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Impact of polypharmacy burden, drug-drug interactions, and pharmacist-led deprescribing interventions on chronic kidney disease progression in elderly patients: a multicenter prospective cohort study with embedded randomized controlled trial.

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Abstract

Background:
Polypharmacy is highly prevalent among elderly patients with chronic kidney disease (CKD) and is associated with accelerated renal deterioration. However, data on the combined impact of polypharmacy burden, drug-drug interactions (DDIs), and structured deprescribing on eGFR trajectory remain limited.

Objective:
To evaluate the relationship between polypharmacy burden, DDI severity, and eGFR decline in elderly patients with CKD, and to assess the effect of pharmacist-led deprescribing interventions.

Methods:
This prospective cohort study enrolled 1,284 patients aged ≥65 years with CKD stages 3–4 across four tertiary care centers in India (2021–2024). Polypharmacy burden was categorized (1–4, 5–9, 10–14, ≥15 medications). DDIs were screened using Micromedex®, and a validated deprescribing intervention was applied to 644 patients. The primary outcome was eGFR slope over 36 months.

Results:
The mean participant age was 71.4 ± 6.2 years; 58.3% were male. Severe polypharmacy (≥15 drugs) was associated with an annual eGFR decline of −9.7 mL/min/1.73 m² vs −2.1 mL/min/1.73 m² in the low-burden group ($p<0.001$). Major DDIs were present in 19.3% at baseline. Pharmacist-led deprescribing significantly attenuated eGFR decline (−2.1% vs −8.4% in controls at 12 months; $p<0.001$) and reduced the prevalence of major DDIs by 38.6%. Multivariable Cox regression identified polypharmacy burden (HR 2.84; 95% CI 1.97–4.09), major DDI (HR 2.31; 95% CI 1.58–3.38), and absence of deprescribing (HR 1.76; 95% CI 1.22–2.54) as independent predictors of rapid renal decline.

Conclusion:
Polypharmacy burden and DDI severity independently accelerate CKD progression in elderly patients. Structured pharmacist-led deprescribing significantly preserves renal function and reduces adverse drug event burden. Routine medication reconciliation and structured pharmacist-led deprescribing programs should be integrated into multidisciplinary CKD care for elderly patients to minimize inappropriate polypharmacy and preserve renal function.

Keywords: *polypharmacy; drug-drug interactions; deprescribing; chronic kidney disease; elderly; estimated glomerular filtration rate; geriatric nephrology*
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1. Introduction

Chronic kidney disease (CKD) is one of the most serious challenges of the 21st century, with 850 million people worldwide affected, and disproportionately in the elderly [1]. India's estimated CKD prevalence in adults aged ≥60 years ranges from 15-20%, with a predicted rise in parallel with an ageing population [2]. Renal senescence in the elderly is due to progressive renal cortex thinning and reduction in glomerular filtration and tubular secretion, which renders the aged kidney susceptible to nephrotoxic damage [3].

Polypharmacy - commonly defined as the simultaneous use of five or more prescription medications - is common in the elderly with CKD, given the high burden of multimorbidity that often requires multiple medications. In India, national surveys show that over 70% of hospitalised elderly have polypharmacy [4]. Unfortunately, both the quantity of medications and pharmacologically complex medication regimens are linked with poor medication adherence, ADRs, and clinically relevant DDIs [5]. CKD amplifies these risks by modulating the pharmacokinetics of drugs that are renally eliminated, diminishing drug binding to plasma proteins (due to hypoalbuminemia), and enhancing susceptibility to toxic tubular damage from nephrotoxins [6].

Drug-drug interactions pose a particular risk in elderly patients with CKD. In elderly outpatients taking five or more medications, a minimum of one significant DDI is present in up to 40% of patients, with the risk increasing with the number of medications taken [7]. Nephrotoxic DDIs, such as those involving non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, ACE inhibitors, and contrast agents, play a role in acute-on-chronic renal failure and progression of CKD [8]. Combined use of renin-angiotensin-aldosterone system (RAAS) inhibitors and potassium-sparing diuretics can lead to hyperkalemia-related arrhythmias, while loop diuretics and NSAIDs can induce acute tubular necrosis [9].

