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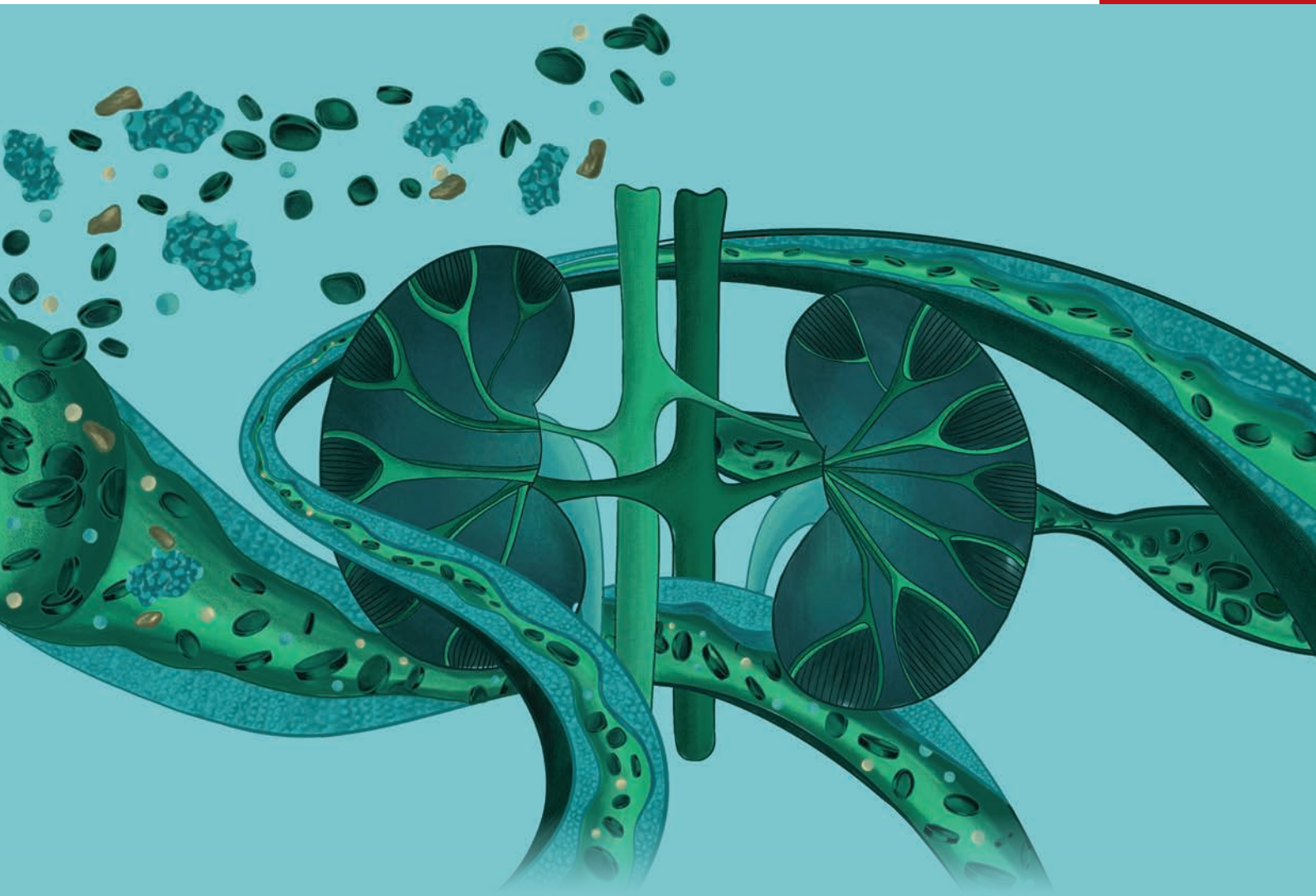

Five-year outcomes of a holistic programme for managing early chronic kidney disease in primary care

A multidisciplinary team approach in primary care is ideal in chronic kidney disease (CKD) management. Outcomes of the HALT-CKD programme have been reported to be positive. (See full article, p.597)

Illustration by Ladyfingers Co.

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EDITORIAL

Stemming the tide of chronic kidney disease: A focus on primary care prevention

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The prevalence of chronic kidney disease (CKD) among Singapore residents aged 18 to 74 years rose significantly from 8.8% in 2019–2020 to 13.8% in 2021–2022.[1,2] Singapore ranks third globally for treated end-stage kidney disease (ESKD), with a median survival of 6 years post-dialysis.[3] Diabetic nephropathy was the leading cause of stage 5 CKD, accounting for 64.6% of new dialysis patients in 2022.[4] This is particularly concerning given Singapore's rapidly ageing population and rising lifestyle-related CKD risk factors. Notably, CKD prevalence is higher among those with pre-diabetes (21.8%), diabetes mellitus (DM) (42.3%) and hypertension (24.2%) compared to those without diabetes (10%).

Primary care plays a crucial role in CKD prevention, screening and diagnosis, particularly in managing risk factors such as DM and hypertension. Since 2017, the Holistic Approach in Lowering and Tracking Chronic Kidney Disease (HALT-CKD) programme has tracked polyclinic patients across all 3 public healthcare clusters with CKD stages G1–G3A to control risk factors and delay CKD progression.

In this issue of the *Annals*, Koh et al. present a retrospective cohort study evaluating the 5-year outcomes of 3800 CKD G1–G3A patients enrolled in the HALT-CKD programme across 5 polyclinics within 1 of the 3 healthcare clusters.[5] Interventions included counselling and lifestyle modification, initiation and optimisation of angiotensin-converting enzyme inhibitors (ACEi)/angiotensin II receptor blockers (ARB), sodium-glucose cotransporter-2 inhibitors (SGLT2i) initiation, and optimisation of DM and hypertension control. The prevalence of DM and hypertension among the patients was 92.9% (median HbA1c 7.4%) and 92.4% (median blood pressure [BP] 132/73) respectively, reflecting relatively well-controlled conditions.

The study highlights the importance of addressing reasons behind ACEi/ARB discontinuation in CKD patients. Patients on the maximum dose of ACEi/ARB rose from 35.7% to 49.2%, while those not on ACEi/ARB increased from 7.5% to 10.1%. Patients who had their ACEi/ARB dose reduced or stopped had an increased risk of progression to CKD stages G3B–G5 compared to those who maintained their doses (hazard ratio [HR] 1.92, 95% confidence interval [CI] 1.50–2.45). While the observational design of this study cannot establish causality, their findings are consistent with the robust evidence from randomised controlled trials (RCTs) and meta-analyses, and established clinical guidelines advocating for renin-angiotensin system blockade in CKD management.[6,7] Notably, the study mentioned that ACEi/ARB cessations commonly occurred following hospital discharge for acute kidney injury, but the reasons were neither documented nor adjusted for in the study. Other common reasons for ACEi/ARB discontinuation encountered in clinical practice include hyperkalaemia and hypotensive events. Hyperkalaemia may be mitigated by reviewing concurrent drugs, moderating dietary potassium intake and considering the addition of diuretics, sodium bicarbonate and potassium binders. Resonium is available in public primary care clinics, but not lokelma, which is more palatable. Enhancing their availability and affordability in primary care, along with increasing physicians' confidence in their use, could help overcome barriers to continued ACEi/ARB use. Hypotension could be managed by switching to ARBs with weaker anti-hypertensive effects, such as losartan. Further research could investigate reasons for ACEi/ARB discontinuation, explore re-initiation, examine the duration of maximal-dose ACEi/ARB use and assess their impact on renal outcomes.

Increasing ACEi/ARB dosage did not significantly delay progression to CKD G3B–G5 (HR 1.01, 95% CI 0.77–1.32), contrasting with evidence and guidelines that support maximal tolerated doses.[6] Baseline data show 35.7% of patients were already on maximal doses of ACEi/ARB, and a proportion

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not on maximal doses may have been on optimal or maximally-tolerated doses. Subgroup analyses restricted to patients not already on maximally-tolerated doses may provide further insights.

The study found that SGLT2i, prescribed to 39.6% of patients, did not significantly delay progression to CKD stages G3B–G5. This contrasts sharply with multiple RCTs (EMPA-REG OUTCOME, CANVAS Program, CREDENCE and DECLARE-TIMI 58) as well as a meta-analysis which demonstrated substantial risk reduction for ESKD as well as dialysis, transplantation or death due to kidney disease.[8] Additionally, Koh et al.'s finding is inconsistent with Liu et al.'s local real-world study, which showed that SGLT2i reduced the risk of CKD progression and ESKD.[9] Given the robust evidence from renal outcome trials, the utilisation of SGLT2i has been incorporated as a key performance indicator for the HALT-CKD programme, with empagliflozin included in the Ministry of Health's standard medication list since November 2023. Since Koh et al.'s study predates these changes, the lack of observed benefit may reflect delayed SGLT2i initiation for patients with poorer HbA1c control, more significant albuminuria or later CKD stages. Additionally, the relatively shorter exposure of SGLT2i use towards the end of a 5-year follow-up may have limited the detection of its long-term benefits. The findings underscore that an "absence of evidence is not evidence of absence."

Other medications, such as mineralocorticoid receptor antagonists (MRAs) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), could further reduce albuminuria and delay CKD progression if included in HALT-CKD. Spironolactone is available in public primary care clinics, but not finerenone, a non-steroidal MRA with fewer side effects. GLP-1 RAs have shown significant benefits in HbA1c control, weight management and cardiovascular risk reduction. Incorporating these medications into primary care practice would enhance the armamentarium for slowing CKD progression.

Albuminuria improvements were noted, with an increase in patients with albuminuria stage A1 from baseline (P<0.001). Although there were statistically significant improvements in HbA1c (from 7.4% to 7.3%), systolic BP (from 132 to 130 mmHg) and diastolic BP (73 to 70 mmHg), these changes were less clinically significant. Overall, 12.6% of patients progressed to advanced CKD (stages 3B and above). Comparable figures for CKD progression using similar definitions are not available, but pre-HALT-CKD analyses may enable comparisons. Additionally, subgroup analyses might reveal differing progression rates, particularly between CKD G1 and CKD G3A. HALT-CKD is a nationwide programme, while this study focused on patients from 5 polyclinics within 1 cluster. Future studies across other public healthcare clusters could provide comparative data. While major interventions, such as ACEi/ARB therapy, are consistent across clusters, differences in counselling approaches and care models can affect the programme outcomes. Some study variables might reach statistical significance with a larger study population.

Despite 92.9% of patients receiving CKD counselling and lifestyle modification advice, progression to advanced CKD stages was not delayed. It is unclear if this is due to the high percentage receiving counselling, resulting in insufficient variation to detect a difference, or the nature of the counselling, typically limited to 1 or 2 sessions. Effective patient education programmes should be tailored to their specific needs, should enhance CKD knowledge, teach strategies to prevent CKD progression, empower self-management and focus on improving health literacy.[10] Ho et al. found limited health literacy and male gender correlated with poorer self-care in CKD among Singaporean patients.[11] Hwang et al. identified limited CKD awareness and ineffective patient-physician communication in a qualitative study exploring perceived barriers and facilitators to CKD care among patients in Singapore.[12] A suggested solution is the use of "health coaches" who can spend more time to provide education and support behaviour change. Another qualitative study exploring healthcare professionals' perspectives highlighted knowledge and practice gaps, systemic constraints for nephrology referrals, short consultation times, suboptimal care coordination, and patients' lack of CKD awareness and self-management skills as barriers.[13] CKD training for primary care physicians, structured CKD care protocols, multidisciplinary team-based care and prioritising nephrology referrals based on risk assessment were identified as key facilitators.

Koh et al.'s study is one of the first to assess the real-world effectiveness of the HALT-CKD programme. While findings, such as the importance of maintaining ACEi/ARB therapy, align with existing literature, the limited impact of SGLT2i and counselling and lifestyle modifications highlights areas for primary care improvement to better align clinical outcomes with the promising results observed in controlled trials.

Healthier SG will further strengthen existing preventive care efforts through healthy lifestyle promotion, increased screening and improved management of chronic conditions, including DM, hypertension and CKD. Starting in January 2025, the HSG CKD Care Protocol will further empower

primary care in managing CKD stages G1–G3A.[14] This protocol recommends (1) patient education, (2) optimising management of risk factors and comorbidities, (3) initiating workup for complications and (4) initiating and titrating ACEi/ARB to maximally tolerated dose in CKD patients with DM or albuminuria, as well as initiating SGLT2i for persistent albuminuria. Aligned with Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, this protocol bridges critical knowledge and implementation gaps, enabling primary care to play a central role in delivering comprehensive CKD management to stem the tide of CKD.

Declaration

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

Keywords: *ACE inhibitor, ARB, chronic kidney disease, CKD, diabetic nephropathy, primary care, SGLT2i*

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EDITORIAL

Journey towards a smoke-free nation

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"A journey of a thousand miles begins with a single step." Singapore's journey towards a smoke-free society started early in the 1970s when legislations were introduced to restrict smoking in certain public spaces and ban tobacco advertising.[1] The National Smoking Control Programme was launched in 1986 with important objectives set to prevent youths from picking up the smoking habit, help current smokers quit, protect non-smokers from second-hand smoke, and tighten regulations against smoking. Public health campaigns and outreach programmes to schools, youth organisations, army camps and workplaces were conducted. There was widespread dissemination of information on the hazards of smoking through mass media coverage and printed materials. Singapore was among the first 40 countries to ratify the World Health Organization (WHO) Framework Convention on Tobacco Control, with its 6 recommendations supporting tobacco cessation—including monitoring tobacco use, protecting people from tobacco smoke, offering smoking cessation assistance, warning dangers of tobacco, enforcing bans on tobacco advertising, and raising taxes on tobacco.[2]

An important part of Singapore's tobacco control efforts is the provision of assistance for smokers on their attempts to quit. Smoking cessation services were incorporated in primary healthcare settings from the 1990s and have since expanded to form a vast network including hospitals, polyclinics and retail pharmacies with over 150 touchpoints where smokers can easily access counselling services and pharmacotherapy. In addition, the "I Quit" programme under the Singapore Health Promotion Board offers tools such as daily tips and encouragement, motivational exercises and other support services such as the QuitLine where smokers can access consultants for personalised advice. There is even a Facebook community club where individuals can share experiences and form a support network for smokers and ex-smokers. Leveraging technology, online modules and mobile applications have enabled smokers who are more technologically proficient, especially youths, to easily access help for smoking cessation. All these measures are well aligned with recommendations in the recently published WHO clinical treatment guidelines on tobacco cessation, highlighting the roles of evidence-based behavioural interventions, pharmacological treatment and digital cessation interventions.[3]

The smoking prevalence rate in Singapore declined remarkably from 23% in 1977 to 13.6% in 2007, but subsequently plateaued and remained in the range of 10 to 15% for more than a decade despite successive increases in the excise duty on cigarettes and expansion of public spaces where smoking is prohibited.[4] In the fourth quarter of 2023, the smoking prevalence rate in Singapore fell below 10% for the first time.[5] This may be attributable to behavioural changes associated with health and financial concerns or tobacco accessibility during the COVID-19 pandemic, as well as the raise in minimum legal age for access to tobacco from 18 to 21 years old since January 2021.

To advance further from the current situation to our goal of becoming a smoke-free nation, we should consider strategies beyond the existing prohibitive measures to prevent young people from taking up the smoking habit and explore factors that motivate smoking cessation to develop solutions tailored to specific needs among current smokers. For example, imposing a generational ban on the sale of tobacco to those born after a certain year, a proposal that had been conceptualised by Singapore back in 2010, is now being considered in the UK as a potential step to phase out smoking.

The study by Koh et al. provides useful insights into tobacco consumption behaviour in Singapore, a high-income country with a multi-ethnic population and a well-established framework for provision of support for tobacco cessation.[6] The findings showed 31.3% and 41.2% of current smokers in Singapore had intentions to quit and made quit attempts in the previous year, respectively. Among ever-smokers, the overall prevalence of smoking cessation was 25.25%. These figures highlight the gap between intention and action, as well as the importance of finding ways to translate quit intentions to concrete actions and eventual success.

Unlike most other studies, Koh et al. focused on identifying factors that may be associated

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with quit intention, quit attempts and successful cessation. Significant factors as highlighted below include ethnicity, education level, marital status, doctors' advice and the perception of risks from smoking.

Malay and Indian smokers were more likely to have contemplated or attempted quitting compared to Chinese smokers. This is notable given that previous surveys consistently showed an increased prevalence of current smokers among these minority races. Notwithstanding the lack of successful smoking cessation outcomes, this suggests a need for more attention and resource allocation to address barriers to successful quitting in this population of motivated smokers.

Education affects health literacy and the perception of smoking-related risks. The level of education attainment may also be an indirect measure of socioeconomic status. Therefore, a decreased understanding and responsiveness to health messages, or a lack of means to access smoking cessation treatment may explain the association between lower education level and reduced likelihood of quit intent and poorer smoking cessation outcomes. It would be important to design interventions that are both literacy- and culturally appropriate, and simple enough for everyone to grasp. These may include simplified messaging, improving support services to these groups, and addressing the social determinants of health.

Marital status also appears to have an impact on smokers' intention and attempts to quit smoking. Current smokers were less likely to quit if they are single, separated, divorced or widowed. Separately, a longitudinal study by Falba and Sindelar found that if a spouse quits smoking, the odds of the partner's cessation increased by up to 7.5 times among men and 8.5 times among women.[7]

Smokers who receive advice from their doctors to quit were more than twice as likely to attempt quitting, a finding that is supported by global literature citing benefits of doctors' advice on smoking cessation rates. For example, Stead et al. found that even with a brief and simple doctor's smoking cessation advice, a smoker is more likely to quit successfully and remain smoke-free after 12 months.[8] Doctors should make it a priority to identify opportunities for the systematic provision of smoking cessation advice in various settings such as peri-operative care, hospitalisation for smoking-related diseases, or as part of chronic disease management in both primary and specialist care.

The link between perceived level of risk from smoking and likelihood of quitting further emphasises the importance of appropriate communication between doctors and patients about the harms of smoking. On this note, the inclusion of graphic warning labels on cigarette packs is also an effective means to convey the health risks of tobacco and motivate smokers to consider quitting.

