



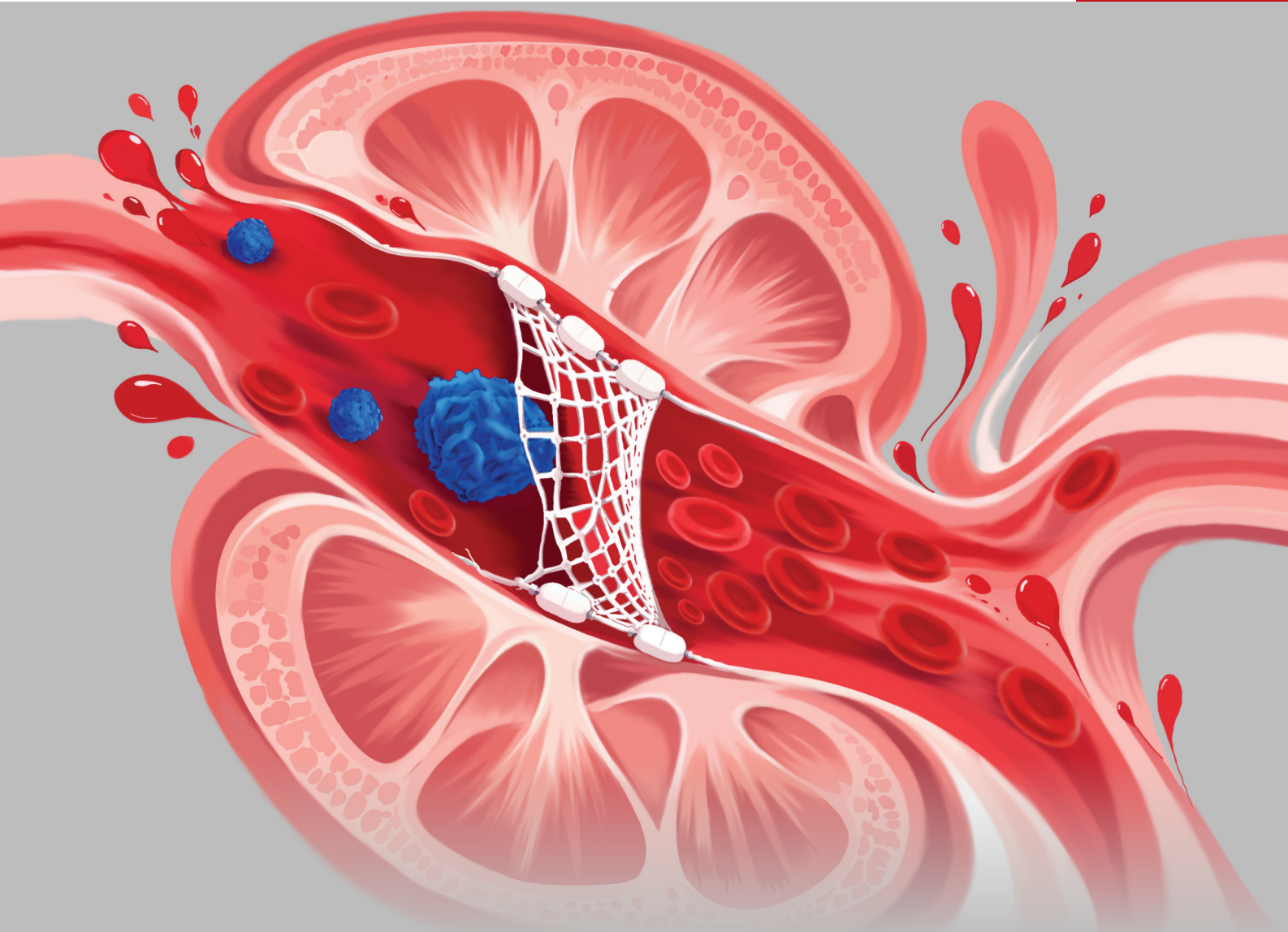
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A randomised controlled study of canagliflozin in improving diabetic kidney disease through a podocyte protection mechanism

Canagliflozin protects the diabetic kidney by preserving podocyte integrity and reducing proteinuria, while additional mechanisms contribute to sustained renal protection (See full article, p. 450)

Illustration by Maria De-Castro

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Coblation intracapsular tonsillectomy outcomes in paediatric obstructive sleep disordered breathing: A Singapore study

Traditional Chinese Medicine in Singapore:
Integrating education, practice, and research in a modern healthcare system

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Beyond haemodynamics: Do SGLT2 inhibitors protect the podocyte?

Arshvini Vijaya Kumar¹ MRCP (UK), Emmett Tsz Yeung Wong^{1,2,3} FRCP (Edin)

Over the past decade, sodium-glucose cotransporter 2 (SGLT2) inhibitors have evolved from glucose-lowering agents into a cornerstone of kidney-protective therapy. Landmark trials, including CREDENCE, DAPA-CKD, and EMPA-KIDNEY, demonstrated reductions in kidney disease progression across a broad spectrum of patients with chronic kidney disease (CKD), beyond those attributable to glycaemic control.¹⁻³ A subsequent collaborative meta-analysis of 13 large placebo-controlled trials reported an approximately 37% reduction in the risk of kidney disease progression, with benefits observed irrespective of diabetes status.⁴ These findings have reshaped contemporary CKD management, with SGLT2 inhibitors now strongly recommended by the KDIGO 2024 guidelines for eligible patients with CKD.⁵

The renoprotective effects of SGLT2 inhibition have traditionally been attributed largely to the restoration of tubuloglomerular feedback. Increased sodium delivery to the macula densa promotes afferent arteriolar vasoconstriction, reducing glomerular hyperfiltration and intraglomerular pressure. However, an expanding body of evidence suggests that kidney protection may extend beyond haemodynamic effects, with proposed mechanisms including reduced tubular workload and hypoxia, modulation of inflammatory and fibrotic pathways, attenuation of inflammasome activation and oxidative stress, and favourable metabolic adaptations.⁶

Podocytes are particularly relevant in this context. These highly specialised, terminally differentiated epithelial cells form a critical component of the glomerular filtration barrier and provide structural support to the glomerular capillary wall. Because their capacity for regeneration is limited, sustained podocyte injury and loss can disrupt the filtration barrier, resulting in proteinuria and progressive glomerulosclerosis. Podocyte dysfunction is therefore considered a central feature of diabetic kidney disease (DKD) progression. While the haemodynamic effects of SGLT2 inhibition are well established, whether these agents confer additional protection through direct or indirect effects on podocytes remains less certain.⁷

Against this background, a randomised, double-blind, placebo-controlled trial by Gu et al. in this issue of the *Annals* provides a valuable clinical opportunity to examine the relationship between SGLT2 inhibition and markers of podocyte injury.⁸ The investigators randomised 180 patients with type 2 diabetes and DKD to 12 weeks of standard therapy plus either canagliflozin or placebo; 172 completed the study and were included in the analysis. Glycaemic control during follow-up was comparable between groups, allowing differences in kidney outcomes and podocyte-associated biomarkers to be interpreted with less concern that they reflected differential glucose-lowering.

A notable strength of this study is the assessment of podocyte-associated biomarkers alongside conventional measures of kidney injury. In addition to blood urea nitrogen, serum creatinine, urinary albumin-to-creatinine ratio (UACR), and 24-hour urinary protein (24h-UP), the investigators serially assessed urinary podocyte count and the urinary podocalyxin-to-creatinine ratio (UPCX/Ucr) as markers of podocyte injury. Canagliflozin was associated with progressive reductions in urinary podocyte shedding, UACR, and 24h-UP over 12 weeks, with significant treatment-by-time interactions. By week 12, urinary podocyte counts were approximately 52% lower and UACR approximately 28% lower than in the control group. Serum creatinine also followed a different trajectory between groups, although the between-group difference was no longer statistically significant at week 12. Taken together, the parallel changes in podocyte-associated biomarkers and proteinuria support the possibility that reduced podocyte injury may contribute to the kidney-protective effects of SGLT2 inhibition.

Several considerations are important when interpreting these findings. The 12-week follow-up and single-centre design necessarily focused the study on short-term biomarker responses rather than sustained preservation of kidney function. The study population was also relatively selected: patients with rapid estimated glomerular filtration rate (eGFR) decline (>5 mL/min/1.73 m² per year), a doubling or

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greater increase in UACR within 2 years, nephrotic syndrome, or other features suggestive of non-diabetic kidney disease were excluded. While these criteria increase confidence that the enrolled cohort had a relatively well-defined DKD phenotype, they also select for a more clinically stable cohort and may limit extrapolation to patients with rapidly progressive disease. The relatively preserved mean baseline eGFR of approximately 74–76 mL/min/1.73 m² should also be considered when applying the findings to patients with more advanced CKD. Urinary podocyte count and UPCX/Ucr should also be regarded as surrogate markers of podocyte injury rather than direct measures of podocyte structure or function. In the absence of complementary structural assessment, reductions in urinary biomarkers should therefore be interpreted as consistent with reduced podocyte injury rather than definitive evidence of preservation of podocyte architecture. Manual podocyte quantification may also introduce measurement variability, although the high reported inter-observer agreement provides reassurance regarding measurement consistency.

The mediation analysis represents a particularly interesting aspect of the study. Rather than asking only whether canagliflozin reduces proteinuria, mediation analysis examines whether part of the treatment effect may operate through an intermediate variable in the proposed pathway between treatment and outcome. Here, treatment assignment was considered the exposure; change in UPCX/Ucr the mediator; and changes in UACR, 24h-UP, and serum creatinine the outcomes. Under the assumptions of the mediation model, the statistically significant indirect effects, with estimated mediation proportions of 84.39% for UACR and 86.42% for 24h-UP, support the hypothesis that reduced podocyte injury may lie on the pathway linking canagliflozin treatment with reduced proteinuria.

These estimates, however, require careful interpretation. Although treatment allocation was randomised, the mediator itself was not, and randomisation therefore does not eliminate potential confounding of the mediator–outcome relationship.⁹ In addition, mediator and outcome changes were assessed over the same follow-up interval, making temporal ordering difficult to establish. For the UACR model, the mediator and outcome also share urinary creatinine as the denominator, potentially introducing correlated measurement variation, although the similar finding for 24h-UP is less susceptible to this concern. Mediation analysis in this setting, therefore, strengthens a biologically plausible mechanistic hypothesis but does not, by itself, establish that reduced podocyte injury causally mediates the antiproteinuric effect of canagliflozin.

These findings also raise a broader question regarding residual kidney risk despite contemporary SGLT2 inhibitor therapy. Even with substantial reductions in kidney disease progression, some patients continue to experience progressive loss of kidney function, reflecting the multiple haemodynamic, inflammatory, fibrotic, metabolic, and structural pathways involved in CKD progression.¹⁰ If reductions in podocyte injury contribute to the clinical effects of SGLT2 inhibition, persistent podocyte injury despite therapy may represent 1 component of this residual risk. Further studies incorporating longer follow-up, serial assessments of podocyte biomarkers and kidney function trajectories, and, where feasible, complementary structural or molecular assessments could help determine whether podocyte preservation is a mediator, biomarker, or consequence of SGLT2 inhibitor-associated kidney protection.

Large cardiovascular and kidney outcome trials have established that SGLT2 inhibitors protect the kidney. The present study contributes to the complementary question of how that protection may occur, providing clinical evidence linking canagliflozin treatment with reduced podocyte injury and proteinuria. Clarifying the causal relationships between these processes will be an important next step in understanding the full spectrum of SGLT2 inhibitor-mediated kidney protection.

Ethics statement

Not applicable, as no study participants were recruited.

Declaration

The authors declare that they have 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: *canagliflozin, diabetes mellitus type 2, diabetic nephropathies, podocalyxin, podocytes*

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A randomised controlled study of canagliflozin in improving diabetic kidney disease through a podocyte protection mechanism

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ABSTRACT

Introduction: This study aimed to investigate whether canagliflozin improves diabetic kidney disease (DKD) through a podocyte protective mechanism.

Methods: DKD patients were randomly assigned to the experimental group (87 patients: standard therapy plus canagliflozin 100 mg/day) and the control group (85 patients: standard therapy plus placebo tablets), with a treatment course of 12 weeks. Investigators and outcome assessors were blinded to allocation. Changes in blood glucose, DKD-related indicators (serum albumin, serum creatinine, blood urea nitrogen [BUN], 24-hour urinary protein [24h-UP], urinary albumin-to-creatinine ratio (UACR), and podocyte injury markers (urinary podocyte count, urinary podocalyxin-to-urinary creatinine ratio [UPCX/Ucr]) were compared. Linear mixed-effects models were used to compare intergroup differences, and mediation effect analysis was performed to evaluate the role of UPCX/Ucr in the improvement of DKD-related indicators by canagliflozin.

Results: Under comparable blood glucose control, the experimental group showed superior outcomes in reducing BUN (between-group difference at week 12: -0.67 mmol/L, 95% confidence interval [CI] -1.10 to -0.24), 24h-UP (geometric mean ratio 0.73, 95% CI 0.65 to 0.82), UACR (geometric mean ratio 0.72, 95% CI 0.65 to 0.80), urinary podocyte count (geometric mean ratio 0.48, 95% CI 0.43 to 0.54), and UPCX/Ucr (geometric mean ratio 0.72, 95% CI 0.66 to 0.79) compared to the control group. Mediation analysis revealed that UPCX/Ucr exerted a significant indirect effect in the reduction of UACR (indirect effect = -0.968 , 95% CI -1.171 to -0.774) and 24h-UP (indirect effect = -0.783 , 95% CI -1.127 to -0.655) by canagliflozin, with no statistically significant direct effects. For serum creatinine reduction, UPCX/Ucr played a partial mediating role with a small indirect effect (indirect effect = -0.301 , 95% CI -0.437 to -0.153), alongside a significant direct effect.

Conclusion: Canagliflozin provides significant renal protective effects for DKD patients, effectively lowering blood glucose while reducing urinary protein, lowering serum creatinine from baseline, and protecting podocytes. The reduction in urinary protein appears to be statistically mediated by podocyte protection, rather than being solely dependent on blood glucose control. However, this mediation analysis does not establish causality.

Keywords: canagliflozin, diabetic kidney disease, podocalyxin, podocyte, type 2 diabetes mellitus, urinary

CLINICAL IMPACT

What is New

- Canagliflozin, a sodium-glucose cotransporter 2 inhibitor, provides favourable glycemic control and renal protection in diabetic kidney disease (DKD), reducing urinary protein and serum creatinine while preserving podocytes.
- Mediation analysis suggests that podocyte protection partially mediates canagliflozin's reduction of urinary protein, with other mechanisms also likely contributing.

Clinical Implications

- Canagliflozin demonstrates significant renoprotective effects in DKD, primarily evidenced by a substantial reduction in urinary protein excretion—an effect that appears to be statistically mediated by the preservation of podocyte integrity.
- Its effect on serum creatinine, however, appears to involve a combination of podocyte protection and additional mechanisms. Given its favourable safety profile, canagliflozin may be an effective therapeutic option for slowing the progression of DKD.

INTRODUCTION

Diabetic kidney disease (DKD) is a common and severe microvascular complication of diabetes mellitus, a leading cause of chronic kidney disease (CKD), the primary aetiology of end-stage renal disease (ESRD), and a contributor to increased patient mortality.¹ Early DKD is characterised by microalbuminuria, which progressively advances to macroalbuminuria. As serum creatinine and blood urea nitrogen levels

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rise, the condition eventually progresses to renal failure. Podocyte dysfunction and pyroptosis play a significant role in the development and progression of albuminuria.² Podocytes, also known as glomerular epithelial cells, are highly terminally differentiated cells that, together with the glomerular basement membrane and endothelial cells, constitute the glomerular filtration barrier. Podocalyxin (PCX), a specific podocyte marker protein, is a crucial component of glomerular podocytes—elevated levels in urine indicate podocyte damage.³ Current research has established a causal relationship between podocyte depletion and the severity of proteinuria in progressive glomerular diseases.⁴ Therefore, investigating mechanisms that protect against podocyte injury may offer new therapeutic strategies for DKD. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a novel class of anti-diabetic drugs widely used clinically. They may exert protective effects against podocyte injury, but the underlying mechanisms remain incompletely understood.⁵ Hence, this study investigates whether canagliflozin, an approved SGLT2i, exerts protective effects on podocytes in DKD patients, for potential insights into DKD treatment.

METHODS

Study population

Inclusion criteria

At the start, a total of 180 patients with type 2 diabetes mellitus who attended Shangyu People's Hospital of Shaoxing City in China from January 2023 to July 2025 and met the diagnostic criteria for DKD were enrolled. Patients with type 2 diabetes mellitus (diagnosed according to the 2022 American Diabetes Association criteria)⁶ and DKD were included. DKD was diagnosed based on an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² or a urinary albumin-to-creatinine ratio (UACR) ≥ 30 mg/g persisting for more than 3 months.⁷

Exclusion criteria

Exclusion criteria are as follows. (1) rapid decline in eGFR (>5 mL/min/1.73 m² per year) suggestive of non-diabetic kidney disease,⁸ a doubling or more of UACR within 2 years,⁹ or presentation with nephrotic syndrome. (2) initiation or dose change of angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), aldosterone antagonists (stable therapy for ≥ 3 months was allowed), or SGLT2i within 3 months prior to enrolment. (3) Liver dysfunction: alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal, or gamma-glutamyl transferase >5 times the upper limit of normal. (4) Abnormal findings in urine erythrocytes, leucocytes, or cellular casts. (5) Presence of other types

of kidney disease, severe cardiac or cerebrovascular disease, malignancy, autoimmune disease, acute conditions such as diabetic ketoacidosis, hyperosmolar hyperglycaemic state, severe infection, or other physiological stress states. (6) Pregnancy or lactation.

Study design and randomisation

This was a prospective, randomised, placebo-controlled, double-blind, parallel-group trial (Supplementary Annex S1). Eligible patients were randomly assigned (1:1) to either the experimental group or the control group using a computer-generated random number sequence with a block size of 4. Allocation concealment was achieved using sequentially numbered, opaque, sealed envelopes. Participants, care providers, outcome assessors, and data analysts were all blinded to group assignment.

Study interventions

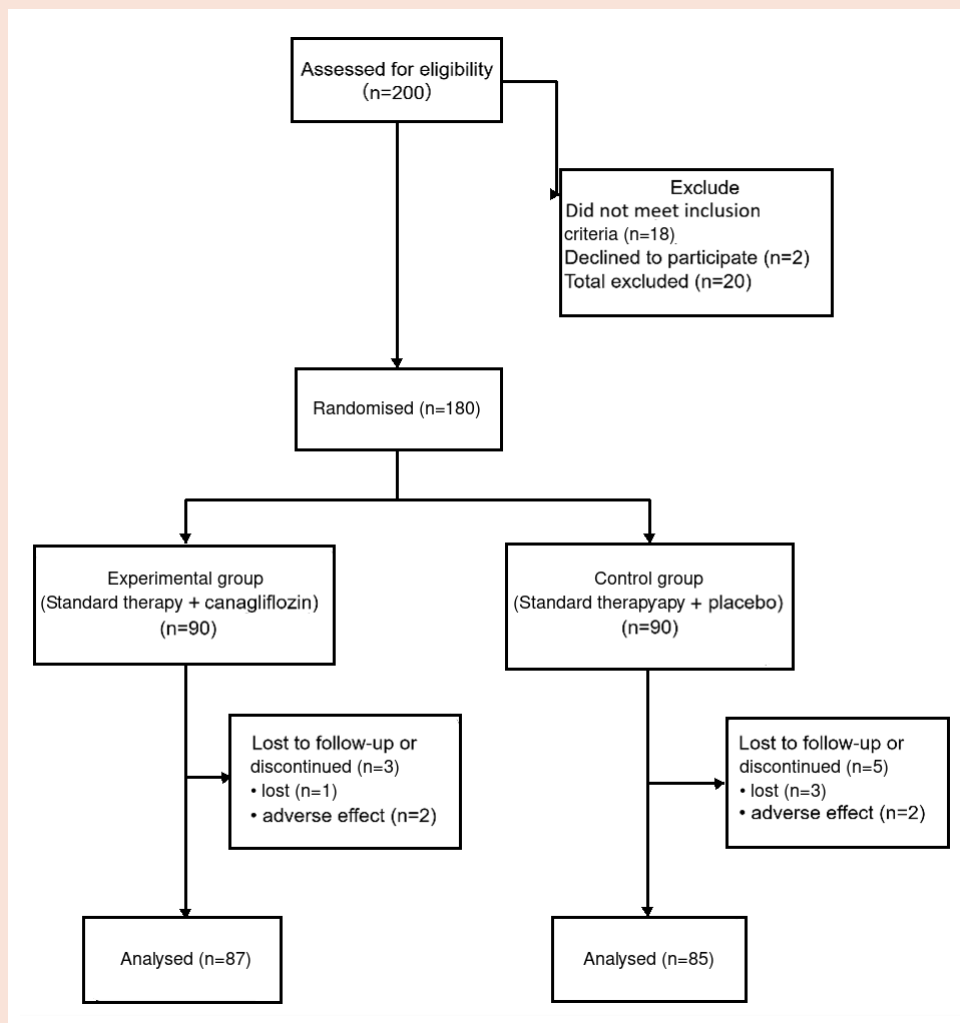
Patients in the experimental group received standard therapy plus canagliflozin (100 mg orally once daily; Janssen-Cilag S.p.A., Italy). Patients in the control group received standard therapy plus placebo tablets identical in appearance to canagliflozin (100 mg orally once daily). Standard therapy included lifestyle intervention combined with glucose-lowering agents (insulin or oral hypoglycaemic drugs), statins for dyslipidaemia, and stable ARB or ACEi for proteinuria reduction, excluding SGLT2i and glucagon-like peptide-1 receptor agonists.

