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Original Research Article

Assessment of Potential Drug–Drug Interactions and Associated Risk Factors among Patients with Multiple Chronic Diseases: A Prospective Observational Study

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Abstract

Background: Patients with multiple chronic diseases frequently require complex medication regimens, increasing the likelihood of potential drug–drug interactions (pDDIs) and clinically important medication-related harm.

Objectives: To determine the prevalence, pattern, and severity of pDDIs and identify factors associated with their occurrence among patients with multiple chronic diseases.

Methods: This prospective observational study included 100 adults receiving treatment for two or more chronic diseases at Alluri Sitarama Raju Academy of Medical Sciences, Eluru, Andhra Pradesh, India, from August 2025 to May 2026. Demographic details, comorbidities, and prescribed medications were recorded prospectively. Potential interactions were screened and classified by severity. Polypharmacy was defined as concurrent use of five or more medications. Factors associated with pDDIs were evaluated using appropriate comparative tests and multivariable logistic regression.

Results: The mean age was 59.3 ± 12.1 years; 57% were male. Participants had a mean of 3.1 ± 1.0 chronic diseases and received 6.8 ± 2.2 medications; 78% had polypharmacy. At least one pDDI was identified in 67% of patients, with 184 interactions overall. Moderate interactions predominated (58.7%), followed by major (26.6%) and minor (14.7%) interactions. Major pDDIs occurred in 29% of patients. Increasing medication burden, age ≥60 years, and ≥4 chronic diseases were independently associated with pDDIs; use of ≥8 medications showed the strongest association.

Conclusion: Potential drug–drug interactions were common among patients with multimorbidity. Systematic medication review, particularly in older adults and patients with high medication burden, can support safer prescribing and targeted clinical monitoring.

Keywords: Drug–Drug Interactions; Multimorbidity; Polypharmacy; Chronic Diseases; Medication Safety; Risk Factors.

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Introduction

Multimorbidity, commonly defined as the coexistence of two or more chronic health conditions in the same individual, has become an increasingly important challenge in contemporary clinical practice. Longer life expectancy, improved survival from cardiovascular and metabolic diseases, and the rising prevalence of diabetes, hypertension, chronic kidney disease, and other long-term disorders have expanded the population requiring sustained pharmacotherapy.

Management of several diseases frequently involves prescriptions from different therapeutic classes and, at times, multiple prescribers. Consequently, polypharmacy is common, particularly among older adults and patients receiving care for complex chronic conditions [1-3]. Polypharmacy is often clinically necessary, but increasing medication burden introduces additional risks. These include adverse drug reactions, medication errors, non-adherence, therapeutic duplication, and drug-drug interactions [1,3].

A drug-drug interaction occurs when the pharmacological effect or disposition of one medicine is altered by another concurrently administered medicine. Potential drug-drug interactions represent combinations with a recognized capacity to interact, even when a clinically evident adverse event has not yet occurred.

Their clinical relevance varies considerably according to the interacting agents, dose, duration, patient susceptibility, organ function, and availability of appropriate monitoring. Studies among geriatric and internal-medicine populations have consistently shown that pDDIs are frequent and are strongly related to the number of medicines prescribed [4,5].

Patients with multiple chronic diseases are particularly vulnerable because several disease-specific treatment recommendations can accumulate into complex regimens. Age-related changes in pharmacokinetics and pharmacodynamics can further modify drug exposure and response. Renal dysfunction is another important determinant because impaired elimination can increase systemic drug concentrations and intensify interactions involving renally cleared medicines or agents that influence electrolytes and renal haemodynamics [6]. Cardiovascular and antidiabetic medicines are frequently implicated because they are commonly co-prescribed in patients with hypertension, diabetes, ischemic heart disease, dyslipidaemia, and kidney disease. International studies have reported wide variation in the frequency of pDDIs, reflecting differences in patient characteristics, clinical setting, medication burden, interaction databases, and definitions used [4-7].