Among the biggest concerns faced in our efforts to completely phase out tobacco is the growing popularity of electronic cigarettes (e-cigarettes) from early last decade. Studies have repeatedly shown evidence confirming the association between the use of e-cigarettes by non-smoking adolescents and subsequent tobacco smoking initiation, suggesting that vaping provides a gateway to smoking for the youth.[9,10] One survey reported 85% of youths between 15 and 30 years of age were exposed to e-cigarette advertising across multiple media platforms despite restrictions on tobacco advertising.[11] Such exposure leads to a higher rate of e-cigarette use among the youths, increasing their likelihood by nearly 3 times of becoming traditional cigarette smokers in the longer term.

Vaping-related offences in Singapore have continued to increase in consecutive years despite its ban on vaping since 2018 and tightening enforcement measures. This rising trend can be explained by multiple factors—strong addictive potential of vaping, ease of access and concealability of e-cigarettes, and lower cost compared to traditional cigarettes. The tobacco and related industries today have more communication channels to engage youths through various global digital platforms such as Instagram and TikTok. A large cigarette company in Indonesia has even experimented with marketing cigarette brands as part of a music campaign in the Metaverse.[12] In addition, delivery services like Uber that offer delivery of e-cigarettes in South Africa, have made it easier for one to access these products.[12] Therefore, more enforcement efforts, more public health education and certainly more research would be needed to find new strategies to counter these exploitative practices by the tobacco industry.

The cost of smoking cessation therapy is often seen as a barrier to help-seeking among smokers. Perhaps more consideration should be given to weigh the expense of treatment against the economic impact of continued smoking and emphasise the potential financial benefits of smoking cessation. According to a study on the expenditure of smokers in Asia-Pacific countries, the estimated annual expense (USD3777; approx. SGD 4950) and lifetime spending (USD 207,398; approx. SGD271,769) of purchasing a pack of cigarettes per

day in Singapore were among the highest in the region.[13] Besides the direct expenses of smoking, indirect expenditures such as a loss of productivity due to smoke breaks and absenteeism from work, as well as the costs of treating smoking-related illnesses, contribute to a much higher economic burden on both the individual and society. Studies on the economic impact of integrating smoking cessation interventions in the care of certain patient populations such as cardiac, respiratory and oncology patients have demonstrated cost-effectiveness with significant clinical benefits achieved at low incremental costs.[14,15]

Other factors that impede delivery of smoking cessation assistance, although less studied, include a lack of time and training reported by healthcare providers, as well as the perception of smokers' responsibility for smoking. The former can be addressed through greater emphasis on smoking cessation teaching in medical education, as well as using smoking cessation templates and protocols, supported with electronic prompts to improve the rate of smoking cessation treatment delivery. More effort should be made to help healthcare providers, particularly in their junior years of training, recognise smoking as an addiction and disease rather than simply a lifestyle choice.

Singapore's journey towards becoming a smoke-free nation offers valuable lessons for tobacco control regionally and globally. The country's comprehensive approach—combining strong policies, cessation support and public education—has achieved significance in reducing smoking rates thus far. The study by Koh et al. provides a better understanding of factors influencing smoking cessation in Singapore's unique context, which would help our healthcare providers, policymakers and researchers refine strategies to address persistent challenges and target interventions more effectively. With a solid foundation for future research and policy development, we hope that Singapore can tackle the "last mile" of tobacco control and realise its vision of a truly smoke-free society.

Declaration

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Keywords: *epidemiology, public health, pulmonary, respiratory medicine, smoking cessation*

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ORIGINAL ARTICLE

Five-year outcomes of a holistic programme for managing early chronic kidney disease in primary care

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ABSTRACT

Introduction: Holistic Approach in Lowering and Tracking Chronic Kidney Disease (HALT-CKD) is a nationwide programme that was introduced in 2017 to combat CKD in Singapore. This study aims to evaluate outcomes of the HALT-CKD programme and identify factors influencing disease progression among early CKD patients.

Method: We conducted a retrospective cohort study involving adult patients aged 21 to 80 with CKD stages G1–G3A, recruited from 5 Singapore polyclinics between 2017 and 2018. The primary outcome—time to progression to advanced CKD (G3B–G5)—was tracked until March 2023, based on patients' last known serum creatinine levels. Descriptive statistics and Cox regression were used. Patients who followed up with other institutions, were deceased or defaulted without developing (or experiencing) the outcome were censored.

Results: We studied 3800 patients (mean age: 61.9 years) for a median of 4.7 years. Among them, 12.6% developed advanced CKD despite statistically significant improvements in HbA1c, blood pressure and albuminuria levels. Increasing age, female sex, clinic, baseline creatinine, diastolic blood pressure and HbA1c significantly shortened time to CKD progression. Macro-albuminuria at baseline (hazard ratio [HR] 1.77, 95% confidence interval [CI] 1.19–2.61) and at analysis (HR 2.22, 95% CI 1.55–3.19) significantly accelerated advanced CKD progression. Patients who had their angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) dose reduced or discontinued progressed to advanced CKD earlier (HR 1.92, 95% CI 1.50–2.45). Counselling and sodium-glucose cotransporter-2 inhibitor (SGLT2i) use did not significantly delay CKD progression.

Conclusion: Maintaining optimal ACEi/ARB dosage is essential to delay CKD progression. Premature cessation or reduction of this dosage should be discouraged. Further research on counselling and SGLT2i use in early CKD is needed to address the growing burden of CKD.

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Keywords: chronic kidney disease, CKD progression, primary care interventions, renin-angiotensin system inhibitors, Singapore healthcare

CLINICAL IMPACT

What is New

- Despite significant improvements in HbA1c, blood pressure and albuminuria across 5 years, 12.6% of patients progressed to advanced chronic kidney disease (CKD).
- Early cessation or reduction of angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) dosage resulted in earlier development of CKD stages G3B–G5.

Clinical Implications

- Recognise and diagnose CKD early, initiate ACEi/ARB therapy, consider sodium-glucose cotransporter-2 inhibitor, provide counselling on lifestyle modifications, and target treatment of existing chronic diseases.
- Avoid early cessation or dose reduction in ACEi or ARB. Doing so can hasten CKD progression.

INTRODUCTION

Singapore has the third highest incidence and sixth highest prevalence of end-stage kidney disease (ESKD) in the world.[1] Globally, chronic kidney disease (CKD) is estimated to affect over 850 million people, with a prevalence of 13.4% among adults worldwide.[2] Diabetes is the main cause of ESKD in new patients initiating dialysis, accounting for two-thirds of cases in 2021.[3] The Ministry of Health's (MOH) war on diabetes has reaped benefits in stabilising its crude prevalence at 8.5% in 2022. However, CKD prevalence increased significantly from 8.7% in 2020 to 13.8% in 2022.[4] This trend is consistent with global patterns, where CKD prevalence is expected to increase by 17% between 2020 and 2030.[5] CKD-related deaths had risen by 76% from

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2009 to 2019, as it remained in the top 10 most common causes of death in Singapore.[6] CKD is also a significant economic burden, with $300 million spent annually on dialysis treatment.[7] By 2035, about a quarter of Singapore residents are projected to develop CKD[8]; the mortality, morbidity and economic burden of CKD will be unfathomable.

Addressing this issue requires an emphasis on optimal management through large-scale primary care programmes to delay CKD progression and improve patient outcomes.[9] The increasing number of patients with CKD being managed in primary care[10] led to the development and rollout of the Nephrology Evaluation, Management and Optimisation (NEMO) programme from 2011 to 2016. It was expanded and continued as the Holistic Approach to Lowering and Tracking Chronic Kidney Disease (HALT-CKD) programme in 2017, covering all 3 healthcare clusters at primary and tertiary care in Singapore.[11,12]

HALT-CKD aims to slow down CKD progression and prevent ESKD development by systematically recruiting and tracking patients with risk factor control at the primary care level. The programme aligns with global health initiatives and policies on CKD management, such as the World Health Organization's goal to reduce the number of deaths from non-communicable diseases, including CKD, by 25% by 2025.[13] HALT-CKD also focuses on medication optimisation to reduce proteinuria, improving blood pressure and glycaemic control in patients with CKD stages G1–G3A in primary care. Moreover, the programme encourages shared-care collaboration between primary and tertiary (nephrology) care for patients with CKD stages G3B–G5.[11] It features the designation of coordinators in each polyclinic, whose role focuses on patient recruitment, education on low-sodium diet, weight management and smoking cessation and making referrals to these services as required. The coordinators also assist the team in tracking key performance indicators, calling up patients to remind them of appointments, and in turn, provide holistic care through continual follow-ups.[14]

HALT-CKD has garnered much success over the years, with over 49,000 patients having benefitted from the programme as of March 2019, with 90% being placed on kidney protective medications and improved chronic disease control since joining the programme. However, local studies have found suboptimal care in specific patient groups, such as in ethnic minorities and the elderly, with resultant poorer chronic disease control.[15,16] To our knowledge, there has not been any studies published based on NEMO or HALT-CKD data. As patients with varying chronic disease control are recruited at different timepoints throughout the ongoing programme, the severity profile of the CKD cohort is diluted over time. This makes it challenging to rigorously track disease progression and assess key performance indicators in individual patients over an extended period. Furthermore, the study of specific cohorts recruited under the HALT-CKD programme has not been performed, despite the ease and ability to do so with close patient tracking and follow-up in primary care. With the first group of patients being recruited in to the programme in April 2017, it will now be possible to assess their health outcomes after 5 years of adequate follow-up. Therefore, our study critically analysed the patients recruited in the first year of the HALT-CKD programme and reviewed their health status and outcomes after 5 years. Our study also evaluated the outcomes of the HALT-CKD programme and identified factors influencing disease progression among early CKD patients. We hypothesised that primary care has achieved its objectives—pharmacological interventions (e.g. medication initiation and up-titration) and non-pharmacological interventions (e.g. lifestyle counselling) have delayed progression to CKD stages G3B–G5. By examining the 5-year outcomes of the programme's initial cohort, we also sought to determine the effectiveness of the HALT-CKD programme in slowing down CKD progression and identified key factors that contribute to successful disease management.

METHOD

Study population and sampling

This retrospective cohort study was conducted among patients aged 21 to 80 with CKD stages G1–G3A who were seen from April 2017 to March 2018 at 5 public primary care clinics (polyclinics) within a public primary healthcare institution in Singapore. These patients were recruited as part of the HALT-CKD programme, based on the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 classification for CKD.[17] Patients included in the study were followed up for 5 years, from date of recruitment (defined as baseline) to March 2023 (defined as at analysis).

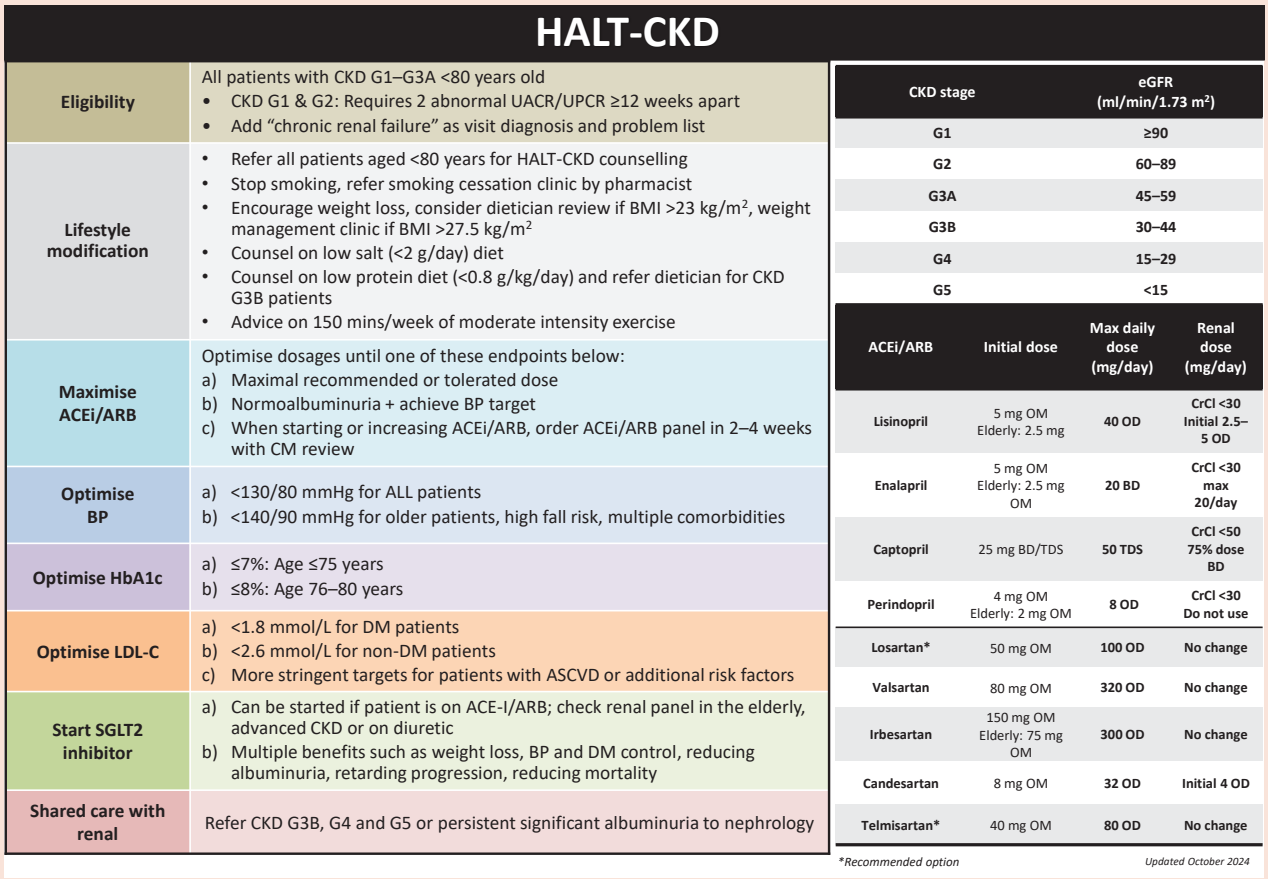
Study definition and parameters

Patient data from the HALT-CKD programme were accessed following ethics approval (Institutional Review Board of the National Healthcare Group, 2023/00314). This included sociodemographic data such as age, race, sex, operations information (e.g. clinic visited and recruitment date), clinical data (e.g. presence of chronic diseases: diabetes, hypertension and hyperlipidaemia), smoking

status, height, weight and body mass index (BMI), blood pressure (BP) and laboratory data (e.g. serum creatinine, HbA1c and urine albumin/creatinine ratio). The register also contained data on medication use, such as angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB) and sodium-glucose cotransporter-2 inhibitor (SGLT2i) (available only at analysis), as well as management (e.g. whether they had received counselling by our HALT-CKD coordinator). Fig. 1 shows specific protocols on management, medication adjustments and lifestyle counselling. Outcomes data were also documented, such as discharged due to age criteria (≥80 years), death, discharged to follow-up with other institutions or lost to follow-up, with dates of outcomes appended. The register is maintained and updated by HALT-CKD coordinators of each polyclinic daily. To minimise risks of breach of confidentiality, patient data were de-identified by the approved centralised trusted third party before analysis by study team.

Variable engineering and data cleaning were performed using Python version 3.11.3 (Python Software Foundation, Wilmington, DE, US), with missing data excluded from the study. Patients who were above the age of 80 at time of analysis (March 2023) were also excluded from the study, as this was the end-point of follow-up within the HALT-CKD programme. Additional variables were engineered, such as number of days from recruitment to event, which was based on the earliest duration of sustained progression to CKD stages G3B–G5 of more than 3 months apart or last known measured serum creatinine before March 2023. As CKD is a chronic progressive disease that develops across years, we excluded all patients with number of days to event ≤90 to reduce overestimation of outcome due to late recruitment, and right-censored patients who did not develop

Fig. 1. HALT-CKD protocol in-clinic poster.



ASCVD: atherosclerotic cardiovascular disease; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; BP: blood pressure; CKD: chronic kidney disease; CM: care manager; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HALT-CKD: Holistic Approach to Lowering and Tracking Chronic Kidney Disease; Hb1Ac: haemoglobin 1Ac; LDL-C: low-density lipoprotein cholesterol; SGLT2i: sodium-glucose cotransporter-2 inhibitor; UACR: urine albumin-creatinine ratio; UPCR: urine protein-creatinine ratio

CKD stages G3B–G5 at time of analysis. For patients who died, defaulted or transferred care to another institution without developing CKD stages G3B–G5, we utilised theirlast available estimated glomerular filtration rate (eGFR) measurement to estimate the time to censoring, as they did not experience the outcome of interest during the study period. Albuminuria stage (i.e. A1–3) was calculated based on existing cutoffs as defined by KDIGO except stage A1, where we used gender specific cutoffs (2.5 and 3.5 mg/mmol for males and females, respectively),[18] a continuation from the previous NEMO programme. eGFR was calculated using the Chronic Kidney Disease Epidemiology 2009 Creatinine equation[19] for all eGFR values before classification into CKD stage. The outcome variable of CKD progression was defined as progression to CKD stages G3B–G5, with an eGFR <45 ml/min/1.73 m^2, as defined by KDIGO.[17] We chose this outcome for this study, as stage G3B was the threshold to refer nephrology (outlined by the HALT-CKD programme), making it a practical and clinically relevant outcome to monitor. Furthermore, individuals with more advanced CKD face a higher risk of renal-related complications.

Statistical analysis

Statistical analyses were performed with SPSS Statistics software version 28.0 (IBM Corp, Armonk, NY, US), with a *P* value of <0.05 in the 2-sided test considered as statistical significance. Descriptive statistics were performed. Numerical variables were represented as mean with standard deviation (SD) and categorical variables as no. (%). Numerical variables that were not normally distributed were represented as median with interquartile range (IQR). McNemar tests were used to evaluate differences in categorical variables between baseline and at analysis, with the Wilcoxon signed-ranks tests used for continuous variables that did not meet the assumptions of normality. A Cox proportional hazards model was used to assess the relationship between the time to CKD stages G3B–G5 using the abovementioned independent variables. Patients who did not develop the outcome but died, defaulted or followed up with other institutions were censored by the model. Patients who developed CKD stages G3B–G5 during the follow-up period were events, and duration to event was used in Cox regression. Results were presented as estimated hazard ratios (HRs) for each covariate with 95% confidence intervals (CIs).

