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Mechanisms and roles of hydroxychloroquine in pregnancy in rheumatic diseases

Research explores the latest advanced role, mechanism, treatment and safety of hydroxychloroquine (HCQ) in rheumatic diseases during pregnancy and application prospects of HCQ in preeclampsia. (See full article, p.113)

Illustration by Maria De-Castro

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Development and validation of the sarcopenia composite index: A comprehensive approach for assessing sarcopenia in the ageing population

Prevalence of complexity in primary care and its associated factors: A Singapore experience

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Adolescent self-harm and suicide attempts in the emergency department in Singapore

Say How Ong¹ MMed (Psy)

The youth mental health crisis has taken centre stage globally in recent years with increased reporting of young persons suffering from mental health problems and mental illnesses. Singapore is not spared. The COVID-19 pandemic has been largely blamed for the onset of the mental health crisis due to its disruptive effects on the young persons' lives. Circuit breaker or lockdown measures, movement restrictions and social isolation may have led to exacerbations of pre-existing mental health conditions and delays in seeking treatments, further fueling the mental health crisis. A systematic review by Jones et al. reported evidence on the potential negative impact of the pandemic on adolescent mental health.¹ The uncertainty of the future, spanning worries about the new pandemic to that of climate change, also weighed heavily on young minds. Additionally, excessive and unrestricted use of the internet and social media has been identified as having a strong association with poor mental health and suicide attempts among the young,² due to the mechanism of harm such as cybervictimisation, accessibility to harmful online content, and social media serving as an "echo chamber" that reinforces maladaptive behaviours such as self-harm and suicide. The interplay of these and other psychosocial factors may have led to elevated distress among children and adolescents.³

During the COVID-19 pandemic, there was a surge in adolescents seeking emergency assistance for depression, self-harm and suicide attempts.³ In Singapore, between the period of 2020 and 2021, an increase in requests in mental health services and hospitalisations for mental health reasons were reported,⁴ mirroring overseas reports of surges in emergency attendances for suicidal behaviours in young persons aged 12 and above.^{3,5}

In this issue of the *Annals*, Chong et al. aptly bring readers' attention to self-harm and suicidal behaviours in Singapore during the pandemic.⁶ The authors collected data from January to December 2021, and studied the sociodemographic profile and suicidal behaviours of 221 adolescents who

presented to a paediatric hospital emergency department (ED). There was a higher proportion of females (85.5%) than males (14.5%) who attempted suicide or engaged in self-harm behaviour. The mean age was the same for both sexes. Differences in methods chosen between sexes were noted, with a higher proportion of males compared to females with suicidal intent (46.% versus [vs] 33.3%) and males adopting more lethal methods like jumping from heights to end their lives. A significantly higher proportion of females presented with intentional paracetamol overdose compared to males (46.6% vs 28.1%). The most common method of suicide attempt was through intentional drug overdose with majority using paracetamol followed by psychotropic drugs (in patients on existing treatment for mental disorders). It is important to appreciate the difference in suicide risk between the 2 sexes. Despite both having common risk factors of suicidal behaviours, such as previous mental or substance abuse disorder and exposure to interpersonal violence, clinicians should be cognisant of female-specific mental health risk factors, such as having severe mood disorders, eating disorders and post-traumatic stress disorder, while males were more likely to have received diagnoses of disruptive behavioural disorders and conduct problems.⁷

The most common mental health issue noted in this current paper was stress-related and emotional coping difficulties (e.g. acute stress reaction, emotional dysregulation and maladaptive coping), followed by mood and anxiety difficulties (e.g. major depressive disorder and anxiety disorder). Slightly more than a quarter of the subjects had both emotional coping and mood problems. In many studies on suicidal behaviours,⁸ a history of past suicide or self-harm attempt confers a high risk for subsequent attempts. Hence besides asking about past suicide attempts, Carballo et al. suggested that attending physicians should look out for factors that appear to increase the risk of suicidality: psychological factors (depression, anxiety, previous suicide attempt,

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drug and alcohol use and other comorbid psychiatric disorders); stressful life events (family problems and peer conflicts); and personality traits (neuroticism and impulsivity).⁹ Impulsivity, lack of foreplanning and unfavourable decision-making are frequent characteristics observed in adolescents who engage in self-harm. Studies have suggested that non-suicidal self-injury is associated with neurocognitive impulsivity, especially in the presence of a history of abuse, depression or post-traumatic stress disorder.¹⁰ More frequent and recent self-harm behaviours were also reported to be occurring in negative emotional contexts, such as perceived or actual criticisms in close relationships.¹¹ Trait impulsivity and catastrophic thinking could therefore be a target for interventions like cognitive behavioural therapy and mindfulness practices.

Of interest is this paper's finding that in the 1 year prior to some of the adolescents' suicide or self-harm attempt, 19.5% of them had presented to a hospital ED or polyclinic in the healthcare cluster at least once for a medically unexplained symptom which could possibly be due to somatisation, and 15.4% had sought healthcare for common mild illnesses like upper respiratory tract infection or gastroenteritis. This means that there could be opportunities for healthcare professionals in a primary health setting to ask more about their adolescent patients' emotional and mental well-being while attending to their medical ailments.

In busy medical clinics or EDs, it can be difficult to perform a thorough psychosocial and mental health screen. Eliciting psychological and emotional symptoms can be even more daunting if the healthcare worker is inexperienced. Clinicians are not necessarily trained to be sensitive to the psychosocial circumstances of young persons and to how adverse psychosocial factors could predispose them to self-harm or attempt suicide. The Home, Education, Activities, Drugs, Sexuality, Suicidality, Safety (HEADSSS) assessment tool used in this present paper is an easy-to-perform face-to-face interview that could be used by a junior doctor, resident, allied health staff or nurse.¹² Based on the verbatim responses, the medical team would be in a better position to make a referral to a child psychiatrist, a psychologist or a medical social worker. For medical staff who do not know how to approach a teen with self-harm, the use of a structured interview in addition to the HEADSSS tool to elicit psychosocial factors and suicide intentions can come in handy. The Pediatric Symptom Checklist is another good and brief screening questionnaire used by pediatricians and other health professionals to improve the

recognition and treatment of psychosocial problems in children.¹³

The study's finding that home conflicts feature highly as a psychosocial risk factor, with many adolescents experiencing parent-child problems and parental conflict, indicates that inclusion of a family assessment by the medical social worker or referral to social services (e.g. family service centre or social service agency) may help to address the ongoing stressors that the adolescents experience at home, thereby reducing the risk of self-harm. Similarly, if school- and academic-related stress plays a significant role in contributing to self-harm behaviours, consultation liaison with the school's senior management and counsellor would be most appropriate.

Suicide research is still very much in its infancy in Singapore and needs to be encouraged and developed. The evidence to date highlights the complex nature of suicidal behaviours and how such behaviours are often a result of the interaction of various psychosocial factors together. Research can help us form an aetiological understanding on individual mechanisms, and aid in the development of suitable interventions and short-term prediction models by integrating research findings.¹⁴ With so much more still to be understood regarding the complexities of suicidal and self-harm behaviours, the findings of this study should spur the community, schools, clinicians and researchers towards cognisance of its predictive factors for early intervention and further research.

Ethics statement

Not applicable.

Declaration

The author declares he 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: *emergency medicine, mental health, paediatrics, psychiatry, psychology, suicide reporting*

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Complexity in primary care: Beyond multimorbidity in Healthier SG

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The global ageing population, particularly older adults with complex biopsychosocial needs, drives increased healthcare utilisation, burdening both the health system and wider society.^{1,2} Primary care physicians (PCPs) may be uniquely positioned to manage patients with complex health needs, given their role in providing continuous, comprehensive, and coordinated care as a first point-of-contact.³ Effectively managing complex patient needs poses a critical challenge for the primary care system, extending beyond financing to encompass the targeted allocation of resources, including time, human resources and ancillary services.

In this issue of the *Annals*, Quek et al. present a cross-sectional study assessing the prevalence of complex care needs in Singapore primary care and identify associated factors of care complexity across 6 polyclinics within 1 of the 3 healthcare clusters.⁴ The study found that 33.5% of 4327 unique patient encounters involved complex care needs, with common medical needs, including polypharmacy and poor control of chronic conditions, and non-medical needs including poor health literacy. The authors divided those with complex care needs into 2 groups: medically challenging and complex care. Factors independently associated with complexity included low socioeconomic status, mobility issues and higher healthcare utilisation, highlighting the need for effective methods to identify and manage complex care needs. The study also revealed that complex care encounters required significantly more resources. For example, physician consultation times increased from 12.7 minutes (routine care) to 17.8 minutes (complex care), while overall costs of care increased from SGD 705 to SGD 1254, highlighting the need for adequate resource allocation for managing complex care patients.

This study leveraged a robust methodology, utilising routinely collected, real-world medical records data from patients treated by a randomly selected and diverse group of experienced primary care physicians in active practice. The dataset was complete, with no missing data, thereby ensuring

the results are relevant and directly applicable to real-world primary care. Its exploratory nature and use of mixed-effects regression to account for potential clustering between individual physicians are commendable. However, the study falls short in addressing potential clustering effects at the clinic level and inter-rater reliability. In essence, determining complexity is a classification task, where patients are categorised into different levels according to predefined criteria. To improve robustness, future studies could employ strategies such as random audit, benchmarking or standardisation, using a small group of expert raters and removing assessor bias. AI-driven models, such as simple Large Language Models (LLMs), may also be useful in determining complexity, offering a potential solution to reduce respondent burden.⁵

This study adds to the increasing body of knowledge on patient complexity, which has been skewed towards the characterisation of multimorbidity using a range of approaches.⁶ A significant merit of this study is the shift from complexity as a characteristic of an individual to the consideration of complexity as a property of a particular interaction between a patient and a healthcare professional. Although not a new idea, it is a path that has been less explored in recent years. Future studies would benefit from considering multiple visits for the same patients, thereby providing stronger evidence both for the differentiation of this construct from patient complexity and for its validity. Additionally, stronger evidence may come from studies in which the different categories are operationalised explicitly and unambiguously.

The study's approach to identifying classification factors through a questionnaire and reporting significant differences across groups may raise concerns about independence, rather than circular reasoning, for factors not extracted from the survey. Specifically, some factors were obtained from medical records, which may not be directly influenced by the classification criteria. While the current model has limitations—including the close relationship between independent variables (e.g.

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number of issues managed, ambulation status, housing type, number of chronic conditions, resource utilisation) and measures (e.g. medical, functional, social, resource utilisation)—the complex interrelationships and overlapping influences between predictors and outcomes are not fully accounted for. Future studies should aim to explore more nuanced relationships between variables and incorporate additional data sources for triangulation; and by doing so, researchers can refine the classification criteria and develop more robust models to adequately capture complexities of patient needs.

As Singapore embarks on the nationwide Healthier Singapore (Healthier SG) initiative, a significant health reform launched in July 2023 that aims to provide integrated and longitudinal care via enrolment with PCPs, numerous concerns have arisen. First is the adequacy of compensation for PCPs both in the private as well as public sectors.⁷ While the Ministry of Health will provide reimbursement through per capita payments (based on numbers enrolled) and key performance indicators, there are concerns that this compensation may not accurately reflect the additional time and effort required to manage complex care for patients, particularly given Singapore's rapidly ageing population.⁸ The second is whether there is an adequate number of physicians to provide the envisioned primary care services. This study highlights the imperative for innovative care systems that redistribute responsibilities beyond physicians, leveraging more cost-effective and sustainable workforce models to meet the needs of an ageing population, thereby reducing reliance on expensive physician manpower. Without such transformative changes, the ambitious goals of Healthier SG will remain elusive.

The study's findings make a significant contribution to the existing literature on measuring complexity in primary care, highlighting the need for a more comprehensive and coordinated approach to managing complex patient needs. In the context of Healthier SG, which prioritises effective primary care, this study's emphasis on care complexity beyond multimorbidity is particularly pertinent. To develop targeted and sustainable solutions, re-examining funding and care coordination models is crucial. Consideration should be given to allocating a protected amount of capitation funding for primary care, similar to National Health Service England's dedicated allocation of 9.5%.⁹ Moreover, new care models must be developed to address the complex

interplay of social determinants of health, such as social isolation, education, employment and mental health, which influences health outcomes and worsen care complexity.^{10,11} By embracing a nuanced understanding of care complexity beyond a sole focus on multimorbidity, we can develop appropriate solutions to improve outcomes and yet reduce costs, and ultimately transforming our primary care into a more sustainable, equitable and patient-centred system.

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: care complexity, family medicine, Healthier SG, multimorbidity, primary care

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Adolescent self-harm and suicide attempts: An analysis of emergency department presentations in Singapore

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ABSTRACT

Introduction: The rising rate of adolescent suicide, and the burden of self-harm and mental health disorders, pose significant threats to Singapore's future health outcomes and human potential. This study sought to examine the risk profile and healthcare utilisation patterns of Singaporean adolescents who presented to the emergency department (ED) for suicidal or self-harm behaviour.

Method: A retrospective review of medical records for patients aged 10 to 19 years who visited Singapore's KK Women's and Children's Hospital ED for suicidal or self-harm attempts from January to December 2021 was conducted.

Results: A total of 221 patients were identified, with a predominance of female patients (85.5%) over males (14.5%). The mean age was 14.2 ± 1.4 years. Intentional drug overdose (52.0%) was the most commonly used method. Significantly more females presented for intentional paracetamol overdose (46.6% versus [vs] 28.1%, $P=0.049$), whereas jumping from a height was more common among males (18.8% vs 5.8%, $P=0.022$). The most frequently observed mental health challenges were stress-related and emotional coping difficulties (50.7%), followed by mood and anxiety symptoms (53.4%). A history of self-harm and suicidal behaviours were the most common psychosocial risk factors. Within the year prior to their ED presentation, 15.4% had accessed healthcare services for mild medical ailments, 19.5% for medically unexplained symptoms, and 17.2% for previous self-harm or suicide attempts.

Conclusion: Most cases involved psychosocial and emotional regulation difficulties, some of which displayed sex-specific patterns, rather than complex psychiatric disorders. The identified predictive factors can help inform Singapore's National Mental Health and Well-being Strategy, to guide targeted and transdiagnostic interventions in schools and community settings.

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Keywords: emergency medicine, mental health, paediatrics, psychiatry, psychology

CLINICAL IMPACT

What is New

- This study provides insights into the nature of adolescent suicide attempts and self-harm behaviour that confronts Singapore today.

Clinical Implications

- Although the cases presented during the COVID-19 restrictions, the identified psychosocial stressors, risk profiles and associations can guide strategies for early recognition and targeted intervention for this vulnerable age group in this post-pandemic era.
- Findings provide justification for mental healthcare strategies to harness the resources in schools, and youth social services to provide psychosocial support and interventions.

INTRODUCTION

Within 3 years from 2019 to 2021, adolescent suicide rates in Singapore almost doubled from 5.35 to 9.14 per 100,000 population.^{1,2} This is against a backdrop of a silently brewing adolescent behavioural and mental health crisis locally and globally, which started before the COVID-19 pandemic but has since been further exacerbated by the disruptions associated with it.^{3,4} According to the Burden of Disease in Singapore report in 2017, self-harm contributed to over 35% of years of life lost in adolescents.⁵ These statistics are gravely concerning because they signal a threat to population health and human potential.

Suicidal attempts and self-harm behaviour in adolescents are often contributed by a myriad of behavioural and mental health factors such as

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mood disorders and eating disorders, as well as psychosocial factors such as home conflict, and peer and romantic relationship problems.^{6,7} It is important to elucidate the unique risk factors in Singapore's adolescent population when they present for suicide or self-harm to the ED to identify strategies for early intervention.

This study aims to identify the demographics, psychosocial risk factors, psychiatric comorbidities and prior healthcare utilisation patterns of adolescents in Singapore who present to a paediatric ED for suicidal and self-harm attempts.

METHOD

The study was approved by the SingHealth Centralised Institutional Review Board (reference 2022-2291). A retrospective review of the electronic health records of adolescents who presented for suicidal or self-harm attempts to the ED of KK Women's and Children's Hospital from January to December 2021 was conducted.

Patients aged 10 to 19 years old were identified using a combination search of ED triage complaints and diagnosis codes for "drug overdose", "ingestion of toxic substance", "paracetamol overdose", "self-harm", "laceration", "fall from height" and "suicide attempt".

Data collected include patient demographics; ED clinical presentation; and inpatient evaluation and management including psychosocial and psychiatric evaluations, past medical history and healthcare utilisation of EDs and SingHealth polyclinics in the past 1 year prior to the episode of suicide or self-harm attempt. Descriptive statistics for the demographic and psychosocial risk profiles were based on the first presentation of patients in 2021 (n=221) as the denominator.

Frequencies and percentages were used to describe categorical data, while mean and standard deviation (SD) were used for continuous data. Secondary analysis was done to compare the demographic and psychosocial risk profiles between the 2 sexes as the approaches to interventions may differ by sex. Univariate analysis for continuous variables was assessed using t-test for parametric data, and chi-square or Fisher's Exact test for categorical and binary variables. STATA Standard Edition version 18.0 (Stata Corp, College Station, TX, US) was used for statistical analysis.

RESULTS

From January to December 2021, there was a total of 221 patients who presented to the ED. Among them, 27 had subsequent repeated attendances for suicide or self-harm in the same year.

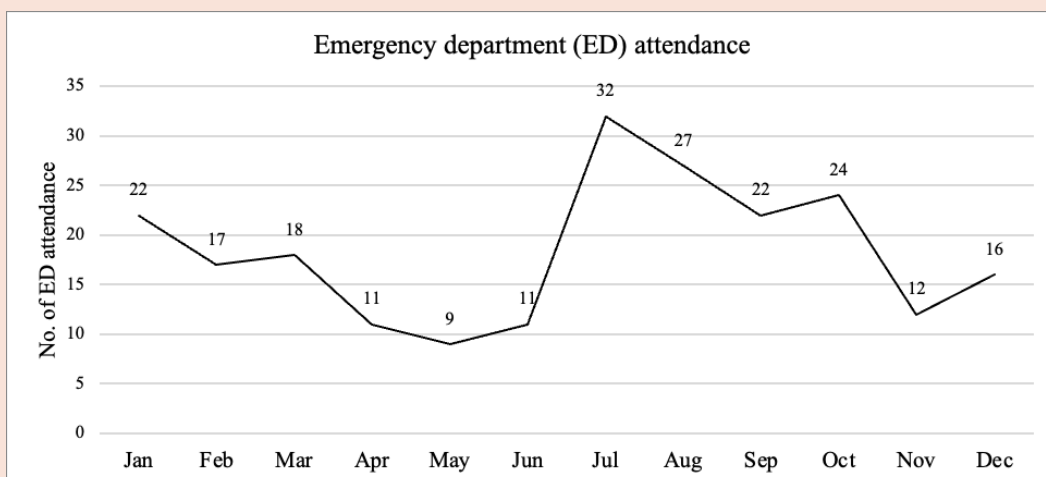
Demographics

Among the 221 patients, there were more females at 189 (85.5%) than males at 32 (14.5%). The mean age among females was 14.2 ± 1.4 (range 10.0–16.2) years and 13.9 ± 1.3 (range 11.0–17.0) years among males. There was no statistically significant difference in age between the sexes (95% CI -0.892 to 0.166; $P=0.178$). The racial distribution between males and females was not statistically significant (Table 1).

Seasonality

ED attendance was the highest in July, after the lowest troughs from April to June in 2021. The incidence remained high from July onwards before markedly decreasing in the last 2 months of November and December 2021 (Fig. 1).

Fig. 1. Emergency department attendances for self-harm and suicide attempts from January to December 2021.



Intent and method of suicide or self-harm attempt

More than one-third of cases had suicidal intent (35.3%), while the majority had ambivalent intent (52.0%). There was a higher proportion of males who had suicidal intent (46.9% versus [vs] 33.3%), but this difference did not reach statistical significance. The most common method of attempt was through intentional drug overdose (72.4%), with majority using paracetamol (44.1%), followed by psychotropic drugs (15.9%) (Table 1).

Less common methods employed included self-laceration, jumping from a height and others (e.g. suffocation). Of note, more common among females compared to males were self-laceration (15.3% vs 9.4%) and intentional drug overdose (74.1% vs 62.5%). In fact, females were more likely than males to present with intentional paracetamol overdose (46.6% vs 28.1%, $P=0.049$). In contrast, jumping from a height was more common among males (18.8% vs 5.8%, $P=0.022$).

Mental health issues

The most common mental health issues noted were stress-related and emotional coping difficulties (e.g. acute stress reaction, emotional dysregulation and maladaptive coping) (50.7%), and mood and anxiety difficulties (e.g. major depressive disorder and anxiety disorder) (53.4%) (Table 1). There were 27.1% of cases that had both emotional coping and mood problems, while 21.7% only had emotional coping difficulties with no other psychopathology. Neurodevelopmental and conduct disorders (e.g. attention deficit hyperactivity disorder, autistic spectrum disorder and oppositional defiant disorder) were more common in males (21.9% vs 6.3%, $P=0.01$), whereas eating disorders were higher in females (18.0% vs 3.10%, $P=0.033$). None of the cases had any substance abuse problems.

A total of 107 (48.4%) patients had already been receiving mental health care by either psychiatrists or psychologists, and 63 (28.5%) had been receiving psychosocial support from their school or community prior to their presentations.

Healthcare services utilisation 1 year prior to suicide or self-harm attempt

In the 1 year prior to their suicide or self-harm attempt, 43 (19.5%) had presented to a hospital ED or polyclinic in the SingHealth healthcare cluster at least once for a medically unexplained symptom that could possibly be due to somatisation. Thirty-four (15.4%) had sought healthcare for common mild illnesses like upper respiratory tract infection or gastroenteritis, and 38 (17.2%) had sought healthcare services for deliberate self-harm or suicide attempt. A previous history of deliberate

suicide or self-harm attempt was shown to be statistically significant, with more females having this risk factor (19.6% vs 3.1%, $P=0.023$) (Table 1).

Psychosocial stressors

Home, Education, Activities, Drugs, Sexuality, Suicidality, Safety (HEADSSS) is an internationally recognised approach in paediatric and primary care settings to conduct a bio-psychosocial assessment and facilitate rapport with an adolescent. Disclosures from psychosocial assessment using the HEADSSS framework are categorised in Table 2.

Family conflict, and anxieties related to academic performance are separately associated with approximately one-third of the cases. Sleep was a problem in 40.3% of the adolescents. There were significantly more males who had problems with excessive recreational screen time beyond the recommended 2 hours (37.5% vs 18.5%, $P=0.015$).⁸ Peer relationship problems like bullying caused distress in more than one-quarter of cases.

There were 17.6% of cases who experimented with vaping, cigarette smoking or alcohol. In addition, 4.1% of cases were sexually active and 16.7% of them had gender identity issues.

For 18.6% of the cohort, there had been a history of being abused. Significantly more females disclosed problems with non-suicidal self-injury (80.4% vs 37.5%, $P<0.001$) and previous suicide attempts (45.0% vs 18.8%, $P=0.005$).

DISCUSSION

Our study describes the 221 patients who presented to the ED for suicide/self-harm attempts in 2021. We have identified the population's demographic profiles, ED presentation details, mental and general health issues, healthcare utilisation patterns in the 1 year prior to presentation and psychosocial risk factors. The identified factors have both confirmed prior studies on adolescent risk behaviour and unveiled new risk profiles that could inform future strategies for early recognition and early intervention.⁹

The higher proportion of females than males in this population is consistent with previous studies, which report that females are more likely to attempt suicide or engage in self-harm behaviour.^{6,10} Possible attributable risk factors include higher prevalence of sexual abuse and depression.^{11,12} Comparing sexes, significantly higher proportion of females presented with intentional paracetamol overdose (46.6% vs 28.1%), while higher proportion of males attempted jumping from a height (18.8% vs 5.8%). In terms of accessibility, paracetamol is widely available without prescription. Similarly, high-rise buildings are ubiquitous in Singapore. The

Table 1. Risk profile of adolescents presenting to the emergency department for suicide or self-harm attempt; factors evaluated include demographics, intent and method of suicide or self-harm attempt, mental health issues and prior healthcare service utilisation.

		Total	Male	Female	P value
Race, no. (%)	No. of patients	221	32	189	NA
	Age (mean $\pm$ SD)	14.2 $\pm$ 1.4	13.9 $\pm$ 1.3	14.2 $\pm$ 1.4	NA
	Chinese	126 (57.0)	24 (75.0)	102 (54.0)	0.103
	Malay	48 (21.7)	3 (9.4)	45 (23.8)	
	Indian	26 (11.8)	4 (12.5)	22 (11.6)	
Intent, no. (%)	Others	21 (9.5)	1 (3.1)	20 (10.6)	
	Suicidal	78 (35.3)	15 (46.9)	63 (33.3)	0.189
	Ambivalent	115 (52.0)	12 (37.5)	103 (54.5)	
	Non-suicidal	28 (12.7)	5 (15.6)	23 (12.2)	
Method of suicide/ self-harm attempt, no. (%)	Intentional drug overdose	160 (72.4)	20 (62.5)	140 (74.1)	0.176
	Nature of medicine ingested	Paracetamol	9 (28.1)	88 (46.8)	0.049
		Psychotropic drugs	7 (21.9)	28 (14.9)	0.318
	Ingestion of toxic substance	7 (3.2)	2 (6.3)	5 (2.6)	0.268
	Jumping from height	17 (7.7)	6 (18.8)	11 (5.8)	0.022
	Self-laceration	32 (14.5)	3 (9.4)	29 (15.3)	0.586
	Others	5 (2.3)	1 (3.1)	4 (2.1)	NA
Mental health issues from psychiatric evaluation, no. (%)	Stress-related and emotional coping difficulties	112 (50.7)	17 (53.1)	95 (50.3)	0.765
	Mood and anxiety difficulties	118 (53.4)	14 (43.8)	104 (55.0)	0.237
	Psychosis or psychotic-like symptoms and disorders	8 (3.6)	3 (9.4)	5 (2.6)	0.093
	Neurodevelopmental and conduct disorders	19 (8.6)	7 (21.9)	12 (6.3)	0.01
	Personality difficulties and disorders	3 (1.4)	0 (0)	3 (1.6)	0.624
	Eating disorders	35 (15.8)	1 (3.1)	34 (18.0)	0.033
	Post-traumatic stress disorder	14 (6.3)	1 (3.1)	13 (6.9)	0.698
	Somatoform disorders	2 (0.9)	0 (0)	2 (1.1)	0.731
	Obsessive compulsive disorder	4 (1.8)	1 (3.1)	3 (1.6)	0.468
	Bipolar disorder	7 (3.2)	2 (6.3)	5 (2.6)	0.268
	Substance abuse	0 (0)	0 (0)	0 (0)	NA
Prior mental health support before ED presentation, no. (%)	Receiving help by psychiatrist/ psychologist	107 (48.4)	12 (37.5)	95 (50.3)	0.181
	Receiving psychosocial support from school counsellor/ community youth worker	63 (28.5)	7 (21.9)	56 (29.6)	0.369

Table 1. Risk profile of adolescents presenting to the emergency department for suicide or self-harm attempt; factors evaluated include demographics, intent and method of suicide or self-harm attempt, mental health issues and prior healthcare service utilisation. (Cont'd)

		Total	Male	Female	P value
Healthcare service utilisation 1 year prior to ED presentation, no. (%)	At least 1 visit for a mild medical ailment ^a	34 (15.4)	4 (12.5)	30 (15.9)	0.428
	At least 1 visit for medically unexplained symptoms	43 (19.5)	5 (15.6)	38 (20.1)	0.554
	At least 1 visit for deliberate self-harm/suicidal attempt	38 (17.2)	1 (3.1)	37 (19.6)	0.023

ED: emergency department; SD: standard deviation; NA: not available

^a Examples include upper respiratory tract infection and gastroenteritis.

