

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

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ABSTRACT

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

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

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

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

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

CLINICAL IMPACT

What is New

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

Clinical Implications

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

INTRODUCTION

Singapore has the third highest incidence and sixth highest prevalence of end-stage kidney disease (ESKD) in the world.¹ Globally, chronic kidney disease (CKD) is estimated to affect over 850 million people, with a prevalence of 13.4% among adults worldwide.² Diabetes is the main cause of ESKD in new patients initiating dialysis, accounting for two-thirds of cases in 2021.³ The Ministry of Health's (MOH) war on diabetes has reaped benefits in stabilising its crude prevalence at 8.5% in 2022. However, CKD prevalence increased significantly from 8.7% in 2020 to 13.8% in 2022.⁴ This trend is consistent with global patterns, where CKD prevalence is expected to increase by 17% between 2020 and 2030.⁵ CKD-related deaths had risen by 76% from

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2009 to 2019, as it remained in the top 10 most common causes of death in Singapore.⁶ CKD is also a significant economic burden, with \$300 million spent annually on dialysis treatment.⁷ By 2035, about a quarter of Singapore residents are projected to develop CKD⁸; the mortality, morbidity and economic burden of CKD will be unfathomable.

Addressing this issue requires an emphasis on optimal management through large-scale primary care programmes to delay CKD progression and improve patient outcomes.⁹ The increasing number of patients with CKD being managed in primary care¹⁰ led to the development and rollout of the Nephrology Evaluation, Management and Optimisation (NEMO) programme from 2011 to 2016. It was expanded and continued as the Holistic Approach to Lowering and Tracking Chronic Kidney Disease (HALT-CKD) programme in 2017, covering all 3 healthcare clusters at primary and tertiary care in Singapore.^{11,12}

HALT-CKD aims to slow down CKD progression and prevent ESKD development by systematically recruiting and tracking patients with risk factor control at the primary care level. The programme aligns with global health initiatives and policies on CKD management, such as the World Health Organization's goal to reduce the number of deaths from non-communicable diseases, including CKD, by 25% by 2025.¹³ HALT-CKD also focuses on medication optimisation to reduce proteinuria, improving blood pressure and glycaemic control in patients with CKD stages G1–G3A in primary care. Moreover, the programme encourages shared-care collaboration between primary and tertiary (nephrology) care for patients with CKD stages G3B–G5.¹¹ It features the designation of coordinators in each polyclinic, whose role focuses on patient recruitment, education on low-sodium diet, weight management and smoking cessation and making referrals to these services as required. The coordinators also assist the team in tracking key performance indicators, calling up patients to remind them of appointments, and in turn, provide holistic care through continual follow-ups.¹⁴

HALT-CKD has garnered much success over the years, with over 49,000 patients having benefitted from the programme as of March 2019, with 90% being placed on kidney protective medications and improved chronic disease control since joining the programme. However, local studies have found suboptimal care in specific patient groups, such as in ethnic minorities and the elderly, with resultant poorer chronic disease control.^{15,16} To our knowledge, there has not been any studies published based on NEMO or HALT-CKD data. As patients with varying chronic disease control are

recruited at different timepoints throughout the ongoing programme, the severity profile of the CKD cohort is diluted over time. This makes it challenging to rigorously track disease progression and assess key performance indicators in individual patients over an extended period. Furthermore, the study of specific cohorts recruited under the HALT-CKD programme has not been performed, despite the ease and ability to do so with close patient tracking and follow-up in primary care. With the first group of patients being recruited in to the programme in April 2017, it will now be possible to assess their health outcomes after 5 years of adequate follow-up. Therefore, our study critically analysed the patients recruited in the first year of the HALT-CKD programme and reviewed their health status and outcomes after 5 years. Our study also evaluated the outcomes of the HALT-CKD programme and identified factors influencing disease progression among early CKD patients. We hypothesised that primary care has achieved its objectives—pharmacological interventions (e.g. medication initiation and up-titration) and non-pharmacological interventions (e.g. lifestyle counselling) have delayed progression to CKD stages G3B–G5. By examining the 5-year outcomes of the programme's initial cohort, we also sought to determine the effectiveness of the HALT-CKD programme in slowing down CKD progression and identified key factors that contribute to successful disease management.

METHOD

Study population and sampling

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

Study definition and parameters

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

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

centralised trusted third party before analysis by study team.

