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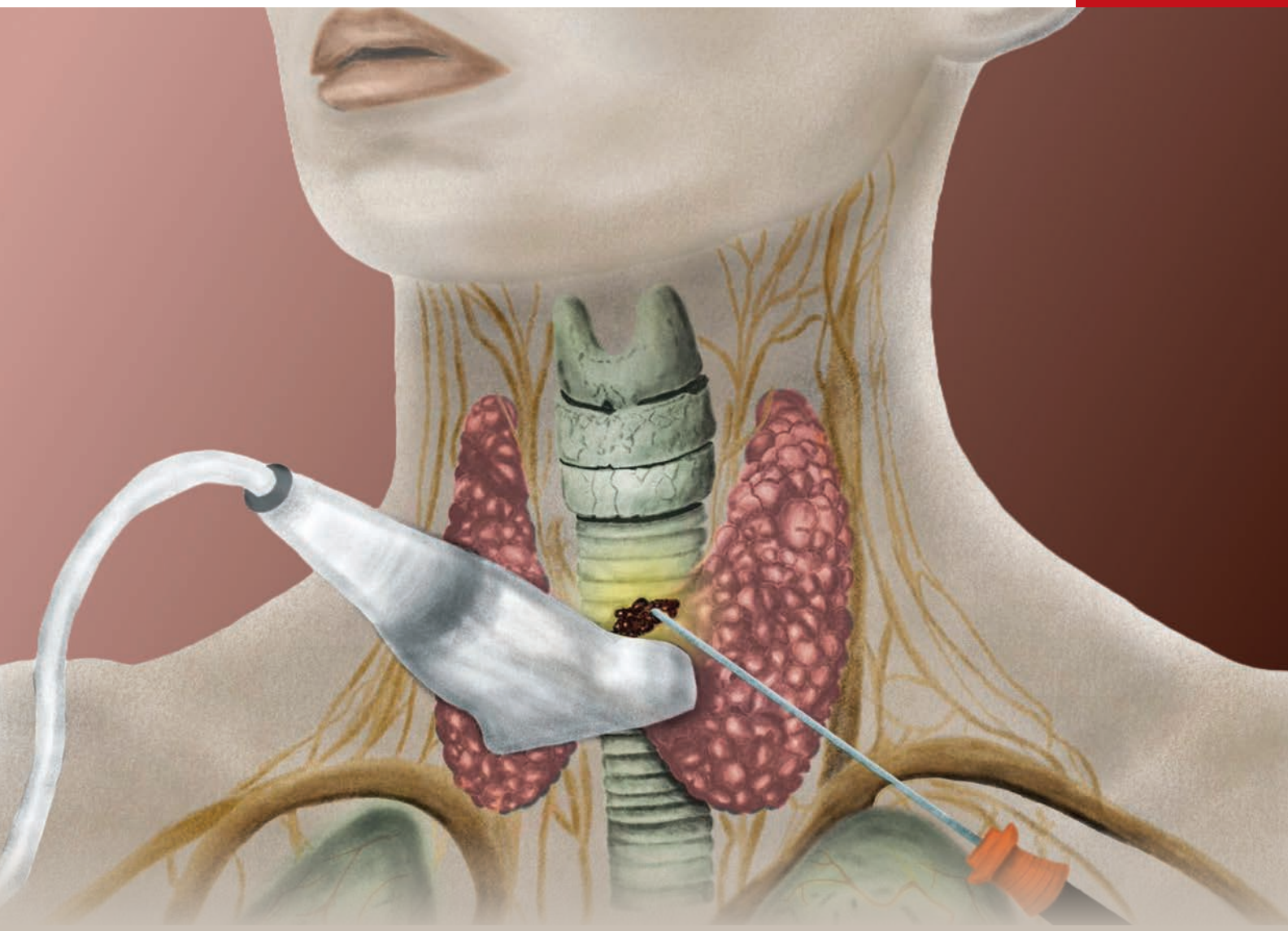

The efficacy and safety of radiofrequency ablation in papillary thyroid carcinoma: A systematic review and meta-analysis

Radiofrequency ablation may be an effective and safe alternative treatment choice to treat papillary thyroid carcinoma, particularly for patients with comorbidities who are not surgical candidates. (See full article, p.170)

Illustration by Maria De-Castro

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EDITORIAL

Strengthening HRQOL assessment in Singapore: Updated norms for EQ-5D-5L and EORTC QLQ-C30

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Health-related quality of life (HRQOL) is increasingly used as an important indicator of health outcomes for measuring the impact of illness and treatment among individuals with mental or physical conditions. The EuroQol 5-dimension (EQ-5D) questionnaire is one of the most widely used generic measures for HRQOL and estimating the quality-adjusted life-years gained for economic evaluations of health treatments and programmes. The original version EuroQol 5-dimension 3-level (EQ-5D-3L) questionnaire contains 5 items covering 5 dimensions of HRQOL using 3 response levels, while the new version EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire has been expanded to 5 response levels to improve its sensitivity and reduce the ceiling effects.[1] The scores from each dimension can be converted into an index score by applying country-specific value sets elicited from the general population. Given the lack of a gold standard in HRQOL measures, interpretation of the index scores requires population norm data as a reference point for identifying the burden of disease in patients with certain conditions or groups of patients. This can be done by comparing their profiles against an average person from similar characteristics, such as age and/or sex, in the general population.[2]

In Singapore, since 2013, the population norm data for the original version of EQ-5D-3L index scores—based on Singapore[3] and UK[4] preference weights—have been established and widely used in previous studies to assess health outcomes. In this issue of the *Annals*, Tan et al. provide updated population norms for the new EQ-5D-5L using Singapore preference weights.[5] This study is timely, given that it has been more than a decade since the new version of the EQ-5D-5L was introduced by the EuroQol Group. Regrettably, population norm data for the instrument are not yet available for the Singapore population.

In a cross-sectional household survey of a representative sample of adult Singapore residents aged 21 years and above, Tan et al. found that the EQ-5D-5L index scores decreased with increasing age, and are slightly lower in females than males and in non-Chinese populations than the Chinese group.[5] The current findings are consistent with the previously published studies that established the population norm data for the original EQ-5D-3L index values based on Singapore and UK preference weights.[6,7] The study also found that the mean EQ-5D-3L index scores decreased with increasing age, were lower among females than males, and were lower among other ethnic groups such Indians and Malays compared to Chinese.[6,7] These findings seem to suggest that the estimates generated by the 2 versions of the EQ-5D for the Singapore general population are similar and consistent over time. However, further longitudinal studies are needed to explore the consistency of the trends of HRQOL over time by these 2 instruments in this population.

The study by Tan et al. is also one of the first to provide population norm data for the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire 30 (EORTC QLQ-C30) in Singapore.[5] EORTC QLQ-C30 is a disease-specific measure commonly used to measure HRQOL in those with cancer, including lung, colorectal and breast cancer. The instrument contains 30 items covering 5 functional scales (15 items), 9 symptoms' scales (13 items) and 1 summary score for a global quality-of-life scale (2 items). The scores range from 0 to 100, with higher scores on the global quality-of-life scale indicating a higher level of HRQOL. The study shed light on the fact that the EQ-5D-5L was significantly correlated with all the EORTC QLQ-C30 subscales. These findings seem to suggest that generic and cancer-specific measures are measuring similar constructs of the HRQOL in the Singapore population. This finding is consistent with the earlier validation study by Luo et al., which also suggests that the EORTC QLQ-C30 was measuring similar dimensions of HRQOL as generic measures like the 36-Item Short Form Survey.[8] The study by Tan et al. also highlighted that the mean of the global

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quality-of-life subscale was higher among those aged 45–64 years than both younger and older age groups. This curvilinear relationship between the scores and age could be attributed to many factors including the ever-increasing healthcare and living costs in Singapore, which affects older adults more because of their greater healthcare needs and diminishing income compared to younger adults.[5] However, future longitudinal research is needed to explore the underlying mechanism of this association using more complex analysis including mediation analysis.

One of the key strengths of this study is that it was conducted using a representative sample of the adult population in Singapore and utilised marginal means from multivariable linear regression models to adjust for confounding in generating population norm data. This makes the estimates generalisable to the multiethnic local population. Hence, future studies are encouraged to use this normative data as a benchmark for comparison and to further examine the HRQOL within different subgroups of the population.

Ethics statement

Not applicable.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Keywords: *EQ-5D, health-related quality of life, population norms, QLQ-C30, Singapore*

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EDITORIAL

Enhancing HIV pre-exposure prophylaxis using telehealth: Insights from the iPARTY study

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Human immunodeficiency virus (HIV) infections are increasing globally despite significant advancements in preventive and treatment programmes.[1] This alarming trend is particularly pronounced within high-risk popula-tions, especially among young men who have sex with men (YMSM). Given these rising infection rates, studies such as the iPARTY study are highly pertinent and essential. The study provides valuable insights into the implementation of pre-exposure prophylaxis (PrEP) among YMSM in Singapore, shedding light on critical factors that influence adherence, such as sexual practices and mental health.[2] Despite the well-documented efficacy of PrEP in significantly reducing the risk of HIV transmission, its uptake remains suboptimal. This is especially true for younger individuals who may encounter barriers such as financial difficulties, lack of awareness and social constraints.

One of the key strengths of the iPARTY study is its focus on teleconsultations for PrEP implementation. The study found that telehealth services were well-received by participants, indicating a promising avenue for increasing PrEP accessibility. Telehealth has emerged as a crucial tool in ensuring that high-risk individuals can access preventive healthcare without fear of stigma or logistical challenges.[3] This is particularly relevant in regions where YMSM and other at-risk groups face societal stigma, which may discourage them from seeking in-person services. Teleconsultations also provide convenience and cost savings, especially for individuals who do not reside near healthcare facilities that offer PrEP services.

Another significant finding of the study is the decline in adherence to daily PrEP over the study period. While adherence rates were initially high, they declined significantly towards the study's conclusion. This trend aligns with findings from other PrEP-related studies, underscoring the challenge of not only initiating PrEP but also ensuring long-term adherence. Several factors contribute to this decline, including medication fatigue, the perception of reduced risk and concerns about the long-term impact of PrEP use. Addressing these issues requires the implementation of adherence strategies such as regular counselling, peer support, and reminder systems. These interventions could help mitigate the decline in adherence and improve overall PrEP outcomes.[4]

The study also reported a reduction in condom use among participants and a concurrent rise in sexually transmitted infections (STIs). This phenomenon, known as risk compensation, is commonly observed in PrEP-related research.[5] It suggests that some individuals develop a false sense of security when using PrEP, leading them to engage in higher-risk sexual behaviours, including reduced condom use. While PrEP is highly effective at preventing HIV transmission, it does not protect against other STIs, making the integration of behavioural counselling into PrEP programmes essential. Addressing risk compensation through education and counselling can help ensure that PrEP users maintain comprehensive sexual health practices.

Interestingly, the study also observed a reduction in the number of sexual partners over time among participants. This suggests that while some aspects of risk behaviour may increase (such as reduced condom use), others may simultaneously decrease. This complex dynamic highlights the need for tailored interventions that address both biomedical and behavioural aspects of HIV prevention. By incorporating behavioural counselling, healthcare providers can reinforce safe sex practices, promote condom use, and help PrEP users make informed decisions about their sexual health.

A particularly noteworthy finding of the study is the statistically significant reduction in participants' PHQ-9 scores, indicating improvements in mood and mental health. Given the well-established intersection between mental health and HIV risk, incorporating psychological support into PrEP programmes is crucial. Many individuals in high-risk populations experience mental health challenges, including depression and anxiety, which can impact

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their ability to adhere to PrEP and engage in safe sex practices.[6] The study highlights the potential of telehealth services not only in delivering PrEP but also in providing mental health support. By leveraging telehealth, healthcare providers can offer integrated care that addresses both the physical and psychological well-being of individuals at risk for HIV.

Telehealth initiatives have already been successfully implemented in other Southeast Asian countries, such as Vietnam and Thailand, to enhance PrEP accessibility.[7] These programmes demonstrate the feasibility of using technology to overcome barriers to healthcare access. By expanding telehealth services, Singapore and other countries in the region can improve PrEP uptake and adherence while simultaneously addressing the mental health needs of at-risk populations. Telehealth platforms also allow for more discreet and confidential healthcare interactions, which can be particularly beneficial for individuals who may fear discrimination or stigma when seeking in-person PrEP services.

Despite its valuable contributions, the iPARTY study has certain limitations that should be acknowledged. One major limitation is the high dropout rate, which may introduce bias and affect the generalisability of the findings. Additionally, the study relied on self-reported data, which can be subject to recall bias and social desirability bias. Participants may have over- or under-reported certain behaviours, leading to potential inaccuracies in the data. Furthermore, while the study was conducted in Singapore, its findings may not be entirely applicable to other settings with different healthcare infrastructures and cultural attitudes toward PrEP and sexual health. Future research should explore strategies to improve retention and adherence in PrEP programmes, particularly among younger populations and in Southeast Asian contexts where accessibility and stigma remain significant concerns.

Another potential area for future research is the role of long-acting injectable PrEP in addressing adherence challenges. While daily oral PrEP is effective, some individuals struggle with the commitment to taking a pill every day. Long-acting PrEP formulations, which require less frequent dosing, may help improve adherence and overall effectiveness.[8] Studies exploring the feasibility and acceptability of long-acting PrEP among YMSM could provide valuable insights into how to optimise HIV prevention strategies.

The study also underscores the importance of community engagement and peer support in PrEP implementation. Community-based approaches, including peer-led education and support groups, can enhance PrEP uptake and adherence.[9] By involving community members in the design and delivery of PrEP programmes, healthcare providers can create more culturally competent and accessible services that meet the unique needs of YMSM and other high-risk populations.

Overall, the iPARTY study adds to the growing body of evidence supporting the use of PrEP and telehealth in HIV prevention. Its findings reinforce the need for integrated, patient-centred approaches that address both biomedical and behavioural aspects of HIV risk. Expanding PrEP access, improving adherence strategies and leveraging telehealth innovations will be critical in achieving more widespread and effective HIV prevention in Singapore and the broader Southeast Asian region. By addressing the challenges identified in this study—such as adherence decline, risk compensation and mental health support—healthcare providers and policymakers can develop more comprehensive strategies to combat the ongoing HIV epidemic.

In conclusion, while PrEP represents a significant advancement in HIV prevention, its full potential can only be realised through strategic implementation that considers behavioural, psychological and logistical factors. The insights gained from the iPARTY study highlight the importance of continued research, innovation and collaboration in the fight against HIV. By integrating PrEP into broader sexual health initiatives, leveraging technology to enhance access and addressing the complex factors that influence adherence, we can move closer to reducing HIV transmission rates and improving the overall health and well-being of high-risk populations. Future studies should build upon these findings to refine and optimise PrEP delivery models, ensuring that all individuals who can benefit from PrEP have the support and resources they need to stay protected against HIV.

Declaration

The author has no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: *HIV, infectious diseases, pre-exposure prophylaxis, sexually transmitted diseases, YMSM*

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ORIGINAL ARTICLE

Health-related quality of life in Singapore: Population norms for the EQ-5D-5L and EORTC QLQ-C30

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ABSTRACT

Introduction: Comparison of patient health-related quality of life (HRQOL) scores to a reference group is needed to quantify the HRQOL impact of disease or treatment. This study aimed to establish population norms for 2 HRQOL questionnaires—EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire 30 (EORTC QLQ-C30) according to age, sex and ethnicity—and to explore relationships between the EQ-5D-5L, EORTC QLQ-C30 and sociodemographic characteristics. We used a representative sample of adult Singapore residents aged 21 years and above.

Method: This study used data collected from a cross-sectional household survey in which 600 adult Singaporeans completed questions on sociodemographic characteristics—the EQ-5D-5L and the EORTC QLQ-C30. Multiple linear regression analyses were conducted to explore associations between sociodemographic characteristics, the EQ-5D-5L scores and the EORTC QLQ-C30 scores. Regression-based population norms were computed for each subgroup using a post-stratification method.

Results: In multiple linear regression analysis, age was significantly associated with EQ-5D-5L index and visual analogue scale (VAS) scores, while no sociodemographic characteristics were significantly associated with EORTC QLQ-C30 summary scores. The normative EQ-5D-5L index and VAS scores decreased in adults aged 65 years and above, and EQ-5D-5L index scores were slightly lower in females than males and in non-Chinese than Chinese. The normative EORTC QLQ-C30 summary scores were slightly higher in Chinese than in the non-Chinese group and in the 45–64 age group than other age groups.

Conclusion: This study provides population norms for the EQ-5D-5L and EORTC QLQ-C30 for the general adult population in Singapore. Future studies of patient populations in Singapore using EQ-5D-5L or QLQ-C30 can use these normative data to interpret the HRQOL data collected.

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Keywords: EQ-5D, health-related quality of life, population norms, QLQ-C30, Singapore

CLINICAL IMPACT

What is New

- Normative EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L) index scores in Singapore decreased with increasing age and were lower in females and non-Chinese individuals.
- Normative Quality of Life Questionnaire-Core Questionnaire 30 (QLQ-C30) summary scores are higher in middle-aged individuals than in young and older individuals.

Clinical Implications

- Future studies of patient populations in Singapore using EQ-5D-5L or QLQ-C30 can use these regression-based norms to interpret data.
- These normative data can also facilitate population health monitoring in Singapore through informing the priorities of public health programmes and evaluating the effectiveness of disease management policies.

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INTRODUCTION

Health-related quality of life (HRQOL) is a multidimensional assessment of the impact of disease and treatment on physical, psychological and social aspects of individuals' lives.[1,2] HRQOL is an important outcome measure of healthcare interventions that is increasingly used in clinical research and practice.[1,3] HRQOL instruments may be generic or disease-specific.[4] Generic instruments are broadly applicable across disease groups, whereas disease-specific instruments are designed for particular diseases and patient populations.[5] While generic instruments are useful for comparing HRQOL among different populations, they are usually less sensitive than disease-specific instruments to the impact of particular aspects of diseases and their treatments on HRQOL.[4,5] Hence, using generic and disease-specific HRQOL instruments in conjunction allows for both cross-population comparisons and deep dive into symptoms or health aspects particular to the condition.[5]

For quantifying the HRQOL impact of disease or treatment, comparison of HRQOL scores of a target patient group with a reference group is needed.[6] In randomised trials, the control group provides the ideal reference group for assessing specific effects of alternative treatment options. The general population is another relevant reference group, providing interpretive value about the impact of any specific disease relative to the background level of health in a general population. Therefore, HRQOL scores of the general population provide useful information for interpreting patients' HRQOL scores for any study design and may be the only option for single-arm clinical studies.

These scores, also called population norms, are usually derived from general population health surveys using the questionnaires of certain HRQOL instruments.[6] Population norms are published as means and standard deviations (SDs) of HRQOL scores for subgroups stratified by sociodemographic variables such as age, sex and ethnicity[6] so that adjusted comparisons can be made when quantifying disease burden, given that the prevalence of health conditions may vary by sociodemographic variables. The HRQOL of general populations in different countries may differ due to real health differences and different perceptions of and responses to HRQOL questionnaires influenced by respondents' cultural background including values, beliefs and religion.[6,7] As a result, it is necessary to establish country-specific population norms for HRQOL instruments.

EQ-5D is a generic HRQOL instrument developed by the EuroQol Group in 1990.[8] The original version of the EQ-5D (the EQ-5D-3L) includes 3 response levels for each of its 5 dimensions including mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.[9] The EQ-5D-5L, which has 5 response levels for each dimension, was introduced in 2009 to increase sensitivity and reduce ceiling effects in measurement.[8] According to a recent systematic review, the EQ-5D-5L was associated with better measurement properties compared to the EQ-5D-3L.[10] Population norms for the EQ-5D-5L have been established for many countries including the US,[11] China[12] and Spain.[13] The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core Questionnaire 30 (EORTC QLQ-C30) is the core of a series of cancer-specific HRQOL instruments that cover the most commonly seen cancers such as lung, colorectal and breast cancers.[14] Population norms for the EORTC QLQ-C30 have been established for several countries including Germany,[15] the Netherlands[16] and Australia.[17]

The EQ-5D has been shown to be a valid HRQOL instrument for various health conditions including cancers in Singapore,[18] a city-state in Southeast Asia inhabited by a multicultural, multi-ethnic population of 6 million consisting of Chinese (74.0%), Malays (13.5%), Indians (9.0%) and other ethnic groups (3.4%).[19] However, Singaporeans' population norms are available for only EQ-5D-3L based on a survey conducted from 2009 to 2010.[20] Similarly, EORTC QLQ-C30 was validated in local cancer patients,[21] but local normative data have not been available.

The present study aimed to establish population norms for both the EQ-5D-5L and the EORTC QLQ-C30 according to age, sex and ethnicity using a representative sample of adult Singapore residents aged 21 years and above. In addition, the study explored relationships between the EQ-5D-5L, EORTC QLQ-C30 and the sociodemographic characteristics of the Singapore population.

METHOD

Study design and data collection

In a cross-sectional household survey, we used a 3-stage sampling method to recruit community-dwelling adult Singaporeans according to demographic quotas for age, sex, ethnic group and apartment size. Eligibility criteria were: (1) 21 years old or above (age of adult by law in Singapore), (2) Singapore citizen or permanent resident, (3) ability to read and communicate in English or Chinese, (4) able to provide informed consent. The survey form was available in 2 languages (English and Chinese)

for participants to choose from. Detailed sampling and data collection processes are reported in Supplementary Material S1. This study received ethical approval from the SingHealth Centralised Institutional Review Board (CIRB 2018/2345).

Instruments

EQ-5D-5L

The EQ-5D-5L is a self-administered questionnaire describing respondents' health on the day of survey in 5 dimensions (i.e. mobility, self-care, usual activities, pain or discomfort, and anxiety or depression). The questionnaire includes a hash-marked EuroQol visual analogue scale (EQ VAS) for respondents to rate their overall health on the day of survey. Detailed scoring methods are reported in Supplementary Material S2.

QLQ-C30

The QLQ-C30 is a questionnaire designed to measure the HRQOL of cancer patients.[22] It consists of 30 questions. Detailed scoring methods are provided in Supplementary Material S3.

Statistical analysis

Statistical analyses were carried out using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio version 2022.07.2 (Posit, Boston, MA, US). Means and SDs were calculated for continuous variables, and frequencies and percentages for categorical variables. Data were presented separately by age, sex, ethnicity and language of survey used. We used 3 categories of age to present the data: 21–44, 45–64 and ≥65 years. Multiple linear regression analyses were used to identify sociodemographic characteristics that were statistically significant predictors of EQ-5D-5L and QLQ-C30 scores, which would be accounted for in the computation of population norms. Age, sex, ethnicity, language, marital status, educational level and housing type were included as categorical variables in the regression models (see Table 1 for categories of each variable). We examined the associations between EQ-5D-5L and QLQ-C30 scores using Spearman's correlations. For all analyses, a P value of <0.05 was considered statistically significant.