Identification of pDDIs before they translate into clinically important harm is therefore an essential component of medication safety. Electronic interaction-screening tools can assist clinicians, but their alerts require interpretation in the context of indication, patient-specific risk, and monitoring requirements. Indian evidence remains heterogeneous across specialties, and data specifically addressing patients with multimorbidity are comparatively limited [5].

Local assessment can help identify high-risk groups and interaction patterns that deserve focused surveillance. The present study was undertaken to assess potential drug-drug interactions among patients with multiple chronic diseases at a tertiary-care teaching hospital. The objectives were to determine the prevalence and severity of pDDIs, describe commonly involved drug combinations, examine their relationship with medication burden and clinical characteristics, and identify independent risk factors associated with the occurrence of pDDIs.

Methodology

Study Design and Setting: This prospective observational study was conducted at Alluri Sitarama Raju Academy of Medical Sciences, Eluru, Andhra Pradesh, India, a tertiary-care teaching institution providing specialist and general medical services to patients from Eluru and surrounding areas. The study was carried out from August 2025 to May 2026. Adult patients receiving pharmacological treatment for multiple chronic diseases were prospectively evaluated during routine clinical care.

Study Participants: Patients aged 18 years or older with at least two documented chronic diseases and receiving two or more systemic medications were eligible. Patients with incomplete medication information, those unable or unwilling to provide consent, and patients not fulfilling the predefined eligibility criteria were excluded. Consecutive eligible patients were approached to reduce selection bias. Of 108 patients assessed, eight were excluded and 100 were included in the final analysis.

Sample Size: Sample size estimation was guided by an earlier South Indian study reporting a pDDI frequency of approximately 76% among patients with chronic kidney disease [12]. Using a 95% confidence level and an absolute precision of approximately 8.5%, the minimum required sample was about 97. Allowing for incomplete records or non-participation, approximately 108 patients were screened, yielding a final analytical sample of 100.

Data Collection: A structured case-record form was used to capture age, sex, chronic diseases, current prescriptions, and the total number of medications. Diagnoses were obtained from the treating team's records. Medication lists were reviewed using generic drug names wherever possible. Polypharmacy was defined as concurrent use of five or more medications, consistent with the commonly used numerical definition in the literature [2]. Patients were categorized by age, number of chronic diseases, and medication burden for risk-factor analysis.

Assessment of Potential Drug-Drug Interactions: Prescribed drug combinations were screened for pDDIs using an electronic drug-interaction database based on the IBM Micromedex Drug-Reax approach, which has been used in comparable observational studies [5,9]. Identified interactions were categorized as minor, moderate, or major according to clinical severity. The likely clinical consequence of each commonly encountered interaction was recorded. A pDDI was considered present when at least one recognized interacting drug pair occurred in the patient's active regimen.

Statistical Analysis: Continuous variables were summarized as mean ± standard deviation or median with interquartile range, as appropriate. Categorical variables were expressed as frequency and percentage. Associations between pDDI status and categorical characteristics were assessed using the chi-square test or Fisher's exact test where required. Continuous medication-burden measures were compared between relevant groups.

Variables considered clinically important or associated with pDDIs in univariate analysis were entered into a multivariable binary logistic

regression model. Adjusted odds ratios with 95% confidence intervals were reported. A two-sided p-value <0.05 was considered statistically significant.

Ethical Considerations: The study was conducted in accordance with the principles of the Declaration of Helsinki. Necessary Permissions were obtained before starting the studyand written informed consent was obtained from participating patients. Patient identifiers were excluded from the analytical dataset.

Results

Participant Characteristics: A total of 108 patients with multiple chronic diseases were assessed for eligibility. Eight were excluded because of incomplete medication records (n=4), unwillingness to participate (n=2), or failure to satisfy the predefined inclusion criteria (n=2). Thus, 100 patients were included in the final analysis. The mean age was 59.3 ± 12.1 years (range, 32-84 years); 57 (57.0%) were male and 43 (43.0%) were female. Patients aged ≥60 years constituted 48.0% of the cohort. The mean number of chronic diseases was 3.1 ± 1.0 and the mean medication count was 6.8 ± 2.2 per patient. Polypharmacy was present in 78 (78.0%) patients. Hypertension and type 2 diabetes mellitus were the most frequent chronic conditions (Table 1).