P values in bold are statistically significant.

Table 2. Psychosocial factors identified in adolescents who presented for suicide or self-harm attempt. Domains for HEADSSS include home, education, activities and peer relationships, sexuality, suicidality, safety.

	Total (n=221)	Male (n=32)	Female (n=189)	P value
Home, no. (%)				
Parental separation/conflict	75 (33.9)	12 (37.5)	63 (33.3)	0.645
Family financial difficulties	5 (2.3)	1 (3.1)	4 (2.1)	0.546
Sibling relationship problems	12 (5.4)	2 (6.3)	10 (5.3)	0.687
Parent-child relationship problems	77 (35.0)	11 (34.4)	66 (35.1)	0.906
Family history of psychiatric issues/suicidal attempts	13 (5.9)	3 (9.4)	10 (5.3)	0.409
Education, no. (%)				
Academic stress	75 (33.9)	9 (28.1)	66 (34.9)	0.453
Absence from school more than 1x per month	63 (28.5)	9 (28.1)	54 (28.6)	0.959
Activities and peer relationships, no. (%)				
Sleep difficulties/deprivation	89 (40.3)	11 (34.4)	78 (41.3)	0.462
Excessive recreational screen time	47 (21.3)	12 (37.5)	35 (18.5)	0.015
Peer relationship conflict (including bullying and cyberbullying)	58 (26.2)	10 (31.3)	48 (25.4)	0.486
Romantic relationship problems	22 (10.0)	3 (9.4)	19 (10.1)	0.602
Drugs/substance use, no. (%)				
Exposed to the influence of substance abuse, cigarettes or alcohol	39 (17.6)	6 (18.8)	33 (17.5)	0.860
Sexuality, no. (%)				
Sexually active	9 (4.1)	3 (9.4)	6 (3.2)	0.126
Gender identity issues	37 (16.7)	5 (15.6)	32 (16.9)	0.855
Suicidality, no. (%)				
Disclosed about non-suicidal self-injury	164 (74.2)	12 (37.5)	152 (80.4)	<0.001
Disclosed about previous suicide attempts	91 (41.2)	6 (18.8)	85 (45.0)	0.005
Safety, no. (%)				
Past history of non-accidental injuries, neglect or sexual abuse	41 (18.6)	5 (15.6)	36 (19.1)	0.645

P values in bold are statistically significant.

difference in methods chosen between the sexes could be explained by our finding that there was a higher proportion of males with suicidal intent (46.9% vs 33.3%). Despite a lower attempt rate, the mortality rate of suicide is higher in males, suggesting a tendency to employ more lethal methods.⁹ Identification of sex-specific risk factors such as autistic spectrum disorder and excessive recreational screen time in males, and eating disorders and past history of self-harm or suicide attempts in females can inform risk management in screening strategies.^{9,13}

In a study published by Wong et al., adolescents were at risk of mental health symptoms, which were often associated to their immature psychological resilience.¹⁴ This explains the vulnerabilities in our study population. The increased vulnerability during this specific period of transition calls for targeted interventions to build psychological resilience in this age group.

In 2021, the months of July to October had the highest number of attendances, which coincided with the second school semester and year-end academic examinations. Meanwhile, the lowest was from April to June, which overlaps with the mid-semester break. This seasonality in relation to the academic examinations is consistent with findings by Matsubayashi et al.¹⁵ The sharp uptick from the June school holidays to the peak in July suggests the return of school could be a particularly stressful period for vulnerable adolescents. Future interventions could thus consider introducing school-based screening and mental health resilience programmes from July onwards, or at the start of all semesters and the period leading up to examinations.

In relation to COVID-19 in 2021, restrictions due to the Omicron and Delta variants of concern, which started in May, continued to impact the school calendar until October, when restrictions were eased.¹⁶⁻¹⁸ These restrictions included limitations in social gatherings, in-person school lessons and co-curricular activities. The higher ED attendance in the second semester could also possibly be attributed to the social isolation adolescents were subjected to during this period.¹⁹ Our study findings, together with other studies that investigate psychosocial support service utilisation associated with the COVID-19 pandemic, may inform strategies for adolescent mental health support should a similar crisis occur in the future.⁹

More than half of our study cohort has ambivalent intent. They were confused themselves on whether they truly wanted to end their own lives. This further highlights the immaturity in emotional regulation and impulsivity in adolescents.²⁰ Population health and community-based strategies that consist of social interventions, together with

process-based and transdiagnostic psychological interventions to strengthen emotional regulation capabilities, are therefore likely to be cost-effective and impactful.²¹⁻²³

The high proportions of patients who disclosed previous suicide attempts (41.2%) and non-suicidal self-injury (NSSI) (74.2%) concur with similar studies demonstrating that prior suicidal attempts and NSSI are known risk factors for subsequent suicide attempts. The postulation is that each attempt desensitises the individual to pain and fear, thus leading to more perilous and serious subsequent attempts.^{9,24} This underscores the importance obtaining honest disclosures about past attempts through psychosocial screening. In contrast, Klonsky et al. suggest that self-injury is anti-suicide because the intent is self-punishment to alleviate negative affect.²⁵

Home conflicts featured highly as another psychosocial risk factor, with many experiencing parent-child problems (35.0%) and parental conflict (33.9%). Research has shown that such adverse social determinants of health are significantly associated with self-harm.²⁶ Working with community partners, such as family service centres to address relationship difficulties within the family, is therefore crucial.²⁷

Similarly, other researchers have found that sleep problems, academic stress and increased recreational screen time have been linked with higher risk of depression and suicide.^{9,28,29} Those with a history of sexual or physical abuse are known to have higher rates of suicidal ideation and attempts.^{9,28,30} Peer conflict and school absenteeism are also associated with higher rates of suicidal ideation.^{9,28,30,31} As demonstrated in our study cohort, patients often present with multiple inter-related psychosocial problems. From the preventive perspective, opportunistic psychosocial screening covering these issues should be integral to holistic care of adolescents at healthcare touchpoints.

In terms of psychopathology, stress-related and emotional coping difficulties (50.7%), together with mood and anxiety difficulties (53.4%), make up the 2 most prevalent issues in this cohort. In this study, surprisingly, only 21.7% had the former without any other psychopathology. The role of emotional dysregulation in causing distress leading to self-harm and suicidal behaviour cannot be underestimated.²⁰ Investments in community-based transdiagnostic interventions to build psychological resilience will likely yield high returns in enhancing adolescent well-being and reducing suicidal behaviour.^{21-23,32} Process-based psychological interventions hold promise by targeting bio-psychosocial processes contributing to mental health symptoms.²² It is apt because evidence-based psychological change

processes may be applied and individualised for the young person at the at-risk and pre-diagnosis stages. Trained school counsellors and community mental health practitioners may be best placed to deliver psychological interventions to augment counselling.³³

Almost half of the patients had ongoing psychiatric or psychological support (48.4%), while over a quarter were receiving psychosocial support from the school or community (28.5%). This could indicate that the current system of support might be inadequate. Studies have suggested that patients treated within a collaborative care model have better health outcomes.³⁴ Thus, from a systems perspective, there is an urgency to address this gap to improve efficiency and coordination of care.

In the 1 year prior to presentation, 17.2% of patients had attended a non-mental healthcare institution in the SingHealth cluster for suicidal or self-harm behaviour, 19.5% for medically unexplained symptoms that might possibly be somatisation episodes, and 15.4% for common mild illnesses. Hence, these healthcare visits provide opportunities for psychosocial and suicide risk screening.^{9,35,36} Indeed, psychosomatic symptoms and frequent healthcare seeking behaviour for minor ailments may be red flags for mental health distress.³⁷ Therefore, EDs and primary care clinics have an important role to play in conducting efficient psychosocial and suicide risk screening of adolescents, particularly those who seek medical care for non-mental health issues.³⁸

We found that adolescents at risk of self-harm and suicidal behaviours typically do not have serious mental health disorders, but instead have psychosocial problems and emotional regulation difficulties. However, their mental health distress can rapidly escalate and manifest in risk-to-self behaviours. This yields fresh insights that may impact strategies for school-based screening and sex-specific mental health support. The findings also give guidance to the current Tiered Care Model in Singapore’s National Mental Health and Well-being Strategy (Fig. 2) whereby resources for transdiagnostic psychosocial support of young people are strategically invested in schools and the community.³⁹ Through this collaborative care model, doctors who encounter adolescents with psychosocial distress in non-mental healthcare settings like primary care clinics, EDs and paediatric specialist clinics may partner with school counsellors and youth social service agencies to provide psychosocial support through counselling, social work and transdiagnostic psychological interventions (Fig. 3). This model is aligned with the preventive and pre-emptive stance advocated by McGorry et al. in the Lancet Psychiatry Commission on youth mental health.³³ We hope that our findings will prove valuable to inform strategies for early recognition and targeted intervention for adolescents with mental health distress in Singapore and in other high-income countries with similar socio-cultural context in Asia and globally.

Fig. 2. Singapore’s Tiered Care Model for mental healthcare with examples applicable to adolescents.

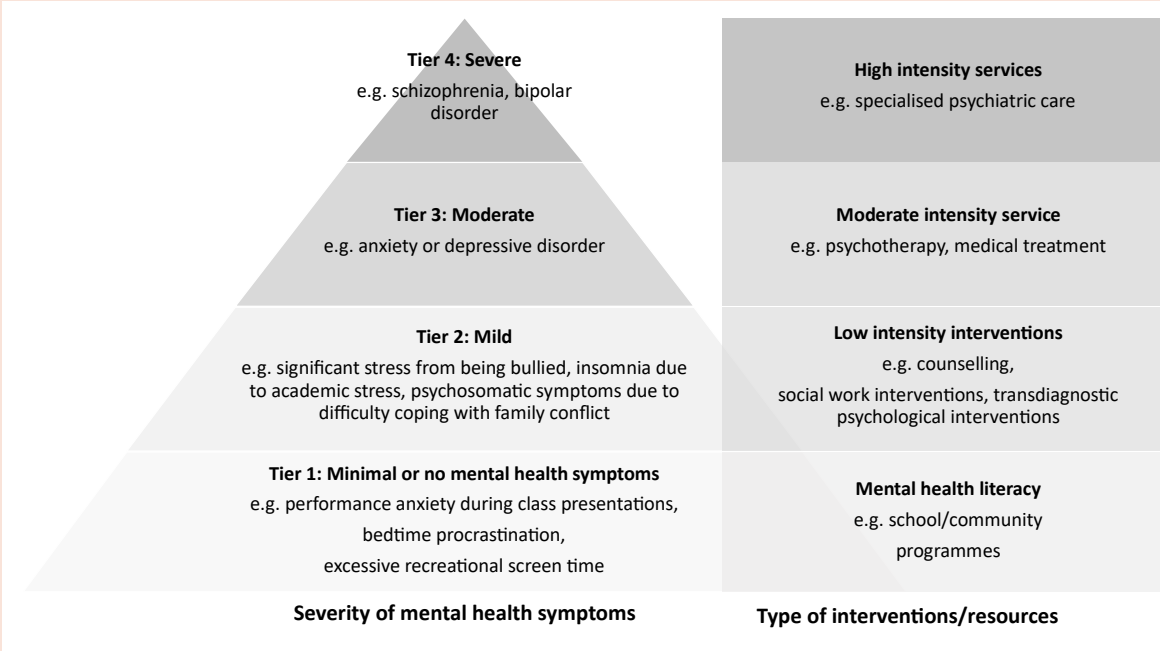
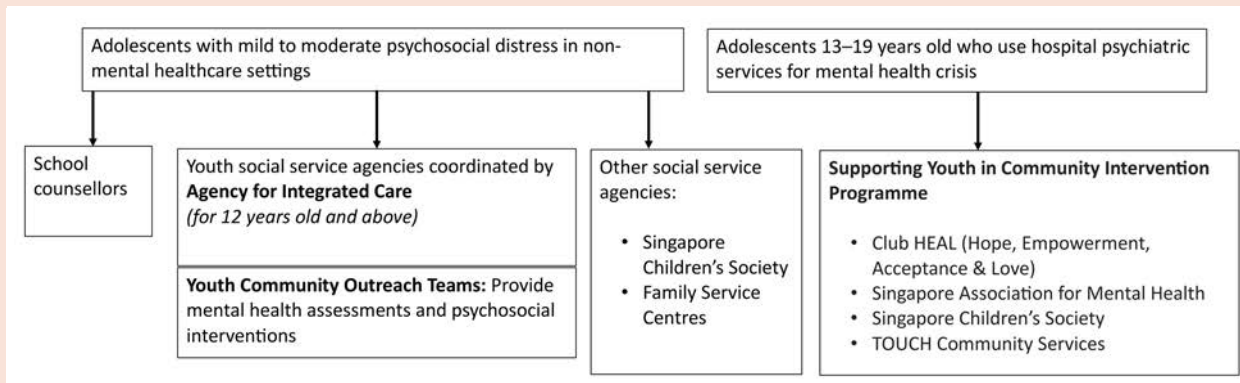


Fig. 3. Continuum of care of adolescents with psychosocial distress; right-siting from hospitals or clinics to the community for psychosocial support and interventions.



Note: Services by school counsellors in Ministry of Education schools, Youth Community Outreach Teams, Youth Integrated Teams and Family Service Centres are fully funded by the government.

Limitations

Given the cross-sectional and retrospective nature of the study, our data are subject to recall bias. The temporal direction of associations is unclear, and there is a certain degree of subjective judgement needed to interpret free-text entries in the medical records. Also, there is likely under-reporting of psychosocial problems because adolescents are known to be hesitant in disclosing stigmatised issues or disapproved behaviours to healthcare providers.⁴⁰ Moreover, there was no examination of the motivations that drive the actions, which may differ between adolescents with non-suicidal, ambivalent or suicidal intent.

The medical records access for this study was limited to SingHealth institutions. Past medical history and visits to other healthcare institutions were not available. Hence, this study's data likely underestimate the extent of patients' prior healthcare utilisation.

This study does not include patients who had been critically injured or died from completed suicide attempts. Such patients would have been directed to other public hospitals in closer proximity based on the country's public ambulance zoning system or might have been certified dead at the scene. Therefore, the patient profile and risk factors in this study do not represent adolescents with completed suicide. Our research findings may not translate to adolescent populations with socioeconomic and cultural backgrounds, or healthcare and social support infrastructure that are different from that of Singapore's.

CONCLUSION

This study has identified the demographic and psychosocial risk profiles of adolescents who

presented to the ED for suicide and self-harm attempts amid the COVID-19 pandemic in 2021. We hope this will further inform a coherent, holistic and bio-psychosocial approach to supporting vulnerable adolescents. Additionally, the findings give reassurance that Singapore's strategy to harness the resources in schools and social services to tackle the youth mental health crisis is in the right direction.³⁹

Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (reference 2022-2291).

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.

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Prevalence of complexity in primary care and its associated factors: A Singapore experience

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ABSTRACT

Introduction: As the population ages, patient complexity is increasing, intensifying the demand for well-resourced, coordinated care. A deeper understanding of the factors contributing to this complexity is essential for optimising resource allocation. This study evaluates the prevalence of complex care needs in Singapore's primary care settings and identifies the factors associated with these needs.

Methods: Using a qualitative study design, we developed a patient complexity questionnaire to assess how Singapore family physicians recognise patient complexity. Sixty-nine experienced primary care physicians applied this tool to assess patient encounters, categorising each as "routine care" (RC), "medically challenging" (MC), or "complex care" (CC). We compared the care needs across these categories and used mixed-effects multinomial logistic regression to determine the independent predictors of complexity.

Results: Of the 4327 encounters evaluated, 15.0% were classified as CC, 18.5% as MC, and 66.4% as RC. In both CC and MC encounters, the most common medical challenges were polypharmacy (66.2% in CC, 44.9% in MC); poorly controlled chronic conditions (41.3% in CC, 24.5% in MC); and treatment interactions (34.4% in CC, 26.0% in MC). Non-medical issues frequently identified included low health literacy (32.6% in CC, 20.8% in MC); limited motivation for healthy lifestyle behaviours (27.2% in CC, 16.6% in MC); and the need for coordinated care with hospital specialists (24.7% in CC, 17.1% in MC). The top 3 independent predictors of complexity included mobility limitations requiring assistance (odds ratio [OR] for requiring wheelchair/trolley: 7.14 for CC vs RC, 95% confidence interval [CI] 4.74–10.74); longer consultation times with physicians (OR for taking >20 minutes for doctor's consultation: 3.96 for CC vs RC, 95% CI 2.86–5.48); and low socioeconomic status (OR for living in 1- or 2-room HDB flats: 2.98 for CC vs RC, 95% CI 1.74–5.13).

Conclusion: High care needs, encompassing both CC and MC encounters, were prevalent in primary

care interactions. These findings highlight that relying solely on chronic disease count is insufficient to capture the full spectrum of patient complexity.

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Keywords: complex care, epidemiology, family medicine, multimorbidity, public health, social science

CLINICAL IMPACT

What is New

- The prevalence of complexity in primary care was 15.0%, with another 18.5% of encounters deemed medically challenging.
- Complex care encounters were associated with longer doctor, nursing and allied health consultation time with higher overall cost of care.

Clinical Implications

- Patients with complex needs require adequate consultation time and an integrated, well-coordinated, team-based care approach.
- Medical education should incorporate complexity training.
- Imperative for a better way to systematically and accurately capture complexity.

INTRODUCTION

As Singapore's population ages, the incidence of non-communicable chronic diseases will rise in tandem.¹ There exists a subset of individuals, oftentimes elderly with multiple chronic conditions, whose care needs are particularly complex.² While

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there is no universal definition of a person with complex needs, these individuals have been found to consume more healthcare resources, yet often have poorer health outcomes.³⁻⁵ There is a need to improve care for these individuals, but much is unknown about their prevalence, their needs and the ways to improve their outcomes, particularly in Asian settings.⁶

The prevalence of complexity in primary care varies greatly internationally, ranging from 3.98% to 42.5%.⁷⁻¹¹ These differences stem from discrepant healthcare contexts across localities, as well as varying definitions of complexity used.¹² For instance, a Spanish study¹¹ that found a complexity prevalence of 3.98% relied primarily on the clinical judgment of general practitioners among primary care patients over 14 years old with chronic conditions, while an English study¹⁰ that employed a model with a predetermined definition of complexity derived using a Delphi methodology arrived at a complexity prevalence of 41.6–42.5%.

In Singapore, polyclinics are large publicly-funded primary care clinics with a comprehensive suite of services including medical, nursing, allied health, laboratory and basic radiology. Many patients with chronic conditions choose polyclinics for their care due to low out-of-pocket costs and care accessibility.¹³ An estimated 6.9 million visits were made to polyclinics in 2023, and the top conditions were hyperlipidaemia, hypertension and diabetes mellitus.¹⁴ With the high volume of care for chronic conditions at polyclinics, we hypothesise that prevalence of complexity is also high.

In terms of definition of complexity, some studies and health systems equate complexity with multimorbidity.¹⁵ The Singapore Ministry of Health (MOH), for instance, uses number of chronic conditions to define complexity.¹⁶ However, most experts recognise that non-biomedical aspects like mental health, socioeconomic factors and patient preferences contribute to complexity and should be considered.¹² To better account for complexity, multiple frameworks¹⁷⁻¹⁹ and measurement tools have been developed. For example, a Canadian group developed a complexity framework with 5 health dimensions: demographics, mental health, social capital, medical/physical health, and health and social experiences, that considers a patient's sociopolitical and physical environmental contexts.¹⁹ While frameworks are helpful for understanding complexity conceptually, they are less useful for clinical implementation. Additionally, many frameworks highlight the influence of cultural, community and local healthcare system factors on patient

complexity.^{17,19} These factors differ from country to country, underscoring the importance of contextual evidence.²⁰ The paucity of Asian studies on this topic is a significant barrier to understanding and addressing these complex care (CC) needs in the local setting.^{12,20,21}

Some studies have developed various tools to quantify complexity, such as the Cumulative Illness Rating Scale (CIRS), INTERMED and Patient Centered Assessment Method (PCAM).²²⁻²⁴ However, these tools come with their own limitations, such as lack of contextual adaptation to the local setting, omission of key factors, and insufficient granularity.

Recognising the limitations of existing tools and acknowledging primary care physicians' knowledge of complexity—given their unique positions as first-line providers and coordinators of care for many individuals with complex needs,^{7,11} we undertook a foundational approach. We decided to first gain a deeper understanding of the nature of complexity in Singapore's primary care, rather than prematurely applying a measurement tool with limited scope. To this end, we previously undertook a qualitative study to understand how family physicians in Singapore recognise complexity.²⁵ Through this study involving physicians practising in both private and public primary care settings, we found 2 distinct groups of patients that required more clinical effort and resources (i.e. high care needs): patients with CC needs and those with medically challenging (MC) issues. In CC, 1 or more difficult medical issues were encountered, with concomitant issues in 1 or more of the following domains: psychological, socioeconomic and behavioural; and these factors adversely impacted medical care and outcomes. In contrast, with MC, issues were mainly limited to the medical domain. Patients not fitting the above characteristics were considered routine care (RC). The qualitative study findings suggested that while CC and MC patients could both be considered "complex", CC patients had higher level care needs than MC patients. We were interested to identify the complexity-related factors that may differ between MC and CC.

This study aimed to further characterise complexity by assessing the prevalence of CC needs and identifying factors associated with high care needs (i.e. CC and MC) in a real-world primary care population. Understanding the magnitude (i.e. prevalence) of complexity and its associated factors is a critical first step in guiding future research and informing efforts to effectively manage complexity in primary care.

METHOD

Study design, population and recruitment

Experienced primary care physicians (PCPs) with postgraduate Family Medicine (FM) qualifications—Graduate Diploma in FM (GDFM), Master of Medicine in FM (MMed[FM]) or Fellowship of the College of Family Physicians Singapore (FCFP[S])—from National Healthcare Group Polyclinics (NHGP) were invited to participate in this cross-sectional study, where PCPs code patients that they had seen. We included physicians with FM training and experience, to mitigate the perception of complexity that may stem from underdeveloped professional competencies.¹²

NHGP has 6 polyclinics in central and northwest Singapore, providing subsidised primary care to an estimated population of 1.5 million residents, ranging from acute care services to chronic disease management and women and child health services.²⁶ Each polyclinic is a publicly-funded “one-stop” facility that houses physicians, nurses and allied healthcare professionals, with laboratory and radiological capabilities.²⁷

To determine the prevalence of patient encounters with high care needs in a representative population from NHGP, weighted random sampling was carried out from 24 August 2022 to 30 November 2022. Physicians were recruited from all 6 polyclinics according to the proportion of patients in NHGP seen at each clinic. PCPs were randomly selected using a random number generator and invited via email. Informed consent was obtained.

Patient complexity questionnaire

Based on the findings of a local qualitative study²⁵ and triangulating with other studies,^{3,7,10,12,17–20,28–30} a questionnaire on CC needs in Singapore primary care was formulated with inputs from an expert panel of experienced PCPs over a few meetings. The questionnaire was pre-tested (n=8) and pilot-tested (n=13), with revisions done iteratively before study commencement.

Participating PCPs assigned a complexity rating for each patient encounter, based on 3 categories: RC, MC and CC. CC needs were also identified and were categorised according to the following domains: (1) medical (7 issues); (2) functional (3 issues); (3) mental health (9 issues); (4) social (4 issues); (5) behavioural (6 issues); as well as (6) resource utilisation (7 issues) (see Supplementary Material Annex A). An encounter was considered CC if there was 1 or more medical domain issues that interacted with a concomitant issue in another non-medical domain (2–6) impacting medical care and outcomes. MC encounters were mainly medical

domain issues with little interacting issues in other domains that affected medical care or outcomes. RC encounters were routine encounters that were not considered CC or MC.

PCP participants attended training sessions—each lasting an hour and held virtually over a video-conferencing platform—on questionnaire-filling to standardise the categorisation of CC, MC and RC, using case studies to illustrate each category of patient encounters.

Sample size

The estimated sample size was 3450 according to the following formula³¹: $n = [Z^2 P(1-P)] / d^2$, where Z is the statistic for level of confidence of 1.96, P is the expected prevalence of 42.5% (based on prior studies^{7–10}), d is precision of 2%,³² and after multiplying a variance inflation factor (VIF) of 1.47 to take into account the possible clustering of data within PCPs,³³ where $VIF = 1 + ICC(\text{cluster size} - 1)$, using a conservative intraclass correlation (ICC) of 0.01³⁴ and an estimated cluster size of 48 patients seen per PCP. Assuming each PCP would see 42–54 patients over 4 half-day sessions, 64–82 PCPs were required.