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

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

HALT-CKD				
Eligibility	All patients with CKD G1–G3A <80 years old - CKD G1 & G2: Requires 2 abnormal UACR/UPCR ≥12 weeks apart - Add “chronic renal failure” as visit diagnosis and problem list			
Lifestyle modification	- Refer all patients aged <80 years for HALT-CKD counselling - Stop smoking, refer smoking cessation clinic by pharmacist - Encourage weight loss, consider dietician review if BMI >23 kg/m², weight management clinic if BMI >27.5 kg/m² - Counsel on low salt (<2 g/day) diet - Counsel on low protein diet (<0.8 g/kg/day) and refer dietician for CKD G3B patients - Advice on 150 mins/week of moderate intensity exercise			
Maximise ACEi/ARB	Optimise dosages until one of these endpoints below: a) Maximal recommended or tolerated dose b) Normoalbuminuria + achieve BP target c) When starting or increasing ACEi/ARB, order ACEi/ARB panel in 2–4 weeks with CM review			
Optimise BP	a) <130/80 mmHg for ALL patients b) <140/90 mmHg for older patients, high fall risk, multiple comorbidities			
Optimise HbA1c	a) ≤7%: Age ≤75 years b) ≤8%: Age 76–80 years			
Optimise LDL-C	a) <1.8 mmol/L for DM patients b) <2.6 mmol/L for non-DM patients c) More stringent targets for patients with ASCVD or additional risk factors			
Start SGLT2 inhibitor	a) Can be started if patient is on ACE-I/ARB; check renal panel in the elderly, advanced CKD or on diuretic b) Multiple benefits such as weight loss, BP and DM control, reducing albuminuria, retarding progression, reducing mortality			
Shared care with renal	Refer CKD G3B, G4 and G5 or persistent significant albuminuria to nephrology			

CKD stage	eGFR (ml/min/1.73 m ²)		
G1	≥90		
G2	60–89		
G3A	45–59		
G3B	30–44		
G4	15–29		
G5	<15		

ACEi/ARB	Initial dose	Max daily dose (mg/day)	Renal dose (mg/day)
Lisinopril	5 mg OM Elderly: 2.5 mg	40 OD	CrCl <30 Initial 2.5–5 OD
Enalapril	5 mg OM Elderly: 2.5 mg OM	20 BD	CrCl <30 max 20/day
Captopril	25 mg BD/TDS	50 TDS	CrCl <50 75% dose BD
Perindopril	4 mg OM Elderly: 2 mg OM	8 OD	CrCl <30 Do not use
Losartan*	50 mg OM	100 OD	No change
Valsartan	80 mg OM	320 OD	No change
Irbesartan	150 mg OM Elderly: 75 mg OM	300 OD	No change
Candesartan	8 mg OM	32 OD	Initial 4 OD
Telmisartan*	40 mg OM	80 OD	No change

*Recommended option

Updated October 2024

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

CKD stages G3B–G5 at time of analysis. For patients who died, defaulted or transferred care to another institution without developing CKD stages G3B–G5, we utilised their last available estimated glomerular filtration rate (eGFR) measurement to estimate the time to censoring, as they did not experience the outcome of interest during the study period. Albuminuria stage (i.e. A1–3) was calculated based on existing cutoffs as defined by KDIGO except stage A1, where we used gender specific cutoffs (2.5 and 3.5 mg/mmol for males and females, respectively),¹⁸ a continuation from the previous NEMO programme. eGFR was calculated using the Chronic Kidney Disease Epidemiology 2009 Creatinine equation¹⁹ for all eGFR values before classification into CKD stage. The outcome variable of CKD progression was defined as progression to CKD stages G3B–G5, with an eGFR <45 ml/min/1.73 m², as defined by KDIGO.¹⁷ We chose this outcome for this study, as stage G3B was the threshold to refer nephrology (outlined by the HALT-CKD programme), making it a practical and clinically relevant outcome to monitor. Furthermore, individuals with more advanced CKD face a higher risk of renal-related complications.

Statistical analysis

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

RESULTS

Of 35,195 patients on the HALT-CKD register, 3800 patients fit the inclusion criteria (Fig. 2). Majority (58.3%) were male, Chinese (68.2%), with a mean

age of 61.9 years and followed-up for a median of 4.7 (IQR 4.0–5.0) years. More than 90% of patients had 1 or more chronic diseases, with significant increment of patients developing hypertension and diabetes mellitus after 5 years.