The practice of deprescribing - the supervised, planned reduction and withdrawal of medications where the harms outweigh the benefits - has become an important aspect of medication management in the elderly [10]. Medication review and deprescribing interventions led by pharmacists have been shown to decrease medication burden, adverse drug reactions (ADRs), and hospital admissions in the general elderly population [11]. But research on the effect of deprescribing on the course of renal disease in CKD patients remains scarce and primarily based on small, single-center studies [12]. Previous systematic reviews have noted the heterogeneity in study designs, definitions of deprescribing, and short follow-up periods as impediments to firm conclusions [13].

Additionally, the relationship of polypharmacy, DDI burden, and deprescribing has not been explored in a holistic longitudinal manner in Indian older adults with CKD. Genetic differences, dietary habits, herbal medication practices, and socioeconomic factors influencing health care may also contribute to a unique disease burden in the South Asian population that may not be reflected in Western epidemiological studies [14,15]. These associations are critical to inform culturally sensitive, evidence-based guidelines.

This study aimed to describe the relationship between different categories of polypharmacy burden, DDI severity levels, and the eGFR trajectory over 36 months in the elderly CKD stage 3-4 population. Further aims included assessing the effect of a pharmacist-led deprescribing program on renal function, ADR rates, hospital admissions, and quality of life measures, and to determine independent predictors of rapid renal decline in this population [16,17].

2. Materials and methods

2.1 study design and setting

This was a multicenter, prospective cohort study with an embedded randomized controlled sub-trial of deprescribing intervention, conducted across four tertiary care centers in India: King George's Medical University (KGMU), Lucknow; All India Institute of Medical Sciences (AIIMS), New Delhi; Christian Medical College (CMC), Vellore; and Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGI), Lucknow. The study was conducted from January 2021 to December 2024.

2.2 ethical

Ethical approval was obtained from the Institutional Ethics Committees of all participating centers before commencement of the study: KGMU/IEC/2020/287; AIIMS/IEC/2020/1043; CMC/IRB/2020/412; and SGPGI/IHEC/2020/156. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

2.3 participants

Eligible participants were adults aged ≥65 years with confirmed CKD stages 3–4 (eGFR 15–59 mL/min/1.73 m², measured by CKD-EPI 2021 creatinine equation) on two occasions at least 90 days apart. Patients were required to be on ≥1 chronic medication. Exclusion criteria included: CKD stage 5 or dialysis dependency; malignancy with expected

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survival <12 months; acute kidney injury within the preceding 3 months; inability to provide informed consent; and prior renal transplantation. The sample size was calculated based on detecting a minimum clinically significant difference of 2.0 mL/min/1.73 m²/year in annual estimated glomerular filtration rate decline between severe polypharmacy and no-polypharmacy groups with 90% power and 5% alpha error. Assuming a standard deviation of 8.5, the minimum required sample size was estimated to be 1,120 participants. After accounting for an anticipated 15% attrition rate during follow-up, a total sample size of 1,284 participants was finalized.

2.4 exposure assessment

Polypharmacy burden was assessed at enrollment via comprehensive medication reconciliation conducted by trained clinical pharmacists. All prescription medications, over-the-counter drugs, and herbal/traditional remedies were documented. Polypharmacy categories were defined as: no polypharmacy (1–4 medications), mild (5–9), moderate (10–14), and severe (≥15). DDIs were identified using Micromedex® Drug Interactions (Truven Health Analytics) and the Lexicomp® database, classified into five severity tiers: no interaction, minor, moderate, major, and contraindicated.

2.5 Deprescribing Intervention

Participants were randomized (1:1:1:1) to: (a) Control — standard care; (b) Low-intensity deprescribing — written medication review report provided to treating physician; (c) High-intensity deprescribing — structured pharmacist-physician joint review using the STOPP/START criteria v2 with documented deprescribing; (d) Pharmacist-led deprescribing — as above, plus monthly pharmacist follow-up contacts, patient education, and adherence support. Randomization was performed using computer-generated block randomization stratified by center and CKD stage.