Assuming a 29% reduction in UACR in the canagliflozin group compared to placebo based on a previous study,¹⁰ with a two-sided alpha of 0.05 and power of 80%, a minimum of 70 patients per group was required. Accounting for a 15% dropout rate, the authors enrolled 180 patients (90 per group). Following loss to follow-up or inability to tolerate drug side effects, 87 patients in the experimental group and 85 in the control group completed the study and were included in the final analysis (Fig. 1).

Laboratory measurements

Blood and urine samples were collected before treatment and at weeks 4, 8, and 12 post-treatment. Measurements included fasting plasma glucose (FPG), 2-hour postprandial glucose (2hPG), glycated haemoglobin (HbA1c), serum albumin, serum creatinine, blood urea nitrogen (BUN), 24-hour urinary protein (24h-UP), UACR, urinary podocyte count, and urinary PCX/urinary creatinine (UPCX/Ucr). For urinary podocyte count, due to the lack of automated urinary sediment analysers, urinary podocyte counting was performed manually. Morning urine sediment smears were stained with anti-podocalyxin antibody and examined under light microscopy by 2 independent experienced technicians who were blinded to group allocation.

Fig. 1. CONSORT flow diagram.



Adapted from Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.

Standard therapy included lifestyle intervention combined with glucose-lowering agents (insulin or oral hypoglycaemic drugs), statins for dyslipidaemia, and stable angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors for proteinuria reduction, excluding SGLT2i and glucagon-like peptide-1 receptor agonists.

The average number of podocytes in 20 high-power fields was recorded. Inter-observer agreement was high ($\kappa=0.86$, 95% confidence interval [CI] 0.78–0.94). For UPCX/Ucr, urine samples (5.0 mL) were centrifuged at 4000 rpm for 10 minutes, the supernatant discarded, and the sediment resuspended in 2 mL normal saline. After mixing thoroughly and recentrifuging under the same conditions, the supernatant was discarded. The sediment was dissolved in 2 mL normal saline, stored in cryotubes at -20°C , and subsequently analysed using enzyme-linked immunosorbent assay.

Outcomes

The primary outcome was the change in UACR from baseline to week 12. Secondary outcomes included

changes in 24h-UP, serum creatinine, eGFR, BUN, urinary podocyte count, and UPCX/Ucr, as well as the mediation proportion of UPCX/Ucr in the reduction of UACR, 24h-UP, and serum creatinine reduction. Safety outcomes included the incidence of adverse events (genitourinary infection, hypoglycaemia, hypotension, clinically significant weight loss).

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 27 (IBM Corp, Armonk, NY, US). Normally distributed continuous variables are presented as mean $\pm$ standard deviation and compared between the groups using the independent-sample t-test. Non-normally distributed variables (UACR,

24h-UP, UPCX/Ucr, urinary podocyte count) were log-transformed before analysis and are presented as median (interquartile range) and compared using Mann-Whitney U tests. Categorical variables are expressed as counts (percentages) and compared using the chi-square test.

For longitudinal data, linear mixed-effects models were used with fixed effects for treatment assignment, time, and treatment-by-time interaction, and a random intercept for each participant. This approach handles missing data under the missing-at-random assumption, using all available data without requiring imputation. Kenward-Roger correction was applied for small samples. Results are presented as estimated mean difference (95% CI).

Multivariable linear regression was performed to assess the independent effect of canagliflozin on the change in UACR, adjusting for age, sex, diabetes duration, body mass index (BMI), baseline eGFR, systolic blood pressure, and baseline HbA1c.

Mediation analysis to assess the role of UPCX/Ucr in the improvement of DKD-related indicators by canagliflozin was performed using the PROCESS v4.2 macro for SPSS by Andrew F. Hayes.¹¹ A two-sided *P* value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

Table 1 shows the baseline demographic and clinical characteristics of the 2 groups. There were no statistically significant differences between groups for any variable, indicating successful randomisation.

Glycaemic control

FPG, 2hPG, and HbA1c decreased significantly over time in both groups (time effect *P*<0.001). However, there were no statistically significant differences between groups (treatment effect *P*>0.05 for all), nor were there significant treatment-by-time interactions, indicating comparable glycaemic control throughout the study (Table 2).

DKD-related indicators

Overall treatment effect

Linear mixed-effects models revealed significant group-by-time interactions for all DKD-related indicators. They include serum albumin, serum creatinine, BUN, 24h-UP, UACR, urinary podocyte count, and UPCX/Ucr (all *P*<0.001), indicating that the trajectory of these parameters differed significantly between groups over the 12-week period (Table 3).

Between-group comparisons at each time point

At weeks 4, 8, and 12, the experimental group showed significantly lower values than the control group for BUN, UACR, urinary podocyte count, and UPCX/Ucr. For 24h-UP, significant differences emerged from week 8 onwards. Serum albumin showed significant differences at weeks 4 and 8 but not at week 12; serum creatinine showed a significant difference only at week 8 (Table 3).

Within-group changes over time

Within both groups, all DKD-related indicators improved significantly over time (time effect: *P*<0.001 for all). Pairwise comparisons with Bonferroni correction showed statistically significant reductions between consecutive time points for most parameters (Table 3).

Multivariable linear regression for UACR change

To assess the independent effect of canagliflozin on UACR reduction, the authors constructed a multivariable linear regression model with log-transformed change in UACR (week 12 value minus baseline) as the dependent variable. Univariate analysis showed that treatment with canagliflozin, baseline eGFR, and baseline HbA1c were associated with UACR change. In the multivariable model, after adjusting for age, sex, diabetes duration, BMI, baseline eGFR, systolic blood pressure, and baseline HbA1c, canagliflozin remained significantly associated with UACR reduction (adjusted β =−0.89, 95% CI −1.21 to −0.57, *P*<0.001). This result suggests that the improvement in proteinuria by canagliflozin is independent of glycaemic control and other confounders.

Mediation analysis of UPCX/Ucr in the improvement of DKD markers by canagliflozin

To further explore whether canagliflozin delays DKD progression by protecting podocytes, mediation analysis was performed with treatment group as the independent variable; change in UPCX/Ucr as the mediator; and changes in UACR, 24h-UP, and serum creatinine as dependent variables. Results showed that for reducing UACR and 24h-UP, the direct effects of canagliflozin were not statistically significant, while the indirect effects through UPCX/Ucr were significant. For reducing serum creatinine, both the direct and indirect effects were statistically significant, suggesting that UPCX/Ucr plays a partial mediating role (Table 5).

Comparison of adverse reactions

There was no statistically significant difference in the incidence of adverse reactions between the 2 groups (Table 6).

Table 1. Baseline demographic and clinical characteristics.

Characteristics	Experimental (n=87)	Control (n=85)	Mean/median difference (95% CI)
Age, mean $\pm$ SD, years	60.48 $\pm$ 16.16	63.20 $\pm$ 16.60	−2.72 (−7.65 to 2.22)
Male, no. (%)	47 (54.0)	44 (51.8)	−
Asian, no. (%)	87 (100)	85 (100)	−
Diabetes duration, mean $\pm$ SD, years	11.71 $\pm$ 5.66	12.50 $\pm$ 6.59	−0.79 (−2.62 to 1.04)
BMI, mean $\pm$ SD, kg/m ²	23.65 $\pm$ 3.80	24.20 $\pm$ 4.51	−0.55 (−1.82 to 0.72)
Current smoker, no. (%)	19 (21.8)	21 (24.7)	−
SBP, mean $\pm$ SD, mmHg	132.5 $\pm$ 12.3	134.1 $\pm$ 13.0	−1.6 (−5.3 to 2.1)
DBP, mean $\pm$ SD, mmHg	80.2 $\pm$ 8.1	81.4 $\pm$ 8.5	−1.2 (−3.7 to 1.3)
HbA1c, mean $\pm$ SD, %	11.30 $\pm$ 1.92	11.63 $\pm$ 2.33	−0.33 (−0.97 to 0.31)
Serum albumin, mean $\pm$ SD, g/L	39.36 $\pm$ 3.71	38.75 $\pm$ 3.67	0.61 (−0.52 to 1.74)
Serum creatinine, mean $\pm$ SD, μ mol/L	96.96 $\pm$ 6.89	95.08 $\pm$ 6.78	1.88 (−0.18 to 3.94)
BUN, mean $\pm$ SD, mmol/L	9.02 $\pm$ 1.69	9.46 $\pm$ 2.18	−0.44 (−1.03 to 0.15)
eGFR, mean $\pm$ SD, mL/min/1.73 m ²	75.5 $\pm$ 15.2	73.8 $\pm$ 16.1	1.7 (−3.0 to 6.4)
UACR, median (IQR), mg/mmol ^a	36.2 (29.8 to 42.5)	36.8 (30.1 to 43.9)	−0.6 (−2.9 to 1.7)
24h-UP, median (IQR), g/24h ^a	0.65 (0.52 to 0.78)	0.63 (0.50 to 0.76)	0.02 (−0.03 to 0.07)
TC, mean $\pm$ SD, mmol/L	4.82 $\pm$ 1.01	4.95 $\pm$ 1.12	−0.13 (−0.45 to 0.19)
TG, mean $\pm$ SD, mmol/L	2.45 $\pm$ 1.10	2.52 $\pm$ 1.15	−0.07 (−0.41 to 0.27)
HDL-C, mean $\pm$ SD, mmol/L	1.15 $\pm$ 0.30	1.12 $\pm$ 0.28	0.03 (−0.06 to 0.12)
LDL-C, mean $\pm$ SD, mmol/L	3.05 $\pm$ 0.85	3.12 $\pm$ 0.90	−0.07 (−0.33 to 0.19)
Use of statin, no. (%)	52 (59.8)	50 (58.8)	−
Use of ACEi/ARB, no. (%)	68 (78.2)	65 (76.5)	−

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BMI: body mass index; BUN: blood urea nitrogen; CI: confidence interval; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; HDL-C: high-density lipoprotein cholesterol; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; SD: standard deviation; TC: total cholesterol; TG: triglycerides; UACR: urinary albumin-to-creatinine ratio; 24h-UP: 24-hour urinary protein

^a For skewed variables, the Hodges-Lehmann estimate of median difference (experimental – control) with 95% CI is presented.

For normally distributed variables, mean difference (experimental – control) with 95% CI is shown. All between-group comparisons were non-significant (all $P > 0.05$).

DISCUSSION

DKD is primarily characterised by albuminuria, glomerulosclerosis, and progressive loss of kidney function, ultimately leading to ESRD and contributing significantly to global mortality. Its pathogenesis is complex and not yet fully elucidated. Current research indicates that immune dysregulation-mediated chronic inflammation and podocyte pyroptosis are key factors in DKD onset and progression.^{5,12} Podocytes are specialised cells within the kidney, crucial for maintaining the glomerular filtration barrier. They regulate the passage of macromolecular proteins, stabilise the

glomerular capillary structure, and protect glomerular endothelial cell function. However, under pathological conditions, podocytes can be injured, depleted, and their regenerative capacity impaired, ultimately leading to proteinuria and kidney damage. Therefore, podocyte injury and dysfunction are critical triggers in the progression of DKD.¹³ PCX is a transmembrane protein located on the apical surface of glomerular podocytes and serves as a major surface antigen. As a negatively charged sialoprotein, it contributes to the charge-selective barrier of glomerular filtration, preventing the leakage of negatively charged proteins

Table 2. Glycaemic parameters over time by group.

Parameters	Time point	Experimental (n=87)	Control (n=85)	Between-group mean difference (95% CI)	P for interaction
FPG, mean $\pm$ SD, mmol/L	Baseline	9.64 $\pm$ 1.67	9.87 $\pm$ 1.72	−0.23 (−0.74 to 0.28)	0.246
	Week 4	8.48 $\pm$ 1.60	8.58 $\pm$ 1.74	−0.10 (−0.60 to 0.40)	
	Week 8	7.02 $\pm$ 1.48	7.15 $\pm$ 1.81	−0.13 (−0.63 to 0.37)	
	Week 12	6.26 $\pm$ 1.95	6.37 $\pm$ 1.56	−0.11 (−0.64 to 0.42)	
2hPG, mean $\pm$ SD, mmol/L	Baseline	17.74 $\pm$ 2.73	17.29 $\pm$ 2.45	0.45 (−0.33 to 1.23)	0.209
	Week 4	13.21 $\pm$ 2.22	12.90 $\pm$ 1.62	0.31 (−0.28 to 0.90)	
	Week 8	11.22 $\pm$ 2.24	11.14 $\pm$ 2.01	0.08 (−0.55 to 0.71)	
	Week 12	9.00 $\pm$ 2.07	8.74 $\pm$ 1.64	0.26 (−0.31 to 0.83)	
HbA1c, mean $\pm$ SD, %	Baseline	11.30 $\pm$ 1.92	11.63 $\pm$ 2.33	−0.33 (−0.97 to 0.31)	0.096
	Week 12	7.00 $\pm$ 1.34	7.11 $\pm$ 1.38	−0.11 (−0.51 to 0.29)	

2hPG: 2-hour postprandial glucose; CI: confidence interval; FPG: fasting plasma glucose; HbA1c: glycated haemoglobin; SD: standard deviation
Between-group mean difference (experimental – control) at each time point was estimated from linear mixed-effects model.

P value for group $\times$ time interaction from linear mixed-effects model (F-test).

into the urine, maintaining the separation between adjacent podocytes (foot processes), and preventing adhesion between epithelial cells and the glomerular capillary tuft.¹⁴ UPCX levels are significantly elevated in DKD patients,¹⁵ making it a reliable indicator of the extent of podocyte injury in DKD. Furthermore, as a biomarker of early podocyte injury in DKD, PCX may appear earlier than proteinuria, potentially serving as a more sensitive indicator of renal damage.¹⁵ Human and animal studies have also demonstrated that podocyte injury is evident in the early stages of DKD progression.^{17,18} Therefore, exploring effective measures and pathways to protect podocytes from injury holds significant clinical importance for DKD prevention and treatment.

SGLT2i are a novel class of glucose-lowering drugs widely used in current clinical practice. Numerous studies have demonstrated their renoprotective effects, and they are recommended by several authoritative guidelines as first-line therapy for DKD. Clinical studies have shown that SGLT2i can prevent the progressive increase in urinary excretion of podocyte-specific molecules in DKD patients, thereby protecting podocytes.^{19,20} The protective effects of SGLT2i on podocytes are considered multifaceted, involving various mechanisms, such as maintaining podocyte integrity, reducing foot process effacement, enhancing podocyte autophagy, attenuating lipotoxicity, reducing oxidative stress and inflammation, and reversing podocyte epithelial-mesenchymal transition.²¹ Canagliflozin, one of the approved SGLT2i, primarily lowers blood glucose

by increasing renal glucose excretion. Concurrently, it reduces proteinuria, demonstrating good efficacy and safety in treating early-stage DKD,²² and lowering the risk of adverse renal events in DKD patients.²³ Animal studies indicate that canagliflozin treatment significantly improves serum creatinine levels, 24-hour urinary albumin excretion, and UACR in DKD mice. Additionally, canagliflozin reduces the expression of key inflammatory markers in the renal cortex and prevents podocyte pyroptosis, thereby attenuating glomerular and podocyte injury, and reducing overall pathological damage.⁵

This study investigated whether canagliflozin exerts podocyte-protective effects and explored the association between podocyte protection and DKD improvement, aiming to elucidate the possible mechanisms by which canagliflozin delays DKD progression. Baseline characteristics were comparable between groups. After treatment, glycaemic control was similar in both groups, minimising the confounding effect of glucose reduction on renal parameters. However, the experimental group showed significantly greater reductions in 24h-UP, UACR, urinary podocyte count, and UPCX/Ucr compared with the control group, demonstrating the beneficial effects of canagliflozin in reducing proteinuria and protecting podocytes. Subsequent mediation analysis revealed that UPCX/Ucr played a significant mediating role in the improvement of proteinuria by canagliflozin, with mediation proportions of 84.39% for UACR and 86.42% for 24h-UP. The direct effects were not statis-

Table 3. Diabetic kidney disease-related indicators over time by group.

Parameters	Time point	Experimental (n=87)	Control (n=85)	Between-group difference (95% CI)	Geometric mean ratio (experimental/control) (95% CI)	F value (group × time)	η ²	P value for interaction
Serum albumin, mean ± SD, g/L	Baseline	39.36 ± 3.71	38.75 ± 3.67	0.61 (−0.52 to 1.74)		138.258	0.452	<0.001
	Week 4	39.68 ± 3.72	38.31 ± 3.75	1.37 (0.25 to 2.49)				
	Week 8	40.73 ± 3.68	39.20 ± 3.74	1.53 (0.41 to 2.65)				
	Week 12	40.51 ± 3.67	40.31 ± 3.68	0.20 (−0.91 to 1.31)				
Serum creatinine, mean ± SD, μmol/L	Baseline	96.96 ± 6.89	95.08 ± 6.78	1.88 (−0.18 to 3.94)		102.977	0.380	<0.001
	Week 4	96.51 ± 6.88	96.61 ± 7.16	−0.10 (−2.20 to 2.00)				
	Week 8	86.63 ± 7.10	90.30 ± 6.77	−3.67 (−5.73 to −1.61)				
	Week 12	86.64 ± 6.95	88.10 ± 7.37	−1.46 (−3.61 to 0.69)				
BUN, mean ± SD, mmol/L	Baseline	9.02 ± 1.69	9.46 ± 2.18	−0.44 (−1.03 to 0.15)		96.139	0.365	<0.001
	Week 4	8.21 ± 1.44	9.19 ± 1.42	−0.98 (−1.42 to −0.54)				
	Week 8	7.38 ± 1.36	8.47 ± 1.35	−1.09 (−1.50 to −0.68)				
	Week 12	7.69 ± 1.35	8.36 ± 1.51	−0.67 (−1.10 to −0.24)				
24h-UP, geometric mean, g/24h ^a	Baseline	0.64	0.61	0.03 (−0.02 to 0.08)		89.588	0.348	<0.001
	Week 4	0.58	0.59	−0.01 (−0.05 to 0.03)				
	Week 8	0.45	0.55	−0.10 (−0.13 to −0.07)				
	Week 12	0.38	0.52	−0.14 (−0.18 to −0.10)	0.73 (0.65 to 0.82)			
UACR, geometric mean, mg/mmol ^a	Baseline	34.5	34.9	−0.4 (−2.7 to 1.9)		41.832	0.200	<0.001
	Week 4	30.1	33.8	−3.7 (−5.7 to −1.7)				
	Week 8	27.0	32.9	−5.9 (−7.8 to −4.0)				
	Week 12	21.0	29.0	−8.0 (−9.8 to −6.2)	0.72 (0.65 to 0.80)			

Table 3. Diabetic kidney disease-related indicators over time by group. (Cont'd)

Parameters	Time point	Experimental (n=87)	Control (n=85)	Between-group difference (95% CI)	Geometric mean ratio (experimental/control) (95% CI)	F value (group x time)	η^2	P value for Interaction
Urinary podocyte count, geometric mean, cells/mL ^a	Baseline	6.1	6.0	0.1 (−0.3 to 0.5)		82.954	0.331	<0.001
	Week 4	5.2	6.2	−1.0 (−1.4 to −0.6)				
	Week 8	3.7	5.5	−1.8 (−2.2 to −1.4)				
	Week 12	2.4	5.0	−2.6 (−2.8 to −2.4)	0.48 (0.43 to 0.54)			
UPCX/Ucr, geometric mean, $\mu\text{g/g}^a$	Baseline	8.8	8.9	−0.1 (−0.8 to 0.6)		105.230	0.385	<0.001
	Week 4	7.9	8.6	−0.7 (−1.5 to 0.1)				
	Week 8	6.1	8.2	−2.1 (−2.8 to −1.4)				
	Week 12	5.5	7.6	−2.1 (−2.5 to −1.7)	0.72 (0.66 to 0.79)			

24h-UP: 24-hour urinary protein; BUN: blood urea nitrogen; CI: confidence interval; SD: standard deviation; UACR: urinary albumin-to-creatinine ratio; UPCX/Ucr: urinary podocalyxin-to-urinary creatinine ratio; η^2 : partial eta-squared (effect size)

Between-group difference (experimental – control) at each time point, estimated from linear mixed-effects model.

F value and P value for group x time interaction from linear mixed-effects model (df₁=3, df₂=684 for all parameters).

Partial eta-squared (η^2): small ≥ 0.01 , medium ≥ 0.06 , large ≥ 0.14 .

The ratio with 95% CI is presented only at week 12 for log-transformed variables, derived directly from the mixed-effects models on the log scale.

^a Values are geometric means back-transformed from linear mixed-effects models performed on log-transformed data; between-group differences and CIs were computed on the log scale and back-transformed.

Table 4. Univariate and multivariable linear regression for change in urinary albumin-to-creatinine ratio.