Table 1: Baseline characteristics of the study population (n=100)

Characteristic	Value
Age, years, mean ± SD	59.3 ± 12.1
Age <60 years	52 (52.0)
Age ≥60 years	48 (48.0)
Male	57 (57.0)
Female	43 (43.0)
Number of chronic diseases, mean ± SD	3.1 ± 1.0
Number of prescribed medications, mean ± SD	6.8 ± 2.2
Polypharmacy (≥5 medications)	78 (78.0)
Hypertension	76 (76.0)
Type 2 diabetes mellitus	64 (64.0)
Dyslipidaemia	42 (42.0)
Ischemic heart disease	31 (31.0)
Chronic kidney disease	22 (22.0)
Chronic respiratory disease	18 (18.0)

Data are presented as n (%) unless otherwise specified. SD: standard deviation.

Prevalence and Severity of Potential Drug-Drug Interactions: At least one pDDI was identified in 67 (67.0%) patients, while 33 (33.0%) had no identified interaction. Overall, 184 pDDIs were detected. Among patients with at least one pDDI, the median number of interactions was 2 (interquartile range: 1-4). Moderate interactions were the most frequent, accounting for 108 (58.7%) of all pDDIs, followed by 49 (26.6%) major and 27 (14.7%) minor interactions.

Twenty-nine patients had at least one major pDDI and 55 had at least one moderate interaction (Table 2).

Table 2: Distribution and severity of potential drug-drug interactions

Variable	n (%)
Patients with ≥1 pDDI	67 (67.0)
Patients without pDDI	33 (33.0)
Patients with 1 pDDI	21 (21.0)
Patients with 2-3 pDDIs	25 (25.0)
Patients with ≥4 pDDIs	21 (21.0)
Patients with ≥1 major pDDI	29 (29.0)
Patients with ≥1 moderate pDDI	55 (55.0)
Total identified pDDIs	184
Minor interactions	27 (14.7)*
Moderate interactions	108 (58.7)*
Major interactions	49 (26.6)*

*Percentage calculated using the total number of identified pDDIs (n=184) as the denominator. pDDI: potential drug-drug interaction.

Common Potential Drug-Drug Interactions: The most frequent interaction pair was aspirin plus clopidogrel, accounting for 18 (9.8%) pDDIs, followed by aspirin plus an angiotensin-converting enzyme inhibitor in 15 (8.2%) and amlodipine plus simvastatin in 13 (7.1%). Interactions involving beta-blockers with insulin or sulfonylureas were documented in 12 (6.5%) instances. The principal anticipated clinical consequences included

bleeding, altered antihypertensive response, renal dysfunction, hyperkalaemia, hypoglycaemia, and enhanced drug exposure (Table 3).

Table 3: Frequently identified potential drug-drug interaction pairs

Drug combination	Potential clinical consequence	Frequency, n (%)
Aspirin + clopidogrel	Increased bleeding risk	18 (9.8)
Aspirin + ACE inhibitor	Reduced antihypertensive effect/renal impairment	15 (8.2)
Amlodipine + simvastatin	Increased statin exposure/myopathy risk	13 (7.1)
Beta-blocker + insulin/sulfonylurea	Masking or prolongation of hypoglycaemia	12 (6.5)
ACE inhibitor/ ARB + spironolactone	Hyperkalaemia	11 (6.0)
Aspirin + anticoagulant	Increased bleeding risk	9 (4.9)
Diuretic + ACE inhibitor/ARB	Hypotension/renal dysfunction	8 (4.3)
Other interaction pairs	Variable	98 (53.3)
Total		184 (100.0)

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker.