Data collection

Participating PCPs retrospectively assessed the complexity and care needs of patients they saw over 4 half-day sessions, referring to electronic case notes. To reduce recall bias, PCPs completed each questionnaire no later than 1 day after the clinic session. Questionnaires were hosted on REDCap.³⁵ To ensure the confidentiality of PCPs and their patients, participants entered a uniquely-assigned physician code and each patient's masked identity number into the questionnaires, without any other identifiers. Each PCP participant received reimbursement of SGD60 (USD44) in grocery vouchers for each half-day clinic session of case notes review and questionnaire filling.

We obtained patient characteristics based on routinely-collected data in the NHGP database, including clinical and resource utilisation data in the preceding year. Time of consultation was extracted electronically based on time spent between the successful “call” of the patient's queue number and the transfer of the patient's queue number to the next provider. The medical conditions included were selected based on clinical judgment, local practice guidelines (Chronic Disease Management Programme¹⁶) and evidence on multimorbidity,^{36,37} and extracted based on coding in electronic medical records (EMR). A member of the data analytics department who was not part of the study team extracted the data and clarified any missing

fields on questionnaire with individual participants to ensure data completeness. Only de-identified data were sent to the study team for analysis.

Data analysis

We analysed the prevalence of complex patient encounters and CC needs. We compared EMR-derived sociodemographic, disease status and resource utilisation characteristics between the 3 groups of patients (RC, MC and CC), applying Kruskal-Wallis test for comparison of continuous variables, and Pearson's chi-squared test or Fisher's Exact test for categorical variables. Similarly, we compared the frequency of questionnaire complex factors between RC, MC and CC using Pearson's chi-squared test or Fisher's Exact test. We developed a mixed-effects multinomial logistic regression model to identify independent predictors of complexity (that were derived from EMR data), comparing RC with MC and CC, while accounting for potential clustering effects at the PCP level, fitted using the Mclogit R package version 0.9.6 (Elff, 2022). We also compared physician-identified complexity with the MOH definition of complexity,¹⁶ which is based on the number of chronic conditions present: simple being 1 chronic condition, moderate being 2 or 3 chronic conditions and complex being 4 or more chronic conditions.

For patients with 2 or more visits recorded, we only considered the first visit to eliminate multiple levels of clustering. We did not detect significant collinearity using VIF. All analyses were performed using R version 4.4.1 (R Core Team, 2021). The National Healthcare Group Domain Specific Review Board approved our study (2022/00226).

RESULTS

Sociodemographic characteristics

Seventy-two PCPs consented to participate (80.2% response rate). Eventually, 69 PCPs (95.8% completion rate) from 6 polyclinics assessed the complexity of 4327 unique patients, after excluding 24 second-visit encounters (see Supplementary Material Annex B). The mean age of patients was 61.2 years (standard deviation [SD] 17.4) with approximately equal proportion of genders. Among them, 73.7% were Chinese, 11.8% Malay, 8.8% Indian and 5.7% others. Socioeconomic status was represented by housing type: 3.6% lived in 1- or 2-room Housing & Development Board (HDB) government-subsidised flats,³⁹ 49.2% lived in 3- or 4-room HDB flats, and the remaining 47.2% in 5-room HDB, private housing and others (Table 1).

Prevalence of patient complexity

In terms of prevalence, 15.0% of patient encounters were CC, 18.5% deemed MC and 66.4% RC (Table 1).

Demographic, medical and resource factors

Demographic and encounter-related factors

Table 1 describes the demographic- and encounter-related factors between CC, MC and RC. Patients with CC encounters were more likely to be older (67.5 years for CC, 65.3 years for MC and 58.7 years for RC, $P<0.001$), residing in 1- or 2-room HDB flats (7.8% in CC, 2.2% in MC, 3.0% in RC, $P<0.001$), and require assistance for ambulation (27.7% in CC, 12.6% in MC and 4.4% in MC, $P<0.001$). Patients with CC encounters had statistically significantly more issues managed (4.06 for CC, 3.51 for MC, 2.19 for RC, $P<0.001$) and more medications dispensed at the encounter (5.32 for CC, 4.45 for MC, 2.87 for RC, $P<0.001$).

Medical conditions

The top 5 medical conditions experienced by patients with high care needs were: hyperlipidaemia (81.4% in CC, 80.3% in MC), hypertension (75.9% in CC, 70.7% in MC), diabetes (60.7% in CC, 51.8% in MC), chronic kidney disease (23.2% in CC, 17.4% in MC) and ischaemic heart disease (19.8% in CC, 17.0% in MC) (Table 2).

Resource utilisation data

Patients with CC encounters utilised significantly more resources across all types of resources studied, including number of medications, cost of care, number and duration of visits to doctors, nurses, medical social workers, psychologists and financial counsellors (Table 2). Doctors spent a mean duration of 17.8 (SD 13.5) minutes attending to CC patients per consultation, compared to 14.9 (SD 9.8) minutes for MC patients, and 12.7 (SD 11.8) minutes for RC patients.

Prevalence of complex care needs

CC needs in CC and MC encounters were categorised as medical, functional, mental health, social, behavioural and related to resource utilisation, and are described in Table 3.

Medical care needs

The most common medical domain issues among CC and MC patients were polypharmacy (66.2% in CC, 44.9% in MC), poor control of chronic conditions (41.3% in CC, 24.5% in MC) and treatment interactions (34.4% in CC, 26.0% in MC).

Table 1. Sociodemographic and encounter-related information of patients.

	Total	Routine care (RC)	Medically challenging (MC)	Complex care (CC)	P value
Prevalence, no. (%)	4327 (100.0%)	2875 (66.4%)	801 (18.5%)	651 (15.0%)	NA
Age, mean (SD)	61.2 (17.4)	58.7 (17.7)	65.3 (16.0)	67.5 (14.9)	<0.001
Gender, no. (%)					0.081
Female	2243 (51.8%)	1511 (52.6%)	421 (52.6%)	311 (47.8%)	
Male	2084 (48.2%)	1364 (47.4%)	380 (47.4%)	340 (52.2%)	
Ethnicity, no. (%)					0.079
Chinese	3191 (73.7%)	2132 (74.2%)	592 (73.9%)	467 (71.7%)	
Malay	509 (11.8%)	316 (11.0%)	101 (12.6%)	92 (14.1%)	
Indian	380 (8.8%)	256 (8.9%)	74 (9.2%)	50 (7.7%)	
Others	247 (5.7%)	171 (5.9%)	34 (4.2%)	42 (6.5%)	
Housing type, no. (%)					<0.001
1- and 2-room HDB	155 (3.6%)	86 (3.0%)	18 (2.2%)	51 (7.8%)	
3- and 4-room HDB	2128 (49.2%)	1389 (48.3%)	393 (49.1%)	346 (53.1%)	
5-room HDB ¹ , private housing and others	2044 (47.2%)	1400 (48.7%)	390 (48.7%)	254 (39.0%)	
Ambulation status, no. (%)					<0.001
Ambulant	3917 (90.5%)	2746 (95.5%)	700 (87.4%)	471 (72.4%)	
Ambulant with aid	147 (3.4%)	53 (1.8%)	37 (4.6%)	57 (8.8%)	
Wheelchair / Trolley / Others	263 (6.1%)	75 (2.6%)	64 (8.0%)	123 (18.9%)	
No. of issues managed, mean (SD)	2.72 (1.72)	2.19 (1.35)	3.51 (1.83)	4.06 (1.94)	<0.001
No. of medications dispensed, mean (SD)	3.53 (3.46)	2.87 (2.81)	4.45 (3.91)	5.32 (4.48)	<0.001

P values in bold are statistically significant. Kruskal-Wallis test applied for comparison of continuous variables; Pearson's chi-squared test or Fisher's Exact test applied for categorical variables. HDB: Housing & Development Board flat; NA: not applicable; SD: standard deviation

Non-medical care needs

The most common non-medical domain issues faced by CC and MC patients were largely from the behavioural and resource utilisation domains. They were poor health literacy (32.6% in CC, 20.8% in MC); poor motivation for healthy lifestyle behaviours (27.2% in CC, 16.6% in MC); required coordination of care with hospitalists (24.7% in CC, 17.1% in MC); refused or non-adherent to medications (22.4% in CC, 10.4% in MC); and required multidisciplinary team intervention (19.2% in CC, 9.7% in MC).

Independent indicators of complexity and care needs

Based on our mixed-effects multinomial logistic regression model (Table 4), factors that indepen-

dently predicted for high care needs (both CC and MC) included: requiring aid for ambulation and/or requiring wheelchair/trolley (odds ratio [OR] 2.63 for MC versus [vs] RC, 95% confidence interval [CI] 1.77–3.91; OR 7.14 for CC vs RC, 95% CI 4.74–10.74); a greater number of issues managed during the encounter (OR 1.64 for MC vs RC, 95% CI 1.52–1.77; OR 2.16 for CC vs RC, 95% CI 1.96–2.38); longer duration of doctor consultation (OR for taking >20 minutes for doctor's consultation was 2.03 for MC vs RC, 95% CI 1.56–2.66; OR for taking >20minutes for doctor's consultation was 3.96 for CC vs RC, 95% CI 2.86–5.48); and higher cost of care over the past 1 year. Factors that independently predicted for CC (but not MC) included living in 1- or 2-room HDB flats (OR 2.98 for CC vs RC, 95% CI 1.74–

Table 2. Disease status and resource utilisation data of patients.

	Total	Routine care (RC)	Medically challenging (MC)	Complex care (CC)	P value
Prevalence, no. (%)	4327 (100.0)	2875 (66.4)	801 (18.5)	651 (15.0)	NA
Medical diagnosis, no. (%)					
Hypertension	2608 (60.3)	1548 (53.8)	566 (70.7)	494 (75.9)	<0.001
Hyperlipidaemia	3001 (69.4)	1828 (63.6)	643 (80.3)	530 (81.4)	<0.001
Type 2 diabetes	1695 (39.2)	885 (30.8)	415 (51.8)	395 (60.7)	<0.001
Stroke/TIA	361 (8.3)	151 (5.3)	95 (11.9)	115 (17.7)	<0.001
Ischaemic heart disease	516 (11.9)	251 (8.7)	136 (17.0)	129 (19.8)	<0.001
Congestive cardiac failure	55 (1.3)	13 (0.5)	13 (1.6)	29 (4.5)	<0.001
Atrial fibrillation	166 (3.8)	55 (1.9)	60 (7.5)	51 (7.8)	<0.001
Peripheral vascular disease	30 (0.7)	9 (0.3)	8 (1.0)	13 (2.0)	<0.001
Chronic kidney disease	471 (10.9)	181 (6.3)	139 (17.4)	151 (23.2)	<0.001
Asthma and/or COPD	263 (6.1)	154 (5.4)	60 (7.5)	49 (7.5)	0.022
Chronic liver disease	406 (9.4)	238 (8.3)	92 (11.5)	76 (11.7)	0.003
Dementia and/or cognitive impairment	82 (1.9)	24 (0.8)	22 (2.7)	36 (5.5)	<0.001
Rheumatoid arthritis	22 (0.5)	12 (0.4)	8 (1.0)	2 (0.3)	0.129
Peptic ulcer disease/gastritis/GERD	410 (9.5)	277 (9.6)	74 (9.2)	59 (9.1)	0.875
Malignant neoplasm	148 (3.4)	74 (2.6)	38 (4.8)	36 (5.5)	<0.001
Osteoporosis	235 (5.4)	122 (4.2)	60 (7.5)	53 (8.1)	<0.001
Disorder of thyroid	343 (7.9)	217 (7.5)	71 (8.9)	55 (8.4)	0.412
Depression	111 (2.6)	48 (1.7)	25 (3.1)	38 (5.8)	<0.001
Anxiety disorder	84 (1.9)	33 (1.1)	19 (2.4)	32 (4.9)	<0.001
Hyperplasia of prostate	211 (4.9)	107 (3.7)	52 (6.5)	52 (8.0)	<0.001

Table 2. Disease status and resource utilisation data of patients. (Cont'd)

	Total	Routine care (RC)	Medically challenging (MC)	Complex care (CC)	P value
No. of chronic conditions, mean (SD)	3.0 (2.1)	2.5 (1.9)	3.7 (2.0)	4.1 (2.0)	<0.001
MOH definition, no. (%)					<0.001
No chronic condition (0 condition)	689 (15.9)	591 (20.6)	61 (7.6)	37 (5.7)	
Simple (1 condition)	444 (10.3)	363 (12.6)	48 (6.0)	33 (5.1)	
Moderate (2-3 conditions)	1428 (33.0)	1011 (35.2)	243 (30.3)	174 (26.7)	
Complex (≥4 conditions)	1766 (40.8)	909 (31.7)	449 (56.1)	407 (62.5)	
Resource utilisation in last 1 year, mean (SD)					
Unique medications dispensed	7.80 (5.71)	6.80 (5.27)	9.13 (5.72)	10.56 (6.32)	<0.001
Doctor visits	3.36 (2.54)	2.99 (2.36)	3.90 (2.61)	4.30 (2.88)	<0.001
Nurse visits	0.33 (0.66)	0.30 (0.59)	0.40 (0.78)	0.41 (0.76)	<0.001
MSW visits	0.01 (0.15)	0.01 (0.09)	0.01 (0.12)	0.05 (0.30)	<0.001
Psychologist visits	0.02 (0.24)	0.01 (0.18)	0.02 (0.22)	0.04 (0.42)	0.036
Financial counsellor visits	0.06 (0.31)	0.04 (0.25)	0.06 (0.30)	0.15 (0.51)	<0.001
Consult time per doctor visit (min)	13.9 (11.9)	12.7 (11.8)	14.9 (9.8)	17.8 (13.5)	<0.001
Total doctor consult time (min)	62.2 (68.6)	54.3 (65.1)	68.0 (60.6)	89.6 (83.3)	<0.001
Total nursing consult time (min)	32.3 (67.0)	25.6 (41.9)	38.1 (53.1)	55.1 (133.6)	<0.001
Total allied health consult time (min)	9.0 (33.5)	7.3 (30.5)	9.3 (31.4)	16.2 (45.6)	<0.001
Total cost of care (SGD)	851.8 (684.6)	705.2 (561.8)	1050.8 (705.3)	1254.4 (897.2)	<0.001

P values in bold are statistically significant. Kruskal-Wallis test applied for comparison of continuous variables; Pearson's chi-squared test or Fisher's Exact test applied for categorical variables.

COPD: chronic obstructive pulmonary disease; GERD: gastroesophageal reflux disease; HDB: Housing & Development Board flat; min: minutes; MOH: Ministry of Health, Singapore; MSW: medical social worker; NA: not applicable; SD: standard deviation; SGD: Singapore dollar; TIA: transient ischaemic attack

5.13); a greater number of medications dispensed during the encounter (OR 1.05 for CC vs RC, 95% CI 1.01–1.09); longer total nursing time; and total allied health time. The number of chronic conditions did not independently predict for complexity or high care needs.

DISCUSSION

Our study categorised complexity in 4327 primary care encounters. The prevalence of complexity in our polyclinic sample was 15.0%, with another 18.5% deemed medically challenging. Different demographics, biopsychosocial characteristics and resource utilisation patterns were associated with each group. The independent indicators of complexity included lower socioeconomic status (by housing type)³⁸; requiring assistance for mobility; a greater number of issues managed and medications dispensed during the encounter;

longer duration of doctor; nursing and allied health consultation time; and higher cost of care over the past year.

Sociodemographic data of the sample population were reasonably representative of the general population in Singapore. In terms of ethnicity, 73.7% of study sample vs 74.1% of the general population were Chinese; 11.8% of study sample vs 13.6% of the general population were Malay; 8.8% of study sample vs 9.0% of the general population were Indian; and 5.7% of the study sample vs 3.3% of the general population were “others” in 2022.³⁹ For housing status, 3.6% of the study sample vs 6.7% of the general population lived in 1- or 2-room HDB flats; 49.2% of the study sample vs 48.6% of the general population lived in 3- or 4-room HDB flats; and 47.2% of the study sample vs 44.4% of the general population lived in 5-room HDB flats or private housing in 2022.³⁹

Table 3. Frequency of questionnaire complexity factors.

	Total	Routine care (RC)	Medically challenging (MC)	Complex care (CC)	P value
	(%)	(%)	(%)	(%)	
Prevalence	100.0	66.4	18.5	15.0	
Medical issues					
Polypharmacy	28.5	15.4	44.9	66.2	<0.001
Treatment for 1 condition affects another	13.5	5.2	26	34.4	<0.001
Poor disease control at risk of complications/deterioration	13.2	3.7	24.5	41.3	<0.001
Declined specialist referral or follow-up	3.8	0.7	7.5	13.4	<0.001
Diagnostic uncertainty/ambiguous diagnosis	6	1.8	16.9	11.1	<0.001
Somatisation disorders	0.7	0.2	0.9	2.9	<0.001
Chronic pain	2.4	1.7	2.2	5.8	<0.001
Functional issues					
Recent worsening of function	3.7	1.3	6.5	11.2	<0.001
Poor function that affects work	1.8	0.8	2.6	4.9	<0.001
Poor function requiring caregiver/bADL assistance	2.2	0.6	3	8.4	<0.001
Mental health issues					
Major depressive disorder	1	0.4	1.1	3.7	<0.001
Anxiety disorders	1.9	0.6	2.9	6.5	<0.001
Obsessive compulsive disorders	0.1	0	0.2	0.2	0.038
Schizophrenia	0.6	0.5	0.4	1.8	<0.001
Bipolar disorder	0	0	0	0	1
Personality disorder	0.1	0	0.1	0.2	0.262
Addictions/substance abuse	0.3	0.2	0.5	0.8	<0.043
Bereavement	0.3	0.1	0.2	1.1	<0.001

Legend	
Prevalence:	
	<5.0%
	5.0-9.9%
	10.0-14.9%
	15.0-19.9%
	20-24.9%
	25.0-29.9%
	30-34.9%
	35.0-39.9%
	40.0-44.9%
	45.0-49.9%
	50.0-54.9%
	55.0-59.9%
	60.0-64.9%

Table 3. Frequency of questionnaire complexity factors. (Cont'd)

	Total	Routine care (RC)	Medically challenging (MC)	Complex care (CC)	P value
Intellectual disability	0.2	0.1	0.2	0.5	0.038
Dementia	1.4	0.3	2.5	4.5	<0.001
Other psychiatric disorders	0.8	0.1	1.4	3.2	<0.001
Social issues					
Family or relationship difficulties	1.4	0.3	2	5.7	<0.001
Caregiver issues or stress	2.1	0.4	1.9	10	<0.001
Financial issues	2.1	0.6	2.6	8.4	<0.001
Social isolation	1.4	0.3	1.6	6	<0.001
Behavioural issues					
Poor health literacy	11.6	4.3	20.8	32.6	<0.001
Poor motivation for healthy lifestyle behaviours	10.4	4.9	16.6	27.2	<0.001
Refused or not adherent to medications	7.5	3.4	10.4	22.4	<0.001
Difficulty with healthcare system navigation	2.9	0.9	5.1	9.2	<0.001
Lack of trust in medical providers	1.8	0.5	2.7	6.6	5.2
Misaligned/unusual health beliefs	3.9	1.4	6.4	11.8	<0.001
Resource utilisation issues					
Frequent polyclinic attendances	2.9	1.3	4.4	8.4	<0.001
Requires multidisciplinary team intervention	5.5	1.2	9.7	19.2	<0.001
Frequent ED attendances or hospitalisations	0.6	0.1	0.5	3.4	<0.001
Recent admission to hospital	3.6	1.2	4.4	12.9	<0.001
Coordination with hospital specialist(s)	9.8	4.5	17.1	24.7	<0.001
Coordination with community partner(s)/agencies	1.3	0.4	1.1	5.2	<0.001

P values in bold are statistically significant. Pearson's chi-squared test/Fisher's Exact test applied for categorical variables. bADL: basic activities of daily living; ED: emergency department

Legend	
Prevalence:	
	<5.0%
	5.0-9.9%
	10.0-14.9%
	15.0-19.9%
	20-24.9%
	25.0-29.9%
	30-34.9%
	35.0-39.9%
	40.0-44.9%
	45.0-49.9%
	50.0-54.9%
	55.0-59.9%
	60.0-64.9%

Table 4. Multinomial logistic regression for predictors of complexity.

	Routine care (RC)			Medically challenging (MC)			Complex care (CC)		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Demographics									
Age	Ref	1.00	0.99-1.01	0.78	0.99-1.01	0.24			
Housing type									
• 5-room HDB & others	Ref			Ref					
• 3 & 4-room HDB	Ref	0.94	0.78-1.12	0.49	0.97-1.53	0.10			
• 1 & 2-room HDB	Ref	0.65	0.37-1.16	0.14	1.74-5.13	<0.001			
Encounter-related									
Ambulation status									
• Ambulant	Ref			Ref					
• Ambulant with aid	Ref	1.94	1.17-3.20	0.01	2.18-6.48	<0.001			
• Wheelchair/trolley/others	Ref	2.63	1.77-3.91	<0.001	4.74-10.74	<0.001			
No. of issues managed	Ref	1.64	1.52-1.77	<0.001	1.96-2.38	<0.001			
No. of chronic conditions	Ref	1.06	0.99-1.13	0.11	0.92-1.09	0.98			
No. of medications dispensed	Ref	1.03	0.99-1.06	0.10	1.01-1.09	0.01			
Database resource utilisation									
Mean doctor visit time									
• ≤10min	Ref			Ref					
• 10 to ≤15min	Ref	1.61	1.29-2.02	<0.001	1.57-2.84	<0.001			
• 15 to ≤20min	Ref	2.08	1.59-2.72	<0.001	2.12-4.24	<0.001			
• >20min	Ref	2.03	1.56-2.66	<0.001	2.86-5.48	<0.001			
Nursing time in last 1 year (min)	Ref	1.00	1.00-1.00	0.07	1.00-1.01	0.002			
Allied health time in last 1 year (min)	Ref	1.00	1.00-1.00	0.83	1.00-1.01	0.03			
Cost of care over last 1 year (SGD)	Ref	1.00	1.00-1.00	0.007	1.00-1.00	<0.001			

P values in bold are statistically significant.
CI: confidence interval; HDB: Housing & Development Board flat; min: minutes; OR: odds ratio; Ref: reference; SD: standard deviation; SGD: Singapore dollar

Unsurprisingly, the sample population had more chronic conditions than that of the general population—with 69.4% of the study sample vs 31.9% of the general population with hyperlipidaemia; 60.3% of the study sample vs 37.0% of the general population having hypertension; and 39.2% of the study sample vs 8.5% of the general population diagnosed with diabetes.⁴⁰

The combined prevalence of high care needs (CC and MC) of 33.6% in our study more closely mirrored the midpoint of prevalence of complexity reported in other western studies, which ranged from 3.98% to 42.5%.^{5,10-12} The differences likely stemmed from different definitions used for complexity. Our study is the first to differentiate complex care from medically challenging encounters. We did so because our qualitative study with PCPs had previously differentiated CC from MC, identifying that persons with CC required a multidisciplinary approach with longer time for consultation.²⁵ The requirement for increased consultation time and resource utilisation was elucidated in our study, with CC encounters requiring a mean duration of 17.8 minutes for their doctor's consultation, compared to 14.9 minutes for MC patients and 12.7 minutes for RC patients. It is uncertain if the consultation time in our study truly reflected the ideal time required, as the time pressures of a busy polyclinic could have constrained the time that doctors could dedicate to CC and MC encounters. Additionally, longer nursing and allied health consultation times were independent predictors for complexity, highlighting the importance of a multidisciplinary approach in managing complexity.

Asian studies on complexity were limited. They had largely focused on inpatients,⁴¹⁻⁴³ specific conditions (e.g. alcohol misuse),⁴⁴ validation of specific complexity tools⁴⁵ or equated multimorbidity with complexity.^{21,46} Among Asian studies that studied complexity in primary care contexts, 2 were qualitative studies regarding primary care physicians' perceptions of complexity.^{25,47} There was only 1 study⁴⁸ that showed a medium positive relationship between patient complexity (identified via PCAM) and healthcare costs. Our study adds to the literature describing how the use of an intuitive questionnaire could identify individuals with complex needs—who were more likely to have incurred higher cost and consumed more resources. This questionnaire could be easily administered in a form suited to any resource setting—integrated seamlessly with electronic medical records systems, or filled manually via pen and paper. On top of higher resource utilisation, our study further identified other independent indicators of complexity, including lower socioeconomic status, requiring

assistance for mobility and a greater number of issues managed during the encounter, providing an opportunity for the pre-emptive identification of these individuals for earlier intervention and prior to resource consumption.

Our study found that while 62.5% of CC and 56.1% of MC patients had 4 or more conditions, using multimorbidity alone to identify complexity would miss a large proportion of patients who required additional care. Rather than the number of chronic conditions, we discovered that complexity was better predicted by the number of issues addressed during the encounter,²⁵ many of which were non-medical in nature. This echoed other studies showing that chronic disease count did not equate to complexity or medical difficulty.^{3,7,29,49} Even among RC patients, two-thirds had 2 or more chronic conditions. It appeared that many PCPs considered the management of multimorbidity as routine, reflecting the high prevalence of multimorbidity.^{50,51} Policymakers in Singapore tend to identify complexity through multimorbidity, which could lead to inaccurate projections of resource requirements. Our findings suggest that funding models for primary care can be adjusted to account for complexity rather than focusing solely on multimorbidity. Such adjustments would better reflect resource utilisation, including appropriately capturing doctor time required for effective management and funding for multidisciplinary teams. This is particularly relevant in the era of population health and national enrolment with primary care providers under the nationwide Healthier SG initiative.⁵² Our study further identified common complex care needs in CC and MC encounters, yet these needs are often not coded in routine clinical care. More efficient and precise methods of identifying CC and MC encounters using electronic medical records are required to support accurate resource projections and provider reimbursements.

We found that living in 1- or 2-room HDB flats independently predicted for physician-defined complexity, agreeing with previous studies showing similar associations with lower socioeconomic status.^{7,19,29} Requirement of assistance for mobility was an independent indicator of physician-defined complexity, perhaps because these individuals require functional support in the form of caregivers or community resources such as day care/rehabilitation centres. The mobility aids could have also served as visual cues for PCPs to explore the impact of their patients' functional status on their medical care.