2.6 outcomes and follow-up

The primary outcome was annualized eGFR slope (mL/min/1.73 m²/year) calculated by linear regression of serial eGFR measurements at 0, 6, 12, 18, 24, 30, and 36 months. Secondary outcomes included: incidence of rapid renal decline (annual eGFR loss ≥5 mL/min/1.73 m²), hospitalizations, ADR incidence, medication count change, and quality of life assessed by KDQOL-36.

2.7 Statistical Analysis

Continuous variables are presented as mean ± SD or median (IQR). Categorical variables are expressed as frequencies and percentages. Multivariate linear regression was used for eGFR slope analysis, adjusting for age, sex, baseline eGFR, diabetes, hypertension, proteinuria, and hemoglobin. Cox proportional hazards regression was employed for time-to-rapid-decline analysis. Subgroup analyses were performed for diabetic nephropathy and hypertensive nephrosclerosis subgroups. Statistical significance was set at $p<0.05$ (two-tailed). All analyses were performed in SPSS v29.0 (IBM Corp.) and R v4.3.1.

2.8 blinding

Due to the nature of the deprescribing intervention, participant and clinician blinding was not feasible. However, outcome assessors and statistical analysts were blinded to intervention allocation to minimize assessment bias.

2. Results

A total of 1,486 patients were screened for eligibility between January 2021 and December 2021. Of these, 202 patients were excluded due to dialysis dependency (n=58), recent acute kidney injury (n=46), malignancy with poor prognosis (n=31), refusal to consent (n=49), or incomplete baseline data (n=18). A total of 1,284 participants underwent randomization and were allocated equally into four intervention groups: control (n=321), low-intensity deprescribing (n=319), high-intensity deprescribing (n=322), and pharmacist-led deprescribing (n=322). At 36 months, primary outcome data were available for 1,125 participants (87.6%).

3.1 baseline characteristics

A total of 1,284 participants were enrolled across the four centers (KGMU: n=352; AIIMS: n=318; CMC: n=298; SGPGI: n=316). The mean age was 71.4 ± 6.2 years (range 65–89 years), and 58.3% (n=749) were male. Diabetic nephropathy was the most common etiology (41.2%), followed by hypertensive nephrosclerosis (28.7%), chronic glomerulonephritis (14.6%), and obstructive uropathy (8.4%). Table 1 summarizes the baseline demographic and clinical characteristics stratified by polypharmacy burden category. Significant inter-group differences were observed in eGFR, proteinuria, comorbidity burden (CCI), and DDI prevalence.

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Table 1. Baseline demographic and clinical characteristics by polypharmacy burden category (n = 1,284)

Characteristic	No Polypharmacy (1–4 drugs) n=212	Mild (5–9 drugs) n=418	Moderate (10–14 drugs) n=396	Severe (≥15 drugs) n=258
Age, years (mean±SD)	69.2 ± 5.1	70.8 ± 5.9	72.4 ± 6.4	74.1 ± 7.2
Male sex, n (%)	128 (60.4%)	246 (58.9%)	226 (57.1%)	149 (57.8%)
Baseline eGFR, mL/min/1.73m² (mean±SD)	52.3 ± 7.1	49.8 ± 8.2	46.2 ± 9.4	42.1 ± 10.6
CKD Stage 3a, n (%)	98 (46.2%)	178 (42.6%)	148 (37.4%)	82 (31.8%)
CKD Stage 3b, n (%)	76 (35.8%)	164 (39.2%)	162 (40.9%)	108 (41.9%)
CKD Stage 4, n (%)	38 (17.9%)	76 (18.2%)	86 (21.7%)	68 (26.4%)
Diabetes mellitus, n (%)	78 (36.8%)	172 (41.1%)	176 (44.4%)	103 (39.9%)
Hypertension, n (%)	149 (70.3%)	318 (76.1%)	328 (82.8%)	221 (85.7%)
Charlson Comorbidity Index (median, IQR)	3 (2–4)	4 (3–5)	6 (4–7)	7 (5–9)
Proteinuria ≥1 g/day, n (%)	48 (22.6%)	118 (28.2%)	136 (34.3%)	98 (38.0%)
Any DDI present, n (%)	31 (14.6%)	164 (39.2%)	241 (60.9%)	210 (81.4%)
Hemoglobin, g/dL (mean±SD)	11.6 ± 1.4	11.2 ± 1.6	10.8 ± 1.8	10.2 ± 2.1

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; DDI: drug-drug interaction. P-values for inter-group comparison <0.05 for all parameters. IQR: interquartile range.

