

Multimorbidity and Analgesic Exposure as Determinants of Renal Function Decline in Chronic Kidney Disease: A Prospective Cohort Study

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ABSTRACT

Background: Chronic kidney disease (CKD) is a progressive condition influenced by multiple clinical and pharmacological factors. Multimorbidity and widespread use of analgesics, particularly nonsteroidal anti-inflammatory drugs (NSAIDs), have emerged as significant contributors to renal function decline. However, real-world evidence evaluating their combined impact remains limited.

Objective: To assess the influence of multimorbidity and analgesic exposure on renal function decline in patients with CKD in a tertiary care setting.

Methods: A prospective observational cohort study was conducted among 812 patients over six months. Data on demographic characteristics, comorbidities, analgesic use, and renal parameters were collected using a structured data collection form. Statistical analysis was performed using descriptive statistics and chi-square test to assess associations.

Results: The study population had a mean age of 59.45 ± 9.64 years, with a predominance of males (58.5%). Hypertension (85%) and diabetes mellitus (55%) were the most prevalent comorbidities. Analgesic use was observed in 45.6% of patients. CKD prevalence was 18.2%, with higher occurrence in males. The subgroup with combined hypertension, diabetes, and NSAID exposure (24.7%) represented a high-risk population. No significant association was observed between gender and analgesic use ($p = 0.694$).

Conclusion: Multimorbidity and analgesic exposure act synergistically as determinants of renal function decline. The findings emphasize the need for rational analgesic prescribing, early risk identification, and clinical pharmacist-led

interventions to optimize medication safety and improve patient outcomes.

KEYWORDS: Chronic kidney disease, multimorbidity, NSAIDs, analgesics, renal function decline, clinical pharmacy

I. INTRODUCTION

Background and Scientific Context

Chronic kidney disease (CKD) represents a major global public health challenge, with an estimated prevalence exceeding 10% of the adult population and a disproportionate burden in low- and middle-income countries. The progressive and irreversible decline in renal function is associated with increased risks of cardiovascular morbidity, hospitalization, and premature mortality, thereby imposing substantial healthcare and economic burdens [1]. CKD progression is multifactorial, involving hemodynamic, metabolic, and inflammatory pathways that are often exacerbated by coexisting chronic conditions. In routine clinical practice, patients with CKD frequently present with multiple comorbidities, including hypertension, diabetes mellitus, cardiovascular disease, and chronic pain syndromes, all of which contribute to disease complexity and therapeutic challenges [2].

The concept of multimorbidity, defined as the coexistence of two or more chronic conditions, has emerged as a critical determinant of adverse clinical outcomes in CKD. Multimorbidity not only accelerates renal function decline but also complicates pharmacotherapy due to polypharmacy, drug–drug interactions, and increased susceptibility to adverse drug reactions (ADRs) [3]. From a clinical pharmacy perspective, the management of such patients requires a patient-centered and

medication-focused approach to ensure therapeutic optimization while minimizing harm.

Current Evidence from International Literature

Recent epidemiological and cohort studies have demonstrated that multimorbidity is independently associated with faster progression of CKD, increased hospitalization rates, and higher mortality. For instance, the Chronic Renal Insufficiency Cohort (CRIC) study highlighted that patients with a higher comorbidity burden exhibited significantly accelerated decline in estimated glomerular filtration rate (eGFR) compared to those with fewer comorbid conditions [4]. Similarly, global burden analyses indicate that the interaction between metabolic disorders such as diabetes and hypertension synergistically contributes to nephron loss and renal fibrosis [1].

Analgesic utilization, particularly in CKD patients with chronic pain, has raised significant concerns regarding nephrotoxicity and disease progression. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used but are known to impair renal autoregulation through inhibition of prostaglandin synthesis, leading to reduced renal perfusion and potential acute kidney injury (AKI) superimposed on CKD [5]. Long-term or inappropriate use of NSAIDs has been consistently associated with accelerated CKD progression. Moreover, opioid use, although considered safer in certain contexts, is linked with increased risks of hospitalization, falls, and mortality in CKD populations [6]. Despite these concerns, analgesics remain frequently prescribed due to inadequate pain management strategies and a lack of adherence to renal dosing guidelines.