The most common non-medical domain issues in CC encounters included poor health literacy, low motivation for healthy behaviours, the need

for coordination with hospitalists, medication non-adherence and requiring multidisciplinary intervention. Given the high prevalence of complexity in primary care, family medicine education, particularly at the postgraduate level, must emphasise skill development for managing CC needs. Findings from our study can inform the identification of specific knowledge, skills, attitudes and partnerships essential for complexity management in the local context, thereby guiding curriculum design with the explicit aim of building learners' confidence in caring for individuals with complex needs.⁵³ This curriculum should involve broad-based transdisciplinary training, such as enhancing communication skills to tackle health literacy issues, practising motivational interviewing, and adopting team-based care approaches.

Our study corroborated the findings of numerous studies, affirming that complexity is a multidomain concept.^{12,18–20} The complexity questionnaire data clearly demonstrated that the issues faced by patients with high care needs are highly heterogeneous, highlighting the necessity of an individualised, rather than one-size-fits-all, approach. This underscores the importance of a holistic, multidisciplinary team-based care approach,²⁶ as well as the necessity of allocating sufficient resources to primary care practices. Such team-based care may need to extend beyond traditional team members, such as nurses, medical social workers and psychologists, to include community partners and social service agencies. For instance, scheduled physical or virtual multidisciplinary case discussions could be organised for patients with particularly complex psychosocial needs, allowing for a more holistic and coordinated approach to care. These resources and collaborations are essential for delivering the comprehensive and customised care required to effectively manage individuals with high care needs.

Strengths and limitations

To our knowledge, this is the first local study investigating the prevalence and associated factors of complexity in primary care. It builds on previous work and provides rich data on an important but previously unidentified group of patients in Singapore. We ensured the robustness of the estimate of prevalence via sample size calculation and undertook measures to standardise the definition of complexity through compulsory briefing sessions for participants. The study was adequately powered and the study sample was fairly representative of the general population sociodemographically. PCPs were randomly selected to mitigate potential biases—at the level

of individual physician in recognising complexity, and systemic biases arising from variations in the patient profiles seen by different doctors. We also performed mixed-effects multinomial logistic regression to further account for PCP-level clustering due to variability in the training and experience of individual PCPs.

There are several limitations. First, this is a cross-sectional study and causation cannot be determined. We were unable to investigate patients' progression and longer-term outcomes. Second, this study involved only PCPs from a public healthcare organisation in Singapore, precluding the generalisability of our findings to other primary care contexts like private general practices in Singapore or primary care practices in other countries. Different settings might have different resources, styles of practice, patient profiles, cultural norms and healthcare infrastructure that would affect the perception of complexity. Third, the identification of issues was limited to what the PCP was aware of or had time to ask about. Fourth, we were unable to obtain the perspectives of patients or other healthcare providers. Fifth, we acknowledge that some of the independent variables used in our multinomial logistic regression model (e.g. ambulation status, housing type, number of chronic conditions) may be closely related to the definition of our outcome measures (i.e. MC/CC, which were based on medical, functional, social and resource utilisation domains being affected). This overlap introduces complexity in fully disentangling the relationships between predictors and outcomes using the current regression framework.

Future research

To better model the complex interplay between predictors and the definition of complexity (MC/CC), a follow-up study that employs advanced analytical techniques, such as Structural Equation Modelling (SEM) can be undertaken. In addition to validating this questionnaire and replicating this study in other family medicine settings, other potential areas of future research could also include cohort studies that examine the relationship between complexity factors and clinical or resource utilisation outcomes prospectively. This questionnaire could also be utilised in interventional studies to identify patients with complex needs and demonstrate effectiveness of clinical programmes.

CONCLUSION

The prevalence of complexity in Singapore primary care was 15.0%, and an additional 18.5% was medically challenging. Our study identified key

areas for improving care for patients with complex care needs: adequate consultation time, multidisciplinary teamwork, complexity training in medical education, and refined methods for identifying complexity.

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Ethics statement

This study was approved by the National Healthcare Group Domain Specific Review Board (2022/00226).

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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Development and validation of the sarcopenia composite index: A comprehensive approach for assessing sarcopenia in the ageing population

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ABSTRACT

Introduction: The diagnosis of sarcopenia relies on key indicators such as handgrip strength, walking speed and muscle mass. Developing a composite index that integrates these measures could enhance clinical evaluation in older adults. This study aimed to standardise and combine these metrics to establish a z score for the sarcopenia composite index (ZoSCI) tailored for the ageing population. Additionally, we explore the risk factors associated with ZoSCI to provide insights into early prevention and intervention strategies.

Method: This retrospective study analysed data between January 2017 and December 2021 from an elderly health programme in Taiwan, applying the Asian Working Group for Sarcopenia criteria to assess sarcopenia. ZoSCI was developed by standardising handgrip strength, walking speed and muscle mass into z scores and integrating them into a composite index. Receiver operating characteristic (ROC) curve analysis was used to determine optimal cut-off values, and multiple regression analysis identified factors influencing ZoSCI.

Results: Among the 5047 participants, the prevalence of sarcopenia was 3.7%, lower than the reported global prevalence of 3.9–15.4%. ROC curve analysis established optimal cut-off points for distinguishing sarcopenia in ZoSCI: -1.85 (sensitivity 0.91, specificity 0.88) for males and -1.97 (sensitivity 0.93, specificity 0.88) for females. Factors associated with lower ZoSCI included advanced age, lower education levels, reduced exercise frequency, lower body mass index and creatinine levels.

Conclusion: This study introduces ZoSCI, a new composite quantitative indicator for identifying sarcopenia in older adults. The findings highlight specific risk factors that can inform early intervention. Future studies should validate ZoSCI globally, with international collaborations to ensure broader applicability.

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Keywords: composite index, early diagnosis, elderly, risk factors, sarcopenia

CLINICAL IMPACT

What is New

- Z score for the sarcopenia composite index (ZoSCI), a novel composite index for diagnosing sarcopenia, is introduced.
- This study integrates grip strength, walking speed and muscle mass into a standardised single score.

Clinical Implications

- A more accurate clinical evaluation of sarcopenia in older adults is enhanced.
- This study highlights key risk factors, including advanced age, lower educational attainment, reduced exercise frequency, lower body mass index and decreased creatinine levels.
- This study also facilitates early prevention and the development of targeted intervention strategies for sarcopenia.

INTRODUCTION

Sarcopenia, characterised by a reduction in muscle mass and a progressive decline in muscle function, presents a significant and growing challenge to the health and well-being of older adults worldwide.¹

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Studies indicate that the prevalence of sarcopenia among community-dwelling older adults aged 60 years and above ranges from 3.9% to 15.4%, depending on the diagnostic criteria used, such as those from the European Working Group on Sarcopenia in Older People (EWGSOP) and the Asian Working Group for Sarcopenia (AWGS), as well as demographic variations.^{2,3} As global populations age, sarcopenia is increasingly recognised as a critical health concern linked to adverse outcomes, including hospitalisation, reduced quality of life, disability, falls and increased mortality.⁴ Thus, identifying high-risk groups and influencing factors, along with implementing early interventions, is crucial for reducing the risk of sarcopenia.^{5,6}

Since the 1980s, geriatricians worldwide have worked to establish diagnostic criteria and definitions for sarcopenia, continuously refining measurement methods, diagnostic protocols and threshold values to account for racial and sex differences.⁵⁻⁸ The EWGSOP initially developed diagnostic tools and cut-off points for sarcopenia classification.⁷ In 2018, EWGSOP2 updated these guidelines, incorporating the Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls (SARC-F) questionnaire to identify probable cases of sarcopenia. This revision redefined low muscle strength as indicative of probable sarcopenia (low grip strength), sarcopenia as low muscle quantity or quality combined with low muscle strength, and severe sarcopenia with the addition of low physical performance.⁵ Recognising regional physiological differences, the AWGS developed a criteria specifically tailored for Asian populations.⁸ In 2019, AWGS updated its classification to include probable sarcopenia (low grip strength or walking speed), sarcopenia and severe sarcopenia, using similar indicators adjusted for Asian contexts.⁶ Both EWGSOP and AWGS emphasise the assessment of grip strength, walking speed and muscle mass as core indicators, highlighting the importance of evaluating both muscle mass and function to comprehensively capture sarcopenia progression.

The screening process for sarcopenia typically begins with tests of grip strength and walking speed, with muscle mass evaluated if these initial measurements reveal declines. Diagnostic cut-offs for these indicators are then applied to determine whether values are within normal ranges or indicate deficiencies. Since both muscle function and muscle mass are crucial indicators for diagnosing sarcopenia, it is important to assess elderly individuals who may have normal muscle function but reduced muscle mass or low muscle function but preserved muscle mass. However, using

diagnostic cut-offs represents a categorical approach, which may not fully capture the continuum of sarcopenia severity across diverse populations. To address this issue, this study transformed measurements of grip strength, walking speed and muscle mass among elderly individuals into standardised scores. These scores were then combined to generate a z score of the sarcopenia composite index (ZoSCI). By quantifying sarcopenia indicators along a continuum, ZoSCI can capture subtle variations in sarcopenia risks, making it particularly useful for identifying at-risk populations globally. We also investigated the relationship between influencing factors and ZoSCI to identify sarcopenia risks and at-risk populations at an early stage.

METHOD

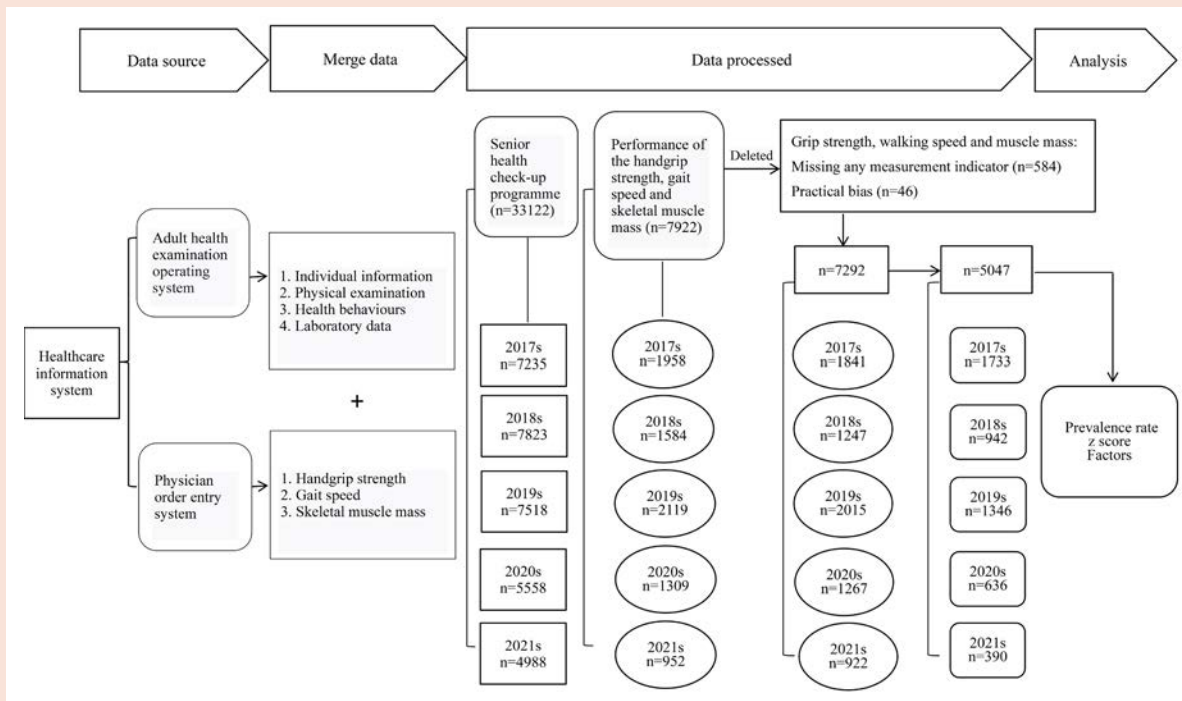
Participants and study design

This retrospective study collected data from individuals aged 65 years and older who participated in the elderly health service programme between January 2017 and December 2021. Data were obtained from the medical centre's system database in Taiwan and included basic demographic information, health-related behaviours, laboratory test results, grip strength, 6-meter walking speed, muscle mass and other relevant data.

Initially, 33,122 cases were included over the 5-year period. Participants with missing data on any of the 3 key measures (i.e. grip strength, walking speed or muscle mass) were excluded, resulting in a final sample size of 5047 cases for final analysis (Fig. 1). All procedures in the present study were approved by the institutional review board of the authors' hospital and conducted in accordance with the Declaration of Helsinki.

We specifically selected the AWGS criteria for diagnosing sarcopenia in this study, as these standards are tailored to Asian populations, accounting for regional differences in body composition, lifestyle and genetics.⁶ By using the AWGS criteria, we aimed to enhance the relevance and accuracy of our findings, ensuring alignment with the characteristics of the elderly population in Taiwan under investigation. Sarcopenia was evaluated using 3 key assessment criteria—(1) muscle strength: assessed via handgrip strength using a spring-loaded electronic grip strength meter (Smedley hand dynamometer FEI 12-0286, Fabrication Enterprises Inc, NY, US). The maximum value of 3 measurements was recorded, with cut-offpoints of <18 kg for women and <28 kg for men. (2) Physical performance: evaluated using the 6-meter walking speed test. A gait speed of <1 m/s indicated low physical fitness.

Fig. 1. Data processing flow chart.



(3) Muscle mass: measured using bioelectrical impedance analysis (Tanita BC-418, Tokyo, Japan). Skeletal muscle mass of the limbs divided by the square of height (ASM/ht^2), with cut-off points were $<5.7 \text{ kg}/\text{m}^2$ for women and $<7.0 \text{ kg}/\text{m}^2$ for men.⁶

Data collection and definitions

Collected data included demographic information (e.g. sex, age, education level) and health-related behaviours (e.g. smoking, drinking, exercise frequency). Body mass index (BMI) was calculated by dividing body weight by the square of height and was categorised as underweight ($<18.5 \text{ kg}/\text{m}^2$), healthy ($18.5\text{--}24 \text{ kg}/\text{m}^2$), overweight ($24\text{--}27 \text{ kg}/\text{m}^2$) and obese ($>27 \text{ kg}/\text{m}^2$).⁹ Laboratory test values included the following: (1) creatinine, with reference range of $0.6\text{--}1.2 \text{ mg}/\text{dL}$ for women and $0.7\text{--}1.3 \text{ mg}/\text{dL}$ for men; (2) estimated glomerular filtration rate (eGFR), categorised into 5 levels from normal renal function to end-stage renal disease;¹⁰ (3) fasting blood glucose ranging $70\text{--}99 \text{ mg}/\text{dL}$; (4) total cholesterol $<200 \text{ mg}/\text{dL}$; (5) triglycerides $<150 \text{ mg}/\text{dL}$; (6) low-density lipoprotein cholesterol (LDL-C) $<130 \text{ mg}/\text{dL}$; and (7) high-density lipoprotein cholesterol (HDL-C) of $>50 \text{ mg}/\text{dL}$ for women and $>40 \text{ mg}/\text{dL}$ for men.¹¹

Statistical analyses

The age- and sex-specific cut-offs for sarcopenia were developed to account for physiological

variations related to ageing and sex differences in muscle mass and function. This tailored approach ensures that the diagnostic criteria are sensitive to the distinct physical characteristics of each subgroup, thereby enhancing the accuracy of sarcopenia detection. To address age-related muscle decline and sex differences, measurement scores for grip strength, walking speed and muscle mass were standardised in 5-year age intervals. These intervals allowed us to adjust for physiological changes associated with ageing that influence sarcopenia risk.

To calculate these cut-offs, raw data were first converted to z scores using the formula: $Z = (x - \mu) / \sigma$, and these standardised scores were then summed to generate the ZoSCI. Optimal ZoSCI cut-off points for each age interval were determined through ROC curve analysis in conjunction with the AWGS criteria, with Youden's index applied to maximise the combined sensitivity and specificity for sarcopenia diagnosis. Youden's index, calculated as (sensitivity + specificity - 1), ranges from 0 to 1, with higher values indicating stronger discriminative ability. For each sex, Youden's index was computed across all points on the ROC curve, and the point with the maximum index value was selected as the optimal cut-off for ZoSCI. This method provided a precise, sex-specific threshold tailored to optimise diagnostic accuracy within the study population. Additionally,

Table 1. Characteristics of study participants.

Variables	Female				Male			
	65–69 years old	70–74 years old	75–79 years old	≥80 years old	65–69 years old	70–74 years old	75–79 years old	≥80 years old
	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)
Education								
Elementary school	464 (47)	243 (60)	164 (69.5)	103 (81.1)	277 (33.6)	163 (36.1)	130 (52.4)	86 (50)
Junior high school	143 (14.5)	59 (14.6)	31 (13.1)	11 (8.7)	112 (13.6)	79 (17.5)	40 (16.1)	29 (16.9)
Senior high school	221 (22.4)	59 (14.6)	26 (11)	5 (3.9)	231 (28)	129 (28.5)	41 (16.5)	25 (14.5)
University or above	160 (16.2)	44 (10.9)	15 (6.4)	8 (6.3)	204 (24.8)	81 (17.9)	37 (14.9)	32 (18.6)
Health behaviours								
Smoke	28 (2)	7 (1.2)	6 (1.5)	2 (0.9)	162 (13.7)	47 (7.7)	44 (12.3)	23 (8.1)
Alcohol	25 (1.8)	6 (1)	1 (0.3)	0 (0)	177 (14.9)	51 (8.4)	35 (9.8)	18 (6.4)
Exercise								
No exercise	210 (14.9)	89 (14.9)	60 (15.3)	57 (26.4)	143 (12.1)	67 (11)	44 (12.3)	52 (18.4)
<150 minutes/week	1050 (74.5)	436 (73)	285 (72.9)	143 (66.2)	894 (75.5)	447 (73.4)	268 (74.9)	194 (68.6)
≥150 minutes/week	149 (10.6)	72 (12.1)	46 (11.8)	16 (7.4)	147 (12.4)	95 (15.6)	46 (12.8)	37 (13.1)
BMI, mean ± SD	24.88 ± 3.83	24.75 ± 3.82	24.74 ± 3.81	24.28 ± 3.8	25.52 ± 3.39	25.06 ± 3.36	24.73 ± 3.54	24.61 ± 3.33
Normal: 18.5–23.9 kg/m ²	595 (42.2)	243 (40.7)	157 (40.2)	89 (41.2)	380 (32.1)	219 (36)	133 (37.2)	108 (38.2)
Underweight: <18.5 kg/m ²	60 (4.3)	31 (5.2)	25 (6.4)	18 (8.3)	43 (3.6)	30 (4.9)	23 (6.4)	15 (5.3)
Overweight: 24–26.9 kg/m ²	391 (27.8)	174 (29.1)	107 (27.4)	61 (28.2)	388 (32.8)	191 (31.4)	111 (31)	93 (32.9)
Obese: ≥27 kg/m ²	363 (25.8)	149 (25)	102 (26.1)	48 (22.2)	373 (31.5)	169 (27.8)	91 (25.4)	67 (23.7)
Handgrip strength, mean ± SD	21.5 ± 3.82	20.04 ± 3.72	18.84 ± 3.95	16.97 ± 4.4	33.13 ± 6.06	31.01 ± 5.56	29.28 ± 5.43	25.47 ± 5.77
Gait speed, mean ± SD	1.03 ± 0.11	0.99 ± 0.11	0.94 ± 0.12	0.87 ± 0.13	1.05 ± 0.12	1.02 ± 0.11	0.99 ± 0.13	0.89 ± 0.13
Skeletal muscle mass, mean ± SD	6.85 ± 0.82	6.8 ± 0.87	6.88 ± 0.88	6.74 ± 1.03	8.57 ± 1.17	8.29 ± 1.14	8.23 ± 1.21	8.1 ± 1.29

Table 1. Characteristics of study participants. (Cont'd)

Variables	Female				Male			
	65–69 years old	70–74 years old	75–79 years old	≥80 years old	65–69 years old	70–74 years old	75–79 years old	≥80 years old
	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)
Laboratory data								
Creatinine, mean ± SD	0.73 ± 0.31	0.76 ± 0.24	0.81 ± 0.28	0.96 ± 0.56	1 ± 0.24	1.06 ± 0.42	1.1 ± 0.34	1.21 ± 0.46
M: <0.7, F: <0.6 mg/dL	228 (17)	71 (12.6)	48 (12.9)	15 (7.4)	35 (3.1)	9 (1.5)	6 (1.8)	2 (0.8)
M: 0.7–1.3, F: 0.6–1.2 mg/dL	1091 (81.4)	475 (84.4)	302 (81.4)	160 (79.2)	1003 (88.8)	509 (87)	273 (82.2)	186 (70.7)
M: >1.3, F: >1.2 mg/dL	21 (1.6)	17 (3)	21 (5.7)	27 (13.4)	92 (8.1)	67 (11.5)	53 (16)	75 (28.5)
eGFR (mL/min/1.73 m²), mean ± SD	90.52 ± 21.76	84.84 ± 21.01	79.5 ± 21.04	69.78 ± 23.18	83.58 ± 19.19	78.47 ± 18.84	75.03 ± 19.94	67.11 ± 20.4
Stages 1–2	1267 (94.6)	503 (89.3)	313 (84.4)	132 (65.3)	1027 (90.9)	495 (84.6)	264 (79.5)	173 (65.8)
Stages 3a–3b	66 (4.9)	56 (9.9)	53 (14.3)	63 (31.2)	101 (8.9)	83 (14.2)	62 (18.7)	85 (32.3)
Stage 4	7 (0.5)	4 (0.7)	5 (1.3)	7 (3.5)	2 (0.2)	7 (1.2)	6 (1.8)	5 (1.9)
Glucose, mean ± SD	109.54 ± 27.23	110.26 ± 30.56	109.83 ± 27.42	113.89 ± 33.51	114.77 ± 29.67	113.07 ± 26.25	110.12 ± 22.17	108.16 ± 22.64
<70 mg/dL	3 (0.2)	0 (0)	0 (0)	0 (0)	1 (0.1)	1 (0.2)	1 (0.3)	0 (0)
70–99 mg/dL	522 (39)	220 (39.1)	154 (41.5)	78 (38.6)	347 (30.7)	172 (29.4)	123 (37)	99 (37.8)
≥100 mg/dL	815 (60.8)	343 (60.9)	217 (58.5)	124 (61.4)	782 (69.2)	412 (70.4)	208 (62.7)	163 (62.2)
Cholesterol, mean ± SD	189.77 ± 34.69	185.17 ± 31.83	180.16 ± 32.59	175.77 ± 34.39	172.99 ± 33.71	169.84 ± 33.23	169.24 ± 33.47	162 ± 32.26
≥200 mg/dL	472 (35.2)	176 (31.3)	89 (24)	42 (20.8)	226 (20)	102 (17.4)	61 (18.4)	31 (11.8)
Triglyceride, mean ± SD	132.89 ± 108.62	123.34 ± 57.97	127.44 ± 65.25	130.36 ± 59.1	132.8 ± 82.45	126.55 ± 80.26	118.63 ± 58.7	119.02 ± 69.77
≥150 mg/dL	363 (27.1)	138 (24.5)	97 (26.1)	64 (31.7)	337 (29.8)	161 (27.5)	69 (20.8)	59 (22.4)
LDL cholesterol, mean ± SD	103.77 ± 31.11	99.88 ± 29.16	95.15 ± 28.28	93.59 ± 32.63	97.23 ± 30.07	94.61 ± 29.69	94.42 ± 29.91	87.22 ± 28.39
>130 mg/dL	243 (18.2)	83 (14.7)	44 (11.9)	26 (12.9)	147 (13.1)	67 (11.5)	42 (12.7)	22 (8.4)
HDL cholesterol, mean ± SD	60.11 ± 15.28	60.92 ± 15.63	59.72 ± 16.19	56.18 ± 15.78	49.71 ± 13.11	50.44 ± 14.6	51.38 ± 14.57	51.05 ± 13.95
M: <40, F: <50 mg/dL	356 (26.6)	146 (25.9)	107 (28.8)	83 (41.1)	244 (21.6)	139 (23.8)	71 (21.4)	55 (20.9)

BMI: body mass index; eGFR: estimated glomerular filtration rate; F: female; HDL: high-density lipoprotein; LDL: low-density lipoprotein; M: male; SD: standard deviation

ZoSCI values were converted to percentile ranks to enhance comparability across populations. To assess the impact of independent variables on ZoSCI, forward selection multiple regression analysis was conducted. Data were analysed using SPSS version 22 (IBM Corp, NY, US), with statistical significance set at $P < 0.05$.

RESULTS

Demographic characteristics and prevalence of sarcopenia

A total of 5047 participants met the inclusion criteria, with an average age of 71.1 ± 5.92 years, ranging from 65 to 103 years. Participants were divided into 5-year age groups: 65–69 (51.4%), 70–74 (23.9%), 75–79 (14.9%) and 80+ years (9.9%). The sample included 2613 women (51.8%), with an average age of 70.69 ± 5.61 years, and 2434 men (48.2%) with an average age of 71.56 ± 6.27 years (Table 1). The overall prevalence of sarcopenia was 3.7%, with a higher rate in men (5.2%) than in women (2.3%); 1.3% of participants were classified as having severe sarcopenia. The prevalence of probable sarcopenia was 27.7%, increasing with age; nearly 50% of those aged over 75 years and 70% of those over 80 years were at risk. Approximately 2.7% exhibited muscle mass loss only (Fig. 2).

Generation of ZoSCI

The ZoSCI distribution was analysed using percentile ranking and AWGS diagnostic grading. ZoSCI values below the 50th percentile was negative, indicating values lower than average. At the 20th percentile, ZoSCI was approximately 1.5 standard deviation (SD) below the average, and within the 5th–95th percentile range, it ranged

around ± 3.2 SD. ZoSCI values were positive for the non-sarcopenia group, indicating values above average. For the probable sarcopenia group, ZoSCI values were approximately 1.5 SD below average, and for the sarcopenia group, ZoSCI values were 3–4 SD below average (Table 2 and Supplementary Tables S1–S3).