Variable	Univariate β (95% CI)	P value	Multivariable adjusted β (95% CI)	P value
Canagliflozin (vs control)	-0.85 (-1.18 to -0.52)	<0.001	-0.89 (-1.21 to -0.57)	<0.001
Age (per year)	0.01 (-0.02 to 0.04)	0.45	0.02 (-0.01 to 0.05)	0.142
Male (vs female)	0.08 (-0.26 to 0.42)	0.65	0.11 (-0.23 to 0.45)	0.521
Diabetes duration (per year)	0.02 (-0.03 to 0.07)	0.42	0.03 (-0.02 to 0.08)	0.213
BMI (per kg/m ²)	0.04 (-0.03 to 0.11)	0.26	0.05 (-0.02 to 0.12)	0.168
Baseline eGFR (per mL/min/1.73 m ²)	-0.03 (-0.05 to -0.01)	0.04	-0.01 (-0.03 to 0.01)	0.289
Baseline SBP (per mmHg)	0.01 (-0.01 to 0.03)	0.35	0.01 (-0.01 to 0.03)	0.402
Baseline HbA1c (per %)	0.18 (0.02 to 0.34)	0.03	0.12 (-0.03 to 0.27)	0.115

BMI: body mass index; CI: confidence interval; eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; SBP: systolic blood pressure; UACR: urinary albumin-to-creatinine ratio; vs: versus

Adjusted $R^2=0.34$, $F=6.82$, $P<0.001$ for the multivariable linear regression model.

Table 5. Mediation analysis of UPCX/Ucr in the improvement of diabetic kidney disease markers by canagliflozin.

	Point estimate	SE	t	P value	95% CI	Mediation proportion
Path 1: Treatment→UPCX/Ucr→UACR						
Direct effect (treatment→UACR)	−0.180	0.121	−1.481	0.141	−0.419 to 0.060	84.39%
Indirect effect (treatment→UPCX/Ucr→UACR)	−0.968	0.100	-	-	−1.171 to −0.774	
Total effect	−1.147	0.124	−9.230	<0.001	−1.393 to −0.902	
Path 2: Treatment→UPCX/Ucr→24h-UP						
Direct effect (treatment→24h-UP)	−0.022	0.100	−0.224	0.823	−0.220 to 0.175	86.42%
Indirect effect (treatment→UPCX/Ucr→24h-UP)	−0.783	0.119	-	-	−1.127 to −0.655	
Total effect	−0.906	0.124	−7.323	<0.001	−1.150 to −0.662	
Path 3: Treatment→UPCX/Ucr→serum creatinine						
Direct effect (treatment→serum creatinine)	−0.892	0.280	−3.198	0.002	−1.450 to −0.343	25.13%
Indirect effect (treatment→UPCX/Ucr→serum creatinine)	−0.301	0.071	-	-	−0.437 to −0.153	
Total effect	−1.198	0.238	−5.039	<0.001	−1.667 to −0.728	

24h-UP: 24-hour urinary protein; CI: confidence interval; SE: standard error; UACR: urinary albumin-to-creatinine ratio; UPCX/Ucr: urinary podocalyxin-to-urinary creatinine ratio

All paths are adjusted for age, sex, diabetes duration, BMI, and baseline HbA1c.

tically significant, suggesting that the reduction in proteinuria is largely statistically mediated by changes in UPCX/Ucr, a marker of podocyte integrity. While this supports the authors' hypothesis, it is important to emphasise that mediation analysis demonstrates statistical association, not direct biological causality. Regarding renal function, canagliflozin significantly reduced serum creatinine and BUN compared to

baseline. While it showed an advantage over standard therapy in reducing BUN, its effect on serum creatinine reduction was comparable to standard therapy. Current evidence on whether canagliflozin reduces serum creatinine is inconsistent; animal studies have confirmed its creatinine-lowering effect in diabetic models,^{5,24} but a systematic review of 20 randomised controlled trials suggested that canagliflozin does

Table 6. Comparison of adverse reactions between experimental and control groups.

Adverse events	Experimental (n=87), no. (%)	Control (n=85), no. (%)	Risk difference (95% CI)	P value
Genitourinary infection	3 (3.45)	1 (1.18)	2.27% (−1.97% to 6.51%)	
Hypoglycaemia	1 (1.15)	3 (3.53)	−2.38% (−6.70% to 1.94%)	
Hypotension	1 (1.15)	0 (0)	1.15% (−1.10% to 3.40%)	
Clinically significant weight loss	1 (1.15)	1 (1.18)	−0.03% (−3.39% to 3.33%)	
Any adverse event	6 (6.90)	5 (5.88)	1.02% (−6.18% to 8.22%)	0.786

CI: confidence interval

Hypoglycaemia was defined as random blood glucose <3.9 mmol/L.

Hypotension was defined as blood pressure <90/60 mmHg.

Weight loss was defined as >5% body weight loss within 3 months affecting daily life (e.g. persistent fatigue or weakness interfering with routine activities; difficulty climbing stairs or carrying groceries; reduced ability to perform usual household chores).

not significantly alter eGFR.²⁵ Therefore, the authors included serum creatinine as a dependent variable in the mediation analysis. The results showed that while UPCX/Ucr had a mediating effect, the proportion was approximately 25.13%, and both direct and total effects were statistically significant. This finding indicates that canagliflozin does reduce serum creatinine in this study, but podocyte protection only accounts for about a quarter of the effect, suggesting that other mechanisms (such as haemodynamic effects) also play substantial roles. Why did the authors not observe the initial rise in creatinine often seen with SGLT2i and ACEi/ARB in this study? The most plausible explanation for the absence of this phenomenon in this study is the well-preserved baseline renal function in the cohort (mean eGFR 73–75 mL/min/1.73 m²). Large clinical trials of canagliflozin have consistently demonstrated that the initial haemodynamic dip in eGFR is modest in magnitude (approximately 3.75 mL/min/1.73 m²),²⁶ such a subtle change may be difficult to detect statistically in the small sample size. Future studies with a longer follow-up period and a broader range of baseline eGFR are needed to clarify this. Regarding safety, canagliflozin did not increase the incidence of adverse reactions compared to standard therapy, suggesting a favourable safety profile.

Several limitations should be acknowledged. First, this was a single-centre study with a modest sample size, which may limit generalisability. Second, the authors used UPCX as a surrogate marker of podocyte injury rather than direct histological confirmation (kidney biopsy). While PCX is well-validated, direct visualisation of podocyte foot process effacement would be stronger evidence. Third, the authors did not employ advanced techniques, such as immunofluorescence, flow cytometry, or PCR for

podocyte quantification, which could reduce measurement variability. Fourth, the follow-up duration (12 weeks) is relatively short; longer-term renal outcomes (eGFR slope, ESRD) were not assessed. Fifth, despite multivariable adjustment, residual confounding cannot be excluded (e.g. dietary salt intake). Sixth, a placebo-controlled design was used, but the absence of an active comparator (e.g. another SGLT2i or GLP-1RA) limits comparison of class effects. Seventh, the mediation analysis assumes a causal ordering (treatment → podocyte protection → proteinuria), which is supported by biological plausibility but not proven by this observational mediation approach.

CONCLUSION

Canagliflozin, as a established SGLT2i, effectively improves glycaemic control and provides significant renal protective benefits in DKD patients by reducing proteinuria, lowering serum creatinine, and protecting podocytes. The reduction in proteinuria appears to be largely statistically mediated by podocyte protection, with a very high mediation proportion. Canagliflozin is a safe and effective agent for improving DKD, although longer-term studies are warranted to confirm the durability of these effects and their translation into hard renal endpoints.

Supplementary material

Annex S1. CONSORT 2025 checklist of information to include when reporting a randomised trial.

Ethics statement

This study was approved by the Hospital Ethics Committee of Shangyu People's Hospital of Shaoxing City (Ethics Approval Number: PJ2022-Res 032-01). All participants provided written informed consent.

Declarations

All participants provided written informed consent. This study was funded by the Shaoxing Municipal Health and Health Technology Plan (Grant no. 2022KY091) and the Zhejiang Provincial Medical and Health Science and Technology Project (Grant no. 2024KY496). 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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Endoscopic combined intrarenal surgery versus conventional percutaneous nephrolithotomy for complex renal calculi: A retrospective study

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ABSTRACT

Introduction: This study aimed to compare the clinical outcomes of endoscopic combined intrarenal surgery (ECIRS) in the prone hip-flexed split-leg position with conventional percutaneous nephrolithotomy (PCNL) for the treatment of complex renal calculi.

Methods: We retrospectively analysed 168 patients with complex renal calculi, including 82 who underwent ECIRS and 86 who underwent conventional PCNL. Baseline demographic and stone characteristics, perioperative outcomes, initial stone-free rate (SFR) within 1–3 days after surgery, final SFR after completion of all planned treatments, auxiliary procedures, double-J stent indwelling duration, length of hospital stay, and postoperative complications were compared between groups. Logistic regression analyses were performed to evaluate factors associated with residual stones after the initial procedure, with additional clinically informed sensitivity analysis using prespecified covariates.

Results: Baseline demographic characteristics, stone features, and postoperative outcomes, including intraoperative ureteral catheterization time, complication rates, Clavien–Dindo classification, and final SFR after completion of all planned treatments, were comparable between the two groups (all $P > 0.05$). In this retrospective cohort, ECIRS in the prone hip-flexed split-leg position was associated with earlier stone clearance after the index procedure, reflected by a higher initial SFR (74.39% versus [vs] 50.00%, $P = 0.001$) and a lower requirement for auxiliary procedures (29.27% vs 46.51%, $P = 0.021$). These findings were accompanied by a shorter hospital stay (6.44 vs 8.61 days, $P < 0.001$), shorter double-J stent indwelling duration (2.81 vs 4.79 weeks, $P = 0.002$), and shorter operative time ($P = 0.012$). Multivariable and sensitivity analyses further demonstrated that ECIRS was independently associated with lower odds of residual stones after the initial procedure (odds ratio 0.40, 95% confidence interval 0.20–0.80, $P = 0.009$).

Conclusion: Single-position ECIRS in the prone hip-flexed split-leg configuration was feasible for selected patients with complex renal calculi and was associated

with earlier stone clearance and shorter perioperative recovery metrics. However, the final SFR after completion of all planned treatments was comparable between groups, and whether this positional configuration confers benefit beyond ECIRS in alternative positions could not be determined from this comparison. Further prospective studies are required to validate these findings.

Keywords: kidney calculi, nephrostomy, percutaneous, retrospective studies, treatment outcome

CLINICAL IMPACT

What is New

- This study showed that ECIRS in the modified prone hip-flexed split-leg position was associated with a significantly higher initial stone-free rate (74.39% versus [vs] 50.00%), shorter hospital stay (6.44 vs 8.61 days), and shorter double-J stent indwelling time (2.81 vs 4.79 weeks) compared with conventional PCNL for complex renal calculi, without an associated increase in complication rates.
- The modified position eliminates the need for intraoperative repositioning, optimising surgical access and efficiency.

Clinical Implications

- Our findings suggest that ECIRS in the prone hip-flexed split-leg position may represent a feasible alternative for selected patients with complex renal calculi in centres with established endourological infrastructure.
- This approach was associated with earlier stone clearance and shorter perioperative recovery metrics; however, residual confounding inherent to the retrospective study design precludes causal interpretation of these associations.

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INTRODUCTION

Renal calculi are among the most prevalent urological diseases worldwide, severely impairing patients' quality of life and increasing the healthcare burden. Epidemiological data from China showed that the national prevalence of renal calculi was 6.4% in 2013–2014,¹ and the hospitalisation-related healthcare burden has continued to increase in recent years.² Among these, complex renal stones—such as staghorn calculi, multiple stones, or stones associated with anatomical abnormalities—pose substantial clinical challenges due to their high recurrence rate, treatment difficulty, and increased risk of complications. These cases require efficient and safe treatment strategies.

Percutaneous nephrolithotomy (PCNL) is regarded as the gold standard for treating complex renal stones, enabling stone fragmentation and removal through a percutaneous tract.³ However, in the presence of multiple complex calculi, PCNL may require multiple tracts or repeated procedures, which can be associated with greater trauma, delayed recovery, and higher complication risks. In addition, the conventional prone position has inherent limitations, including the need for patient repositioning and technical constraints when simultaneous retrograde ureteroscopic access is required.⁴

Endoscopic combined intrarenal surgery (ECIRS) integrates the advantages of percutaneous nephroscopy and ureteroscopy, facilitating stone fragmentation and fragment retrieval through dual access. Since its introduction with the Galdakao-modified supine Valdivia position in 2008,⁵ ECIRS has undergone multiple modifications in positioning techniques, including the reverse lithotomy position, prone hip-flexed split-leg position, and knee-chest prone position. These innovations have expanded positioning strategies for ECIRS; however, adoption may still be influenced by surgeon familiarity, equipment availability, and institutional workflow.

To facilitate simultaneous antegrade and retrograde access during ECIRS, we adopted a prone hip-flexed split-leg position that allows the procedure to be completed without intraoperative repositioning. The present study aimed to evaluate the feasibility and perioperative outcomes of ECIRS performed in this position compared with conventional PCNL for the treatment of complex renal calculi.

METHODS

Study design

A retrospective cohort analysis was conducted on the clinical data of patients diagnosed with complex renal stones at Jinhua Hospital, Zhejiang University School of Medicine, between May 2022 and July 2024.

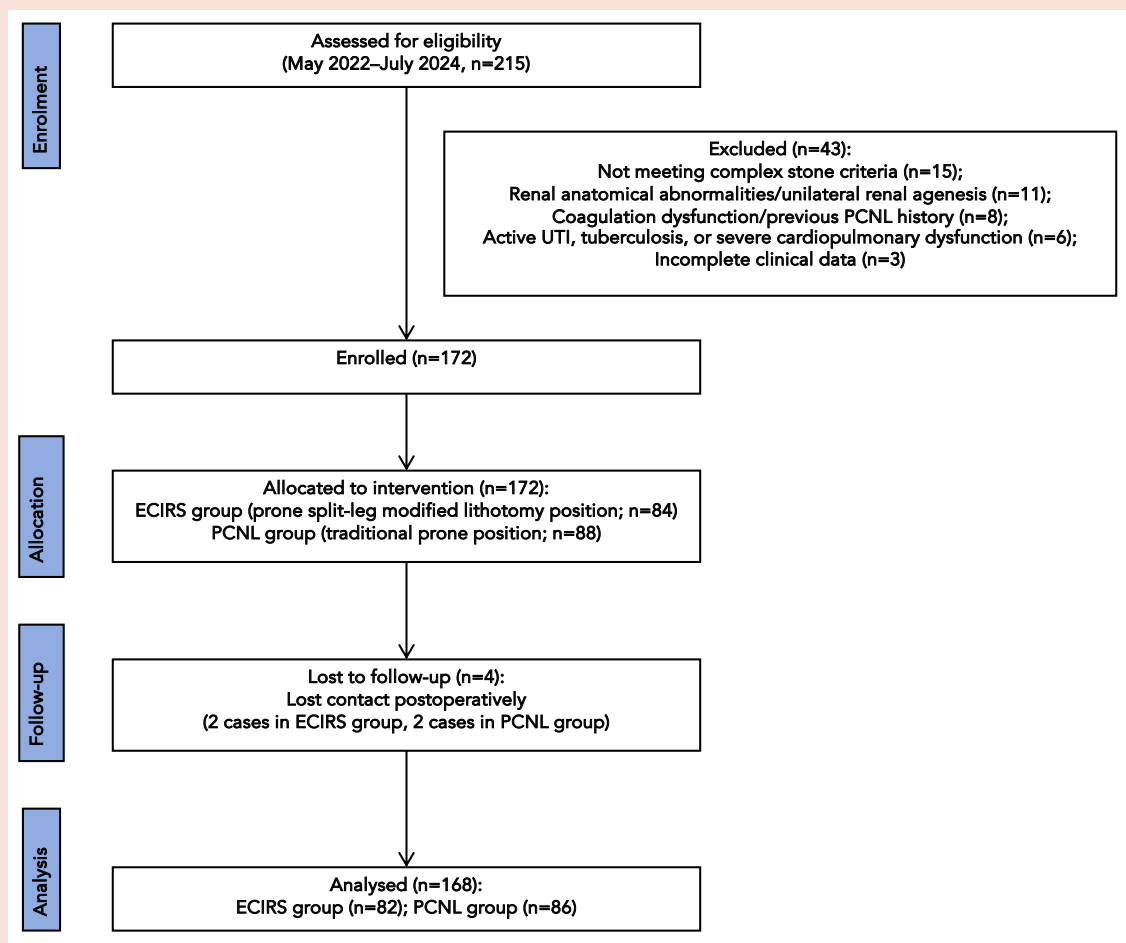
Patients who underwent either PCNL or ECIRS for stone removal were included. The inclusion criteria were as follows: (1) age ≥ 18 years; (2) preoperative confirmation of complex renal stones by ultrasonography and computed tomography (CT), defined as stones meeting any of the following criteria: (a) a maximum diameter > 2 cm; (b) staghorn calculi; or (c) multiple renal stones (≥ 2 stones) with a S.T.O.N.E. score ≥ 7 points⁶; (3) patients treated with ECIRS in the prone hip-flexed split-leg position or with traditional PCNL; and (4) complete clinical data available. The exclusion criteria were as follows: (1) anatomical abnormalities of the kidney or functional/anatomical absence of a unilateral kidney; (2) coagulation disorders or a history of prior PCNL; (3) concomitant active urinary tract infection uncontrolled after standard preoperative treatment, tuberculosis, or severe cardiopulmonary dysfunction; and (4) incomplete clinical data compromising data integrity assessment. The distribution of patients meeting each criterion for complex renal stones is provided in Supplementary Table S1. Cases with missing key variables were excluded from the final analysis, and no missing data imputation was performed.

This study was approved by the respective ethics committee. Written informed consent was obtained from all enrolled patients. The patient grouping was determined through comprehensive evaluation by 3 experienced urologists, based on the S.T.O.N.E. score quantifying stone complexity, renal anatomical characteristics, and the patient's informed consent. The detailed process of patient screening, inclusion, exclusion, and final grouping is illustrated in Fig. 1.

Preoperative evaluation

All patients underwent standardised preoperative preparation, including detailed medical history collection, physical examination, routine laboratory tests, and imaging evaluation. Preoperative workup included urinalysis, urine culture, and antibiotic susceptibility testing. For patients with urinary tract infection, targeted antibiotic therapy was administered preferentially according to urine culture and susceptibility test results. In the absence of definitive susceptibility test results, empirical antibiotics, primarily cephalosporins, and selected quinolones based on local antimicrobial susceptibility patterns were administered under antimicrobial stewardship principles; and the use of broad-spectrum antibiotics was strictly controlled to avoid the development of drug resistance. For patients with confirmed preoperative urinary tract infection, targeted anti-infective therapy was continued for 7 days, followed by repeat urine culture and urinalysis before surgery. Patients were included in the surgical protocol only when the urine

Fig. 1. Flow diagram of patient screening.



ECIRS: endoscopic combined intrarenal surgery; PCNL: percutaneous nephrolithotomy; UTI: urinary tract infection

culture result turned negative, the white blood cell count in urinalysis returned to normal, and the infection was confirmed to be effectively controlled. Postoperative antibiotic therapy was administered according to perioperative infection status, urine culture results, and institutional antimicrobial stewardship protocols. The complexity of renal stones was objectively assessed using the S.T.O.N.E. scoring system,⁷ based on non-contrast CT images. This scoring system comprises 5 parameters: S (stone size), T (tract length), O (obstruction), N (number of involved calyces), and E (essence/Hounsfield units). The sum of these 5 items yielded a total score ranging from 5 to 13.

Surgical technique

Percutaneous nephrolithotomy

Patients in the PCNL group underwent the conventional 2-step puncture method. Under general anaesthesia in the lithotomy position, a 5 Fr open-ended ureteral catheter was inserted into the upper urinary tract and an 18 Fr Foley catheter into the

bladder. The patient was then repositioned to the traditional prone position, with pressure points (chest, iliac crest, and knees) adequately protected. Retrograde pyelography was subsequently performed, and renal calyx puncture was achieved under fluoroscopic and ultrasonographic guidance. A 0.035-inch stiff guidewire was advanced and coiled within the renal pelvis or ureter to ensure stability. Serial fascial dilators (16 Fr, 18 Fr, or 24 Fr) were used to sequentially establish a 16 Fr, 18 Fr, or 24 Fr percutaneous tract, followed by placement of a corresponding working sheath. A 20 Fr nephroscope was typically introduced through the standard 24 Fr tract, whereas an appropriately sized endoscope was selected for smaller-calibre tracts. Lithotripsy and stone extraction were then performed under direct endoscopic vision.