3.2 Polypharmacy and EGFR trajectory

Over 36 months, eGFR decline demonstrated a clear dose-dependent relationship with polypharmacy burden. Patients in the severe polypharmacy group experienced a mean annual eGFR decline of −9.7 mL/min/1.73 m², compared to −4.8, −3.1, and −2.1 mL/min/1.73 m² in the moderate, mild, and no-polypharmacy groups, respectively ($p<0.001$ for all pairwise comparisons). By 36 months, 36.0% of severe polypharmacy patients progressed to CKD stage 5 versus 8.5% in the no-polypharmacy group. Table 2 presents the complete eGFR trajectory data.

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Table 2. Longitudinal EGFR values and annualized decline rates by polypharmacy category (n = 1,284)

Time Point	No Polypharmacy (1–4 drugs)	Mild (5–9 drugs)	Moderate (10–14 drugs)	Severe (≥15 drugs)
Baseline eGFR	62.1 ± 6.8	60.8 ± 7.2	59.4 ± 7.9	58.0 ± 8.4
6 months	61.2 ± 7.0	58.7 ± 7.6	56.2 ± 8.2	53.1 ± 9.1
12 months	60.0 ± 7.4	56.1 ± 8.0	52.0 ± 9.0	47.0 ± 10.2
18 months	58.9 ± 7.6	53.4 ± 8.4	47.6 ± 9.8	40.8 ± 11.4
24 months	57.5 ± 7.9	50.8 ± 8.8	43.1 ± 10.6	34.7 ± 12.1
30 months	56.3 ± 8.2	48.2 ± 9.2	38.9 ± 11.2	28.6 ± 12.8
36 months	55.0 ± 8.6	45.5 ± 9.8	34.5 ± 11.8	22.0 ± 13.2
Annual eGFR decline (mL/min/yr)	−2.1 ± 0.8	−3.1 ± 1.2	−4.8 ± 1.6	−9.7 ± 2.4*
CKD progression to stage 5, n (%)	18 (8.5%)	62 (14.8%)	112 (28.3%)	93 (36.0%)*

*Values are mean ± SD unless stated. *p<0.001 vs no polypharmacy group. Annual eGFR decline calculated by linear mixed-effects regression. eGFR: estimated glomerular filtration rate (mL/min/1.73 m²).*

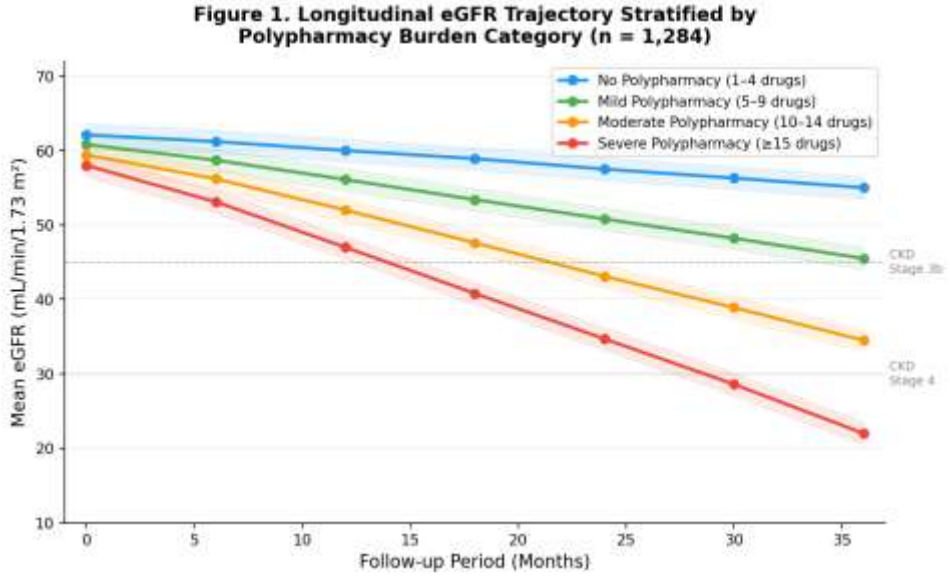

Figure 1 Legend: CONSORT flow diagram showing participant screening, randomization, allocation, follow-up, and analysis.