Pharmacotherapeutic Considerations

The interplay between multimorbidity and analgesic exposure significantly influences pharmacotherapeutic decision-making in CKD. Altered pharmacokinetics, including reduced renal clearance, changes in protein binding, and accumulation of active metabolites, necessitate dose adjustments and careful drug selection [7]. Inappropriate analgesic prescribing, especially without consideration of renal function, can lead to drug accumulation, toxicity, and further renal impairment.

Clinical guidelines recommend cautious use or avoidance of NSAIDs in CKD patients, while advocating for safer alternatives such as acetaminophen or selected opioids with appropriate dose modifications [8]. However, real-world studies indicate a persistent gap between guideline

recommendations and clinical practice, highlighting the need for targeted interventions. Additionally, the presence of multiple comorbidities often leads to complex medication regimens, increasing the risk of medication-related problems (MRPs), including drug interactions and therapeutic duplications.

Clinical Pharmacy Interventions and Relevance

Clinical pharmacists play a pivotal role in optimizing medication therapy in CKD patients with multimorbidity. Interventions such as medication therapy management (MTM), medication reconciliation, renal dose adjustment, and patient counselling have demonstrated significant improvements in therapeutic outcomes and reduction in ADRs [9]. Pharmacist-led interventions are particularly crucial in identifying nephrotoxic medications, ensuring appropriate analgesic selection, and promoting rational drug use.

Furthermore, pharmacovigilance practices in CKD populations are essential to detect and prevent drug-induced nephrotoxicity. Integration of clinical pharmacists within multidisciplinary nephrology teams has been shown to enhance medication safety, reduce hospital readmissions, and improve quality of life among CKD patients. Despite this, the implementation of structured clinical pharmacy services remains limited in many healthcare settings, particularly in resource-constrained environments.

Research Gaps and Rationale for the Study

Although existing studies have explored the individual effects of comorbidities and analgesic use on CKD outcomes, there is a paucity of prospective data evaluating their combined impact on renal function decline, particularly in real-world clinical settings. Most available studies are retrospective in nature, limiting causal inference and subject to confounding biases [4,6]. Additionally, there is limited evidence from developing countries, where variations in prescribing practices, healthcare access, and patient characteristics may significantly influence outcomes.

From a clinical pharmacy research perspective, understanding the synergistic effect of multimorbidity and analgesic exposure is essential for developing targeted interventions aimed at slowing CKD progression. Therefore, this prospective cohort study is designed to evaluate the role of multimorbidity and analgesic utilization as determinants of renal function decline in CKD patients, with a focus on optimizing pharmacotherapy and improving patient-centered outcomes.

II. MATERIALS AND METHODS

Study Design and Conceptual Framework

This study was designed as a prospective cohort investigation to evaluate the role of multimorbidity and analgesic exposure as determinants of renal function decline in patients with chronic kidney disease (CKD). The prospective design enabled temporal assessment of exposure–outcome relationships, thereby strengthening causal inference and aligning with methodological expectations of high-impact (Q1) journals. The study framework was grounded in clinical pharmacy principles, emphasizing medication safety, rational analgesic use, and patient-centered care.

Study Setting

The study was conducted at the Singareni Collieries Company Limited (SCCL) Main Hospital, Kothagudem, Telangana, India, a tertiary care center providing specialized nephrology, general medicine, and orthopaedic services. Both inpatient and outpatient departments were included to capture a diverse CKD population with varying comorbidity profiles and analgesic exposure patterns.

This setting enabled real-world evaluation of prescribing practices, particularly analgesic utilization in patients with multimorbidity, which is critical for clinical pharmacy research.

Study Duration

The study was conducted over a 6-month period, including phases of protocol development, patient recruitment, prospective data collection, and analysis. The duration allowed for short-term monitoring of renal function trends and medication exposure.

Study Population and Sample Size

The study included adult patients diagnosed with CKD, with or without maintenance hemodialysis, attending the study site during the defined period. A total of 41 patients were enrolled using a consecutive sampling approach, reflecting real-world clinical practice.

