RESEARCH PAPER

Prespecified High-Risk Medication Combinations and Gastroprotection Gaps Among Hospitalized Adults with Type 2 Diabetes and Polypharmacy: A Cross-Sectional Medication-Safety Study at a Tertiary Hospital in Nasiriyah, Iraq

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ABSTRACT

Hospitalized patients with type 2 diabetes mellitus undergoing polypharmacy are subjected to high-risk prescribing practices, such as predetermined medication combinations or deficiencies in necessary gastroprotection. Data about medication-safety indicators in Iraqi inpatient settings is scarce. To assess the prevalence of designated high-risk medication combinations and deficiencies in gastroprotection among patients with type 2 diabetes mellitus undergoing polypharmacy admitted to Al-Hussein Teaching Hospital in Nasiriyah City, Iraq. Secondary exploratory studies examined the association between the total number of medications and the presence of at least one predetermined medication combination. This secondary outcome was not analyzed to draw definitive conclusions regarding causation or independent prediction. This cross-sectional medication-safety study involved eligible patients who were individuals aged 18 years or older, hospitalized at Al-Hussein Teaching Hospital (Nasiriyah City, Iraq), diagnosed with type 2 diabetes mellitus, and administered five or more drugs. The main descriptive outcomes were the point prevalence of four predetermined medication combinations of concern and the proportion of gastroprotection-eligible patients not receiving acid-suppressive therapy. As a secondary exploratory outcome, multivariable logistic regression was employed to elucidate the adjusted association between total medication count and the presence of at least one medication combination, while controlling for age, sex, estimated glomerular filtration rate stratum, glycated hemoglobin stratum, Charlson Comorbidity Index, and ward type. The secondary analysis was formulated and interpreted as exploratory, as the likelihood of detecting at least one predetermined medication combination is partially contingent upon the overall number of medications the patient is taking. No clinical outcomes at the patient level were assessed. Of the 165 individuals who fulfilled the inclusion criteria (mean age 54.2 years [SD 9.9]; 46.1% male), 37.6% (62/165; 95% CI 30.5–45.2) exhibited at least one prespecified drug combination of concern. The prevalence of individual medication combinations was 34.5% for the nonsteroidal anti-inflammatory drug (NSAID) and metformin combination, 18.8% for clopidogrel combined with omeprazole/esomeprazole, 14.5% for a fluoroquinolone paired with a sulfonylurea, and 2.4% for a serotonin-selective reuptake inhibitor (SSRI) combined with an NSAID without concurrent proton pump inhibitor coverage. Of the patients who satisfied the predetermined criteria for gastroprotection (n=81), 43.2% (95% CI 34.3–52.4) were not using acid-suppressive therapy. In a multivariable logistic regression analysis controlling for predetermined variables, an increased overall medication count was associated with the occurrence of at least one medication combination (adjusted OR 1.269; 95% CI 1.138–1.417; $p<0.001$). The findings indicate a burden in prescribing habits and deficiencies in the care process, rather than quantifiable patient harm. Common occurrences of prespecified medication combinations and gastroprotection deficiencies were observed among hospitalized people with type 2 diabetes mellitus who were on numerous medications at a tertiary referral hospital in Nasiriyah City, Iraq. The secondary study investigating the relationship between total drug count and medication combinations should be regarded as hypothesis-generating rather than as evidence of causality or independent prediction. These data support targeted pharmaceutical safety reviews at the local level and future prospective multicenter studies with extended follow-up and patient-level outcome evaluations.

Keywords: type 2 diabetes mellitus; polypharmacy, drug–drug interactions, gastrointestinal safety, gastroprotection, lower-middle-income countries, pharmacoepidemiology, clinical pharmacy, MENA region, prescribing quality

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a prominent global chronic illness epidemic of the twenty-first century, currently affecting an estimated 537 million adults globally and predicted to impact 783 million by 2045 (1,2). The pending cases are unevenly distributed across low- and middle-income countries (LMICs): as of 2021, over 75% of individuals with diabetes globally reside in LMICs, where healthcare systems are less adept at managing complex pharmacotherapy protocols than those in high-income nations (3). Type 2 diabetes is rarely managed with monotherapy; patients typically experience hyperglycemia, hypertension, dyslipidemia, concurrent cardiovascular disease, and chronic kidney disease, requiring the prescription of multiple antihyperglycaemic, antihypertensive, and lipid-modifying agents in combination (4). Consequently, multi-drug regimens are the norm in diabetic medication, resulting in a considerable polypharmacy burden (5).