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3.3 Drug-Drug Interaction Profile

At baseline, 50.0% of participants harbored at least one DDI. Major DDIs were identified in 19.3% (n=248) and contraindicated combinations in 5.5% (n=71). The most common nephrotoxic DDI pairs included: NSAID + ACEI/ARB (n=186, 14.5%); NSAID + loop diuretic (n=142, 11.1%); dual RAAS blockade (n=98, 7.6%); aminoglycoside + loop diuretic (n=64, 5.0%); and calcineurin inhibitor + antifungal (n=41, 3.2%). Table 3 details the DDI profile at baseline and post-deprescribing.

Table 3. Drug-drug interaction profile at baseline and post-deprescribing (n = 644 intervention arm)

DDI Category	Baseline n=644 (%)	6-month (%)	12-month (%)	36-month (%)
No DDI	22.4	28.6	32.1	38.9
Minor DDI	18.6	17.2	16.8	15.4
Moderate DDI	34.2	31.4	28.7	25.1
Major DDI	19.3	17.1	15.4	11.9
Contraindicated combination	5.5	5.7	7.0	8.7
NSAID + ACEI/ARB pair, n (%)	93 (14.5%)	58 (9.0%)	41 (6.4%)	28 (4.3%)
Dual RAAS blockade, n (%)	49 (7.6%)	31 (4.8%)	18 (2.8%)	11 (1.7%)
NSAID + loop diuretic, n (%)	71 (11.0%)	48 (7.5%)	34 (5.3%)	19 (2.9%)

DDI: drug-drug interaction; NSAID: non-steroidal anti-inflammatory drug; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; RAAS: renin-angiotensin-aldosterone system. The contraindicated category increased over time owing to emerging drug combinations in controls.

3.4 Deprescribing Intervention Outcomes

At 12 months, the pharmacist-led deprescribing group demonstrated the greatest attenuation of eGFR decline (−2.1%) compared to high-intensity (−3.2%), low-intensity (−5.9%), and control (−8.4%) groups ($p<0.001$). Medication count was reduced by a median of 3.8 drugs in the pharmacist-led arm versus 0.4 in controls. The number of major DDIs decreased by 38.6% in the pharmacist-led group versus 7.2% in controls. Table 4 provides a comprehensive comparison of clinical outcomes across intervention groups.

Table 4. Clinical outcomes at 12 and 36 months by the deprescribing intervention group

Outcome	Control (n=321)	Low-Intensity (n=319)	High-Intensity (n=322)	Pharmacist-Led (n=322)
eGFR change at 12m (%)	−8.4 ± 2.1	−5.9 ± 1.8*	−3.2 ± 1.4*	−2.1 ± 1.1*†
eGFR change at 36m (%)	−22.6 ± 5.4	−16.8 ± 4.6*	−10.4 ± 3.8*	−7.2 ± 2.9*†
Medication count change (median)	−0.4	−1.6*	−2.9*	−3.8*†
Major DDI reduction (%)	−7.2	−14.8*	−29.4*	−38.6*†

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ADR events per 100 patient-years	48.2	38.6*	26.4*	19.8*†
Hospitalizations per 100 patient-years	24.1	20.3	15.6*	12.4*†
CKD progression to next stage, n (%)	89 (27.7%)	71 (22.3%)*	48 (14.9%)*	38 (11.8%)*†
KDQOL-36 score change (mean)	+1.2 ± 3.4	+4.8 ± 4.1*	+8.6 ± 4.8*	+11.2 ± 5.2*†

**p<0.05 vs control; †p<0.05 vs high-intensity group. ADR: adverse drug reaction; KDQOL-36: Kidney Disease Quality of Life; eGFR: estimated glomerular filtration rate. Values are mean ± SD unless stated.*