Endoscopic combined intrarenal surgery

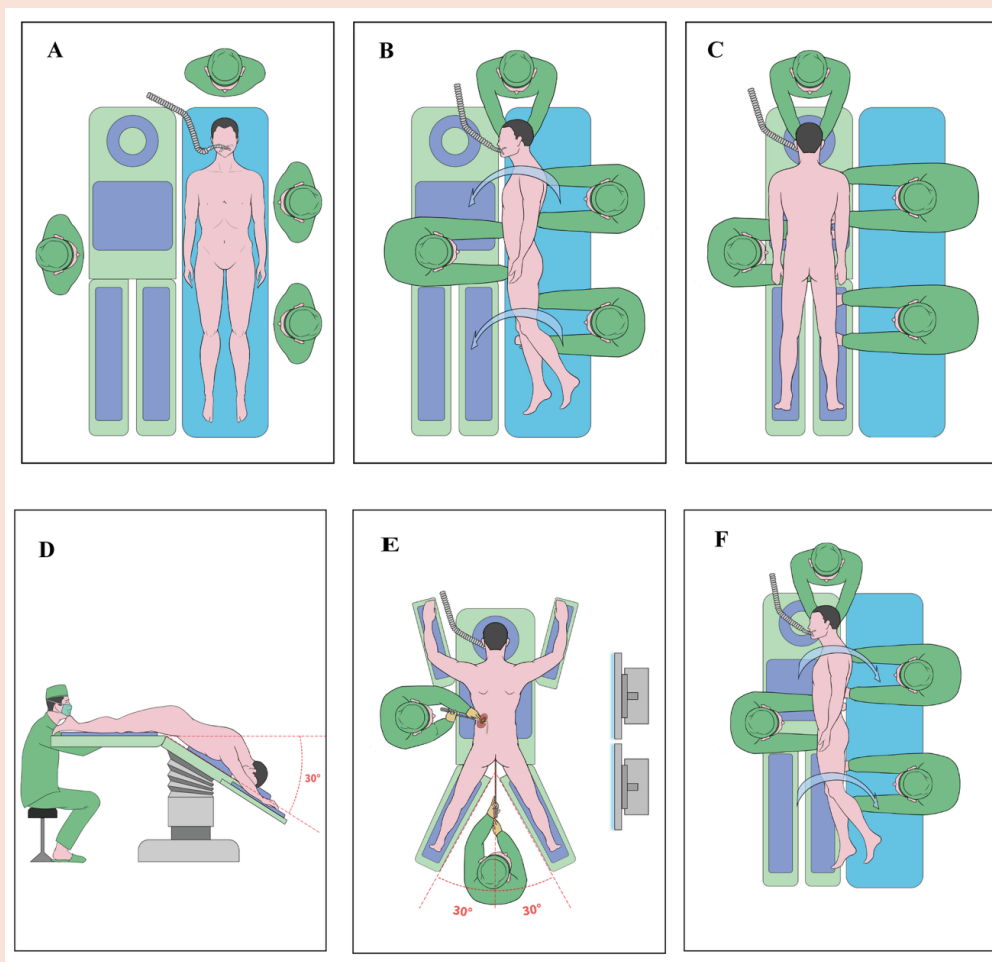
After induction of general anaesthesia, patients were transferred from the transport bed to the operating table in a coordinated team effort and placed in the prone hip-flexed split-leg position. Strategic padding

was applied at pressure points (chest, iliac crest, and knees) to prevent neurovascular injury. Both lower limbs were positioned on padded supports aligned with the operating table, with approximately 20-degree hip flexion and an inter-leg distance of at least 30 cm. The operating table was raised by ~30 cm, the head was tilted downwards, and the foot end was elevated by 30 cm, resulting in a perineal elevation of 60 degrees. The procedure began with cystoscopy, followed by retrograde insertion of a 5–7 Fr open-ended ureteral catheter into the renal pelvis to create artificial hydronephrosis, after which a 12–14 Fr ureteral access sheath was advanced over a 0.035-inch guidewire. The operating table was then levelled, and a 7.5 Fr flexible ureteroscope was inserted. Under combined ultrasound and flexible ureteroscopic guidance, a percutaneous renal tract was established using serial fascial dilators and

corresponding Amplatz sheaths (16 Fr, 18 Fr, or 24 Fr), selected according to stone burden, calyceal anatomy, and intraoperative surgical requirements. Large stones were fragmented with an ultrasonic/pneumatic lithotripter via nephroscopy, while small stones in difficult-to-access locations were treated with holmium laser through the flexible ureteroscope. When patients were transferred to the recovery bed, the same position was maintained (20-degree hip flexion and ≥ 30 cm inter-leg distance), thus avoiding intraoperative repositioning (Fig. 2).

All procedures were performed by three experienced urologists. A ureteral catheter was routinely left indwelling in all patients, and a 6 Fr double-J ureteral stent was placed strictly according to unified objective criteria in patients with intraoperatively confirmed significant ureteral oedema, residual stone fragments ≥ 2 mm with potential risk of postoperative obstruction

Fig. 2. Steps of establishing the prone hip-flexed split-leg position for ECIRS. (A) The patient receives anaesthesia in the supine position on the transport bed prior to transfer. (B) The patient is turned to the prone position on the adjacent operating table with coordinated team assistance. (C) Strategic padding is applied at pressure points (chest, iliac crest, and knees) to prevent neurovascular injury. (D) Retrograde ureteral catheter insertion to establish artificial hydronephrosis prior to percutaneous puncture. (E) Simultaneous manipulation of percutaneous nephroscope (upper image) and transurethral ureteroscope (lower image). (F) Patient transferred to the recovery bed while maintaining the prone hip-flexed split-leg alignment.



ECIRS: Endoscopic combined intrarenal surgery

or requiring subsequent auxiliary treatment, or anticipated need for subsequent intervention. Stent removal was performed by a dedicated urological team after resolution of gross haematuria and flank pain, adequate control of urinary tract infection confirmed by urinalysis, and imaging confirmation of no significant residual calculi or urinary tract obstruction. The ureteral catheter and Foley catheter were removed after confirmation of no urinary extravasation, haematuria, or other abnormalities following evaluation at 24–48 hours postoperatively. Operative time was defined as the interval from the initiation of cystoscopy to the completion of Foley catheter and double-J ureteral stent placement. Length of hospital stay was defined as the duration from patient admission to discharge.

Postoperative assessment

Serum haemoglobin and creatinine levels were measured within 24 hours after surgery and compared with preoperative values. Abdominal CT was performed 1–3 days postoperatively to assess residual stones and determine the initial SFR. CT urography was reserved for patients with severe haemorrhagic complications or when residual stones could not be accurately evaluated on standard postoperative CT. Stone-free status was defined as the absence of residual intrarenal stone fragments ≥ 4 mm on postoperative imaging.⁸ For patients with intrarenal residual stones ≥ 4 mm detected on postoperative imaging, the need for adjuvant intervention was determined comprehensively based on the patients' clinical symptoms and the size and location of the residual stones. Adjuvant interventions included extracorporeal shock wave lithotripsy, secondary percutaneous nephrolithotomy, and flexible ureteroscopic lithotripsy. Postoperative complications were graded according to the Clavien–Dindo classification system⁹: Grade I complications required no specific intervention or symptomatic management only, and included low-grade postoperative fever and mild haematuria, which were managed with fluid support, close vital sign monitoring, and symptomatic treatment. Grade II complications required pharmacological intervention and included febrile infection and minor leakage around the nephrostomy tube. Targeted antimicrobial therapy was administered according to urine culture and antimicrobial susceptibility results, and nephrostomy tube leakage was managed with local disinfection and sterile dressing changes. Grade III complications required invasive intervention and included severe haemorrhage, perirenal haematoma, ureteral mucosal injury, and severe infection. Corresponding treatments included endovascular embolisation for haemostasis, ultrasound-guided percutaneous drainage of hematoma, placement of a 6 Fr double-J ureteral stent for ureteral support and healing, and intensive anti-

infective therapy with broad-spectrum antibiotics, with additional anaerobic coverage when necessary. Follow-up imaging was performed 3 months after completion of all planned treatments, using kidney-ureter-bladder (KUB) radiography and/or CT, to determine the final SFR. Final stone-free status was defined as the absence of residual fragments ≥ 4 mm or the presence of clinically insignificant residual fragments not requiring further intervention.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median (interquartile range). Group comparisons were performed using Student's t-test or the Mann-Whitney U test. Categorical variables were expressed as frequencies (percentages) and compared using the chi-square test or Fisher's exact test. Univariate and multivariable logistic regression analyses were performed to identify factors associated with residual stones after the initial procedure. To reduce potential confounding bias inherent to retrospective analyses, additional clinically informed sensitivity analyses were performed using prespecified clinically relevant covariates. All statistical analyses were conducted using R software version 4.3.1 (R Core Team, Vienna, Austria), and a two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of patients

A total of 168 patients with complex renal stones were included, of whom 86 underwent PCNL and 82 underwent ECIRS. No significant differences were observed in baseline demographic or stone characteristics between the two groups (all $P > 0.05$, Table 1). The mean S.T.O.N.E. score was 8.1 ± 1.1 in the ECIRS group and 8.3 ± 0.9 in the PCNL group, indicating comparable stone complexity between groups.

Surgical and postoperative outcomes

According to the surgical data presented in Table 2, no significant differences were observed between the 2 groups in intraoperative ureteral catheterisation time, haemoglobin change, complication rate, or Clavien–Dindo classification. The operative time was shorter in the ECIRS group than in the PCNL group (102.38 ± 27.64 min vs 114.31 ± 33.18 min, $P = 0.012$). Postoperative serum creatinine was lower in the ECIRS group (89.96 ± 21.68 $\mu\text{mol/L}$ vs 96.78 ± 18.27 $\mu\text{mol/L}$, $P = 0.028$), and creatinine change also differed between groups (median interquartile range [IQR]: ECIRS, -8.92 [-37.34 to 9.68] vs PCNL, 2.22 [-28.05 to 17.79], $P = 0.025$). The double-J stent indwelling duration was likewise shorter in the ECIRS group than in the PCNL group (median IQR: 2.81 [2.04 to 3.88] weeks vs 4.79 [1.64 to 10.73] weeks, $P = 0.002$).

Table 1. Baseline demographic and stone characteristics of patients.

Variables	Total (n=168)	PCNL group (n=86)	ECIRS group (n=82)	P
Age (years)	60.17 ± 11.41	59.59 ± 12.39	60.79 ± 10.32	0.495
BMI (kg/m ²)	24.50 ± 3.99	25.02 ± 4.10	23.93 ± 3.79	0.075
Sex, n (%)				0.388
Female	65 (38.69)	36 (41.86)	29 (35.37)	
Male	103 (61.31)	50 (58.14)	53 (64.63)	
Stone side, n (%)				0.769
Right	80 (47.62)	40 (46.51)	40 (48.78)	
Left	88 (52.38)	46 (53.49)	42 (51.22)	
S.T.O.N.E. score	8.2 ± 1.0	8.3 ± 0.9	8.1 ± 1.1	0.159
S score	1.4 ± 0.5	1.4 ± 0.5	1.4 ± 0.6	0.979
T score	1.3 ± 0.5	1.3 ± 0.5	1.3 ± 0.5	0.659
O score	1.5 ± 0.5	1.5 ± 0.5	1.5 ± 0.5	0.709
N score	2.2 ± 0.6	2.3 ± 0.6	2.2 ± 0.7	0.276
E score	1.8 ± 0.4	1.8 ± 0.3	1.7 ± 0.4	0.407
Preoperative haemoglobin (g/L)	135.49 ± 17.52	136.72 ± 18.30	134.20 ± 16.67	0.351
Preoperative creatinine (µmol/L)	103.63 ± 33.18	101.40 ± 33.92	105.98 ± 32.42	0.372

BMI: body mass index; ECIRS: endoscopic combined intrarenal surgery; PCNL: percutaneous nephrolithotomy; S.T.O.N.E.: stone size, tract length, obstruction, number of involved calyces, and essence

In the S.T.O.N.E. nephrolithometry score, S represents stone size; T, tract length; O, degree of obstruction; N, number of involved calyces; and E, stone essence or stone density. Values for the total S.T.O.N.E. score and its components are presented as means of integer-based scores.

The ECIRS group had a shorter hospital stay than the PCNL group (6.44 ± 1.98 days vs 8.61 ± 3.37 days, $P < 0.001$). Regarding stone clearance, ECIRS was associated with a higher initial SFR within 1–3 days after the index procedure (74.39% [61/82] vs 50.00% [43/86], $P = 0.001$) and a lower rate of auxiliary procedures (29.27% vs 46.51%, $P = 0.021$). Specifically, 24 patients in the ECIRS group required additional procedures after the initial treatment, compared with 40 patients in the PCNL group. However, the final SFR at 3 months after completion of all planned treatments did not differ significantly between the 2 groups (95.12% [78/82] vs 93.02% [80/86], $P = 0.804$).

Factors associated with initial SFR

Following the first treatment, residual stones were observed in 43 patients (50.00%) in the PCNL group and in 21 patients (25.61%) in the ECIRS group. To further explore factors associated with initial stone-free status, patients were stratified according to whether they achieved stone-free status after the initial procedure. As shown in Table 3, significant differences were observed between the stone-free

and residual-stone groups in age, body mass index (BMI), S.T.O.N.E. score, operative time, and operative approach (all $P < 0.05$).

Subsequent univariate logistic regression analysis (Table 4) showed that surgical modality, age, BMI, S.T.O.N.E. score, and operative time were associated with the risk of residual stones after the initial procedure (all $P < 0.05$). Variables with statistical significance in the univariate analysis were subsequently entered into the primary multivariable logistic regression model. Surgical modality, S.T.O.N.E. score, and age remained independently associated with residual stones in the primary multivariable analysis (all $P < 0.05$). To further evaluate the robustness of the findings, an additional clinically informed multivariable model—incorporating prespecified clinically relevant covariates, including age, sex, BMI, S.T.O.N.E. score, stone side, and complication occurrence—was subsequently constructed. Sensitivity analysis demonstrated that the association between ECIRS and residual stones remained generally stable, with only minimal changes in the effect estimate compared with the primary multivariable model (Supplementary Table S2),

Table 2. Surgical and postoperative characteristics.

Variables	Total (n=168)	PCNL group (n=86)	ECIRS group (n=82)	P
Postoperative haemoglobin (g/L)	129.42 ± 21.05	130.18 ± 19.76	128.62 ± 22.41	0.631
Postoperative creatinine (µmol/L)	93.45 ± 20.24	96.78 ± 18.27	89.96 ± 21.68	0.028
Operative time (min)	108.48 ± 31.09	114.31 ± 33.18	102.38 ± 27.64	0.012
Intraoperative ureteral catheterisation time (min)	7.05 ± 2.53	6.95 ± 2.59	7.16 ± 2.49	0.601
Hospital stay (days)	7.55 ± 2.98	8.61 ± 3.37	6.44 ± 1.98	<0.001
Haemoglobin change (postoperative – preoperative, g/L)	–4.48 (–13.68 to 2.38)	–7.92 (–14.10 to –0.49)	–1.95 (–12.54 to 3.29)	0.071
Creatinine change (postoperative – preoperative, µmol/L)	–3.35 (–36.65 to 14.74)	2.22 (–28.05 to 17.79)	–8.92 (–37.34 to 9.68)	0.025
Double-J stent placement, n (%)				0.900
No	24 (14.29)	12 (13.95)	12 (14.63)	
Yes	144 (85.71)	74 (86.05)	70 (85.37)	
Double-J stent indwelling duration (weeks)	3.40 (2.00, 6.19)	4.79 (1.64, 10.73)	2.81 (2.04, 3.88)	0.002
Complications, n (%)				0.952
No	100 (59.52)	51 (59.30)	49 (59.76)	
Yes	68 (40.48)	35 (40.70)	33 (40.24)	
Clavien-Dindo grade, n (%)				0.621
No	100 (59.52)	51 (59.30)	49 (59.76)	
I	40 (23.81)	18 (20.93)	22 (26.83)	
II	14 (8.33)	8 (9.30)	6 (7.32)	
III	14 (8.33)	9 (10.47)	5 (6.10)	
Initial SFR, n (%)				0.001
Stone-free	104 (61.90)	43 (50.00)	61 (74.39)	
Residual stone	64 (38.10)	43 (50.00)	21 (25.61)	
Final SFR, n (%)				0.804
Stone-free	158 (94.05)	80 (93.02)	78 (95.12)	
Residual stone	10 (5.95)	6 (6.98)	4 (4.88)	
Auxiliary treatment, n (%)				0.021
No	104 (61.90)	46 (53.49)	58 (70.73)	
Yes	64 (38.10)	40 (46.51)	24 (29.27)	

ECIRS: endoscopic combined intrarenal surgery; PCNL: percutaneous nephrolithotomy; SFR: stone-free rate

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate. For variables presented as median (IQR), the values in parentheses represent the 25th and 75th percentiles. Haemoglobin and creatinine changes were calculated as postoperative values minus preoperative values. Intraoperative ureteral catheterisation time refers to the time required for retrograde ureteral catheter placement during the procedure. Double-J stent indwelling duration was calculated among patients who received double-J stent placement.

Table 3. Clinical and perioperative characteristics stratified by initial stone-free status.

Variables	Stone-free (n=104)	Residual stone (n=64)	P
Age (years)	58.77 ± 10.82	62.45 ± 12.04	0.042
BMI (kg/m ²)	23.97 ± 3.36	25.32 ± 4.72	0.049
S.T.O.N.E. score	8.0 ± 1.0	8.4 ± 1.1	0.019
Preoperative haemoglobin (g/L)	134.64 ± 16.77	136.87 ± 18.73	0.425
Postoperative haemoglobin (g/L)	129.19 ± 18.87	129.79 ± 24.32	0.868
Preoperative creatinine (µmol/L)	101.84 ± 32.35	106.55 ± 34.53	0.373
Postoperative creatinine (µmol/L)	92.68 ± 21.31	94.71 ± 18.45	0.529
Operative time (min)	104.72 ± 29.98	114.60 ± 32.13	0.045
Haemoglobin change (postoperative – preoperative, g/L)	–4.48 (–12.64 to 1.84)	–4.44 (–14.31 to 3.31)	0.660
Creatinine change (postoperative – preoperative, µmol/L)	–1.21 (–36.65 to 15.95)	–5.16 (–34.55 to 11.33)	0.564
Sex, n (%)			0.088
Female	35 (33.65)	30 (46.88)	
Male	69 (66.35)	34 (53.12)	
Stone side, n (%)			0.880
Right	50 (48.08)	30 (46.88)	
Left	54 (51.92)	34 (53.12)	
Complications, n (%)			0.057
No	69 (66.35)	33 (51.56)	
Yes	35 (33.65)	31 (48.44)	
Operative approach, n (%)			0.001
PCNL	43 (41.35)	43 (67.19)	
ECIRS	61 (58.65)	21 (32.81)	

BMI: body mass index; ECIRS: endoscopic combined intrarenal surgery; PCNL: percutaneous nephrolithotomy; S.T.O.N.E.: stone size, tract length, obstruction, number of involved calyces, and essence

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range [IQR]), as appropriate. For variables presented as median (IQR), the values in parentheses represent the 25th and 75th percentiles.

supporting the robustness of the findings. Specifically, ECIRS was independently associated with a reduced risk of residual stones (odds ratio [OR] 0.40, 95% confidence interval [CI] 0.20–0.80, $P=0.009$), whereas higher S.T.O.N.E. scores (OR 1.50, 95% CI 1.06–2.14, $P=0.023$) and older age (OR 1.04, 95% CI 1.01–1.07, $P=0.017$) were independently associated with higher odds of residual stones.

DISCUSSION

PCNL has long been regarded as the traditional gold standard for the treatment of complex renal stones and is widely applied in clinical practice. The most commonly used position is the prone position.¹⁰ The prone position offers advantages for percutaneous puncture by providing a larger puncture area and

reducing the risk of visceral injury.¹¹ However, this position poses difficulties for retrograde ureteroscopic procedures. To overcome this limitation, the prone hip-flexed split-leg position was developed, aiming to optimise both PCNL and retrograde intrarenal surgery. This modified position not only facilitates percutaneous access and tract establishment by expanding the working space but also reduces the risk of complications during retrograde procedures. The hip-flexed design maintains the balance of the Trendelenburg position, aids instrument navigation, and minimises patient repositioning. Meanwhile, the split-leg modification improves the ureteroscopic access route and reduces interference.¹² This design enhances mobility during retrograde procedures, facilitates ureteroscopic navigation, minimises

Table 4. Univariate and multivariable analyses of factors associated with residual stones.

Variables	Univariate analysis OR (95% CI)	P	Multivariable analysis OR (95% CI)	P
ECIRS vs PCNL	0.34 (0.18–0.66)	0.001	0.40 (0.20–0.80)	0.009
Age, per year	1.03 (1.01–1.06)	0.044	1.04 (1.01–1.07)	0.017
BMI, per kg/m ²	1.09 (1.01–1.18)	0.032	1.09 (1.00–1.19)	0.055
S.T.O.N.E. score, per point	1.46 (1.06–2.02)	0.021	1.50 (1.06–2.14)	0.023
Operative time, per 10-min increase	1.11 (1.01–1.23)	0.047	1.11 (0.99–1.24)	0.074

BMI: body mass index; CI: confidence interval ECIRS: endoscopic combined intrarenal surgery; OR: odds ratio; PCNL: percutaneous nephrolithotomy; S.T.O.N.E.: stone size, tract length, obstruction, number of involved calyces, and essence

interference from the patient's legs, and optimises the operating field, thereby reducing complications during stone extraction.¹³ In addition, the antegrade surgeon can operate in a sitting position with both hands outside the fluoroscopic field, which represents another advantage.¹⁴

The present study demonstrated a significantly higher initial stone-free rate in the ECIRS group than in the PCNL group (74.39% vs 50.00%, $P=0.001$), which was generally consistent with previous ECIRS series.¹⁵ Among Asian populations, the prevalence of complex renal calculi has continued to increase in association with dietary changes and metabolic syndrome.¹ In this context, single-position ECIRS in the prone hip-flexed split-leg position may represent a feasible technical option for selected patients. In the present cohort, this approach was associated with earlier stone clearance, reduced need for auxiliary procedures, shorter double-J stent indwelling duration, and shorter hospital stay. For Asian centres with established endourological infrastructure, the single-position approach may help streamline perioperative surgical workflow. However, broader implementation in resource-constrained settings would require adaptation according to local equipment availability, as well as dedicated cost-effectiveness evaluation.