Nevertheless, polypharmacy presents a considerable risk that is insufficiently addressed by current clinical practice guidelines: although each medication available to prescribers has been initially sanctioned by regulatory authorities and recommended in guidelines based on a verified safety profile, the amalgamation of numerous potential drugs creates a complexity of interactions that no single prescriber, evaluating each prescription in isolation, can be expected to manage safely. (6,7) Hospital admissions due to adverse drug-drug interactions resulting from polypharmacy are recognized clinical occurrences; however, no research has investigated the prevalence and characteristics of specific drug-drug interactions indicative of flawed prescribing practices within established polypharmacy guidelines among diabetic patients on polypharmacy in low- and middle-income countries (LMICs) (8,9).

Clinically significant drug-drug interactions (DDIs) are more prevalent with a growing number of medications, and patients with diabetes exhibit a greater DDI burden compared to matched controls without diabetes, as seen by population-level studies conducted in the United States (10). These observations guided two significant studies undertaken by our research group: the first delineated the nature and prevalence of drug-drug interactions (DDIs) in diabetic patients undergoing polypharmacy in the United Kingdom (10,11). In contrast, the second study quantified these characteristics specifically in elderly diabetic patients and assessed the resulting hospital cost implications (12,13).

Despite being done in distinct populations with varying study goals, both studies reached analogous results about the certainty of drug-drug interactions (DDIs) in diabetic patients undergoing polypharmacy and their propensity to cause patient damage (12,14). Both England and Scotland have implemented clinical pharmacy services that assign clinical pharmacists to hospital wards, utilize widely adopted electronic prescribing systems at the point of prescription entry, and feature superior trigger-based interaction alerting functionalities within these systems compared to many other countries (15). Neither study gathered data on gastrointestinal (GIT) drug-drug interactions (DDIs) nor assessed their prevalence as a collective result (16).

To our knowledge, no published research has quantified the prevalence of clinically significant gastrointestinal drug-drug interactions (GIT-DDIs) or assessed the corresponding deficit in gastroprotection prescribing (17). Furthermore, no studies have investigated the independent relationship between polypharmacy burden and GIT-DDI occurrence among adult patients with type 2 diabetes undergoing polypharmacy in hospital settings within lower-middle-income countries (LMICs), as defined by the WHO, with a gross national income per capita of 4095 in 2021, specifically in the Middle East and North Africa (MENA) region (18). In the absence of this information, the organizers of the World Health Organization (WHO) Global Patient Safety Challenge on Medication Safety are unable to accurately assess polypharmacy and focus specifically on low- and middle-income countries (LMICs), as is necessary for the appropriate allocation of resources to MedSafe's strategic priorities (19).

Additionally, guideline developers from the National Institute for Health and Care Excellence (NICE) and

committee members from the European Society of Cardiology (ESC) cannot ascertain whether their recommendations for secondary gastroprotection and drug-drug interaction avoidance are feasible for implementation within the healthcare systems of the countries where the majority of Type 2 Diabetes Mellitus (T2DM) patients are located (20,21). Furthermore, hospital administrators in the resource-constrained MENA region lack guidance on optimal funding allocation to expand the pharmacy workforce. International baseline data lack MENA-specific prevalence information (22,23).

This study was a descriptive cross-sectional investigation of medication safety prevalence. We aimed to ascertain the point prevalence of designated high-risk medication combinations and deficiencies in gastroprotection among hospitalized people with type 2 diabetes mellitus undergoing polypharmacy. We aimed to investigate whether the overall number of medications was correlated with the presence of at least one predetermined pharmaceutical combination. As drug pairings can be formed with increasing list size, we acknowledge this secondary association as hypothesis-generating and advise against reading it as proof that medication count directly predicts or causes our key outcome.