RESULTS

Of 35,195 patients on the HALT-CKD register, 3800 patients fit the inclusion criteria (Fig. 2). Majority (58.3%) were male, Chinese (68.2%), with a mean age of 61.9 years and followed-up for a median of 4.7 (IQR 4.0–5.0) years. More than 90% of patients had 1 or more chronic diseases, with significant increment of patients developing hypertension and diabetes mellitus after 5 years.

Statistically significant improvements were noted for haemoglobin A1c (Hb1Ac), systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the patients after 5 years, despite worsening of CKD stage. In terms of their management, 92.9% of patients have been counselled regarding their CKD by coordinators. Patients on maximum ACEi/ARB dose have increased from 35.7% to 49.2%, while patients not on ACEi/ARB have also increased from 7.5% to 10.1%. SGLT2i was prescribed for 39.6% of patients.

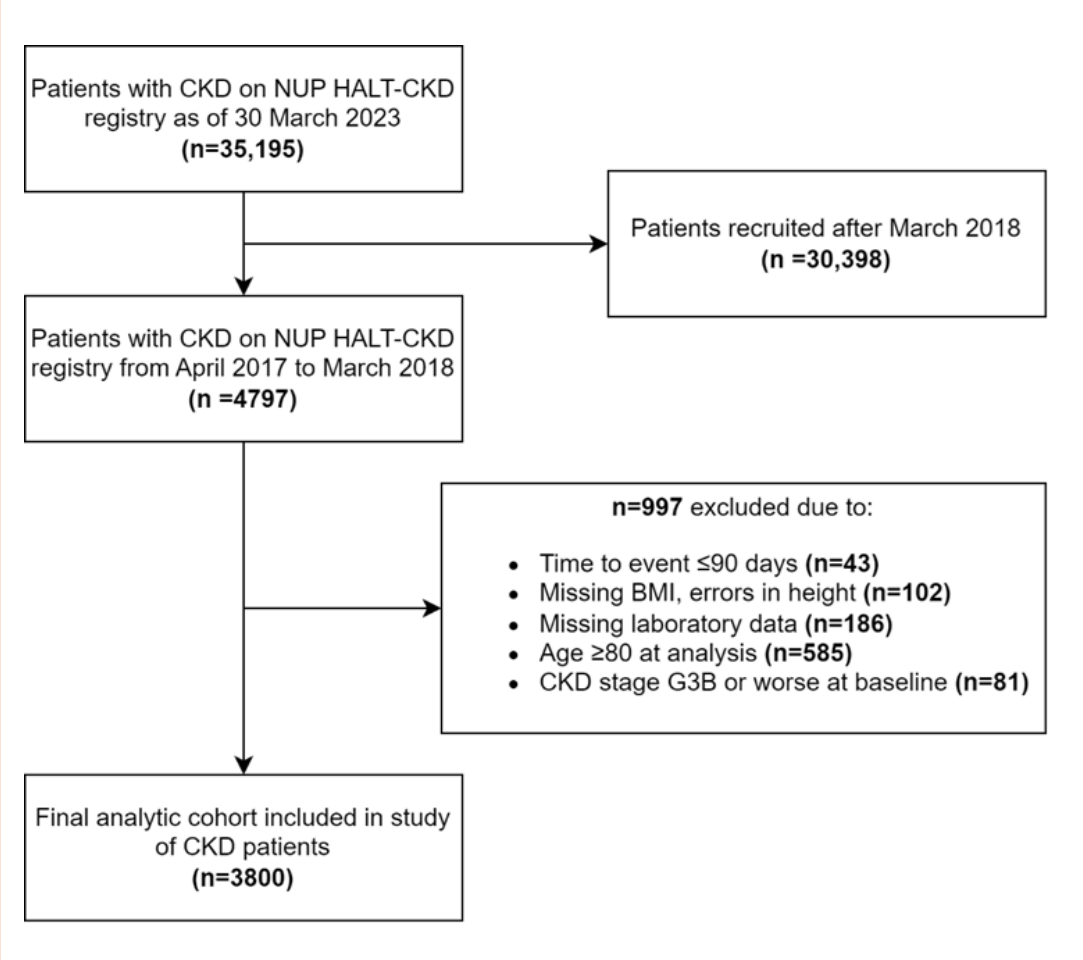
In terms of outcome, progression to CKD stages G3B–G5 occurred in 12.6% over 5 years (Table 1), with more patients progressing into the red zone as shown in Table 2. There was a significant increase in number of patients with albuminuria stage A1 from baseline compared to 5 years later (*P*<0.001) (Table 2).

Our Cox regression analysis (Table 3) yielded a significant *P* value of <0.001 for omnibus tests of model coefficients at each step, with exclusion of 263 (6.9%) cases due to missing HbA1c values (due to non-diabetes patients). Increasing age at baseline, female sex, clinic, increasing HbA1c, serum creatinine and DBP at baseline were associated with a shorter time to CKD stages G3B–G5. Patients with macroalbuminuria (stage A3) at baseline and at analysis developed CKD stages G3B–G5 earlier compared to patients with normoalbuminuria (stage A1) (baseline HR 1.77, 95% CI 1.19–2.61, at analysis HR 2.22, 95% CI 1.55–3.19).

In terms of management, patients who received CKD counselling or started on SGLT2i did not experience a delay in CKD stages G3B–G5. After adjusting for patient sociodemographics, clinical parameters, albuminuria status, counselling and SGLT2i use, patients who had their ACEi/ARB dose reduced or stopped during the 5 years had increased hazards of progression to CKD stages G3B–G5, compared to patients who had maintained at their current doses (HR 1.92, 95% CI 1.50–2.45) (Table 3). Patients who had their ACEi/ARB dosage increased did not significantly delay the time to CKD stages G3B–G5 (HR 1.01, 95% CI 0.77–1.32).

Subgroup analysis was performed to compare patients who had maximised their doses of ACEi/ARB and not on SGLT2i (n=514), versus patients with suboptimal doses of ACEi/ARB and on SGLT2i (n=970). After adjusting for patient sociodemographics, clinical parameters, albuminuria status

Fig. 2. Development of retrospective cohort of CKD patients for study.



BMI: body mass index; CKD: chronic kidney disease; NUP HALT-CKD: National University Polyclinics Holistic Approach to Lowering and Tracking Chronic Kidney Disease

Table 1. Characteristics of patients included in the study from April 2017 to March 2018.

Study characteristics	(n=3800)		*P* value
	At recruitment	At analysis	
Mean age, year (SD)	61.9 (8.1)	67.2 (8.1)	
Sex, no. (%)			
Male	2215 (58.3)		
Female	1585 (41.7)		
Race, no. (%)			
Chinese	2592 (68.2)		
Malay	799 (21.0)		
Indian	301 (7.9)		
Others	108 (2.8)		

Table 1. Characteristics of patients included in the study from April 2017 to March 2018. (Cont'd)

Study characteristics	(n=3800)		*P* value
	At recruitment	At analysis	
Clinic, no. (%)			
Clinic A	1441 (37.9)		
Clinic B	645 (17.0)		
Clinic C	541 (14.2)		
Clinic D	588 (15.5)		
Clinic E	585 (15.4)		
Smoking status, no. (%)			
Non-smoker	NA	2580 (67.9)	
Ex-smoker	NA	408 (10.7)	
Smoker	NA	407 (10.7)	
Unknown	NA	405 (10.7)	
Presence of chronic diseases, no. (%)			
Hyperlipidaemia	NA	3754 (98.8)	
Hypertension	3513 (92.4)	3701 (97.4)	<0.001[a]
Diabetes mellitus	3529 (92.9)	3583 (94.3)	<0.001[a]
Clinical parameters			
Median eGFR, ml/min/1.73 m^2 (IQR)	82.7 (29.6)	69.0 (36.0)	<0.001[b]
Median BMI, kg/m^2 (IQR)	NA	26.6 (6.1)	
Median HbA1c, % (IQR)	7.4 (1.5)	7.3 (1.6)	<0.001[b]
Median SBP, mmHg (IQR)	132 (17)	130 (16)	<0.001[b]
Median DBP, mmHg (IQR)	73 (12)	70 (12)	<0.001[b]
Underwent HALT-CKD counselling, no. (%)	NA	3529 (92.9)	
ACEi/ARB usage, no. (%)			<0.001[a]
Not on medication	286 (7.5)	382 (10.1)	
On medication	2158 (56.8)	1547 (40.7)	
On maximum dose of medication	1356 (35.7)	1871 (49.2)	
SGLT2i usage, no. (%)	NA	1506 (39.6)	
Progression to CKD G3B–G5, no. (%)		480 (12.6)	
Patients with worsening G category,[c] no. (%)		1558 (41.0)	
Patients with worsening A category,[d] no. (%)		641 (16.9)	

[a] McNemar test
[b] Wilcoxon signed-rank test
[c] Worsening CKD G category (e.g. G1–G2 or G3A–G3B)
[d] Worsening CKD A category (e.g. A1–A2 or A2–A3)
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HALT-CKD: Holistic Approach to Lowering and Tracking Chronic Kidney Disease; Hb1Ac: haemoglobin 1Ac; IQR: interquartile range; NA: not applicable; SBP: systolic blood pressure; SD: standard deviation; SGLT2i: sodium-glucose cotransporter-2 inhibitor

Table 2. Comparison of CKD stage, at baseline (2017–2018) and at analysis (2023).

Baseline = 3800			Albuminuria categories		
			A1	A2	A3
GFR categories		Total, no. (%)	335 (8.8)	2629 (69.2)	836 (22.0)
	G1	1436 (37.8)	54 (1.4)	1088 (28.6)	294 (7.7)
	G2	1637 (43.1)	79 (2.1)	1194 (31.4)	364 (9.6)
	G3A	727 (19.1)	202 (5.3)	347 (9.1)	178 (4.7)
	G3B	0 (0)	0 (0)	0 (0)	0 (0)
	G4	0 (0)	0 (0)	0 (0)	0 (0)
	G5	0 (0)	0 (0)	0 (0)	0 (0)

Analysis = 3800			Albuminuria categories		
			A1	A2	A3
GFR categories		Total, no. (%)	747 (19.7)	1991 (52.4)	1062 (27.9)
	G1	884 (23.3)	200 (5.3)	528 (13.9)	156 (4.1)
	G2	1568 (41.3)	286 (7.5)	881 (23.2)	401 (10.6)
	G3A	868 (22.8)	200 (5.3)	414 (10.9)	254 (6.7)
	G3B	461 (12.1)	60 (1.6)	164 (4.3)	237 (6.2)
	G4	17 (0.4)	1 (0.0)	4 (0.1)	12 (0.3)
	G5	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)

CKD: chronic kidney disease; GFR: glomerular filtration rate

Coloured cells indicated severity/likelihood of progress to chronic kidney disease. Green cells indicate low risk (if no other markers of kidney disease, no chronic kidney disease); yellow cells indicate moderately increased risk; orange cells indicate high risk; red cells indicate very high risk.

Table 3. Cox regression for time to CKD stages G3B–G5 across 5 years.

Study variables	*P* value	HR	95% CI for HR	
			Lower	Upper
Age at baseline	<0.01	1.052	1.035	1.070
Race	0.44			
Chinese		1.00		
Indian	0.84	0.96	0.65	1.43
Malay	0.13	1.20	0.95	1.52
Others	0.91	0.97	0.55	1.71
Sex (female)	<0.001	4.15	3.17	5.43
Polyclinic	0.046			
Clinic A		1.00		
Clinic B	0.59	0.92	0.69	1.24

Table 3. Cox regression for time to CKD stages G3B–G5 across 5 years. (Cont'd)

Study variables	*P* value	HR	95% CI for HR	
			Lower	Upper
Clinic C	0.04	1.34	1.01	1.78
Clinic D	0.27	0.85	0.64	1.13
Clinic E	0.18	1.24	0.91	1.69
Chronic diseases at baseline				
Diabetes mellitus	0.22	3.45	0.48	24.9
Hypertension	0.12	0.71	0.46	1.09
Hyperlipidaemia	0.44	1.73	0.42	7.08
Smoker or ex-smoker	0.45	1.10	0.86	1.42
Clinical parameters				
BMI	0.482	1.008	0.986	1.030
Baseline HbA1c	<0.001	1.144	1.071	1.223
Baseline serum creatinine	<0.001	1.063	1.057	1.069
Baseline SBP	0.735	0.999	0.991	1.006
Baseline DBP	0.037	1.013	1.001	1.026
Albuminuria stage (at baseline)	<0.001			
A1		1		
A2	0.65	1.09	0.76	1.55
A3	0.004	1.77	1.19	2.61
Albuminuria stage (at analysis)	<0.001			
A1		1		
A2	0.72	1.06	0.76	1.49
A3	<0.001	2.22	1.55	3.19
Management parameters				
Received CKD counselling	0.14	1.39	0.89	2.16
Started on SGLT2i	0.49	0.93	0.76	1.14
Change in ACEi/ARB dose from baseline to at analysis	<0.001			
Maintained same dose		1		
Increased dose	0.94	1.01	0.77	1.32
Decreased dose[a]	<0.001	1.92	1.50	2.45

[a] Decreased dose includes drug cessation
ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; CI: confidence interval; CKD: chronic kidney disease; DBP: diastolic blood pressure; HR: hazard ratio; Hb1Ac: haemoglobin 1Ac; SBP: systolic blood pressure; SGLT2i: sodium-glucose cotransporter-2 inhibitor

and counselling, we did not find any statistically significant difference between combinations of medication use on time to CKD stages G3B–G5 progression (HR 0.72, 95% CI 0.51–1.01, favouring maximised ACEi/ARB dosage).

A separate subgroup analysis was also conducted to ascertain if albuminuria improvement conferred additional protection against CKD progression. After adjusting for similar factors in our previous Cox regression models, including use of ACEi/ARB and SGLT2i, we did not find any statistically significant difference between improvement, maintenance or worsening of albuminuria stage on our primary outcome (P=0.148).

DISCUSSION

Our study aligns with global studies highlighting the importance of avoiding ACEi/ARB discontinuation in CKD patients.[20] While prior research showed that discontinuation increases mortality and ESKD risk in advanced CKD, we found that earlier reduction or cessation also accelerates progression in early CKD patients (stages G1–G3A). We should also focus on early detection and intervention, particularly in female patients and patients with A3 albuminuria, which have been shown to also hasten progression. The HALT-CKD programme recruits patients based on albuminuria readings across 90 days and follows the strict criteria outlined by KDIGO. Database records are judiciously maintained and updated by full-time coordinators, with routine quarterly updates sent to MOH. Therefore, we were able to maintain a good follow-up rate. Given that this is a multicentre study on a multiethnic representative adult Asian population, we believe that this study cohort is representative of the Singapore primary care landscape.

This is one of the first few studies conducted for early CKD patients in primary care in Singapore looking at CKD progression, with an appropriate follow-up duration and a large sample size. Previous local hospital-based studies showed higher risk of CKD progression, but this was because the patients studied had more advanced CKD, with a similar follow-up duration.[21,22] Nevertheless, they conferred similar findings, highlighting the need to begin the fight early against CKD in primary care. The higher risk must be emphasised to older female patients especially during counselling, where lack of sex hormones post-menopause may accelerate CKD progression.[23] Patients seen at clinic C seemed to have higher risk of CKD progression, which may be linked to their demographic profile. On average, they were 1.07 years older (95% CI 0.33–1.81), had a different ethnic composition (P<0.001) and higher diabetes prevalence at baseline (P<0.001).

Primary care practitioners should prioritise maintaining ACEi/ARB therapy and maximising dosage to reduce CKD progression risk among patients with early CKD. The KDIGO 2022 guidelines recommend that the reduction of dosage or discontinuation of ACEi/ARB should be a last resort, only in patients with hyperkalaemia or symptomatic hypotension.[24] Most ACEi/ARB cessations followed hospital discharge for acute kidney injury (AKI), consistent with international findings of a 7-fold increased risk of discontinuation after AKI episodes.[25] Therefore, we recommend restarting and maintaining ACEi/ARB for patients as tolerated, to significantly reduce the risk of CKD G5 and mortality.[26] Despite the non-significant reno-protective benefits to increase ACEi/ARB dose in CKD patients in this study, we agree that maximising the dosage of ACEi/ARB will improve outcomes.[27] Larger studies will be able to detect a significant dose-dependent improvement.

As SGLT2i usage was not part of the indicators examined under the HALT-CKD programme and not available to primary care at the start of the study (2017–2018), we were unable to determine the start date for patients initiated on SGLT2i, but we found its use in patients at analysis (March 2023). While numerous international studies showcased reno-protective and survival benefits,[28] our study did not show any significant improvement in delaying CKD progression. We believe this was due to the confounding of initiating SGLT2i in patients with poorer HbA1c control, more significant albuminuria and at later CKD stages. While delay in CKD progression was also found in another local study,[29] our multivariate-adjusted subgroup analysis, which compared difference in medication regimens between maximising ACEi/ARB dosage and ACEi/ARB with SGLT2i usage, also did not show any significant benefits in delaying CKD progression. Perhaps future local studies could focus purely on examining SGLT2i effectiveness in patients with early CKD.

Another interventionist approach of HALT-CKD is patient counselling, which has been shown to improve patient-reported outcomes, quality of life and clinical outcomes.[30] Locally, counselling sought to improve knowledge, awareness, motivation and attitudes among CKD patients.[31] This also included explanation of the pathophysiology of CKD and medications conducted by trained and experienced coordinators, which contributed to improving medication adherence and patient empowerment about their own conditions. Adoption of healthy lifestyle factors will have an additive effect on health.[32] However, our study did not detect protective effects of counselling on CKD progression, as a significant majority (92.9%) were counselled

upon recruitment to the programme. Moreover, as patients were only counselled once or twice throughout the programme, the number of counselling sessions can be further studied to potentially examine the role of serial counselling in chronic disease management.