Raking, a post-stratification technique, was used to create sample weights to match the population distributions for age, sex, ethnicity, education level and income shown in Table 1.[23] We utilised a regression-based method to compute the population norms for each subgroup rather than presenting the observed means and SDs of scores, because this would allow us to control for the effect of other sociodemographic variables by including them as predictors in the regression models (Supplementary Material S4).[24,25] This method also allowed us to provide norms for subgroups where there were no or very few observations. Using separate linear regression models, we generated normative data for EQ-5D-5L index, VAS, QLQ-C30 summary scale, functional and symptom subscales, each for a total of 12 subgroups defined by age (21–44, 45–64 and ≥65 years), sex (male and female), ethnicity (Chinese and non-Chinese).

Table 1. Sample sociodemographic characteristics (n=600).

Variable	Sample, no. (%)	Population (%)
Language of survey		Not applicable
English	452 (75.3)	
Mandarin	148 (24.7)	
Sex, male	292 (48.7)	48.7
Age, median (IQR), years	45.0 (34.0–59.0)	42.4
21–44	289 (48.2)	42.9
45–64	215 (35.8)	35.7
≥65	96 (16.0)	21.4
Ethnicity		
Chinese	451 (75.2)	74.0

Table 1. Sample sociodemographic characteristics (n=600). (Cont'd)

Variable	Sample, no. (%)	Population (%)
Malay	76 (12.7)	13.5
Indian	60 (10.0)	9.0
Others	13 (2.2)	3.4
Highest level of education (n=597)		
Primary or lower	65 (10.9)	20.9
Secondary	75 (12.6)	16.0
O level/A level/diploma	195 (32.7)	26.9
University and above	262 (43.9)	36.2
Current marital status (n=597)		
Never married	158 (26.3)	28.6
Currently married	393 (65.5)	61.8
Separated	4 (0.7)	4.7
Divorced	28 (4.7)	
Widowed	14 (2.3)	4.9
Type of housing		Not available
1-, 2- or 3-room HDB flat	149 (24.8)	
4-room HDB flat	251 (41.8)	
5-room or executive HDB flat	200 (33.3)	
Current employment status (n=596)		Not available
Working	406 (67.7)	
Student (full-time)	25 (4.2)	
National Service	3 (0.5)	
Homemaker/housewife	75 (12.5)	
Retired	60 (10.0)	
Unemployed (able to work)	26 (4.3)	
Unemployed (unable to work because of disability or other medical conditions)	1 (0.2)	
Monthly household income, SGD (n=508)		
Below 2000	97 (16.2)	18.4
2000–3999	127 (21.2)	8.5
4000–5999	111 (18.5)	8.8
6000–9999	111 (18.5)	17.1
10,000 and above	62 (10.3)	47.2

IQR: interquartile range; HDB: Housing & Development Board; SGD: Singapore dollar

RESULTS

There was a total of 600 respondents, comprising 452 (75.3%) English-speaking and 148 (24.7%) Chinese-speaking respondents. There were 289 (48.2%) respondents aged 21–44 years, 215 (35.8%) aged 45–64 years and 215 (35.8%) respondents aged ≥65 years; 292 (48.7%) respondents were male; and 451 (75.2%) respondents were Chinese, 76 (12.7%) were Malay, 60 (10.0%) respondents were Indian, and 13 (2.2%) were of other ethnic groups. The total number of participants by sex, age and ethnicity are shown in Supplementary Table S1.

The highest level of education was university degree and above in 262 (43.9%) respondents, O level/A level/diploma in 195 (32.7%), and secondary education or lower in 140 (23.5%). Most respondents (251, 41.8%) were living in 4-room Housing & Development Board (HDB) apartments, were employed (406, 67.7%) and were married (393, 65.5%). The monthly household income was below SGD2000 in 97 (16.2%) respondents, SGD2000–3999 in 127 (21.2%), SGD4000–5999 in 111 (18.5%), SGD4000–9999 in 111 (18.5%) and SGD10,000 and above in 62 (10.3%). The demographic characteristics of the sample were similar to census data except that our sample was slightly younger, better educated and earned less (Table 1).

Spearman's correlations between the EQ-5D-5L and the QLQ-C30 scores were all statistically significant (Table 2). Conceptually similar domains (e.g. the QLQ-C30 pain subscale and the EQ-5D-5L pain/discomfort dimension: 0.61) had higher absolute correlations, while conceptually dissimilar domains (e.g. the QLQ-C30 cognitive functioning subscale and the EQ-5D-5L self-care dimension: -0.05) had lower absolute correlations.

Table 2. Spearman's correlation coefficients between EQ-5D and QLQ-C30 items/scores (n=600).

QLQ-C30	EQ-5D						
	Mobility	Self-care	Usual activities	Pain/ discomfort	Anxiety/ depression	Index	VAS
Global health/QoL	-0.18[a]	-0.14[a]	-0.22[a]	-0.30[a]	-0.28[a]	0.38[a]	0.62[a]
Physical functioning	-0.34[a]	-0.13[b]	-0.24[a]	-0.34[a]	-0.22[a]	0.40[a]	0.33[a]
Role functioning	-0.19[a]	-0.19[a]	-0.34[a]	-0.22[a]	-0.15[a]	0.25[a]	0.15[a]
Emotional functioning	-0.11[b]	-0.08[c]	-0.23[a]	-0.27[a]	-0.46[a]	0.42[a]	0.24[a]
Cognitive functioning	-0.13[b]	-0.05	-0.15[a]	-0.30[a]	-0.31[a]	0.36[a]	0.26[a]
Social functioning	-0.29[a]	-0.23[a]	-0.39[a]	-0.33[a]	-0.31[a]	0.39[a]	0.31[a]
Fatigue	0.19[a]	0.16[a]	0.25[a]	0.39[a]	0.32[a]	-0.45[a]	-0.34[a]
Nausea/vomiting	0.08	0.10[c]	0.20[a]	0.15[a]	0.16[a]	-0.16[a]	-0.14[a]
Pain	0.35[a]	0.17[a]	0.30[a]	0.61[a]	0.21[a]	-0.55[a]	-0.28[a]
Dyspnoea	0.22[a]	0.16[a]	0.29[a]	0.23[a]	0.19[a]	-0.25[a]	-0.21[a]
Insomnia	0.14[a]	0.16[a]	0.14[a]	0.36[a]	0.26[a]	-0.35[a]	-0.21[a]
Appetite	0.18[a]	0.17[a]	0.24[a]	0.28[a]	0.24[a]	-0.31[a]	-0.18[a]
Constipation	0.15[a]	0.06	0.21[a]	0.17[a]	0.19[a]	-0.21[a]	-0.13[b]
Diarrhoea	0.06	0.09[c]	0.08	0.07	0.06	-0.06	-0.05
Financial difficulties	0.24[a]	0.21[a]	0.45[a]	0.27[a]	0.22[a]	-0.30[a]	-0.27[a]
QLQ-C30 summary score	-0.30[a]	-0.16[a]	-0.28[a]	-0.54[a]	-0.40[a]	0.60[a]	0.37[a]

[a]$P<0.001$; [b]$P<0.01$; [c]$P<0.05$
EQ-5D: EuroQol 5-dimension questionnaire; QLQ-C30: Quality of Life Questionnaire-Core Questionnaire 30; QoL: quality of life; VAS: visual analogue scale

In the multivariate linear regression analysis, older age (≥65 years) was associated with lower EQ-5D-5L index (β -0.04; standard error [SE] 0.02; *P*=0.008) and EQ VAS (β -6.0; SE 1.56; *P*<0.001). No variables were significantly associated with the QLQ-C30 summary score (Table 3).

Population norms were computed using estimated marginal means for the EQ-5D-5L index, EQ VAS and QLQ-C30 summary score (Table 4), each functional subscale of the QLQ-C30 (Table 5), and each symptom subscale of the QLQ-C30 and financial difficulties (Supplementary Table S2) for age, sex and ethnicity groups. The normative EQ-5D-5L index and EQ VAS scores were similar for the young and middle-aged subgroups, which were higher than those for the old subgroup; EQ-5D-5L index scores were slightly lower in females and non-Chinese participants.

The normative QLQ-C30 scores decreased with age for the physical functioning, social functioning, nausea/vomiting and appetite loss subscales; increased with age for the emotional functioning, pain and financial difficulties subscales; and exhibited a non-monotonic relationship with age for global health, role functioning, cognitive functioning, fatigue, dyspnoea, insomnia, constipation and diarrhoea subscales. The normative QLQ-C30 scores for males were similar to those for females for the physical functioning, cognitive functioning, social functioning and fatigue scales; higher than those for females for the role functioning, emotional functioning, nausea/vomiting, dyspnoea, insomnia and financial difficulties subscales; but lower than those for females for the global health, pain, constipation and diarrhoea subscales. The normative QLQ-C30 scores for Chinese were similar to or higher than those for non-Chinese for all functional scales, and lower than those for non-Chinese for all the symptom scales and financial difficulties. Following post-stratification weighting, the normative score for Chinese females aged ≥65 years on the fatigue subscale was -0.35. As scores range from 0 to 100, a score of 0 can be considered the normative score for this subgroup.

DISCUSSION

More than a decade has passed since Singapore's population norms for the EQ-5D-3L were published, and before this study, there was a lack of population norms for the EQ-5D-5L and QLQ-C30 in Singapore. Given the improved sensitivity of the EQ-5D-5L compared to the EQ-5D-3L, establishing population norms for the EQ-5D-5L would provide useful reference data for studies in Singapore. Using multivariate linear regression models and estimated marginal means, we produced population norms for the EQ-5D-5L and QLQ-C30 questionnaires for the general adult population in Singapore.

The trends found in the EQ-5D-5L index scores in this study were similar to other countries' population norms and the previously published EQ-5D-3L population norms.[20] EQ-5D-5L index scores were negatively associated with age in both studies, indicating a trend of worsening mobility, self-care, usual activities, pain/discomfort and anxiety/depression with ageing. The normative EQ-5D-5L index scores were slightly higher for male respondents. These findings were consistent with other studies, which showed that EQ-5D-5L index and EQ VAS scores decreased with increasing age[11,20] and that women had lower EQ-5D-5L index scores than men.[12] These trends were also consistent with patterns in population norms of other countries, such as Vietnam, China and Australia.[12,26,27] Normative EQ-5D-5L index scores were slightly higher for Chinese compared to non-Chinese groups. This is consistent with evidence for wide socioeconomic disparities experienced by ethnic minorities in Singapore, which has led to disparities in health literacy, health-seeking behaviours and financial resources.[28,29] The higher EQ-5D-5L index scores for Chinese respondents could also be attributed to face-saving culture, characterised by a greater reluctance to admit health problems due to their social undesirablility.[30]

Consistent with existing studies, the QLQ-C30 subscale scores in our population sample decreased with age for the physical functioning subscales, but increased with age for the emotional functioning subscale.[15-17,31] The non-monotonicity of the QLQ-C30 summary score was likely driven by the non-monotonicity of the global health, role functioning, cognitive functioning and symptom subscales. Similar non-monotonicity has been found in other countries for several of the QLQ-C30 subscales including role functioning, cognitive functioning, fatigue and dyspnoea.[17,31] This differing association with age may be due to the different constituent dimensions of EQ-5D-5L and QLQ-C30. EQ-5D-5L comprises primarily physical health dimensions, while QLQ-C30 consists of psychological, social and symptom dimensions which tend to have complex association with age. The absence of association between age and the QLQ-C30 summary score in multiple linear regression analysis and the minimal non-monotonicity in the normative data could be due to the cancellation of the various monotonic and non-monotonic relationships of the subscales with age after aggregation.

Table 3. Linear regression analysis of QLQ-C30 and EQ-5D scale scores: regression coefficients of sociodemographic characteristics (n=600).

	Global QoL	Physical functioning	Role functioning	Emotional functioning	Cognitive functioning	Social functioning	Fatigue	Pain	Insomnia	C30 summary score	EQ-5D index	EQ-5D VAS
Language												
English	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mandarin	2.8 (1.9)	-2.7[c] (1.2)	1.6 (1.8)	5.6[a] (1.9)	0.04 (1.6)	0.64 (1.6)	-1.6 (1.9)	-0.63 (1.9)	0.36 (2.5)	-0.47 (1.1)	0.01 (0.0)	1.8 (1.3)
Sex												
Male	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Female	1.8 (1.4)	-0.54 (0.9)	-0.11 (1.3)	-2.1 (1.3)	-1.1 (1.1)	1.0 (1.1)	2.3 (1.4)	2.9[c] (1.4)	2.2 (1.8)	0.87 (0.8)	-0.01 (0.0)	-0.11 (0.9)
Age (years)												
21–44	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
45–64	-0.29 (1.8)	-3.7[a] (1.1)	0.19 (1.6)	2.7 (1.7)	-0.38 (2.7)	-0.13 (1.4)	-3.8[c] (1.8)	2.2 (1.8)	-0.44 (2.3)	0.19 (1.0)	-0.01 (0.0)	-2.0 (2.1)
≥65	-3.8 (2.4)	-6.4[a] (1.5)	-1.5 (2.2)	7.1[a] (2.3)	0.59 (1.5)	-0.20 (2.0)	-1.9 (2.4)	4.2 (2.4)	-1.5 (3.1)	0.50 (1.4)	-0.04[a] (0.0)	-6.0[a] (1.2)
Ethnicity												
Chinese/other	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Malay	-1.1 (2.3)	-2.6 (1.5)	-0.14 (2.2)	3.6 (2.2)	3.1 (1.9)	-0.52 (1.9)	3.3 (2.3)	-0.48 (2.3)	-0.79 (3.0)	0.32 (1.3)	-0.03 (0.0)	0.77 (1.5)
Indian	3.9 (2.3)	-5.6[a] (1.5)	-5.1[c] (2.2)	1.6 (2.3)	-1.6 (2.0)	-2.4 (1.9)	-2.4 (2.3)	0.21 (2.4)	0.00 (3.0)	-1.4 (1.3)	-0.02 (0.0)	-0.08 (1.5)
Highest level of education												
PSLE/ primary or lower	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Secondary	0.80 (2.8)	-1.0 (1.8)	-2.2 (2.7)	-3.7 (2.8)	-1.3 (2.4)	1.4 (2.3)	2.8 (2.8)	5.2 (2.9)	1.3 (3.6)	-0.60 (1.6)	-0.02 (0.0)	-2.1 (1.9)

Table 3. Linear regression analysis of QLQ-C30 and EQ-5D scale scores: regression coefficients of sociodemographic characteristics (n=600). (Cont'd)

	Global QoL	Physical functioning	Role functioning	Emotional functioning	Cognitive functioning	Social functioning	Fatigue	Pain	Insomnia	C30 summary score	EQ-5D index	EQ-5D VAS
O level/N level or NTC 3 certificate or its equivalent/A level or NTC 1–2 or certificate in office/business skills or its equivalent/ other diploma and professional qualification	0.46 (2.6)	0.67 (1.6)	-1.0 (2.4)	3.0 (2.5)	4.7[c] (2.2)	1.1 (2.1)	-1.0 (2.6)	-0.51 (2.6)	-2.0 (3.3)	1.7 (1.5)	0.01 (0.0)	-0.72 (1.7)
Polytechnic diploma/ university and above	5.4 (2.9)	0.91 (1.8)	0.01 (2.7)	4.0 (2.8)	4.9[c] (2.4)	2.7 (2.4)	-3.2 (2.9)	-2.3 (3.0)	-2.1 (3.7)	3.1 (1.7)	0.01 (0.0)	2.0 (1.9)
Current marital status												
Never married	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Currently married	1.4 (1.7)	0.32 (1.1)	0.84 (1.6)	0.35 (1.6)	1.0 (1.4)	-1.2 (1.4)	-1.8 (1.7)	-1.7 (1.7)	-1.5 (2.1)	0.79 (1.0)	0.01 (0.0)	0.65 (1.1)
Separated/divorced/ widowed	-0.19 (2.9)	-1.3 (1.8)	-2.1 (2.7)	-1.3 (2.8)	-0.71 (2.4)	-0.52 (2.4)	-2.4 (2.9)	-2.0 (2.9)	-2.2 (3.7)	1.0 (1.7)	-0.03 (0.0)	1.2 (1.9)
Type of housing												
1-, 2- or 3-room HDB flat	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
4-room HDB flat	-0.44 (1.8)	0.27 (1.1)	0.66 (1.7)	-1.4 (1.7)	0.27 (1.5)	-0.27 (1.5)	0.93 (1.8)	-1.9 (1.8)	-1.4 (2.3)	0.17 (1.0)	0.00 (0.0)	0.08 (1.2)
5-room or executive HDB flat	1.0 (1.9)	-1.1 (1.2)	-0.60 (1.8)	-0.57 (1.9)	2.1 (1.6)	-1.3 (1.6)	2.0 (1.9)	-2.1 (2.0)	-2.0 (2.5)	-0.03 (1.1)	0.00 (0.0)	0.48 (1.3)

EQ-5D: EuroQol 5-dimension questionnaire; HDB: Housing & Development Board; NA: not applicable; NTC: national technical certificate; PSLE: primary school leaving examination; QLQ-C30: Quality of Life Questionnaire-Core Questionnaire 30; QoL: quality of life; VAS: visual analogue scale

[a]$P<0.001$; [b]$P<0.01$; [c]$P<0.5$

Table 4. Model-predicted mean (standard error) EQ-5D index, EQ-5D visual analogue scale and QLQ-C30 summary scores by sex, age and ethnicity.

	EQ-5D index score						Visual analogue scale						QLQ-C30 summary score					
	Male			Female			Male			Female			Male			Female		
	21–44 years	45–64 years	≥65 years	21–44 years	45–64 years	≥65 years	21–44 years	45–64 years	≥65 years	21–44 years	45–64 years	≥65 years	21–44 years	45–64 years	≥65 years	21–44 years	45–64 years	≥65 years
Chinese, no. (%)	0.982 (0.018)	0.976 (0.011)	0.940 (0.018)	0.968 (0.015)	0.962 (0.012)	0.926 (0.021)	81.9 (2.2)	81.8 (2.1)	77.7 (3.3)	82.9 (2.1)	82.8 (2.2)	78.6 (2.7)	91.8 (2.0)	93.7 (1.2)	92.2 (1.0)	91.4 (1.5)	93.3 (1.5)	91.8 (1.3)
Non-Chinese, no. (%)	0.939 (0.016)	0.933 (0.021)	0.897 (0.027)	0.925 (0.022)	0.920 (0.027)	0.883 (0.034)	81.6 (1.9)	81.5 (2.0)	77.3 (3.6)	82.5 (2.0)	82.4 (2.2)	78.3 (3.1)	89.6 (1.8)	91.5 (2.2)	90.1 (2.2)	89.2 (2.1)	91.1 (3.0)	89.7 (2.9)

EQ-5D: EuroQol 5-dimension questionnaire; QLQ-C30: Quality of Life Questionnaire-Core Questionnaire 30

Table 5. Model-predicted mean (SE) QLQ-C30 global health/QoL and functional subscale scores by sex, age and ethnicity.

	Male			Female		
	21–44 years	45–64 years	≥65 years	21–44 years	45–64 years	≥65 years
Global health/QoL, no. (%)						
Chinese	72.8 (2.7)	76.2 (2.5)	71.4 (2.7)	75.2 (2.7)	78.6 (2.4)	73.8 (2.6)
Non-Chinese	72.8 (2.7)	76.2 (3.2)	71.4 (3.7)	75.2 (2.8)	78.5 (3.3)	73.7 (3.8)
Physical functioning, no. (%)						
Chinese	95.7 (2.2)	94.1 (1.5)	89.9 (2.0)	95.1 (1.7)	93.5 (1.8)	89.3 (2.0)
Non-Chinese	91.3 (1.7)	89.7 (2.5)	85.5 (2.9)	90.7 (2.1)	89.1 (3.2)	84.9 (3.4)
Role functioning, no. (%)						
Chinese	97.2 (2.2)	98.0 (1.2)	95.5 (1.8)	95.7 (1.7)	96.4 (1.6)	94.0 (2.2)
Non-Chinese	93.0 (1.8)	93.7 (2.9)	91.3 (3.0)	91.5 (2.6)	92.2 (3.9)	89.8 (4.0)
Emotional functioning, no. (%)						
Chinese	86.5 (2.8)	89.1 (2.5)	92.2 (1.9)	83.4 (2.5)	86.0 (2.8)	89.1 (2.2)
Non-Chinese	86.3 (2.2)	89.0 (3.1)	92.0 (3.3)	83.2 (2.9)	85.9 (4.0)	88.9 (4.1)
Cognitive functioning, no. (%)						
Chinese	90.8 (2.5)	93.3 (1.8)	91.1 (2.3)	91.2 (2.1)	93.8 (1.8)	91.5 (2.0)
Non-Chinese	90.5 (2.2)	93.0 (2.0)	90.8 (2.7)	90.9 (2.4)	93.5 (2.6)	91.2 (3.0)
Social functioning, no. (%)						
Chinese	97.2 (1.7)	96.7 (1.3)	94.6 (1.8)	97.6 (1.4)	97.1 (1.2)	95.0 (1.9)
Non-Chinese	95.0 (1.5)	94.5 (1.9)	92.5 (2.2)	95.4 (1.8)	94.9 (2.3)	92.8 (2.7)

QoL: quality of life

The trend in the QLQ-C30 global health/quality of life and social functioning scores differed from that in other studies. Our study showed higher levels of global health for the 45–64 age group than both younger and older groups. In contrast, the results of a multinational study showed higher global health/quality of life for the youngest and oldest age groups, compared to the middle-aged group (30–59 years old).[31] In an Australian study, participants aged 70 years or more had the highest mean scores on the global health/quality-of-life functional subscale.[17] While social functioning scores increased with age in several countries' population norms,[16,17] social functioning decreased with age in our study. These opposite trends between Singapore and other countries could be attributed to the ever-increasing healthcare and living costs in Singapore, which affects older adults more because of their greater healthcare needs and diminishing income compared to younger adults. The high living costs may have reduced social participation among the elderly.[16,17,32]

Non-Chinese respondents in our study had significantly lower QLQ-C30 physical and role functioning scores. This finding supported the previously published study that established the EQ-5D-3L norms, which had also showed that non-Chinese respondents reported more problems with mobility and self-care compared to Chinese respondents in Singapore,[20] as well as a study that found poorer 36-Item Short Form Survey physical functioning scores in non-Chinese respondents compared to Chinese respondents.[33] Factors influencing the physical functioning dimension of HRQOL may have differed across ethnic groups.[33] Otherwise, there may have been differences in how individuals from different ethnic groups answered these questions.[33] This underlines the importance

of accounting for differences in sociodemographic characteristics when analysing and interpreting HRQOL outcomes, particularly in unrandomised comparisons and when estimating population norms.