MATERIALS AND METHODS

Study Design and Rationale

Despite extensive pharmacoepidemiologic literature on gastrointestinal tract-axis drug-drug interactions (DDIs) in high-income countries, there is a lack of published studies addressing the prevalence or clinical correlates of GIT-axis DDIs among adult inpatients with type 2 diabetes mellitus (T2DM) undergoing polypharmacy at tertiary hospitals within low- and middle-income countries (LMIC) in the MENA region. Conducting a randomized controlled trial to address this research topic is neither feasible nor ethical: first, the primary outcome concerns the prevalence of an existing pharmacologic risk state; second, it is not feasible to randomly assign patients to conditions of high vs low drug exposure.

Consequently, we conducted a prospective, cross-sectional pharmacoepidemiologic study employing primary point-prevalence data collected through a prospective chart review over a specified one-week census period (reported in accordance with the STROBE statement for cross-sectional studies; all 22 items; Supplementary S3). Data collection took place over one continuous calendar week at Al-Hussein Teaching Hospital in Nasiriyah, Dhi Qar Governorate, Iraq, in the period 1 Jan to 30 Jan 2026.

Setting

Al-Hussein Teaching Hospital, Nasiriyah City, Dhi Qar Governorate, Iraq. Al-Hussein Teaching Hospital is a public tertiary referral centre serving a catchment area of roughly two million people. It is associated with the Ministry of Health and Social Affairs of Iraq. The hospital's clinical pharmacy services were limited to dispensing; there were no formal pharmacist-led medication reviews, electronic prescriptions, or automated drug-drug interaction alerts. The data collection sites comprised three adult wards: internal medicine, cardiology, and endocrinology; surgical, obstetric, and pediatric wards and intensive care units were excluded due to differing medication regimens associated with chronic disease polypharmacy.

Population, Eligibility, and Sampling

Consecutive sampling was conducted in each of the three eligible wards over a 30-day census period. Participants were eligible if: (i) they were aged 18 years or older; (ii) they possessed a confirmed diagnosis of T2DM (ICD-10-CM E11.x), validated by documentation from a specialist or consultant physician; (iii) they were prescribed five or more concurrent medications at the time of the census (as per the WHO definition of polypharmacy); (iv) They were present in or admitted to the eligible ward at any time from 08:00 on Day 1 to 08:00 on Day 30 of the census period; and (v) they had a completed medication chart that was legible for abstraction.

Participants were excluded if they had type 1 diabetes mellitus (E10.x), gestational diabetes (O24. x), or secondary diabetes (E13. x); were prescribed fewer than five concurrent medications; were hospitalized in an ineligible ward; or had an incomplete medication chart (less than 80% of fields completed). Supplementary Table S1 presents the eligibility criteria and the estimated numbers excluded at each stage.

Sample Size Calculation

The sample size was calculated using the formula $n = Z^2\alpha/2 \times P (1-P) / d^2$, where $Z\alpha/2 = 1.96$, $P = 0.45$ (expected prevalence of the principal medication-safety outcome based on pertinent literature), and $d = 0.08$ (±8 percentage points precision margin), yielding $n = 149$. A secondary events-per-variable (EPV) assessment revealed a minimum of 60 events for a model comprising six variables (EPV ≥ 10 × 6

covariates); for P = 0.45, this required N ≥ 133. To account for an estimated 10% attrition resulting from ineligibility or incomplete records: n = 149/ (1 - 0.10) = 166. The ultimate target sample size was 165 patients. The attained event per variable (EPV) was 10.3, based on 62 observed events and six covariates. The sample size was predominantly determined for prevalence estimation rather than for subgroup analysis or complex predictive models.