Multivariable analysis further identified ECIRS as an independent factor associated with a reduced risk of residual stones (OR 0.40). In additional clinically informed sensitivity analysis adjusting for prespecified clinically relevant covariates, the association between ECIRS and residual stones remained generally stable, further supporting the robustness of the primary findings. This may be related to the dual-access capability of ECIRS, which facilitates the clearance of fragments that might otherwise be inaccessible to a rigid nephroscope. Older age also emerged as an independent predictor of residual stones after the initial procedure (OR 1.04), corresponding to an approximately 4% increase in odds per year. Although the per-year effect size was modest, its cumulative impact across broader age ranges may still be clinically meaningful. This finding is consistent with previous studies reporting similar ORs¹⁶ and highlights the need for further research to clarify the role of age in pre-

dicting stone-free outcomes. Hamamoto et al.¹⁷ reported that stone size, stone surface area, complete staghorn stones, and the number of stone branches are risk factors for residual stones in ECIRS. This is consistent with this study's finding that a higher S.T.O.N.E. score was independently associated with residual stones, underscoring the importance of preoperative stone complexity assessment when evaluating surgical effectiveness.

Although this positioning strategy is technically more complex, this study showed that the postoperative complication rate was not significantly different between the ECIRS and PCNL groups, and no position-related complications (e.g nerve injury, pressure ulcers) occurred. This observation is in line with previous reports suggesting that avoiding intraoperative repositioning may help reduce cardiovascular stress and anaesthesia-related burden, particularly in elderly or frail patients.¹⁸ During the postoperative recovery phase, ECIRS was associated with lower postoperative serum creatinine levels and greater reductions in creatinine. Serum creatinine is influenced by multiple perioperative factors, including hydration status, perioperative medication use, and antibiotic administration, rather than surgical technique alone. In addition, although no significant difference was observed in the final SFR at 3 months after completion of all treatments between the 2 groups (95.12% vs 93.02%, $P=0.804$), ECIRS was associated with more favourable perioperative recovery-related metrics. The shorter indwelling duration of double-J stents in the ECIRS group likely reflected earlier stone clearance and reduced the need for auxiliary procedures or staged treatment.¹⁹ Collectively, these findings were associated with a shorter hospital stay in the ECIRS group, suggesting a potential advantage in perioperative recovery.

Nevertheless, the present study has several limitations. First, as a non-randomised retrospective study, the selection of surgical protocols for ECIRS and PCNL was determined by the surgeons' technical preferences and individualised assessment of stone characteristics, which inevitably introduced selection bias. Even though no significant differences were observed in baseline data between the 2 groups, unanalysed

potential confounding factors such as the anatomical structure of the calyceal neck and the degree of renal pelvic rotation might have exerted a hidden impact on surgical decision-making and final outcomes. Second, time data related to position conversion were not systematically recorded in this study, making it impossible to quantify the potential effect of positional manipulation on the total anaesthesia duration. This limited the comprehensive comparison and evaluation of the overall perioperative efficiency of the 2 surgical procedures. Third, although multivariable analysis was performed, complete correction for all potential confounding factors could still not be achieved. In particular, tract size distribution was not systematically recorded in the original retrospective database, and its potential confounding effect on perioperative outcomes could not be completely excluded. In addition, surgeon-related factors and potential learning-curve effects were not specifically analysed in the present study. Although all procedures were performed by experienced urologists using standardised perioperative protocols, potential temporal bias related to increasing ECIRS experience, case allocation patterns, and evolving intraoperative equipment availability could not be completely excluded, which may have influenced the observed perioperative outcomes. Furthermore, given the retrospective nature and limited sample size of the present study, the cohort was considered more suitable for inference regarding major perioperative outcomes such as initial SFR and length of hospital stay, whereas findings related to secondary or exploratory outcomes, including creatinine change, complication subtypes, and BMI-associated residual stone risk, should be interpreted with caution. Therefore, the conclusions of this study should be interpreted cautiously in combination with clinical practice. Currently, stricter cut-off values are widely applied to evaluate residual stones. Because fragments smaller than 4 mm were not uniformly documented under the original study design, sensitivity analyses adopting stricter cut-off criteria could not be performed. Future research should conduct large-sample prospective randomised controlled trials to further verify the clinical efficacy and safety of ECIRS in the prone hip-flexed split-leg position by standardising the collection of position-related time parameters and optimising the strategy for confounding factor control.

CONCLUSION

ECIRS in the prone hip-flexed split-leg configuration was feasible for the management of complex renal calculi. In the present cohort, ECIRS was associated with earlier stone clearance, reduced need for auxiliary procedures, shorter double-J stent indwelling duration, and shorter hospital stay, whereas no significant difference was observed in the final stone-free rate after completion of all planned treatments. Whether

the prone hip-flexed split-leg position provides additional benefit beyond other established ECIRS positioning techniques requires further prospective evaluation.

Supplementary materials

Supplementary Table S1. Distribution of patients according to the predefined criteria for complex renal calculi.

Supplementary Table S2. Sensitivity analysis using prespecified clinically relevant covariates.

Supplementary Table S3. STROBE checklist for the reporting of retrospective cohort study.

Ethics statement

This study was approved by the Medical Ethics Review Committee of Jinhua Municipal Central Hospital (Approval No.: [Research] 2026-Ethics Review-195) and conducted in accordance with the Declaration of Helsinki to protect participants' rights and interests.

Declaration

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Availability of data and materials

The data and materials in the current study are available from the corresponding author on reasonable request.

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Coblation intracapsular tonsillectomy outcomes in paediatric obstructive sleep disordered breathing: A Singapore study

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ABSTRACT

Introduction: Coblation intracapsular tonsillectomy (ICT) may offer a more favourable post-operative morbidity profile compared with extracapsular tonsillectomy for paediatric obstructive sleep-disordered breathing (oSDB). Data from the Singapore paediatric population remain limited. This study examines the outcomes of coblation ICT in children with oSDB at a tertiary centre in Singapore.

Methods: This was a single-centre prospective cohort study of 102 consecutive children aged 21 months to 15 years undergoing coblation ICT for oSDB (April–October 2023). Concurrent adenoidectomy was performed in 98.0% of patients. Primary outcomes included complications and disease-specific quality of life (QoL) via the Obstructive Sleep Apnea-18 Quality of Life (OSA-18) questionnaire (where higher scores indicate greater symptom burden and poorer quality of life), assessed pre-operatively and at 3 months. Secondary outcomes included pain, analgesia, diet, and snoring resolution.

Results: No post-operative haemorrhage or major complications occurred. All 102 patients completed a 3-month review. The median OSA-18 score improved significantly from 74 (interquartile range [IQR] 54–89) to 29.5 (IQR 23–40) post-operatively ($P < 0.001$), representing a shift from the moderate to the minimal impact band. The mean change of 39.3 points exceeded twice the published minimal clinically important difference (standardised response mean 2.17). Perceived QoL score improved from median 5 (IQR 4–6.6) to 8 (IQR 8–9) ($P < 0.001$). At 3 months, 82.4% had no snoring. Post-operative pain was mild, with 75.5% requiring analgesia for 3 days or fewer.

Conclusion: In this uncontrolled single-arm cohort, coblation ICT with concurrent adenoidectomy was associated with low morbidity and clinically meaningful improvements in caregiver-reported outcomes. These hypothesis-generating findings warrant further investigation through multicentre comparative studies with longer follow-up.

Keywords: coblation, intracapsular tonsillectomy, otorhinolaryngology, paediatrics, quality of life, sleep apnoea

CLINICAL IMPACT

What is New

- To the authors' knowledge, this is the first Singapore data on coblation intracapsular tonsillectomy outcomes for paediatric obstructive sleep-disordered breathing in Singapore, benchmarked against international cohorts.
- Clinically meaningful OSA-18 quality-of-life improvement, with effect size well above published minimal clinically important difference, supporting larger, longer-term Singapore validation studies.

Clinical Implications

- Low morbidity in real-world use (zero haemorrhage, mild pain, rapid diet recovery), pending long-term validation.
- Reflects real surgical practice (98% concurrent adenoidectomy), useful for setting expectations pending comparative trials.
- Findings may guide patient selection: children with greater baseline symptom burden showed the largest gains, useful for counselling families.

INTRODUCTION

Obstructive sleep-disordered breathing (oSDB) in children, ranging from snoring to severe obstructive sleep apnoea (OSA), is associated with significant neurocognitive, behavioural, and cardiovascular sequelae.¹ While tonsillectomy remains the standard surgical intervention, it is sometimes complicated by significant post-operative pain, bleeding, and delayed recovery, particularly in paediatric populations.^{2,3} Coblation intracapsular tonsillectomy (ICT), which involves removal of tonsillar tissue while preserving the capsule, has emerged as a promising alternative that may reduce post-operative morbidity while

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maintaining clinical efficacy. The intracapsular approach is particularly suited to children with obstructive symptoms, as the preserved tonsillar capsule acts as a natural barrier to reduce pain and bleeding; in contrast, extracapsular tonsillectomy is generally preferred for recurrent tonsillitis, where complete removal of tonsillar tissue is required to reduce infection recurrence.³ However, data on its safety and effectiveness in the Singapore paediatric population remain limited.

To the authors' knowledge, this represents the first prospective study in Singapore examining the outcomes of coblation ICT for patients with oSDB at a paediatric otolaryngology practice, with a particular focus on post-operative outcomes, symptom resolution, and quality of life (QoL).

METHODS

Study design

This was a single-centre, prospective cohort study conducted at KK Women's and Children's Hospital in Singapore, from April 2023 to October 2023. All eligible patients underwent coblation ICT performed by a single, experienced surgeon, which reflects the current practice model at the institution where this technique was introduced and standardised during the study period. All eligible patients presenting during the study period were enrolled consecutively. No additional selection criteria were applied beyond the eligibility criteria stated below.

Inclusion and exclusion criteria

Children aged between 21 months and 15 years with oSDB and tonsillar hypertrophy undergoing coblation ICT were included in this study.

Exclusion criteria included children with a history of recurrent tonsillitis (to isolate oSDB as the primary indication for surgery), bleeding disorders (due to increased perioperative risk), previous tonsil surgery (to avoid confounding due to altered anatomy), or suspected malignancy (where complete tissue excision is needed for definitive histopathological assessment).

Surgical technique

All eligible patients with oSDB underwent coblation ICT performed by a single surgeon, under general anaesthesia. Adenoidectomy was concurrently performed in cases where adenoid hypertrophy was clinically relevant. Surgery was performed using the EVAC 70 XTRA coblator wand (Smith & Nephew, London, UK).

Outcome measures

Outcome measures were assessed before patients' discharge and at outpatient follow-ups 1 week and 3 months after surgery.

Primary outcomes of interest included: (1) perioperative and postsurgical complications (including haemorrhage and other adverse events requiring intervention), and (2) disease-specific QoL, assessed via the Obstructive Sleep Apnea-18 Quality of Life (OSA-18) questionnaire⁴ pre-operatively and at the 3-month post-operative visit. The OSA-18 is an 18-item disease-specific QoL instrument with a total score ranging from 18 to 126, where higher scores indicate greater symptom burden and poorer QoL.

Secondary outcomes included post-operative pain control (measured by the Wong-Baker FACES Scale⁵ [WBS]), time to resume diet (both soft and normal), snoring resolution (reported by caregivers), hospital readmissions, and any incidents of tonsil regrowth.

Statistical analysis was conducted using the Wilcoxon signed-rank test to compare pre- and post-operative OSA-18 and QoL scores, with significance set at $P < 0.05$. Change in OSA-18 score was calculated as the paired pre- to post-operative difference for each patient, and effect size was expressed as standard response mean (SRM), calculated as the mean change divided by standard deviation. All analyses were conducted using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp, Armonk, NY).

RESULTS

Demographics

A total of 102 children with oSDB secondary to adenotonsillar hypertrophy were enrolled in the study. The mean age was 6.0 ± 2.5 years (71.3 ± 31.7 months), with a median of 5.5 years (range: 21 months to 15.0 years). The majority were male (64.7%, $n=66$), with 35.3% female ($n=36$). The cohort was ethnically diverse, comprising 45.1% Chinese ($n=46$), 20.6% Malay ($n=21$), 15.7% Indian ($n=16$), 2.9% Caucasian ($n=3$), and 15.7% from other ethnic backgrounds ($n=16$) (Table 1).

Surgical indications and concurrent procedures

The primary indication for surgery was snoring without a formal diagnosis of OSA, accounting for 86.3% ($n=88$) of cases. Formal OSA, confirmed by polysomnography, was present in a minority: 3.9% ($n=4$) had mild OSA, 2.9% ($n=3$) had moderate OSA, and 6.9% ($n=7$) had severe OSA. All children meeting the American Academy of Otolaryngology–Head and

Table 1. Demographics and duration of hospital stay.

	n	%
Age (years)		
Mean	6.0	
Median	5.5	
Standard deviation	2.5	
Minimum	1.7 (21 months)	
Maximum	15.0	
Sex		
Male	66	64.7
Female	36	35.3
Ethnicity		
Chinese	46	45.1
Malay	21	20.6
Indian	16	15.7
Caucasian	3	2.9
Others	16	15.7
Indications for ICT		
Snoring	88	86.3
Mild OSA	4	3.9
Moderate OSA	3	2.9
Severe OSA	7	6.9
Adenoid size (Grade)		
1	3	2.9
2	32	31.4
3	45	44.1
4	22	21.6
Tonsil size (Brodsky scale grades)		
1	1	1.0
2	35	34.3
3	49	48.0
4	17	16.7
Days of hospitalisation		
0 (day surgery)	8	7.8
1	84	82.4
2	10	9.8
Total	102	100

ICT: intracapsular tonsillectomy; OSA: obstructive sleep apnoea

Days of hospitalisation: Day 0 = day-surgery discharge;

Day 1 = post-operative day 1 discharge;

Day 2 = post-operative day 2 discharge

Neck Surgery's high-risk criteria underwent pre-operative polysomnography. In the remaining snoring-only cases, the decision to operate was based on the clinical assessment of significant adenotonsillar hypertrophy and caregiver-reported symptoms, without routine pre-operative polysomnography, consistent with guideline-concordant practice for uncomplicated presentations (Table 1).

Concurrent procedures were performed in 36.3% (n=37) of patients. The most common was myringotomy with ventilation tube insertion (50.0%), followed by inferior turbinate (IT) diathermy alone (31.6%). Additional procedures included Little's area diathermy for epistaxis (5.3%, n=2), and isolated cases of microlaryngobronchoscopy, diagnostic laryngoscopy, tongue-tie release, and drug-induced sleep endoscopy (2.6% each, n=1).

Concurrent adenoidectomy was performed in the majority of cases (98.0%, n=100), reflecting real-world clinical practice. The outcomes reported represent combined surgical effect, consistent with how coblation ICT is delivered in a specialist paediatric otolaryngology setting. The 2 patients who did not receive adenoidectomy represent too small a subgroup for meaningful stratified analysis.

Tonsil and adenoid grading

Adenoid and tonsil hypertrophy were assessed clinically and intraoperatively. The majority of patients had moderate to severe adenoid enlargement, with Grade 3 (44.1%, n=45) being the most common, followed by Grade 2 (31.4%, n=32), Grade 4 (21.6%, n=22), and Grade 1 (2.9%, n=3).

Tonsil size was graded separately for each side using the Brodsky scale (Grades 1–4). The mean tonsil grade was Grade 3 bilaterally, and the most frequent grade per side⁶ was Grade 3 (48.0%, n=49), followed by Grade 2 (34.3%, n=35), Grade 4 (16.7%, n=17), and Grade 1 (1.0%, n=1). These findings reflect a study population predominantly exhibiting moderate to severe adenotonsillar hypertrophy—consistent with the surgical indication for coblation ICT in paediatric oSDB (Table 1).

Duration of hospital stay

The majority of patients (82.4%, n=84) were discharged after 1 day, with 7.8% (n=8) of patients discharged as day cases, and 9.8% (n=10) requiring 2-day stays. All patients who stayed for 2 days were elective admissions without complications (Table 1).

Postsurgical complications and quality of life (primary outcomes)

No episodes of post-operative haemorrhage requiring surgical intervention were reported. At 3 months, there were no readmissions for morbidity, recurrent tonsillitis, or further significant complications. Two

cases of small tonsil fossa clots were observed, which both resolved with conservative management without the need for surgical intervention. One case of focal tonsil regrowth in the left superior pole was noted, but this did not lead to any clinical symptoms or require intervention (Table 2).

Post-operative recovery and pain management (secondary outcomes)

Post-operative pain assessment was completed in 94.1% (n=96) of patients. Pain scoring was limited in 6 patients due to age-related or developmental challenges—3 were aged 24 months or younger, 1 had autism spectrum disorder, and 2 had Down syndrome. Pain was evaluated using the WBS, and was generally mild. On post-operative days 0–1 (POD 0–1), 43.8% (n=42) of patients reported no pain (WBS 0), while 35.4% (n=34) reported minimal pain (WBS 2). Only 2.1% (n=2) experienced severe pain (WBS 8 or 10). The median pain score on POD 0–1 was 2 (IQR 0–2), indicating generally mild pain. By the first outpatient review on POD 7, 85.4% (n=82) of patients reported no pain (Table 3).

Analgesia use was brief in most cases, with 75.5% (n=77 of 102) requiring pain relief for 3 days or fewer. Dietary recovery was similarly rapid: by POD 0–1, 94.1% (n=96 of 102) of patients were able to tolerate at least half portions of a soft diet. By POD 7, 84.3% (n=86 of 102) had resumed a normal diet, while the remaining 15.7% (n=16 of 102) transitioned to a normal diet between POD 7 and 14 (Table 3).

Snoring resolution (secondary outcome)

Snoring showed significant improvement by POD 7, with 66.7% (n=68) of patients reporting no snoring and 16.7% (n=17) experiencing a reduction in snoring intensity. The remaining 16.7% (n=17) were still experiencing snoring at a level comparable to pre-operative levels at POD 7 (Table 3).

All 102 enrolled patients completed the 3-month review with complete outcome data. At 3 months, 82.4% (n=84) of patients were no longer observed to be snoring. Of the remaining 18 patients, 11.8% (n=12) had minimal residual snoring occurring predominantly during respiratory tract infections, and 5.9% (n=6) had stable snoring comparable to pre-operative levels (Table 3).

Importantly, oSDB in children is often multifactorial in aetiology. Contributing factors beyond adenotonsillar hypertrophy include obesity, significant allergic rhinitis with associated nasal obstruction, and craniofacial anomalies. These comorbidities may independently affect symptom severity and surgical outcomes and should be considered when interpreting results. In this study's cohort, patients with concurrent IT hypertrophy—suggestive of allergic rhinitis based on clinical history and nasal endoscopic findings—were identified and managed with concomitant IT diathermy where clinically indicated. Patients with significant obesity or syndromic conditions were not specifically excluded but represented a minority of cases; these are acknowledged as potential confounders of post-operative outcomes.

A significant improvement was observed in both the OSA-18 and QoL scores. The median pre-operative OSA-18 score was 74 out of 126 (interquartile range [IQR] 54–89), which decreased significantly to 29.5 (IQR 23–40) post-operatively ($P<0.001$). Similarly, the perceived QoL score—a single global item rated on a scale of 0 to 10, where 0 represents the worst and 10 the best perceived QoL—demonstrated a statistically significant improvement, with the median pre-operative score of 5 (IQR 4–6.6) increasing to 8 (IQR 8–9) postsurgery ($P<0.001$). This represented a shift from the moderate OSA-18 impact band (score 60–80) pre-operatively to the minimal impact band (score <60) post-operatively.⁴ The mean change of 39.3 points (standard deviation 18.1) substantially exceeded the

Table 2. Postsurgical complications (primary outcome)—POD 0 to 3 months.

Complication	n	%
Post-operative haemorrhage requiring intervention	0	0.0
Observed tonsil fossa clots (monitored, conservative management) ^a	2	2.0
Morbidity-related readmissions	0	0.0
Recurrent tonsillitis	0	0.0
Recurrence of snoring ^b	0	0.0
Tonsil regrowth	1	1.0

POD: post-operative day

^a Tonsil fossa clots resolved with conservative management; no surgical intervention required.

^b Recurrence of snoring refers to snoring that resolved, then recurred (distinct from residual/persistent snoring, defined as snoring that never fully resolved after surgery).