The EQ-5D-5L was significantly correlated with the QLQ-C30 on all subscales. This was consistent with existing international research[34] showing that generic HRQOL measures correlated well with measures of cancer-related HRQOL in the Singaporean population. While older age significantly predicted poorer EQ-5D-5L index and EQ VAS scores, age did not significantly predict scores on the QLQ-C30 subscales apart from the physical functioning, emotional functioning and fatigue subscales. Taken together, these suggest that age has a larger impact on the specific constructs assessed by EQ-5D-5L compared to those assessed by the QLQ-C30, especially on the self-care dimension (i.e. whether one has problems washing or dressing oneself). The weak correlations between the self-care item and some QLQ-C30 subscales suggest that problems with self-care may not necessarily impact certain domains of HRQOL, such as cognitive functioning.

These population norms can facilitate population health monitoring by helping to inform the priorities of public health programmes and evaluate the effectiveness of disease management policies. By establishing benchmarks for HRQOL, these norms can guide the allocation of resources according to the needs of the population.[35] Lower normative scores could indicate areas that may benefit from preventative interventions, such as reducing social isolation among the elderly to address the decline in social functioning. Utilising normative data in cost-utility analyses can also inform healthcare interventions and insurance reimbursement policies.[36] Further studies employing these instruments are encouraged to allow for cross-national analyses in both Southeast Asian and global contexts.

The strengths of this study were that it comprised a representative sample of the adult population in Singapore, and provided norms for multiple sociodemographic characteristics of the Singapore population. Singapore offers a case study for population health in a multi-ethnic society, and the findings from this study can contribute to global discussions on HRQOL measurements by providing insights into how culture impacts health perceptions. Additionally, this study utilised marginal means estimated with multivariate linear regression models that adjusted for confounders in computing population norms. We encourage other countries to adopt similar methodologies to establish comparable HRQOL data for cross-national analyses. Our quota sampling strategy—set up to achieve national representativeness by age, sex, ethnicity and housing type—resulted in eligible participants being rejected from the study. Due to the lack of data on non-respondents, response rates could not be estimated. We do not think this incurred response bias because respondents were screened out by a local survey company during home visits rather than opting out. However, some response bias may have occurred in the selection of eligible individuals at that stage of sampling.

In addition, we only surveyed Singaporeans living in HDB apartments. People who live in private housing, who might have better or worse HRQOL, were not represented. As private housing is associated with higher socioeconomic status,[37] this may have introduced a socioeconomic bias, limiting generalisability. It would be helpful for future studies to include a more diverse housing sample to more accurately reflect the Singaporean population. Lastly, due to small sample sizes for some subgroups, Malay, Indian and other races were combined into a non-Chinese subgroup, and English and Chinese language groups were combined. Although this was not ideal, this allowed us to ensure adequate sample sizes for statistical analysis, enhancing the reliability of the results. We believe combining language groups for the EQ-5D-5L was appropriate, given strong evidence for measurement equivalence between the English and Chinese versions of the EQ-5D-5L in Singapore.[38,39] Further research on measurement equivalence between the English and Chinese versions of the QLQ-C30 in Singapore is required.

CONCLUSION

This study provides Singaporean population norms for both the EQ-5D-5L and EORTC QLQ-C30 scores. Future studies involving patient populations in Singapore can use these normative data to aid interpretation of the HRQOL data collected.

Supplementary materials

Material S1. Sampling and data collection.

Material S2. EQ-5D-5L.

Material S3. EORTC QLQ-C30.

Material S4. Regression-based method for computing population norms.

Table S1. Number of participants by sex, age and ethnicity (n=600).

Table S2. Model-predicted mean (SE) QLQ-C30 symptom and financial difficulties subscale scores by sex, age and ethnicity.

Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (CIRB 2018/2345).

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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ORIGINAL ARTICLE

iPARTY study: Increasing pre-exposure prophylaxis access and reach via telehealth for young men who have sex with men in Singapore 2022–2023

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ABSTRACT

Introduction: Although pre-exposure prophylaxis (PrEP) has been available in Singapore since 2016, its uptake among gay, bisexual and other men-who-have-sex-with-men (GBMSM) is low. The iPARTY study was established to evaluate the acceptability and feasibility of PrEP and a PrEP teleconsultation service for young GBMSM aged 18 to 29 years.

Method: A total of 53 young GBMSM were enrolled in the iPARTY study. They had a total of 5 in-person consultations and teleconsultations, at 12-week intervals. Laboratory tests and quarterly baseline surveys were performed to assess PrEP adherence, sexual behaviour, and incidence of human immunodeficiency virus (HIV) and other sexually transmitted infections (STIs).

Results: Thirty-five participants completed the entire 12-month follow-up. Most participants had positive experiences with PrEP teleconsultations. There was a statistically significant fall in participants' aggregate Patient Health Questionnaire-9 scores throughout the study. Self-reported PrEP adherence decreased over the course of the study, denoting improved mental health. Although self-reported condom use for anal intercourse and participants' risk perception of HIV decreased after PrEP adoption, there was no statistically significant increase in STI incidence.

Conclusion: This pilot project has shown that PrEP services provide an opportunity for YMSM to access sexual health testing, treatment and counselling, and may even have tangible benefits on the mental health of this population. Teleconsultation is shown to be a suitable platform for the delivery of such services. Collaborative initiatives are crucial to further enhance the affordability and accessibility of PrEP in Singapore, and to improve patient adherence.

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Keywords: HIV, infectious diseases, pre-exposure prophylaxis, STI, young MSM

CLINICAL IMPACT

What is New

- This pilot study is the first to evaluate the acceptability and feasibility of pre-exposure prophylaxis (PrEP) provision via teleconsultation for young men who have sex with men (YMSM).

Clinical Implications

- The study demonstrates that teleconsultation for PrEP services is practical and well-received by YMSM, providing a foundation to support broader implementation.
- These findings offer guidance to expand PrEP accessibility and enhance sexual health services for this population.

INTRODUCTION

Human immunodeficiency virus (HIV) infection remains a significant global health challenge worldwide, with 39 million people living with HIV as of 2022.[1] In Singapore, there were 209 newly diagnosed cases of HIV infections in 2023, a 3% increase from 2022.[2] Although highly active antiretroviral therapy (HAART) effectively suppresses viral replication, lifelong treatment is required.[3,4] Even with HAART, people living with HIV are more susceptible to various long-term comorbidities, including cardiovascular disease, diabetes, frailty and cognitive disorders.[5]

Without an effective cure, preventive measures to avoid contracting HIV are imperative. Pre-exposure prophylaxis (PrEP), which involves the use of

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antiretroviral drugs before potential HIV exposure, is one such measure.[6,7] Although PrEP services have been available in Singapore since 2016, PrEP uptake among gay, bisexual and other men who have sex with men (GBMSM) has been slow; in a 2023 report, although PrEP awareness was high in this population (93.0%), only a minority (25.0%) of those who had heard of PrEP were current PrEP users.[8] PrEP usage among young men who have sex with men (YMSM) is often even lower than their older counterparts, partially due to their financial limitations. Furthermore, YMSM may benefit from PrEP more than their older counterparts;[9] the former are particularly at risk due to their higher rates of risky sexual behaviours, substance use related to sexual activities, and barriers to accessing healthcare services.[10,11]

Hence, the iPARTY study was conducted, with the aim to establish and pilot a 1-year clinical cohort of 50 YMSM aged 18 to 29 in Singapore to assess the delivery, acceptability and feasibility of daily PrEP, as well as a PrEP teleconsultation service for YMSM. There are also concerns that PrEP utilisation could result in an increase in high-risk sexual behaviours, such as condom-less sexual intercourse, having multiple partners, or not discussing STI statuses, due to a perceived lower risk of HIV infection.[12,13] This is known as risk compensation, and could result in a corresponding increase in other STIs.[14] Therefore, our study further assessed the sexual practices and STI incidence of participants to evaluate this phenomenon. Counselling on sexually transmitted infection (STI) and risk compensation was also performed concurrently with PrEP provision.[15]

METHOD

Participant recruitment

Between June 2021 and 2022, 53 participants were enrolled in the study. Inclusion criteria were Singaporean citizen or permanent resident; assigned male at birth (cisgender man or transgender woman); aged 18 to 29 years; HIV-negative (self-reported at enrolment); self-reported sexual intercourse with men and any of the following risk factors for HIV infection in the past 12 months: (1) self-reported condomless anal sex; (2) diagnosis of 1 or more STIs; (3) self-reported use of recreational drugs during sexual activities. The exclusion criteria included the following: unable to provide informed consent; a positive HIV diagnosis; contraindications to the use of the tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) co-formulation for PrEP, including those with impaired kidney function (estimated creatinine clearance, or CrCl<50 mL/min) and those with active Hepatitis B.

Prospective participants were approached by study team members from Action for AIDS (AfA Singapore), a community-based organisation in Singapore that provides sexual health services to YMSM, who assessed participants' eligibility and willingness to participate using a standardised script. For those keen to participate, written informed consent was obtained in a private, confidential setting at National Centre for Infectious Diseases, Singapore (NCID). To ensure anonymity, all participants were issued unique participant identification numbers, which would become the sole means of identification throughout the study; only the HIV physician and the study coordinator would have access to participants' identities. All consultations, tests and generic daily PrEP were provided at no cost to the participants; participants only needed to pay nominal fees for medication delivery, if required.

This study received funding from the NCID Catalyst Fund 2021/2022 and was approved by the National Health Group Domain Specific Review Board (2021/00810).

Investigations

To determine eligibility, tests for hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (anti-HBs) were conducted at the first visit. Serum creatinine was also measured at the beginning of the study and again at 24 weeks to assess eligibility and tolerability, respectively.

STI screening was performed 5 times throughout the study, with intervals of 12 weeks between each assessment. Tests included a rapid fourth-generation HIV test, rapid syphilis test and polymerase chain reaction (PCR) testing for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* using a urine sample.

Participants with positive HIV tests were withdrawn from the study and referred to a specialist HIV care centre for further care. Participants who tested positive for syphilis, gonorrhoea or chlamydia were also referred to an appointed sexual health centre for appropriate treatment but were not withdrawn from the study.

Consultations

Participants attended a total of 5 consultations, at 12-week intervals, with an infectious disease physician who was also a member of the study team. The first and fifth consultations were conducted in-person, and the others were teleconsultations performed over Zoom platform (Zoom Video Communication, San Jose, CA, US), a secure video-conferencing platform with Advanced Encryption Standard 256-bit encryption, user authentication

and audit trails. These measures complemented institutional IT policies, including password protection for laptops and electronic medical records, malware protection and strict controls on patient data access.

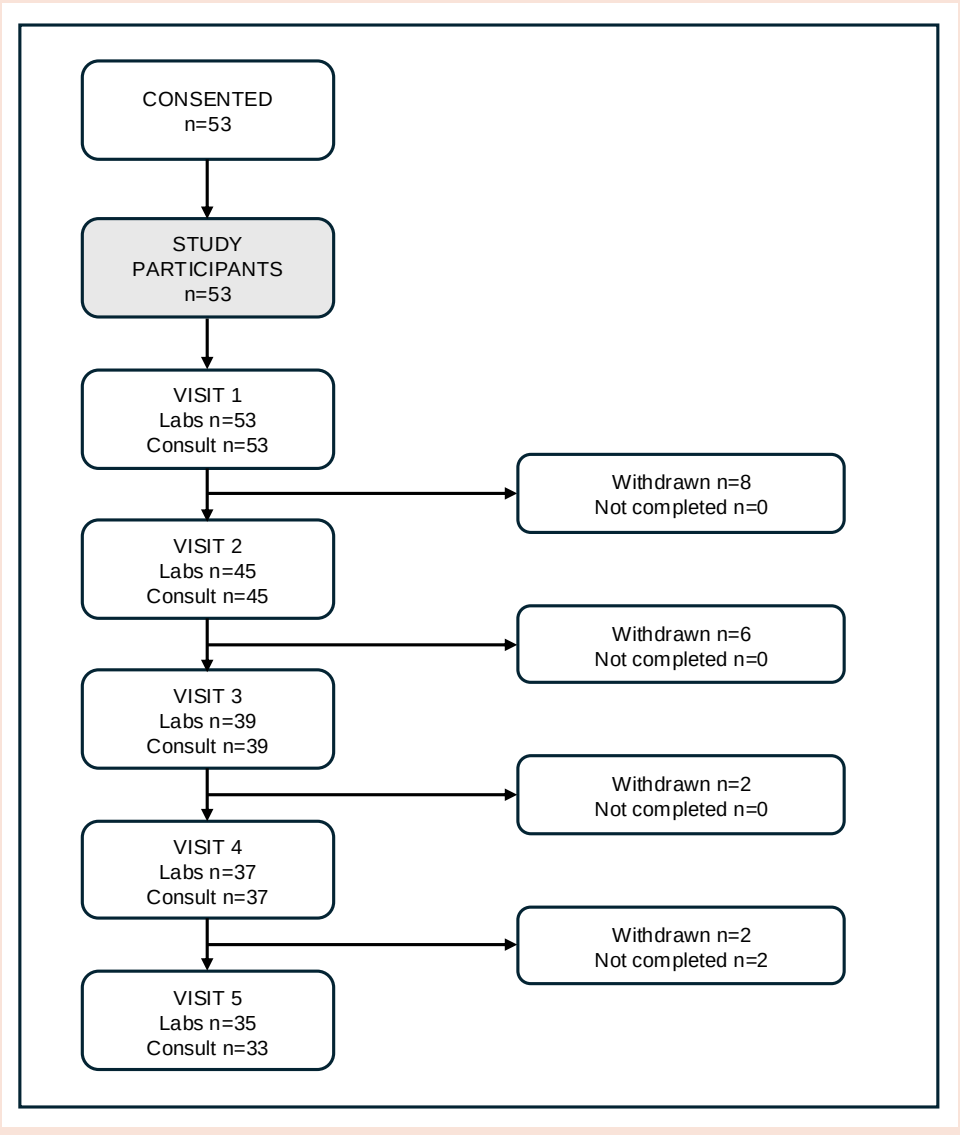
At these consultations, participants' test results would be reviewed. Participants also received counselling on the use of daily HIV TDF/FTC PrEP, in accordance with Singapore's National HIV Programme's PrEP Guidelines,[15] with the following information: (1) that TDF/FTC taken daily has an efficacy of up to 96% in preventing HIV infection in at-risk individuals, if taken as prescribed; (2) that a lead-in period of 14 days is necessary before full protection is achieved, and all sexual intercourse during this lead-in period should be protected with condom use; (3) that PrEP is only effective in preventing HIV infection, and precautions should still be taken to prevent infection with other STIs. At the end of the consultation, participants were given a prescription to purchase their medications from institutional pharmacies or from recommended online sources.

After completing the study, participants were offered the option to continue PrEP follow-up at either the NCID or the Department of Sexual Health Clinic (DSC), a local STI specialist outpatient clinic.

Questionnaires

Three different questionnaires (Supplementary Appendices 1–3) were given to the participants throughout the study, to assess the following: general demographics; sexual outcomes and behaviours; substance use; HIV/STI testing beha-

Fig. 1. Flow diagram for participant recruitment and retention (n=53).



viours; HIV risk perception and complacency; mental health screen, including the Patient Health Questionnaire-9 (PHQ-9), the 12-item HIV stigma scale, and questions on anticipated PrEP stigma, adapted from Calabrese et al.;[16-18] self-reported adherence to PrEP using questions adapted from a study by Blumenthal et al.;[19] and telehealth experience.

Statistical analysis

Statistical analyses were performed using Microsoft Excel 2023 (Microsoft Corporation, Redmond, WA, US). Continuous variables were summarised as mean ± standard deviation (SD), or median and range, as appropriate. For categorical variables, frequencies and percentages were reported.

Student's t-test was used for statistical analysis of continuous variables, and the chi-square test was used for categorical variables, where appropriate. A *P* value of <0.05 was considered statistically significant.

RESULTS

Between June 2021 and June 2022, 53 participants were enrolled in the study. Among them, 62.3% (33/53) of the participants completed the entire 12-month follow-up, and 66.0% (35/53) were able to complete all the surveys (2 participants missed their final doctor's appointment) (Fig. 1). Of the 20 participants who dropped out of the study, 10 were uncontactable, 3 were "busy and unable to commit", 2 were "overseas and unable to commit", 2 were "no longer interested," 1 felt that "medication delivery was inconvenient," 1 felt that there was "no urgent need to start PrEP as [he] feels he is not high-risk", and 1 seroconverted prior to PrEP initiation and was no longer eligible.

Demographics

The mean age of the cohort was 24.2 ± 2.99 years, with the majority of participants being of Chinese ethnicity (37 participants; 69.8%), followed by Malay (12 participants; 22.6%) and Indian (4 participants; 7.6%). All participants had at least secondary school education, with 37.7% (20/53) of participants having completed university education. Among the participants, 75.5% (40/53) lived in public housing and 24.5% (13/53) lived in private housing, with a median income range of SGD 1000 to 2999. Single participants comprised 86.8% (46/53) of the cohort, while 9.4% (5/53) had 1 partner, and 3.8% (2/53) had multiple male partners.

Among the cohort, 90.6% (48/53) were first-time PrEP users. Comparing the participants who completed all study surveys (n=35) against those that defaulted (n=18), there was a statistically significant difference in age (defaulters: 23.2 ± 2.23; non-defaulters: 24.7 ± 3.21; $P<0.05$) and relationship status (defaulters: 78% single, 22% attached; non-defaulters: 91% single, 9% attached; $P<0.05$). While the $P<0.05$ result suggested that the age difference is statistically significant, it is unlikely to be clinically or practically relevant based on the small magnitude of the difference. There were no statistically significant differences in ethnicity, education level, income or housing type ($P>0.05$).

PrEP adherence

There was a significant decrease in self-reported PrEP adherence among participants consistently taking 7 pills per week, with the adherence rate declining from 55.6% at the second visit to 37.1% at the fifth visit ($P<0.05$) (Fig. 2A). Notably, by the second visit, only 30% of the defaulters (n=20) reportedly took 7 pills a week, compared to 62.9% of those who completed the study (n=33) ($P<0.05$) (Fig. 2B).

Sexual practices

As the study progressed, changes in participants' sexual practices were observed. At the first visit, 60.4% of participants had 6 or more sexual partners. This decreased to 42.9% at the fifth visit ($P<0.05$) (Fig. 3A). However, there was a reduction in reported condom use for anal intercourse with both regular and casual partners, from 28.3% to 11.4% for regular partners ($P<0.05$), and from 56.6% to 28.6% for casual partners ($P<0.05$) (Fig. 3B).

Substance use

There was a decrease in the percentage of participants who used substances (e.g. alcohol, poppers, Viagra [sildenafil citrate], etc.) during sex activities, from 60.4% at the first visit to 45.7% at the first visit. However, this was not statistically significant ($P=0.076$).

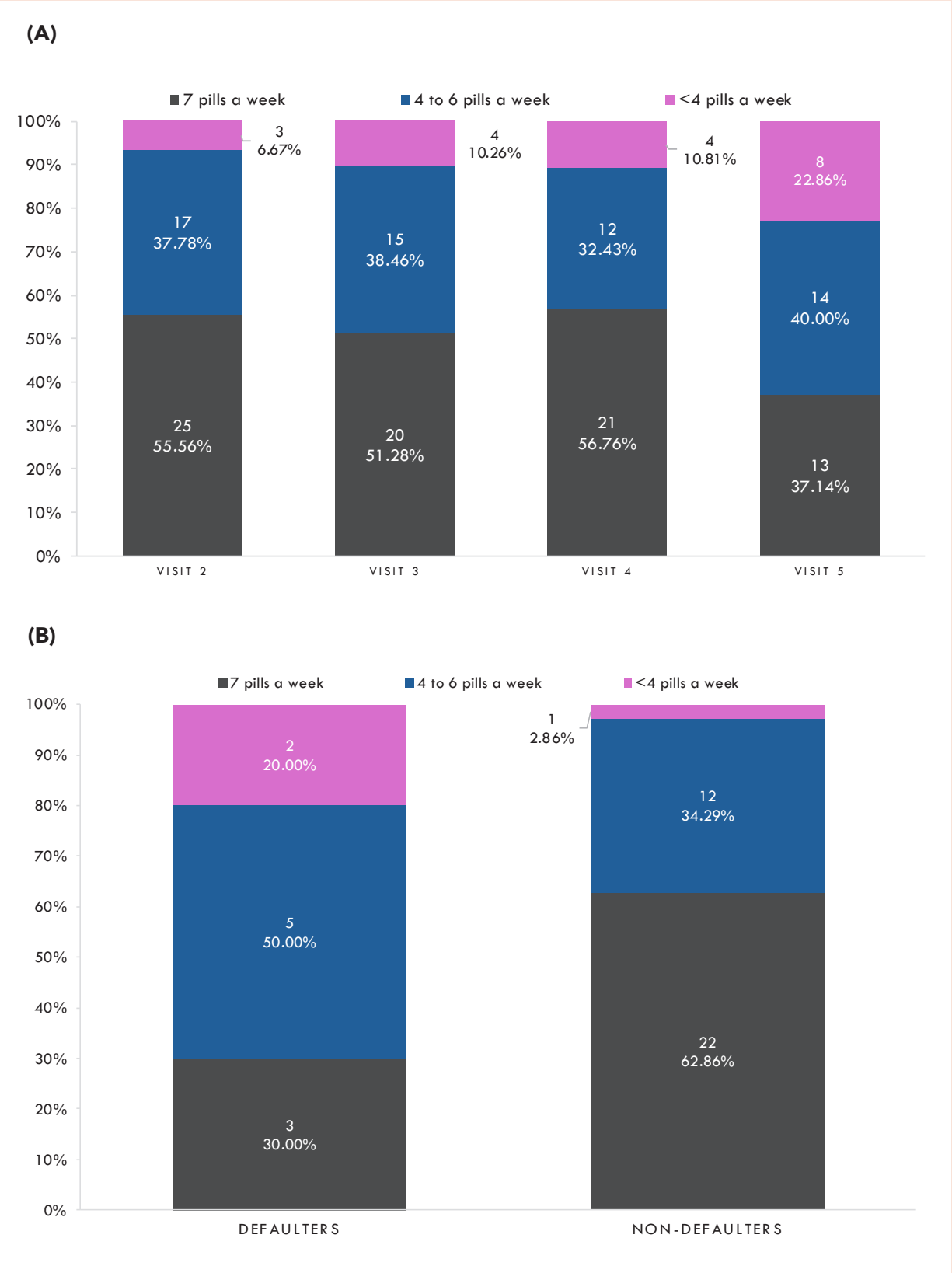
Sexually transmitted infections

An increase in STI incidence was observed after PrEP initiation among participants, from 18.9% (10/53) at the first visit to 28.6% (10/35) at the fifth visit. STI cases, such as chlamydia, gonorrhoea and syphilis were self-reported by participants. The breakdown of self-reported STIs from the first to the fifth visit is shown in Table 1.