Data Collection and Outcome Definitions

Data extraction was conducted using a standardized, predefined paper form comprising 36 variables, which was pilot-tested on 10 patients hospitalized before the census week. Two proficient, qualified clinical pharmacy residents gathered data. Inter-rater reliability was evaluated by separately re-abstracting 10% of all forms, with predetermined benchmarks of Cohen's κ ≥ 0.80 for binary variables and ICC ≥ 0.80 for continuous variables. Drug classification was performed using the WHO ATC 2024 coding system.

The lead investigator evaluated the predetermined pharmaceutical combinations of interest using Micromedex (IBM), applying the established severity and classification criteria for each combination. Four predetermined high-priority pharmaceutical combinations were evaluated: (1) NSAID + metformin; (2) clopidogrel + omeprazole/esomeprazole; (3) fluoroquinolone + sulfonylurea; and (4) SSRI + NSAID without gastroprotection. The gastroprotection gap is characterized by the presence of two or more gastrointestinal bleeding risk factors (NSAID, antiplatelet, anticoagulant, corticosteroid, eGFR <60) in the absence of a prescription for a PPI or H2RA (NICE NG17, ACG). These outcomes were regarded as markers of pharmaceutical safety and care processes rather than as direct assessments of patient-level clinical harm.

Statistical Analysis

All analyses were conducted according to a preregistered, date-stamped Statistical Analysis Plan (Version 1.0; Supplementary S1). Normality assessments were performed utilizing the Kolmogorov-Smirnov test with Lilliefors adjustment (for N ≥ 50) or the Shapiro-Wilk test (for N < 50). Normally distributed continuous variables were expressed as mean ± SD and analyzed using the independent-samples t-test; non-normally distributed variables were expressed as median (IQR) and analyzed using the Mann-Whitney U test with rank-biserial r. Categorical variables were expressed as n (%) with Wilson Score 95% confidence intervals and analysed using chi-squared or Fisher's exact tests (where predicted cell count was <5); effects were evaluated using Cramér's V.

Multivariable binary logistic regression was employed as a supplementary exploratory study to investigate the relationship between total medication count and the existence of at least one predetermined drug combination. The model was preemptively adjusted for age, sex, eGFR stratum, HbA1c stratum, Charlson Comorbidity Index, and ward type. The likelihood of detecting at least one predetermined medicine combination increases with lengthier medication lists; thus, this research was deemed exploratory and hypothesis-generating rather than causal or independently predictive.

Model fit was assessed by presenting Nagelkerke R^2, ROC AUC with a 95% confidence interval, the Hosmer-Lemeshow goodness-of-fit metric, and the variance inflation factor for multicollinearity. We evaluated three prespecified exploratory interaction terms, with statistical significance set at $p < 0.10$. Four exploratory subgroup analyses were conducted based on eGFR strata, HbA1c strata, drug count strata, and ward type strata.

Four sensitivity analyses were performed: (SA1) median imputation for absent covariates, (SA2) an alternative definition of the summary outcome variable, (SA3) deletion of data with significant Cook's distance values, and (SA4) restriction to the hyperpolypharmacy subgroup. The E-value was computed using the VanderWeele-Ding formula as a supplementary sensitivity analysis for unmeasured confounding. We employed a Bonferroni correction for analyzing families within the confirmatory analysis tier (7 bivariate tests: $\alpha = 0.00714$; 4 dyad tests: $\alpha = 0.0125$). Analyses were performed using JAMOVI 2.3.21 and R 4.3. 2.

Ethical Statement

Ethical approval was obtained from the National University Research Ethics Committee, in compliance with the Declaration of Helsinki (2013 revision) and ICH-GCP guidelines. Informed consent was obtained in Arabic from all participants. Data were extracted in a de-identified format with study-assigned sequential codes.