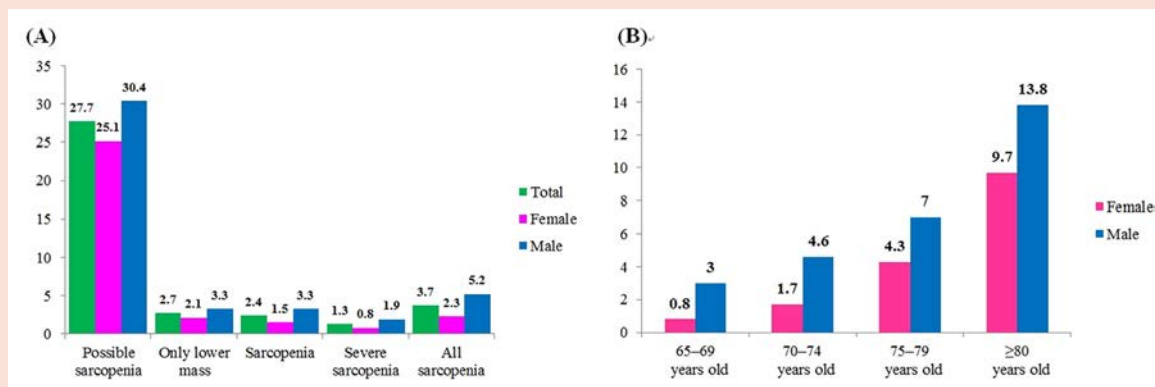
Optimal cut-offs point and accuracy of ZoSCI

Using the AWGS diagnostic criteria as the gold standard, the optimal ZoSCI cut-off for diagnosing sarcopenia in women was -1.97 , with a sensitivity of 0.932, specificity of 0.881 and an area under curve (AUC) of 0.962. Age-specific cut-offs for women were determined as follows: -2.07 for ages 65–69, -3.22 for ages 70–74, -2.26 for ages 75–79 and -1.35 for ages 80+ years, with sensitivity ranging from 0.839 to 0.941, specificity from 0.772 to 0.973 and AUC from 0.886 to 0.963. For men, the optimal cut-off was -1.85 , with sensitivity of 0.913, specificity of 0.880 and an AUC of 0.941. Age-specific cut-offs for men were established as -2.82 for ages 65–69, -1.21 for ages 70–74, -1.41 for ages 75–79 and -0.60 for 80+ years, with sensitivity ranging from 0.872 to 0.920, specificity from 0.775 to 0.964, and AUC from 0.864 to 0.972, respectively (Fig. 3).

Associated factors of ZoSCI

Multiple linear regression identified several factors affecting ZoSCI. For women, each 1-year increase in age was associated with a 0.12 decrease in ZoSCI (standard error [SE] 0.007, $P < 0.001$). Having a college education or higher increased ZoSCI by 0.34 (SE 0.12, $P = 0.004$). Engaging in less than 150 minutes and more than 150 minutes of exercise per week increased ZoSCI by 0.35

Fig. 2. Prevalence of sarcopenia.



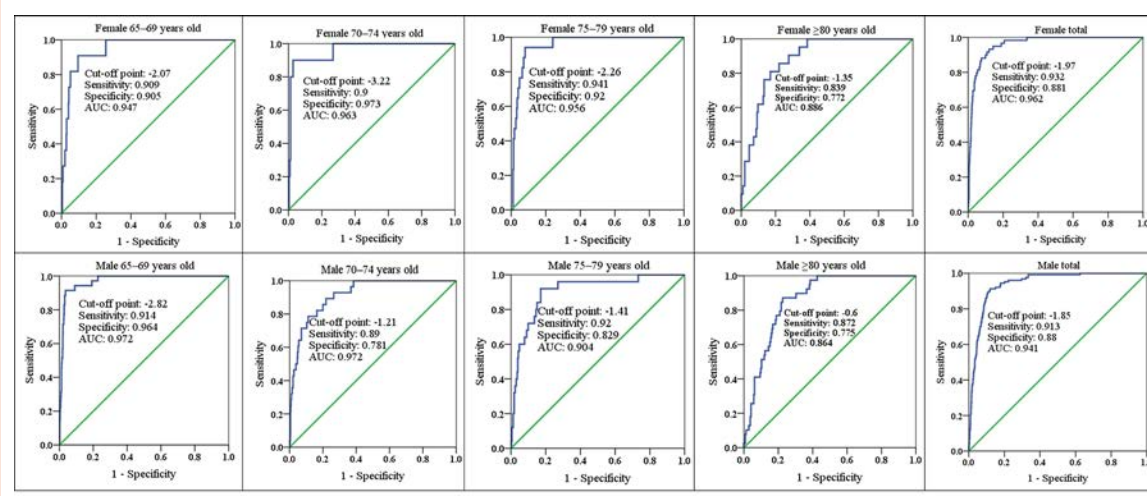
(A) Prevalence of possible sarcopenia, sarcopenia and severe sarcopenia, as well as the proportion of individuals with only low muscle mass, stratified by sex (total: green, female: pink, male: blue). (B) Prevalence of sarcopenia across different age groups (65–69, 70–74, 75–79 and ≥80 years), stratified by sex (female: pink, male: blue).

Table 2. ZoSCI distribution in percentile rank and AWGS diagnosis.

	Percentile rank of the sample						AWGS diagnosis			Non-sarcopenia		
	5th	15th	20th	50th	75th	85th	95th	Non-sarcopenia	Possible sarcopenia	All sarcopenia	Normal	Only lower mass
								Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)
Total												
Female	-3.27	-1.83	-1.39	-0.03	1.19	1.85	3.19	0.72 ± 1.5 (-2.77 to 7.4)	-1.71 ± 1.58 (-6.9 to 3.42)	-4.01 ± 1.44 (-8.39 to -0.61)	0.77 ± 1.47 (-1.88 to 7.4)	-1.07 ± 1.39 (-2.77 to 5.88)
Male	-3.39	-1.95	-1.54	0.001	1.31	2.04	3.21	0.91 ± 1.54 (-3.07 to 8.55)	-1.33 ± 1.66 (-8.48 to 5.32)	-3.42 ± 1.55 (-8.26 to 0.75)	1.02 ± 1.48 (-1.74 to 8.55)	-1.15 ± 1.06 (-3.07 to 3.29)
65–69 years old												
Female	-2.85	-1.72	-1.4	-0.13	1.12	1.86	3.27	0.35 ± 1.63 (-3.23 to 7.39)	-2.14 ± 1.63 (-6.96 to 3.08)	-3.33 ± 1.18 (-4.99 to -1.14)	0.41 ± 1.6 (-2.55 to 7.39)	-1.62 ± 1.26 (-3.23 to 1.49)
Male	-3.02	-1.86	-1.58	-0.03	1.23	1.94	3.1	0.5 ± 1.64 (-3.22 to 8.33)	-1.52 ± 1.66 (-8.3 to 4.95)	-3.72 ± 1.21 (-7.21 to -1.3)	0.56 ± 1.61 (-2.51 to 8.33)	-1.65 ± 1.35 (-3.22 to 2.92)
70–74 years old												
Female	-3.04	-1.73	-1.39	-0.13	1.18	1.85	3.12	0.7 ± 1.52 (-2.07 to 7.32)	-1.51 ± 1.51 (-7.37 to 2.49)	-3.98 ± 1.26 (-5.54 to -0.95)	0.73 ± 1.48 (-1.6 to 7.32)	-0.36 ± 2.44 (-2.07 to 6.87)
Male	-3	-1.75	-1.46	-0.06	1.3	1.96	3.08	0.74 ± 1.52 (-3.16 to 5.33)	-1.22 ± 1.61 (-7.25 to 4.03)	-3.1 ± 1.73 (-6.68 to -0.48)	0.9 ± 1.44 (-1.73 to 5.33)	-1.25 ± 0.92 (-3.16 to 1)
75–79 years old												
Female	-3.28	-1.98	-1.6	-0.07	1.36	1.84	2.93	1.14 ± 1.4 (-1.98 to 6)	-1.13 ± 1.46 (-5.69 to 2.82)	-3.5 ± 1.15 (-5.11 to -0.92)	1.24 ± 1.34 (-1.1 to 6)	-1.18 ± 0.38 (-1.98 to -0.65)
Male	-3.16	-1.82	-1.49	0.03	1.23	1.93	3.33	1.19 ± 1.51 (-2.05 to 6.17)	-0.8 ± 1.63 (-8.34 to 3.35)	-2.85 ± 1.75 (-7.86 to 1.23)	1.37 ± 1.45 (-1.17 to 6.17)	-0.39 ± 1.11 (-2.05 to 1.68)
≥80 years old												
Female	-2.98	-2.04	-1.66	-0.1	1.24	2.18	3.29	1.86 ± 1.16 (0.36 to 5.73)	-0.33 ± 1.59 (-4.36 to 4.29)	-2.34 ± 1.36 (-5.84 to -0.37)	1.88 ± 1.16 (0.36 to 5.73)	0.78
Male	-3.5	-2.17	-1.75	0.13	1.33	2	2.95	2.03± 1.15 (-0.5 to 6.12)	-0.24 ± 1.63 (-5.65 to 3.23)	-2.16 ± 1.46 (-6.28 to 0.14)	2.2 ± 1.03 (0.77 to 6.12)	0.61 ± 1.19 (-0.5 to 2.69)

AWGS: Asian Working Group for Sarcopenia; SD: standard deviation; ZoSCI: z score for the sarcopenia composite index

Fig. 3. Receiver operating characteristic curves for different age and sex groups.



AUC: area under curve

Note: The plots display sensitivity and specificity across age groups (65–69, 70–74, 75–79 and ≥80 years) for females (top), males (bottom) and the total population (rightmost). Each panel includes the cut-off, sensitivity, specificity and AUC.

(SE 0.12, $P=0.003$) and 0.63 (SE: 0.16, $P<0.001$), respectively. Underweight status was associated with a 0.52 decrease in ZoSCI (SE 0.18, $P=0.004$), while overweight and obese were associated with increases of 0.6 (SE 0.09, $P<0.001$) and 1.3 (SE 0.1, $P<0.001$), respectively. Age explained 14% of the variance in ZoSCI, with other factors contributing to a total of 24.2%.

For men, each 1-year increase in age was associated with a 0.14 decrease in ZoSCI (SE 0.007, $P<0.001$). Higher education levels increased ZoSCI by 0.36 (junior high), 0.32 (high school) and 0.47 (university) (SE 0.12, $P=0.002$; SE 0.1, $P=0.002$; SE 0.11, $P<0.001$, respectively). Engaging in less than 150 minutes and more than 150 minutes of exercise per week increased ZoSCI by 0.6 (SE 0.14, $P<0.001$) and 0.78 (SE 0.17, $P<0.001$), respectively. Overweight and obese were associated with increases in ZoSCI of 0.7 (SE 0.09, $P<0.001$) and 1.59 (SE 0.1, $P<0.001$), respectively. Creatinine levels below 0.7 mg/dL were associated with a 0.65 decrease in ZoSCI (SE 0.27, $P=0.014$). Age explained 22% of the variance in ZoSCI, with other factors contributing to a total of 34.5% (Table 3).

DISCUSSION

This retrospective study analysed data from 5047 participants over the past 5 years, revealing a sarcopenia prevalence of approximately 3.7% based on 2019 AWGS criteria, with higher rates in males than females (5.2% versus [vs] 2.3%). This prevalence is lower than global averages, typically reported between 3.9% and 15.4%.^{2,3,13-18} Several factors may account for this disparity. First,

the stricter cut-off points recommended by the AWGS for Asian populations¹⁹ could result in lower prevalence rates compared to studies using other criteria, such as EWGSOP. Second, lifestyle factors in Taiwan, including higher levels of physical activity and dietary habits supportive of muscle retention, may contribute to a healthier ageing population.²⁰ Third, our study focused on a relatively healthy elderly cohort, with 75% of the participants under 75 years old, potentially under-representing individuals with significant health issues that are more prevalent in older and less active populations. Sex differences in sarcopenia prevalence were also observed. This disparity may be attributed to greater age-related muscle loss in men, linked to hormonal changes such as testosterone decline.²¹ Cultural factors could also play a role, as older men in Taiwan tend to have higher sedentary rates than women, potentially exacerbating muscle loss.^{6,22} These findings highlight the importance of considering sex-specific risk factors in sarcopenia research and prevention, particularly in developing tailored intervention strategies for at-risk populations. Furthermore, probable sarcopenia was identified in 27.7% of participants, with significant progression in those over 75 years, while 3% exhibited isolated muscle mass loss, highlighting the need for a standardised score that integrates all indicators.

ZoSCI is a standardised score that integrates grip strength, walking speed and muscle mass into a single measure, offering a comprehensive assessment than individual measurements. At the 5th percentile, ZoSCI was approximately -3.2, which may not fully align with Seashore's standardi-

Table 3. Multiple linear regression analysis of factors affecting ZoSCI.

Variables (reference group)	Female		Male	
	β	SE	β	SE
Age (years)	-0.12 ^a	0.007	-0.14 ^a	0.007
Education (elementary school)				
Junior high school	NA	NA	0.36 ^b	0.12
Senior high school	NA	NA	0.32 ^b	0.1
University or above	0.34 ^b	0.12	0.47 ^a	0.11
Exercise (No exercise)				
<150 mins/week	0.35 ^b	0.12	0.6 ^a	0.14
≥150 mins/week	0.63 ^a	0.16	0.78 ^a	0.17
BMI (healthy body weight)				
Underweight	-0.52 ^b	0.18	NA	NA
Overweight	0.6 ^a	0.09	0.7 ^a	0.09
Obese	1.3 ^a	0.1	1.59 ^a	0.1
Creatinine (M: 0.7–1.3, F: 0.6–1.2 mg/dL)				
M: <0.7, F: <0.6 mg/dL	NA	NA	-0.65 ^c	0.27
Cumulative R2		0.24		0.35
Adjusted R2		0.24		0.34

^a $P < 0.00$; ^b $P < 0.01$; ^c $P < 0.05$

BMI: body mass index; NA: not applicable; SE: standard error; ZoSCI: z score for the sarcopenia composite index

sation principles.²³ For females, below-average ZoSCI values extended to the 50th percentile, while for males, values were positive from the 50th percentile onward. Among younger elders, ZoSCI remained negative at the 50th percentile, indicating that half had values below the mean, suggesting a need for early preventive interventions, such as nutrition, exercise and possibly pharmaceutical options. Further analysis by AWGS classification showed that some non-sarcopenic participants had negative ZoSCI values, reaching as low as 3 standard deviations below the mean. This could reflect performance variability among participants or isolated muscle mass loss. Similarly, some participants classified as “normal” also had negative ZoSCI values, indicating lower muscle mass or quality relative to their peers. These findings underscore the importance of early prevention strategies for sarcopenia.

In applying ZoSCI, ROC curve analysis identified optimal cut-off values for diagnosing sarcopenia, demonstrating high diagnostic accuracy. With increasing age, these cut-offs align more closely

with age group averages, suggesting greater ZoSCI variation among younger elders. The average participant age was 71.1 years, with 54.9% of those over 75 years diagnosed with sarcopenia and 23.5% classified as non-sarcopenic. ZoSCI scores decreased with age, consistent with studies showing increased odds of sarcopenia with age.^{13,16,24,25} This decline is linked to an annual muscle loss rate of approximately 0.5%, which accelerates to 1% per year after age 50 years, and further impacted by factors like inadequate nutrition and decreased physical activity.^{26,27} Furthermore, education level significantly influenced ZoSCI scores, with higher education associated with higher scores. Supporting this, Tyrovolas et al. found that higher education provides protection against sarcopenia, possibly due to better knowledge about diet and physical activity, which positively impacts health outcomes.²⁸ Insufficient physical activity is consistently associated with declines in muscle mass.^{16,18,24,25,29} This study found that higher exercise frequency significantly increased ZoSCI scores in both

sexes, suggesting the importance of regular physical activity in maintaining muscle function and mass, particularly as ageing contributes to muscle atrophy.³⁰ The World Health Organization recommends regular physical activity to mitigate sarcopenia and prevent disability.³¹ Our results showed that being overweight or obese was associated with higher ZoSCI scores across sexes, while being underweight was linked to lower scores among elderly females. This finding aligns with studies that associate low BMI and underweight status with a higher risk of sarcopenia.^{18,25,32} Low body weight may indicate poor nutrition, especially insufficient protein intake, while higher body weight may support muscle mass retention.^{18,33} However, sarcopenic obesity, characterised by excessive fat coupled with low muscle mass, presents additional health risks, including metabolic syndrome, cardiovascular disease and osteoporosis.^{34,35} Excess adipose tissue increases the production of cytokines and adipokines, leading to inflammation, insulin resistance and muscle breakdown, which contribute to muscle loss.³⁶ In this study, BMI was used to assess body composition but did not differentiate between types of fat, making it challenging to identify sarcopenic obesity among overweight or obese individuals. Further research should establish precise BMI cut-offs for sarcopenic obesity and enhance health databases for the elderly with measures of abdominal and visceral fat. Creatinine, a marker for eGFR, serves as an indicator of renal function. Elevated creatinine levels suggest reduced eGFR, while low levels may indicate muscle mass loss, as 90% of creatine phosphate is stored in muscle.^{37,38} In this study, lower creatinine levels were associated with reduced ZoSCI scores in elderly males. Sarcopenia diagnosis may benefit from assessing both muscle function and serum creatinine concentrations. Thongprayoon et al. identified a U-shaped distribution of serum creatinine, linking low muscle mass and renal dysfunction to higher mortality rates.³⁹

The study's findings highlight several advantages of using ZoSCI, which could substantially influence clinical pathways for sarcopenia diagnosis and intervention. First, ZoSCI uses continuous numerical values to assess sarcopenia indicators, allowing for more precise evaluation compared to categorical tools. This approach provides a nuanced understanding of each patient's condition, facilitating early detection of sarcopenia progression. Unlike the SARC-F questionnaire, which relies on subjective self-reports and is susceptible to variability, ZoSCI generates objective, quantifiable data that enhance diagnostic accuracy, particularly for mild cases that subjective assessments may overlook. Furthermore, ZoSCI offers a streamlined, single-score approach

in contrast to the multi-step EWGSOP process, making it more efficient for high-volume clinical settings. Another significant advantage of ZoSCI is its focus on early intervention from a preventive healthcare perspective, without prioritising whether muscle function or mass declines first. By providing a balanced risk profile, ZoSCI allows clinicians to identify at-risk individuals early and initiate targeted interventions at optimal stages. This emphasis on prevention and early intervention represents a shift from traditional sarcopenia assessments, supporting the integration of ZoSCI into routine screening and proactive care.

This study has some limitations that should be acknowledged. First, the retrospective design and exclusion of participants with incomplete data may have introduced selection bias, potentially resulting in a healthier sample and underestimating the prevalence of sarcopenia. Moreover, the final sample may represent a younger and generally healthier elderly demographic, biased toward individuals more inclined to participate in health check-ups. This limitation may affect the generalisability of the findings to the broader elderly population, particularly those with compromised health. Additionally, the study did not account for variables such as nutritional status, cognitive function and other lifestyle factors known to influence sarcopenia risk and progression.⁶ Future research should adopt a prospective design and incorporate these factors to provide a more comprehensive understanding of sarcopenia risk across diverse elderly populations. Second, while widely used sarcopenia diagnostic criteria, such as AWGS for East Asian populations and EWGSOP for Western populations, utilise similar measurement tools, they establish different cut-off points, leading to regional variations in sarcopenia prevalence. This variation underscores the global importance of sarcopenia research and highlights the potential for adapting ZoSCI for diverse populations. Based on AWGS criteria and data from an elderly Asian population, ZoSCI offers a valuable model for assessing sarcopenia among East Asian populations. Although these norms provide a strong foundation for use in Taiwan and similar demographic groups, further validation against international standards, such as EWGSOP, is essential to ensure compatibility and accuracy beyond East Asia. Future studies should investigate ZoSCI's adaptability across diverse regions and ethnic groups, making physiological calibrations as needed. Furthermore, international collaborations could facilitate standardisation efforts, enabling comparative studies and promoting ZoSCI's broader global application. Third, ZoSCI was developed by combining standardised scores for grip strength, walking speed and muscle mass

without assessing each component's individual contribution to the overall evaluation. Future research should investigate the impact of each component and evaluate their predictive value for adverse outcomes. Such studies would allow for adjustments in the weighting of each indicator, enhancing ZoSCI's accuracy and clinical relevance. Finally, while ZoSCI provides a standardised tool for diagnosing sarcopenia, its implementation may face challenges in resource-limited settings due to specific equipment requirements. However, ZoSCI's flexible framework allows for adaptation across diverse healthcare systems. In well-resourced settings, ZoSCI can be integrated into routine screening, whereas in lower-resource environments, alternative methods, such as simplified body composition measures, may approximate diagnostic criteria.⁶ Furthermore, variations in ZoSCI normative scores across healthcare systems highlight the need for regional calibrations.⁴⁰ Aligning ZoSCI with local tools, infrastructure and norms enhances its diagnostic utility, facilitating early sarcopenia detection across diverse contexts.

CONCLUSION

To the best of authors' knowledge, this study is the first attempt to develop and validate ZoSCI, a composite index that combines standardised scores of grip strength, walking speed and muscle mass to assess sarcopenia. ZoSCI's continuous, quantitative evaluation enhances diagnostic precision and facilitates early sarcopenia detection. By providing a standardised framework, ZoSCI supports consistent research across populations, helping to identify sarcopenia risk factors and guide targeted interventions. Its adaptability across various healthcare settings makes ZoSCI a valuable tool for global use. With international validation, ZoSCI has the potential to standardise sarcopenia assessment, foster preventive strategies and ultimately improve outcomes for ageing populations worldwide.

Supplementary materials

Table S1. Z handgrip strength distribution in percentile rank and AWGS diagnosis.

Table S2. Z gait speed distribution in percentile rank and AWGS diagnosis.

Table S3. Z muscle mass distribution in percentile rank and AWGS diagnosis.

Ethics statement

This study was approved by the Institutional Review Board of Far Eastern Memorial Hospital, New Taipei City, Taiwan (111059-F).

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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Mechanisms and roles of hydroxychloroquine in pregnancy in rheumatic diseases

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ABSTRACT

Introduction: Hydroxychloroquine (HCQ), originally an antimalarial drug, is currently used to treat multiple disorders, especially rheumatic diseases. Given its good efficacy and safety, HCQ is widely administered in pregnant patients. However, the safety profile of HCQ during pregnancy remains controversial due to limited research. In addition, HCQ has been reported to reduce preeclampsia in patients with systemic lupus erythematosus (SLE) and could potentially alleviate the symptom of preeclampsia. However, the clinical profile and molecular mechanism of HCQ in preeclampsia is yet to be fully understood.

Method: We reviewed the literature on HCQ treatment in pregnancy with rheumatic diseases and preeclampsia in PubMed and Web of Science. We also discussed the safety of long-term therapy with HCQ during pregnancy.

Results: HCQ mainly modulates autoimmune response through inhibition of lysosomal function, toll-like receptor (TLR) signalling, nicotinamide adenine dinucleotide phosphate-mediated oxidative stress and autophagy. Benefits of HCQ in treating rheumatic diseases, including antiphospholipid syndrome, rheumatoid arthritis and Sjogren's syndrome during pregnancy, has been demonstrated in clinics. In particular, multiple clinical guidelines recommend HCQ as an indispensable therapeutic drug for pregnant patients with SLE. Additionally, it may potentially function in preeclampsia to improve clinical symptoms.

Conclusion: HCQ is effectively used for rheumatic diseases during pregnancy. The benefits of HCQ treatment in rheumatic diseases outweigh the risk of adverse reactions it induces in pregnant women.

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Keywords: efficacy and safety, HCQ, preeclampsia, pregnancy, rheumatic diseases

CLINICAL IMPACT

What is New

- This presentation summarised the latest advanced role, mechanism, treatment and safety of hydroxychloroquine (HCQ) in rheumatic diseases during pregnancy.
- Meanwhile, we discussed the application prospects of HCQ in preeclampsia.

Clinical Implications

- To provide the pharmaceutical perspective on the effect and safety of HCQ in pregnancy, aiming to help clinicians use HCQ or any other anti-rheumatic drugs more reasonably and safely in the treatment of pregnant women.

INTRODUCTION

With the prevalence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) around the world, hydroxychloroquine (HCQ) has once again come into public attention due to its potential therapeutic role in COVID-19. HCQ is a classic antimalarial drug that belongs to the 4-aminoquinoline phospholipase A2 inhibitors. It was first introduced in 1955 and quickly gained popularity in the treatment of systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS) and other rheumatic diseases. Apart from its immunomodulatory function, the effect of HCQ has extended to antiviral, hypolipidaemic, hypoglycaemic and antithrombosis, as well as anti-malignancies (Fig. 1).¹ Due to its good efficacy,

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safety profile and low cost, HCQ is now commonly administered as a single agent or in combination with other immunosuppressants during pregnancy to treat rheumatic diseases.²

Rheumatic diseases occur primarily in females of childbearing years, including SLE, APS, rheumatoid arthritis (RA) and Sjogren's syndrome (SS). HCQ predominantly alleviates the symptoms of typical rheumatic diseases, particularly skin problems and joint pain, by reducing the inflammatory response in patients. Since pregnant women with rheumatic diseases are always considered to be at higher possibility of pregnancy complications and adverse pregnancy outcomes (APOs), they should require more intensive observation and prompt pharmacotherapy. With the development and use of HCQ in clinical therapy, recent research has generally recognised the benefit of HCQ in improving pregnancy outcomes and its safety profile in pregnant women with rheumatic disorders.

Although the application of HCQ in reproductive immunity has become a new research hotspot, the molecular mechanism is not yet entirely understood. This review primarily focused on the mechanism and clinical treatment of HCQ in pregnancy with rheumatic diseases, such as SLE, APS, SS and RA. It also discussed the relevance and potential use of HCQ in preeclampsia. Finally, we further presented our opinion on the safety of pregnant patients taking HCQ for rheumatic disorders. Keywords

such as "rheumatic disease" OR "rheumatism" OR "antiphospholipid antibody syndrome" OR "Sjogren's syndrome" OR "rheumatoid arthritis" OR "systemic lupus erythematosus" OR "preeclampsia" AND "hydroxychloroquine" AND "pregnancy" OR "gestation" were used in the literature search in PubMed and Web of Science. We also checked reference lists for relevant publications, recent reviews and editorials.