Risk perception

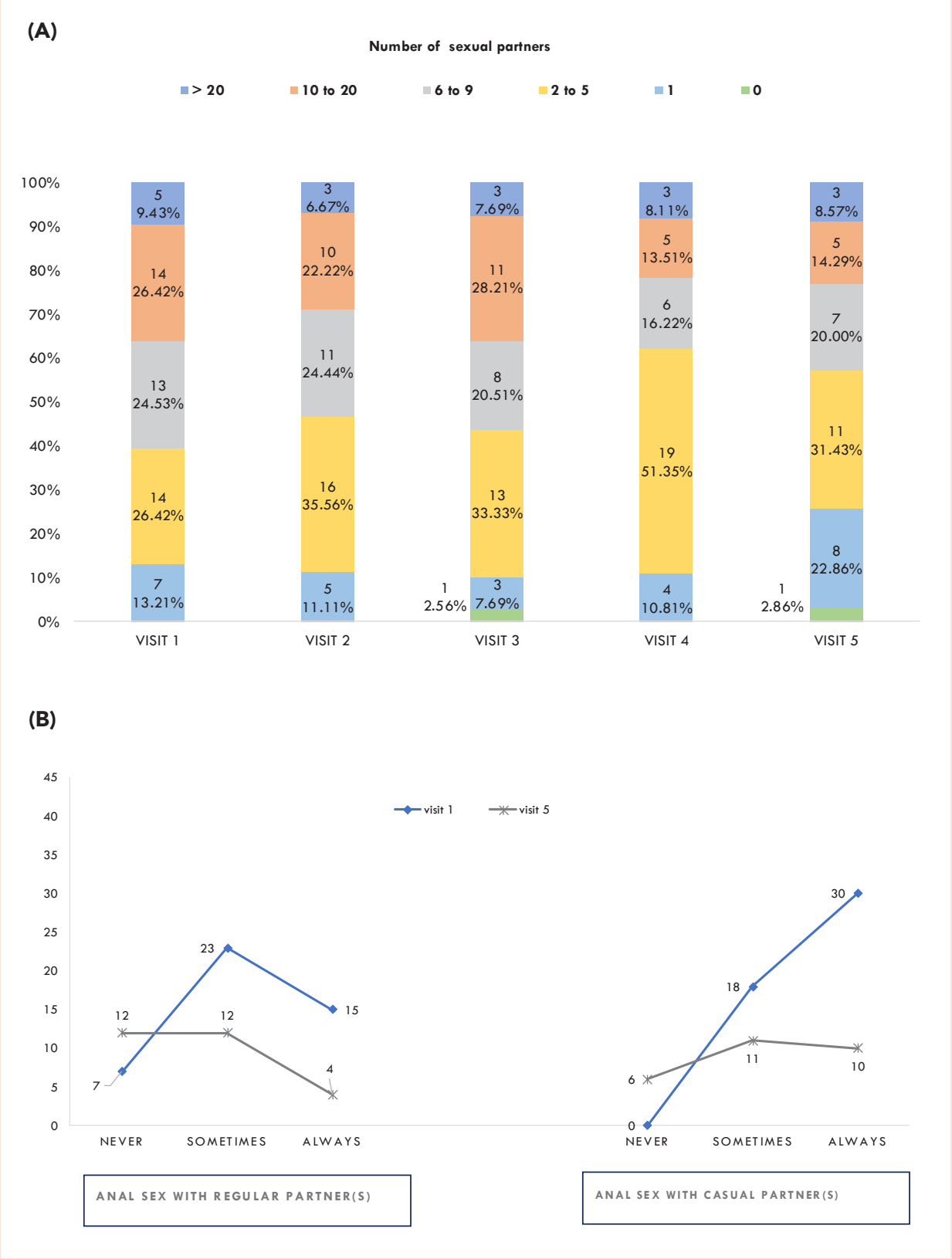
From the first to the fifth visit, there was an overall decrease in participants' risk perception of HIV. At the first visit, 69.8% of participants agreed that "HIV was a less serious threat than it used to be";

Fig. 2. Defaulters versus non-defaulters.



(A) Self-reported PrEP adherence from visits 2–5; (B) Self-reported PrEP adherence at visit 2 (defaulters versus non-defaulters).

Fig. 3. Changes in sexual practices.



(A) Number of sexual partners (visits 2–5); (B) Condom use when having anal sex with regular versus casual male partner(s) in the last 6 months.

Table 1. Cumulative incidence of sexually transmitted diseases from visits 1–5, no. (%).

STIs	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Chlamydia	4 (7.55%)	6 (1.33%)	4 (1.03%)	3 (8.1%)	6 (17.14%)
Gonorrhoea	2 (3.77%)	2 (4.44%)	5 (1.28%)	5 (13.5%)	3 (8.57%)
Syphilis	1 (1.89%)	1 (2.22%)	1 (2.56%)	1 (2.70%)	1 (2.86%)
Genital herpes	0	0	0	0	0
Genital warts	2 (3.77%)	0	0	0	0
Others	1 (1.89%)	0	0	1 (2.70%)	0
Total participants	53	45	39	37	35

STIs: sexually transmitted infections

this increased to 88.6% at the fifth visit (P<0.05). There was also a significant increase in the percentage of participants who agreed that they "practised safe sex less often due to advancements in medical treatment for HIV/AIDS", from 16.4% at the first visit to 48.6% at the fifth visit (P<0.05).

Mental health screen

There was a statistically significant fall in participants' aggregate mean (SD) PHQ-9 scores from the first visit (17.7 ± 3.54) to the fifth visit (13.1 ± 3.04) (P<0.05), indicating an overall improvement in mood. There were no significant temporal differences in the aggregated scores for either the HIV Stigma Scale or the PrEP Stigma Scale.

At the first visit, the PHQ-9 scores of the participants who defaulted the study (16.3 ± 3.38) were noted to be lower than the PHQ-9 scores of those who completed the study (18.3 ± 3.46) (P<0.05). There were no significant differences in the aggregated scores for either the HIV Stigma Scale or the PrEP Stigma Scale between the defaulters and non-defaulters.

Telehealth experience

Overall, participants had positive feedback about the telehealth experience; at the fifth visit, 80% of participants either agreed or strongly agreed that they had had positive experiences with PrEP teleconsultations. All participants agreed that their questions and concerns could be addressed adequately by doctors via teleconsultation.

DISCUSSION

This pilot project has shown that telehealth services can significantly improve PrEP uptake among YMSM. Prior to the study, only 9.6% of the surveyed YMSM were taking PrEP, which was even lower than the overall PrEP uptake of 25% in the 2023 Singaporean study.[8] By the end of the study, despite some defaulters, 62.3% of participants continued to take PrEP and attend follow-up PrEP appointments.

While PrEP provision has demonstrated its benefits, there was a significant decrease in self-reported PrEP adherence among participants throughout the study. Key barriers to PrEP adherence previously identified include forgetting to take PrEP daily, not wanting to take a chemical substance for a prolonged period, and low perceived vulnerability to HIV.[20] Changes in lifestyle and relationship status could also result in a diminished need for PrEP.[21]

PrEP providers must thus emphasise the importance of consistent PrEP use at each consultation, and provide education on prevention-effective PrEP adherence.[22-25] To address the key barriers identified, digital platforms can be leveraged to increase adherence, especially among the younger, tech-savvy population.[26] For instance, medication reminders via mobile applications can increase PrEP adherence among YMSM by developing medicine-taking habits, especially when first commencing PrEP.[27,28] Further providing incentives for good adherence may also improve retention in PrEP programmes.[29] Peer navigators can also be engaged, to address individual barriers to PrEP and provide peer motivation.[30]

PrEP may also offer significant psychological benefits for recipients. A statistically significant decrease in PHQ-9 scores from the first to the last visit indicates an overall improvement in mental health after starting PrEP. A few mechanisms have been proposed for this positive change. First, PrEP may alleviate the fear of HIV infection, providing reassurance for PrEP users.[31] Second, PrEP could independently lead to better sexual satisfaction, ultimately culminating in greater life satisfaction.[32] However, maintaining adherence to PrEP regimens can introduce stress, particularly for those concerned

about the consequences of missed doses. Some younger participants also felt that taking PrEP could negatively impact how others perceive them. This perception was particularly common among younger individuals and those who were more psychologically vulnerable, as reflected by lower self-esteem scores and higher depression scores, which could, in turn, affect PrEP adherence.[33] Additionally, the high initial PHQ-9 scores observed in the study, with many participants showing moderately-severe depression, suggest potential benefits to integrating routine mental health screening into PrEP services, to identify and address mental health challenges in this vulnerable population early.[34]

Participants also did not partake in regular STI testing prior to this study. However, STI screening conducted during the study revealed that many individuals tested positive for various STIs. Additionally, 1 individual was found to have seroconverted at the start of the study, prior to PrEP initiation. Therefore, expanding PrEP services, along with accompanying STI tests, could be highly beneficial for the early detection and treatment of STIs, including HIV, in this at-risk population.

The study also highlighted concerns that, despite the benefits, PrEP uptake may lead to riskier sexual practices. Although counselling was provided during PrEP consultations, there was still a statistically significant reduction in reported condom use for anal intercourse. Nevertheless, while PrEP provision could lead to riskier sexual practices that confer a high risk of acquiring STIs, the incidental detection and treatment of these STIs as part of PrEP provision, and the benefits of HIV prevention may partially offset risk compensation.[35,36]

Nevertheless, in the provision of PrEP services, it is essential for clinicians to continue emphasising that PrEP does not prevent other STIs, and to recommend concurrent condom use with PrEP use, which is consistent with national PrEP Guidelines.[15,37] Recently published cases of PrEP failure in Singapore further underscore the critical importance of risk counselling and adherence to PrEP to maintain its efficacy, as these cases were patients on self-directed PrEP, who had adherence issues.[38]

This study has several limitations. First, the cost for PrEP and associated investigations were borne by the study. Eventually, barring policy changes, the participants will have to pay out-of-pocket to continue receiving PrEP services. This financial aspect may deter consistent PrEP usage, especially given the relatively low median income range (SGD 1000 to 2999) among the surveyed YMSM population. Second, the reasons for defaulting were not always fully explored, as some defaulters become uncontactable; such information could provide valuable insights into improving PrEP services. Third, the small sample size in this study limits its statistical power, making it difficult to detect significant effects. There are also potential selection biases, as the population, recruited at STI testing sites from community-based organisations, could have greater familiarity, knowledge and awareness of PrEP than the broader population of YMSM, reducing generalisability. Future studies should be conducted on a larger scale to validate the findings of this pilot study. Finally, while this pilot study focused solely on daily PrEP, future studies could focus on other modalities of PrEP delivery. In particular, on-demand PrEP could be an alternative for individuals poorly adherent to daily PrEP.[39] Recently, novel long-acting, extended-delivery injectable PrEP formulations have demonstrated excellent outcomes, offering potential to enhance adherence.[40,41]

CONCLUSION

In conclusion, this study demonstrates that PrEP services provide an opportunity for YMSM to access sexual health testing, treatment and counselling, and may even have a positive impact on their mental health. Telemedicine has proven to be a suitable platform for the delivery of such services. Given these immense benefits of improving PrEP uptake, top-down policy changes should be implemented in Singapore to scale up PrEP initiatives, enhancing both its affordability and accessibility. This would serve the public good and better protect the vulnerable YMSM population. While clinicians should emphasise the effectiveness of PrEP in preventing HIV, individuals using PrEP must remain aware that it does not protect against other STIs; engaging in risky sexual behaviours while on PrEP may still increase their vulnerability to these infections.

Supplementary Table S1

Supplementary Appendices 1–3

Ethics statement

Patient consent was sought for this study. This study received funding from the NCID Catalyst Fund 2021/2022 and was approved by the National Healthcare Group Domain Specific Review Board (2021/000810).

Declaration

The authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

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REVIEW ARTICLE

The efficacy and safety of radiofrequency ablation in papillary thyroid carcinoma: A systematic review and meta-analysis

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ABSTRACT

Introduction: Radiofrequency ablation (RFA) avoids the complications of general anaesthesia, reduces length of hospitalisation and reduces morbidity from surgery. As such, it is a strong alternative treatment for patients with comorbidities who are not surgical candidates. However, to our knowledge, there have only been 1 systematic review and 3 combined systematic review and meta-analyses on this topic to date. This systematic review and meta-analysis seeks to evaluate the efficacy and safety of RFA in the treatment of papillary thyroid carcinoma (PTC) with longer follow-up durations.

Method: PubMed, Embase and Cochrane databases were searched for relevant studies published from 1990 to 2021; 13 studies with a total of 1366 patients were included. The Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines and Sandelowski et al.'s approach[1] to "negotiated consensual validation" were used to achieve consensus on the final list of articles to be included. All authors then assessed each study using a rating scheme modified from the Oxford Centre for Evidence-Based Medicine.

Results: Pooled volume reduction rates (VRRs) from 1 to 48 months after RFA, complete disappearance rates (CDR) and complications were assessed. Pooled mean VRRs were 96.59 (95% confidence interval [CI] 91.05–102.13, I^2=0%) at 12 months[2-6] and 99.31 (95% CI 93.74–104.88, I^2=not applicable) at 48 months.[2,5] Five studies showed an eventual CDR of 100%.[2,4,7-9] No life-threatening complications were recorded. The most common complications included pain, transient voice hoarseness, fever and less commonly, first-degree burn.

Conclusion: RFA may be an effective and safe alternative to treating PTC. Larger clinical trials with longer follow-up are needed to further evaluate the effectiveness of RFA in treating PTC.

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Keywords: efficacy, otorhinolaryngology, papillary thyroid cancer, radiofrequency ablation, safety

CLINICAL IMPACT

What is New

- In the treatment of papillary thyroid carcinoma (PTC) using radiofrequency ablation (RFA), pooled mean volume reduction rates after 6 months were above 90%.
- Eventual complete disappearance rates of 100% were reported in 5 studies.

Clinical Implications

- No life-threatening complications from RFA were recorded; the most common complications were pain, transient voice hoarseness, fever and less commonly, first-degree burn.
- RFA may be an effective and safe alternative treatment choice to treat PTC, particularly for patients with comorbidities who are not surgical candidates.

INTRODUCTION

Malignant nodules account for 5–15% of all thyroid nodules and papillary thyroid carcinoma (PTC) accounts for 85% of that.[10] Most guidelines recommend surgery as the first-line treatment for PTC.[11] However, surgery does carry a risk for complications, such as hypothyroidism and recurrent laryngeal nerve damage leading to voice hoarseness.[12-17] Thus, other treatment strategies, such as active surveillance (AS) [18] and thermal ablation[19] have been explored.

Thermal ablation can be broadly categorised into 3 main techniques: microwave ablation (MWA), laser ablation and radiofrequency ablation (RFA). In recent years, RFA has been shown to yield successful results in the treatment of a variety of

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thyroid diseases. This paper will focus on this technique. RFA utilises an alternating current with a frequency ranging between 200 kHz and 1200 kHz to produce local thermal energy, generating temperatures between 50°C and 100°C resulting in tissue necrosis, and this process may be guided using an ultrasound.

RFA avoids complications of general anaesthesia, reduces length of hospitalisation and reduces morbidity from surgery.[20] It has shown promising outcomes in thyroid disease, specifically PTC.[2,5,8,21,22] Long-term observation of RFA in the treatment of PTC showed a good volume reduction rate (VRR), low tumour recurrence and low lymph node metastasis rate. This presents a strong alternative treatment choice for patients who are not surgical candidates due to the presence of comorbidities. In fact, the 2021 Cardiovascular and Interventional Radiology Society of Europe/European Thyroid Association clinical practice guidelines[23] proposed AS and ultrasound-guided minimally invasive treatment (MIT) for suitable cases of PTC. This multidisciplinary consensus statement also states that AS and ultrasound-guided MITs may be used as an alternative management option to thyroidectomy for selected cases of papillary thyroid microcarcinoma (PTMC). It may even be considered for patients with differentiated thyroid carcinoma in the following conditions: PTMC, unresectable thyroid cancer, neck lymph node recurrence of differentiated thyroid cancer and distant metastases.[24]

According to the 2015 American Thyroid Association clinical practice guidelines, AS is a recommended option for the management of PTMCs.[11] However according to the data provided by Oh et al.,[25] nearly half of their patient cohort with PTMC (48.3%) who accepted AS had experienced anxiety during their follow-up and underwent delayed thyroid surgery thereafter.

In 2023, the American Thyroid Association updated a statement on utilising ablation techniques on benign thyroid nodules[26]—however, there has not been a statement on utilising ablation techniques on PTCs. Nevertheless, it provides a general framework of recommendations for RFA such as using a moving shot technique with hydrodissection, and guidelines on the management of periprocedural complications.

To our knowledge, there have only been 5 combined systematic review and meta-analyses on this topic to date.[27-31] Our systematic review and meta-analysis seeks to evaluate the efficacy and safety of RFA in the treatment of PTC, with the aim of updating the information presented in previous studies, given the emergence of several new findings and to examine the benefits of longer follow-up durations.

METHOD

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for this paper. The study team consulted a team of experts that comprised the head and neck surgical oncologists at the Department of Otorhinolaryngology of Tan Tock Seng Hospital, a tertiary care teaching hospital in Singapore.

Guided by the Population, Intervention, Comparison, Outcome and Study (PICOS) design elements of the inclusion criteria, the primary research question was determined as follows: How efficacious is RFA as a treatment for PTC? The secondary research question was determined as: How safe is RFA as a treatment for PTC? Efficacy may be defined by VRR and complete disappearance rate (CDR), which are the main outcomes examined in this study. Evaluation of safety encompassed the risk of post-procedure complications.

The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) and is available online with the registration number: CRD42023432383. No amendments have been made to the protocol.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for the systematic review, guided by the PICOS framework are outlined in Table 1.

Search strategy

The PubMed, Embase and Cochrane databases were searched to identify articles that evaluated the efficacy and safety of RFA as a treatment for PTC.

Articles published from 1 January 1990 to 30 February 2023 were searched using the terms "radiofrequency ablation" and "papillary thyroid carcinoma". All articles published in English or had English translations were included. The search was carried out between 5 March 2023 and 9 March 2023. The search process is summarised in the PRISMA flowchart (Fig. 1).

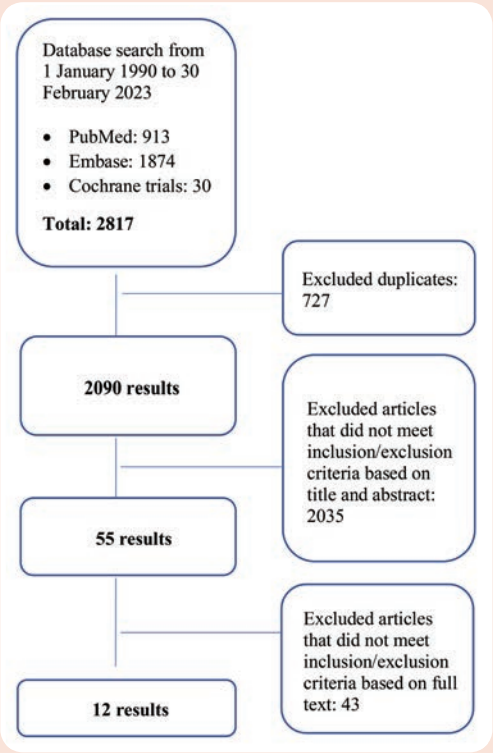
Two reviewers (WSCC and XYJA) independently assessed the titles and abstracts found in each database to compile the definitive list of articles for review. The method of "negotiated consensual validation" by Sandelowski et al. (2007)[1] was used to establish agreement on the final list of articles selected. In cases where consensus between the 2 initial reviewers was not achieved, the article

Table 1. Inclusion and exclusion criteria.

PICOS elements	Inclusion	Exclusion
Population	• Papillary thyroid cancer • Age older than 18 years	• Extra-thyroidal tissue • Benign neoplasms
Intervention	• RFA	• Other types of ablation • Non-ablative therapies
Comparison	• Comparisons of the number of nodules ablated by RFA • Mean size (volume) of ablated nodules • Amount of energy delivered per treatment • Treatment time • Complications • VRR	
Outcome	• Complete follow-up data of the number of nodules ablated by RFA • Mean size (volume) of ablated nodules • Amount of energy delivered per treatment • Treatment time • Complications • VRR	
Study design	• Articles in English or translated to English • Randomised controlled trials, cohort studies, case-control studies, cross-sectional studies • Year of publication: 1 January 1990 to 30 February 2023 • Databases: PubMed, Embase, Cochrane	• Grey literature/electronic and print information not controlled by commercial publishing • Case reports or series with 10 or fewer 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 treated nodules

PICOS: Population, Intervention, Comparison, Outcome and Study; RFA: radiofrequency ablation; VRR: volume reduction rate

Fig. 1. PRISMA flowchart for inclusion of selected articles in this systematic review and meta-analysis.



in question underwent review by 4 additional reviewers.

Data extraction

A standardised excel spreadsheet was used to extract data from all included articles. Data extracted is summarised in Supplementary Table S1.

Statistical analysis

The main outcomes of this study were VRR of the treated nodule at 1, 3, 6, 12, 18, 24, 30, 36 and 48 months. The CDR was analysed as well—this was defined as 100% disappearance of lesions based on ultrasound findings. Meta-analytic pooling was performed using inverse variance for calculating weights, and Der Simonian-Laird random-effects model was used 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 with $P<0.1$ indicating statistical significance. According to the Cochrane Handbook for Systematic Reviews of Interventions,[32] while a statistically significant result may indicate a problem with heterogeneity, a non-significant result must not

be taken as evidence of no heterogeneity. Interpretation of the I^2 statistic may be interpreted as follows: slight (0–40%), moderate (30–60%), substantial (50–90%) or considerable (75–100%) heterogeneity.[32] The $P<0.1$ threshold was employed given the low statistical power of the chi-square test. A random-effects model was applied throughout. All statistical analyses were performed using RevMan 5.4 software (Review Manager [RevMan] [Computer program]. Version 5.4, The Cochrane Collaboration, 2020).

Risk of bias

The quality of evidence of each study was rated according to a rating scheme modified from the Oxford Centre for Evidence-Based Medicine.[33] Only studies conducted on non-palliative cases of PTC were included in this study to ensure a more uniform analysis of VRRs. However, other confounding factors, such as tumour size and location, could not be controlled as the studies did not provide specific details regarding the patient selection criteria, such as tumour size and location.

RESULTS

The search from the 3 databases retrieved 2817 articles. There were 2090 articles after the exclusion of 727 duplicates. After reviewing the titles and abstracts, 55 articles were included. The full texts of these 55 articles were retrieved. After reviewing these, 12 were included in both the systematic review and the meta-analysis (Supplementary Table S1). Of the excluded articles, 8 were suspected to have overlapping populations, 10 did not discuss the main subject, 4 had less than 10 patients, 5 were reviews, 11 could not be retrieved, 3 were case reports and 2 did not report any VRR. An additional search of their bibliographies did not return any relevant studies.