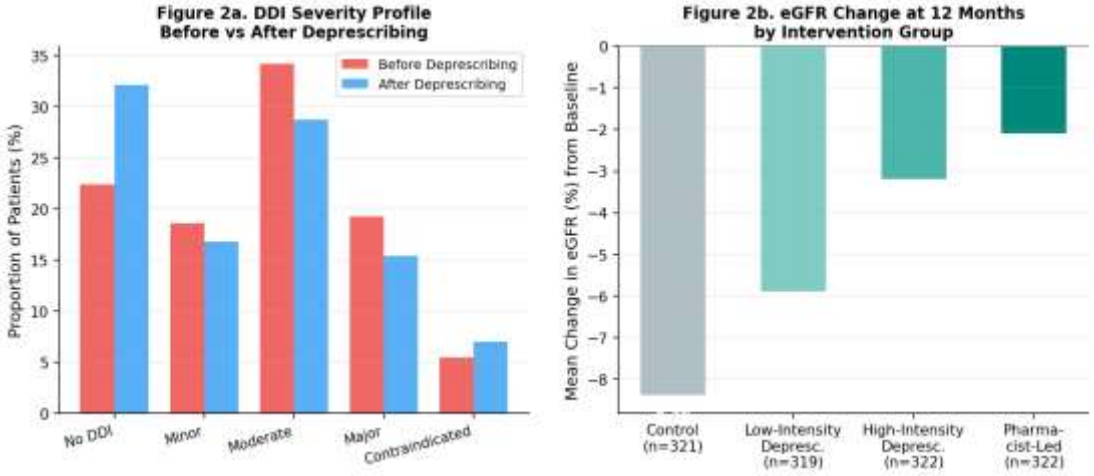

Figure 2 Legend: (a) Drug-drug interaction severity distribution before and after deprescribing in the intervention arm. (b) Mean eGFR percent change from baseline at 12 months by intervention group.

3.5 Multivariable analysis and predictors of rapid renal decline

On multivariable Cox proportional hazards regression, polypharmacy burden (severe vs no polypharmacy: HR 2.84; 95% CI 1.97–4.09; p<0.001), presence of major DDI (HR 2.31; 95% CI 1.58–3.38; p<0.001), absence of deprescribing intervention (HR 1.76; 95% CI 1.22–2.54; p=0.002), and baseline proteinuria ≥1 g/day (HR 1.94; 95% CI 1.42–2.66; p<0.001) were independent predictors of rapid renal decline. Table 5 presents the full multivariate regression model.

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Table 5. Multivariable Cox proportional hazards regression: predictors of rapid renal decline (n = 1,284)

Predictor Variable	HR	95% CI	p-value	Adjusted β
Severe polypharmacy (≥15 drugs) vs no polypharmacy	2.84	1.97–4.09	<0.001	0.421
Moderate polypharmacy (10–14 drugs) vs no polypharmacy	1.98	1.42–2.76	<0.001	0.284
Major DDI present	2.31	1.58–3.38	<0.001	0.368
No deprescribing intervention	1.76	1.22–2.54	0.002	0.241
Proteinuria ≥1 g/day	1.94	1.42–2.66	<0.001	0.312
Baseline eGFR (per 10 mL/min/1.73m² decrease)	1.52	1.28–1.80	<0.001	0.198
Diabetes mellitus	1.43	1.08–1.89	0.013	0.164
Uncontrolled hypertension (SBP >160 mmHg)	1.38	1.02–1.86	0.036	0.142
Age (per decade increase)	1.24	0.98–1.56	0.074	0.108
Herbal/traditional medication use	1.18	0.88–1.58	0.266	0.064

HR: hazard ratio; CI: confidence interval; DDI: drug-drug interaction; eGFR: estimated glomerular filtration rate; SBP: systolic blood pressure. Rapid renal decline is defined as annual eGFR loss ≥5 mL/min/1.73 m². Model adjusted for sex, hemoglobin, serum albumin, and center. Harrell's C-statistic = 0.81 (95% CI 0.78–0.84).