This study is not without its limitations. While patients recruited in the HALT-CKD programme demonstrated statistically significant improvements in albuminuria staging, HbA1c and BP readings, the clinical significance of these modest improvements may be limited, and their impact on patient outcomes may not be clinically apparent. Our study also assumed that CKD progression was a one-way regression. However, in reality, early stage CKD is often reversible and influenced by multiple factors. Moreover, fluctuations in serum creatinine due to acute kidney injury and hospital admissions can result in inaccurate representation of CKD severity. The underlying cause of CKD was postulated to be due to diabetes and hypertension, but not definitively determined. This is important because differences in aetiology directly impact the rate of CKD progression.[33] Moreover, the actual relationship between albuminuria status and medication use could be better understood if the study had captured the exact duration of these circumstances, allowing for a continuous variable to be collected and utilised in model development. Discontinuation or suboptimal dosing of ACEi/ARB may be driven by underlying comorbidities, leading to worse outcomes, and the reasons for discontinuation are not accounted or adjusted for. Prescription data may not reflect actual medication use or adherence.

Impact of other clinical parameters such as low-density lipoprotein cholesterol, medications like statins, other anti-hypertensive drugs or diabetes medications, and presence of other cardiovascular comorbidities are known to affect CKD, but these indicators were not captured as part of the HALT-CKD programme. Additionally, we recognise that our retrospective cohort design may be susceptible to unmeasured confounding variables, for which we may not be able to adjust for. For our Cox regression, we only recorded 12.6% of events in 5 years of follow-up. The study duration could be extended to get a more representative picture in predicting CKD progression for early-stage CKD patients. Given our study population of early CKD patients with low CKD-related mortality risk, we did not account for death as a competing risk. This risk is negligible in this population and unlikely to impact the analysis. Future studies can make these adjustments to build a more robust model, which will directly impact clinical guidelines and practice.

CONCLUSION

Our study on HALT-CKD patients demonstrated the programme's positive impact on tracking, monitoring and intervening among CKD patients. Early detection and intervention are crucial in CKD management, best achieved through a multidisciplinary team approach within primary care. Continuing ACEi/ARB significantly delayed CKD progression to stages G3B–G5. Future studies could explore the cardiovascular benefits of improved CKD control, evaluate the cost-effectiveness of nationwide CKD management programmes and assess the true impact of counselling and SGLT2i use among primary care CKD patients.

Ethics statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of the National Healthcare Group (2023/00314) on 29 June 2023.

Declaration

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

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ORIGINAL ARTICLE

Factors influencing smoking cessation: Insights from Singapore's nationwide health and lifestyle survey

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ABSTRACT

Introduction: Singapore has implemented an evidence-based smoking cessation framework to support smokers in quitting. Our study investigated the prevalence and correlates of (1) quit attempts (QA) and quit intentions (QI) among current smokers, and (2) smoking cessation (SC) among ever-smokers in Singapore.

Method: Data was collected from a nationwide survey conducted between 2020 and 2022. QA was defined as attempting to stop smoking at least once in the past 12 months, while QI was defined as planning to quit smoking within the next 30 days or the next 6 months. SC referred to individuals who quit smoking over 6 months ago. Sociodemographic factors, doctor's advice to quit and perceived harm from smoking were assessed using logistic regression among current smokers (n=1024) and ever-smokers (n=1457).

Results: Among current smokers, 31.3% and 41.2% reported QI and QA, respectively. Smokers with secondary or pre-tertiary education were less likely to report QI compared to those with a degree or higher. Doctor's advice to quit was associated with a higher likelihood of QA. Among ever-smokers, 25.3% reported SC, and this was more likely when they perceived smoking 1 or more packs of cigarettes daily as posing a moderate or high health risk.

Conclusion: Educational campaigns should focus on simplifying messages for individuals with lower literacy levels. Smoking cessation training can be incorporated into medical education, and graphic health warnings on cigarette packs can help effectively communicate the dangers of smoking.

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Keywords: epidemiology, public health, quit attempt, quit intention, smoking cessation

CLINICAL IMPACT

What is New

- This study adds to global knowledge on of smoking cessation by identifying key factors within a diverse, multi-ethnic population.
- Higher educational attainment and perceived harm from smoking increased the likelihood of quitting.

Clinical Implications

- Smoking cessation campaigns should be designed to be easily understood, especially by those with lower literacy levels.
- Singapore's current approach, including graphic health warning on cigarette packs, can serve as a model for other countries looking to boost smoking cessation rates.

INTRODUCTION

The global prevalence of smoking has declined over the years. According to authors utilising data from the Global Burden of Disease, Injuries, and Risk Factors Study, from 1990 to 2020, the number of male smokers fell by 27.2%, whereas female smokers fell by 37.9%.[1] Moreover, the decline in smoking prevalence was higher in countries with a higher sociodemographic index than those with a lower sociodemographic index.[1] Despite the fall in smoking prevalence worldwide, challenges in smoking cessation remain. One prominent challenge is the emergence of the e-cigarette, the novelty

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of which has enticed younger individuals to start smoking.[2] Developing countries face additional challenges such as limited awareness and poor access to smoking cessation services.[3]

Similar to other countries, Singapore faces several challenges in improving its smoking cessation rates. A Singapore-based study on patients with substance use disorders identified several hurdles to cessation, including withdrawal symptoms, high cost of smoking cessation treatments, and lack of motivation.[4] Nonetheless, smoking prevalence in Singapore has declined from 13.9% to 10.1% between 2010 to 2020.[5] This decline can be attributed to Singapore's multiprolonged approach to reducing smoking rates, which involves the enforcement of 2 primary legislative acts: the Tobacco (Control of Advertisement and Sale) Act and the Smoking (Prohibition in Certain Places) Act.[6] The former act encompasses measures such as prohibiting the sale of tobacco products to individuals below 21 years old and banning advertisements of tobacco products. The latter act restricts smoking in specific public places, including public transport and hospitals. Additionally, there is the "I Quit" smoking cessation programme that tailors cessation plans for smokers according to their characteristics.[7] These successful strategies to reduce smoking prevalence can be a blueprint for other countries with high smoking prevalence.

International studies, brought together through systematic reviews, have identified factors that influence smoking quit attempts and cessation.[8,9] They found that individuals were more likely to attempt quitting if they had made previous attempts to quit, had longer duration of abstinence and had motivation to quit.[8] Moreover, individuals were more likely to cease smoking if they smoked more cigarettes per day and had a negative perception of smoking.[9] However, a common limitation of these systematic reviews is methodological heterogeneity, whereby the study methods are so diverse that it is difficult to compare findings for several correlates.[8,9] With Singapore's multicultural context and multiprolonged approach to smoking cessation, understanding the factors behind its success can provide a complementary perspective for other countries struggling with low cessation rates.

Hence, our study aimed to examine the prevalence and correlates of different stages of smoking cessation in Singapore, which include intentions and attempts to quit and smoking cessation.

METHOD

This cross-sectional study is part of a larger study that aimed to examine drug consumption in Singapore (i.e. Health and Lifestyle Survey). In addition to drug consumption, the study captured comprehensive information on participants' sociodemographic and lifestyle habits. The methodology is explained in a previous publication.[10] Briefly, the study obtained its sample (n=6509) from an administrative database and adopted a disproportionate stratified sampling design. The analysis was weighted to account for disproportionate stratified sampling, non-response and post-stratification by age, sex and ethnicity. These processes are similar to those used in other population-based studies,[11,12] ensuring that the analysis is representative of Singapore's population.

Individuals were included if they were (1) Singapore citizens or permanent residents living in Singapore, (2) aged 15–65 years old, and (3) literate in English, Mandarin, Malay or Tamil. The exclusion criteria were (1) inability to do the interview and (2) hospitalised or institutionalised during the study period.

The study team employed a survey company to carry out the study between April 2021 and July 2022. The study team also trained lay interviewers to conduct the interviews. Due to COVID-19 restrictions, after obtaining consent from the participant face-to-face, a QR code or link was given to the participants, followed by a unique number for them to complete the online survey.

As the study involved asking sensitive questions such as illicit drug use, steps were taken to protect the participants' identity. No identifiers were collected. The questionnaire was self-administered using tablets, and only verbal consent was taken to avoid documentation. Consent was not documented to minimise the risk of identifying the participants and to protect them from potential legal issues due to their responses. Moreover, parental consent was waived for participants who were minors. All questions had choices such as "I prefer not to answer" and "I don't know" so that participants could skip questions they found personal. Three months after the survey's completion, the survey company destroyed all contact information. The study protocol adhered to the ethical standards of the responsible committee on human experimentation (institutional and national) and with the principles of the Declaration of Helsinki. The study was approved by the Domain Specific Review Board from the National Healthcare Group.[1]

Smoking-related outcomes

The outcome variables were intentions to quit, attempts at quitting, and smoking cessation. Participants were asked to indicate their smoking status using one of the following options: smoker (daily or sometimes a week), former smoker, and

non-smoker. Among current smokers (i.e. participants who smoked daily or a few times a week), intentions to quit were assessed by asking them if they had planned to quit in the next 30 days, next 6 months or not at all in the next 6 months. Those who had planned to quit in the next 30 days or next 6 months were considered to have intentions to quit. Attempts at quitting were evaluated among the current smokers using the question: "How many times have you tried to stop smoking in the past 12 months?" Those who had tried to stop smoking at least once in the past 12 months were classified as having attempted to quit. In examining smoking cessation, the study used the term "ever-smoker" to denote participants who answered either "smoker (daily or sometimes a week)" or "former smoker". Smoking cessation was assessed by asking former smokers whether they "quit more than 6 months ago" or "quit within the last 6 months". Those who had quit more than 6 months ago were considered to have successfully achieved smoking cessation.

Independent variables

Our study examined the association between the outcome variables with the following variables: age, sex, ethnicity, education, marital status, having children, employment, personal income, number of chronic conditions, age of initiation of smoking, perceived risk of harm for occasional smoking and smoking 1 or more packs daily. The perceived risks of harm associated with smoking were self-reported using a 4-point Likert scale (i.e. no risk, little risk, moderate risk and great risk of harm). In this analysis, perceived risk of harm was dichotomised into no/little risk of harm and moderate/great risk of harm. For intentions and attempts to quit, additional variables were examined. These variables were doctor's advice to quit smoking and nicotine dependence.

Chronic conditions were self-reported by individuals using a modified checklist of 18 chronic conditions. These conditions were asthma, arthritis, back problems, cancer, chronic inflammatory bowel disease, chronic lung diseases, congestive heart failure, diabetes, heart disease, hyperlipidaemia, hypertension, kidney failure, migraine, neurological conditions including Parkinson's disease, stomach ulcer, stroke and thyroid disease. Our study classified the responses into 3 groups: no chronic condition, 1 chronic condition, and 2 or more chronic conditions.

Nicotine dependence was assessed using the Fagerstrom test for nicotine dependence.[13] Individuals were classified as having very low nicotine dependence if the score was 0–2, low nicotine dependence if the score was 3–4, and moderate-to-high nicotine dependence if the score was 5 and above.[13]

Statistical analysis

Weighted percentages and unweighted counts were presented for all categorical variables. Multiple logistic regression was conducted to determine the correlates of each smoking-related outcome. For each outcome, the following steps were performed: (1) a univariate logistic regression model was generated to identify potential correlates, and (2) variables with *P* value <0.05 were included in the initial multivariable logistic regression using the enter method. Subsequently, variables with *P* value >0.05 were removed and another multivariable logistic regression analysis was performed to determine the final model.

The results of the models were presented in odds ratio (OR) and 95% confidence interval (CI). Standard error was estimated using Taylor linearisation. The analysis was generated using IBM SPSS version 23 (IBM Corp, Armonk, US) and Stata/MP 18.0 (StataCorp, College Station, US), with 2-tailed tests at a 5% significance level.

RESULTS

The analysis included 1457 ever-smokers, of which 1024 were current smokers. Among the 1024 current smokers, 1021 answered the question on intention to quit and 881 answered the question on attempts to quit.

Most participants in both groups were male (current smokers: 82.99%, ever-smoker: 80.54%), of Chinese ethnicity (current smoker: 63.48%, ever-smoker: 63.15%), married (current smoker: 59.24%, ever-smoker: 59.71%), had no children (current smoker: 65.94%, ever-smoker: 64.97%), and were either employed or self-employed (current smoker: 86.82%, ever-smoker: 86.26%) (Table 1). Regarding smoking-related variables, most participants in both groups started smoking at 18 years of age or later (current smoker: 51.55%, ever-smoker: 52.53%), and received advice from a doctor to quit smoking (current smoker: 84.55%, ever-smoker: 87.66%) (Table 1). Additionally, most participants in both groups believed that smoking occasionally or smoking at least 1 pack per day presented a moderate to great risk of harm (Table 1).

Among current smokers, the prevalence of intentions and attempts to quit were 31.27% (n=385) and 41.21% (n=427), respectively (Fig. 1). Among ever-smokers, the prevalence of smoking cessation was 25.25% (n=345).

Table 2 presents the logistic regression models for intentions to quit. In the multivariable model, current smokers were more likely to contemplate quitting if they were of Malay (versus [vs] Chinese, OR 1.62, 95% CI 1.004–2.61) or Indian ethnicity (vs

Table 1. Characteristics of current smokers and ever-smokers.

	Current smokers (n=1024)		Ever-smokers (n=1457)	
	Weighted %	Unweighted n	Weighted %	Unweighted n
Age groups, years				
15–34	33.97	369	35.10	554
35–49	32.16	368	33.73	524
50–65	33.87	287	31.17	379
Sex				
Female	17.01	183	19.46	308
Male	82.99	841	80.54	1149
Ethnicity				
Chinese	63.48	233	63.15	335
Malay	23.92	493	24.05	700
Indian	9.65	262	9.45	366
Others	2.95	36	3.36	56
Education				
Degree/professional qualification and postgraduate and above	15.82	117	20.44	222
No formal education/primary	12.96	128	10.31	165
Secondary school	34.17	320	31.49	426
Pre-tertiary education [a]	37.06	447	37.75	630
Marital status				
Married	59.24	602	59.71	856
Single	32.71	324	32.88	469
Separated/widowed/divorced	8.05	94	7.41	125
Have children				
No	65.94	632	64.97	902
Yes	34.06	392	35.03	555
Employment				
Employed/self-employed	86.82	874	86.26	1217
Economically inactive/students	9.05	89	9.84	153
Unemployed/temporarily laid off	4.13	44	3.90	64
Personal income, SGD				
No income/below 2000	39.51	355	37.04	484
2000 to 3999	35.72	341	35.27	483
4000 to 6999	13.31	97	14.63	147
7000 and above	11.47	68	13.07	113

Table 1. Characteristics of current smokers and ever-smokers. (Cont'd)

	Current smokers (n=1024)		Ever-smokers (n=1457)	
	Weighted %	Unweighted n	Weighted %	Unweighted n
Number of chronic conditions				
0	51.94	521	48.74	711
1	29.61	269	30.03	391
2 or more	18.44	222	21.23	339
Age of onset for smoking				
<18 years old	48.45	406	47.47	569
≥18 years old	51.55	418	52.53	608
Received advice from doctor to stop smoking				
Yes	15.45	182	12.34	
No	84.55	839	87.66	
Nicotine dependence				
Very low	52.63	533		
Low	28.57	285		
Moderate to high	18.79	203		
Perceived risk of harm (smoke occasionally)				
No/little risk of harm (reference)	46.96	379	42.35	494
Moderate/great risk of harm	53.04	476	57.65	741
Perceived risk of harm (smoke 1 or more packs per day)				
No/little risk of harm (reference)	13.86	127	10.91	142
Moderate/great risk of harm	86.14	733	89.09	1104

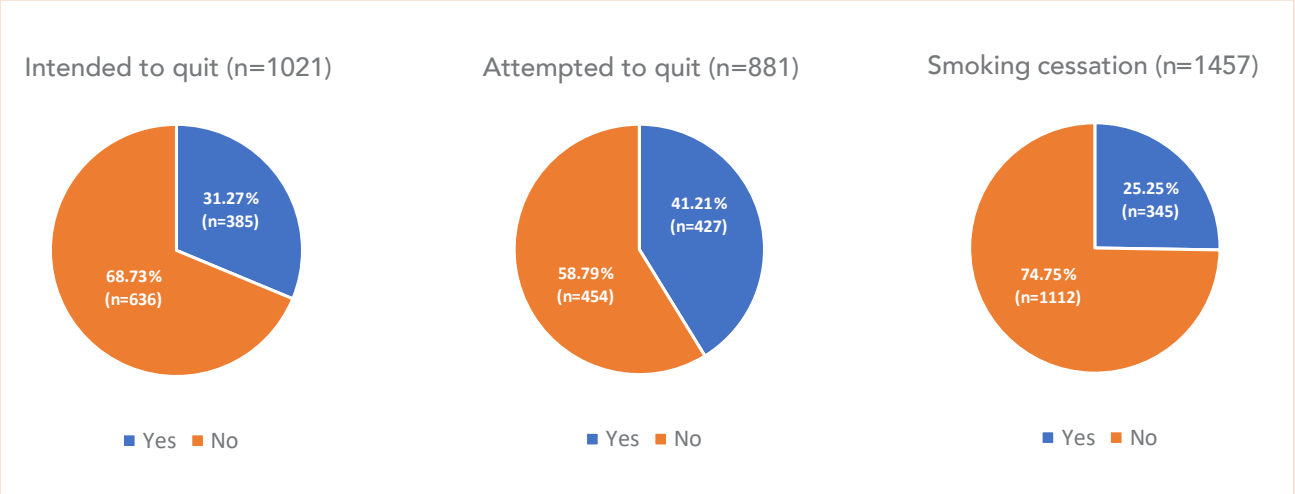
Missing data: education (current smoker [n=12], ever-smoker [n=14]); marital status (current smoker [n=4], ever-smoker [n=7]); employment (current smoker [n=17], ever-smoker [n=23]); personal income (current smoker [n=163], ever-smoker [n=230]); number of chronic conditions (current smoker [n=12], ever-smoker [n=16]); age of initiation to smoking (current smoker [n=200], ever-smoker [n=280]); received advice from doctor to stop smoking (current smoker [n=3]); nicotine dependence (current smoker [n=3]); perceived risk of harm (smoke occasionally) (current smoker [n=169], ever-smoker [n=222]); perceived risk of harm (smoke 1 of more packs per day) (current smoker [n=164], ever-smoker [n=211])

[a] Pre-tertiary education includes vocational institute/institute of technical education/pre-university/junior college/diploma/International Baccalaureate

Chinese, OR 2.59, 95% CI 1.61–4.18), and had attempted to quit previously (OR 8.15, 95% CI 5.02–13.22). Current smokers were less likely to have intentions to quit if they had secondary school education (vs degree and above, OR 0.32, 95% CI 0.14–0.69) or pre-tertiary education (vs degree and above, OR 0.37, 95% CI 0.17–0.80), separated/ widowed/ divorced (vs married, OR 0.34, 95% CI 0.17–0.69), and had low (vs very low, OR 0.53, 95% CI 0.31–0.89) or moderate-to-high nicotine dependence (vs very low, OR 0.53, 95% CI 0.29–0.97).