Characteristics of included studies

Supplementary Table S1 summarises the characteristics of the 13 included studies for meta-analysis. One was a prospective study and 12 were retrospective studies. All were cohort studies and from Asia. The mean total energy of RFA was 2 kJ (range 0.86 to 3.169 kJ) and the mean duration of RFA was 23.0 min (range 1.32 to 136.8 min). The mean age of patients was 45.6 (range 41 to 66 years). All nodules were confirmed as PTC by fine needle aspiration cytology. From the studies that reported mean volumes, the mean volume of the target nodules was 0.379 mL (0.03 to 156.67 mL). From the studies that reported follow-up periods, the mean follow-up period was 27.7 months.

Efficacy

Follow-up schedules of these studies were not standardised—not all had studied VRRs for the same duration of follow-up. There were 7 studies that reported VRRs at 1, 3, 6 and 12 months. Only 4 studies reported VRRs at 18 months, 6 studies reported VRRs at 24 months, 2 studies reported VRRs at 30 months, 6 studies reported VRRs at 36 months and 2 studies reported VRRs at 48 months. This review pooled mean VRRs over common follow-up durations found across each study. The pooled mean VRRs at 1, 3, 6, 12, 18, 24, 30, 36 and 48 months were 60.52% (95% CI 36.45–84.58, I^2=27%) (Fig. S1), 83.47% (95% CI 68.34–98.59, I^2=0%) (Fig. S2), 92.23 (95% CI 81.61–102.86, I^2=0%) (Fig. S3), 96.59% (95% CI 91.05–102.13, I^2=0%) (Fig. S4), 98.95% (95% CI 95.76–102.14, I^2=0%) (Fig. S5), 99.47% (95% CI 97.89–101.05, I^2=0%) (Fig. S6), 98.43% (95% CI 93.85–103.02, I^2=0%) (Fig. S7), 99.70% (95% CI 98.32–101.08, I^2=0%) (Fig. S8) and 99.31% (95% CI 93.74–104.88, I^2=not applicable) (Fig. S9), respectively. Reported I^2 statistics indicate little heterogeneity across all studies. Five studies recorded 100% complete disappearance of the nodules[2,4,7-9] between the periods of 24 months and 48 months. One study[8] divided nodules into 2 groups by their T stage and another study divided nodules into groups by age of patients.[21] Each group was analysed separately. One study reported a recurrence rate of 1%.[3] Publication bias was not evaluated due to the small number of included studies.

Cost

Three papers also reported that patients undergoing RFA incurred lower costs compared to patients undergoing surgical resection.[21,34,35]

Factors affecting efficacy

Staging

There is an association between earlier stages of tumours and higher disappearance rates. Xiao et al. (2021)[8] showed that the CDRs for T1a tumours were higher than that of T1b tumours (81.7% and 52.7%, respectively). This may be because the volume of coagulative necrosis was larger in the T1a group than in the T1b group. Moreover, Xiao et al. also in 2021,[4] studied the efficacy of RFA on T2N0M0 tumours and reported that tumour size reduced significantly with a VRR of 93.7% at 30-month follow-up after RFA and a disappearance rate of 16.7%.

Wu et al. (2020) reported that RFA is effective in reducing the VRR of multiple malignant

nodules as well.[36] There were 6 patients who had 2 PTMC nodules at the same time and all nodules were successfully treated.

Safety

No studies recorded life-threatening complications. The most common complication was transient voice hoarseness[2,3,5,7,9,22,34-37] though none of the studies reported permanent voice changes. This is usually caused by thermal damage to the recurrent laryngeal nerve, with damage occurring in 0.75% to 17.39% of patients. Other complications include the development of pain,[5,21,36] transient hypoparathyroidism,[34] hyperthyroidism post-operation 2.9%,[9] hypothyroidism post-operation 1.9%,[9] haematoma,[2,22,37] fever[3] and first-degree burns.[2,22]

Temporary thyroid function abnormalities (both hyper- and hypothyroidism)[9] also occurred as thyroid follicular cells are destroyed during the treatment. Thus, thyroid hormones are released into the blood, causing thyroid function abnormalities.[9] In Zhu et al. (2021), 2 out of 102 patients (1.9%) who underwent RFA developed hypothyroidism post-operation and 3 out of 102 patients (2.9%) developed hyperthyroidism.[9]

Moreover, 4 papers reported a higher quality of life associated with RFA compared to surgical resection[5,21,35,38] in view of the reduced rate of complications, such as recurrent laryngeal nerve paralysis, hypoparathyroidism and hypothyroidism. The studies did not report the differences in outcomes of procedures performed by operators of varying experiences, hence no definite conclusion can be drawn on the association between operator experience and complication rate.

DISCUSSION

The management of PTC has traditionally revolved around surgical interventions, such as total thyroidectomy or lobectomy. However, the recent clinical practice guidelines proposed by the Cardiovascular and Interventional Radiological Society of Europe/European Thyroid Association[23] have introduced AS and MIT options for suitable cases of PTC.

The findings of this study provide compelling evidence supporting the efficacy of RFA in the volume reduction of PTC. The pooled VRRs after 6 months were above 90%. Mean VRRs at 6, 12, 18, 24, 30, 36 and 48 months were 92.23 (95% CI 81.61–102.86, I^2=0%) (Fig. S4), 96.59% (95% CI 91.05–102.13, I^2=0%) (Fig. S5), 98.95% (95% CI 95.76–102.14%, I^2=0%) (Fig. S6), 99.47% (95% CI 97.89–101.05, I^2= 0%) (Fig. S7), 98.43% (95% CI 93.85–103.02, I^2=0%) (Fig. S8), 99.70% (95% CI 98.32–101.08, I^2=0%) (Fig. S9) and 99.31% (95% CI 93.74–104.88, I^2 not applicable) respectively, indicating significant tumour shrinkage. Moreover, the eventual CDRs of 100% reported in 5 studies[2,5,8,21,22] further underscore the potential of RFA to effectively eradicate PTC. These results align with previous systematic reviews, highlighting the ability of RFA to achieve tumour control and reduction in PTC volume.

The lack of heterogeneity can be explained by our selective inclusion criteria—only papers citing RFA as a treatment for curative purposes for PTC were included. Moreover, most of the studies also included fewer than 200 patients, which may have contributed to the homogeneity and overestimate treatment efficacy.

The bio-pathophysiological mechanism of RFA in the treatment of PTC further enhances our understanding of its efficacy. RFA utilises thermal energy generated by an alternating current to induce localised tissue destruction.[39] The hyperthermic effects of RFA cause coagulative necrosis, protein denaturation, disruption of cell membranes and destruction of blood vessels within the tumour. Additionally, RFA triggers an immune response within the tumour microenvironment, promoting the clearance of residual tumour cells and enhancing the antitumor immune response.[40]

Importantly, the safety profile of RFA appears favourable, with no life-threatening complications recorded in the included studies. The reported adverse events, including pain, transient voice hoarseness,[2,3,5,7,9,22,34-37] fever[3] and first-degree burns,[2,22] were generally manageable and of a transient nature. The lower incidence of complications after RFA may be due to accurate tumour targeting under ultrasound guidance, the protection of vital organs via the hydrodissection technique and the abundant experience of the ultrasound physician.[5] However, the safety margin of RFA (defined as margins of adjacent tissue to be ablated) has not yet been described. Xiao et al. (2022)[8] reported that all patients in their cohort had solitary low-risk tumours and that the safe margin of RFA was ≥3 mm.[8]

The introduction of minimally invasive therapeutic options for suitable cases of PTC in the latest clinical practice guidelines reflects a growing recognition of the benefits of non-surgical approaches. RFA, as a minimally invasive technique, offers several advantages over surgery. This includes the avoidance of complications—risks of general anaesthesia, damage to the recurrent laryngeal nerve, scarring, hypothyroidism, hypoparathyroidism and the requirement for lifelong medication. Additional advantages comprise shorter hospital

stays and decreased morbidity. These advantages make RFA an attractive option for patients who are not surgical candidates due to the presence of comorbidities or personal preferences.

There exist alternative non-invasive options to treat PTC as well. This includes MWA and high-intensity focused ultrasound. There are currently no definitive guidelines that describe how these methods should be used to treat PTCs and few studies have compared these therapies as well.

In a systematic review by Tong et al. (2019)[30] studying MWA, laser ablation and RFA, the efficacy of these 3 methods was found to be similar.[30] There were no life-threatening complications resulting from these ablation methods; the pooled proportions of complications of RFA (1.7%), MWA (6.0%) and laser ablation (0.92%) were low and there was also no significant difference among these (P>0.05). However, it was noted that MWA resulted in more transient voice changes compared to RFA. This may be attributed to the fact that the temperature in RFA increases slowly and heat is readily removed. This limits the coagulation zone size of RFA. MWA, on the other hand, depends less on tissue impedance and rapidly increases in temperature, resulting in coagulative necrosis that can inactivate tumours quickly. However, for PTCs eligible for RFA, they are usually small in size and it may not be easy for operators to manipulate MWA, which may result in a larger zone of active heating than necessary, increasing the likelihood of adjacent nerve injury.

One question remains: how can healthcare policies in Singapore promote the adoption of RFA in treating PTC? First, health insurance providers should recognise RFA as a reimbursable procedure so as to encourage more healthcare facilities to adopt the technology. Second, clinical guidelines should be established specifically for RFA. Third, policies that allocate resources for training healthcare professionals in RFA techniques will enhance the competency of providers, making them more likely to incorporate this method into their practice. Last, policies that support research initiatives or provide funding for studies on RFA might encourage more medical facilities to implement RFA, as positive outcomes and evidence could help alleviate concerns about its efficacy and safety.

Limitations

It is essential to acknowledge the limitations of this study. The number of studies included in the analysis was relatively small, which may limit the generalisability of the findings. A larger number of studies would provide a more robust and comprehensive analysis of the efficacy and safety of RFA in the treatment of PTC.

The studies did not provide specific details regarding the patient selection criteria, such as tumour size and location. This lack of standardised criteria makes it difficult to determine the ideal candidates for RFA and compare its efficacy with surgical interventions in specific subsets of PTC patients.

Our study also relied on published literature and may be susceptible to publication bias, as studies with positive or significant results are more likely to be published. This bias may affect the overall assessment of the efficacy and safety of RFA in treating PTC.

The duration of follow-up in the included studies was relatively short, ranging from 1 to 60 months. Durations of follow-up were also not standardised. Only 1 study reported a recurrence rate of 1%. Longer-term follow-up is essential to evaluate the sustained effectiveness of RFA in tumour control and recurrence rates. This is especially so as recurrence for PTC usually takes many years. Ywata et al. (2021) reported the median time of recurrence to be 56.8 months.[41] Additionally, long-term data would provide valuable insights into the durability of the treatment and potential late complications.

The publications included also focused primarily on Asian cohorts. One may postulate that this may be due to a wider acceptance of MITs in East Asia, though no studies have been done on why this is so. More prospective randomised trials that compare RFA directly with surgery in low-risk versus high-risk patients should be conducted as well. There were also no randomised controlled trials in the field of RFA for PTC. There is a need for multicentre trials with Asian populations to validate the generalisability of these findings.

The included studies only evaluated the efficacy of RFA on low-risk PTCs (defined as a PTMC without extrathyroidal extension, vascular invasion or metastases).[11] More studies need to be conducted on higher-risk PTCs. The studies also did not address lymph node metastases, for which the standard treatment remains to be surgical resection according to current guidelines. However, it was found in 3 studies (not included in our study in view of the inclusion criteria) that volume reduction rates were high for metastatic cervical lymph nodes ablated by RFA.[42-44]

Only Chen et al. (2022)[35] and Chung et al. (2021)[7] utilised RFA on recurrent tumours after surgery. We were unable to analyse the differences in VRR

between recurrent and primary PTCs as Chung et al. did not report VRRs at specific intervals, leaving only 1 such study[35] for our comparison. Nevertheless, it should be noted that at 6 months, VRR was 86.6 ± 22.2 as reported by Chen (2022),[35] which is comparatively lower than that of the other studies.

CONCLUSION

In conclusion, our meta-analysis provides a summary of the current literature on the efficacy and side effects of RFA on PTC. The results suggest that RFA may be an effective and safe alternative treatment modality. However, it is not yet a standard treatment due to the lack of long-term data. Larger clinical studies and randomised controlled trials with longer follow-up durations are needed to evaluate the recurrence rate of this treatment.

Further studies with larger populations are required to assess the risks and benefits of using different combinations of energy depending on the size, type and location of the nodule. Comparative analyses can be done with other methods of ablation such as MWA. These findings may provide a deeper insight into the efficacy and safety associated with RFA, and help guide future management of PTC using RFA as a treatment modality.

Supplementary materials

Table S1. Characteristics of included studies.
Fig. S1. Volume reduction rate (VRR) 1 month.
Fig. S2. VRR 3 months.
Fig. S3. VRR 6 months.
Fig. S4. VRR 12 months.
Fig. S5. VRR 18 months.
Fig. S6. VRR 24 months.
Fig. S7. VRR 30 months.
Fig. S8. VRR 36 months.
Fig. S3. VRR 48 months.

Ethics statement

The protocol is registered in PROSPERO (CRD42023432383).

Declaration

The authors declare they have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Availability of data and materials

All data generated or analysed during this review are included in this published article and its supplementary files.

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REVIEW ARTICLE

Premature ovarian insufficiency: When ovaries retire early

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ABSTRACT

Introduction: Premature ovarian insufficiency (POI) refers to loss of ovarian activity before the age 40 years. POI has significant detrimental effects on health (infertility, cardiovascular diseases, type 2 diabetes, reduced bone density, dementia), well-being and longevity. This summary is a practical toolkit for health-care professionals (HCPs) looking after women with POI.

Method: A workgroup comprising specialists in gynaecology, reproductive medicine, endocrinology, genetics and family medicine reviewed relevant guidelines and literature on POI to establish recommendations for the diagnosis and management of POI in Singapore.

Result: A summary to assist HCPs manage POI was produced, outlining: (1) the aetiology and consequences of POI; (2) making the diagnosis; (3) hormone therapy (HT) prescribing options including for those with additional medical conditions; (4) counselling women with POI about HT; and (5) long-term management of POI.

Conclusion: Timely diagnosis and management of POI is vital to prevent long-term adverse consequences, except infertility. HT is the mainstay of treatment and there are no alternatives as effective. Contraindications are very few; estrogen-sensitive cancer is the main contraindication, and caution in prescribing may be needed with established coexisting cardiovascular disease. Estrogen dosage is higher than when treating normal menopause, and as a result, the patient might require more progestogen for endometrial protection. Minimising cardiovascular risk factors by following a healthy lifestyle is important. POI is a significant public health issue and it is imperative that women have affordable access to appropriate HT. Large-scale research on POI in Asian women is needed.

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Keywords: amenorrhoea, cardio-metabolic disease, hormone replacement therapy, hormone therapy, obstetrics and gynaecology, osteoporosis, premature menopause, premature ovarian failure

CLINICAL IMPACT

What is New

- Untreated POI has health consequences, affects quality of life and reduces longevity.

Clinical Implications

- Women at risk should be counselled regarding measures to reduce risk of POI and about fertility preservation options, when appropriate.
- Women with POI should be treated with hormone therapy until usual age of menopause as primary prevention for cardio-metabolic diseases and osteoporosis; contraindications are few.
- All stakeholders need to improve access to medical treatment for women with POI.

INTRODUCTION

Premature ovarian insufficiency (POI, also known as primary ovarian insufficiency) refers to loss of ovarian activity before the age of 40 years, leading to hypergonadotropic hypoestrogenism and 4 months or more of menstrual disturbance.[1] In ovarian insufficiency, the ovarian dysfunction is not necessarily definitive, which is why the terms premature menopause and premature (or primary) ovarian failure are not accurate. Twenty-five percent of women with POI may experience fluctuating ovarian function and intermittent menstrual disturbance or symptoms of hypoestrogenism.[2] Women with POI are at risk of long-term consequences including infertility, cardiovascular disease (CVD), type 2 diabetes, low bone mineral density (BMD), sexual dysfunction, reduced quality of life and premature mortality. Hormone therapy

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(HT) is therefore recommended (in most women) to mitigate these long-term complications. Early menopause occurs between the ages of 40 and up to 45 years. It is recognised to have similar long-term consequences as POI; as such HT is also indicated in this group of women.

METHOD

A workgroup consisting of specialists in gynaecology, reproductive medicine, endocrinology, genetics and family medicine reviewed relevant guidelines and literature on POI to establish recommendations for the diagnosis and management of POI in Singapore. A consensus document on the management of POI was published in 2024 after collaboration between European, North American and Australian specialist societies, plus the International Menopause Society.[1] Our review supports the recommendations but with an emphasis on Asian women, especially where their needs may differ from other populations. We conducted a search on PubMed using keywords, which include: "premature ovarian insufficiency", "hormone therapy" and "Asian". Relevant studies published in English were included.

RESULTS

Prevalence

Recent global studies have estimated the prevalence of POI and early menopause to be 3.5–3.7% and 12.2%, respectively.[3,4] The prevalence of POI was higher in medium and low Human Development Index countries.[3] In a large cross-sectional study in the US, the prevalence of POI appears to be lower in Asian women: Chinese at 0.5% (95% confidence interval [CI] 0.1–1.9) and Japanese at 0.1% (95% CI 0.02–1.1), compared to Caucasian at 1.0% (95% CI 0.7–1.4), African-American at 1.4% (95% CI 1.0–2.1) and Hispanic at 1.4% (95% CI 0.8–2.5).[5] However, studies from China, Korea and India report the prevalence of POI at 2.2–3.2% and early menopause at 7.2–16.2%.[6-8] This might reflect the roles of genetics and environment influencing the prevalence of POI. To our knowledge, there is no study on rates of POI in Singapore to date.

Aetiology

The aetiology of POI is diverse; it can be divided into non-iatrogenic or iatrogenic causes (Table 1). Non-iatrogenic POI can be associated with chromosomal or genetic defects, autoimmune diseases and environmental factors. In approximately 60% of cases, no cause is found and it is currently described as idiopathic.[9] There is increasing evidence, however, that idiopathic POI may be genetic in origin[10] and may represent a syndrome of premature ageing. Iatrogenic causes of POI include chemotherapy, abdomino-pelvic radiation and pelvic surgeries, especially repeated ovarian surgeries.

In view of the long-term health consequences of POI, efforts should be made to reduce its incidence. Modifiable factors may include advising women to stop smoking, reducing ovarian surgeries for benign ovarian conditions and modifying treatment regimens for malignant and chronic disease to protect ovarian function. Women facing any gonadotoxic treatment should be counselled about the risks; when there is sufficient time and the individual is well enough, she should be offered a referral to a reproductive medicine specialist to discuss fertility preservation options.

Long-term consequences

The key long-term consequences are shown in Table 1 and summarised below. Women with POI are at risk of premature mortality, largely due to CVD, which may be worsened by the presence of other modifiable CVD risk factors.[11] Although the exact mechanism is unclear, adverse changes in lipid profile and impaired endothelial function related to estrogen deficiency may lead to premature atherosclerosis.[13] Women with POI have a 50% increased risk of type 2 diabetes compared to those aged between 45 and 55 years at menopause.[14,15] The impact of POI on CVD may be disproportionately higher in Asians compared to Caucasians as Asians are at risk of higher visceral fat, insulin resistance and dyslipidaemia at a lower level of body mass index (BMI).[16]

Low BMD (z score less than 2 standard deviations below age-matched pre-menopausal populations) is another consequence of POI, associated with earlier age at onset, later induction of puberty and reduced use of estrogen replacement.[1] Certain causative factors for POI may themselves be associated with lower BMD, such as Turner's syndrome, some chemotherapies (e.g. for breast cancer) and possibly autoimmunity.[1] The prevalence of low BMD in POI was estimated to be 8–14% in an American study, with African-American or Asian women more commonly affected than Caucasians.[17] However, ethnicity was not an independent predictor, and instead may have been a marker for a combination of modifiable risk factors, especially reduced use of HT. Evidence from an Australian cohort supports the biologically plausible expectation that POI is associated with an increased risk of fracture.[18]

Evidence for the association between age at natural menopause and all-cause dementia has been inconsistent.[19,20] However, more recent studies show that shorter lifetime endogenous estrogen

exposure may be associated with higher risk of all-cause dementia.[21-23] For example, a recent UK Biobank study with a large cohort of 160,080 women reported that compared to women with age at menopause of 46–50 years, women with non-iatrogenic POI or early menopause (age 41–45 years) had a higher risk of all-cause dementia, with hazard ratio (HR) of 1.36 (95% CI 1.01–1.83) and 1.19 (95% CI 1.03–1.37); respectively. However, late natural menopause (over 55 years) was linked to lower risk of dementia (HR 0.83, 95% CI 0.71–0.98).[23] Women with surgical menopause before the age of 40 years (HR 1.94; 95% CI 1.38–2.73) and after the age of 55 years (HR 1.65; 95% CI 1.21–2.24) were both linked to an increased risk of all-cause dementia.[23]

POI is an irreversible cause of infertility, although natural pregnancies may occur in an estimated 5% of women, with most occurring within the first year of POI onset.[2] Infertility may contribute to reduced quality of life in several domains, including psychological and psychosexual well-being. Inadequate estrogen replacement may contribute to dyspareunia and poor sexual health.

Clinical presentation

The clinical presentations of POI can be variable. The most common presenting symptom is menstrual disturbance, particularly amenorrhoea. Amenorrhoea may be followed by temporary resumption of cycles, which may be regular or irregular. There may be symptoms of low estrogen, including vasomotor symptoms (VMS) such as hot flushes and night sweats, vaginal dryness and/or dyspareunia. Other symptoms such as joint pain, labile mood, low energy, low libido as well as impaired memory and concentration may be present.

Symptoms experienced by women with POI may vary in intensity and can be intermittent due to fluctuations in ovarian activity. Some experience few or no VMS, especially when the onset of POI occurs at a very young age (before or during early adulthood). This may indicate that VMS are due to estrogen withdrawal rather than estrogen deficiency. Women who undergo surgical POI often have more sudden onset and severe symptoms, and have a greater risk of impaired cognitive function at least in the short-term.

Diagnosis

Fig. 1 is a diagnostic algorithm for POI. POI is diagnosed when there is or has been an episode of menstrual disturbance for at least 4 months and an elevated follicle-stimulating hormone (FSH) level of ≥25 IU/L.[1] FSH test only needs to be repeated if there is any doubt about the diagnosis. The FSH level must be interpreted with caution in women using hormonal contraceptives or hormone replacement therapy (HRT) within the last 6 weeks.

Serum anti-mullerian hormone (AMH) is produced by small ovarian antral follicles. The number of these follicles and therefore serum AMH declines throughout the reproductive years. AMH cannot predict when menopause will occur and is not useful to diagnose POI as it can be undetectable for years before the onset of menstrual disturbance.

Further evaluation

In the absence of clear iatrogenic causes of POI, genetic and autoimmune screening should be offered to evaluate possible underlying causes and associations.