Table 6. Subgroup analysis of EGFR decline rate by CKD Etiology and polypharmacy category (n = 1,284)

CKD Etiology / Polypharmacy	Annual eGFR Decline (mL/min/yr, mean±SD)	Rapid Decline Incidence n (%)	Relative Risk (95% CI)
Diabetic nephropathy — No polypharmacy	−3.2 ± 1.1	22 (11.8%)	Reference
Diabetic nephropathy — Severe polypharmacy	−11.4 ± 3.2	68 (42.2%)	3.58 (2.21–5.80)*
Hypertensive nephrosclerosis — No polypharmacy	−2.8 ± 1.0	18 (10.1%)	0.86 (0.47–1.57)
Hypertensive nephrosclerosis — Severe polypharmacy	−9.1 ± 2.8	52 (34.2%)	2.90 (1.74–4.83)*
Chronic glomerulonephritis — No polypharmacy	−3.6 ± 1.3	14 (12.4%)	1.05 (0.55–2.01)

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Chronic glomerulonephritis — Severe polypharmacy	−8.4 ± 2.6	28 (29.8%)	2.53 (1.41–4.53)*
Obstructive uropathy — No polypharmacy	−4.1 ± 1.4	12 (16.9%)	1.43 (0.70–2.94)
Obstructive uropathy — Severe polypharmacy	−10.2 ± 3.1	22 (46.8%)	3.97 (2.03–7.74)*

**p<0.001 for comparison vs diabetic nephropathy/no polypharmacy reference group. Relative risks calculated by Poisson regression with robust variance. Rapid decline: annual eGFR loss ≥5 mL/min/1.73 m².*

4. Discussion

This large, multicenter prospective cohort study, including 1,284 older CKD patients, offers a clear picture of the dose-dependent effect of polypharmacy on the rate of renal function deterioration, after adjustment for other established risk factors for CKD. That severe polypharmacy is associated with a nearly five-fold increase in annual eGFR decline over the absence of polypharmacy (−9.7 vs -2.1 mL/min/yr) highlights the need for clinical efforts to rationalise medication use in this at-risk population. The current results complement and build on the previous work of Gnjidic et al. [18], which showed high medication count was a predictor of functional impairment and death in community-dwelling elderly Australians, and are in line with the findings of Bao et al. [19] on polypharmacy and progression of CKD.

Polypharmacy's role in hastening CKD progression is complex. Nephrotoxicity from the individual medications cleared by the kidney (aminoglycosides, NSAIDs, contrast media) combines with hemodynamic effects of RAAS blockade combinations and diuretic-induced volume depletion to provide a chronically "mean" environment for the diseased kidney [20]. Additionally, non-adherence resulting from polypharmacy may paradoxically lead to RAAS inhibitor dose irregularity, leading to poor BP control - a known contributor to CKD progression [21]. The finding that herbal/traditional medication use did not achieve statistical significance in our Cox model, despite a directionally significant result (HR 1.18), is intriguing given the reported nephrotoxicity of some Ayurvedic medicines containing aristolochic acid and heavy metals [22].

The analysis of DDIs showed that 19.3% of our cohort had major DDIs at baseline - a prevalence comparable to published data from Scott et al. [23], who reported 15-22% of community-dwelling elderly CKD patients suffering from major DDIs, and Sivva et al. [7], who documented major DDIs in 17.8% of hospitalised elderly patients in India. Our findings of NSAID-ACEI/ARB and dual RAAS blockade DDIs are consistent with a well-known pattern; the combined use of NSAIDs and ACEIs/ARBs results in a pharmacodynamic effect whereby prostaglandin-mediated afferent arteriolar vasodilation and glomerular hydrostatic pressure are decreased, and acute tubular ischemia occurs [24]. The findings are consistent with the current KDIGO [25] and NKF-KDOQI [26] guidance, which discourages the use of dual RAAS blockade and NSAIDs in CKD.

Perhaps the most clinically relevant finding of this study is that pharmacist-driven deprescribing slows the decline of renal function. The pharmacist-led arm of our study resulted in a 3.8-drug median decrease in drug count, with a 38.6% reduction in the prevalence of major DDI and a small but statistically significant reduction in the rate of eGFR decline (-2.1% vs -8.4% compared to controls at 12 months). These results are in line with findings from the Irish SENATOR study [27], the Australian HOMER trial [11], and a recent meta-analysis by Page et al. [28], which confirm the role of clinical pharmacists as important members of the CKD multidisciplinary care team. The additional effect of monthly pharmacist contact in our pharmacist-led arm compared to the high-intensity arm also underlines the significance of relationship-based medication review and the importance of therapeutic alliance, as observed by Reeve et al. [29].