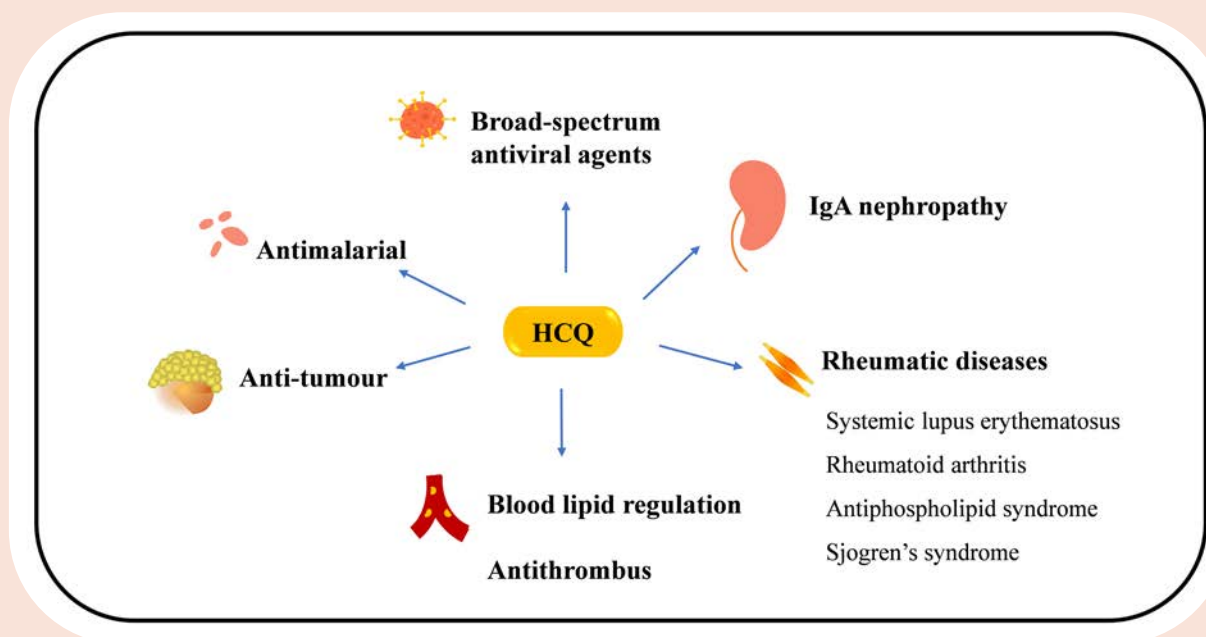
Mechanism of action of HCQ

The exact mechanism of how HCQ regulates immune function has not been entirely delineated. HCQ has been reported to function mainly in rheumatic diseases through versatile immunomodulatory and anti-inflammatory responses, with additional roles such as antiplatelet and antioxidant effects.³ In general, HCQ could exert therapeutic effects via modulating different cellular signals, especially the inhibition of endolysosomal activities, innate inflammatory signalling pathways, oxidative stress and thrombosis (Fig. 2).

Inhibition of lysosomal function

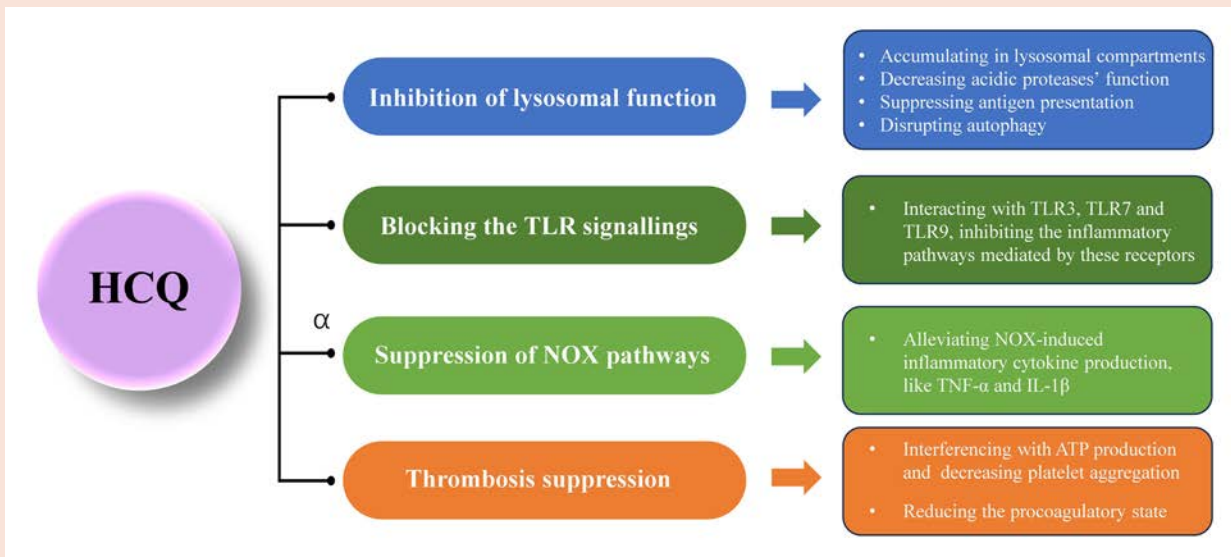
Due to its hydrophobicity and alkalescence, HCQ disperses quickly into acidic lysosomes across cell membranes. It accumulates in lysosomal compartments, stabilises cell membrane and decreases the functions of acidic proteases, thereby increasing the pH of acidic subcellular

Fig. 1. Benefits of HCQ in various diseases.



HCQ: hydroxychloroquine; IgA: immunoglobulin A

Fig. 2. Major mechanisms of HCQ.



ATP: adenosine triphosphate; HCQ: hydroxychloroquine; IL-1 β : interleukin-1 beta; NOX: nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; TLR: toll-like receptor; TNF- α : tumour necrosis factor-alpha

compartments. Meanwhile, alteration in acid enzyme activity reduces the formation and transport of major histocompatibility class II complex molecules, leading to suppression of antigen presentation and autoimmune responses. Furthermore, HCQ disrupts autophagy, a lysosomal-dependent degradation process that degrades damaged cytoplasmic materials and organelles to maintain cell homeostasis.¹

Inhibition of toll-like receptor (TLR)-mediated innate immune response

HCQ inhibits several typical inflammatory pathways, particularly the signalling mediated by TLRs. TLRs expressed primarily by immune cells are significant receptors in the innate immune system, and mediate the induction of inflammatory cytokine genes. TLR3, TLR7 and TLR9 of the innate immune system are present in the intracellular compartments like endosomes. TLR3 mainly induced the expression of type I interferon (IFN) and IFN-inducible genes via TRIF/IRF3. Sensitive to synthetic imidazoquinoline-like molecules, TLR7 triggered the induction of type I IFN and inflammatory cytokines via the myeloid differentiation primary-response protein 88 (MyD88)- and nuclear factor-kappaB (NF- κ B)-dependent pathways. TLR9, activated by DNA in the endosome of immune cells, leads to the robust production of IFN. HCQ prefers to interact with TLR3, TLR7 and TLR9, and specifically blocks the activation of these receptors that mediate inflammatory pathways and cytokines. Therefore,

it prevents the activation of these receptors that mediate inflammatory pathways and cytokines.³

Suppression of other signalling pathways

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs)—exclusive enzyme complexes in the generation of reactive oxygen species (ROS)—are involved in numerous proinflammatory signalling cascades. HCQ has been proven to alleviate NOX-mediated production of TNF- α and IL-1 β by directly blocking the translocation of gp91phox.⁴ It also protects the endothelium by suppressing NADPH and activating extracellular signal-regulated kinase 5 (ERK5),⁴ because overproduction of ROS is the main cause of vascular endothelial dysfunction. With regard to second messenger-mediated signal transduction, HCQ impairs the expression and secretion of immune cytokines and factors in T- and B-cells by interfering with intracellular Ca²⁺ mobilisation.⁵

In addition, before low molecular weight heparin was widely applied in clinical practice, HCQ was used to prevent pulmonary embolism after arthroplasty for its potential antithrombotic effect. Its anticoagulant and antithrombotic effects have gradually been recognised with the use of HCQ in treating diverse diseases. Belizna et al. found HCQ dose dependently reduced collagen-induced platelet aggregation and platelet α -granule release. It suppresses platelet aggregation via adenosine diphosphate (ADP) inhibition and inhibits the release of arachidonic acid caused by activated platelets.⁶

HCQ treatment in pregnancy with rheumatic diseases

Systemic lupus erythematosus (SLE)

SLE is an autoimmune rheumatic disease presented with multiple organ injury. Although the pathogenesis of SLE remains incompletely understood, the autoimmune attack theory may be the essential hypothesis so far. Pregnancy with SLE increases the obstetric risk of APOs, such as preterm birth, intrauterine growth restriction and preeclampsia.² Generally, therapy for SLE aims to alleviate immune damage in cells, tissues and organs. HCQ benefits SLE from diverse perspectives, particularly through amelioration of systemic symptoms as well as improvement in musculoskeletal and cutaneous mucosal performance. Apart from HCQ-moderate inflammatory response, HCQ obviously decreased the possibility of thrombosis in SLE. Another advantage of HCQ is its potential role in preventing severe complications. It reduces the incidence of diabetes in a dose-dependent manner, as shown in a study of HCQ treatment with 200 mg/day for 1.8 years in SLE patients.⁷ HCQ may also be beneficial for osteoporosis, a common complication in SLE patients, by increasing spinal bone mineral density, especially in women receiving prolonged steroid therapy. HCQ-treated group showed a trend towards lower prednisone dosage and reduced the occurrence of preeclampsia and preterm delivery in pregnant women with lupus.^{8,9} HCQ treatment during pregnancy also significantly decreased flares during pregnancy and postpartum. Substantial evidence suggests that lupus activity and symptoms in pregnant women could be alleviated by HCQ without any risk to the fetus.¹⁰⁻¹² Significantly, most studies currently indicate that HCQ treatment in SLE women throughout pregnancy remarkably improved birth outcomes, in contrast to pregnant lupus mothers who did not take HCQ.^{10,13-15} It also reduced recurrent miscarriages, the occurrence of hypertension, gestational diabetes and pregnancy complications.¹⁶ Based on these findings (Table 1), HCQ should be continued during pregnancy. This is also supported by many clinical guidelines from different countries. A Chinese guideline for pregnancy with SLE suggests that HCQ reduces the activity and recurrence of SLE in pregnant women, improves pregnancy outcomes, and even benefits for the prevention of preeclampsia and neonatal heart block, without harmful effects on newborns.¹⁷ HCQ plus low molecular weight heparin plus low-dose aspirin (LDA) is more suitable than HCQ in addition to LDA or glucocorticoid or Ig for pregnant patients undergoing SLE with antiphospholipid antibodies (aPL) and recurrent

pregnancy loss, according to the Latin American group for the study of lupus (GLADEL).¹⁸ Practice guidelines of the British society for rheumatology (BSR) and the British health professionals in rheumatology recommend HCQ for all pregnant SLE patients, with the exception of contraindications.^{19,20} The 2020 American College of Rheumatology (ACR) practice guideline strongly advises all SLE women to take HCQ during pregnancy if possible, showing that HCQ is beneficial to the outcomes of both mothers and fetuses.²¹ Furthermore, the European League Against Rheumatism (EULAR) suggests that pregnancies with SLE should be treated with HCQ at a maintenance dose to stabilise the condition and improve pregnancy outcomes. However, the dose of HCQ should not exceed 5 mg/kg/real of body weight (BW) (Table 2).²²

Antiphospholipid syndrome (APS)

APS, characterised by thrombotic events and pathological pregnancies, is an autoimmune disorder that is more likely to lead to unfavourable pregnancy outcomes. Although low-dose aspirin and heparin treatment for pregnant women with APS has increased the live birth rate by approximately 70%, HCQ has commonly been administered as an adjunctive medication for the treatment of APS-related thrombosis.²³ It decreases the combination of aPL- β 2GP1 complex and platelet aggregation by suppressing aPL-activated overexpression of GPIIb/IIIa on the platelet membrane.²³ Treatment of HCQ in patients with aPL during pregnancy increased the live birth rate (67% HCQ group versus [vs] 57% control group, $P=0.05$) and decreased the prevalence of aPL-related pregnancy morbidity and complication (2% vs 10.9%, $P=0.05$).²⁴ Emerging clinical studies also showed that treatment with 200–400 mg HCQ in refractory APS pregnant women could improve the pregnancy outcome, like lower rates of pregnancy loss, live birth and pregnancy complications (Table 3).²⁵⁻²⁷ A retrospective study of 194 pregnant primary APS patients revealed that high dose HCQ (400 mg) and initiation prior to pregnancy were linked to a higher live birth rate in contrast to a low dose (200 mg) and treatment only during pregnancy.²⁷ To our knowledge, HCQ is currently not included in the standard therapy of primary APS, but it definitely benefits the refractory cases, involving refractory obstetrical APS. EULAR recommends the addition of HCQ in the first trimester may be conducive to APS patients with pregnancy, despite receiving a combination of LDA and heparin.²⁸ The other compelling clinical guideline has recommended HCQ used routinely

Table 1. Clinical studies on HCQ treatment in pregnant women suffering from SLE.

Author or committee	Year	No. of pregnancies	HCQ dosage	HCQ duration	Results and conclusion
Kroese SJ, et al. ⁷	2017	110 pregnancies, 30 of which were treated with HCQ	200 mg or 400 mg per day	Throughout pregnancy	HCQ decreased the occurrence of flares (non-HCQ group: 6.4% mild and 2.6 severe; HCQ group: 2.6.7% mild and 0 severe) and the dosage of prednisone (OR 0.2, 95% CI 0.0–1.4; <i>P</i> =0.10), as well as increased the duration of pregnancy (95% CI 1.0–3.8; <i>P</i> ≤0.001).
Alle G, et al. ¹⁰	2024	174 pregnant women with SLE	200 mg daily (6.9%), 400 mg daily (85.1%), different dose (8%)	Throughout pregnancy	SLE patients with subtherapeutic (HCQ ≤500 ng/mL: 8.8% versus [vs] 0.7%) and non-adherent HCQ levels (≤200 ng/mL: 13.3% vs 1.3%) had more severe flares during pregnancy.
Levy RA, et al. ¹¹	2001	20 consecutive pregnant patients, 10 treated with HCQ	Not available	Beginning between 8 and 18 weeks of pregnancy until 12 weeks after delivery	HCQ group lowered prednisone dosage and improved pregnancy duration and Apgar scores compared to the placebo group.
Braga A, et al. ¹²	2021	215 pregnancies from 143 patients, 63.7% with HCQ	Not available	During gestation	HCQ reduced the risk of flare in SLE patients during pregnancy.
Leroux M, et al. ¹³	2015	118 SLE patients totally, HCQ group (n=41) and no HCQ group (n=77)	400 mg daily	Before pregnancy or during the first 8 weeks	The HCQ group has a lower rate of preterm birth (15.8% vs 44.2%) and IUGR (10.5% vs 28.6%).
Balevic SJ, et al. ¹⁴	2019	145 serum samples from 50 patients with RD, 56% of whom had SLE	400 mg per day commonly	Throughout pregnancy	Of patients with SLE, more pregnancies (83%) with average HCQ levels ≤100 ng/mL delivered prematurely than 21% with average levels >100 ng/mL.
Canti V, et al. ¹⁵	2021	74 pregnancies in 53 SLE patients, 45 pregnancies were treated with HCQ	300 mg/day	Throughout pregnancy	SLE patients with HCQ treatment reduced the IUGR rate (10% vs 32%) and showed significantly longer time to delivery (37.8 ± 1.72 vs 36.3 ± 4.11).
Abd Rahman R, et al. ¹⁶	2020	82 SLE pregnancies included 47 treatments with HCQ	Not available	Not available	Recurrent miscarriages (17.1% vs 0%, <i>P</i> =0.003), occurrence of hypertension (42.9% vs 6.4%, <i>P</i> = 0.01), gestational diabetes mellitus (14.3% vs 0%, <i>P</i> =0.01) and concurrent medical illness (42.9% vs 14.9%, <i>P</i> =0.005) were reduced in HCQ group.

For superscript numbers, please see REFERENCES.

CI: confidence interval; HCQ: hydroxychloroquine; IUGR: intrauterine growth retardation; OR: odds ratio; RD: rheumatoid disease; SLE: systemic lupus erythematosus; RD: rheumatoid disease

Table 2. Recommendations of guidelines for HCQ therapy in pregnant women with SLE.

Committee	Year	Recommendation for HCQ treatment in SLE patients with pregnancy	Grade
CHOPARD ¹⁷	2022	HCQ should be treated throughout pregnancy.	Weak
GLADEL ¹⁸	2018	HCQ plus LMWH plus LDA is advised for pregnant SLE women with antiphospholipid antibodies and recurrent pregnancy loss.	Moderate
BSR and BHPR ¹⁹	2016	HCQ should be treated and continued during pregnancy at a maximum of 400 mg/day.	LOE 1 ++, GOR A, SOA 100%
BSR ²⁰	2018	HCQ can be used at doses of up to 6.5 mg/kg/day, compatible with pregnancy and breastfeeding.	LOE 1 ++, GOR A
ACR ²¹	2020	All women with SLE should take HCQ during pregnancy if possible.	Strong
EULAR ²²	2019	HCQ is suggested for all patients with SLE, at a dose not exceeding 5 mg/kg/real BW.	1B/A 3B/C

For superscript numbers, please see REFERENCES.
ACR: American College of Rheumatology; BHPR: British Health Professionals in Rheumatology; BSR: British Society for Rheumatology; BW: body weight; CHOPARD: Chinese Research Committee of Pregnancy and Reproduction in Autoimmune Rheumatic Diseases; EULAR: European League Against Rheumatism; GLADEL: Grupo Latino Americano de Estudio del Lupus; GOR: grade of recommendation; HCQ: hydroxychloroquine; LDA: low-dose aspirin; LMWH: low molecular weight heparin; LOE: level of evidence; SLE: systemic lupus erythematosus; SOA: strength of agreement

alone or adding to therapeutic schemes for pregnant women with refractory APS or who experience recurrent complications,²⁹ with a safe dose of 200–400 mg.

Sjogren’s syndrome (SS)

SS occurs more predominantly in women than in men, with a female-to-male ratio of about 9:1. Women with SS are likely to experience more complicated pregnancies than healthy women.²⁹ Although the therapeutic benefit of HCQ in classic SS symptoms remain controversial, there is research illustrating that HCQ alleviates oral domain symptoms and several indicators like unstimulated salivary flow rate (uSFR), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and immunoglobulin M (IgM) as well as immunoglobulin A (IgA) in general patients. Regarding the research on pregnant patients, a retrospective study included 109 pregnant women as control group and 26 pregnancies with SS group showed HCQ were used in 15 patients (57.7%) and may also help ameliorate obstetric outcomes.³⁰ In 853 autoimmune pregnancies with 49 SS patients, HCQ therapy decreased preeclampsia (19.8% vs 8.91%, $P<0.001$), early-onset preeclampsia (7.78% vs 2.51%, $P=0.007$) and pregnancy loss (2.99% vs 0.56%, $P=0.036$) significantly. Forty-two (85.71%) of 49 SS patients had taken HCQ.³¹ On the contrary, Ballester C et al. found there was no premature delivery or low birth weight percentile child in primary SS pregnant patients with HCQ.³² However, the insufficient number of HCQ group ($n=6$) limited the evaluation of the possible beneficial effects of HCQ. Several

reports also indicated that there is no association between HCQ and a good pregnancy outcome in SS,^{33,34} but these findings need to be confirmed in larger sample size studies (Table 4). Furthermore, both EULAR and Sjogren’s Syndrome Foundation suggested that first-line therapy for SS should concentrate on symptom relief, with HCQ (200 mg/day) to treat musculoskeletal pain treatment.^{35,36} They also recommended assessing the benefits and risks for patients during pregnancy. BSR also advised the administration of HCQ (6 mg/kg) in SS, especially in patients with skin and joint lesions or fatigue symptoms. Besides, it was mentioned that HCQ might be continued throughout pregnancy and breastfeeding.³⁷

Rheumatoid arthritis (RA)

RA is a long-term inflammatory joint disorder with a variable progression. Historically, methotrexate (MTX), sulfasalazine, leflunomide, HCQ or chloroquine (CQ) are referred to as disease-modifying anti-rheumatic drugs (DMARDs), generally used in RA. Regrettably, although considerable reviews have established that HCQ is appropriate for pregnant patients with mild and moderate RA, we found few clinical studies on the effectiveness of HCQ treatment in pregnant patients with RA. However, the potential role of HCQ has been widely studied in general patients with RA. Combination of MTX with HCQ in RA treatment was more efficient than MTX alone.³⁸ According to the 2021 ACR guideline, HCQ is more appropriate than other DMARDs in the therapy of DMARDs-naïve patients with mild RA.³⁹ EULAR recommends HCQ

Table 3. Clinical studies on HCQ treatment in pregnant women with APS.

Author or committee	Year	No. of pregnancies	HCQ dosage	HCQ duration	Results and conclusion
Sciascia S, et al. ²⁴	2016	170 pregnancies in 96 women	400 mg (200 mg twice daily) or 200 mg (once daily)	At least 6 months prior to pregnancy and continued throughout pregnancy	HCQ group has a higher live birth rate (67% vs 57%, $P=0.05$), prolonged pregnancy (27.6 weeks vs 21.5 weeks, $P=0.03$) and lower occurrence of aPL-related pregnancy morbidity and complication (2% vs 10.9%, $P=0.05$).
Mekinian A, et al. ²⁵	2015	35 pregnancies from 30 APS patients	200–400 mg	80% started before pregnancy	HCQ decreased pregnancy losses from 81% to 19% and improved the rate of live born babies to 78% in patients with refractory obstetrical APS.
Gerde M, et al. ²⁶	2021	101 pregnancies of 87 refractory primary OAPS women	200 mg per day or 200 mg twice daily	At least 2 months before pregnancy (200 mg) or initiation of pregnancy, both throughout the entire pregnancy	The live birth rates were obviously higher in the group receiving with HCQ (97.1%, 67/69) with regard to the control group (62.5%, 20/32) ($P<0.001$). The occurrence of pregnancy complications was also reduced in the HCQ group (8.7% vs 37.5%, $P<0.001$).
Ruffatti A, et al. ²⁷	2018	194 pregnant PAPS patients	200–400 mg daily	112 patients (57.7%) before pregnancy and 82 (42.3%) during pregnancy	Treatment with HCQ markedly increased the live birth rate ($P=0.027$). A higher dosage (400 mg vs 200 mg, $P=0.036$) and treatment before pregnancy (before vs during pregnancy, $P=0.027$) contributed to a higher live birth rate.

For superscript numbers, please see REFERENCES.

aPL: antiphospholipid antibodies; APS: antiphospholipid syndrome; HCQ: hydroxychloroquine; OAPS: obstetric APS; PAPS: primary APS

to be considered only in a particular circumstance when the other DMARDs failed or with MTX and sulfasalazine.⁴⁰ Furthermore, the Asia Pacific League of Associations for Rheumatology notes HCQ can only be used in combination with other DMARDs in patients with RA, primarily considering its possible metabolic and cardiovascular benefits.⁴¹ Thus, reviews summarise and conclude that HCQ is beneficial for RA patients with a mild or moderate disease during pregnancy and suggest continuing treatment in these patients who were willing to conceive. Regarding the guideline recommendation for RA pregnant patients, recommendations for medication therapy in pregnancy just points out HCQ did not increase the occurrence of congenital malformations and can be used throughout pregnancy with rheumatic diseases.¹⁹ HCQ efficiency on pregnant women with RA should be further studied.

Potential use of HCQ in preeclampsia

Preeclampsia (PE) is an obstetric complication leading to high neonatal and maternal morbidity and mortality. Rheumatic diseases tend to increase the incidence of preeclampsia. Since HCQ is generally used for thrombosis prevention, anti-inflammation and anti-oxidation in rheumatic diseases, the researchers investigated whether HCQ directly plays a preventive role in preeclampsia, which has similar standard features and pathophysiology to SLE.^{8,42} In terms of molecule mechanism,

endothelial dysfunction is one of the most persuasive opinions on preeclampsia development. Researchers preliminarily speculate that HCQ may benefit PE by suppressing oxidative stress and inflammatory mediators like cytokines, chemokines and cell adhesion molecules (i.e. intercellular adhesion molecule 1 [ICAM-1], vascular cell adhesion molecule 1 [VCAM-1]), which could result in endothelial damage.⁴² Generally, HCQ restores NOX availability and disrupts vascular ROS overproduction induced by NADPH oxidase. HCQ also mitigated endothelial injury of PE by inhibiting the release of TNF- α and VCAM-1 as well as ICAM-1 to keep monocyte from adhering to the endothelium.⁴² Despite HCQ being the major medication in the treatment of pregnancy with SLE, no randomised controlled trials (RCTs) and observational studies have been conducted to report the efficiency of HCQ treatment in preeclampsia women without rheumatoid diseases. Previous clinical studies only focused on the treatment of HCQ in preeclampsia induced by rheumatoid disorders. Rector et al. indicated no statistically significant correlation between HCQ and preeclampsia in either nulliparous or multiparous lupus pregnancies.⁴³ Conversely, it reported that HCQ treatment in pregnant women with autoimmune diseases reduced the occurrence of preeclampsia.²⁴ A meta-analysis including 709 HCQ-treated pregnancies and 1055 pregnancies without HCQ showed that the additional use of HCQ apparently

Table 4. Clinical studies of HCQ therapy in pregnancy with SS.

Author or committee	Year	No. of pregnancies	HCQ dose	HCQ duration	Results and conclusion
Barros T, et al. ³⁰	2022	109 normal pregnant women and 26 SS pregnancies, 15 pregnancies with HCQ therapy	Not reported	Not reported	Treatment with HCQ might benefit the obstetric results in SS patients.
Ye S, et al. ³¹	2023	Among 853 pregnancies with autoimmune, 49 pregnancies with SS, of whom 42 treated with HCQ	≤400 mg/day	32 initiated before pregnancy, 5 from early pregnancy, 5 from mid or late pregnancy	HCQ treatment significantly reduced preeclampsia, early-onset preeclampsia and pregnancy loss in 853 pregnancies with autoimmune abnormalities, including 49 SS cases.
Ballester C, et al. ³²	2017	54 pregnancies in 19 women with pSS	At least 200 mg/day	Started before pregnancy and throughout the pregnancy	6 patients treated with HCQ (n=6) did not deliver prematurely or give birth to a child in the LBW percentile.
Fierro JJ, et al. ³³	2023	48 SLE and 21 pSS pregnancies with 70 fetuses (1 twin)	Not reported	Not reported	No significance of APO in patients with pSS between HCQ use and non-HCQ use.
Priori R, et al. ³⁴	2013	45 pregnancies in 36 women, 11% of which were treated with HCQ	Not reported	Not reported	No differences in pregnancy and fetal outcome no matter whether treated with medications, including HCQ.