Genetic

The prevalence of chromosomal abnormalities in women with POI is 10–12%, of which the majority are X chromosomal abnormalities, e.g. Turner's syndrome.[25,26] Women diagnosed with Y chromosome gonadal dysgenesis are at high risk of gonadoblastoma,[27] and should be advised to have their gonads removed. Karyotype analysis should be offered in all cases of unexplained POI.[1] If there are financial reasons to limit testing, a pragmatic approach would be to offer it to those with young onset (usually taken to be under the age of 30 years) or those planning for a pregnancy.

Fragile X *(FMR1)* premutation is present in 0.8–7.5% of women with non-iatrogenic POI and up to 13% in women with a positive family history of POI.[28] However, in Asian studies, there was a lower incidence (0.5–1.6%) of fragile X premutation among Chinese women with POI,[29,30] and no association between fragile X premutation and POI in an Indian population.[31] Since being a carrier of fragile X syndrome has significant implications for the individual and their family, we recommend referring the woman to genetic services for counselling prior to performing *FMR1* premutation testing. For cost considerations, clinicians may offer karyotype first, then *FMR1* premutation testing if the karyotype is normal.

Whole genome analysis is likely to uncover further genetic causes for POI in the foreseeable future.[32] In the current literature, there are approximately 100 monogenic causes identified.[10] Other studies have suggested that the majority of cases are likely oligogenic or polygenic in nature, with 2 or several different genes having synergistic effects.[10] Genetic variants have to be classified as pathogenic (class 5) or likely pathogenic (class 4) for POI according to the American College of Medical Genetics and Genomics criteria.[33] Interna-

Table 1. Aetiology and consequences of premature ovarian insufficiency.

Aetiology		Long-term consequences without HT
Non-iatrogenic POI	**Iatrogenic POI**	
Idiopathic (most common cause of non-iatrogenic POI)	**Chemotherapy** • Particularly cyclophosphamide and other alkylating agents; dependent on cumulative dose and combination of cytotoxic agents	**Infertility**
Genetic causes (10%) • Turner's syndrome (45XO): most common genetic cause • Fragile X pre-mutation: prevalence may be lower in Asians than other populations • Y chromosome gonadal dysgenesis • Autosomal gene mutations, e.g. BPES[a]	**Radiotherapy to the pelvis and/or abdomen** • Dependent on cumulative dose and field of exposure	**Increased risk of:** • Low bone mineral density, osteoporosis and possibly of fractures • CVD: coronary artery disease, heart failure and stroke • Type 2 diabetes • All-cause dementia and cognitive impairment (probably resulting from CVD) • Premature mortality
Autoimmune associations (20%) • Addison's disease • Autoimmune polyendocrine syndromes 1 and 2 • Autoimmune thyroid disorders, especially Hashimoto's thyroiditis • Other autoimmune conditions: coeliac disease, type 1 diabetes mellitus, myasthenia gravis, systemic lupus erythematous, thrombocytopenic purpura, vitiligo, alopecia, pernicious anaemia, rheumatoid arthritis, Crohn's disease, Sjogren's syndrome, primary biliary cirrhosis	**Bilateral oophorectomy** • Other pelvic surgery has been associated with early age of menopause and/or reduced ovarian reserve, including single oophorectomy, hysterectomy, uterine artery embolisation, bilateral or repeated ovarian surgery for cysts or endometriosis	**Reduced quality of life, including**: • Psychosexual well-being • Psychological well-being
Inborn error of metabolism (rare cause) • Galactosaemia[a]		**Reduced risk of breast cancer**
Environmental associations • Smoking: associated with earlier onset of menopause		

BPES: blepharophimosis syndrome; CVD: cardiovascular disease; HT: hormone therapy; POI: premature ovarian insufficiency

[a] These are usually diagnosed in infancy.

Aetiology segment is modified from Nguyen HH, Milat F, Vincent A. Premature ovarian insufficiency in general practice: Meeting the needs of women. Aust Fam Physician 2017;46(6):360-6, with permission from The Royal Australian College of General Practitioners.[24]

Superscript number: refer to REFERENCES

tional large cohort studies, including a Chinese study,[34] have shown gene positivity in up to 26% and 36.7% of women with sporadic and familial POI, respectively.[2,35] Higher gene positivity was observed in syndromic POI (58.3%)[35] and in women with primary amenorrhoea (28.5%) compared to secondary amenorrhoea (17.8%).[34] The recent 2024 European Society of Human Reproduction and Embryology guidelines on POI has made a conditional recommendation that next-generation sequencing can be offered to all women with non-iatrogenic POI after genetic counselling.[1] This is available for women with POI in some countries, such as China, the UK and France. However, in most countries including Singapore, it is still not part of routine screening for POI, unless there are specific clinical indications (e.g. blepharophimosis, ptosis and epicanthus inversus syndrome).

Autoimmune

Autoimmune disorders are more frequent in women with POI than in the general population, and non-iatrogenic POI is more frequent in women with certain autoimmune disorders.[1] The most clinically important autoimmune conditions associated with POI are adrenal insufficiency in the context of autoimmune polyendocrine syndrome, and thyroid hormone disorders.

The prevalence of Addison's disease (autoimmune adrenal insufficiency) is estimated to be 40–60 cases per 1 million population in Western countries, but only 4.17 per 1 million population in Korea.[36] Between 10–20% of women with Addison's disease have POI, while approximately 2.5–20% of women with POI develop adrenal autoimmunity.[37] Antibodies against 21-hydroxylase antibodies (21OH-Ab) are currently the marker with the highest diagnostic accuracy for autoimmune POI and should be looked for in women with non-iatrogenic POI. Although currently there is no specific treatment option for autoimmune POI, the diagnosis is clinically relevant for identifying subclinical or latent autoimmune adrenal insufficiency.[1] Women with a positive 21OH-Ab should be referred to an endocrinologist for testing of adrenal function and to rule out Addison's disease.

Approximately 20% of adults with idiopathic POI will experience autoimmune thyroid hormone disorders, most commonly Hashimoto thyroiditis.[1] Thyroid function should be assessed by measuring thyroid-stimulating hormone (TSH) at diagnosis and repeated every 5 years or earlier if symptoms of hypothyroidism occur. TSH should also be measured when the woman desires pregnancy due to the detrimental effects of hypothyroidism on fetal neurodevelopment. Testing for thyroid peroxidase (TPO) antibodies should not be performed for screening purposes in women with POI due to the high prevalence of positive TPO antibodies in the general community.[38]

Hormone therapy

Hormone therapy (HT) is indicated for POI, primarily to reduce the risks of CVD, type 2 diabetes, low BMD (with potential future fracture risk) and possibly dementia and cognitive impairment, irrespective of the presence or severity of symptoms of low estrogen. HT can be provided as physiological hormone replacement therapy (HRT) or combined hormonal contraception (CHC). There are few contraindications to HRT, the main one being personal history of estrogen-sensitive cancer. Healthcare professionals (HCPs) prescribing HT for women with POI after cancer treatment should ensure the cancer was not estrogen-sensitive and check with the patient's oncologist if in doubt. The contraindications to CHC are the same with functioning ovaries (refer to the UK Medical Eligibility Criteria for Contraceptive Use guideline[39]).

HT should be initiated early unless contraindicated and this includes for girls requiring pubertal induction, who should be referred to a paediatric endocrinologist for management (which is outside the scope of this review). HT should be continued until the usual age of menopause (approximately 50 years). Thereafter, ongoing HRT could be considered on the basis of personalised risk-benefit assessment, including need to improve bone health. Table 2 provides a summary for counselling women with POI about HT.

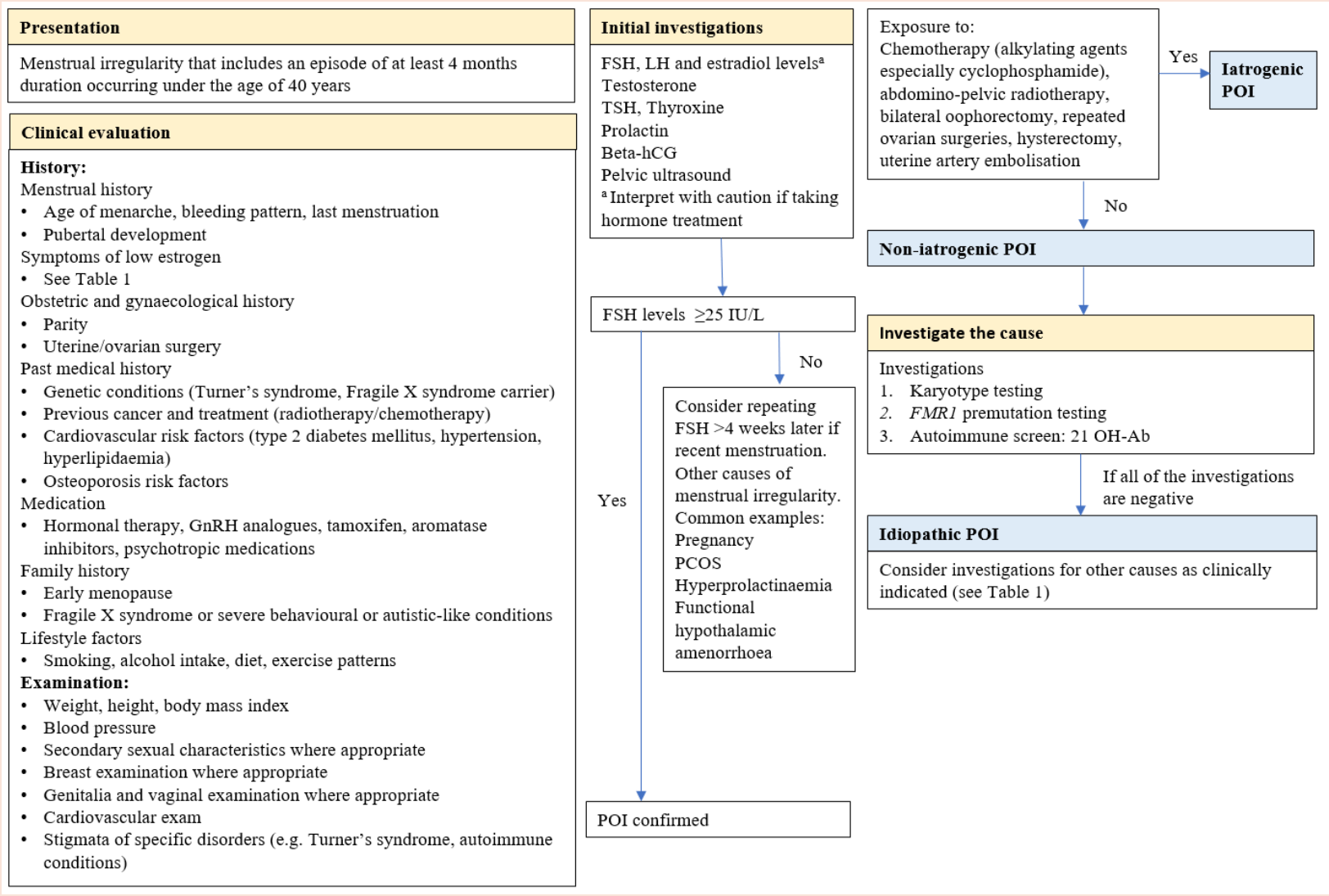
HRT is not a contraceptive, and women desiring pregnancy should be reassured that HRT will not interfere with their chance (albeit low) of natural pregnancy. If pregnancy is not desired, sexually active women should be advised on the need for contraception.

Various factors require consideration in the selection of HT preparations. HT should be individualised to improve adherence, taking into account personal preferences including any need for contraception. CHC may be more appealing due to familiarity with its use among younger women. Although there may be theoretical advantages to transdermal estradiol with oral cyclical progesterone or Mirena (52 mg levonorgestrel intrauterine device [IUD]; Bayer, Leverkusen, Germany), most young women prefer oral HT.[40] Fig. 2 includes an algorithm to assist with this decision-making process.

HT regimens

HT must consist of an estrogen plus a progestogen for endometrial protection in those with an

Fig. 1. Premature ovarian insufficiency diagnostic algorithm.



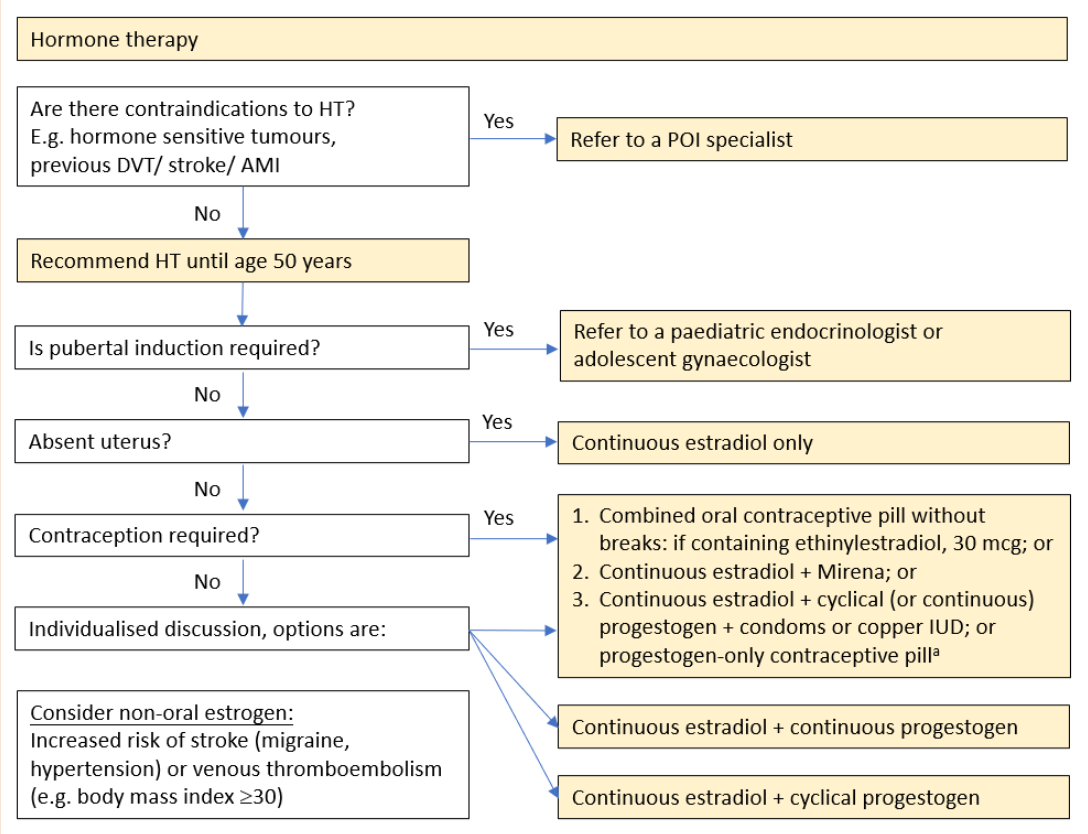
FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; hCG: human chorionic gonadotropin; LH: luteinizing hormone; PCOS: polycystic ovarian syndrome; POI: premature ovarian insufficiency; TSH: thyroid-stimulating hormone; 21-OH-Ab: 21-hydroxylase antibodies
Modified from Nguyen HH, Milat F, Vincent A. Premature ovarian insufficiency in general practice: Meeting the needs of women. Aust Fam Physician 2017;46(6):360-6, with permission from The Royal Australian College of General Practitioners.[24]
Superscript number: refer to REFERENCES

Table 2. Counselling women with premature ovarian insufficiency about hormone therapy.

Points for counselling
• HT is **indicated for women with POI or early menopause** (unless contraindicated) until the usual age of menopause (50 years of age).
• HT **protects your long-term health**, by reducing the risk of developing cardiovascular disease, type 2 diabetes, low bone density and dementia.
• HT can provide **relief of symptoms of low estrogen** and improve quality of life.
• Women with POI taking HT until the age of 50 years **are not thought to have higher risk of breast cancer** than women with normal ovarian function.
• Different formulations of HT allow for **personalised therapies** according to women's preferences and risk factors.
• Women who have a uterus require both estrogen replacement and **progestogen for protection of the endometrium**.
• HT can be physiological HRT or CHC.
• HRT is **not a contraception** and has fewer side effects than **CHC**.
• Transdermal HT has minimal or no increased risk of venous thromboembolism.
• **Complementary therapies are not a substitute for HT.**
• Women with POI need **long-term follow-up** with a healthcare professional.

CHC: combined hormonal contraception; HT: hormone therapy; HRT: hormone replacement therapy; POI: premature ovarian insufficiency

Fig. 2. Algorithm for prescribing hormonal therapy.



AMI: acute myocardial infarction; DVT: deep vein thrombosis; IUD: intrauterine device; HT: hormonal therapy; POI: premature ovarian insufficiency
[a] Progestogen-only contraception pill does not provide adequate endometrial protection within a hormone replacement therapy regime, hence additional progestogen is required.

intact uterus and those who have a history of endometriosis, as combined HT may reduce the risk of activating or causing malignant transformation of endometriosis.[1,41] Estrogen alone can be used otherwise.

Sequential HRT (sHRT: progestogen for 12–14 days/month) is prescribed for women who prefer monthly withdrawal bleeds, while continuous HRT (cHRT) is for those who do not. sHRT is preferable for women who are within 1 year of their last menstrual period to reduce unscheduled bleeding, as well as in women who wish to maximise their (low) chance of natural pregnancy or planning to have embryo transfer as a result of oocyte donation in the near future.[42] Long sHRT regimens with progestogen for a minimum of 12 days every 3 months can be considered for women who struggle to tolerate progestogens, although the risk of endometrial cancer with such regimens is higher. Extrapolating from older postmenopausal women using HRT, sHRT may be associated with a lower risk of breast cancer but a higher risk of endometrial cancer compared to cHRT.

If CHC is prescribed, it should be taken continuously, i.e. without any days omitting hormone, as this results in reduced total exposure to estrogen, and VMS can occur, which may be distressing. If breakthrough bleeding occurs, a break of 4–7 days can be taken at the end of every 2nd or 3rd calendar strip of pills to allow a withdrawal bleed.[42]

Type of estrogen

There have been no studies published to date to inform which of the current commercially available HT options are best for women with POI. Most of the research has been for hormone contraception in younger women or HRT for use by older women with usual age at menopause. A UK trial is ongoing at the time of writing which randomises combined oral contraception or HRT for women with POI.[43]

Estradiol (also known as 17-beta estradiol or E2) is the main and most potent estrogen produced by the pre-menopausal ovary. Natural estrogen is commercially available as estradiol hemihydrate, and is found in oral and transdermal (patch, gel and spray) formulations or as the oral pro-drug estradiol valerate. Oral estradiol undergoes extensive hepatic first-pass metabolism, resulting in low bio-availability of estradiol (under 5%), high levels of the weak natural estrogen estrone and also a variety of other metabolites. These may be responsible for the side effects noted in older postmenopausal women, e.g. increased risk of venous thromboembolism (VTE) and stroke. In contrast, transdermal estradiol undergoes little metabolism and in the older age group appears not to affect the clotting cascade or VTE risk.[44,45]

Ethinyl estradiol (EE) is a synthetic estrogen that was developed for CHC, i.e. for women of reproductive age. EE is much more potent than estradiol and causes unfavourable effects on lipid profile and blood pressure, and increases the risk of VTE and stroke. These adverse effects are increased in smokers, those with obesity and those aged over 35 years. Side effects are also dependent on the progestogen delivered alongside EE in the doses used for CHC. Oral CHC may be less favourable for maintenance of BMD compared to HRT;[46] this could be because EE is less beneficial than natural estradiol or due to the suppressive effect on insulin-like growth factor 1 production by CHC. It is not known if the risk-benefit ratio of CHC may be improved in the newer pills containing the natural estrogens (estradiol or estetrol produced by the feto-placental unit). Estetrol is a weak estrogen thought to have fewer adverse effects than EE and is available with drospirenone as an oral contraceptive in some countries (Australia, US and Europe; licence granted in Hong Kong, Taiwan and Japan in 2024). An HRT version may be available soon.

Most POI specialists do not recommend prescribing conjugated equine estrogen since it contains estrogens not found in humans and is more thrombogenic than estradiol, unless a natural estrogen product is not available and CHC is contraindicated.[1] Tibolone, a synthetic molecule that can stimulate estrogen, progestogen and androgen receptors,[47] is not recommended. Its safety with long-term use or in pregnancy is unknown. It does not improve BMD in women with POI,[48] and is unlikely to favour pregnancy due to its thinning effect on the endometrium.

Progestogen for endometrial protection

There are no data to indicate the preferred progestogen for endometrial protection in women with POI. In older postmenopausal women, micronised progesterone (Utrogestan, Besins Healthcare, Monaco) and dydrogesterone (Duphaston, Abbot Laboratories, Chicago, IL, US: a synthetic isomer of natural progesterone) may be preferrable over synthetic progestogens, e.g. medroxyprogesterone acetate or norethisterone, as they are associated with a lower risk of breast cancer[49] and avoid the androgenic and thrombotic side effects of norethisterone. The 52 mg levonorgestrel IUD (Mirena) may also be considered to avoid systemic effects of progestogens or when contraception is required. The Mirena probably provides protection

against endometrial hyperplasia within an HRT regimen for up to 5 years[50] and this is supported by the Faculty of Sexual and Reproductive Health (UK). Depot preparations of medroxyprogesterone acetate, oral progestogen-only contraceptive pills, vaginal progesterone gel and compounded micronised progesterone creams should not be used for endometrial protection due to concerns that their hypoplastic effects are inadequate.[1]

HT dosage

Women with POI generally require higher doses of estrogen for prevention of long-term sequelae, especially for bone health, than those required to control menopausal symptoms in older women. The recommended doses of estrogen for women with POI are oral estradiol 2 to 4 mg or transdermal estradiol 50–100 mcg patches or 2–3 mg gel daily (or 2–3 estradiol sprays).[1] Doses required to attain maximum BMD in the youngest of those with POI (post-puberty) are probably at the higher end of these ranges.[1] Future studies are needed to determine the optimal dosage across the reproductive age range. Ethnicity needs to be taken into consideration in such studies, not only because of different background levels of prevalence and risk for cardio-metabolic disease and osteoporotic fractures. Asian women have significantly higher serum estradiol levels during treatment with transdermal estradiol compared with Caucasian women, suggesting an ethnic difference in steroid metabolism.[51] This may have implications for treating POI in Asians. If CHC containing ethinyl estradiol is used for HT, 30 mcg taken continuously is needed, instead of 20 mcg or 30 mcg cyclically.

The dose of progestogen required for endometrial protection depends on the dose of estrogen and the regimen. For a standard estradiol dose of oral 2 mg per day, continuous regimens require 5 mg dydrogesterone or 100 mg of micronised progesterone, while cyclical regimens require 10 mg dydrogesterone or 200 mg micronised progesterone for 12–14 days per month.[52] Women who require higher doses of estrogen may require an increased dose of progestogen to ensure adequate endometrial protection.