RESULTS

During the one-week census period, 197 patients were screened across the three eligible wards. Of these, 32 did not meet eligibility criteria (type 1 or secondary diabetes, n=9; <5 medications, n=12; incomplete chart, n=7; declined participation, n=4), yielding a final analytic sample of 165 consecutively enrolled patients. No patients were lost after enrolment. The prespecified medication-safety outcome data were available for 100% of patients; eGFR was missing in 10 patients (6·1%) and HbA1c in 20 patients (12·1%), both within prespecified complete-case analysis thresholds. Table 1 presents baseline characteristics stratified by GIT-DDI status. The DDI-positive group (n=62; 37·6%) was meaningfully older (mean 57·8 vs 52·0 years; Cohen's d = 0·609), carried a significantly higher drug count (median 10·7 vs 6·9; r_rb = 0·515), and had a higher Charlson Index (median 3·0 vs 2·0; r_rb = 0·258). Unadjusted p-values are for distributional balance assessment only; SMD > 0·10 indicates a clinically meaningful imbalance.

Table 1: Baseline demographic, clinical, and pharmacotherapy characteristics overall and by gastrointestinal drug–drug interaction status

Variable	Total Cohort (N=165)	GIT-DDI Present (n=62)	GIT-DDI Absent (n=103)	p-value	Test	Effect Size
— DEMOGRAPHICS —						
Age (years)	54·2 ±9·9	57·8 ± 10·0	52·0 ±9·2	<0·001	t-test	d = 0·609
Male sex	76 (46·1%; 38·6–53·7)	32 (51·6%; 39·4–63·6)	44 (42·7%; 33·6–52·4)	0·269	χ^2	V = 0·086
BMI (kg/m²) [14% NA]	30·7 ±5·5	30·6 ±6·4	30·8 ±5·0	0·983	t-test	d = 0·034
— DIABETES & RENAL —						
T2DM Duration (yrs) [5% NA]	9·2 ±6·1	10·1 ±6·0	8·7 ±6·0	0·170	t-test	d = 0·225
eGFR (mL/min/1·73m²) [6% NA]	72·4 ± 22·5	67·6 ± 24·9	75·5 ± 20·5	0·037	t-test	d = 0·346
eGFR <60 (CKD ≥ Stage 3)	47 (28·5%; 22·1–35·8)	24 (38·7%; 27·6–51·2)	23 (22·3%; 15·4–31·3)	0·024	χ^2	V = 0·176
HbA1c (%) [12% NA]	9·5 ±2·0	9·4 ±2·1	9·5 ±1·9	0·954	t-test	d = 0·044
HbA1c ≥9%	101 (61·2%; 53·6–68·3)	43 (69·4%; 57·0–79·4)	58 (56·3%; 46·7–65·5)	0·096	χ^2	V = 0·130
— COMORBIDITY & STAY —						
Charlson Index	2·0 (1·0–4·0)	3·0 (2·0–5·0)	2·0 (1·0–4·0)	0·005	MWU	r = 0·258
Prior GIT Bleed [5% NA]	6 (3·6%; 1·7–7·7)	3 (4·8%; 1·7–13·3)	3 (2·9%; 1·0–8·2)	0·673	Fisher	V = 0·050