Table 3. Post-operative recovery outcomes (secondary outcomes).

	n	%
Pain (POD 0/1) — WBS		
WBS 0 (no pain)	42	43.8
WBS 2 (minimal)	34	35.4
WBS 4	11	11.5
WBS 6	7	7.3
WBS 8	1	1.0
WBS 10 (severe)	1	1.0
Total assessed	96	100
Pain (POD 7) — Wong-Baker FACES Scale^a		
WBS 0 (no pain)	82	85.4
WBS 2 (minimal)	12	12.5
WBS 4	2	2.1
WBS 6	0	0.0
WBS 8	0	0.0
WBS 10 (severe)	0	0.0
Total assessed	96	100
Analgesia requirement		
≤3 days	77	75.5
>3 days	25	24.5
Total assessed	102	100.0
Diet		
Tolerated at least ½ portion soft diet (POD 0–1): Yes	96	94.1
Tolerated at least ½ portion soft diet (POD 0–1): No	6	5.9
Total assessed	102	100.0
Return to normal diet (POD 7): Yes	86	84.3
Return to normal diet (POD 7): No	16	15.7
Total assessed	102	100.0
Snoring (POD 7)		
No snoring	68	66.7
Yes (improved, minimal)	17	16.7
Yes (stable, comparable to pre-op)	17	16.7
Total assessed	102	100.0
Snoring (3 months)		
No snoring	84	82.4
Yes (improved, minimal)	12	11.8
Yes (stable, comparable to pre-op)	6	5.9
Total assessed	102	100.0

POD: post-operative day; WBS: Wong-Baker FACES Scale (0 = no pain, 10 = worst pain)

^a Pain scoring was completed in 96 of 102 patients; 6 patients were unable to complete scoring due to age or developmental factors.

published minimal clinically important difference (MCID) of 15–18 points for the OSA-18,⁴ and the standardised response mean (SRM) of 2.17 indicates a very large effect size by conventional thresholds (Table 4).

DISCUSSION

In this uncontrolled single-arm cohort, ICT—performed with concurrent adenoidectomy in 98.0% of patients and additional nasal or middle-ear procedures in 36.3%—was associated with low post-operative morbidity and significant caregiver-reported improvements in symptom burden and QoL. Most participants experienced low to minimal pain, an early return to normal diet, and significant post-operative improvements in both OSA-18 symptom scores and overall QoL. The magnitude of OSA-18 improvement is clinically meaningful, not merely statistically significant: the cohort moved from the moderate to the minimal impact severity band, the mean change of 39.3 points exceeded twice the published MCID threshold, and the SRM of 2.17 reflects a very large effect size—indicating substantial caregiver-perceived improvement in disease-specific QoL.

These findings are consistent with those reported by Amin et al., whose large cohort study of 1257 paediatric patients found significant improvements in health-related QoL across all domains, with a median analgesia requirement of 6 days, no returns to theatre for post-operative haemorrhage, rapid recovery, and a low revision rate of 2.6%—primarily due to tonsillar regrowth. Patients in that study had a median direct follow-up of 101.5 days, with longer-term outcomes estimated over a median of 1419 days based on patient age at entry and anticipated follow-up duration (as reported by Amin et al.).⁷ A recent single-arm pooled-proportion meta-analysis by Lin et al. (14 studies, 9821 patients) reported a post-tonsillectomy haemorrhage rate of 1.0% (95% confidence interval [CI] 0.5–1.6) and a rate of further tonsil surgery of 1.4% (95% CI 0.6–2.2) following coblation ICT, providing a useful benchmark against which the zero haemorrhage rate may be contextualised.⁸ This study was not designed as a head-to-head comparison with extracapsular techniques and does not establish superiority of the intracapsular approach.

The choice of intracapsular versus extracapsular tonsillectomy depends on the primary indication for surgery. The intracapsular approach is particularly well-suited to children with oSDB, as preservation of the tonsillar capsule reduces exposure of the pharyngeal musculature, thereby limiting post-operative pain and bleeding risk. In contrast, extracapsular tonsillectomy remains the preferred approach for recurrent tonsillitis, where complete removal of tonsillar tissue is necessary to prevent recurrent infection.³

Importantly, no major post-operative complications, including secondary haemorrhage, were observed in this study's cohort. Tonsillar capsule preservation and reduced thermal damage have been proposed in the literature as mechanisms underlying the favourable morbidity profile observed with this technique, potentially contributing to faster recovery and reduced analgesic requirements.^{7–11} The authors acknowledge, however, that this study's cohort comprised cases performed by a single, experienced surgeon, which may have contributed to the low complication rate. This potential selection bias should be considered when interpreting these results, and multicentre data including surgeons at varying stages of the learning curve would be necessary to fully characterise the safety profile of this technique.

Children with greater pre-operative symptom burden—reflected in higher OSA-18 scores and lower baseline QoL—experienced the most substantial gains following surgery. These results are consistent with the existing literature suggesting that children with more pronounced oSDB symptoms derive the greatest functional and QoL gains from surgical intervention,^{3,4} and support the internal consistency and construct validity of the OSA-18 as a disease-specific outcome measure.⁵

A subset of patients demonstrated persistently elevated post-operative OSA-18 scores and suboptimal QoL outcomes. Post-operative OSA-18 scores were negatively correlated with both post-operative QoL and degree of QoL improvement, suggesting that residual symptoms after surgery continue to meaningfully affect caregiver-perceived well-being. These patients were more likely to harbour concomi-

Table 4. Pre- and post-operative OSA-18 and QoL scores.

	Pre-operative median (IQR)	Post-operative median (IQR)	P value
OSA-18 total score	74 (54–89)	29.5 (23–40)	<0.001
Perceived QoL score	5 (4–6.6)	8 (8–9)	<0.001

IQR: interquartile range; OSA-18: Obstructive Sleep Apnea-18 Quality of Life questionnaire; QoL: quality of life
Wilcoxon signed-rank test was performed using SPSS version 29.0; $P < 0.05$.

tant risk factors for oSDB beyond tonsillar hypertrophy, including obesity and significant allergic rhinitis, the latter reflected by the need for IT diathermy. It is also relevant that the majority of patients in this cohort underwent surgery on the basis of caregiver-reported snoring and clinical examination findings without pre-operative polysomnography, and may therefore include children in whom the true severity of oSDB was not formally quantified pre-operatively. This is a recognised limitation of clinically driven surgical decision-making in this population, and may contribute to the residual symptom burden observed in a subset of patients. Identifying such patients pre-operatively is therefore clinically important, as they may benefit from additional or alternative interventions alongside or instead of surgery, including weight management, intranasal corticosteroid therapy, or further sleep investigations. These findings underscore the importance of pre-operative counselling regarding realistic surgical expectations in children with complex or multifactorial oSDB, and may help refine patient selection for coblation ICT. Formal identification of independent predictors of residual symptoms was beyond the scope of this study. Future larger multi-centre studies should prospectively investigate predictors of surgical outcome following coblation ICT.

The improvement in snoring observed at both POD 7 and 3 months is encouraging, though the durability of this benefit beyond 3 months—and in particular the rates of tonsillar regrowth and revision surgery—cannot be determined from the present study. Given that snoring is often the most distressing symptom for caregivers, its improvement significantly affects perceived surgical success and family well-being.

Despite this subset of patients with residual symptoms, the overall results support the broader utility of coblation ICT in paediatric oSDB. The short length of stay and rapid return to normal diet observed in this cohort may have favourable cost implications, though no formal economic analysis was performed in this study. This warrants evaluation in future research.

Limitations

Despite the strengths of this study's prospective design and comprehensive outcome assessment, several limitations merit consideration. First, as this was a single-centre study conducted by a single, experienced surgeon at a tertiary paediatric hospital, the generalisability of the findings may be limited. The low complication rate may partly reflect the surgeon's experience and the centre's established perioperative protocols, rather than being solely attributable to the technique itself. Broader adoption of coblation ICT across surgeons with varying experience levels and across different institutions would be needed to confirm the generalisability of these

safety outcomes. Future multicentre studies, ideally including a comparison arm of standard extracapsular tonsillectomy, would provide more robust evidence.

Second, the follow-up period was limited to 3 months postsurgery. All 102 enrolled patients completed the 3-month review. While this timeframe captures early post-operative recovery and short-term symptom resolution, it is insufficient to assess the outcomes on which the intracapsular technique is most contested—specifically tonsillar regrowth and revision surgery. The principal long-term concern specific to intracapsular techniques is regrowth of preserved tonsillar tissue with recurrent obstruction requiring revision. Amin et al. reported a revision rate of 2.6% accruing over a median estimated follow-up of 1419 days, with younger age, severe OSA, and severe comorbidity identified as independent risk factors.⁷ The present study's cohort includes children with precisely these risk profiles—including a child aged 21 months, 7 with severe OSA, and children with Down syndrome—yet the 3-month follow-up window is too short for meaningful regrowth or revision data to have accrued. The single case of asymptomatic focal regrowth identified at 3 months and the absence of revision surgery in this cohort should therefore not be interpreted as evidence of long-term durability; these outcomes cannot yet be assessed. The authors are committed to the extended follow-up of this cohort and recommend that future studies prospectively report regrowth and revision rates over a minimum of 1 year.

Third, this is a single-arm observational study and lacks a concurrent comparison group receiving standard extracapsular tonsillectomy. The absence of a control arm limits the ability to directly attribute observed outcomes to the intracapsular technique rather than to the natural history of oSDB or non-specific effects of surgery. The authors acknowledge that concurrent adenoidectomy was performed in 98.0% of patients and other additional procedures in 36.3%. However, the authors believe that this reflects real-world practice where coblation ICT is seldom performed in isolation. The outcomes reported therefore represent the combined effect of the surgical package, which is consistent with how this procedure is delivered clinically. While the independent contribution of the ICT component cannot be isolated from this design, this pragmatic approach strengthens the external validity and clinical applicability of the findings.

This study also relied on caregiver-reported measures for key outcomes—such as snoring frequency and QoL—which introduce the potential for subjective bias. While objective assessments such as post-operative polysomnography would provide a more robust evaluation of surgical efficacy, routine pre- or post-

operative polysomnography is not standard practice for children with uncomplicated oSDB. The reliance on caregiver reports therefore reflects current clinical practice and aligns with real-world management, though it remains a limitation in terms of objective outcome measurement.

As noted above, comorbidities such as obesity and allergic rhinitis—which were not formally characterised in all patients—may have independently influenced symptom severity and post-operative outcomes. Future studies should incorporate systematic documentation of these comorbidities to better isolate the effect of surgical intervention.

Finally, pain assessment using WBS proved challenging in some younger children and those with developmental delays, which may have affected the accuracy of reported pain scores. These limitations should be addressed in future multicentre studies with extended follow-up and incorporation of objective outcome measures.

CONCLUSION

In this uncontrolled single-arm cohort, coblation ICT was associated with low post-operative morbidity and significant improvement in caregiver-reported symptom and QoL scores. Further investigation through multicentre, comparative studies with longer follow-up periods is warranted to validate the long-term efficacy of coblation ICT and to establish its role relative to traditional extracapsular tonsillectomy.

Supplementary material

Fig. S1. Participant flow diagram.

Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (2023/2287). Written informed consent was obtained from the legal guardian of each participant prior to enrolment. This study did not receive external funding and was conducted

independently of the device manufacturer (Smith & Nephew, London, UK); the manufacturer had no role in study design, data collection, analysis, or reporting.

Declaration

The authors declare that they have no other 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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Traditional Chinese Medicine in Singapore: Integrating education, practice, and research in a modern healthcare system

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ABSTRACT

Traditional Chinese Medicine (TCM) is gaining prominence within Singapore's predominantly Western medicine (WM) system, reflecting a broader shift towards integrative care. This commentary argues that education is the primary engine of TCM integration, with reforms in professional recognition, competency-based assessments, bilingual curricula, and structured clinical training aligning TCM with contemporary standards and enabling collaboration with WM. These educational advances have catalysed changes in clinical practice, most notably the incorporation of acupuncture into public healthcare institutions, and strengthened research through targeted funding, formal ethics oversight, and TCM–WM partnership.

Despite progress, persistent barriers remain. Limited interprofessional education and communication impede collaborative care and fuel uncertainty about concurrent TCM–WM use. Financial constraints, including restricted subsidies, shape access and care-seeking for TCM. Safety concerns about Chinese proprietary medicines, including risks of adulteration, affect public and professional trust. Foundational differences in diagnostic frameworks and research methodologies complicate evaluation and standardisation, while patient non-disclosure of TCM use fragments care.

Singapore's experience illustrates that safe, evidence-informed TCM integration depends on sustained investment in interprofessional education, equitable financing, robust safety surveillance, and high-quality translational research. Advancing these priorities can support holistic, person-centred care across both systems.

Keywords: education, integrative medicine, interprofessional, patient-centred care, traditional medicine

INTRODUCTION

Complementary medicine refers to a non-mainstream therapeutic approach used alongside Western medi-

cine (WM) to improve outcomes, with acupuncture alone and the full range of Traditional Chinese Medicine (TCM) therapies being the most widely accepted.¹ Reflecting global momentum, the World Health Organization (WHO) Global Traditional Medicine Strategy 2025–2034 sets out principles,² and the WHO publishes benchmarks for TCM and acupuncture on terminology,³ training,⁴ and clinical practice.⁵ Singapore, shaped by Asian and Western traditions, offers a salient case of TCM's adoption within a predominantly WM system. This commentary reviews Singapore's TCM landscape across education, practice, and research, highlighting advances and persistent challenges.

TCM, introduced during the colonial era, is now used by 20% of adults in Singapore, with nearly 40% reporting concurrent use with WM for the same condition (Singapore's National Population Health Survey 2022).¹ This prevalence is comparable to estimates from China (19%),² Taiwan (27%),³ and South Korea (26%).³ Regional approaches to TCM integration vary: South Korea's National Health Insurance covers the full range of traditional medicine treatments,⁴ while Hong Kong SAR has developed a dedicated Chinese Medicine Hospital, provided government-subsidised TCM, integrated TCM–WM services, and supported education and research.⁵ In contrast, Singapore has taken a selective, evidence-based path, focusing on targeted subsidies and the integration of specific modalities, most notably acupuncture, into public healthcare institutions. In Singapore, the TCM Practitioners Board (TCMPB) regulates the registration of TCM practitioners (TCMPs), registration, accreditation of approved training institutions, continuing professional education, and ethical and professional conduct.¹ According to the latest TCMPB annual report, Singapore has 3242 TCMPs and 260 acupuncturists,⁶ with more than half aged 50–69 years.⁷

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SUCCESSES OF TCM

Education

TCM education has evolved from apprenticeship to recognised academic and professional pathways. Fig. 1 maps key milestones in this development.

Recent reforms aim to meet local needs, raise training standards, and attract younger entrants. Nanyang Technological University (NTU) is transitioning to a 4-year, bilingual Bachelor of Chinese Medicine (BCM), replacing its previous 5-year double-degree programme with Beijing University of Chinese Medicine. The first cohort is expected to graduate in 2028. The curriculum integrates technology-enabled and team-based learning, longitudinal clinical training, and TCM research, with emphasis on ageing and preventive care, aligned with Healthier SG—Singapore's national initiative to shift the healthcare system from treating illnesses to preventive care.⁸ NTU also launched a Master of Science in Chinese Medicine in 2026, expanding annual capacity to about 40 Bachelor's⁹ and 30 Master's graduates¹⁰—up from 30 undergraduates previously.

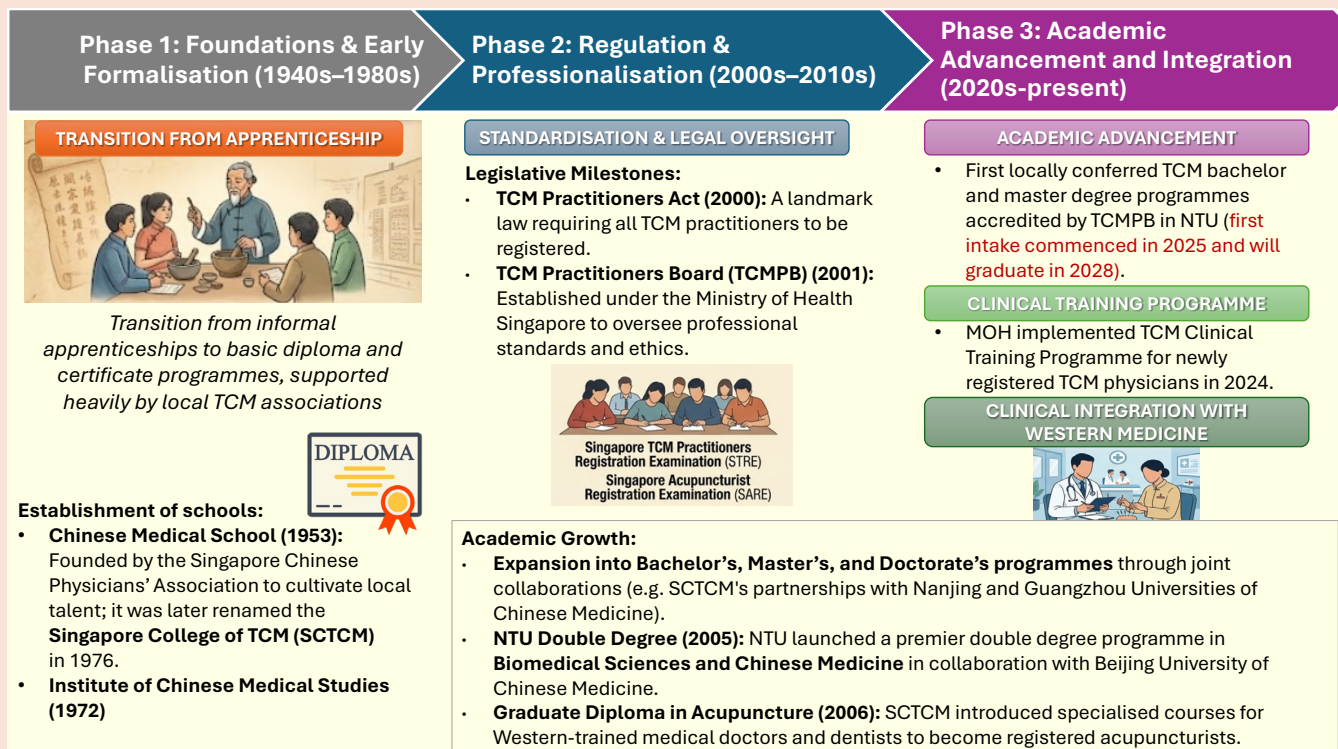
The Singapore TCM Physicians Registration Examination and the Singapore Acupuncturists Registration Examination were revamped in 2025 to emphasise

clinical competency.¹¹ From 2027, both examinations will adopt an Objective Structured Clinical Examination format, aligning TCM assessment with practices familiar to medical, nursing, and allied health training.

In 2024, Singapore's Ministry of Health (MOH) implemented a 1-year TCM clinical training programme that places selected TCMP trainees in 3-month rotations across 4 participating TCM institutions, mirroring housemanship in WM. The programme uses a competency-based framework, Entrustable Professional Activities (EPAs), to progressively entrust trainees with patient care under the supervision of clinical mentors.¹² This structured transition from training to independent practice is intended to raise care standards. MOH also supports TCMPs' professional development and service provision through the TCM Development Grant.¹³

Adoption of bilingual instruction and the EPA framework signals Singapore's commitment to modernising TCM education and aligning it with contemporary standards. Standardised competencies foster an integrated, person-centred workforce. While bilingual instruction may strengthen communication between TCM and WM professionals and prepare graduates for practice and research, reduced emphasis on Mandarin could limit engagement with classical TCM

Fig. 1. Roadmap of TCM education development in Singapore.



MOH: Ministry of Health Singapore; NTU: Nanyang Technological University; SCTCM: Singapore College of TCM; TCM: Traditional Chinese Medicine; TCMPB: TCM Practitioners Board

texts and weaken cultural transmission. Preserving classical literacy and the cultural foundations of TCM should remain a priority within bilingual curricula.

Practice

Singapore's 3 public healthcare clusters—National Healthcare Group Health, National University Health System, and Singapore Health Services (SingHealth)—practise predominantly evidence-based WM. Since 2005, acupuncture, supported by research and broad acceptance, is available in most public health institutions (PHIs). In 2020, the Agency for Care Effectiveness, Singapore's health technology assessment and clinical guidance agency, has recommended subsidies at PHIs for needled acupuncture, with or without electrostimulation, for adults with neck and low back pain.¹⁴ Expanding access reflects growing institutional recognition of acupuncture as an adjunct therapy that delivers clinical value, and signals a more pluralistic model in which treatments are valued for their outcomes rather than their origins.

WM–TCM integration in Singapore is supported by interdisciplinary dialogue. Through events such as the annual Forum on the Use of Evidence-Based TCM in WM Practice, co-organised by SingHealth and the Academy of Chinese Medicine Singapore,¹⁵ practitioners from both fields explore incorporating evidence-based TCM into mainstream care, aiming to build mutual understanding, shape common evidence-based practices, and promote high-value care, collaborative research, and education. This aligns with MOH's sandbox initiative, launched in 2025, which examines how integrative care affects outcomes.¹⁶ Ongoing reviews of the clinical-effectiveness and cost-effectiveness of acupuncture and Chinese proprietary medicines for chronic and non-chronic disease management¹ and further position Singapore's healthcare system to deliver holistic care.