Association Between Patient Characteristics and Potential drug-drug Interactions: The prevalence of pDDIs increased progressively with medication burden. Among patients receiving fewer than five medications, 6 of 22 (27.3%) had a pDDI, compared with 35 of 51 (68.6%) receiving 5-7 medications and 26 of 27 (96.3%) receiving eight or more medications ($p<0.001$). Potential drug-drug interactions were also more frequent among patients aged ≥60 years than among younger patients (79.2% vs. 55.8%, $p=0.013$).

Patients with four or more chronic diseases had a higher prevalence than those with two or three chronic diseases (85.3% vs. 57.6%, $p=0.006$). Chronic kidney disease was significantly associated with pDDIs (86.4% vs. 61.5%, $p=0.027$), whereas sex was not significantly associated ($p=0.624$) (Table 4).

Table 4: Factors associated with potential drug-drug interactions

Characteristic	pDDI present, n (%)	pDDI absent, n (%)	p-value
Age <60 years (n=52)	29 (55.8)	23 (44.2)	0.013
Age ≥60 years (n=48)	38 (79.2)	10 (20.8)	
Male (n=57)	39 (68.4)	18 (31.6)	0.624
Female (n=43)	28 (65.1)	15 (34.9)	
2-3 chronic diseases (n=66)	38 (57.6)	28 (42.4)	0.006
≥4 chronic diseases (n=34)	29 (85.3)	5 (14.7)	
<5 medications (n=22)	6 (27.3)	16 (72.7)	<0.001
5-7 medications (n=51)	35 (68.6)	16 (31.4)	
≥8 medications (n=27)	26 (96.3)	1 (3.7)	
Chronic kidney disease present (n=22)	19 (86.4)	3 (13.6)	0.027
Chronic kidney disease absent (n=78)	48 (61.5)	30 (38.5)	

pDDI: potential drug-drug interaction. Values are based on the supplied study dataset.

Independent risk factors for potential drug-drug interactions: In the multivariable logistic regression analysis, use of eight or more medications was the strongest independent predictor of pDDIs (adjusted odds ratio [AOR] 8.42; 95% CI: 2.05-34.61; $p=0.003$). Having four or more chronic diseases was independently associated with higher odds of pDDIs (AOR 3.16; 95% CI: 1.08-9.24; $p=0.036$), and age ≥60 years was also significant (AOR 2.48; 95% CI: 1.01-6.10; $p=0.048$).

Chronic kidney disease did not remain statistically significant after adjustment (AOR 2.37; 95% CI: 0.72-7.80; $p=0.156$) (Table 5).

Table 5: Multivariable logistic regression analysis of factors associated with potential drug-drug interactions

Risk factor	Adjusted OR	95% CI	p-value
Age ≥60 years	2.48	1.01-6.10	0.048
Male sex	1.18	0.46-3.02	0.729
≥4 chronic diseases	3.16	1.08-9.24	0.036
5-7 medications	2.94	1.02-8.48	0.046
≥8 medications	8.42	2.05-34.61	0.003
Chronic kidney disease	2.37	0.72-7.80	0.156

OR: odds ratio; CI: confidence interval. Reference categories were age <60 years, female sex, 2-3 chronic diseases, <5 medications, and absence of chronic kidney disease, respectively.

Relationship between medication burden and interaction status

Patients without a pDDI received a mean of 4.8 ± 1.5 medications, compared with 7.8 ± 1.9 medications among those with at least one pDDI ($p<0.001$). Patients with major pDDIs also had a higher medication burden than those without major interactions (8.1 ± 2.0 vs. 6.3 ± 2.0 medications, $p<0.001$) (Table 6). Overall, the findings showed that pDDIs clustered among older patients, those with greater multimorbidity, and particularly those exposed to larger medication regimens.

Table 6: Medication burden according to potential drug-drug interaction status

Comparison	Mean number of medications	p-value
No pDDI vs. ≥1 pDDI	4.8 ± 1.5 vs. 7.8 ± 1.9	<0.001
No major pDDI vs. major pDDI	6.3 ± 2.0 vs. 8.1 ± 2.0	<0.001

pDDI: potential drug-drug interaction.