Monitoring of HT

Women should be reviewed every 3 months while starting on HT to allow for any necessary adjustments. Once optimum HT is established, consultations should occur at least annually. At each visit, HCPs should enquire about symptoms of estrogen deficiency, any unscheduled bleeding, adherence to therapy and reiterate the reasons for needing HRT, including the requirement for progestogen protection of the endometrium.

Serum measurement of estradiol levels is not required routinely but may be helpful to check compliance or absorption if symptoms persist despite a seemingly adequate dose (for estradiol preparations only). It is reasonable to aim for physiological estradiol levels as found in the serum of women with normal menstrual cycles of approximately 200–400 pmol/L.[53] Serum estradiol levels do not increase in a linear fashion with oral estradiol.[54]

Risks of HT

There is a lack of studies investigating the risks of HT for women with POI. Untreated POI is associated with a reduced risk of breast cancer, likely due to reduced lifetime exposure to estrogen.[55,56] Large studies have not found an increased risk of breast cancer in women less than 50 years taking HRT.[56,57] A more recent report brings this into question, noting an increased risk of breast cancer in the small number of women identified starting HRT between 30 and 39 years of age.[58] Statistical significance may be due to index case selection. Although Asian women have lower incidence rates of invasive breast cancer than women of European origin, its incidence in East and Southeast Asia has increased rapidly over the past 40 years.[59] Given that women with POI will usually be taking HT for over a decade, it is a reminder that the HT of choice should be those with the minimal risk of breast cancer.

CHC administered via any route is associated with risk of VTE and very small risk of thrombotic stroke. Oral HRT has similar adverse effects in older, postmenopausal users and may occur in women with POI, especially in the presence of other risk factors (e.g. smoking and obesity). This risk can be mitigated by using transdermal estrogen,[44,45] and it is the preferred estrogen for women with migraine or hypertension, or who are at increased risk of VTE (e.g. BMI ≥30).[1,60] The choice of progestogen used alongside estradiol replacement may also influence VTE risk, although there was no adverse effects of different progestogens on the clotting cascade with transdermal estrogen.[61] Nonetheless, using a progestogen with a low thrombogenic profile would be reasonable (e.g. Mirena, oral micronised progesterone or dydrogesterone).

Prolonged use of progestogen is associated with a small risk of meningioma, but not for micronised progesterone, dydrogesterone and Mirena.[62]

Non-hormonal and complementary therapy

Many Asian women accept menopause as a natural process and would prefer natural or herbal treatment (37%) over HT (19%) for the treatment of menopausal symptoms.[63] Women with POI may

also turn to complementary therapies, but they should be advised that these do not replace HT for the prevention of long-term sequelae of POI.

Women with a personal history of hormone-sensitive cancer who are unable to take HT may benefit from non-hormonal pharmacologic (e.g. selective serotonin reuptake inhibitors) and non-pharmacologic therapies (e.g. cognitive behavioural therapy). These can be helpful in relieving menopausal symptoms in older peri- and postmenopausal women, but evidence specific to POI is lacking.

A new class of centrally-acting drugs, neurokinin (NK) blockers, to reduce VMS in peri-menopausal women was launched for women age 45 to 55 years in Australia, the UK and the US in 2022. The licence applications are pending for various markets, including Singapore. NK blockers may have a future role for women with POI for whom HT is contraindicated.

Management of POI

The diagnosis of POI can be extremely distressing for women. Several consultations may be required to provide emotional and psychological support, including for sharing the diagnosis with family and/or partner. All women with POI should be given lifestyle advice and long-term follow-up to monitor their cardiovascular, bone and psychological health, as summarised in Table 3. Women with POI who are keen for fertility should be offered referral to a reproductive medicine specialist.

Lifestyle intervention

Women with POI should be given lifestyle advice to optimise bone and cardio-metabolic health and to reduce risks of dementia. They should be advised to avoid smoking, moderate alcohol intake and maintain a healthy body weight (BMI of 18.5–22.9 kg/m^2). Diet should be low in fat and salt but rich in calcium and vitamin D—the recommended daily dietary intake for bone health is calcium 1000–1200 mg and vitamin D 600–800 IU.[64] The average Singaporean diet contains 625 mg calcium daily.[65] Women who are not getting enough dietary calcium and vitamin D should receive supplementation. Vitamin D measurement could be considered for all women diagnosed with POI, since the prevalence of deficiency in Singapore is up to 42%,[66] possibly contributing to low BMD. Vitamin D can be obtained with 5–30 minutes of sun exposure between 10 am and 3 pm, for at least twice a week. Women should be advised to do 150–300 minutes/week of moderate-intensity aerobic for cardio-metabolic health, ideally including some weight-bearing (e.g. dancing, jogging, skipping rope), muscle-strengthening (e.g. light weights, elastic band exercises) and balance exercises (e.g. yoga, pilates, tai chi) for bone health.

Fertility options

Women should be informed that 5% of women with POI spontaneously conceive, especially within the first year of amenorrhoea.[2] There is no reliable intervention to increase ovarian activity and natural conception rates. Oocyte or embryo donation are the only proven treatments to achieve pregnancy.[1] Several novel approaches have recently been described, including in vitro activation of follicle growth in biopsied ovarian tissue, administration of mesenchymal stem cells and injection of platelet rich plasma into the ovary. More robust studies are required to determine if these treatments are effective. The opportunity for fertility preservation is missed in women with established POI.

Fitness for pregnancy requires assessment in the preconception period as some women with POI may be of high obstetric risk, such as women with Turner's syndrome, those who have had pelvic irradiation (also associated with a reduced chance of pregnancy), mediastinal irradiation or high-dose anthracycline exposure. Women who are planning pregnancy with egg donation are at higher risk of obstetric complications such as hypertensive disorders in pregnancy.

Relatives of women with POI

The risk of POI in a woman who has a relative diagnosed with POI may be up to 15%.[1] Female relatives (such as sisters or daughters) of women with non-iatrogenic POI who are concerned about their risk for developing POI should be advised that they may be at risk, and informed of the signs and symptoms of POI, with the recommendation to seek medical advice if these occur. Unfortunately, there are no established methods for predicting or preventing POI in this group of women. Some relatives may wish to consider earlier family planning and/or fertility preservation options, although the role of fertility preservation in women with a familial link to POI is not established. There may be financial constrains or legal restriction in some countries for egg freezing.[68,69] Relatives of women with the fragile X premutation should be offered genetic counselling and testing.

DISCUSSION

POI affects an estimated 3.5% of women globally and the long-term consequences of POI, especially on CVD and osteoporosis, should make health policymakers prioritise and allocate health resources

Table 3. Long-term management of premature ovarian insufficiency.

Long-term management of POI

1. Cardiovascular risk factors
- **Blood pressure, weight** and **smoking** status: monitor each visit
- **Lipid profile** and **diabetes screening**: assess at diagnosis
  - Treat/reassess according to local CVD risk assessment tools (none currently available weighted for POI/age of menopause) and protocols

2. Bone health risk factors
- **Vitamin D**: consider screening at baseline and treat if deficient
- **DEXA** scan: consider at diagnosis (especially if diagnosis or start of HT was delayed, low BMI or family history of osteoporosis)
  - Normal BMD (z score >-2.0) and adequate HT: value of repeat DEXA scan within 5 years is low
  - Low BMD (z score £-2.0): repeat DEXA 1–3 years after HT commenced

If BMD declines despite seemingly adequate HT, compliance should be checked, screening for other secondary causes of osteoporosis undertaken and consideration given to increasing dose of estrogen/changing preparation. Referral to an osteoporosis specialist may be required: bisphosphonates should be avoided unless there is no chance of future pregnancy (including from egg donation).

3. Fertility
- Adjust HT according to fertility plans: e.g. stop/start contraceptive HT or sHRT
- Refer to reproductive medicine specialist if patient wishes to consider fertility treatment

4. Sexual dysfunction
- **Enquire** after sexual function
- Optimise **HT**
- Treat persisting urogenital symptoms (e.g. **vaginal estrogen, moisturisers and lubricant** to treat dyspareunia)
- Review medications potentially impacting sexual function (e.g. antidepressants)
- **Psychosexual counselling** if required
- **Testosterone** therapy: consider for HSDD especially in surgical POI but:
  - Insufficient evidence regarding efficacy and long-term safety to support routine use[67]
  - No licenced testosterone preparation for females available in Singapore currently

5. Quality of life
- **Psychological symptoms**: e.g. grief at the loss of femininity and fertility, fear of long-term health consequences, concerns regarding impact on relationship with their (future) partner
  - Refer for psychological support when needed
  - Signpost to support groups and educational resources

6. Autoimmune screening (for idiopathic or autoimmune POI and Turner's syndrome)
- **TSH measurement** every 5 years or if symptoms develop
- Low threshold to investigate symptoms suggestive of other autoimmune conditions

7. Cancer screening
- **Enquire after unscheduled vaginal bleeding**, investigate and manage as indicated
- Breast and cervical cancer screening **as per national guidelines**

BMD: bone mineral density; BMI: body mass index; CVD: cardiovascular disease; DEXA: dual-energy x-ray absorptiometry; HSDD: hypoactive sexual desire disorder; HT: hormonal therapy; POI: premature ovarian insufficiency; sHRT: sequential hormone replacement therapy; TSH: thyroid-stimulating hormone

for preventive and treatment interventions for affected women. Healthcare policies should ensure that appropriate HT choices are available and more affordable. Fertility-sparing treatments for cancer and non-cancer conditions should be used whenever possible to reduce iatrogenic POI, with more research into these options. Artificial reproductive techniques and fertility preservation should be made more available for women at risk of POI.

There are barriers for prescribing HT, for both women and HCPs, often still related to the publication of the Women's Health Initiative Studies in 2002, which reported an increased breast cancer prevalence associated with HRT use. HCPs may have had inadequate training in menopausal medicine, resulting in a lack of confidence for prescribing these treatments, even for women with POI. Many women have a lack of knowledge of as well as concerns about the risks of HRT, that is, not understanding the differences between its use to manage symptoms of normal menopause in contrast to reducing the consequences of POI. These barriers need to be broken, by providing training and education to HCP to provide evidence-based counselling to women with POI, in order for them to make informed decisions about their health.[70]

The field of genetics in POI is expanding and it is hoped that this will allow a better understanding of the condition, its prognosis and development of novel prevention or treatment strategies. Last, setting up a POI registry and collaborative research across the region can facilitate much needed large-scale research to be conducted for Asian women with POI.

CONCLUSION

The diagnosis and management of POI can be challenging for HCPs. Practitioners should include POI in their differential diagnosis of women presenting with onset of menstrual irregularity under 40 years of age and be able to confirm the diagnosis, investigate the underlying cause and screen for factors that may potentiate the long-term consequences. Women should be started on HT, unless contraindicated (for which there are very few). Multidisciplinary team involvement is often required. Women require long-term follow-up to monitor therapies and to screen for consequences of POI.

Ethics statement

Not applicable.

Declaration

The authors do not have any affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript. No generative artificial intelligence (AI) or AI-assisted technologies was used in writing this manuscript.

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LETTER TO THE EDITOR

Barriers to cervical cancer screening and the potential role of HPV self-sampling in Singapore: A cross-sectional study

Edwin Aik Chen Chng[1] *MBBS*, Helen Elizabeth Smith[2] *MBBS*

Dear Editor,

Cervical cancer is a common female cancer and a leading cause of cancer deaths, with about 170 deaths annually in Singapore.[1] Despite a population-based screening programme, with government subsidies and affordable co-payments, the current screening rate of 45.4% among 25–74 year-olds,[2] falls far below the 70% national target. In other countries, the introduction of self-testing for human papillomavirus (HPV) has improved cervical cancer screening uptake.[3] Our cross-sectional survey explored the barriers to screening among Singaporean women, their attitudes towards self-testing, and the potential increase in cervical cancer uptake should HPV self-sampling be made available.

Consecutive women aged ≥30–70 years attending 1 general practice clinic were invited to complete the survey on whether they had ever participated in cervical screening. Women were excluded if they had a total hysterectomy, a history of cervical cancer, or never had sexual intercourse. A recruitment quota for each age group ensured population representation.[4] Women <30 years were excluded in view of international guidelines that recommend HPV test for ages above 30.

The online self-administered questionnaire collected sociodemographic data, cervical cancer screening history, knowledge of the national screening programme, together with the barriers (personal, professional and organisational) challenging compliance to recommendations.

Over 90% of women were aware of screening for cervical cancer and believed that screening was beneficial, recognising that cervical cancer can be serious and fatal (95%) and recognising their own risk (75%). Of concern was that far fewer women knew the correct frequency (20%) or eligibility (29%) for screening, and 1 in 10 women previously or sexually active thought they were not at risk of developing cervical cancer. These observations suggest that there is a need to enhance women's awareness of the need for repeat and regular cervical cancer screening, something that could be supported by a personalised reminder system.

Although three-quarters of the women had screened at least once for cervical cancer, only 62% had screened within the required previous 5 years. While the intention for future screening was high (63% indicating they were "very likely" and 24% "somewhat likely"), three-quarters indicated 1 or more barrier to screening. Common barriers were pain/discomfort (25%), fear of abnormal result (24%), embarrassment/lack of privacy (21%) and cost/financial concerns (21%). Less common barriers included lack of female doctors (16%), shortage of time (13%), uncertainty of screening interval (12%) and unawareness of screening venues (10%). The 2024 Healthier SG initiative is expected to reduce financial concerns, as national screening programmes are now fully subsidised for women ≥40 years. However, lack of knowledge and experiential barriers require attention from healthcare professionals and policymakers to increase further cervical cancer screening uptake.

In many regions (e.g. Australia, North America, Europe, Asia, Central Africa), cervical cancer screening uptake has been boosted between 4.1–46.2% after the introduction of HPV self-sampling.[5-8] We wanted to estimate its potential impact among Singaporean women, but first had to describe the procedure for self-sampling as it is not used routinely in Singapore, and awareness is low (7%). Even with such unfamiliarity, almost two-thirds (64%) expressed willingness to participate in self-administered HPV testing, 27% being accepting of both clinician and self-sampling methods, 18% preferred the idea of self-testing but were happy with either, and 6% wanted only self-sampling.

Concerns expressed about self-sampling included, but to a slightly lesser extent than for a clinician-sampled Pap smear, pain/discomfort

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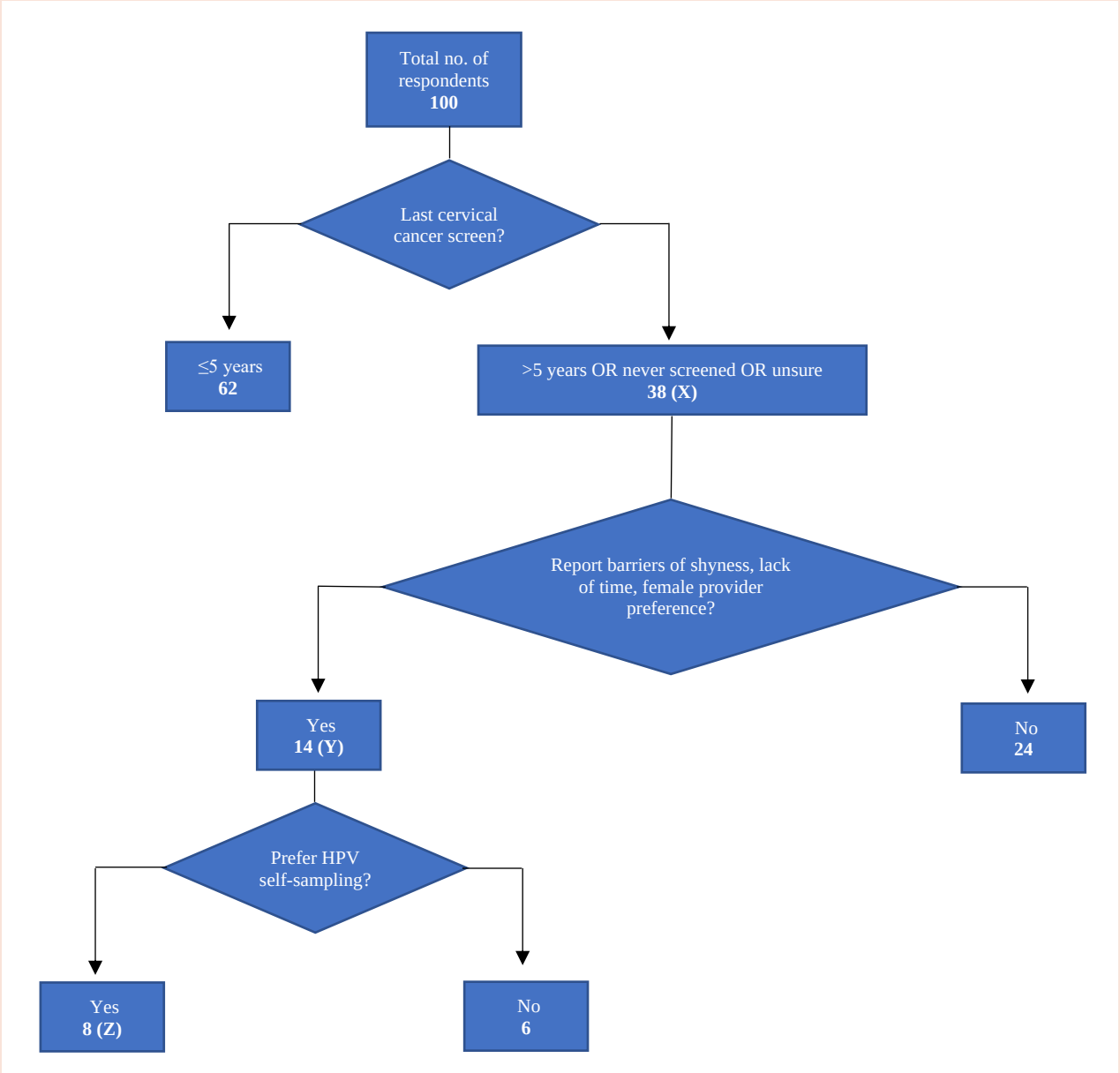
(18%) and cost (13%). The method-specific barrier for women was doing the test incorrectly (67%). They described how willingness to self-test would be enhanced by discussing with a doctor (48%), to get more information (41%) and reassurance about reliability (36%). They suggested that it would also be helpful to meet with women who had self-sampled (25%).

Fourteen of the 32 women in our sample who were not compliant with cervical cancer screening (out of date or never screened), were challenged by embarrassment, lack of time and preference for a female health provider. Each of these 3 barriers can be reduced by self-sampling, and 8 of these women indicated they would prefer self-sampling. Using the formula [(X ∩ Y ∩ Z)/n] x 100%, the expected percentage increase in screening rates with the introduction of HPV self-sampling would be (8/100) x 100=8% (Fig. 1). As most respondents expressed a favourable response to self-sampling, if allowed, its introduction could also impact on sustained 5-yearly cervical cancer screening.

The introduction of self-sampling is not without its challenges. Self-collected vaginal samples are deficient in ectocervical and/or endocervical cells, resulting in a lower sensitivity for detecting

Fig. 1. Workflow map to calculate the potential increase of cervical cancer screening rate with availability of HPV self-sampling.



HPV: human papillomavirus

high-grade cervical lesions compared to clinician-collected samples.[9] When patients who have self-sampled are found to be positive for non-HPV type 16 or 18 (high-risk strains), they need to return for a clinician-sampled Pap test, whereas if conventional screening methods are used, reflex cytology can be conducted on the same sample. In Singapore, about 21.0–25.6% of women are positive for high-risk HPV on testing[10,11]; if so, up to 1 in 4 women who undergo self-sampling will possibly need to be recalled for a clinician-sampled Pap test to complete the screening process. Our respondents were not informed about the potential for a second screening test, and if aware may have been less enthusiastic about self-sampling. However, as mentioned above, other countries have boosted their screening rates with the introduction of HPV self-sampling.[5-8]

Our study summarises the ways in which the current cervical cancer screening programme is perceived as challenging, focusing on these barriers has the potential to boost women's future compliance. We have also estimated that with the introduction of self-sampling cervical cancer screening, an additional 8% of women would be willing to be screened. Unfortunately, the current funding for cervical cancer screening is targeted on clinician-sampling only. Thus, women would need to do both self-sampling and self-funding in the short-term. The costs of a self-sampling programme (i.e. initial test, recall for inadequate test, recall for further testing) are needed and set against the benefits (i.e. quality of life and number of years of life gained). With this objective data, a decision can be made about the cost-effective target for self-sampling (unscreened only, unscreened and inadequately screened, or all women eligible for screening who wish to self-sample) and the extra investment required.

Ethics statement

Ethics approval was obtained from Parkway Independent Ethics Committee (PIEC/2022/059).

Declaration

The authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: *cancer, cervical, HPV, screening, self-sampling*

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LETTER TO THE EDITOR

vNOTES hysterectomy with a homemade glove port: Initial experience in Singapore

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Dear Editor,

Vaginal natural orifice transluminal endoscopic surgery (vNOTES) is an established surgical method of performing hysterectomy via the vaginal route and is one of the latest editions to the realm of minimally invasive surgery. Since the first vNOTES performed by Su et al. in Taiwan in 2012, vNOTES has been gradually gaining popularity as more surgeons become familiar with the technique.[1] Since our initial foray into performing vNOTES hysterectomy at Singapore General Hospital, we have been able to perform even more successful cases and across a wider spectrum of patients.[2] This is a discussion of our surgical outcomes and subgroup-tailored techni-ques in performing vNOTES since our index cases.

We conducted a retrospective review of patients that underwent vNOTES hysterectomy for benign gynaecological conditions at Singapore General Hospital from March 2021 to December 2023. Since our initial foray in performing vNOTES hysterectomy, patients are determined to be candidates for vNOTES hysterectomy if they are candidates for laparoscopic surgery. SingHealth Centralised Institutional Review Board approval was not required for the use of anonymised patient data. Length of stay, operative duration and complication rates were the main outcomes assessed. Continuous variables were summarised using median and range. Categorical variables were represented by percentages. Surgical complications encountered were classified according to the Clavien-Dindo Classification.[3] Patients were followed-up until the first clinic visit (3 weeks) for any post-operative complications.

From March 2021 to December 2023, 92 cases of vNOTES hysterectomy were performed. The clinical demographic and perioperative outcomes of our study are shown in Table 1.