Digital health is reshaping TCM practice. China's experience with TCM internet hospitals,¹⁷ artificial intelligence (AI)-powered language models (e.g. TCMChat, MedChatZH)¹⁸ and disease-specific databases (e.g. TCM2COVID for COVID-19, TCM-ADIP for Alzheimer's disease)¹⁸ illustrates potential gains in access and decision support. In Singapore, teleconsultation, AI-assisted technologies (e.g. TCM Tuina robot), and digital diagnostic tools (e.g. automated pulse analyser, AI-based tongue analysis) are being piloted. These innovations aim to enhance diagnostic accuracy, improve reproducibility, and integrate TCM into modern healthcare through evidence-based data—but they must first secure the Health Sciences Authority's clearance or registration exemption, supported by robust research studies on validation, reliability, and data governance. Rigorous evaluation is essential before routine adoption.

Research

The MOH's TCM Research Grant (TCMRG) funds collaborative studies between TCM organisations and PHIs or academic institutions. For interventional studies, a WM principal investigator is required to ensure rigorous, safe evaluation and credible translation into evidence-based policy and practice.¹⁹ Research is further supported by the Academy of Chinese Medicine, Singapore Institutional Review Board, an independent ethics review committee that applies standards equivalent to those in conventional research, to enhance integrity and public confidence.²⁰

CHALLENGES OF TCM

Education

Opportunities for collaboration between WM and TCM students are limited, creating a barrier to integration. Earlier structured exposure may improve interdisciplinary work. The National University of Singapore's Yong Loo Lin School of Medicine runs a pre-clinical common curriculum for medical, nursing, dentistry, and pharmacy students to cultivate teamwork and interprofessionalism.²¹ Without an equivalent platform linking WM and TCM students, mutual understanding remains limited, risking future silos. From 2027, final-year NTU TCM students will begin clinical rotations at Tan Tock Seng Hospital to observe integrated TCM–WM practice.²² While promising, this initiative currently involves only 1 TCM school, 1 medical school, and 1 hospital. Expanding placements across more PHIs would broaden exposure and better prepare future TCMs.

Limited TCM knowledge among WM practitioners can compromise advice on concurrent TCM use and potential herb–drug interactions.²³ As integration grows, incorporating foundational TCM content into WM undergraduate curricula and continuing professional education and, conversely, introducing WM fundamentals into TCM training would strengthen interdisciplinary understanding and support safer, coordinated care.

Practice

Although acupuncture for neck and low back pain has been subsidised since 2020, MediSave coverage remains limited (capped at SGD200), and patients seeking acupuncture for other indications in PHIs pay private rates. By contrast, MediSave and other government financing schemes (Community Health Assist Scheme, Chronic Disease Management Programme) primarily support WM-based inpatient care and outpatient chronic disease management, respectively, with limited coverage for TCM. Local healthcare providers sometimes attribute adrenal insufficiency or Cushing's syndrome to prior TCM

use because of the perceived steroid-like effects of TCM herbs. Only a limited number of herbs have well-established steroidal activity, and much of the evidence is pre-clinical.²⁴ The addition of medicinal substances such as steroids and heavy metals is also prohibited by the Health Sciences Authority.²⁵ Adulteration of herbal products with exogenous glucocorticoids, falsely marketed as TCM, remains a recurring issue.²⁶

Non-disclosure of TCM use to WM doctors is common and increases the risk of unrecognised potential herb–drug interactions. A local study revealed that 70% of breast cancer patients did not share TCM use with their WM doctors, citing perceived opposition or limited understanding of TCM among WM doctors.²⁷ Such non-disclosure, driven by fear of dismissal or misunderstanding, fragments care. These findings underscore the need for deeper TCM–WM integration to safeguard patient safety and improve outcomes. Equity of access across Singapore's multi-ethnic population also warrants attention. Although TCM is used most by Chinese patients, followed by Malay and Indian patients,²⁸ ethnic differences in TCM access, acceptance, and utilisation remain understudied. Research is needed to identify potential disparities and ensure benefits are equitable.

Research

While the sandbox creates pathways for WM–TCM integration, it also surfaces potential friction. Differences in ontology lead to gaps in understanding. TCM's diagnostic approach centres on syndrome differentiation and patterns of disharmony, whereas scientific explanations for TCM mechanisms remain varied. These divergent frameworks can hinder communication, underscoring the need for mutual literacy.

Methodological differences add complexity. TCM care is often individualised via syndrome differentiation, while WM typically applies disease-specific treatments that are guided by quantitative indicators. WM research prioritises standardisation and precise endpoints, an approach that can struggle to capture the dynamic nature of TCM interventions. Aligning methods and evaluating outcomes across both systems remain challenging.

CONCLUSION

Singapore's healthcare system remains predominantly WM-based, yet TCM, particularly acupuncture, is widely accepted and increasingly relevant for preventive care and chronic disease management. Advances in TCM education, practice, and research have strengthened its place within the national healthcare landscape. As education underpins effective integration, Singapore should prioritise mandatory interprofessional exposure within healthcare

curricula to foster mutual understanding and collaborative practice. System-level measures—including expanded financing for selected evidence-based TCM indications and routine documentation of TCM use during medication reconciliation—can improve accessibility and safety. Together, these strategies support safer, more coordinated, and person-centred care across both systems.

Ethics statement

Not applicable, as no patient data was used.

Declaration

The authors declare that 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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Achieving restraint-free care for frail older patients with cognitive impairment in the acute hospital

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Dear Editor,

In a fast-paced, task-oriented acute hospital setting, frail older patients face significant risks of functional decline, delirium, and iatrogenic harm, including the use of physical restraints. While person-centred care models are well established in long-term care settings, their implementation in acute hospitals—characterised by high patient turnover, time pressures, and staff unfamiliar with geriatric care principles—presents unique challenges.

Recognising this imperative, the authors developed a person-centred care ethos and culture based on Donabedian's Structure-Process-Outcome framework,¹ which links organisational resources and processes to improvements in care quality. This framework underpinned the milestone of over 1 year of restraint-free care across all acute geriatric wards in Khoo Teck Puat Hospital, a first in Singapore. Achieving sustainable change requires deliberate investment in building care culture, infrastructure, training, and specialised expertise (Structure); the consistent application of evidence-based approaches at the bedside (Process); and comprehensive evaluation of impact (Outcome).

The success of any culture-change initiative depends fundamentally on having the right resources and organisational structures in place. New nurses receive foundational training in the age-friendly 6Ms framework² for older and vulnerable patients during induction, with ongoing training and e-learning modules available for existing staff. A customised 3-level Humanitude training programme systematically develops competency across the nursing workforce. Approximately 25% of the hospital's nursing workforce has completed Level 1 training, including two-thirds of all geriatric nurses. Beyond Level 1, 13 staff hold Level 2 certification and 4 hold Level 3 certification, qualifying them to train others. The authors also adopted supportive design principles³ to create safe, familiar, and empowering environments through ward refurbishments, indoor greenery, activity trolleys, and

therapeutic programmes in music, drama, reminiscence, and horticulture. Families are regarded as integral partners in care, with extended visiting hours and opportunities for active participation during hospitalisation. A specialist cognitive-behavioural support team provides guidance to ward staff navigating complex care scenarios, ensuring that frontline staff have access to the necessary expertise when standard approaches prove insufficient.

Person-centred care in the acute setting is operationalised through 2 interconnected evidence-based approaches. The 6Ms age-friendly framework—an expansion of the Institute for Healthcare Improvement's 4Ms model²—provides a systematic, evidence-based structure for care planning, ensuring that every clinical decision considers what Matters most to the patient, alongside their Medications, Mentation, Mobility, Multimorbidity, and Meals. The authors operationalise the 6Ms through approaches that prioritise patient safety while promoting independence and dignity—using the Johns Hopkins Highest Level of Mobility Scale, providing bedside assistive devices, supporting cognition with spectacles and hearing aids, and encouraging home-cooked foods with dietitian input and modified utensils to promote independent eating.

Complementing this, the Humanitude care methodology equips staff with techniques for respectful, dignity-preserving interactions with older patients, particularly those with cognitive impairment or care resistance.⁴ Humanitude builds positive caregiver-patient relationships through 5 stages: (1) announcing presence respectfully, (2) establishing trust and consent, (3) delivering care using 4 pillars (horizontal eye contact, affirming speech, gentle touch, and upright posture), (4) providing positive reinforcement, and (5) planning future encounters.⁴ This methodology preserves human dignity while securing positive emotional memories that facilitate ongoing care acceptance.⁴

Translating these frameworks into consistent practice requires ongoing support and accountability. The

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authors implemented robust monitoring systems, including counting consecutive restraint-free days to enable transparent accountability, and regular direct observations of staff at the bedside to facilitate mentoring and constructive feedback. Resetting the restraint-free day counter to zero proved particularly demoralising, as a single restraint application erased months of progress. An After-Action Review is undertaken whenever physical restraints are used. For instance, a review of an after-office-hours restraint incident led to the development of pharmacological escalation guidelines supporting on-call doctors and nurses in managing complex situations, with daily review to ensure that pharmacological measures remain judicious and time-limited. Expansion from 1 pioneer ward to 4 additional wards during 2024–2025 introduced new challenges arising from differing patient profiles, ward cultures, and staff resistance, requiring sustained education, mentoring, and strong leadership to overcome.

The ultimate test of this initiative lies in its measurable impact across 3 interconnected levels: patients, staff, and the organisation. Patient outcomes were evaluated in 2 complementary studies. In a pilot quasi-experimental trial ($n=20$), patients receiving Humankind care showed significant improvements in activities of daily living, with median Modified Barthel Index scores increasing from 20 to 54.3 ($P=0.002$), compared with a median increase of 0 in the usual-care group. Measures of mental wellness also improved, with the Bradford Well-being Index increasing from 7.0 to 20.0 and the ill-being index decreasing from 7.0 to 2.5 (both $P=0.002$). In a larger ongoing study ($n=1374$; mean age 82 years) in which 75.3% had a diagnosis of dementia (Table 1), care refusal was reduced, with Refusal of Care Informant Scale scores decreasing from 1.96 to 0.31 (mean difference 1.64; 95% confidence interval [CI] 1.44–1.85; $P<0.001$), and functional mobility improved, with Johns Hopkins Highest Level of Mobility scores increasing from 4.63 to 5.10 ($P<0.001$).

These patient-level gains were mirrored by meaningful changes in the staff delivering care. Two complementary studies examined the impact of Humankind training on staff. A qualitative study ($n=196$) revealed shifts towards compassionate, person-centred care, with staff reporting increased respect for patient choice, reduced coercion in care, stronger staff-patient relationships, and greater confidence in promoting patient independence. A quantitative pre-post study ($n=106$) found statistically significant improvements in staff attitudes towards dementia 6 months after training, with mean Dementia Attitudes Scale scores increasing from 60.05 ± 8.64 to 66.79 ± 9.97 ($P<0.001$; Cohen's $d = 0.55$).

Table 1. Baseline characteristics of participants.

Variable (n=1374)	no. (%)
Age, mean (SD)	82.0 (8.5)
Length of stay, mean (SD)	16.6 (20.2)
CFS, ^a median (IQR)	6 (5–6)
CFS groups ^a	
Non-frail (CFS 1–3)	18 (1.4)
Mild frailty (CFS 4–5)	366 (29.4)
Moderate–severe frailty (CFS 6–9)	859 (69.1)
Sex, male	618 (45.0)
Dementia	1034 (75.3)
Dementia severity ^b	
Mild dementia	295 (23.7)
Moderate-to-severe dementia	732 (58.9)
Restraint use at baseline	231 (16.8)

CFS: Clinical Frailty Scale; IQR: interquartile range; SD: standard deviation

^a Data available for $n=1243$.

^b Mild dementia = dementia with CFS <6 ; moderate-to-severe dementia = dementia with CFS ≥ 6 .

At the organisational level, these structural and process investments culminated in more than 365 consecutive restraint-free days across 5 geriatric wards caring for more than 150 patients, without a significant increase in injurious falls—demonstrating that safety and dignity can be maintained simultaneously. Building on this foundation, the next phase involves implementing a bundled intervention programme to improve care for frail older patients in non-geriatric wards and to reduce hospital-associated disability. Using a stepped-wedge design, the authors will systematically spread person-centred care practices across the hospital, ensuring that all older patients receive age-friendly and dignified care.

Ethics statement

Not applicable, as no study participants were involved.

Declaration

The authors declare no affiliations or financial involvement with any commercial organisation with a direct financial interest in the subject or materials discussed in this manuscript. Generative AI tools were used to assist with language refinement and editing of the manuscript text, with no involvement in data collection, analysis, or interpretation of results.

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Keywords: acute hospital, Donabedian, frailty, geriatric medicine, person-centred care, restraint-free

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AI-assisted analysis of public data to identify diabetes stakeholder priorities in Singapore: A proof-of-concept study

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Dear Editor,

The exponential growth of publicly available healthcare data from open-access journals, news articles, and online forums has created an extensive repository for data mining and knowledge generation.¹ The wealth of information presents unprecedented opportunities for understanding stakeholder needs within healthcare systems. Data from online forums are increasingly recognised as a legitimate qualitative research methodology, offering access to large amounts of spontaneous and unfiltered perspectives that all stakeholders can share naturally in public domains.²

Artificial intelligence (AI) technologies in healthcare represent one of the most promising frontiers for improving health services and health outcomes. Natural language processing and machine learning in AI offer promising capabilities to systematically collect and analyse large-scale public domain data.³

Diabetes is a common chronic condition that affects approximately 400,000 people in Singapore, with a prevalence of 8.5%.⁴ The condition's management involves multiple stakeholders: patients requiring daily self-management, caregivers providing support, healthcare providers (HCPs) delivering care, and governments formulating policies and managing resources.⁵ This complexity makes diabetes particularly suitable for demonstrating how AI can capture diverse stakeholder perspectives from public domain data.

The study was conducted in 3 main phases using Accenture's UberSight platform (Accenture SG Services Pte Ltd, Singapore), a downstream analytics and forecasting layer that ingests licensed or otherwise permitted datasets, applies analytical processing, and generates forecast-oriented insights. It does not independently crawl, scrape, or extract data from external platforms. The 3 phases were: (1) data collection and preparation, (2) holistic AI application using generative AI and machine learning models, and (3) visualisation and insights development. "Data collection" here refers to the study methodology for sourcing and preparing input datasets, rather than a direct platform capability.

In phase 1, researchers collected 132,708 artefacts over 12 months (between September 2023 and August 2024) from diverse diabetes-related sources, including academic databases (e.g. PubMed) and social media platforms (e.g. YouTube, Reddit, X, Instagram, TikTok). The proportions of the data sources were: PubMed (67.6%), X (8.0%), online news (12.6%), blogs (4.2%), forums/message boards (3.4%), YouTube (1.1%), newspapers (0.8%), magazines (0.7%), Reddit (0.7%), TikTok (0.6%), Instagram (0.3%), and television/radio (0.03%). Keywords and topic clusters specific to Singapore's diabetes landscape were curated, with human supervision ensuring contextual validity and relevance. The list of search terms is in Supplementary Table S1.

In phase 2, the sources obtained were mapped systematically into a robust master data model using a defined data ingestion schema that tagged content types, date of publication, and source credibility, so that AI analysis could be conducted effectively. The data ingestion schema served as a standardised blueprint for how data was collected, structured, and stored. Each incoming data point was automatically tagged with key attributes such as content type (e.g. article, report, image, transcript) to differentiate modalities; date of publication to enable trend analysis; and source credibility to assess reliability and prioritise authoritative information. AI algorithms were assigned weightages based on relevance to diabetes topics. The study was conducted under applicable usage-rights and data governance restrictions. Access was limited to authorised personnel and use restricted to the approved analytical purpose. Redistribution of vendor data was prohibited, and project-specific data were deleted upon conclusion of the use case. Accenture's responsible AI governance framework ensured compliance with data privacy requirements, including Singapore's Personal Data Protection Act and the European Union's General Data Protection Regulation. Only anonymised, aggregated data were processed.

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The comprehensive discovery corpus incorporated contextual understanding, linking content to social, cultural, policy, and behavioural frameworks. For instance, “insulin” references were analysed beyond mere mentions to understand specific contexts regarding cost, accessibility, or medical effects. The system addressed missing values, outliers, and format inconsistencies, using natural language processing models and metadata extraction techniques to standardise diverse multimodal data formats (e.g. PDF, HTML, .mp4, .jpg, .txt, video, text, images) into unified structures optimised for generative AI models.

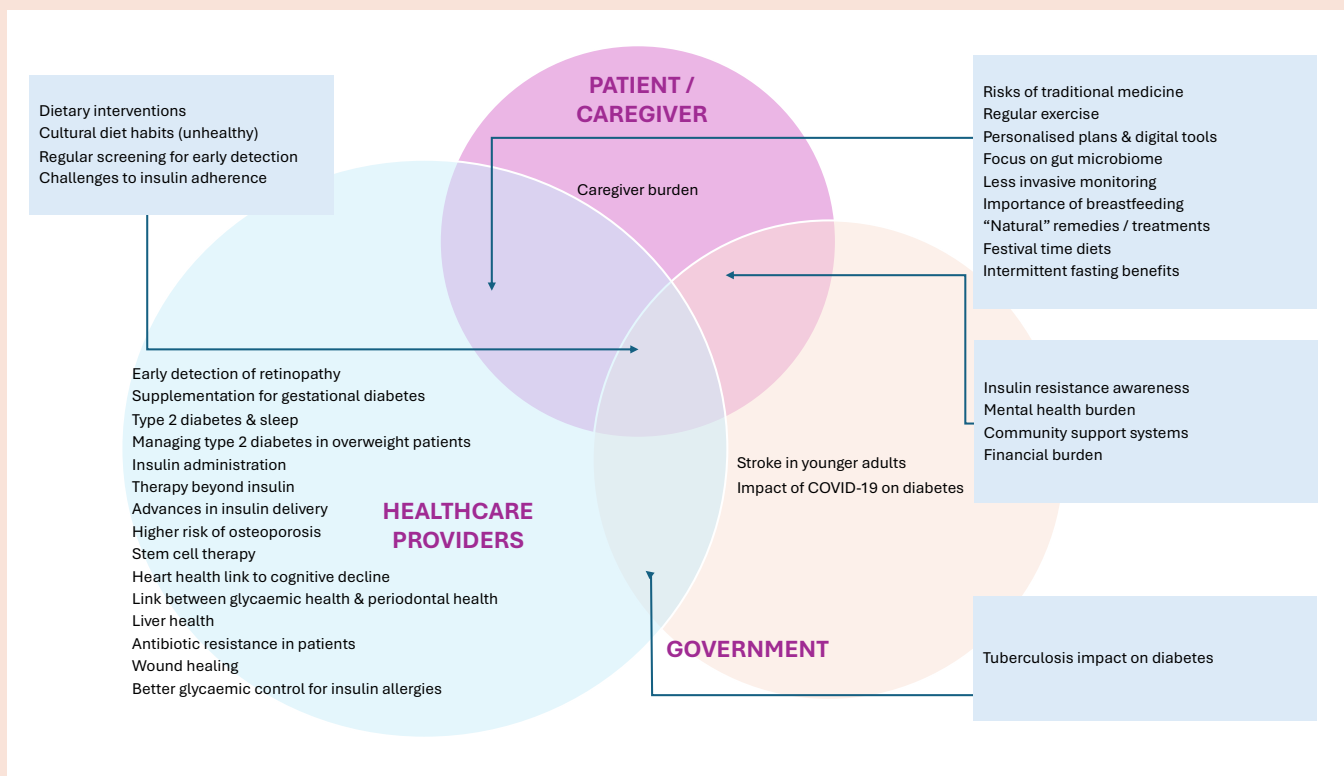
Using large language model-assisted topic generation, the researchers extracted unique topics from the master dataset to identify microtrends. Generative AI algorithms grouped semantically similar discussions. UberSight’s Trend Intensity model used its Power and Momentum dimensions to distil information into 52 unsupervised themes through AI-led topic modelling. The Power vector included topic volume, referrer volume, and sentiment, while Momentum measured pace, recency, and directional trajectory over time. Themes scoring high on both vectors emerged as significant trends. Healthcare specialists, clinicians, and researchers manually reduced the 52 themes to 36 supervised themes of

importance to Singapore’s diabetes management. These were analysed across 3 stakeholder groups: patients and caregivers, HCPs, and government.

Phase 3 involved data designers creating interactive presentations and dashboards. Themes most salient to patients and caregivers were presented through detailed vignettes and segment-specific implications. Sensitivity analysis validated final model outputs through topic coherence scores (interquartile range 0.25–0.69, median 0.35), followed by manual cross-checks to refine clustering assignments. When the sensitivity analysis was run by individual data type, a slightly higher median coherence of 0.49 was found. The low coherence scores can be attributed to the dataset comprising heterogeneous content types, including biomedical literature, transcripts, and online discussions. As topic coherence metrics are sensitive to linguistic variation across content types, the observed distribution of scores is consistent with the dataset’s composition.