For superscript numbers, please see REFERENCES.
APO: adverse pregnancy outcomes; HCQ: hydroxychloroquine; LBW: low birth weight; pSS: primary Sjogren’s syndrome;
SLE: systemic lupus erythematosus; SS: Sjogren’s syndrome

decreased the total risk of preeclampsia in pregnancies with SLE by 46%, but it had no effect on the incidence of preeclampsia for APS/aPLs patients.⁴⁴ In parallel with that conclusion, Liu et al. summarised that treatment with 200–400 mg of HCQ daily significantly lowered the incidence of preeclampsia in autoimmune disorders.⁹ Therefore, the clear efficiency of HCQ in preeclampsia induced by rheumatic diseases needs more evidence from further RCTs and large-scale prospective cohort studies. Next, more basic and clinical studies should examine the benefit of HCQ treatment in preeclampsia patients without rheumatic diseases.

Safety of HCQ therapy during pregnancy

Drug safety during pregnancy is a significant consideration for medical treatment. HCQ is an oral medication that is rapidly and completely absorbed from the upper intestinal tract.³ It is primarily metabolised into N-desethylhydroxychloroquine in the liver via cytochrome P450 enzymes.³ A large apparent volume of distribution leads to an elimination half-life of approximately 40 to 60 days.³ Since creatinine clearance is not associated with the response to HCQ bioavailability, dosage adjustment is not necessary in patients with

renal insufficiency. Notably, HCQ readily crosses the placenta with the ratio of fetal concentration to maternal concentration being 1.04.⁴⁵ Various adverse reactions of HCQ have been found, of which ocular, skin and cardiac toxicity represent the most potential, especially when long-term therapy and large doses are used.⁴⁵ A small number of investigations indicate that HCQ treatment during pregnancy may be associated with ocular damage in fetuses.^{46,47} This is debatable because normal newborns are likely to have malformations and these are just a few cases in the control group. A cohort study proposed the risk of malformations in first trimester pregnancy was slightly increased by HCQ, showing an adjusted relative risk (RR) of 1.26.⁴⁸ A clinical trial showed 5 of 45 (11%) infants exposed to 400 mg HCQ in utero had a prolonged corrected QT interval of more than 2 standard deviation (SD), without other symptoms.⁴⁹ Meanwhile, numerous clinical studies recently consider HCQ has no harmful effect on fetal outcomes (Table 5). In a retrospective study, 14 mothers who received HCQ treatment for an average of 7.2 months during their pregnancies at an average dose of 317 mg reported that their newborns’ visual acuity was normal with no

Table 5. Clinical studies on the safety of HCQ treatment during pregnancy.

Authors	Type of study	Year	HCQ duration	HCQ dosage	No. of pregnancies	Results and conclusion
Huybrechts KF, et al. ⁴⁸	Retrospective study	2021	During the first trimester versus no use	371 mg mean daily dose	2045 pregnancies exposed to HCQ and 3,198,589 pregnancies without HCQ exposure	A small increase in the risk of malformations associated with HCQ use in the first trimester, particularly with a daily HCQ dose ≥400 mg.
Friedman DM, et al. ⁴⁹	Clinical trial	2020	Throughout pregnancy	400 mg daily	45 infants exposed to HCQ during gestation	HCQ treatment during pregnancy is associated with a low incidence of infant QTc prolongation.
Klinger G, et al. ⁵⁰	Retrospective study	2001	7.2 months mean duration of HCQ exposure	317 mg average daily dose	14 HCQ-treated cases in 21 pregnancies	No ophthalmic abnormality was found in children exposed to HCQ in uterus.
Costedoat-Chalumeau N, et al. ⁵¹	Retrospective study	2003	At least 6 months prior to pregnancy and throughout gestation	200 mg twice daily or once daily	133 pregnancies treated with HCQ, 70 pregnancies without HCQ	Pregnancy outcomes were not statistically different between 2 groups.
Reynolds JA, et al. ⁵²	Retrospective study	2023	Prescribed during pregnancy	Not recorded	284 live births of 199 mothers, 149/284 (52.5%) exposed to HCQ	No obvious negative outcomes in children exposed to HCQ during pregnancy.
Chambers CD, et al. ²	Prospective study	2022	HCQ treatment in the first day of the last menstrual period to the end of pregnancy	324.8 mg average daily dose	837 pregnancies, of which 279 exposed to HCQ	HCQ exposure showed no abnormality in the rates of structural defects or other adverse outcomes. Risks did not differ at HCQ doses ≥400 mg/day.
Andersson NW, et al. ⁵³	Retrospective study	2021	Women with HCQ prescriptions from 14 days before conception	200 mg (IQR, 200–250)	1,240,875 pregnancies, of which 303 exposed to HCQ	Pregnancies treated with HCQ have no increased risk of major birth defects, preterm birth or SGA.
Bérard A, et al. ⁵⁴	Prospective study	2021	71.8 days on average	204.3 mg mean daily dose	233,748 pregnancies, including 105 HCQ-exposed cases	No data showed the increased risk of prematurity, LBW or MCM in HCQ-exposed pregnancy.
Leroux M, et al. ¹³	Retrospective study	2015	Before pregnancy or during the first 8 weeks	400 mg daily	118 SLE patients, containing HCQ group (n=41) and group without HCQ (n=77)	No malformation was found in fetuses exposed in utero to HCQ.
Diav-Citrin O, et al. ⁵⁵	Prospective study	2013	98.2% of patients were treated with HCQ at least in the first trimester of pregnancy	300 mg (IQR, 200–400)	455 pregnant women without HCQ exposure compared to 114 HCQ-exposed pregnancies	HCQ treatment in pregnancy is not a major malformation.
González R, et al. ⁵⁶	Clinical trials	2024	400 mg/day for 3 days and 200 mg/day for 11 days	400 mg/day and 200 mg/day	55 women in HCQ group and 60 women in control	No differences were in the occurrence of adverse pregnancy outcomes between 2 groups.

For superscript numbers, please see REFERENCES
HCQ: hydroxychloroquine; IQR: interquartile range; LBW: low birth weight; MCM: major congenital malformations; QTc: heart rate-corrected QT interval; SGA: small size for gestational age; SLE: systemic lupus erythematosus

ophthalmological abnormalities.⁵⁰ The conclusion was also confirmed by a study that included 90 women and 133 pregnancies treated with 200 mg HCQ per day (11 pregnancies) or twice daily (122 pregnancies).⁵¹ Reynolds et al. showed no significant differences in the incidence of congenital malformations or intrauterine growth restriction, regardless of whether children were exposed to HCQ in utero or not.⁵² Additionally, HCQ treatment did not increase the risk of spontaneous abortion or preterm delivery, birth defects and low birth weight, compared to the control group without HCQ.^{2,13,53,55} This is consistent with data from an RCT of 115 pregnant women with mild SARS-CoV-2 infection, which found no obvious differences in the occurrence of adverse pregnancy outcomes and newborns with health problems at birth between the HCQ group and the control.⁵⁶ A meta-analysis comprising 3948 immune-disordered pregnancies, of which 1617 patients were in the HCQ group and 2331 in the control group, revealed that there was no significant correlation between HCQ and adverse fetal outcomes and congenital malformation.⁸ Although the safety evidence of HCQ during pregnancy in clinical studies remains insufficient to evaluate teratogenicity, most researchers insist that the benefits of HCQ treatment in pregnant women could outweigh the potential risks in the clinic.⁵⁷ Furthermore, we discover the amount of HCQ in these articles, which showed no effect on fetal safety, varies approximately from 200 to 400 mg during pregnancy. Huybrechts et al. showed that a daily dose of ≥ 400 mg HCQ in the first-trimester had a higher risk of malformations than < 400 mg daily (RR 1.33 vs 0.95).⁴⁸ Therefore, the possibility of the HCQ side reactions occurring may be dose dependent. This is verified by a consensus from the Netherlands, which states that HCQ treatment at a dose of 200–400 mg/day during pregnancy and lactation may be safe for pregnant women.⁵⁸ EULAR also announced that the recommended dose of less than 5 mg/kg carries a low risk of toxicity in pregnant SLE patients.²²

CONCLUSION

Undoubtedly, HCQ is extensively used as a safe modulator in pregnant women with rheumatic diseases. Based on previous evidence, there is less risk of adverse fetal outcomes when treated with HCQ at a dose below 400 mg. However, there are insufficient prospective studies and no large-scale RCTs on the efficacy and safety of HCQ in rheumatic diseases. Currently, a multicentre, double-blind, prospective clinical trial called HIBISCUS is ongoing in order to investigate HCQ safety and whether additional treatment with HCQ improves the fetal outcomes in a population of

patients with primary APS.⁵⁹ HYPATIA, another international multicentre RCT, is also underway to explore the effectiveness of HCQ in improving pregnancy outcomes in patients with persistently positive aPL, as well as its safety.⁶⁰ With its low cost, HCQ might be an extremely valuable adjunct to the treatment of rheumatic diseases during pregnancy.

Ethics statement

Not applicable

Declaration

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Beyond BMI: The Janus-like effect of muscle versus fat on midlife women's health

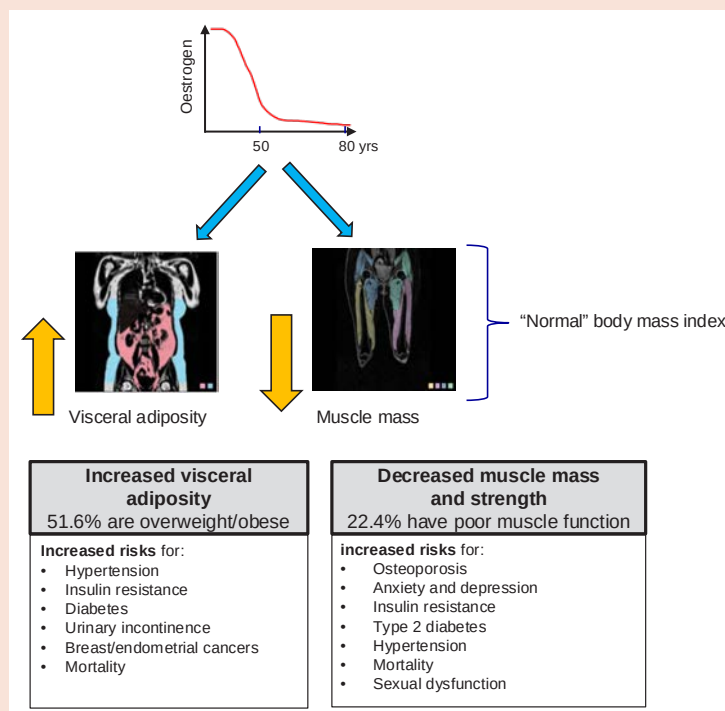
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Janus—the Roman goddess of natural cycles, change and transitions—is an appropriate symbol for the life-changing shift from the reproductive period to the post-menopausal stage of life. Since the average age of menopause is 50 years,¹ it is a universal life stage for long-living Singaporean women. The menopausal transition is associated with a profound decline in circulating oestrogen levels, resulting in the slowing of basal metabolism and marked changes in body composition.² On average, women gain approximately 2 to 3 kg during the menopause transition. Remarkably, many Singaporean women maintain relatively stable “healthy” BMI, even though deleterious changes in their body composition are occurring.² These changes in body composition involve 2 variables, both of which increase BMI. However, 1 variable

has positive, while the other has negative health effects. Muscle mass/strength—a positive factor that increases BMI—is necessary for cardiometabolic and skeletal health, activities of daily living and mobility.³ Lack of muscle mass, or sarcopenia, results in frailty and increased risk of death.³ On the other hand, abdominal (visceral) adiposity also increases BMI but is a strong negative factor for cardiometabolic health.²

This commentary considers the consequences of oestrogen decline to increase visceral adiposity and decrease muscle mass on cardiometabolic health and other important conditions important to midlife women. We argue that beyond BMI, it is appropriate to measure the Janus-like changes in visceral adiposity and muscle mass/strength as women face the menopause transition.

Fig. 1. Visceral adiposity and muscle mass at onset of menopause.



Abrupt drop in oestrogen around menopause (~50 years) causes increase in visceral adiposity (pink) and reduced muscle mass (coloured) as indicated by the MRI scans. Reduction in muscle mass/strength coupled with increase in visceral adiposity can result in apparently “normal” body mass index despite abnormal body composition and associated increased health risks.

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Menopause onset is associated with decreasing energy expenditure and fat oxidation leading to increasing abdominal (i.e. visceral) fat (Fig. 1). Asian women tend to transit from a pre-menopausal gynaecoid “pear” shape with fat around the hips, buttocks and thighs, to the post-menopausal “apple” shape with increasing fat deposition around the abdomen. Asian women appear to store more fat abdominally than Caucasian women of comparable BMI.⁴

Ovariectomy stops oestrogen production and is used as a model of menopause in laboratory animals to study how the loss of ovarian function causes fat mass accumulation. Ovariectomy is associated with increased body weight and abdominal adiposity, and oestrogen replacement reverses this effect.⁵ Oestrogen receptor knockout mice were shown to have increased fat mass, as well as adipocyte number and size.⁶ Brain-specific oestrogen receptor knockout mice have increased abdominal obesity, mediated through hyperphagia and hypometabolism, and induced by decreased heat production and decreased physical activity.⁷

The Study of Women’s Health Across the Nation (SWAN)—the most comprehensive study on menopause funded by the US National Institutes of Health—provided very compelling evidence that an accelerated gain in fat mass and loss of muscle mass were related to the menopause transition rather than ageing.⁸ Although an increase in fat mass and a decline in fat-free mass were observed during pre-menopause, these changes accelerated during peri-menopause before stabilising in the postmenopausal years.⁹ This perimenopausal increase in fat mass was attributed to increased abdominal fat.² Several large randomised clinical trials on oestrogen replacement therapy indicate that women who received oestrogens gained less body weight and had smaller increases in waist girth than women randomised to placebo.^{10,11}

Collectively, these studies suggest that the loss of ovarian oestrogen promotes abdominal fat accumulation and a decline in energy expenditure, leading to markedly poorer cardiometabolic health, an effect that is more marked in Asian women. Oestrogen replacement tends to slow down this trend towards abdominal adiposity.

Emerging evidence indicate that oestrogen has important functions related to muscle mass and strength (Fig. 1). In animal studies, ovariectomy results in a 10% decrease in strength that corresponded with an 18% decrease in fibre cross-sectional area¹² and, in the absence of oestrogen, muscle is more prone to injury and regrowth is limited.¹³

In human studies, postmenopausal women experience a rapid decrease in muscle mass and

strength and are more vulnerable to age-related frailty.¹⁴ Muscle area and grip strength were greater in oestrogen replacement therapy users than in non-users, and oestrogen replacement therapy can improve muscle protein synthesis following resistance training.¹³ Although less extensive than for visceral adiposity, there is increasing evidence that oestrogen decline at menopause decreases muscle mass and physical performance, and oestrogen replacement therapy can slow down this process.¹⁵

One of the main challenges in assessing disease risk for postmenopausal women is the over-reliance on BMI as an indicator of health. BMI encompasses both fat and muscle, which does not sufficiently account for shifts in body composition during menopausal transition. For example, women from the SWAN cohort had a simultaneous occurrence of an accelerated increase in fat mass and reduction in lean mass, leading to a 3.6% cumulative rise in proportion fat mass and 1.9% cumulative decline in proportion of lean mass over the course of the menopause transition.⁹ This phenomenon presents a Janus-like effect wherein many women undergoing menopausal transition may experience a concurrent loss of muscle mass and gain in excessive levels of visceral fat, while retaining a “normal” BMI. This gives rise to a unique scenario—the Y-Y paradox in which 2 individuals possessing similar BMI can have different adiposity levels.¹⁶

Studies from the Singapore Integrated Women’s Health Program (IWHP) cohort¹⁷ indicate that visceral adiposity and poor physical performance were independent determinants of insulin resistance.^{18,19} Muscle strength was also a risk factor of diabetes, independent of visceral adiposity.²⁰ The risk of developing type 2 diabetes was significantly reduced in postmenopausal women who used oestrogen therapy in several randomised clinical trials, including the Women’s Health Initiative and Heart and Estrogen/progestin Replacement Study from the US.² Although those studies were not unanimous, the evidence indicate a plausible link between visceral adiposity during the menopause transition to increased risk of insulin resistance and risk of type 2 diabetes.

Vascular function appears to be preserved up until the menopause transition, after which it progressively deteriorates, possibly due to a shift in redox balance and the loss of the antioxidant and anti-inflammatory effects of oestradiol.²¹ Postmenopausal women experience an increase risk in cardiovascular disease (CVD), that is primarily thought to be due to ovarian failure and the loss of oestrogen that occurs across the menopause transition.² The Framingham Heart Study found that visceral adiposity, compared to BMI, was

more strongly associated with incident diabetes, hypertension, low HDL and CVD events in women, including CVD death.²² Studies from the Singapore IWHP cohort indicate that visceral adiposity increased systolic blood pressure by 9.8 mmHg (95% confidence interval [CI] 6.2–13.4).²³ In addition, reduced physical performance was independently associated with increased risk for hypertension (adjusted odds ratio 2.83, 95% CI 1.46–5.47), even after adjustment for visceral obesity.²⁴

During menopause, obesity was reported as a protective factor against osteoporosis, due to the mechanical effect of body weight on bone.²⁵ However, the true protective effect on bone density comes from an increase in muscle, not fat.^{25,26} While visceral adipose tissue (VAT), not BMI, was associated with a greater fracture risk in men,²⁷ the effects of VAT and BMI on fracture risk and bone microarchitecture were similar in women.^{27,28} We found that handgrip strength reduced the likelihood of spinal osteoporosis by 50% in Singaporean women,²⁹ supporting findings that resistance training increases bone mineral density in other studies.³⁰

Sarcopenic obesity, defined using visceral fat attenuation, was linked to poorer survival rates, regardless of BMI.³¹ In the UK Biobank, women in the top VAT quintile had the highest hazard ratio for all-cause mortality.³² These findings highlight mechanisms of fat inflammation, sex-related body fat distribution and hormonal differences. In addition to a low muscle mass, poor handgrip strength was also associated with mortality prediction.³³ although some studies argue that muscle strength is a better predictor.³⁴

Over the past decade, the IWHP cohort has inspired publications giving unique insights on the Janus-like opposing effects of adiposity and muscle strength. Visceral adiposity was independently associated with increased risks for hypertension,²⁴ insulin resistance,¹⁸ incident diabetes¹⁹ and mortality²² (Fig. 1). Besides visceral adiposity, our studies highlight the important contribution of poor muscle function to midlife women's health. Weak hand grip strength, present in 22.1% of Singaporean women, was independently associated with increased risks for osteoporosis,²⁹ hypertension, insulin resistance,¹⁸ type 2 diabetes,¹⁹ and mortality.³³ The 2023 Singapore National Population Health Survey found that among midlife women (aged 50–59 years), only 26.4% reported sufficient muscle strengthening activities. The population attributable risk of sarcopenia for mortality is 5.2% in the US National Health and Nutrition Examination Survey.³⁵ The total costs of hospitalisation among those with sarcopenia was USD19.12 billion, with total costs higher in women than men.³⁶ The evidence presented above strongly supports

the current Singapore Ministry of Health recommendation to improve physical performance as outlined in the Singapore Clinical Practice Guidelines for Sarcopenia.³⁷

Women with a higher waist circumference (≥ 95 cm) have 22% increased future healthcare costs compared to those with a normal waistline.³⁸ Visceral adiposity contributed to 50.4% of type 2 diabetes cases in the Shanghai Men's and Women's Health Studies.³⁹ Menopausal hormone therapy for 15 years among younger women (about 50 years old) was associated with a higher gain in quality-adjusted life years (1.49 versus 0.11) compared to older women (around 65 years old),⁴⁰ suggesting it might be more cost-effective to start hormone therapy at a younger age.

In summary, beyond BMI and reduction of visceral obesity, exercises to improve physical performance and muscle strength and menopausal hormone therapy have emerged as key lifestyle factors that would increase healthy lifespan in midlife Singaporean women.²⁰ Targeted implementation programmes are needed to improve muscle strength especially in Chinese women with Chinese language preference, Indians and Malays.⁴¹

Ethics statement

This study was approved by the National Healthcare Group's Domain Specific Review Board (Reference numbers: 2014/00356 and 2020/00201).

Declaration

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Keywords: *menopausal symptoms, muscle function, obstetrics and gynaecology, visceral adipose tissue, women's health*

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Digital health's impact on the patient-doctor relationship in a primary healthcare setting: A qualitative study

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Dear Editor,

The integration of digital health is reshaping the patient-doctor relationship in primary care by challenging its core principles of trust, knowledge, regards, empathy and care continuity. While digital health improves access and empowers patients, it also destabilises the delicate nature of this relationship. Our qualitative study—conducted in 6 public primary care clinics in central and north Singapore on 21 doctor and patient participants over 15 months across 2023 and 2024—explores these paradoxical effects of digital health and offers insights into how we can mitigate them. Our findings are summarised into 4 major themes.

Digital health heralds a paradigm shift in the patient-doctor dynamic. It has empowered patients with tools for self-monitoring and increased their self-efficacy. Through wearable devices, shared medical records and mobile health application portals, patients now have greater visibility and timely feedback on their health status. This empowerment has transitioned the doctor's role from "a sage on the stage"—a sole authority dispensing knowledge—to a "guide on a side". Now, doctors often help patients curate information to facilitate informed decision-making. Doctors who are slow to embrace the insidious shift may feel challenged by the new power acquired by patients.

With easy access to online health resources, patients frequently approach consultations armed with unverified information, compelling doctors to address misinformation while preserving professional credibility. One doctor from our study remarked, "There's a lot of information out there, but if the patient has no insight on the right information, it can lead to more harm." This phenomenon reflects tensions introduced by digital health into the patient-doctor relationship, eroding trust in doctors. The onus is now on the doctor to keep up with "Dr Google" and adapt generic online information into personalised advice for patients.

Remote consultation via video consultation poses another threat to relational trust. Video consultation

has enhanced accessibility to care. These tools have enabled timely care for minor ailments and psychological support, bringing convenience to patients, and increasing healthcare reach and care continuation for healthcare providers. Unfortunately, such convenience is a double-edged sword that has led to potential abuse of healthcare encounter, such as the unwarranted issuance of medical certificates.

The delicate patient-doctor relationship has always been threatened by external forces such as healthcare financing, organisation efficiency and data-centric health informatics design. Despite these challenges, patients and doctors have intuitively known what is most important in the healthcare system—that of a strong patient-doctor relationship, which is based upon trust, knowledge, regard and empathy. Digital health, though empowering, paradoxically endangers the humanistic qualities essential in care. A patient reflected, "Sometimes, the doctor seems more focused on the screen than on me, and that makes me feel like I'm not really being listened to." Therefore, digital health's promise must be carefully balanced with strategies that sustain empathetic engagement.

Finally, our study uncovered critical insights regarding the digital divide. Both doctors and patients emphasised the need for equity in digital health, advocating inclusivity in adoption. One patient lamented, "For me, it's easy because I understand English, but my parents [...] won't understand the apps." Doctors echoed these concerns, emphasising the need for user-centric designs and tailored digital literacy programmes to ensure inclusivity. This disparity underscores the ethical imperative to bridge digital divide, and alienates those unable to engage with emerging technology, thereby exacerbating health inequities.

Based on these findings, our study team presents the following implications to harness the promises of digital health while safeguarding the core tenets of patient-doctor relationship:

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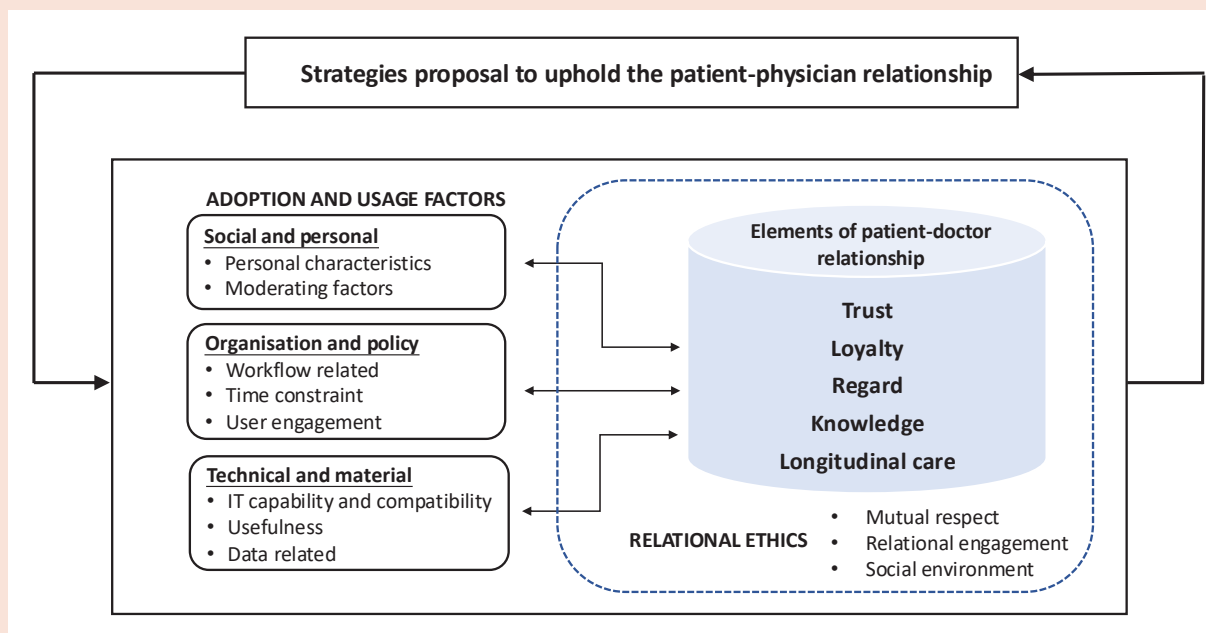
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Fig. 1. Strategies to uphold patient-doctor relationship.