For correlates for attempts to quit, current smokers were more likely to attempt quitting if they were of Malay (vs Chinese, OR 2.21, 95% CI 1.49–3.29) or Indian ethnicity (vs Chinese, OR 2.18, 95% CI 1.40–3.39), had received doctor's advice to quit smoking (OR 2.36, 95% CI 1.29–4.32), and perceived occasional smoking to have moderate or great risk of harm (vs no/ little harm, OR 1.91, 95% CI 1.24–2.94) (Table 3). They were less likely to attempt quitting if they had moderate-to-high nicotine dependence (vs very low dependence, OR 0.49, 95% CI 0.28–0.85).

Fig. 1. Proportion of current smokers that had intentions or attempts to quit, and proportion of ever-smokers that achieved smoking cessation.



In Table 4, ever-smokers were more likely to cease smoking if they had 2 or more chronic conditions (vs no chronic condition, OR 2.14, 95% CI 1.35–3.38), and perceived smoking 1 or more packs daily to have moderate or great risk of harm (vs no/little harm, OR 4.52, 95% CI 1.89–10.80). They were less likely to quit smoking if they were male (vs female, OR 0.64, 95% CI 0.43–0.94), and had primary school education and below (vs degree and above, OR 0.19, 95% CI 0.10–0.38), secondary school (vs degree and above, OR 0.39, 95% CI 0.23–0.65) or pre-tertiary education (vs degree and above, OR 0.54, 95% CI 0.34–0.84).

DISCUSSION

Our study examined the prevalence of intentions to quit, attempts at quitting and smoking cessation in Singapore. Our study has a higher proportion of current smokers who intended to quit (31.27%) and attempted to quit (41.21%), and the proportion of those who ceased smoking successfully lagged behind (25.25%). Consistent with this finding, a study from the US reported a higher proportion of intention to quit (77.1%) than smoking cessation (7.5%).[14] A similar trend was also found in a Malaysian study, which found that while 49.1% of smokers attempted quitting, the success rate for smoking cessation was lower at 31.4%.[15] These studies imply that globally, smokers face challenges in translating intention and attempts to quit into successful cessation.

A prominent finding in our study was that current smokers who were advised by a doctor to quit smoking were more likely to attempt quitting. Similarly, in a systematic review that examined 42 trials worldwide, brief advice from a physician increased the chance of smoking cessation.[16] These findings suggest that integrating cessation advice into primary healthcare settings can be an important intervention for smoking cessation worldwide. Currently, in Singapore, a framework for addressing tobacco dependence exists within the primary healthcare setting.[17] Moreover, smoking cessation clinics are available in polyclinics and restructured hospitals.[17] Other countries can modify these measures by providing appropriate training to clinicians on offering advice and support based on their cultural context.

Our study also found that individuals with a higher perceived risk of harm from 1 or more packs of cigarettes were more likely to quit smoking successfully. Moreover, those with a higher perceived risk of harm from occasional smoking were more likely to attempt quitting. These findings align with studies in other countries, demonstrating that awareness of the harmful effects of smoking is associated with smoking cessation.[18,19] In a study among Korean adolescents, graphic health warnings increased the odds of attempts to quit by 1.72 times for boys and by 1.74 times for girls.[18] An Australian market research reported that among ever-smokers, 61% of those who quit successfully said that graphic health warnings made them more concerned about their smoking habits, leading them to quit.[19]

Our study found that those with nicotine dependence were less likely to have the intention

Table 2. Logistic regression with intentions to quit as outcome.

	Intentions to quit			
	Univariate regression		Multivariable regression (n=874)	
	OR (95% CI)	*P* value [a]	OR (95% CI)	*P* value [a]
Age groups, years				
15–34 (reference)				
35–49	0.55 (0.37–0.82)	**0.003**		
50–65	0.45 (0.28–0.72)	**0.001**		
Sex				
Female (reference)				
Male	0.84 (0.53–1.33)	0.459		
Ethnicity				
Chinese (reference)				
Malay	1.73 (1.21–2.45)	**0.002**	1.62 (1.004–2.61)	**0.048**
Indian	2.48 (1.69–3.64)	**<0.001**	2.59 (1.61–4.18)	**<0.001**
Others	2.50 (1.20–5.23)	**0.014**	2.01 (0.84–4.82)	0.117
Education				
Degree/professional qualification and postgraduate and above (reference)				
No formal education/primary	0.35 (0.17–0.73)	**0.005**	0.33 (0.11–1.02)	0.054
Secondary school	0.43 (0.24–0.76)	**0.004**	0.32 (0.14–0.69)	**0.004**
Pre–tertiary education [b]	0.68 (0.39–1.16)	0.156	0.37 (0.17–0.80)	**0.011**
Marital status				
Married (reference)				
Single	1.58 (1.08–2.32)	**0.019**	0.92 (0.56–1.52)	0.743
Separated/ widowed/divorced	0.56 (0.28–1.15)	0.113	0.34 (0.17–0.69)	**0.003**
Have children				
Yes (reference)				
No	1.44 (0.98–2.10)	0.060		
Employment				
Employed/self–employed (reference)				
Economically inactive/students	0.73 (0.38–1.40)	0.349		
Unemployed/temporarily laid off	1.37 (0.55–3.39)	0.495		
Personal income, SGD				
No income/below 2000 (reference)				
2000 to 3999	0.85 (0.55–1.31)	0.452		
4000 to 6999	0.60 (0.30–1.18)	0.137		
7000 and above	1.04 (0.51–2.12)	0.917		

Table 2. Logistic regression with intentions to quit as outcome. (Cont'd)

	Intentions to quit			
	Univariate regression		Multivariable regression (n=874)	
	OR (95% CI)	*P* value [a]	OR (95% CI)	*P* value [a]
Number of chronic conditions				
0 (reference)				
1	0.79 (0.51–1.21)	0.275		
2 or more	1.27 (0.79–2.05)	0.327		
Age of initiation to smoking				
<18 years old (reference)				
≥18 years old	1.18 (0.79–1.77)	0.430		
Received advice from doctor to stop smoking				
No (reference)				
Yes	1.56 (0.97–2.49)	0.066		
Nicotine dependence				
Very low (reference)				
Low	0.42 (0.27–0.65)	**<0.001**	0.53 (0.31–0.89)	**0.017**
Moderate to high	0.42 (0.25–0.69)	**0.001**	0.53 (0.29–0.97)	**0.039**
Perceived risk of harm (smoke occasionally)				
No/little risk of harm (reference)				
Moderate/great risk of harm	1.88 (1.26–2.81)	**0.002**		
Perceived risk of harm (smoke 1 or more packs per day)				
No/little risk of harm (reference)				
Moderate/great risk of harm	1.60 (0.88–2.90)	0.125		
Previous attempt to quit				
No (reference)				
Yes	7.87 (4.95–12.52)	**<0.001**	8.15 (5.02–13.22)	**<0.001**

CI: confidence interval; OR: odds ratio
[a] *P* values in bold indicate statistical significance (*P* <0.05).
[b] Pre-tertiary education includes vocational institute/institute of technical education/pre-university/junior college/diploma/ International Baccalaureate

to quit or to attempt to quit smoking. This finding is not surprising, as they likely experienced stronger addiction or more severe withdrawal symptoms. This finding highlights the need for increased support, such as nicotine replacement therapy and counselling, for these individuals. Additionally, future research could explore interventions and communication strategies that might encourage them to develop the intention to quit or take steps towards quitting smoking.

For sociodemographic correlates, a noteworthy finding is that lower educational qualification is significantly associated with a lower likelihood of intention to quit and smoking cessation. These findings corroborate with findings from other population-based studies. A longitudinal Finland-based study found that higher educational levels were associated with higher odds of smoking cessation.[20] Similarly, a study that utilised data from Australia, Canada, the UK and US reported that

Table 3. Logistic regression with attempts to quit as outcome.

	Attempts to quit			
	Univariate regression		Multivariable regression (n=756)	
	OR (95% CI)	*P* value [a]	OR (95% CI)	*P* value [a]
Age groups, years				
15–34 (reference)				
35–49	0.57 (0.38–0.87)	**0.009**		
50–65	0.74 (0.46–1.20)	0.224		
Sex				
Female (reference)				
Male	1.29 (0.79–2.12)	0.310		
Ethnicity				
Chinese (reference)				
Malay	2.17 (1.51–3.11)	**<0.001**	2.21 (1.49–3.29)	**<0.001**
Indian	2.18 (1.46–3.27)	**<0.001**	2.18 (1.40–3.39)	**0.001**
Others	2.46 (1.11–5.45)	**0.027**	2.15 (0.84–5.47)	0.110
Education				
Degree/professional qualification and postgraduate and above (reference)				
No formal education/primary	1.07 (0.49–2.34)	0.865		
Secondary school	1.00 (0.53–1.87)	0.996		
Pre-tertiary education [b]	1.64 (0.91–2.95)	0.099		
Marital status				
Married (reference)				
Single	1.77 (1.18–2.64)	**0.006**		
Separated/widowed/divorced	0.68 (0.32–1.41)	0.297		
Have children				
Yes (reference)				
No	1.11 (0.75–1.63)	0.613		
Employment				
Employed/self-employed (reference)				
Economically inactive/students	1.21 (0.61–2.41)	0.583		
Unemployed/temporarily laid off	1.59 (0.58–4.40)	0.369		
Personal income, SGD				
No income/below 2000 (reference)				
2000 to 3999	1.11 (0.70–1.76)	0.653		
4000 to 6999	0.81 (0.42–1.59)	0.547		
7000 and above	1.17 (0.57–2.43)	0.666		

Table 3. Logistic regression with attempts to quit as outcome. (Cont'd)

	Attempts to quit			
	Univariate regression		Multivariable regression (n=756)	
	OR (95% CI)	*P* value [a]	OR (95% CI)	*P* value [a]
Number of chronic conditions				
0 (reference)				
1	0.81 (0.52–1.27)	0.358		
2 or more	1.18 (0.71–1.94)	0.524		
Age of initiation to smoking				
<18 years old (reference)				
≥18 years old	1.12 (0.74–1.69)	0.580		
Received advice from doctor to stop smoking				
No (reference)				
Yes	2.38 (1.42–3.98)	**0.001**	2.36 (1.29–4.32)	**0.005**
Nicotine dependence				
Very low (reference)				
Low	0.54 (0.35–0.84)	**0.007**	0.62 (0.38–1.03)	0.066
Moderate to high	0.56 (0.34–0.92)	**0.021**	0.49 (0.28–0.85)	**0.011**
Perceived risk of harm (smoke occasionally)				
No/little risk of harm (reference)				
Moderate/great risk of harm	2.12 (1.41–3.20)	**<0.001**	1.91 (1.24–2.94)	**0.003**
Perceived risk of harm (smoke 1 or more packs per day)				
No/little risk of harm (reference)				
Moderate/great risk of harm	1.61 (0.90–2.88)	0.107		

CI: confidence interval; OR: odds ratio
[a] *P* values in bold indicate statistical significance (*P* <0.05).
[b] Pre-tertiary education includes vocational institute/institute of technical education/pre-university/junior college/diploma/ International Baccalaureate

smokers with lower education had 1.4 times higher odds of not intending to quit than those with higher education.[21]

The aforementioned findings can have broader significance to the development of global public health strategies. In Singapore, the perceived risk of harm from cigarette smoking is heightened by putting graphic health warnings on cigarette packs.[22] Moreover, educational programmes were implemented to target students from a young age, raising awareness of the harmful effects of smoking.[23] These approaches can be valuable for other countries seeking to increase smoking cessation prevalence. However, successful adaption may require tailoring their approaches based on their population's education level and awareness level.

One strength of our study is that the use of a structured questionnaire ensured that the methodology could be replicated in other countries. Although the specific questions related to smoking should be tailored according to the cultural context of the country, the overall structure of the questionnaire can be universally applied. By having a standardised questionnaire, the results from different countries can be compared. Another strength is that because the data is from a population-based study, the results can be generalised to the

Table 4. Logistic regression with smoking cessation as outcome.

	Smoking cessation			
	Univariate regression		Multivariable regression (n=1230)	
	OR (95% CI)	*P* value [a]	OR (95% CI)	*P* value [a]
Age groups, years				
15–34 (reference)				
35–49	1.29 (0.90–1.85)	0.169		
50–65	0.8 (0.51–1.25)	0.326		
Sex				
Female (reference)				
Male	0.63 (0.43–0.92)	**0.017**	0.64 (0.43–0.94)	**0.023**
Ethnicity				
Chinese (reference)				
Malay	0.89 (0.65–1.20)	0.444		
Indian	0.70 (0.49–1.00)	0.052		
Others	1.55 (0.83–2.88)	0.170		
Education				
Degree/professional qualification and postgraduate and above (reference)				
No formal education/primary	0.14 (0.08–0.26)	**<0.001**	0.19 (0.10–0.38)	**<0.001**
Secondary school	0.30 (0.18–0.49)	**<0.001**	0.39 (0.23–0.65)	**<0.001**
Pre–tertiary education [b]	0.46 (0.30–0.71)	**<0.001**	0.54 (0.34–0.84)	**0.007**
Marital status				
Married (reference)				
Single	0.93 (0.65–1.33)	0.679		
Separated/widowed/divorced	0.62 (0.30–1.27)	0.190		
Have children				
Yes (reference)				
No	0.76 (0.54–1.07)	0.116		
Employment				
Employed/self–employed (reference)				
Economically inactive/students	1.46 (0.88–2.41)	0.145		
Unemployed/temporarily laid off	0.77 (0.34–1.72)	0.517		
Personal income, SGD				
No income/below 2000 (reference)				
2000 to 3999	1.26 (0.81–1.96)	0.296		
4000 to 6999	2.13 (1.20–3.79)	**0.010**		
7000 and above	2.13 (1.17–3.87)	**0.013**		

Table 4. Logistic regression with smoking cessation as outcome. (Cont'd)

	Smoking cessation			
	Univariate regression		Multivariable regression (n=1230)	
	OR (95% CI)	*P* value [a]	OR (95% CI)	*P* value [a]
Number of chronic conditions				
0 (reference)				
1	1.35 (0.90–2.00)	0.144	1.35 (0.88–2.07)	0.168
2 or more	2.08 (1.36–3.17)	**0.001**	2.14 (1.35–3.38)	**0.001**
Age of onset for smoking				
<18 years old (reference)				
≥18 years old	1.08 (0.74–1.56)	0.699		
Perceived risk of harm (smoke occasionally)				
No/little risk of harm (reference)				
Moderate/great risk of harm	1.79 (1.23–2.60)	**0.002**		
Perceived risk of harm (smoke 1 or more packs per day)				
No/little risk of harm (reference)				
Moderate/great risk of harm	5.37 (2.32–12.42)	**<0.001**	4.52 (1.89–10.80)	**0.001**

CI: confidence interval; OR: odds ratio
[a] *P* values in bold indicate statistical significance (*P* <0.05).
[b] Pre-tertiary education includes vocational institute/institute of technical education/pre-university/junior college/diploma/International Baccalaureate

Singapore population. However, caution should be exercised when generalising to other countries. Although our results aligned with some studies from other countries, policies should be tailored according to the needs of the population.

A limitation of our study is that the study was done during the COVID-19 period. Studies have shown that COVID-19 can act as a hindrance and a catalyst for smoking cessation, due to reasons such as boredom and fear.[24,25] It is unclear whether the effect of COVID-19 on smoking cessation will be sustained over time. Another limitation of our quantitative study is that we are unable to examine the impact of smoking cessation interventions, as well as the reasons that people continue or quit smoking. Future studies can build on this study by examining the efficacy of different smoking cessation messages across countries, as well as the effect of clinician training on smoking cessation behaviours. Moreover, qualitative studies can explore the barriers and facilitators of smoking cessation.

CONCLUSION

In conclusion, our study contributes to the global knowledge of smoking cessation by identifying sociodemographics, perceived risk of harm from cigarette smoking, nicotine dependence, and clinicians' advice associated with smoking cessation behaviour in a multi-ethnic population. As lower education is associated with poorer quit intention and smoking cessation, educational campaigns should be tailored for easy understanding by individuals with lower literacy levels. Moreover, smoking cessation training can be integrated into medical education. Singapore's approach to smoking cessation behaviours, such as graphic health warnings on cigarette packs and smoking cessation clinics, can serve as a model for other countries aiming to improve smoking cessation behaviours.

Ethics statement

The study adhered to the ethical standards of the responsible committee on human experimentation

(institutional and national) and with the Declaration of Helsinki. The study was approved by the Domain Specific Review Board from the National Healthcare Group (NHG-DSRB Ref 2019/0077).

Declaration

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ORIGINAL ARTICLE

Enhancing guidelines for managing cognitively impaired drivers: Insights from Western evidence for Asian adaptation

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ABSTRACT

Introduction: The global incidence of dementia is increasing, and cognitively impaired drivers are at a higher risk of crashes compared to healthy drivers. Doctors face challenges in assessing these at-risk drivers, with questionable adherence to existing guidelines. This study aimed to review and compare guidelines for managing cognitively impaired drivers from various countries.