Discussion

The present prospective study demonstrated a substantial burden of potential drug-drug interactions among patients with multiple chronic diseases. At least one pDDI was identified in 67% of participants, and 184 interactions were detected overall. This prevalence lies within the broad range reported across clinical populations. Bethi et al. documented pDDIs in 46% of patients admitted to internal medicine wards in India [5], whereas Diksis et al. reported a prevalence of 74.4% among hospitalized cardiac patients [6]. In polypharmacy outpatients in Jordan, Nusair et al. found at least one pDDI in 96% [7]. Such variation is expected because interaction frequency depends on disease complexity, medication count, care setting, and the screening database used.

Moderate interactions constituted 58.7% of all pDDIs in the present study, followed by major interactions in 26.6%. This pattern is comparable with Indian internal-medicine data in which moderate interactions were the predominant category [5] and with studies of polypharmacy populations showing a similar dominance of moderate-severity alerts [7,9]. Importantly, a potential interaction does not invariably indicate inappropriate prescribing. Some combinations are therapeutically justified when benefits outweigh risks, provided that clinical and laboratory monitoring is adequate. For example, concomitant antiplatelet therapy can be intentionally prescribed in selected cardiovascular conditions, although bleeding risk requires surveillance.

Medication burden emerged as the most prominent risk factor. Patients receiving eight or more medications had markedly higher adjusted odds of pDDIs, and the mean number of medicines was substantially greater among patients with interactions than among those without interactions. This observation is consistent with previous studies showing a steep rise in interaction probability as the number of concurrently prescribed drugs increases [4,6,9,10]. Polypharmacy creates more possible drug pairs and is also a marker of greater disease complexity. The association of four or more chronic diseases with pDDIs further supports the influence of multimorbidity on pharmacotherapeutic risk.

Older age was independently associated with pDDIs. Ageing frequently coexists with multimorbidity, altered renal and hepatic function, and increased exposure to cardiovascular and metabolic medicines [1,3]. Chronic kidney disease was associated with a higher unadjusted prevalence of pDDIs in this study, although it did not retain statistical significance after multivariable adjustment. This remains clinically relevant because renal impairment can alter drug clearance and amplify pharmacodynamic consequences such as hyperkalaemia, hypotension, and nephrotoxicity [8,11,13].

The most frequent interaction pairs involved aspirin with clopidogrel, aspirin with angiotensin-converting enzyme inhibitors, and amlodipine with simvastatin. Contemporary cardiovascular data also identify aspirin-containing combinations as frequent contributors to pDDI alerts [14]. These findings support structured medication reconciliation, review of cumulative medication burden, and prioritization of high-risk patients for closer monitoring. Incorporating interaction screening into routine clinical review can improve recognition of potentially consequential combinations while avoiding indiscriminate discontinuation of clinically necessary therapy.

Limitations

This study has several limitations. It was conducted at a single tertiary-care centre with a sample of 100 patients, limiting broader generalization. The analysis identified potential rather than confirmed clinical drug-drug interactions, so observed adverse outcomes were not systematically attributed to individual interaction pairs.

Interaction classification depended on an electronic database, and over-the-counter medicines, herbal products, adherence, and pharmacogenetic variability were not comprehensively evaluated.

Conclusion

Potential drug-drug interactions were frequent among patients with multiple chronic diseases, affecting approximately two-thirds of the study population. Moderate interactions formed the largest category, while more than one-quarter of identified interactions were major. Increasing medication burden was the strongest risk factor, with additional contributions from older age and greater multimorbidity.

These findings emphasize the need for systematic medication reconciliation and individualized review whenever several chronic conditions are treated concurrently. Particular attention should be directed toward patients receiving eight or more medicines and those requiring combinations associated with bleeding, renal dysfunction, electrolyte disturbances, or hypoglycaemia. Integrating electronic interaction screening with clinical judgment and appropriate monitoring can strengthen medication safety in routine care.

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