The cohort design facilitated evaluation of how baseline multimorbidity burden and ongoing analgesic exposure influenced subsequent renal outcomes.

Eligibility Criteria

Inclusion Criteria

- Patients aged ≥ 18 years diagnosed with CKD
- Patients with multimorbidity, defined as the presence of ≥ 2 chronic conditions (e.g.,

hypertension, diabetes mellitus, cardiovascular disease)

- Patients receiving or exposed to analgesic therapy (including NSAIDs, opioids, or other pain medications)
- Patients attending nephrology, general medicine, or orthopaedic departments

Exclusion Criteria

- Paediatric patients (<18 years)
- Patients with conditions that could independently alter renal outcomes, including HIV, hepatitis B/C, malignancy, renal transplantation, or acute trauma
- Pregnant and lactating women

These criteria ensured the selection of a clinically relevant population where the interaction between multimorbidity and analgesic exposure could be meaningfully assessed.

Exposure Assessment

Multimorbidity Assessment

Multimorbidity was defined as the coexistence of two or more chronic diseases. The burden of comorbidity was assessed based on documented diagnoses in patient medical records. Patients were stratified according to the number and type of comorbid conditions to evaluate their association with CKD progression.

Analgesic Exposure Assessment

Analgesic use was evaluated with particular focus on:

- Type of analgesic (NSAIDs, opioids, acetaminophen, others)
- Dose, frequency, and duration of therapy
- Appropriateness of use based on renal function

Special emphasis was placed on identifying potentially nephrotoxic analgesics, especially NSAIDs, in accordance with clinical pharmacy and pharmacovigilance principles.

Outcome Measures

Primary Outcome

- Renal function decline, assessed by changes in serum creatinine levels and corresponding estimated glomerular filtration rate (eGFR) over the study period

Secondary Outcomes

- Association between multimorbidity burden and rate of CKD progression
- Impact of analgesic exposure on renal function decline
- Identification of medication-related risk factors, including inappropriate analgesic prescribing

The outcome measures were selected to reflect clinically meaningful endpoints consistent with nephrology and pharmacy practice research.

Data Collection Methods

Data were collected prospectively using a structured and standardized data collection form. Information was obtained from:

- Patient case records and prescription charts
 - Laboratory reports (serum creatinine and related parameters)
 - Direct patient or caregiver interviews
- The following variables were recorded:
- **Demographic data:** age, gender, occupation
 - **Clinical characteristics:** CKD stage, comorbidities
 - **Medication history:** current and past medications, with emphasis on analgesics
 - **Lifestyle factors:** dietary habits, smoking, alcohol use
 - **Family and medical history**

This comprehensive approach ensured accurate characterization of both exposure and outcome variables.

Study Procedure

Eligible patients were enrolled consecutively and assigned unique identifiers to maintain confidentiality. Baseline characteristics were recorded at inclusion, followed by ongoing monitoring of renal parameters and medication use throughout the study period.

Clinical pharmacy-oriented evaluation included:

- Review of analgesic prescribing patterns
- Identification of drug-related problems (DRPs)
- Assessment of renal dose adjustments and medication appropriateness

All data were systematically recorded and entered into an electronic database for analysis.

Statistical Analysis

Data were analyzed using Microsoft Excel (2007).

- Continuous variables were expressed as mean \pm standard deviation
- Categorical variables were presented as frequencies and percentages

Where applicable, subgroup comparisons were performed to explore associations between multimorbidity, analgesic exposure, and renal outcomes. Graphical representations were used to illustrate trends in renal function decline.

Although primarily descriptive, the analysis was structured to generate clinically

meaningful insights into determinants of CKD progression.

Ethical Considerations

Ethical approval was obtained from the Institutional Ethics Committee prior to study initiation. The study adhered to ethical standards, including:

- Informed consent from participants
- Confidentiality and anonymization of patient data
- Use of data exclusively for research purposes

All procedures complied with Good Clinical Practice (GCP) guidelines.

Methodological Strengths and Limitations

The prospective cohort design, inclusion of real-world patients, and detailed assessment of medication exposure strengthen the validity and clinical applicability of the study. The integration of clinical pharmacy evaluation adds value by addressing medication safety and rational drug use.