Method: A scoping review was conducted to identify relevant guidelines, which were then descriptively compared with Singapore's guideline.

Results: Eleven guidelines from 8 countries: US (n=2), Canada (n=2), UK (n=2), Ireland, Belgium, Australia, New Zealand and Singapore were reviewed. All guidelines support driving assessments and conditional licensing in ordinary (i.e. non-professional) drivers with dementia. Canada stands out for not allowing co-piloting and geographical restrictions in conditional licensing practice. Few guidelines provide indemnity for doctors reporting to licensing authorities, and communication about the impact of dementia on car insurance is rarely addressed. Most Western guidelines include evidence-based approaches, provisions for drivers with mild cognitive impairment and early discussions on transitioning from driving. A clinic-based functional screening toolbox and 2 clinical algorithms (1 with and 1 without the Clinical Dementia Rating scale) were identified as having universal applicability. Singapore's guideline, by comparison, is outdated and lacks both developmental rigour and guidance on managing mild cognitive impairment and transitioning drivers out of driving.

Conclusion: Comprehensive, evidence-based guidelines from Western countries provide valuable resources that can help Singapore design or update its guideline.

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Keywords: cognitively impaired drivers, family medicine, fitness-to-drive, geriatric medicine, guidelines

CLINICAL IMPACT

What is New

- This study identified gaps in the current Singapore guideline for managing cognitively impaired drivers and provides useful insights from Western countries that could be adapted to the Asian context.
- A clinic-based functional screening toolbox and 2 clinical algorithms could have potential universal applications.

Clinical Implications

- Singapore's guideline for managing cognitively impaired drivers requires updates to improve its developmental rigour and content.
- This study's findings offer useful evidence-based resources that can assist Asian countries in designing or updating their guidelines.

INTRODUCTION

Licensing authorities rely on medical certifications of fitness-to-drive when renewing licence for drivers who are at higher risk of crashes. Drivers with cognitive impairment are 2 to 8 times more likely to be involved in a crash compared to those without such impairments,[1] and studies show they have a significantly higher risk of accidents in real-world driving situations.[2] However, many doctors have reported challenges with self-confidence and ethical dilemmas in evaluating these drivers, leading to inconsistent adherence to existing guidelines.[3-4] The ambiguity in these guidelines on when drivers with cognitive decline should cease driving is partly due to insufficient evidence linking

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cognition decline to crash risk.[5] This has prompted calls for more rigorous updates to guidelines, grounded in expert opinion.[6] Assessing medical fitness-to-drive in individuals with early-stage cognitive impairment or dementia is more difficult than evaluating those with moderate to advanced dementia. While some drivers in the early stages of cognitive decline may continue to drive safely for some time after diagnosis, others may fail on-road driving tests.[7] The unpredictable progression of the disease makes it challenging to predict when driving becomes unsafe. At the same time, concerns have emerged about the negative impact of stopping driving on health and well-being.[8] With dementia cases rising globally and Asia's population ageing more rapidly than the West,[9] it is crucial to review and summarise current guidelines on managing cognitively impaired drivers to support timely updates and inform policymakers in Asia.

METHOD

A scoping review was conducted between October 2022 and October 2023 to identify guidelines for managing cognitively impaired drivers. Three authors independently screened the titles and abstracts of 4850 English publications (from 2018 to 2022) across 6 databases (Table 1). Out of these, 92 studies were selected for full-text review. Initial thematic analysis identified 5 studies that highlighted guidelines from the US, Canada, UK, Ireland, Belgium, Australia and New Zealand. The most recent versions of these guidelines were then accessed online for a comparative descriptive analysis with Singapore's guideline.

RESULTS

A total of 11 guidelines from 8 countries: US (n=2),[10,11] Canada (n=2),[12,13] UK (n=2),[14,15] Ireland (n=1),[16] Belgium (n=1),[17] Australia (n=1),[18] New Zealand (n=1)[19] and Singapore (n=1) were reviewed.[20] All guidelines were designed to assist healthcare professionals in assessing fitness-to-drive, while acknowledging the licensing authority as the ultimate decision-maker regarding a driver's licensing status. Each guideline includes a legal disclaimer. The specific characteristics and designs of the guidelines are outlined in Table 2.

All countries allow conditional licensing for ordinary (i.e. non-professional) drivers who are deemed fit based on individualised assessments, although the frequency of medical and driving reviews varies. Canada has the strictest standards, prohibiting compensatory measures such as co-piloting or geographic restrictions, and instead mandates regular medical/driving reviews to maintain licence status. Conditional licensing for professional or heavy vehicle drivers varies between countries, with New Zealand prohibiting it altogether. Singapore's guideline for this group is unclear (Table 3).

Table 1. Scoping review literature search.

Databases	Medline, PubMed, CINAHL, Cochrane Library, Web of Science, APA PsycInfo
Keyword search	automobile driving, driver, driving, cognitive dysfunction, dementia, cognitive decline, cognitive impair, mental deterioration, mild neurocognitive disorder, cognition disorder, Alzheimer
Inclusion criteria	Editorials, policies, guidelines, statements, driving risks, accident rates on 4-wheel motor vehicles
Exclusion criteria	Studies from Africa, and on tricycles and motorbikes
Thematic contents of full-text reviewed studies	Recommendations/guidelines/guidance, doctors, literature reviews (scoping/systematic), off- and on-road tests, driving simulator, motor-vehicle risk, types of dementia, naturalistic driving, driving cessation, caregiver, biomarkers, vision and frontier research
Identified studies with guidelines on the management of cognitively impaired drivers	Rapoport MJ, Chee J N, Carr DB et al. An international approach to enhancing a national guideline on driving and dementia. Curr Psychiatry Rep 2018;20:16. Selway JS. To drive or not to drive: when there is dementia. J Nurse Pract 2018;14:202-9. Walsh L, Chacko E, Cheung G. The process of determining driving safety in people with dementia: a review of the literature and guidelines from 5 English speaking countries. Australas Psychiatry 2019;27:480-5. Stamatelos P, Economou A, Stefanis L, et al. Driving and Alzheimer's dementia or mild cognitive impairment: a systematic review of the existing guidelines emphasizing on the neurologist's role. Neurol Sci 2021;42:4953-63. Staplin L, Lococo KH, Mastromatto T, et al. CE: Can Your Older Patients Drive Safely? Am J Nurs 2017;117:34-43.

Table 2. Characteristics and design of guidelines on cognitively impaired drivers.

Origins	Each of the Western countries has at least 1 guideline published with a government-linked transportation/licensing agency. Six out of these 7 guidelines from Western countries are joint publications with local medical associations. Sole publications by medical associations also exist (US, Canada, UK and Singapore).
Endorsements	Ten guidelines are officially endorsed by 1 or more (range 1–10) organisations related to healthcare. One guideline (US) did not receive endorsement due to public administration protocol.
Year of publication and version number	Latest publications: 2022 (Ireland, UK, Australia) 2021 (Canada) 2019 (US, Canada) 2018 (UK) 2017 (Belgium) 2014 (New Zealand) 2011 Singapore 2010 (US, reaffirmed 15 May 2023) Earliest publication: 1974 (Canada) First publication: 2015 (Ireland) 1997 (Singapore)
Online access	Free public access: Western guidelines except Belgium Free online access: Singapore Medical Association members
Length of document	A4 pages: range 2–289 pages
Key-points or bolded statements; appendices	All guidelines
Algorithms, flowcharts/pathways, figures, case studies	Some guidelines
Design	
Type 1	Medical standards of licensing in ordinary and professional/heavy vehicle groups of drivers (n=6)
Type 2	Clinical information to guide the process of assessment and decision-making on driving fitness (n=5)

The requirement for doctors to report at-risk drivers to licensing authorities differs across countries. In British Columbia (Canada) and New Zealand, a hybrid system is used, where doctors are only required to report if the driver disregards medical advice to stop driving (Table 3).

Legal protection for doctors who report at-risk drivers also varies. In Australia, indemnity is provided to all informants reporting such drivers. Canadian doctors have explicit indemnity and protection when reporting (Table 3). All guidelines promote a functional approach to determining driving fitness, combining medical assessment with practical off-road and on-road tests. In 6 countries, occupational therapists are involved in driving assessments (Table 3).

Most guidelines are developed using evidence-based approaches.[10-16,18] US and Canada are notable for explicitly citing levels of evidence supporting their practices,[11,12] while Belgium and Singapore rely on local expert panel review, with Singapore's literature references being outdated. In Singapore's guideline, the sources of information are dated between 1983 and 1995, with references in the Cognitive Disorder section specifically ranging from 2006 to 2008.

The Clinical Assessment of Driving-Related Skills (CADReS) is an evidence-based off-road functional screening toolbox that can be used within the "Plan for Older Drivers' Safety" algorithm (Table 4).[10] Additionally, an algorithm is available to assess driving risk levels across a continuum, integrating the Clinical Dementia Rating (CDR) (Level A evidence) with other risk factors (Level B or C or no evidence). A CDR score of 2.0 identifies a driver as a high-risk driver and recommends immediate cessation of driving.[11]

There is also an evidence-based guideline that assesses driving risk without using the CDR scale.[12] In this approach, after evaluating the patient's condition, comorbidities, medication use, behavioural issues, driving history, cognitive tests and physical examination findings, clinicians are asked 2 key questions: (1) Would I let a loved one get into a car that this patient is driving? and (2) Would I want to have a loved one cross the street

Table 3. Summary of guidelines in managing drivers with cognitive impairment and dementia, and development of these guidelines.

	US	Canada	UK	Ireland	Belgium	Australia	New Zealand	Singapore
Conditional licensing for ordinary drivers:								
Stated time of day	Allowed	No	Allowed	Allowed	Allowed	Allowed	Allowed	Allowed
Stated locations	Allowed	No	Allowed	Allowed	Allowed	Allowed	Allowed	Allowed
With companion	Allowed	No	Allowed	Allowed	Allowed	Allowed	Allowed	Allowed
Frequency of medical and driving reviews	Varies between states	Every 6–12 months or earlier	Annually	Every 6–12 months or earlier	Based on individualised recommendations	Annually	Based on individualised recommendations	Every 6–12 months or earlier
Conditional licensing for professional/heavy vehicle drivers	Varies between states	Same as ordinary drivers	No for those with dementia	No for those with dementia	Aware of higher standards but not specified	Same as ordinary drivers	No for those with cognitive impairment and dementia	Unclear: no for those with behavioural symptoms
Mandatory reporting by doctors to licensing authorities	Varies between states	Yes in 9 provinces and only if medical advice is ignored in British Columbia No in Alberta, Quebec	No	No	No	Yes in South Australia and Northern Territory No in other states	No unless driver ignores given medical advice during licence renewal stage	No
Explicit indemnity for reporting to licensing authorities	Varies between states	Yes by the state and Canadian Medical Association	No	Yes by the Irish Medical Association for at-risk, non-compliant drivers	No	Yes irrespective of professional status	Only when driver ignores given medical advice during licence renewal stage	No
Functional model to driving fitness (medical, off-road and on-road assessment)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Driving assessments/by occupational therapists	Yes	Yes	Not stated; licensing authorities will arrange	Yes	Not stated; licensing authorities will arrange	Yes	Yes; licensing authorities will arrange	Yes
Development of guidelines/evidence-based approach reported	Yes	Yes with international experts	Yes	Yes	Literature review by local experts	Yes with international experts	Unclear: draft reviewed by local health experts and disability groups	Literature review by local experts

Table 4. Clinical Assessment of Driving-Related Skills toolbox: summary of screening contents and tools.

General driving assessment	Driving history (Modified Driving Habits Questionnaire), instrumental activities of daily living, changes in medication
Vision	Visual perception, visual processing, visual spatial skills, visual acuity (Snellen chart), visual field screening, contrast sensitivity (Pelli-Robson contrast sensitivity chart)
Cognition	Montreal Cognitive Assessment test, Trail Making tests, Clock Drawing test; Snellgrove Maze Test
Motor/sensory	Rapid Pace test, Get-Up-and-Go test, functional range of motion tests (normal vs impaired)

Adapted from Pomidor A (Ed). Clinician's Guide to Assessing and Counselling Older Drivers. 4th ed. New York: American Geriatrics Society; 2019.

in front of a car that this patient is driving? If the response is "uncertain", the driver is referred for on-road testing. If the response is "absolutely not", the driver is considered high-risk and advised to stop driving, pending further investigation by the licensing authority.[12]

Only guidelines from Western countries emphasise early engagement with patients to discuss eventual driver retirement and provide support for transitioning to alternative transportation and lifestyle adjustments. In the UK, doctors are required to inform drivers diagnosed with dementia of their legal obligation to inform their car insurance company. Failure to do so can invalidate the patient's insurance policy, and driving without valid insurance is a criminal offence.[15]

DISCUSSION

Assessing driving risk across the spectrum from mild cognitive impairment to moderate dementia remains a global challenge. Our findings indicate that, to date, no test—including cognitive assessments—or historical risk factors can precisely quantify driving risk in individuals with cognitive impairment or dementia. As a result, clinicians must integrate both qualitative and quantitative assessments in their decision-making. Notably, we identified several evidence-based tools from Western guidelines with potential for application: (1) the CADReS toolbox,[10] (2) the algorithm incorporating the CDR scale,[11] (3) the algorithm without the CDR scale,[12] and (4) early discussions about driver retirement with individuals and caregivers, alongside practical support for transportation alternatives and monitoring health and well-being outcomes after retirement from driving. Since the CDR scale requires specific training and familiarity, in areas where doctors are not trained in its use, the non-CDR algorithm offers a valuable alternative for clinical decision-making, with potential for broader application in the Asian context.

All guidelines recommend a functional-based approach to assess driving ability, combined with individualised practical driving evaluations, which permit conditional licensing for ordinary drivers. Notably, Canada takes a stricter approach, prohibiting geographical restrictions and co-piloting as part of conditional licensing for drivers with cognitive impairment or dementia. While the evidence on the safety of conditional licensing remains inconclusive, there is strong evidence that retiring from driving negatively impacts health and well-being.[8] Therefore, allowing conditional licensing with geographical restrictions and co-piloting, coupled with regular medical and driving reviews (every year or less), may provide a balanced approach to support ordinary and compliant drivers. The limited availability of conditional licensing for cognitively impaired professional drivers in most countries reflects a tiered approach, as professional drivers are generally at greater risk of accidents due to longer driving hours and higher fatality rates compared to ordinary drivers.[20] In licensing frameworks where mandatory reporting by doctors is not required, physicians may feel conflicted about breaching patient confidentiality when reporting non-compliant, at-risk drivers. This can strain the doctor-patient relationship[3,4,16] and expose doctors to potential legal challenges from dissatisfied drivers. Practical strategies emerging from this study include implementation of a hybrid model, where doctors are required to report only non-compliant drivers,[13,19] or providing full legal indemnity and protection for reporting doctors,[12,16,19] followed by further investigation by the licensing board.

The UK clinical guideline uniquely emphasises the doctor's responsibility to inform the driver or caregiver to verify the validity of car insurance following a dementia diagnosis,[15] a point often overlooked in previous research. Further revisions of guidelines and public education efforts should incorporate this important message. This study

identified only 1 Asian guideline (Singapore). The focus on English language sources and recent publications (2018–2022) may have excluded other relevant Asian guidelines. Given the rapid ageing of populations in Asia, policymakers must acknowledge the public health risks posed by cognitively impaired drivers. Adapting initiatives from Western countries could help accelerate the development of regional policies. Policymakers should work closely with medical associations and licensing authorities, taking into account cultural factors such as family dynamics, societal needs and public transportation availability. Additionally, cross-national research on leveraging technologies like telemedicine, artificial intelligences and virtual reality to assess driver safety should be prioritised.

CONCLUSION

Managing cognitively impaired older drivers to maintain road safety and promote optimal health outcomes is a challenging and complex responsibility for clinicians tasked with assessing fitness-to-drive. Clear, reliable and up-to-date guidelines are essential for this purpose. Comprehensive, evidence-based guidelines from Western countries can serve as valuable models to inform future developments in Asia.

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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LETTER TO THE EDITOR

Intravenous epoprostenol therapy in the treatment of pulmonary arterial hypertension in Singapore

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Dear Editor,

Pulmonary arterial hypertension (PAH) is a progressive disease characterised by significant morbidity and mortality. Intravenous (IV) epoprostenol (Veletri, Johnson & Johnson, US), a prostacyclin analogue, has been shown to improve exercise tolerance, PAH symptoms, haemodynamics and survival.[1,2] However, there is a lack of data on feasibility and tolerability of this therapy in Singapore. A previous study examined the use of selexipag, an oral prostacyclin analogue, in a Singapore population.[3] We aimed to describe the first Singapore experience of initiating and maintaining IV epoprostenol therapy for treating PAH patients in Singapore, and highlight the various issues and challenges encountered.

Patients from National Heart Centre Singapore who were diagnosed with PAH and remained in intermediate to high risk class with progressive symptoms, despite being on maximum tolerable doses of oral/inhaled phosphodiesterase-5 inhibitors, endothelin-1 receptor antagonists and/or prostacyclin analogues were assessed and counselled for initiation of IV epoprostenol.

A set of protocols were developed, encompassing a comprehensive assessment and support from a multidisciplinary team of physicians, specialist nurses and pharmacists (see Supplementary Materials for detailed protocol). Suitable patients underwent counselling, were given hard and soft copy information, and connected with fellow IV epoprostenol users. Another group of suitable patients were identified and underwent training sessions held by specialist nurses with simulation on the preparation of IV epoprostenol, ambulatory pump and Hickman line care. Weekly review of training and competency was done.

An admission was arranged for a Hickman line insertion followed by initiation and gradual up-titration of IV epoprostenol in a high dependency setting with close monitoring of clinical parameters and biochemical markers for the first day, followed by further titration in the general ward in the subsequent days. Regular inpatient review was done by a multidisciplinary team, and the patient was discharged when an acceptable IV epoprostenol infusion rate was achieved. Follow-up (both telephone and in-person) was done at regular intervals. Emergency contacts were given to patient/caregiver, and emergency protocols were drafted in cases of pump or line dysfunction and other scenarios.