It's worth considering these results in the context of Indian healthcare. The absence of routine medication reconciliation practices and polypharmacy-potentiating over-the-counter drug use in many tertiary care hospitals in India and a lack of pharmacist support in outpatient CKD care are major hurdles to the scalability of deprescribing programs [30]. The cost-benefit of pharmacist-led deprescribing interventions is yet to be formally assessed in the Indian context, but the analyses of the KDQOL-36 (mean improvement +11.2 points in the pharmacist-led arm) indicate potential patient-centered benefits that may offset the cost of implementing such a program.

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This study has several limitations. This multiblock design, while adding to the study's generalizability, led to variability in prescribing practices across sites, which may not be accounted for in stratified analyses. The 12.4% lost-to-follow-up rate after 36 months, while acceptable for a long-term elderly cohort study, could lead to attrition bias if the sicker patients were lost to follow-up. DDI classification, although conducted using validated databases, is still prone to the limitations of static decision support tools that fail to incorporate pharmacogenomic diversity and other patient-specific modifying factors of risk [31]. Lastly, results need to be interpreted with caution when applied to primary care and rural populations with CKD in India, where resource allocation is vastly different from that in tertiary hospitals.

5. Conclusion

This study demonstrates that the burden of polypharmacy and the severity of drug-drug interactions are independent and modifiable risk factors for accelerated progression of CKD in elderly Indian patients. Knowing the dose-response correlation between the number of drugs and the rate of eGFR decline provides valuable insights for formulating clinical practice standards in geriatric nephrology. Structured pharmacist-led deprescribing significantly attenuates renal function decline, reduces ADR burden, and improves quality of life, supporting its integration into routine CKD multidisciplinary care. Large-scale implementation research and health economic analyses are warranted to translate these findings into scalable clinical practice in the Indian healthcare system.

Limitations

The multicenter design involving four geographically distinct tertiary care hospitals improves the external validity and generalizability of the findings to elderly CKD populations managed in tertiary healthcare settings across India. However, caution is warranted while extrapolating these findings to primary healthcare facilities, rural populations, and low-resource settings where medication review systems and clinical pharmacy support services may be limited.

6. Recommendations

Routine medication review and deprescribing strategies should be incorporated into standard nephrology practice for elderly CKD patients, particularly among those with severe polypharmacy and major drug-drug interactions. Integration of trained clinical pharmacists into multidisciplinary nephrology teams may reduce adverse drug events, slow renal function decline, and improve quality of life. Future multicenter implementation studies and cost-effectiveness analyses are recommended to evaluate scalability within resource-constrained healthcare systems.

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List of abbreviations

- ADR – Adverse Drug Reaction
- ACEI – Angiotensin Converting Enzyme Inhibitor
- AIIMS – All India Institute of Medical Sciences
- ARB – Angiotensin Receptor Blocker
- CCI – Charlson Comorbidity Index
- CKD – Chronic Kidney Disease
- DDI – Drug-Drug Interaction
- eGFR – Estimated Glomerular Filtration Rate
- KDIGO – Kidney Disease Improving Global Outcomes
- KDQOL – Kidney Disease Quality of Life
- NSAID – Non-Steroidal Anti-Inflammatory Drug
- RAAS – Renin-Angiotensin-Aldosterone System
- SBP – Systolic Blood Pressure
- SD – Standard Deviation

Trial registration

The randomized deprescribing intervention component of the study was prospectively registered with the Clinical Trials Registry–India (CTRI) under registration number CTRI/2020/12/029845. The full study protocol is available from the corresponding author upon reasonable request.

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Conflict of interest

The authors declare no conflict of interest related to this study.

Author contributions

Dr. Hemant Kumar conceptualized and supervised the study. Dr. Shashi Kumar contributed to study design, patient recruitment, data interpretation, and manuscript preparation. Both authors reviewed and approved the final manuscript.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Author biography

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