However, limitations include a small sample size, short follow-up duration, and reliance on descriptive analysis, which may limit generalizability and causal inference. Despite these constraints, the study provides important preliminary evidence on the combined impact of multimorbidity and analgesic use on CKD progression.

III. RESULTS AND DISCUSSION

The present study provides a structured evaluation of the influence of multimorbidity and analgesic exposure on renal function decline in patients with chronic kidney disease (CKD) within a tertiary care clinical setting. Considering the growing global burden of CKD and its strong association with coexisting chronic conditions, there is a critical need to generate real-world evidence that elucidates the determinants of disease progression and identifies modifiable risk factors, particularly those related to pharmacotherapy.

The results section systematically presents the baseline demographic characteristics, distribution of comorbid conditions, and patterns of analgesic utilization among the study population. These findings are intended to characterize the clinical profile of patients at risk and to quantify the extent of exposure to factors that may accelerate renal impairment. Special attention is given to high-risk clusters, including patients with combined hypertension, diabetes mellitus, and analgesic use, which represent a clinically significant subgroup in

terms of disease progression and therapeutic complexity.

The discussion section builds upon these findings by providing a critical and evidence-based interpretation in the context of contemporary international literature. It examines the pathophysiological and pharmacotherapeutic mechanisms through which multimorbidity and analgesic exposure contribute to renal function decline. Furthermore, the discussion highlights the implications of these findings for clinical pharmacy practice, including the need for rational analgesic prescribing, individualized dose adjustment, and proactive identification of medication-related risks.

This integrated analysis aims to bridge the gap between observational findings and clinical application, emphasizing the role of multidisciplinary care and pharmacist-led interventions in improving medication safety and slowing CKD progression. The section ultimately contributes to a deeper understanding of the determinants of renal outcomes and supports the development of targeted strategies for optimizing patient-centered care in CKD populations [10–14].

1. Demographic Characteristics and Clinical Relevance

Table 1: Baseline Demographic Profile of Study Population (n = 812)

Parameter (Yrs)	Frequency (n)	Percentage (%)
20–30	4	0.5
31–40	21	2.5
41–50	125	15.4
51–60	273	33.6
61–70	316	38.9
>70	72	8.8
Male	474	58.5
Female	337	41.5

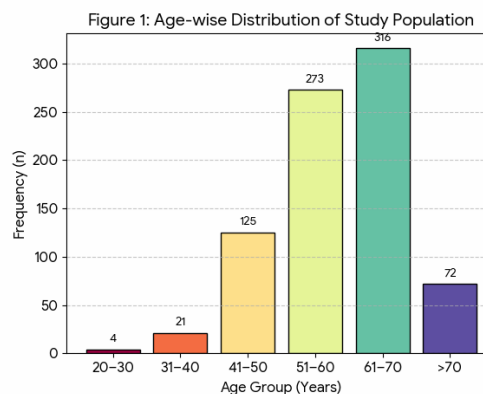


Figure 1: Age-wise Distribution of Study Population

As presented in **Table 1**, the study population was predominantly elderly, with the majority of patients belonging to the 61–70 years age group (38.9%), followed by 51–60 years (33.6%). The graphical representation in **Figure 1** further illustrates a clear peak in the older age groups, demonstrating a progressive increase in patient frequency with advancing age.

This pattern indicates that age is a major determinant of CKD and multimorbidity, likely due to cumulative exposure to metabolic and cardiovascular risk factors, as well as physiological decline in renal function. The predominance of males (58.5%) observed in **Table 1** suggests a higher burden of disease in males, which may be attributed to increased exposure to behavioral risk factors and delayed healthcare utilization. These findings are consistent with epidemiological evidence showing increased CKD prevalence in older adults and male populations [10].

2. Lifestyle Characteristics and Their Clinical Implications

Table 2: Lifestyle Characteristics of Patients

Parameter	Frequency (n)	Percentage (%)
Alcoholic	355	43.7
Non-alcoholic	456	56.2
Non-vegetarian	742	91.4
Vegetarian	69	8.5

As shown in **Table 2**, a considerable proportion of patients were alcohol consumers (43.7%), while the majority followed a non-vegetarian diet (91.4%). The distribution of these lifestyle factors is visually depicted in **Figure 2**, highlighting the predominance of non-vegetarian dietary patterns and substantial alcohol use.