From 2016 to 2021, 12 patients were initiated on IV epoprostenol; 11 were female and mean age was 44 years (interquartile range [IQR] 34.5–49.3). There were 4, 5 and 3 patients who were in New York Heart Association class II, III and IV, respectively. Baseline characteristics on right heart catheterisation showed a mean pulmonary artery pressure of 53 mmHg (IQR 47–54) and pulmonary vascular resistance of 12.6 Wood units (IQR 10.0–14.2). The average time from date of diagnosis of PAH to date of initiation of IV epoprostenol was 7.3 years (IQR 5.2–11.7) and the average maximum IV epoprostenol dose reached was 12.7 ng/kg/min (IQR 9.0–14.7), outlined in Table 1.

IV epoprostenol was generally well tolerated. Diarrhoea was the most common side effect affecting 5 patients, followed by headaches and musculoskeletal complains each of which affected 3 patients. Infective complications occurred a total of 5 times in 2 different patients, necessitating a total of 3 Hickman line changes. Non-infective complications occurred 4 times (2 line dislodgement, 1 cracked line and 1 contact dermatitis from dressing) each of them resulting in a Hickman line change.

As of July 2021, 6 patients had died. In these patients, IV epoprostenol was initiated 7.2 (IQR 4.3–13.2) years after diagnosis of PAH and continued for 11.3 months (IQR 7.7–13.1) until their demise. Of the remaining 6, IV epoprostenol

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Table 1. Clinical characteristics, side effects and line complications of study population.

Baseline characteristics	
Mean age, (IQR), years	44 (34.5–49.3)
Sex, no. (%)	
Male	1 (8.3)
Female	11 (91.7)
Race, no. (%)	
Chinese	8 (66.6)
Malay	3 (25.0)
Other	1 (8.3)
New York Heart Association class, no. (%)	
I	0 (0)
II	4 (33.3)
III	5 (41.7)
IV	3 (25.0)
Comorbidities, no. (%)	
Hypertension, hyperlipidaemia, ischemic heart disease, chronic obstructive pulmonary disease, obstructive sleep apnoea, stroke, chronic kidney disease	0 (0)
Diabetes mellitus	2 (16.7)
Atrial fibrillation	3 (25.0)
Asthma	2 (16.7)
Connective tissue disease	5 (41.7)
Medications, no. (%)	
Phosphodiesterase-5 inhibitor	10 (83.3)
Endothelin-1 receptor antagonist	11 (91.7)
Soluble guanylate cyclase stimulator	2 (16.7)
Oral/inhalational prostacyclin receptor agonist	10 (83.3)
Patients on single therapy, no. (%)	1 (8.3)
Patients on dual therapy, no. (%)	1 (8.3)
Patients on triple therapy, no. (%)	10 (83.3)
Diuretics	9 (75.0)
Warfarin	0 (0)
NT-proBNP at start, median (IQR), pg/mL	1874.5 (913.5–2960.8)
Transthoracic echocardiogram parameters, median (IQR)	
RV inlet size, cm	4.8 (4.5–5.3)
TAPSE, mm	17 (13–24)
RA area, cm^2	27.9 (20.0–38.3)
RA pressure, mmHg	15 (8–15)
PA systolic pressure, mmHg	75 (65.5–86.5)
LV ejection fraction, %	62.5 (57.5–67.8)
Pericardial effusion, no. (%)	7 (58.3)
RV-PA coupling (TAPSE/PASP), mm/mmHg	0.193 (0.158–0.244)

Table 1. Clinical characteristics, side effects and line complications of study population. (Cont'd)

Baseline characteristics	
Right heart catheterisation parameters, median (IQR)	
Mean RA pressure, mmHg	10 (5.8–18.8)
RV systolic pressure, mmHg	82.5 (68.3–86.0)
RV diastolic pressure, mmHg	14.5 (9.8–17.8)
Mean PA pressure, mmHg	52.5 (47.0–54.0)
PA wedge pressure, mmHg	12 (10–16)
Pulmonary vascular resistance, Wood unit	12.6 (10.0–14.2)
LV systolic pressure, mmHg	105 (104.0–111.8)
LV end diastolic pressure, mmHg	11 (7–13)
Cardiac output via Fick's method, L/min	2.8 (2.6–4.1)
Pulmonary hypertension classification, no. (%)	
Group 1	12 (100.0)
Idiopathic	6 (50.0)
Congenital	1 (8.3)
Connective tissue disease	5 (41.7)
Group 2	0 (0)
Group 3	3 (25.0)
Group 4	0 (0)
Group 5	1 (8.3)
Time of diagnosis to time of initiation of epoprostenol (IQR), years	7.3 (5.2–11.7)
Alive (n=6)	7.3 (6.3–9.9)
Demised (n=6)	7.2 (4.3–13.2)
Maximum IV epoprostenol dose achieved (IQR), ng/kg/min	12.7 (9.0–14.7)
Side effects and complications	
Side effects, no. (%)	
Diarrhoea	5 (41.7)
Headache	3 (25.0)
Musculoskeletal complains	3 (25.0)
Flushing	2 (16.7)
Palpitations	1 (8.3)
Pre-syncope	1 (8.3)
Line-related complications, no. (incidence per 1000 catheter days)	
Infective	5 (0.76)
Line changed	3 (0.46)
Line not changed	2 (0.30)
Mechanical	3 (0.46)
Other (contact dermatitis)	1 (0.15)

IQR: interquartile range; LV: left ventricle; NT-proBNP: N-terminal pro-brain natriuretic peptide; PA: pulmonary artery; RA: right atrium; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion

was initiated 7.3 months (IQR 6.3–9.9) after the diagnosis of PAH, continued for 17 months (IQR 13.9–27.3), and continued further as of July 2021. Right ventricle (RV) size on echocardiography in patients who survived remained stable (0.0 mm [IQR–0.2-0.5] RV inlet increase/year) compared to those who demised (0.9 mm [IQR 0.2–1.4] RV inlet increase/year).

While potentially lifesaving, the use of IV epoprostenol presents several medical and social challenges. The reported side effects of IV epoprostenol in this cohort were similar to those listed in the Veletri product insert,[4] though their occurrence varied. The most common side effect in our cohort was diarrhoea and gastrointestinal issues (41.7% vs 32%), followed by headaches (25% vs 49%) and musculoskeletal complaints (25% vs 5%). Another observational study reported a similar side effect profile.[5] These side effects were managed symptomatically, allowing patients to continue the drug if the side effects are tolerable. In our study, no patients discontinued therapy due to side effects.

Infective complications occurred at a rate of 0.76 per 1000 catheter days in our study, compared to other studies which reported a range of 0.32 to 0.43 infections per 1000 catheter days. Mechanical complications occurred at a rate of 0.46 per 1000 catheter days, compared to about 0.23 per 1000 catheter days.[6,7] This higher incidence may be related to a skewed result from a small sample size as over half of these complications occurred in 1 of 12 patients. Regardless, line-related complications remain a significant issue in patients on IV epoprostenol.[8,9]

Furthermore, there are other issues arising from living with an indwelling line. Patients must not only learn to care for it consistently, but also face social and psychological effects from managing an external line.[10] This can significantly influence patients' daily lives as they adapt to these new responsibilities. To mitigate this, patients require strong social support to continue treatment and maintain line integrity. Psychologically, they need to be mentally prepared to live with a central line and to continue lifelong treatment, sometimes with its associated side effects. A multidisciplinary team to support these patients throughout their treatment journey is crucial.

In this study, the longer median duration to initiating IV epoprostenol therapy was partly due to the effort and resources needed to initiate and develop the service to support this therapy. With increasing experience in managing these patients and an established service, the goal is to identify and start suitable high-risk patients on this therapy earlier.

Despite its challenges, establishing concrete protocols with multidisciplinary team support allows for the introduction of IV epoprostenol as an additional potential line of effective therapy for PAH patients in Singapore. This is particularly important as the option of transplantation currently is limited in part due to scarcity in Singapore. The main limitation of this study is the small sample size from a single tertiary centre in a developed country, which may limit the generalisability of the results. Nevertheless, this provides important data and protocols for the region to build on, and may also serve as a basic foundation for centres planning to start their programmes. These will need to be adapted to cater to local needs and setting.

Declaration

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Supplementary Materials: *Detailed protocol.*

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LETTER TO THE EDITOR

Serum progesterone in the management of pregnancy of unknown location: A Singapore experience

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Dear Editor,

The management of pregnancy of unknown location (PUL) currently encompasses multiple blood tests to trend serum beta-human chorionic gonadotropin (hCG) levels every 48 hours and ultrasound scans (USS). This results in multiple hospital visits for patients, causing emotional and economic distress. Therefore, it is important to identify women with PUL at risk of an ectopic pregnancy (EP) requiring close monitoring, and to limit the follow-up for those who are likely to have a viable intrauterine pregnancy (IUP) or a failing pregnancy that may resolve spontaneously. Studies show that a single serum progesterone level can be used for triaging, with centres using cut-offs of 10 nmol/L to 30 nmol/L at which the pregnancy may spontaneously resolve.[1-5]

To determine the feasibility of using a single serum progesterone level to differentiate non-viable pregnancies from viable IUP, and the low-risk PUL from the high-risk PUL requiring intervention, we conducted a prospective cohort study of women with a diagnosis of PUL who attended KK Women's and Children's Hospital, Singapore. The study included women aged 21 years and older who conceived spontaneously. Women who had conceived through assisted reproductive technologies or those on exogenous progesterone were excluded from the study.

All participants underwent serial serum beta-hCG tests and USS as per current practice. Serum progesterone level was obtained from the blood sample that was taken for the serum beta-hCG monitoring at their first or second visit, and compared with their eventual pregnancy outcome. We classified the outcomes into 4 categories: miscarriage, EP, persistent PUL and viable IUP.

Demographic and clinical data were collected concurrently in an electronic form. Data were reviewed and analysed by 2 separate team members using SPSS Statistics software version 29 (IBM Corp, Armonk, US) with comparison of means using the t-test (P<0.05 to determine significance).

A total of 150 pregnant women presenting with PUL were recruited between December 2021 and July 2022. Data from 145 patients were analysed after excluding 5 patients that did not meet the criteria.

The median age of our study population was 31 years. More than half (54.5%, n=79) were nulliparous, 13.1% had at least 1 previous caesarean section, 24.1% had at least 1 previous EP, and 5.5% had 1 or more previous miscarriages.

The serum progesterone levels ranged from 1.6 to 125.7 nmol/L with a mean level of 27.1 nmol/L. The pregnancy outcomes of our study population are summarised in Table 1.

We found that the serum progesterone level was under 10 nmol/L in 44.8% (n=65). A miscarriage had occurred in 90.7% (n=59) of women, all of which resolved spontaneously. There were no women with a viable IUP or persistent PUL. An EP was diagnosed in 6 women (9.2%), of which 4 underwent surgical intervention while 2 were managed with systemic methotrexate (MTX).

Regarding women with serum progesterone between 11–20 nmol/L (12.4%, n=18), there were 11 miscarriages (61.1%), 5 EP (27.7%), 1 IUP (5.5%) and 1 persistent PUL (5.5%). The women with miscarriages did not require intervention. Of the women with EPs, 1 required surgery while 4 were managed with MTX. The woman with persistent PUL was managed with MTX.

When the serum progesterone levels were between 21–30 nmol/L (5.5%, n=8), there were 2 miscarriages (25%), 3 EPs (37.5%) and 3 IUPs (37.5%). Each woman who miscarried had a spontaneous resolution. Of the women with EPs, 2 underwent surgery and 1 received MTX.

In women who had serum progesterone levels above 30 nmol/L (37.2%, n=54), 63% (n=34) had

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Table 1. Summary of pregnancy outcomes.

Pregnancy outcome	Percentage % (no.)	Mean serum progesterone (range) (nmol/L)	Mean number of beta-hCG tests (range)	Mean number of USS (range)	Mean number of visits (range)	Average days to diagnosis (range)	Period of amenorrhoea (weeks)
Viable IUP	26.2 (38)	61.5 (19.5–125.7)	1.9 (1–3)	2.2 (1–4)	2.8 (2–5)	16.8 (2–30)	1.6–13.6
Miscarriage	59.3 (86)	13.0 (1.6–114.9)	2.2 (1–6)	1.7 (0–5)	2.5 (1–8)	7.0 (1–50)	1.4–26.3
EP	13.8 (20)	23.2 (1.6–79.5)	2.7 (1–6)	2.4 (1–5)	2.8 (1–6)	6.1 (1–30)	2.1–9.1
Persistent PUL	0.7 (1)	14.9	4	1	2	11	1.3

hCG: human chorionic gonadotropin; EP: ectopic pregnancy; IUP: intrauterine pregnancy; PUL: pregnancy of unknown location; USS: ultrasound scan

viable IUPs. A miscarriage occurred in 25.9% (n=14), of which 64.3% (n=9) were managed conservatively and 35.7% (n=5) needed intervention (2 surgical evacuations and 3 medical management). An EP was diagnosed in 11.1% (n=6) of patients, all of which required intervention (3 received MTX and the other 3 underwent laparoscopic salpingectomy).

There were no viable pregnancies (n=38) at progesterone levels under 10 nmol/L. At serum progesterone levels under 20 nmol/L (n=83), there was only 1 viable IUP (1.2%), and at levels under 30 nmol/L (n=91), there were 4 viable IUPs (4.4%). When the serum progesterone levels were greater than 30 nmol/L, there were 34 viable IUPs (63%).

Progesterone levels rise in early pregnancy due to its production in the corpus luteum, with levels decreasing in a failing pregnancy.[6] Progesterone levels may hence be used to predict the outcome of PULs.[1-5,9-11] However, studies have also reported a transient decline in progesterone levels during the luteal-placental shift in normal pregnancies, with a nadir between weeks 6 and 8 of gestation.[7,8] As most PULs present at this gestation, it may be difficult to distinguish if a low progesterone level is due to an early gestational age or a luteal production issue. Verhaegen et al. found that the cut-off progesterone range of 10–19 nmol/L predicts a non-viable pregnancy with a pooled sensitivity of 74.6%, specificity of 98.4%, positive likelihood ratio of 45 and negative likelihood ratio of 0.26.[11] Other studies have used cut-off progesterone levels ranging from 20.0 nmol/L[10] to 30 nmol/L[1] to differentiate non-viable pregnancies from viable IUPs.

In our study, there were no women with a viable IUP or persistent PUL at progesterone levels under 10 nmol/L, and 90.7% resolved spontaneously without any complications. Cordina et al. reported that 93.4% of women with serum progesterone levels under 10 nmol/L did not have any complications that required further visits to the hospital.[2] This is also comparable to other studies.[12] However, all women diagnosed with EPs (9.2%, n=6) in our study were managed either with surgery or MTX.

A serum progesterone level under 20 nmol/L has been linked to a higher risk of failing pregnancy.[3] Ghaedi et al. reported that more than 90% of patients with progesterone under 20 nmol/L will be diagnosed with a non-viable pregnancy.[10] In our study, 57.2% (n=83) had serum progesterone level of under 20 nmol/L. Of these, 98.8% had a non-viable pregnancy. Miscarriage occurred in 84.3% (n=70), an EP was diagnosed in 13.2% (n=11), and one woman with persistent PUL received systemic MTX. Only 1 woman (1.2%) had a viable IUP.

Hahlin et al. reported no viable pregnancies when serum progesterone level was under 30 nmol/L.[1] In our study, 62.8% of women (n=91) had a progesterone level of less than 30 nmol/L. Of these, 95.7% were non-viable. A miscarriage occurred in 79.1% (n=72) of women, an EP was diagnosed in 15.4% (n=14), and 1 had persistent PUL. All women with a miscarriage did not require any intervention for resolution. A viable IUP was found in 4.4% (n=4).

Ghaedi et al. reported that more than 90% with a progesterone level greater than 64–80 nmol/L will have a viable pregnancy.[10] In our study, 80.7% (n=21) of PULs with serum progesterone more than 60 nmol/L (n=26) had a viable IUP. There were 2 EPs and 3 miscarriages. In conclusion, though a high single progesterone level has a higher chance of a viable IUP, it may not necessarily exclude a non-viable pregnancy.

Our study demonstrated that among women with PUL who had a final diagnosis of a miscarriage, those with progesterone level under 30 nmol/L had a spontaneous complete miscarriage, while

more than a third of women with levels greater than 30 nmol/L required intervention. Other studies similarly found cut-off serum progesterone levels of between 10 nmol/L[2,12] and 20 nmol/L[3] predicted pregnancies that were likely to resolve without intervention.

While our study did not establish a single serum progesterone cut-off to reliably distinguish high-risk from low-risk PULs, the findings offer valuable insights for managing patient expectations. A progesterone level below 10 nmol/L strongly indicates that a viable IUP is unlikely, with levels below 20 nmol/L offering only a 1% chance of a viable IUP. For levels below 30 nmol/L, the likelihood of a viable IUP increases to 4.4%, while levels above 30 nmol/L raise this likelihood to 63%.

It is crucial to emphasise that serum progesterone levels alone should not determine pregnancy viability, as viable pregnancies have been observed even at lower levels. For women diagnosed with miscarriage, a serum progesterone level below 30 nmol/L suggests the miscarriage will likely resolve without intervention.

Ethics statement

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements. The final study protocol, including the final version of the participant information and consent form, was approved in writing by the Centralised Institutional Review Board (CIRB reference: 2021/2088), prior to the enrolment of any patient into the study. Eligible patients were identified and approached by a member of the study team, and informed consent was taken.