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

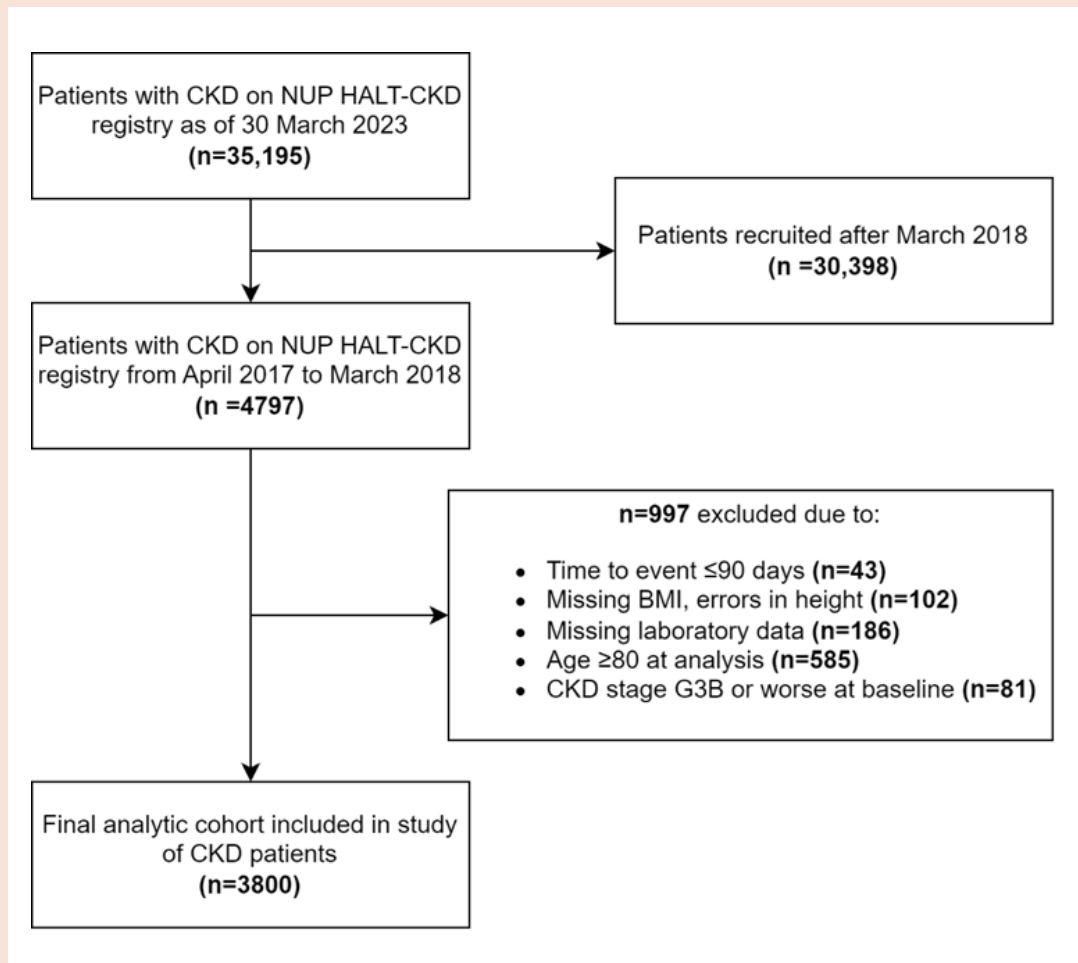
In terms of outcome, progression to CKD stages G3B–G5 occurred in 12.6% over 5 years (Table 1), with more patients progressing into the red zone as shown in Table 2. There was a significant increase in number of patients with albuminuria stage A1 from baseline compared to 5 years later (*P*<0.001) (Table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

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

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

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

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



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

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

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

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

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

^a McNemar test^b Wilcoxon signed-rank test^c Worsening CKD G category (e.g. G1–G2 or G3A–G3B)^d Worsening CKD A category (e.g. A1–A2 or A2–A3)

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HALT-CKD: Holistic Approach to Lowering and Tracking Chronic Kidney Disease; HbA1c: haemoglobin 1Ac; IQR: interquartile range; NA: not applicable; SBP: systolic blood pressure; SD: standard deviation; SGLT2i: sodium-glucose cotransporter-2 inhibitor

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

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

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

CKD: chronic kidney disease; GFR: glomerular filtration rate

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

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

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

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

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

^a Decreased dose includes drug cessation

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

CONCLUSION

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

Ethics statement

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

Declaration

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

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