From 130,000 initial artefacts, the system identified 278 microtrends across the 3 stakeholder groups, consolidated into 52 unsupervised themes, and finally refined to 36 supervised themes by clinical experts (Fig. 1). Three key topics emerged as common priorities across all 3 stakeholders: dietary interventions and

Fig. 1. Categorisation of themes.



cultural diet habits, regular screening, and insulin adherence challenges. Patients/caregivers and HCPs intersected on diabetes management methods including traditional medicine, exercise, intermittent fasting, postpartum breastfeeding, and digital tools. Patients/caregivers and government overlapped in support services, particularly psychological, social, and financial support.

Patients and caregivers were most concerned about the caregiver burden of providing care for a person with diabetes. HCPs were focused on understanding how diabetes interacted with other health conditions, such as sleep, heart, and periodontal health, and developing new therapies for patients with diabetes. The government was investigating increased stroke risk in younger adults with diabetes, and the impact of COVID-19 on diabetes.

This study demonstrates AI-driven methodologies' feasibility for analysing large-scale public domain healthcare data. The approach successfully processed 132,708 artefacts, providing comprehensive insights into Singapore's diabetes care landscape. The Power and Momentum vectors enabled identification of both current priorities and emerging concerns, supporting proactive healthcare planning. Traditionally, data from public domains were collected and analysed manually, which limited both the number of forums that could be accessed and the findings obtained.⁶ However, a systematic review between 2023 and 2024 found 130 articles that used AI for qualitative data analysis, highlighting the rising trend of using AI in this field.⁷

The distinct theme clusters that emerged for each stakeholder group reveal where perspectives align and where gaps may exist. The difference between clinical priorities and public awareness represents an opportunity for targeted intervention. For example, caregiver burden remains a major concern for caregivers and patients with diabetes, but has been overlooked by HCPs and the government, suggesting insufficient translation of research into practice.^{8,9}

The findings also highlighted HCPs' large focus on comorbidities and therapeutic developments, which are crucial for long-term health outcomes. However, these were less frequently discussed amongst patients and caregivers, possibly reflecting gaps in the group's understanding of diabetes. This is supported by a systematic review which found that diabetes knowledge among type 2 diabetes patients in Southeast Asia was unsatisfactory, particularly amongst older patients with lower education levels and poor glycaemic control.¹⁰ This suggests a need for improved patient education and communication about the broader health implications of diabetes.

Although the methodology effectively processed large volumes of data, it might not capture the depth of individual experiences that qualitative research methods provide. Therefore, this approach should complement rather than replace traditional in-depth qualitative interview methodologies. While the authors maintained diversity in the data sources, they cannot guarantee that this translates to demographic diversity amongst contributors. Given that data were collected from public forums where participants remained anonymous, demographic representation could not be verified.

In summary, this AI-driven framework represents a significant advancement in identifying the priorities of various stakeholders in diabetes management. The data have potential for use in healthcare planning and policy development, with future applications extending to other chronic conditions and identifying cross-disease patterns and systemic healthcare challenges.

Supplementary material

Table S1. List of search terms used.

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Ethics statement

Not applicable, as no patient data were used in this study.

Declaration

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

Keywords: access to information, artificial intelligence, data analysis, data collection, diabetes mellitus, public health informatics

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Real-world doxycycline post-exposure prophylaxis and bacterial STI incidence among MSM using HIV PrEP in Singapore

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Dear Editor,

Doxycycline post-exposure prophylaxis (DoxyPEP) is an emerging strategy for preventing bacterial sexually transmitted infections (STIs). Randomised controlled trials have shown reductions of more than 70% in chlamydia and syphilis among men who have sex with men (MSM) and transgender women, with weaker and more variable effects on gonorrhoea.¹⁻³ These results have informed recent international guidance recommending targeted DoxyPEP for MSM and transgender women at increased STI risk.^{4,5} Real-world cohorts from Spain and the US have reported broadly similar findings, generally using within-person before-and-after comparisons.⁶⁻⁸ However, comparable data from Asia are lacking.

At the Department of STI Control, National Skin Centre, Singapore, DoxyPEP has been offered since mid-2025 to MSM at higher STI risk, including those on human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP) with reduced condom use. As DoxyPEP had only recently been introduced, awareness and uptake were still developing among clinicians and patients, and it was not routinely prescribed to all PrEP users. The prescribed regimen was a single 200 mg dose of doxycycline taken as soon as possible, and within 72 hours, of sexual exposure. The authors conducted a retrospective cohort study using electronic medical records from 27 July 2024 to 31 December 2025, including MSM aged 21 years or older who were receiving HIV PrEP and subsequently initiated DoxyPEP.

Among HIV PrEP users who initiated DoxyPEP, person-time was divided into pre- and post-DoxyPEP periods. Incident chlamydia, gonorrhoea, and syphilis, including recurrent episodes, were identified from laboratory records. Incidence rates were calculated as events per 100 person-years to account for differences in follow-up duration. Incidence before and after DoxyPEP initiation was compared using Andersen–Gill recurrent-event Cox models, with DoxyPEP exposure modelled as a time-varying covariate and

robust standard errors used to account for recurrent events within individuals. Age at first visit, ethnicity, marital status, and residential status were included as covariates. Variables causing model singularity were excluded from the final Cox model. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were reported.

Of 735 MSM receiving HIV PrEP, 117 initiated DoxyPEP during follow-up and were included. The median age was 31 years (interquartile range 27–37). Most participants were Chinese (93/117, 79.5%), followed by Malay (11/117, 9.4%), Indian (2/117, 1.7%), and other ethnicities (11/117, 9.4%). Total pre- and post-DoxyPEP person-time was 21.259 and 14.793 person-years, respectively. Chlamydia and gonorrhoea testing frequencies were 1321.8 and 621.9 screening episodes per 100 person-years before and after DoxyPEP initiation, respectively; corresponding syphilis testing frequencies were 258.7 and 142.0 tests per 100 person-years.

In the within-person analysis, chlamydia incidence was significantly lower after DoxyPEP initiation, decreasing from 51.7 to 6.8 per 100 person-years (adjusted HR 0.059, 95% CI 0.008–0.437; $P=0.006$) (Table 1). Gonorrhoea incidence rates were similar before and after DoxyPEP initiation, at 47.0 and 47.3 per 100 person-years, respectively. No statistically significant association was observed (adjusted HR 0.490, 95% CI 0.157–1.532; $P=0.220$). Syphilis incidence was 4.7 per 100 person-years before DoxyPEP initiation and 20.3 per 100 person-years after initiation, but the number of events was small and the difference was not statistically significant (adjusted HR 3.855, 95% CI 0.407–36.555; $P=0.240$).

The reduction in chlamydia is consistent with trial and real-world evidence.⁶ The large effect size in this study should be viewed in the context of the small number of events and short post-initiation follow-up. Gonorrhoea incidence was not significantly reduced, consistent with variable trial efficacy and the high prevalence of tetracycline resistance among circulating

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Table 1. Bacterial STI incidence before and after DoxyPEP initiation among HIV PrEP users (within-person comparison).

Outcome	Pre-DoxyPEP events (per 100 person-years)	Post-DoxyPEP events (per 100 person-years)	Adjusted HR (95% CI)	P
Chlamydia	51.7	6.8	0.059 (0.008–0.437)	0.006
Gonorrhoea	47.0	47.3	0.490 (0.157–1.532)	0.220
Syphilis	4.7	20.3	3.855 (0.407–36.555)	0.240

CI: confidence interval; DoxyPEP: doxycycline post-exposure prophylaxis; HIV PrEP: human immunodeficiency virus pre-exposure prophylaxis; HR: hazard ratio; STI: sexually transmitted infections

Neisseria gonorrhoeae strains in the Western Pacific region.⁹ In addition to the small number of syphilis events, the numerical increase may partly reflect delayed detection of infections acquired before or around DoxyPEP initiation, given the interval between infection, seroconversion, and diagnosis. The wide confidence interval also indicates substantial uncertainty around this estimate. Several limitations should be noted. As this was a retrospective study using routinely collected clinical data, information on sexual behaviour, condom use, number of partners, and DoxyPEP adherence was unavailable. Incident infections were detected only when patients attended for testing, and differences in testing frequency before and after DoxyPEP initiation could have affected the observed incidence. However, the large reduction in chlamydia incidence, with no comparable reduction in co-tested gonorrhoea, suggests that the finding is unlikely to be explained solely by reduced testing frequency. DoxyPEP was also introduced only in mid-2025, resulting in a relatively short post-initiation follow-up and few incident events. This limited the precision of the chlamydia estimate and the power to detect changes in gonorrhoea and syphilis. Finally, this was a single-centre study, and antimicrobial resistance outcomes were not assessed.

To the authors' knowledge, this is among the first real-world evaluations of DoxyPEP outcomes among MSM in Asia. Among MSM receiving HIV PrEP, DoxyPEP initiation was associated with a significant reduction in chlamydia incidence, supporting a potential role for targeted DoxyPEP in chlamydia prevention among MSM already identified as benefiting from biomedical STI/HIV prevention. No significant reduction was observed for gonorrhoea or syphilis in this early cohort. Larger prospective studies with standardised STI testing intervals, assessment of DoxyPEP adherence, sexual behaviour data, and a contemporaneous PrEP-only comparison group would help validate these findings and provide more precise estimates of effectiveness. Replication across other centres and Asian settings would determine

reproducibility and generalisability and inform targeted DoxyPEP implementation in the region. Integration of gonococcal antimicrobial susceptibility and molecular resistance surveillance will also be important in interpreting the absence of an observed reduction in gonorrhoea. A recent longer-term study¹⁰ reported declining DoxyPEP effectiveness against gonorrhoea in association with the expansion of high-level tetracycline-resistant *N. gonorrhoeae*. Although the present study did not assess whether DoxyPEP use was associated with the emergence or increased prevalence of tetracycline-resistant *N. gonorrhoeae*, antimicrobial resistance remains an important consideration with wider implementation. DoxyPEP may nevertheless retain substantial value for the prevention of other bacterial STIs, particularly chlamydia. Wider implementation should therefore be accompanied by antimicrobial resistance surveillance and periodic reassessment of clinical effectiveness. Future Singapore-based studies could compare tetracycline susceptibility and resistance determinants in *N. gonorrhoeae* isolates from DoxyPEP users and non-users.

Ethics statement

The study was approved by the National Healthcare Group Domain Specific Review Board (2025-2028).

Declaration

The authors declare that 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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Keywords: chlamydia, doxycycline post-exposure prophylaxis, HIV pre-exposure prophylaxis, men who have sex with men, sexually transmitted infections

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Diabetes, chronic kidney disease, and annual hospital costs in older patients: A cost decomposition analysis

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Dear Editor,

Diabetes mellitus (DM) and chronic kidney disease (CKD) are prevalent, costly, and frequently co-occur in older adults, yet their independent and joint contributions to hospital spending in Asian public-sector settings remain poorly defined. Compared with those having neither condition, expenditures are about 3 to 4 times higher in CKD and 2.3 times higher in DM.^{1,2} Prior Singapore studies examined CKD progression costs within type 2 DM but did not isolate the independent cost of CKD without DM, nor decompose spending into service components.³ The authors therefore examined the independent and joint associations of DM and CKD with annual hospital costs and the service components driving excess spending.

This is a retrospective cohort study using 1-year data (June 2024 to May 2025) from the 326-bed Alexandra Hospital, a public general hospital in Singapore. Eligible patients were Singapore citizens aged 60 years or older with at least 1 encounter, yielding 4699 patients. Gross annual hospital costs in Singapore dollars (SGD) were disaggregated into 5 components: inpatient care, outpatient care, diagnostics, procedures and therapeutics, and medications/consumables/other. Patients were classified according to International Classification of Diseases 10th Revision (ICD-10) by active diagnoses (DM E10-E14; CKD N18, N19) as “neither” ($n=3016$), “DM-only” ($n=1008$), “CKD-only” ($n=315$), or “both” ($n=360$). A generalised linear model with gamma distribution and log link was used to examine total costs, given the right-skewed distribution of hospital costs, and adjusted for sex, age group, ethnicity, Community Health Assist Scheme tier (i.e. public subsidies extended to Singapore citizens based on household income), and count of other chronic conditions (identified using a validated administrative algorithm).⁴ Diagnosis coding was performed by trained medical record officers in the hospital’s medical records office, following standard institutional coding practice. Covariates were selected a priori based on established socio-demographic and clinical

confounders reported in the DM-CKD cost literature. Ordinary least squares regression was used for decomposition. Because the model uses a log link, each coefficient (β) reflects the proportional, rather than absolute, change in cost; exponentiating the coefficient and subtracting 1 gives the percentage difference in cost relative to the reference group. Significance was pre-specified at $P<0.10$, given the small “CKD-only” subgroup and high cost variability.⁵ Ethical approval was obtained with a waiver of patient consent.

The mean age was 75.3 ± 8.81 years; 56.1% were female and 79.3% Chinese. Total annual costs were highly skewed (median SGD430.46, mean SGD1599.41); 39.8% of patients incurred no inpatient costs at all, so the entirety of inpatient expenditure was borne by the remaining 60% of patients. Consistent with the well-recognised concentration of hospital spending, a relatively small subset within this 60% is likely to account for a disproportionate share of that expenditure. After adjustment, “CKD-only” patients had 45.1% higher total costs than the “neither” group ($\beta=0.372$, $P=0.034$), whereas “DM-only” patients showed no significant difference ($\beta=-0.005$, $P=0.971$) and the “both” group a non-significant 18.6% increase ($\beta=0.171$, $P=0.414$). Patients aged 80 years and above ($\beta=0.576$, $P<0.001$) and each additional chronic condition ($\beta=0.122$, $P=0.046$) incurred higher costs. Compared with Chinese patients, costs were 42.2% higher in Malay patients ($P=0.073$), 65.9% higher in Indian patients ($P=0.008$), and 122.1% higher in other ethnic groups ($P=0.001$). A sensitivity model with a DM $\times$ CKD interaction term yielded an identical CKD coefficient ($\beta=0.372$) and a non-significant interaction ($\beta=-0.196$, $P=0.486$), supporting CKD as the principal independent cost driver.

Decomposition of the SGD520.58 total excess cost for “CKD-only” patients relative to the “neither” group (90% confidence interval [CI] -56.22 to 1097.39 ; $P=0.138$) showed that it was driven mainly by 2 components. Inpatient care contributed the largest share (SGD239.72; 46.0%; $P=0.184$), followed by medications/consumables/other (SGD153.60; 29.5%),

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the only component reaching significance in this model ($P=0.093$); together they accounted for roughly three-quarters of the excess. The remaining 3 components contributed less than a quarter combined: diagnostics (SGD59.45; 11.4%), procedures and therapeutics (SGD55.90; 10.7%), and outpatient care (SGD11.92; 2.3%). Predicted mean costs by group and component are shown in Fig. 1. “CKD-only” patients had the highest total cost (SGD1880.99), driven mainly by inpatient care (SGD697.02) and medications (SGD436.18). Notably, patients with both conditions had the lowest adjusted medication cost (SGD211.19), below even the “neither” group (SGD282.59).

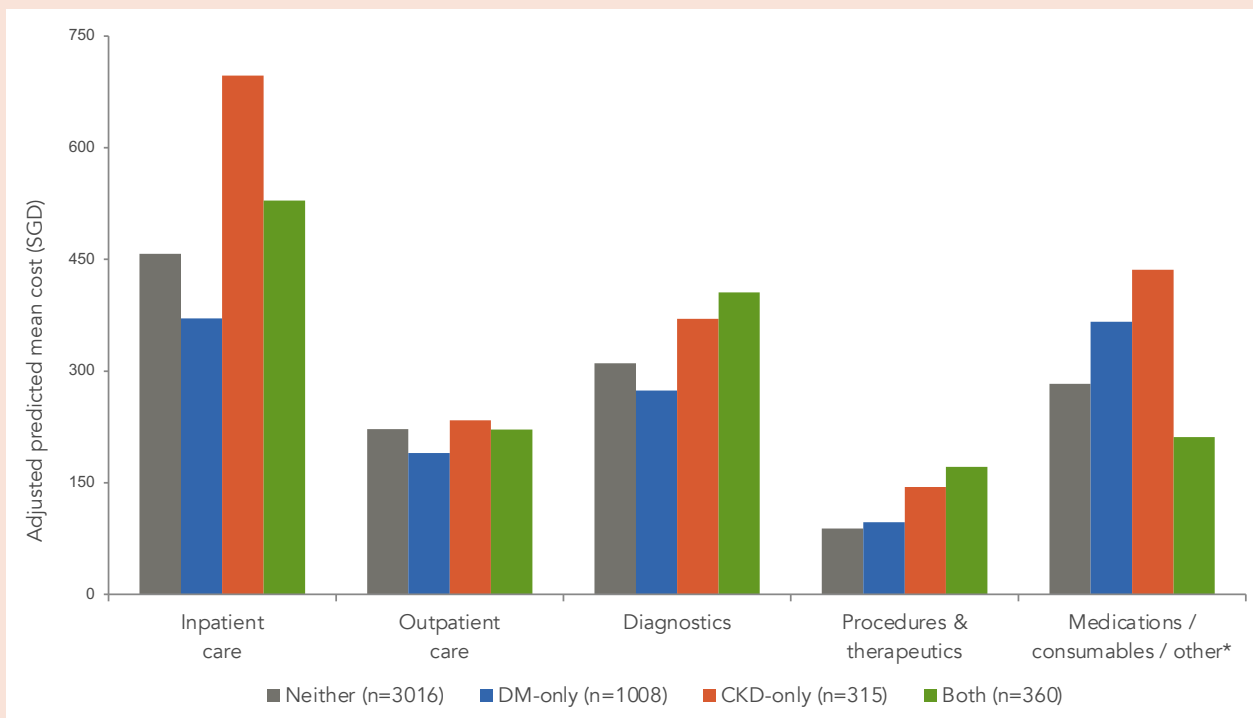
The finding that CKD, but not DM, independently drives hospital costs is consistent with the disproportionate economic burden of kidney disease and the observation that costs track declining renal function more than DM alone.⁶ CKD often remains asymptomatic until complications such as cardiovascular disease, anaemia, and mineral bone disorders demand hospitalisation, specialist care, and complex medication regimens, whereas well-controlled DM is largely managed in primary care. Medications likely reflect the high cost of agents such as erythropoiesis-stimulating agents, phosphate binders, and cardiovascular drugs essential for slowing the progression of CKD.⁷

The paradoxically low medication cost in the “both” group most plausibly reflects care-shifting. Patients with multiple comorbid conditions frequently obtain much of their medication through community pharmacies, dialysis centres, or national programmes outside of hospital billing, so the hospital record captures only a fraction of their true use. Survivor bias may also contribute, as those with the most advanced disease may not survive a full costing year. That the most complex patients appear least expensive within 1 institution is precisely why hospital costs alone understate their true burden.

Ethnic cost disparities persisted after adjustment for DM-CKD status, age, and comorbidity burden, indicating that these differences are not attributable to differential prevalence of DM or CKD across ethnic groups. Rather, they likely reflect a higher underlying severity of disease within each comorbidity category and delayed presentation,⁸ together with differential use of private care outside the public system, given income-related differences in access previously reported locally.⁹

Two intervention targets follow directly from the cost structure. First, structured medication review and adherence support may improve the appropriateness of prescribing and help prevent CKD-related complications and avoidable hospitalisations, given the close interrelationship of multimorbidity, polypharmacy,

Fig. 1. Adjusted predicted mean costs.



CKD: chronic kidney disease; DM: diabetes mellitus; SGD: Singapore dollar

and frailty in older patients; expanded subsidies for evidence-based CKD therapies would primarily ease patient out-of-pocket burden rather than necessarily reduce total system-level medication expenditure. Second, the large inpatient contribution reinforces the case for hospitalisation prevention through multidisciplinary, community-based CKD care, as delivered locally in primary care.¹⁰ Patients aged 80 years and above—the costliest subgroup—warrant age-specific care models.

Limitations include reliance on a single hospital with a care model and patient demographic that may not be generalisable to other institutions; absence of CKD stage and glycaemic control; reliance on ICD-10 diagnosis coding (N18/N19) without dedicated capture of dialysis or transplant status, which may have led to some misclassification; and the observational design, which precludes causal inference and makes residual confounding likely despite adjustment for measured covariates. As patients with milder disease are more likely to be managed in community settings, the hospital-based cohort may not represent the full spectrum of DM-CKD comorbidity, and the inability to capture costs incurred outside this hospital likely understates the true economic burden across all groups, particularly in the “both” group. Furthermore, as this study examined cost alone, without corresponding data on clinical outcomes, quality of life, or cost-effectiveness, higher costs in CKD patients should not be interpreted as inherently undesirable; they may in part reflect necessary and appropriate intensification of care. Consequently, the mechanisms underlying elevated inpatient costs, such as length of stay, admission acuity, dialysis modality, and procedure intensity, could not be examined and represent an important direction for future study using more granular clinical data, such as linkage to renal registries.

In conclusion, CKD independently drives higher hospital costs in older Singapore patients, with inpatient care and medications as the key contributors and clear targets for medication optimisation and hospitalisation prevention. Lower hospital medication costs in comorbid patients highlight the need for linked data systems to capture the true cost of care across settings, while ethnic disparities support culturally tailored chronic disease programmes and community outreach.

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Ethics statement

This is a retrospective analysis of de-identified administrative data. Patient consent was waived by Alexandra Hospital Institutional Review Board (AH-RNR-2025-0002).

Declaration

No funding was received for this study. The authors declare that 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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