Our cohort consisted of a multiethnic population. The median and maximum age of patients were 47 and 75 years, respectively. Fifty-two patients (56.5%) had a body mass index (BMI) of 25 and above and were considered as obese according to our local Asian classifications. Twenty patients (19.2%) were virgo intacta, and 40 cases (43.4%) had previous abdomino-pelvic surgeries. vNOTES hysterectomy for ovarian cysts and fibroids were the most common indication for surgery. Metabolic disease and asthma were the most common medical comorbidities of our cohort. Median estimated blood loss was 100 mL. Median operative duration was 115 min. Ten patients had uterine weight greater than 300 g with 3 cases being more than 500 g. Median duration of hospitalisation (including operative day) was 2 days. All patients were well on first post-operative clinic review. We reported a total of 3 patients that experienced complications. The first patient developed postoperative bleeding from the vaginal vault on postoperative day 2 which was managed conservatively. The second patient required conversion to laparotomy to facilitate delivery of a large ovarian cyst (26.9 cm x 14.1 cm x 16.5 cm) and repair of an inadvertent enterotomy and cystostomy. The third case required closer monitoring in the surgical intensive care unit due to failure to extubate in the operating theatre likely related to morbid obesity (BMI 55.9), poorly controlled asthma and obstructive sleep apnea.

Over the years, we have explored the role of vNOTES and concluded that it is a feasible approach in various patient populations with careful adjustments to surgical technique.

Patients with previous abdominal surgery represent a challenging subgroup for vNOTES surgeons due to the presence of adhesions. For patients with prior lower segment caeserian section (LSCS), which forms an ever-increasing subgroup in our local population as more women opt for LSCS, we perform a posterior colpotomy followed by bladder adhesiolysis and dissection of the uterovesical fold under direct laparoscopic guidance. For patients with previous anterior

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Table 1. Patient characteristics and perioperative outcomes.

	vNOTES (n=92)
Median age, years (range, SD)	50 (23–81, 13.4)
BMI (range, SD)	25.8 (15.6–55.9, 5.5)
BMI ≥25	52 (56.5)
BMI <25	40 (43.5)
Race, no. (%)	
Chinese	53 (57.6)
Indian	19 (20.7)
Malay	12 (13.0)
Others	8 (8.7)
Parity, no. (%)	
Virgin	20 (19.2)
Non-virgin	72 (80.8)
Normal vaginal delivery, no. (%)	
0	47 (51.1)
≥1	45 (48.9)
Previous abdominal surgery, no. (%)	
Yes	40 (43.4)
No	52 (56.5)
Type of abdominal surgery, no. (%)	
Lower segment caeserian section	16 (17.4)
Cystectomy	9 (9.8)
Colectomy	4 (4.3)
Cholecystectomy	6 (6.5)
Exploratory laparotomy	1 (1.1)
Sleeve gastrectomy	2 (2.2)
Hernia repair	2 (2.2)
Others	5 (5.4)
Indication for surgery, no. (%)	
Ovarian cyst	27 (29.3)
Fibroids	21 (22.8)
Genetic risk reduction (BRCA1/2, RAD51C/D, BRIP1, Lynch syndrome)	16 (17.4)
Gender reassignment	9 (9.9)
Atypical hyperplasia	9 (9.9)
Adenomyosis/endometriosis	3 (3.3)
Cervical intraepithelial neoplasia with fibroids	3 (3.3)
Genetic risk reduction and adenomyosis	1 (1.1)
Ovarian cyst and adenomyosis	1 (1.1)
Ovarian torsion	1 (1.1)
Pyometra	1 (1.1)
Medical comorbidities, no. (%)	
Hyperlipidaemia	32 (37.8)
Hypertension	30 (32.6)
Type 2 diabetes mellitus	16 (17.4)
Asthma	13 (14.1)
Ischaemic heart disease	3 (3.3)
Paroxysmal atrial fibrillation	3 (3.3)
Chronic kidney disease	3 (3.3)
Gastroesophageal reflux disease	3 (3.3)
Stroke/transient ischaemic attack	2 (2.2)
Median operative duration, minutes (range, SD)	115 (45–475, 59)
Median estimated blood loss, mL (range, SD)	100 (0–700, 224.9)
Median length of stay, days (range, SD)	2 (1–12, 1.72)
Median uterine weight, g (range, SD)	94 (24–872, 145.2)
Perioperative complications	3 (3.2)
< Clavien-Dindo III	1 (33.3)
≥ Clavien-Dindo III	2 (66.6)

BMI: body mass index; SD: standard deviation; vNOTES: vaginal natural orifice transluminal endoscopic surgery

resections or suspected endometriosis, we perform an anterior colpotomy or lateral approach to minimise the risk of rectal injury.[4,5] Adhesiolysis is then performed prior to the sealing of uterine vessels. The ureters are traced prior to the mobilisation of the uterus to avoid ureteric injury.

vNOTES in virgo intacta patients is technically challenging due to a narrow vagina and introitus. This is made even more challenging in our local Asian population due to our natural Asian anatomy of having a narrower introitus as compared to the Western population. We performed vNOTES for 20 virgo intacta patients without any major complications through the use of a small virgin speculum and small lateral retractors, to provide adequate exposure without causing major vaginal tears. Anterior and posterior colpotomy were performed under laparoscopic guidance to improve anatomical visualisation during routine colpotomy.

Performing vNOTES in patients with large uterus can be challenging due to difficulty with uterine manipulation, visual access and specimen retrieval. In some cases, large fibroids sited at the lower anterior corpus and extrauterine fibroids with caudal extension to the cervix could also complicate routine colpotomy.[6-8] Some studies have also noted increased blood loss in patients with large uteri undergoing vNOTES due to regurgitant bleeding from the large uterus and failure to ligate all engorged vessels associated with a large uterus.[7] To achieve comparable blood loss rates and operative durations in patients with large uteri, we took greater precautions to ensure proper ligation of the engorged vessels by utilising a good energy sealing device. Only 1 case required conversion to laparotomy to facilitate specimen retrieval. The decision for conversion was also partly due to the inadvertent enterotomy and cystostomy.

Performing colpotomy is technically challenging in patients with high BMI (>35) due to crowded introitus. With rising rates of obesity in Singapore, we anticipate an increase in vNOTES performed for patients with high BMI in the following years. We opted to perform the initial circumferential incision under laparoscopic guidance before proceeding with the remaining segments of surgery. We also elected to perform some of the initial stages of surgery vaginally before introducing pneumoperitoneum and performing the remaining segments of surgery.

This study presents our initial experience in performing vNOTES for a wide and varied patient population. With increased experience in vNOTES hysterectomy, we will eventually be able to conduct comparative studies to better evaluate the efficacy of vNOTES against other surgical alternatives and reduce selection bias. With a larger study population, we also aim to conduct multivariate analyses and logistic regressions to identify potential predictors of adverse outcomes to guide the recommendation of vNOTES in different patient populations.

Ethics statement

Not applicable.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Keywords: *epidemiology, general surgery, medical education, minimally invasive surgery, surgery*

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LETTER TO THE EDITOR

Effectiveness of an online patient education video for transcatheter aortic valve implantation

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Dear Editor,

Anxiety and gaps in medical knowledge have been shown to adversely affect treatment decisions amongst patients and their next-of-kin (NOK).[1-3] In a busy clinical setting, physicians may find it time-consuming and challenging to address all aspects of a complex procedure, like transcatheter aortic valve implantation (TAVI) for the treatment of aortic stenosis (AS). We aim to evaluate the effectiveness of an online patient education video in improving patients' and NOKs' knowledge, and reducing their anxiety for TAVI.

Between April 2021 and April 2024, consecutive patients and/or their NOK being considered for TAVI in the National Heart Centre Singapore were recruited. Non-English-speaking participants were excluded. Written informed consent was obtained from the participants and ethical approval was obtained.

In addition to the consult by the heart team, a 5-minute original animated education video, accessible at https://www.youtube.com/watch?v=F56YUQEhj0k, was shown. This was created using a whiteboard sketching video tool, VideoScribe (Sparkol Limited, Bristol, UK) and narrated in English. The video described the clinical symptoms of AS, the indications, procedural details, risks and benefits of TAVI, and post-procedural care (Supplementary material S1). A self-administered written questionnaire (Supplementary material S2) was conducted prior to and after the intervention. In summary, the questionnaire gathered information regarding baseline demographic data, and both objective and subjective assessment of knowledge and anxiety levels. The knowledge component was objectively graded based on 10 questions with a score of 1 for the right answer without negative marking. Anxiety was assessed objectively via the State Trait Anxiety Inventory (STAI).[4] The STAI is a self-reported, validated psychological instrument to assess levels of state anxiety (STAI-S) and trait anxiety (STAI-T). Qualitative feedback on the video was also obtained.

The primary outcomes were objective knowledge scores and STAI scores. Secondary outcomes were participants' own perception of their knowledge and anxiety levels.

All scores were compared pre- and post-intervention using Wilcoxon signed-rank test. A sensitivity analysis was performed separately in the patient and NOK subsets. A *P* value of <0.05 was considered significant. Statistical analysis was performed using Stata version 18 (StataCorp, College Station, Texas).

A total of 32 participants were recruited, with 18 patients and 14 NOKs. Participants were equally represented in sex. Median age was 65.0 (interquartile range [IQR] 46.5–75.5) years, with patients generally older than NOK, at 74.5 (IQR 67–82) and 43.0 (IQR 38–53) years, respectively. Most participants were non-university graduates (78.1%) and lived in public housing (71.9%).

Table 1 summarises the outcomes. For primary outcomes, overall scores on the 10-question questionnaire increased pre-intervention to post-intervention from 5.0 (IQR 4–6.5) to 7.0 (IQR 6–8) (*P*<0.01). In the patient subgroup, scores increased from 4.0 (IQR 3–6) to 7.0 (IQR 7–9) (*P*<0.01). There was a non-significant increase in scores for the NOK group from 5.0 (IQR 5–7) to 6.0 (IQR 6–7) (*P*=0.16).

For assessment of anxiety based on STAI-S and STAI-T scores, there was a decrease from pre-

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Table 1. Knowledge and anxiety levels pre- and post-intervention.

	Median	IQR		*P* value
Overall				
Knowledge				
Objective (pre)	5.0	(4.0,	6.5)	<0.01
Objective (post)	7.0	(6.0,	8.0)	
Subjective (pre)	6.0	(4.0,	7.0)	<0.01
Subjective (Post)	8.0	(77.0,	8.5)	
Anxiety				
STAI-S scale (pre)	44.5	(35.5,	51.5)	<0.01
STAI-S scale (post)	37.0	(31.0,	47.5)	
STAI-T scale (pre)	39.5	(31.0,	47.5)	<0.01
STAI-T scale (post)	37.0	(31.0,	44.5)	
Subjective (pre)	7.0	(5.0,	8.0)	0.02
Subjective (post)	6.0	(4.0,	7.0)	
Patients				
Knowledge				
Objective (pre)	4.0	(3.0,	6.0)	<0.01
Objective (post)	7.0	(7.0,	9.0)	
Subjective (pre)	5.0	(4.0,	6.0)	<0.01
Subjective (post)	7.5	(6.0,	8.0)	
Anxiety				
STAI-S scale (pre)	47.5	(36.0,	53.0)	0.05
STAI-S scale (post)	42.0	(35.0,	53.0)	
STAI-T scale (pre)	40.5	(30.0,	48.0)	0.23
STAI-T scale (post)	36.5	(30.0,	49.0)	
Subjective (pre)	7.0	(5.0,	9.0)	0.12
Subjective (post)	6.0	(5.0,	8.0)	
NOKs				
Knowledge				
Objective (pre)	5.0	(5.0,	7.0)	0.16
Objective (post)	6.0	(6.0,	7.0)	
Subjective (pre)	6.0	(6.0,	8.0)	<0.01
Subjective (post)	8.0	(8.0,	10.0)	
Anxiety				
STAI-S scale (pre)	41.0	(35.0,	50.0)	<0.01
STAI-S scale (post)	33.5	(30.0,	41.0)	
STAI-T scale (pre)	39.5	(34.0,	45.0)	0.01
STAI-T scale (post)	37.0	(32.0,	39.0)	
Subjective (pre)	6.0	(5.0,	8.0)	0.09
Subjective (post)	5.5	(4.0,	6.0)	

IQR: interquartile range; NOK: next-of-kin; STAI-S: State Trait Anxiety Inventory-State; STAI-T: State Trait Anxiety Inventory-Trait

intervention to post-intervention from 44.5 (IQR 35.5–51.5) to 37.0 (IQR 31–47.5) (P<0.01) and 39.5 (IQR 31–47.5) to 37 (IQR 31–44.5) (P<0.01), respectively. There was a significant decrease in scores for NOKs for both STAI-S from 41.0 (IQR 35–50) to 33.5 (IQR 30–41) (P<0.01) and STAI-T from 39.5 (IQR 34–45) to 37.0 (IQR 32–39) (P<0.01); there was a decrease in scores for patients from 47.5 (IQR 36–53) to 42.0 (IQR 35–53) (P=0.05) in STAI-S, without significant difference in STAI-T scores (P>0.05).

For secondary outcomes, subjective perceptions for understanding the TAVI procedure rated on a scale of 10 increased overall from 6.0 (IQR 4–7) to 8 (IQR 7–8.5) (P<0.01). This was seen in both patients (5.0 [IQR4–6] to 7.5 [IQR6-8], P<0.01)and NOKs (6.0 [IQR 6–8] to 8.0 [IQR 8–10] P<0.01]. Median subjective anxiety levels rated on a scale of 10 decreased from 7.0 (IQR 5–8) to 6.0 (IQR 4–7) (P=0.02) overall. Separately, both patient and NOK median scores did not decrease significantly (P>0.05).

Regarding qualitative feedback about the video, all participants reported that they liked the use of videos in patient education. The top reasons are that it was simple to understand (90.1%), and that there were pictures and drawings (81.3%) and clear narration (65.6%).

Our study showed that there was significant increase in knowledge through this simple intervention. Similarly, a prior randomised controlled trial using an animated video with whiteboard sketching tools improved knowledge in patients undergoing coronary angiography and angioplasty.[5] Beyond cardiology, Moe-Byrne et al.

corroborated in a systematic analysis that video animations were useful patient information tools for improving knowledge.[6] Notably, the increase in knowledge scores in the patient subgroup, could be attributed to the increased age of this cohort, where the effectiveness of visual aids in delivering information compared with verbal counselling is accentuated.[7] Additionally, there is significant reduction in anxiety through our intervention. It has been reported that even if patients do agree to a procedure, inadequate understanding in patients with poor health literacy may worsen patient anxiety, increase litigation and confer worse outcomes.[8,9] The use of a video in reducing anxiety in a clinical setting has also been seen in other medical disciplines. For example, Raz et al. found that a video intervention significantly reduced participants sense of dejection through lung cancer screening and promoted psychological preparedness.[10] Our study adds to the body of evidence in demonstrating the utility of video tools in improving knowledge and reducing anxiety.[5]

There are several benefits to this video identified. First, the duration is short allowing good attention span. Second, the video utilises whiteboard sketching tools with layman language, and simple animations with subtitles that increase understandability. Lastly, our video is readily and publicly available.

Several limitations exist. This is a study from a single tertiary cardiac institution. In addition, due to limited resources for translation, only English-speaking participants were recruited. Thus, this may impact the generalisability of the results. The production of this video in other languages is planned.

In conclusion, this is one of the first studies demonstrating that an online patient education video using simple whiteboard sketching tools was effective in improving knowledge and reducing anxiety in patients/NOKs for TAVI. There may be consideration of incorporating this into clinical practice to improve patient care.

Supplementary Material S1 Figure
Supplementary Material S2 TAVI Questionnaire

Ethics statement

Written informed consent was obtained from the participants and ethical approval for the study was obtained from the SingHealth Centralised Institutional Review Board (Reference 2020/3149).

Declaration

The authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: *aortic stenosis, cardiology, patient education, TAVI, video*

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LETTER TO THE EDITOR

A review on adverse airway events during anaesthesia over 6 years in a tertiary referral hospital

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Dear Editor,

Comprehensive reviews of perioperative critical airway events (CAE) have been conducted through audits and closed claims analyses. However, there is currently limited published data specific to Singapore. Our study aims to analyse CAE at a tertiary hospital in Singapore, ascertain their frequency, identify risk factors, and compare findings to international studies.

We conducted a retrospective review of CAE from January 2014 to December 2019, approved by the SingHealth Centralised Institutional Review Board (2020/2008). We thoroughly reviewed all incident reports in the operating theatre, excluding any intensive care unit (ICU) airway emergency activations. We identified 144 patients, documenting 207 CAE out of 165,253 anaesthesia procedures, equating to an incidence rate of 12.5 CAE per 10,000 anaesthesia procedures. Among these patients, 84 had 1 CAE, 57 patients had 2 CAE, and 3 patients had 3 CAE. The analysis of 144 patients (denominator) revealed that 47.1% were 60 years and above, and the sex distribution was nearly equal. Among the patients, 48.8% were classified as American Society of Anesthesiologists (ASA) score 3 or above. Further, 79.7% of CAE occurred during elective surgeries and within office hours (76.4%). Head and neck surgeries accounted for 26.7% of these events. In addition, 80.1% of patients had adverse events during intubation, with 20.3% undergoing rapid sequence induction. Most CAE happened during anaesthesia induction (34.3%).

We classified complications into immediate and final outcomes, with the immediate outcomes further divided into major and minor categories. The most prevalent complications were hypoventilation or hypoxemia (30.0%), followed by failed extubation requiring re-intubation (15.0%) and aspiration (9.7%). Among the immediate outcomes were 115 minor airway complications and 19 cancelled procedures. Major complications included 52 unanticipated ICU admissions, 1 case requiring emergency surgical airway creation, and 5 deaths. Two deaths were related to airway management complications, while the other 3 were unrelated to airway management.

A chi-square test compared the general patient cohort with those who experienced CAE. Statistical analysis revealed significant associations between CAE and patients with an ASA status of 3 or higher ($P<0.001$), as well as in cases where anaesthesia was administered after office hours ($P<0.001$). The ASA Closed Claims Project,[1] the NAP4 audit[2] and research from Australia and New Zealand[3] also emphasise the association between higher ASA status, emergency surgeries and CAE.

Several significant findings emerged from our analysis. A considerable number of CAE occurred in head and neck surgeries, likely due to these procedures' specific challenges. Challenges include airway sharing, anatomical distortions, and contamination from surgical debris.[4] Additionally, most CAE occur during the induction phase of anaesthesia, which is a high-risk period for complications such as hypoxia, aspiration and oesophageal intubation.[5] However, the study also found significant CAEs during the maintenance and emergence phases, emphasising the need for vigilance throughout the anaesthesia process. Another notable finding was that a minority of CAE occurred in the post-anaesthesia care units, suggesting potential deficits in anaesthetic support or experience within those areas.[6]

The prevalent complications include hypoxemia and hypoventilation,[7] frequently stemming from challenges in airway management, laryngospasm, bronchospasm, or aspiration. Our study also found that 31 cases required re-intubation, highlighting the potential for airway-related complications post-extubation, which aligns with similar findings by Xie et al.[3,8] The identified causes of re-intubation were consistent with our findings, encompassing

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insufficient reversal of neuromuscular blockade, obstruction in the upper airway, pulmonary oedema and reduced levels of consciousness. Our analysis elicited that CAE were notably prevalent in patients with an ASA status of 3 or higher, possibly attributed to significant functional impairment and systemic illness, aligning with conclusions drawn by Mayhew et al.[9]

Our study also found that the odds of CAE are statistically higher in surgeries performed after 1700 hours compared to the general cohort of patients undergoing surgical procedures (Table 1). This may be attributed to factors such as inadequate manpower, lack of specialist consultant support, fatigue and disrupted circadian rhythms—all of which have been documented to increase anaesthetic adverse events.[10]

Table 1. Demographics (n=144) and statistical analysis of the demographics.

	No. of patients	Percentage (%)
Age, years		
<60	64	52.9
60 and above	57	47.1
Not available	23	
Sex		
Male	65	52.8
Female	58	47.1
Not available	21	
ASA score		
1	12	9.6
2	52	41.6
3	51	40.8
4	10	8.0
Not available	19	
Elective/emergency		
Elective	106	79.7
Emergency	27	20.3
Not available	11	
Time of incident		
0800 to 1700 (during office hours)	110	76.4
After 1700 (after office hours)	34	23.6
Location of surgery		
Head + neck	36	26.7
Thorax	13	9.6

Table 1. Demographics (n=144) and statistical analysis of the demographics. (Cont'd)

	No. of patients	Percentage (%)
Back	6	4.4
Upper limb	11	8.1
Upper abdomen	25	18.5
Lower abdomen	13	9.6
Genital/gynae	5	3.7
Urology	7	5.2
Lower limb	19	14.1
Not available	9	

Comparing the demographics of patients with critical airway events with the entire cohort of patients who underwent surgery

	Critical airway events	Total (without critical airway events)	*P* value
Sex			
Male	65	68,523	0.466
Female	58	69,738	
ASA score			
≤2	64	135,774	**<0.001**
≥3	61	29,354	
Nature of surgery			
Elective	106	115,080	0.275
Emergency	27	23,171	
Unspecified	11		
Time of incident			
0800 to 1700	110	125,200	**<0.001**
After 1700	34	14,905	

ASA score: American Society of Anesthesiologists score

Of the 5 deaths, only 2 were attributed to challenging anatomy. The first involved airway burns, where 2 intubation attempts failed, resulting in bradycardia, likely secondary to hypoxia. The proceduralist attempted front-of-neck access, which was unsuccessful despite multiple attempts and complicated by bleeding and aspiration, ultimately resulting in the patient's demise. While front-of-neck access was necessary, the insertion of a supraglottic airway device should have been considered after the failure of intubation, in line with the International Difficult Airway guidelines. The second death occurred in a post-coronary artery bypass graft patient, where desaturation after oesophageal intubation led to fatal hypoxia. The other 3 deaths were linked to concomitant cardiac pathologies such as myocardial ischaemia and ventricular fibrillation. These cases underscore the importance of considering contextual factors such as time pressure, remote location, haemodynamic status, and respiratory reserve, all contributing to a "physiologically difficult airway".

One of our study's key strengths is its large patient population and the structured, anonymised data collection through the Risk Management System, a standardised checklist that ensures reliable reporting. The research team thoroughly reviewed each incident report and reached a collective consensus on the interpreta-tion of the data. The study's retrospective nature is a key limitation, as the anonymised data prevented the collection of further details on CAE and limited the ability to establish temporal sequences or causality. Additionally, some data needed to be more consistently documented, and the administrative nature of the dataset means that some CAEs may not have been consistently registered, potentially leading to an underestimation of the actual incidence of the events.

In conclusion, the study underscores the significant impact of CAE that can occur perioperatively, particularly in head and neck surgeries, after 1700 hours, and in patients with a higher ASA score. These events can lead to severe adverse outcomes, including ICU admissions and fatalities. The research emphasises the significance of comprehensive preoperative evaluation for identifying high-risk patient groups, diligent monitoring during high-risk surgical procedures, adherence to international airway management guidelines, and mandatory participation in advanced airway training programmes. These measures are crucial for improving patient safety and decreasing the occurrence of CAEs. The study also emphasises the need for future research to include prospective studies with more detailed and consistent data collection.

Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (2020/2008).

Declaration

No funding was received for this study. The authors have no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in the manuscript.

Keywords: *anaesthesiology, mortality, pneumonia, pulmonary, surgery*

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