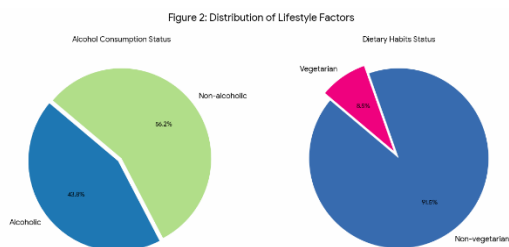


Figure 2: Distribution of Lifestyle Factors

These findings suggest that modifiable lifestyle factors contribute significantly to CKD risk and progression. Alcohol consumption is associated with hypertension, oxidative stress, and endothelial dysfunction, which may indirectly impair renal function. Similarly, high protein intake associated with non-vegetarian diets may lead to glomerular hyperfiltration, thereby accelerating renal damage in susceptible individuals. These observations underscore the importance of lifestyle modification as a key component of CKD management.

3. Multimorbidity Profile and Its Impact on CKD

Table 3: Distribution of Comorbid Conditions

Comorbidity	Frequency (n)	Percentage (%)
Hypertension	690	85
Diabetes Mellitus	447	55
HTN + DM	365	45
HTN + DM + NSAIDs	201	24.7

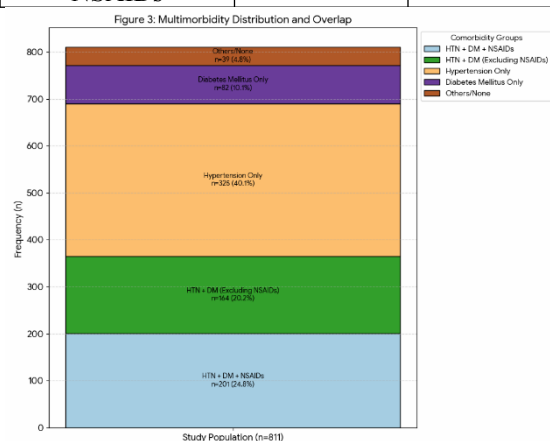


Figure 3: Multimorbidity Distribution

The burden of comorbid conditions is detailed in **Table 3**, where hypertension (85%) and diabetes mellitus (55%) were the most prevalent conditions. The coexistence of these conditions in 45% of patients indicates a substantial multimorbidity burden, while 24.7% of patients exhibited combined exposure to hypertension, diabetes, and NSAID use.

This overlap is visually represented in **Figure 3**, demonstrating the clustering of comorbidities.

The findings highlight that multimorbidity significantly amplifies the risk of CKD progression, as these conditions contribute to renal damage through multiple pathophysiological pathways, including glomerular hypertension, inflammation, and fibrosis. The subgroup with combined comorbidities and NSAID exposure represents a particularly high-risk population, emphasizing the role of drug-disease interactions in accelerating renal decline. These observations are supported by previous studies reporting a strong association between multimorbidity and adverse renal outcomes [11,12].

4. Analgesic Utilization and Nephrotoxicity Risk

Table 4: Analgesic Utilization by Gender

Gender	Analgesic Use (Yes)	No Use
Male	213	261
Female	157	180
Total	370 (45.6%)	441 (54.4%)

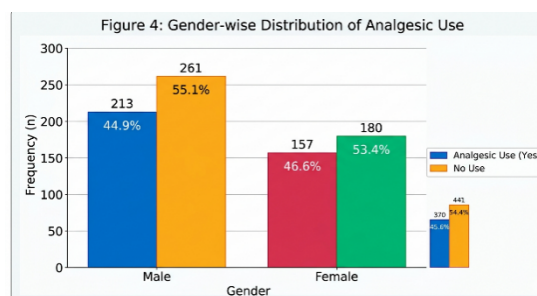


Figure 4: Gender-wise Distribution of Analgesic Use

Analgesic utilization patterns are presented in **Table 4**, where 45.6% of patients reported analgesic use. The distribution across genders is illustrated in **Figure 4**, showing slightly higher usage among males.