Declaration

This study has secured funding from the 7th SingHealth Duke-NUS OBGYN Academic Clinical Programme Research Grant 2020. 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: *early pregnancy loss, ectopic pregnancy, miscarriage, pregnancy of unknown location, progesterone*

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LETTER TO THE EDITOR

Automated Cobb angle measurement in scoliosis radiographs: A deep learning approach for screening

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Dear Editor,

Adolescent idiopathic scoliosis is the most common paediatric spinal deformity, impacting 1 in 300 children.[1] In Singapore and other countries, national screening programmes have been established to detect scoliosis early, with the aim of using bracing to prevent progression to moderate or severe scoliosis, which may require surgical intervention.[1,2] Whole spine radiography is crucial for accurately diagnosing scoliosis using the Cobb method, where scoliosis is defined by a Cobb angle of at least 10°.[3] This method requires precise identification of the most tilted vertebral endplates above and below the curve apex, leading to a classification of mild (10–25°), moderate (25–40°) or severe scoliosis (>40°).[4]

While clinicians can manually calculate the Cobb angle, this approach is labour-intensive and error-prone, especially for inexperienced readers. Recently, deep learning (DL) techniques have shown promise in providing an automated solution for accurate Cobb angle measurement.[5-8] However, it remains uncertain whether these solutions are generalisable across a diverse range of images and suitable for efficient clinical use. We have developed a robust DL model for automated scoliosis grading, deployable on both mobile devices and digital platforms for rapid Cobb angle measurement from hardcopy and digital images. This is particularly pertinent to the Singapore context, where clinicians must assess images obtained from various equipment and systems, necessitating an accessible and cost-effective DL solution to aid their clinical workload.

After approval of waiver of consent from the Institutional Review Board of the National Healthcare Group, Singapore (DSRB: 2021/01084), retrospective extraction of scoliosis radiographs was performed on consecutive patients attending the National University Hospital in Singapore between January 2018 and January 2019. Inclusion criteria were paediatric patients ranging 10–18 years of age, and no history of prior spine surgery, skeletal disorders and other neuromuscular disorders. The dataset included a wide range of radiographic studies for model DL training/validation and testing including EOS imaging (EOS imaging, Paris, France) at standard and low dose, standard radiographic techniques from several vendors and scanned hardcopy radiographs. A total of 630 patients had a single radiograph (mean age ± standard deviation [SD] 12.6 ± 2 years 459/72.9% girls); 580 radiographs were used for training/validation (92%) and 50 (8%) for testing. Supplementary Fig. S1 presents a flow chart of the study design.

Manual vertebral segmentation was performed on the 580 radiographs in the training/validation set by board-certified radiologists: a musculoskeletal radiologist (author JTPDH with 12 years of experience), a neuroradiologist (AM with 7 years of experience) and senior radiologists in training (XZL with 5 years of experience and DSWL with 3 years of experience). The developed DL model used a 2-part approach. First, we trained an attention-based deep neural network, Context Axial Reverse Attention Network (CaraNet) to identify individual vertebrae using the segmented vertebra. Second, we calculated the Cobb angle by fitting a polynomial curve to the centre of the vertebral bodies (Fig. 1). Further details on the DL model development are provided in the Supplementary Material S1.

DL model testing involved 2 methods: screenshots from a high-resolution monitor and photographs from a handphone camera (iPhone 12, Apple Inc, Cupertino, CA, US). The DL model's Cobb angles were compared to those manually calculated by a third-year radiology resident (RWL with no prior experience in scoliosis assessment) and a third-year orthopaedic resident (XL with at least 6-months

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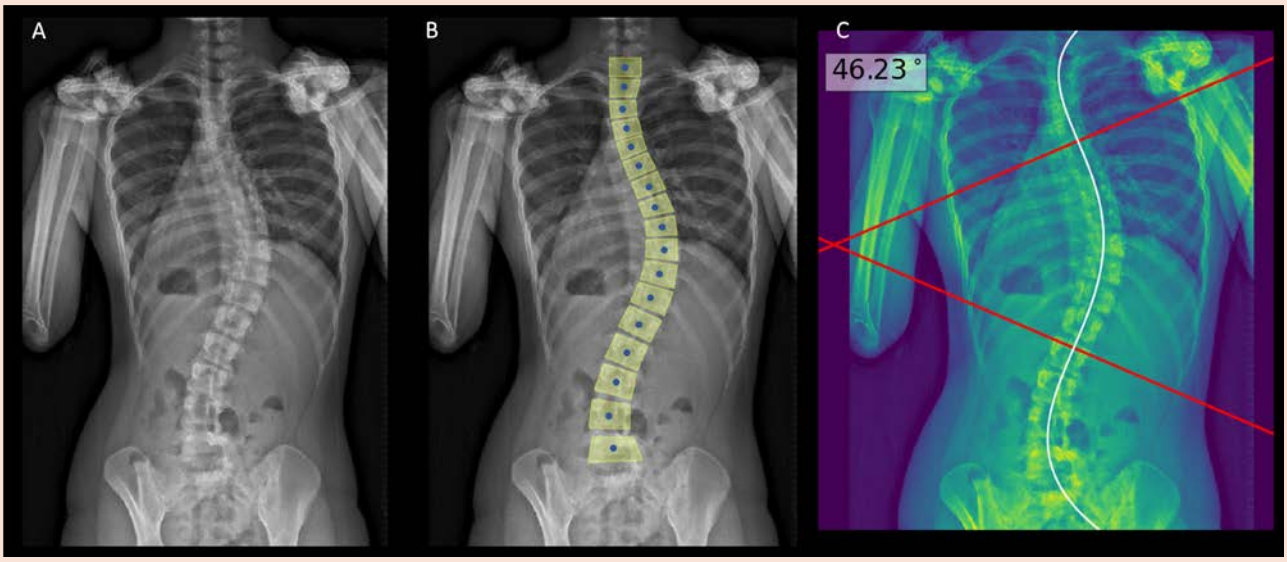

Fig. 1. (A) Original posteroanterior spine radiograph displaying scoliosis. (B) Vertebral segmentation was performed to train the deep learning (DL) model, utilising the 4 vertebral body corners (highlighted by yellow boxes). Subsequently, the centroid of each vertebral body was identified (indicated by blue dots). Finally, (C) illustrates the DL model's output, linking all the vertebral body centroids to form a best-fit spline curve—the maximum Cobb angle is accurately depicted.

experience in scoliosis assessment). Mean angle differences and sensitivity/specificity for referring patients to a specialist clinic (Cobb angle >25°) were assessed using the reference standard angles provided by a spine surgeon (JHT with 6 years of experience).

On the test set of 50 radiographs, the DL model using screenshots demonstrated a mean angle difference of 3.1° ± 2.7° (95% CI 2.3–3.9°), outperforming the radiology resident with a difference of 4° ± 4.5° (95% CI 3.1–5.6°), but slightly reduced compared to the orthopaedic resident with a difference of 2.4° ± 1.9° (95% CI 1.9–2.9°) (P<0.01, for both comparisons). For predicting referral, the DL model using screenshots, radiology residents and orthopaedic residents showed similar sensitivities of 88.5%, 80.8% and 84.6%, respectively (Supplementary Table S1). However, the DL model's performance was lower when using handphone images compared to the screenshot method and other readers, with a mean angle difference of 6.2° ± 6.2° (95% CI 4.5–8.0°); DL model using handphone had the lowest sensitivity (69.2%) for predicting referral needs (P<0.01).

Prior studies exploring the use of AI models for Cobb angle measurement have demonstrated promising results.[5-8] Ha et al. in 2022 trained a Faster R-CNN Resnet-101 object detection model on high-resolution images.[9] They compared the derived Cobb angles to measurements in the medical records, and demonstrated a mean Cobb angle difference of 7.3° (95% CI 5.9–8.8°) against the clinical record. In comparison, our DL model had superior mean angle differences of 3.1° using screenshots and 6.2° using handphone images, which were also within the range of differences reported between DL models and human expert readers (up to 10°).[9,10]

Our DL model could enhance scoliosis screening efficiency and consistency in Singapore. Currently, clinicians from Singapore's Health Promotion Board (HPB) rely on time-consuming manual Cobb angle assessment using printed radiographs, which can lead to errors in vertebral endplate selection. In contrast, our DL model rapidly analyses Cobb angles from original images or screenshots, displaying minimal angle differences compared to our reference standard. Additionally, DL model annotations could be easily integrated into existing radiographs, aiding interpretation and fostering trust with clinicians. To enhance practicality, a handphone application is still a viable option, enabling quick assessment of digitised print radiographs or hardcopy films. However, this technique was not as reliable as the screenshot method, which may relate to reduced image resolution, angulation or incomplete cropping.

Several limitations should be acknowledged. First, the study had a limited range of cases from a single institution and external validation is necessary to confirm the model's performance in different settings. Second, Cobb angle calculation utilised a

vertebral centre point and spline technique, rather than the traditional endplate-based method. This may introduce variability in the measurements and limit acceptability by the clinicians (Supplementary Material S1.2). Additionally, the reference standard was based on a single surgeon, and a panel of expert readers may provide a more robust evaluation.

In conclusion, our DL model's performance in calculating the Cobb angle, particularly with the use of screenshots, surpassed that of a radiology resident and showed only a slight reduction in performance compared to an experienced orthopaedic resident. We hope to expand on these initial results, and integrate DL model annotations into the clinical workflow at the HPB to aid clinicians in scoliosis interpretation (Supplementary Material S2).

Data availability

The datasets generated during and/or investigated during the research study are available from the corresponding author upon reasonable request.

Code availability

Custom code is available at the current site for the deep learning model: https://gitlab.com/futuristicai/vertiai/. Accessed 2 April 2023.

Declaration

No funding was received for this study. There is no conflict of interest or competing interest for this work. No relevant financial activities for any of the authors outside the submitted work.

Ethics statement

The requirement for informed consent was waived due to the retrospective nature of this study and minimal risk involved by the local Institutional Review Board of the National Healthcare Group (NHG), Singapore (DSRB: 2021/01084).

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Keywords: *artificial intelligence, deep learning, orthopaedic surgery, population screening, public health, radiology*

Appendix

Supplementary Fig. S1. Flow chart of the study design.

Supplementary Table S1. Mean Cobb angle differences for each reader and the deep learning mode.

Supplementary Material S1. Deep learning model development, detection of vertebrae, calculating Cobb angle.

Supplementary Material S2. Clinical implementation strategies.

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LETTER TO THE EDITOR

Cost-effectiveness and clinical outcomes of artificial intelligence-enhanced screening for diabetic foot ulcers: A simulation study

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Dear Editor,

Diabetic foot ulcers (DFUs) are a serious complication of diabetes mellitus, with a lifetime risk estimated to be between 19% and 34%.[1] Without timely prevention and management, DFUs can lead to lower extremity amputations (LEAs) and premature death.[2,3] DFUs also impose significant healthcare and societal costs, especially in Southeast Asia.[4,5] Regular foot screenings are essential for preventing these complications.

Countries in Southeast Asia generally follow the guidelines set by the 2023 International Working Group on the Diabetic Foot,[6] which recommend foot screening frequency based on their risk stratification system: annually for very low risk, once every 6–12 months for low risk, once every 3–6 months for moderate risk and once every 1–3 months for high risk. However, adherence to these guidelines reveals significant challenges and variability in practice due to barriers such as resource limitations and staff shortages. In Singapore, the Agency for Care Effectiveness recommends differentiated screening intervals: annually for low-risk patients, every 6 months for moderate-risk patients and every 3–4 months for high-risk patients.[7] Low-risk patients are defined as those without any of the following risk factors: calluses, deformities, peripheral artery disease, neuropathy, previous foot ulcers or amputations. Evidence[8] suggests that the risk of ulceration in low-risk patients remains stable over time. We estimated that 60–80% patients with diabetes can be classified as low risk, and their annual DFU incidence risk is lower than 1% based on data from our cluster's Chronic Disease Management Datamart (CDMD),[9] raising concerns about overscreening and inefficient resource allocation.

Artificial intelligence (AI) offers a potential solution by enabling personalised risk-tailored screening.[10] This study evaluated the cost-effectiveness and clinical outcomes of AI-enhanced screening versus routine annual screening for low-risk patients. Using an XGBoost-based predictive model, the AI-enhanced screening approach involves screening based on individual risk: patients flagged as positive are screened annually, while negative low-risk patients are screened every 3 years. The predictive model achieved an area under the receiver operating characteristics curve of 0.81, with a sensitivity of 0.7 and a specificity of 0.8. A cohort of 500,000 low-risk patients with diabetes in Singapore, with an average age of 50 years, was simulated over a lifetime to assess the long-term impact of the AI-enhanced screening.

A Markov state-transition model was constructed to simulate disease progression through 5 health states: diabetes, DFU, minor LEA, major LEA and death. Model parameters, including both base values and distributions of disease transition probabilities and costs (Table 1), were derived from CDMD[9] and validated against international sources.[11,12] Direct medical cost for foot screening, examination, consultation, DFU treatment and management, LEA procedures, and related services were included in the cost analysis. Effectiveness was measured in quality-adjusted life years (QALYs), based on EuroQoL-5 Dimension data from a Singapore study.[13] A 3% discount rate was applied for both costs and effectiveness. The incremental cost-effectiveness ratio (ICER) was then assessed to determine the most cost-effective screening strategy using gross domestic product (GDP) per capita as the willingness-to-pay (WTP) threshold as commonly used in Singapore. Other outcomes measured in the simulation included the number of patients screened, DFU detections, minor and major LEAs performed, and deaths. Monte Carlo micro-simulations with 1000 samples, randomly drawn from parameter distributions, were performed for probability sensitivity analysis (PSA) to account for

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Table 1. Model parameters and their values[a] used in the study.

Parameter	Base value	Range
Progression rate		
Annual progression risk from DM to DFU	0.8%	N (0.8%, 0.2%)
Annual progression risk from DFU to minor LEA	6.1%	N (6.1%, 1%)
Annual progression risk from DFU to major LEA	3.5%	N (3.5%, 1%)
Annual progression risk from minor LEA to major LEA	23.7%	N (23.7%, 0.5%)
Mortality rate	Gompertz function: $a * e^{b*age}/1000$ where a=0.03, b=0.1	a, b: constant
Increased progression due to delayed detection of DFU	25%	Random sampling from [0–50%]
Cost		
Cost per foot screening	SGD56	Constant
Annual cost of DM-related medical services	SGD1099	N (1099, 116)
Annual cost of DFU-related medical services	SGD4002	N (4002, 1489)
Annual cost of minor LEA-related medical services	SGD7546	N (7546, 9928)
Annual cost of major LEA-related medical services	SGD15,188	N (15,188, 20,587)
Utility		
Utility of low-risk DM patient	0.95	Random sampling from [0.9–0.95]
Utility of DFU	0.8	Random sampling from [0.75–0.85]
Utility of minor LEA	0.6	Random sampling from [0.5–0.7]
Utility of major LEA	0.3	Random sampling from [0.2–0.4]
Sensitivity and specificity		
Sensitivity of AI model	0.7	Random sampling from [0.6–0.7]
Specificity of AI model	0.8	Random sampling from [0.7–0.8]

AI: artificial intelligence; DFU: diabetic foot ulcer; DM: diabetes mellitus; LEA: low extremity amputation
N (mean, standard deviation) stands for normal distribution.
[a] Parameter values were derived from our cluster's Chronic Disease Management Datamart

uncertainties in model parameters. Results were summarised in cost-effectiveness acceptability curves (CEAC) and expected loss curves (ELC) to determine the optimal screening strategy under uncertainty.[14] The CEAC shows the chance of each strategy being the most cost-effective and picks the one with the highest chance. The ELC shows the potential cost of choosing the wrong strategy and selects the one with the lowest risk of loss.

AI-enhanced screening resulted in an average lifelong cost of SGD54,272 per patient, compared to SGD55,587 for annual screening, saving SGD1315 per patient. The lifelong effectiveness for AI-enhanced screening was 23.150 QALYs per patient, which is slightly lower than 23.154 QALYs for annual screening with a minimal difference of 0.004 QALYs per patient. AI-enhanced screening required 4,372,523 DFU screenings, compared to 11,178,861 screenings under annual screening. LEA rates were similar between strategies, with 52,720 minor and 68,646 major LEAs for AI-enhanced screening versus 52,689 minor and 68,710 major LEAs for routine screening. AI screening led to 26 additional deaths. ICER was SGD292,181 per QALY

gained, well below Singapore's GDP per capita in 2023 (SGD110,000), indicating that AI-enhanced screening was more cost-effective than annual screening.

PSA showed that AI-enhanced screening had an average cost of SGD52,178 and effectiveness of 22.866 QALYs, compared to SGD53,993 and 22.876 QALYs for routine screening. ICER from PSA was SGD174,572 (standard deviation SGD13,296) per QALY gained. Both CEAC and ELC indicated that AI-enhanced screening was optimal when WTP was below SGD180,000 per QALY.

AI-enhanced DFU screening optimises healthcare resource allocation by tailoring screening intervals based on individual risk, leading to long-term cost savings. This aligns with government initiatives to reduce healthcare expenditure while maintaining high standards of care, benefiting both patients and healthcare systems. In resource-constrained settings, this approach could alleviate healthcare burdens and enable better resource allocation. The findings are relevant not only for Singapore but also for other countries in Southeast Asia and globally, where diabetes incidence is high and healthcare resources are limited. Malaysia, Indonesia and Thailand could benefit from similar AI-driven strategies, adapted to local healthcare systems. The predictors used in our AI model are routinely collected, facilitating easy adoption and adaptation across different healthcare settings. This flexibility allows the model to be tested and validated in diverse regions, ensuring it can be adjusted for local infrastructure, patient demographics and resource availability. Such adaptability ensures broader applicability and smoother integration into various health systems.

In conclusion, this study demonstrates that AI-enhanced DFU screening can offer significant cost savings while maintaining high standards of care. By tailoring screening intervals based on individual risk, healthcare systems can improve resource efficiency while maintaining high standards of care. Future research should focus on validating these findings in diverse populations and addressing ethical concerns to ensure that AI-driven healthcare innovations are accessible to all.

Ethics statement

This study was approved by the National Healthcare Group Institutional Domain Specific Ethics Review Board (2019/01045). Informed consent from patients was not required as the study used anonymised administrative data.

Declaration

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Keywords: *artificial intelligence, cost effectiveness analysis, diabetic foot ulcers, Markov modelling, microsimulation, screening*

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