Awareness in medical professional to maintain digital competency. Medical professionals are challenged by open-sourced medical information, accelerated use of digital health tools such as wearables, remote monitoring and AI-assisted technologies. While these tools augment doctors' capability, they have inherent limitations when used in different clinical contexts. Medical professionals must maintain digital competency to remain effective when facing a tech-savvy patient. Proficiency is critical for delivering quality care and maintaining patient trust. Resources should also be prioritised towards building healthcare workforce capability before large-scale digital health implementation.

Developing human-centric digital environment. Digital health applications complement, not replace, doctors' humanistic skills such as empathy, moral judgement and clinical reasoning. Doctors should be mindful of the potential for digital tools to depersonalise care and balance technological integration with genuine patient engagement. By providing doctors with a user-centric digital environment, allowing them to navigate seamlessly between the digital and lived space, and refocusing their attention to authentic connections with patients, a healthy patient-doctor relationship can be upheld.

Addressing the digital divide as a social determinant of health. Closing the digital literacy gap requires more than user-friendly tools. System-

wide digital inclusion programmes should support marginalised groups. Healthcare providers may consider introducing digital literacy as part of patient education, ensuring that patients are equipped to use these tools effectively. This may involve collaborating with community partners to tailor digital health education to the needs of older adults; or incorporating it into the care coaching model for patients. The design of universally accessible tools, such as using voice command or audio enhancements, can also help to mitigate disparities among older adults. Such initiatives are essential to uphold healthcare equity in the digital age, ensuring all patients benefit meaningfully from digital health. Without a sociopolitical commitment to inclusivity, digital health risks reinforcing health inequities for vulnerable populations.

Our findings highlighted both the positive and negative impact of digital health within Singapore's primary care ecosystem, illustrating how it has improved access to healthcare and accelerated patient empowerment while simultaneously destabilising patient-doctor relationship. Future research should focus on refining digital health tools to be equitable, relational and adaptable to diverse patient needs, ensuring these tools serve as enablers rather than disruptors of human-centred care. In the evolving landscape of digital healthcare, the integrity of the patient-doctor relationship must remain paramount, fortified by empathy, inclusivity and a commitment to enhance human potential.

Ethics statement

Ethics approval was obtained from National Healthcare Group Domain Specific Review Board (2021/01036), and the study was performed in accordance with the relevant guidelines and regulations laid by it. We used the Consolidated Criteria for Reporting Qualitative Research (COREQ) as our reporting framework. Written informed consent followed by sociodemographic information was obtained physically from the participants before commencing the interviews over Zoom calls. All participants were reimbursed with grocery store vouchers of SGD20 (USD15.50) as token of appreciation. There are individual quotes from qualitative interviews, but no personally identifiable information is designated to each quote.

Declaration

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Keywords: digital health, family medicine, health equity, implementation framework, longitudinal care, patient-doctor relationship, perceptions, primary care, public health, qualitative study

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Navigating the risks of contrast extravasation in CT scans: A 3-year study of 26,544 automated power injector cases

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Dear Editor,

We present findings from our large-scale retrospective study on contrast media extravasation (CME) in computed tomography (CT) examinations. Over 3 years, we analysed 26,544 adult CT examinations with intravenous contrast media administered via a power injector to determine CME incidence and evaluate associated risk factors.

CME is a recognised complication of contrast-enhanced CT, potentially leading to severe outcomes in rare cases. Most instances result in mild, self-limiting symptoms like swelling, erythema and pruritus. However, severe outcomes, including compartment syndrome, extensive skin ulceration and tissue necrosis have been documented, occasionally necessitating surgical intervention.¹

Our study revealed an overall CME incidence of 0.11% (28/26,544), consistent with previously reported ranges.² The majority were mild CME (89.3%), while 3 cases had moderate CME that presented with blistering, altered sensation and severe pain. None had severe CME. This low rate of approximately 1 in 915 patients underscores the relative safety of contrast-enhanced imaging procedures while highlighting the importance of identifying and mitigating risk factors.

Multivariate analysis identified several independent CME risk predictors: injection rate >3 mL/s (odds ratio [OR] 2.8, 95% confidence interval [CI] 1.9–4.1), age >50 years (OR 2.3, 95% CI 1.6–3.3), female sex (OR 1.9, 95% CI 1.3–2.7) and lower limb injection sites (OR 3.5, 95% CI 2.1–5.8).

Higher injection rates (>3 mL/s) were associated with increased CME risk (0.19%) compared to lower rates (≤3 mL/s, 0.06–0.07%; $P<0.001$). This aligns with previous research suggesting a positive relationship between higher injection rates and CME risk.³ However, the absolute risk remains low even at higher rates, with <0.2% incidence across all categories.

We observed that injection rates below 3 mL/s offered no significant advantage over injection rate at 3 mL/s in reducing CME risk (0.07% versus [vs] 0.06%, ($P>0.05$) (Table 1). This is in line with other studies that found no significant advantage in CME rates at lower injection speeds.^{4,5} Radiologists can confidently employ a 3 mL/s injection rate for routine CT examinations, achieving optimal image quality without elevating extravasation risk.

Age and sex emerged as significant factors. Patients older than 50 years showed higher CME incidence (0.13% vs 0.08%, $P=0.02$), as did female patients (0.15% vs 0.07%, $P=0.01$). Women had approximately 2.14 times higher CME risk than men. These findings are consistent with recent studies and may be attributed to vascular fragility and venous access challenges.⁶

CME incidence varied based on intravenous access site. Lower limb cannulation sites had higher CME rates than upper limb sites (0.25% vs 0.10%, $P=0.03$). Lower extremities present higher CME risks due to difficult visualisation, patient movement and reduced blood flow. Obesity and peripheral vascular disease can complicate femoral vein access. Foot veins, being smaller and more fragile, are susceptible to rupture. The limited soft tissue in the foot offers less absorption capacity for extravasated contrast. Upper extremity veins, particularly in the antecubital fossa, are preferred due to their larger size, better stability, lower venous pressure and easier monitoring—these characteristics reduce vein perforation and extravasation risk while allowing for more secure placement.

Overall, injection sites in the lower limbs and small distal veins are less optimal.⁷ No CME cases were reported in central venous access procedures, which agrees with existing literature and suggests that contrast injection via central venous catheters can be performed safely for CECT when using a strict protocol.⁸

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Table 1. Demographics, study variables and incidence of contrast media extravasation (CME) (n=26,544).

	Incidence of CME no. (%)
Injection rate (n)	
<3 mL/s (12,329)	9 (0.07)
3 mL/s (7701) ^a	5 (0.06)
>3–5 mL/s (6270)	12 (0.19)
Unspecific (244)	2 (0.01)
Age group (n)	
≤50 years (8532)	4 (0.05)
>50 years (17,984)	24 (0.13)
≤60 years (13,776)	11 (0.08)
>60 years (12,740)	17 (0.13)
Sex (n)	
Male (14,826)	10 (0.07)
Female (11,690)	18 (0.15)
Injection site (n)	
Wrist and hand (8956)	9 (0.10)
Cubital fossa (7768)	14 (0.18)
Forearm (1902)	3 (0.16)
Groin (29)	1 (3.45)
Foot (28)	1 (3.57)
Central venous line (251)	0 (0)
Unspecified (7610)	0 (0)
Cannula gauge (n)	
14G (2)	0 (0)
16G (92)	1 (1.09)
18G (1869)	7 (0.37)
20G (6086)	15 (0.25)
22G (1462)	4 (0.27)
CVP line, PICC (303)	0 (0)
Unspecified (16,730)	1 (0)

CVP: central venous catheter; PICC: peripherally inserted central catheter

^a Default injection rate for routine scans.

While our study suggests that gauge size may influence CME risk (Table 1), other clinical factors and usage frequency are also important considera-

tions. A comprehensive assessment of patient characteristics is essential, rather than strictly following the “larger gauge size is better” approach.

Our study highlighted the importance of preventive measures. Extravasation during pre-injection saline flush, followed by re-insertion of cannulas, successfully prevented CME in 26 examinations. This underscores the value of careful vascular access assessment and saline test injections before contrast media administration.

Qualitative analysis of procedural notes revealed factors commonly associated with CME cases: limited or difficult IV access (53.6%), multiple venipunctures on the same limb (17.9%) and small peripheral veins (35.7%). The overall low CME incidence (0.11%) may be attributed to a well-established protocol for checking cannulas before contrast injection.

These findings have important clinical implications. While higher injection rates may be necessary for optimal image quality, particularly in CT angiography, they should be used judiciously, especially in high-risk populations. Identifying risk factors such as advanced age, female sex and lower limb injection sites can guide clinicians in taking extra precautions with susceptible patients.

Patient education should address these different risk factors, emphasising the slightly elevated risk for certain groups while noting the low absolute risk. Enhanced monitoring protocols during and after contrast media procedures may benefit high-risk patients.

The study's limitations include its retrospective, single-centre nature, which potentially limits generalisability and applicability to different patient populations and contrast administration protocols. Reliance on electronic medical records may have led to underreporting of minor CME cases. Future research should focus on prospective, multicentre studies to validate these findings. Interventional studies testing the efficacy of preventive measures, such as pre-injection saline flush protocols or ultrasound-guided IV placement would be valuable. Investigating the long-term outcomes of CME patients could inform follow-up care protocols.

In conclusion, our study provides valuable insights into CME risk factors and preventive strategies in CT examinations. Identifying high-risk populations and implementing tailored preventive approaches can enhance contrast-enhanced imaging procedures' safety while maintaining optimal diagnostic quality. The findings underscore the need for standardised cannula assessment and contrast administration protocols, particularly in susceptible patients. While higher injection rates may be necessary

for diagnostic quality, appropriate precautionary measures should be taken to reduce CME risk in high-risk populations.

Ethics statement

Waiver for ethics approval was granted by the National Healthcare Group Domain Specific Review Board following retrospective nature of study and use of de-identified data (DSRB Reference number: 2016/01381).

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.

Keywords: *computed tomography, contrast media extravasation, injection rate, power injector, risk factors*

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Infected ovarian endometrioma: Case series and management outcomes

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Dear Editor,

Infected endometrioma, which is the superimposed infection and abscess formation of ovarian endometrioma, is increasingly understood to be a distinct clinical entity from tubo-ovarian abscess (TOA). The pathophysiology of infected endometriosis has been postulated to be a result of endometriotic fluid acting as a culture medium for pathogens, weakened cyst walls and immune dysregulation.¹ Multiple routes of spread have been identified including haematogenous, lymphatic, gastrointestinal translocation or by ascending vaginal route.² Although the true prevalence of endometriosis is unknown, the burden in Asian populations is likely to be high, especially due to delayed diagnosis.³ However, the current paucity of literature and clinical guidelines on infected endometriosis hampers consensus on its optimal management. We present a series of 10 cases of infected endometrioma with prospectively recruited patients who were treated at the National University Hospital in Singapore from January to October 2023, to provide insights on the identification and treatment of infected endometriosis. Ethical approval from the National Healthcare Group Domain Specific Review Board (Reference: 2023/00017) and patients' written consent were obtained.

The demographic and clinical information for the 10 patients is summarised in Table 1. The patients had a median age of 40 years and 50% were nulliparous. The clinical history of all patients was atypical for TOA; none were immunosuppressed, obese, reported prior sexually transmitted infections (STI) or had preceding pelvic procedures. Interestingly, 4/10 of cases had no prior diagnosis of endometriosis.

The clinical diagnosis of infected endometriosis was made on the basis of abdominal pain, sepsis, raised inflammatory markers, characteristic

ultrasound findings of low-echo ovarian cysts. All patients were admitted and commenced on empirical intravenous broad-spectrum antibiotics based on existing TOA guidelines,⁴ commonly ceftriaxone and metronidazole. Doxycycline cover was included until vaginal swabs for *Chlamydia trachomatis* were negative. Prior to antibiotics, routine STI screening and blood cultures were obtained—the former yielded only 1 positive result for *Trichomonas vaginalis* and the latter were all negative for all causative organisms. Once clinical response was achieved, antibiotics were converted to an oral course for a further 2 weeks. Two patients failed the trial of antibiotics and required drainage of the endometrioma for source control—one transabdominally and the other transvaginally; fluid cultures from drainage were positive for *Haemophilus influenzae* and *Peptoniphilus* species, respectively. On discharge, 9/10 patients were given hormonal suppression for endometriosis and 8/10 underwent definitive surgery with cystectomy or pelvic clearance at an interval of 3–17 months. All surgical candidates had evidence of deep infiltrating endometriosis (DIE), confirmed on histopathology. No recurrences were observed in the 1 year post-surgery.

This case series highlights the unique aspects of managing infected endometriosis. While the presenting symptoms may be similar to TOA, a detailed history may unveil dysmenorrhoea and infertility. Our patient profile was notably older (median 40 years), nulliparous and without typical risk factors for TOA like obesity, immunosuppression and barring 1 case, concomitant STI. Prior series have described iatrogenic inoculation during pelvic surgery² or oocyte retrieval,⁵ but this was not observed in our patients. Ultrasound imaging plays a crucial role in differentiating the 2 conditions. Infected endometrioma is identified by thick smooth walls, low-echo contents and lack

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Table 1. Clinical summary of cases admitted for infected endometrioma at the National University Hospital, Singapore from January to October 2023.

Age, years	Parity	Laterality and size of endometrioma (cm)	Causative organism	Antibiotic therapy	Surgical drainage	Hormonal suppression	Definitive surgery
49	2	Right: 7.6	None isolated	Ceftriaxone, metronidazole, doxycycline	NA	GnRH agonist	THBSO
49	3	Right: 8.7, Left: 3.6	<i>Trichomonas</i>	Ceftriaxone, metronidazole, doxycycline	NA	Dienogest	THBSO
36	VI	Left: 4.5	None isolated	Amoxicillin clavulanic acid	NA	Dienogest	Defaulted
34	2	Right: 5.8, Left: 6.0	None isolated	Ceftriaxone, metronidazole, doxycycline	NA	Dienogest	Cystectomy
46	0	Left: 22.0	<i>Haemophilus Influenza</i>	Piperacillin tazobactam	Percutaneous radiologically-guided	GnRH agonist	THBSO
29	0	Right: 7.6, Left: 2.7	<i>Peptoniphilus sp.</i>	Ceftriaxone, metronidazole	Transvaginal drainage	GnRH agonist	Cystectomy
42	0	Right: 4.8, Left: 9.8	None isolated	Ceftriaxone, metronidazole, doxycycline	NA	Depot medroxyprogesterone acetate	Cystectomy
37	1	Right: 14.6	None isolated	Ceftriaxone, metronidazole	NA	Dienogest	Cystectomy
31	0	Right: 6.0, Left: 6.0	None isolated	Ceftriaxone, metronidazole, doxycycline	NA	GnRH agonist	Cystectomy
51	4	Right: 3.8	None isolated	Ceftriaxone, metronidazole, doxycycline	NA	NA	Declined

GnRH: gonadotrophin-releasing hormone; NA: not applicable; THBSO: total hysterectomy, bilateral salpingo-oophorectomy; VI: virgo intacta bilateral salpingo-oophorectomy

of mobility in the posterior cul-de-sac.³ In contrast, TOA appears as a complex adnexal mass with thickened irregular walls and elongated dilated mass suggestive of pyosalpinx.⁴ Computed tomography provides little additional benefit and should be done only to exclude other intra-abdominal pathology. Colonic or vaginal flora are thought to be implicated in infected endometriosis. We found this to be consistent in our series; the 2 positive cultures identified *Peptoniphilus*, a known vaginal and gut commensal,⁶ and *Haemophilus influenzae*, a commensal of the upper respiratory tract which may cause endometritis.⁷ Only 1 patient tested positive for an STI, *Trichomonas vaginalis*. We propose that empirical antibiotics should be broad-spectrum with anaerobic coverage, and despite the low frequency of STI in our series, coverage for common STIs should be included until swabs return negative.

In patients who fail to respond to antibiotics, surgery for source control is required.⁴ The objective of surgery during acute infection differs from definitive treatment once the flare is over. During active infection, the aim is for drainage of the abscess to treat underlying sepsis, and for cultures to direct antibiotic therapy. Minimally invasive approaches, such as radiologically-guided or laparoscopic drainage, have been described with good outcomes.⁸ The location of the endometrioma should inform a transvaginal or transabdominal approach.

Once infection has been resolved, the underlying endometriosis must be treated. A key difference in management is the introduction of hormonal suppression to down-regulate oestrogen-mediated endometriosis⁹ and complement antibiotic therapy. Hormonal suppression treats symptoms of DIE, reduces risks of recurrence and limits progression

of endometriosis. At our hospital, we have effectively used progestogens (dienogest and depot medroxyprogesterone acetate) or gonadotrophin-releasing hormone agonist. The choice of suppression was at the discretion of the treating clinician.

In patients with infected endometriomas, it is uncertain whether long-term suppression will be sufficient to prevent recurrent infections, or whether surgical clearance should be routinely offered. Extrapolation from data on TOA suggests that the risk of recurrence is significant. Without definitive treatment, patients will remain symptomatic and at risk of recurrence causing further morbidity. We propose definitive surgical treatment to excise all endometriotic tissue should be deferred for at least 6 weeks after an acute flare, as friable inflamed tissues increase risk of complications.⁴ Extent of surgery should be guided by fertility intent and age, for example cystectomy in pre-menopausal, or oophorectomy in peri-menopausal women, along with excision of all endometriotic nodules. Our findings of histologically-confirmed DIE in all our surgical candidates corroborate with findings from Chen et al., in that infected endometriomas were associated with advanced endometriosis.¹⁰

In summary, this case series outlines the acute management and bridge to long-term treatment of infected endometriomas. A 2-pronged treatment approach is required, first to control sepsis with antibiotics and source control, and second to treat the underlying disease with hormonal suppression and eventual excisional surgery. There is a need for more prospective multicentre studies to develop consensus guidelines in the Asian context on the optimal management of this condition.

Ethics statement

Ethical approval from the National Healthcare Group Domain Specific Review Board (Reference:

2023/00017) and patients' written consent were obtained.

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.

Keywords: *endometriosis, infectious diseases, minimally invasive surgery, obstetrics and gynaecology, ovarian endometrioma, pelvic abscess*

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Navigating health challenges: Singapore's National University Health System's approach to child and family well-being

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Dear Editor,

Singapore's progressive commitment to addressing child and family well-being is anchored in its forward-thinking public health agenda. Recognising that long-term population health outcomes are shaped by early-life interventions, Singapore has directed increasing attention towards addressing complex health challenges that emerge during childhood and across the family unit. These challenges are compounded by factors such as rapid urbanisation and rising cost of living, technological shifts and societal transitions that have exacerbated sedentary behaviours. With decreasing total fertility and birth rates, it is of utmost importance to realise each child's maximum potential as early as possible, beginning from preconception.

In response to these multifaceted challenges, Singapore's Ministry of Health developed the Child and Maternal Health and Well-being Strategy and Action Plan (2021), which takes a holistic, life-course approach that highlights the importance of early intervention, preventive care and inter-sectoral collaboration as cornerstones of improving health outcomes for families and children from preconception to adolescence.¹ It is critical to enhance the health, safety and development of children and families through integrated, community-based programmes that prioritise early detection, prevention and sustained health interventions across the lifespan.

Key health challenges

Childhood obesity. There is a worrying increase in the proportion of overweight students aged 6–18 years. In 2021, 16% of school-going youths were classified as overweight (body mass index-for-age ≥ 90 th percentile), a rise from 13% in 2017. A significant spike occurred between 2020 and 2021, likely due to the COVID-19 pandemic, which severely limited opportunities for physical activities in schools.²

This situation mirrors a global trend of rising childhood obesity. This poses significant risks

to long-term health, with conditions like type 2 diabetes, cardiovascular diseases and metabolic syndrome that may manifest in adulthood. Therefore, addressing childhood obesity in Singapore requires comprehensive community-based strategies that prioritise physical activity, promote healthy eating, and reduce sedentary behaviours from a young age.³

Screen time. Excessive screen time has been linked to a variety of negative outcomes, including poor sleep quality, obesity and developmental delays in learning and behaviour.^{4,7} Studies conducted in Singapore have revealed concerning trends regarding children's screen time. With the increasing availability of digital devices, children at a mean age of 13.8 months are engaging in passive screen time daily.^{6,7} Screen time tends to increase as children grow older, contributing to sedentary behaviours that undermine their physical and cognitive development. Research has shown that children with developmental disorders spend more time on screens compared to their peers, which further exacerbates their challenges.⁸

Global studies, such as one by Madigan et al., found that higher screen time at 24 and 36 months is associated with poorer developmental screening test performance at 36 and 60 months.⁹ These findings highlight the importance of reducing screen time and promoting healthier activities, such as interactive play, outdoor activities and face-to-face interactions.

Reducing screen time among young children requires a multi-pronged approach. This includes educating parents about the risks of excessive screen time, providing alternative engagement strategies for children, and working with schools and community organisations to offer more screen-free activities. In a world where digital devices are becoming increasingly integrated into daily life, regulating screen use is crucial for safeguarding the cognitive and social development of children.

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Table 1. Theory of change based on workforce needs assessment at the National University Health System in Singapore.

Domain	Gaps identified	Processes	Outputs	Outcomes
Fragmentation	- System fragmentation - Duplication of efforts - Drop-out rates when referred on - Short-term funding	- Pathway mapping - Seek long-term funding	- Improved access to services in the community and tertiary hospital - Long-term funding for the division	Improved integration of care systems between primary and tertiary care, and health and social systems with health system re-design
Skills-mix/training	- Clinical-focused model - Lack of care navigator roles - Drip effect with repeated drilling of the same message - Lack of motivational interviewing skills	- Skill-mix building teams, recruit non-clinical roles for patient engagement - Provide motivational interviewing skills training for staff - Ensure every contact matters with checklists in place to screen for conditions, i.e. child safety, screen time, sleep, etc.	- Increase hiring of employees in non-clinical roles for patient engagement - Increase number of staff with motivational interviewing skills - Increase detection of previously undiagnosed issues with sleep and screen time with appropriate referrals to relevant partners	- Increased stakeholder engagement through establishment of partnerships with Singapore's healthcare clusters - Improved co-creation and co-production with community partners to enable successful establishment of ground-up and top-down initiatives
Community engagement	- Lack of community engagement - Non-compliance with programmes - Reliance on parents to use literature - Cultural/generational influences instead of evidence-based information	- Carry out focused group discussions to obtain insights into target populations - Recruit community champions - Develop peer support models	- Increase in programmes with co-production and co-creation of initiatives with the community - Increase in participation rate in programmes from the community - Increase in peer support networks, i.e. in breastfeeding, parent support groups	
Health equity	- Relies on parents attending appointments or polyclinics - Parental compliance low if from households that are focused on meeting basic needs. Drop-out rates when referred on	- Collaborate with programmes working with these families focused on meeting basic needs - Work with ministries to allow these families to be directly seen at NUH	- Decrease appointment default rates - Increase parental compliance to appointments	Improved health equity
Safeguarding of children	- No real evidence of staff taking a safeguarding approach - Lack of screening for social determinants of health, domestic abuse and ACE	- ACE awareness training for health staff - Clear safeguarding protocols and training	Increase use of ACE checklist at primary care level	
Data	Lack of insight into current health profile of population other than from the GUSTO study	- Have a central database for measuring KPIs and outcomes across the project - Maintain a service performance outcome dashboard of quality indicators in the hospital and community	- Increase insights into health gaps in the population - Improve programmes based on their KPIs and achieved outcomes	Data repository of child and family health indicators in the Western cluster

ACE: adverse childhood experiences; GUSTO: Growing Up in Singapore Towards healthy Outcomes; KPIs: key performance indicators; NUH: National University Hospital

Maternal mental health. While Singapore has made significant strides in reducing maternal and infant mortality, new challenges have emerged concerning maternal mental health. Factors that affect maternal mental health include maternal sleep and breastfeeding.⁴ Approximately 1 in 10 women experience depression before, during or after pregnancy. This figure is consistent with global data, highlighting the pervasiveness of perinatal mental health disorders. However, these mental health challenges extend beyond depression, encompassing anxiety, stress, and the psychological impact of maternal obesity, all of which can increase the risk of complications during pregnancy and adverse developmental outcomes for offspring.⁵

Singapore has launched several maternal mental health programmes, but there remains a need to scale up support, particularly for mothers in vulnerable or lower-income groups. The stigma associated with seeking help for mental health issues still presents a barrier to care. Addressing maternal mental health issues also involves creating supportive environments for mothers. This includes promoting mental wellness through education, offering peer support groups and ensuring that healthcare professionals are trained to recognise and manage early signs of maternal distress. These efforts can lead to better outcomes for both mothers and their children.

Approach to key health challenges

It is essential to understand the existing processes of community-based programmes, and map them out using a life course framework. As there are multiple existing programme drivers that are targeting different key health challenges, it is important to consolidate, coordinate and support these programmes in order to align programme goals with the overall preventive health strategy for family and child and reduce duplication of efforts. A workforce needs assessment was carried out to understand the strengths of programmes and barriers in their implementation by the National University Health System (NUHS), which forms the Western cluster of healthcare institutions in Singapore (Table 1). This then formed the basis for a theory of change and logic model for health systems transformation at NUHS.

Challenges in implementation and future directions

Implementation is challenging with issues ranging from cross-sector collaboration to resource allocation, and tackling cultural and social barriers. Singapore is transforming through the HealthierSG

movement, which shifts healthcare delivery from a hospital-centric model to a community-focused approach, emphasising value-based care and addressing broader health determinants. This national trend towards holistic healthcare reform shows the importance of addressing fragmentation and promoting alignment within the healthcare system.¹⁰

Future plans involve improving healthcare access through digital health integration, life course approach, telemedicine, data analytics, cross-sector collaborations and developing programmes for at-risk youths, focusing on precision public health. These approaches, while tailored to the Singapore context, may offer valuable insights for addressing similar public health challenges in other regions.

Ethics statement

Not applicable

Declaration

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