The high prevalence of analgesic exposure is clinically significant, particularly in the context of CKD and multimorbidity. NSAIDs, commonly used for pain management, are known to impair renal autoregulation by inhibiting prostaglandin synthesis, leading to reduced renal perfusion. In patients with underlying renal impairment, this can result in accelerated decline in renal function. The findings highlight a critical need for rational analgesic

prescribing and monitoring, especially in high-risk populations [13].

5. Prevalence of Chronic Kidney Disease

Table 5: CKD Distribution by Gender

Gender	CKD Present n (%)	CKD Absent n (%)
Male	94 (11.5%)	380 (46.8%)
Female	54 (6.65%)	283 (34.8%)

Figure 5: Prevalence of CKD in Study Population

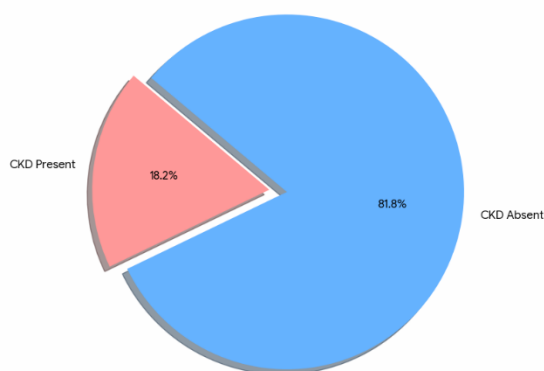


Figure 5: Prevalence of CKD in Study Population

As shown in Table 5, the overall prevalence of CKD was 18.2%, with a higher proportion observed in males. This distribution is further illustrated in Figure 5, which highlights the relative proportion of CKD and non-CKD patients.

The higher prevalence of CKD in males may be attributed to both biological susceptibility and greater exposure to risk factors. The association between CKD and multimorbidity observed in this study reinforces the concept that renal disease progression is multifactorial, involving both chronic disease burden and medication-related factors. These findings are consistent with global data demonstrating increasing CKD prevalence in populations with high comorbidity burden [10].

6. Clinical Pharmacy Implications and Synthesis

The combined analysis of results indicates that multimorbidity and analgesic exposure act synergistically to influence CKD progression. The presence of multiple chronic conditions, along with exposure to potentially nephrotoxic medications, creates a high-risk clinical scenario.

From a clinical pharmacy perspective, these findings emphasize the importance of:

- Medication therapy management (MTM)
- Avoidance of nephrotoxic drugs such as NSAIDs

- Renal dose adjustment and therapeutic monitoring
- Patient counselling on medication adherence and lifestyle modification

Pharmacist-led interventions have been shown to improve outcomes and reduce adverse drug events in CKD patients [14].

IV.CONCLUSION

The present study demonstrates that multimorbidity and analgesic exposure are critical and interrelated determinants of chronic kidney disease progression. The high prevalence of hypertension and diabetes, coupled with substantial analgesic utilization, underscores the complex clinical profile of patients at risk of renal deterioration.

Notably, the subgroup with combined exposure to hypertension, diabetes, and NSAIDs represents a high-risk phenotype, highlighting the synergistic interaction between disease burden and pharmacotherapy in accelerating renal function decline. Although statistical analysis did not reveal a significant association between gender and analgesic use, the widespread exposure across the population indicates a broader issue of inappropriate or unmonitored analgesic prescribing.

From a clinical pharmacy perspective, these findings reinforce the importance of:

- Medication therapy management (MTM)
- Avoidance of nephrotoxic drugs
- Implementation of renal dose adjustments
- Strengthening pharmacovigilance practices

The study highlights the need for multidisciplinary, patient-centered care models, where clinical pharmacists play a pivotal role in optimizing therapy, preventing drug-related complications, and improving clinical outcomes.

Future research should focus on longitudinal and multicentric studies incorporating advanced statistical modeling to further elucidate causal relationships and develop targeted intervention strategies for CKD management.

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CONFLICT OF INTEREST

The authors declare that there is **no conflict of interest** regarding this study.

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