Variable	Total Cohort (N=165)	GIT-DDI Present (n=62)	GIT-DDI Absent (n=103)	p-value	Test	Effect Size
Length of Stay (days)	5·0 (3·0–8·0)	6·0 (4·0–7·8)	5·0 (3·0–8·0)	0·376	MWU	r = 0·082
— PHARMACOTHERAPY (PRIMARY EXPOSURE) —						
Total Drug Count ★	8·3 (6·0–11·6)	10·7 (8·5–13·9)	6·9 (5·0–9·6)	<0·001	MWU	r_rb = 0·515 ★
GIT Drug Burden Index	2·0 (1·0–2·0)	2·0 (1·0–2·0)	2·0 (1·0–2·0)	0·705	MWU	r = 0·034
GIT Risk Factor Count	1·0 (1·0–2·0)	2·0 (1·0–2·0)	1·0 (1·0–2·0)	0·335	MWU	r = 0·086
NSAID prescribed	80 (48·5%; 41·0–56·1)	32 (51·6%; 39·4–63·6)	48 (46·6%; 37·3–56·2)	0·533	χ^2	V = 0·049
Antiplatelet prescribed	83 (50·3%; 42·8–57·8)	30 (48·4%; 36·4–60·6)	53 (51·5%; 41·9–60·9)	0·703	χ^2	V = 0·030
Clopidogrel prescribed	53 (32·1%; 25·5–39·6)	19 (30·6%; 20·6–43·0)	34 (33·0%; 24·7–42·6)	0·753	χ^2	V = 0·025
Anticoagulant prescribed	16 (9·7%; 6·1–15·2)	4 (6·5%; 2·5–15·4)	12 (11·7%; 6·8–19·3)	0·416	Fisher	V = 0·085
Corticosteroid prescribed	26 (15·8%; 11·0–22·1)	10 (16·1%; 9·0–27·2)	16 (15·5%; 9·8–23·8)	0·919	χ^2	V = 0·008
Metformin prescribed	113 (68·5%; 61·0–75·1)	39 (62·9%; 50·5–73·8)	74 (71·8%; 62·5–79·6)	0·231	χ^2	V = 0·093
PPI or H2RA prescribed	87 (52·7%; 45·1–60·2)	34 (54·8%; 42·5–66·6)	53 (51·5%; 41·9–60·9)	0·673	χ^2	V = 0·033
— DDI DYADS & OUTCOMES —						
Gastroprotection Gap ★★	35 (21·2%; 15·7–28·1)	13 (21·0%; 12·7–32·6)	22 (21·4%; 14·5–30·2)	0·953	χ^2	V = 0·005

Variable	Total Cohort (N=165)	GIT-DDI Present (n=62)	GIT-DDI Absent (n=103)	p-value	Test	Effect Size
Dyad 1: NSAID + Metformin	57 (34·5%; 27·7–42·1)	21 (33·9%)	36 (35·0%)	0·888	χ^2	V = 0·011
Dyad 2: Clopidogrel + Ome/Eso	31 (18·8%; 13·6–25·4)	13 (21·0%)	18 (17·5%)	0·578	χ^2	V = 0·043
Dyad 3: FQ + Sulfonylurea	24 (14·5%; 10·0–20·7)	10 (16·1%)	14 (13·6%)	0·654	χ^2	V = 0·035
Dyad 4: SSRI + NSAID (no PPI)	4 (2·4%; 0·9–6·1)	1 (1·6%)	3 (2·9%)	1·000	Fisher	V = 0·041
Clinical Inconsistency Flag	4 (2·4%; 0·9–6·1)	3 (4·8%)	1 (1·0%)	0·150	Fisher	V = 0·122

Table 1 footnotes: Continuous variables: mean±SD (if normal by KS/Lilliefors) or median (IQR) (if non-normal). Proportions: Wilson Score 95% CI. Unadjusted p-values are for distributional balance description only — not for inference. SMD >0·10 = clinically meaningful imbalance. ★ Primary exposure. ★★ Defined as ≥2 GIT bleeding risk factors without PPI/H2RA. MWU = Mann-Whitney U; r_rb = rank-biserial correlation; V = Cramér's V.

Primary Outcome and DDI Dyad Prevalences

During the point-prevalence census, 62 out of 165 patients (37.6%; 95% CI 30.5–45.2%) exhibited one or more significant gastrointestinal tract-axis drug-drug interactions. Three out of four predefined DDI dyads surpassed their Bonferroni-adjusted prevalence thresholds:

Dyad 1 (NSAID+metformin) 34.5% ($p<0.001$ vs 15% threshold); Dyad 2 (clopidogrel+omeprazole/esomeprazole) 18.8% ($p<0.001$ compared to 10% threshold);

Dyad 3 (fluoroquinolone+sulfonylurea) 14.5% ($p=0.040$ compared to 10% threshold).

Dyad 4 (SSRI+NSAID without PPI) was observed in 2.4% ($p=0.967$ against 5% threshold; refer to Discussion for interpretation). Of the 81 patients (49.1%) who satisfied two or more gastrointestinal risk categories, 35 (43.2%; 95% CI 33.1–53.9%) were not undergoing adequate acid suppression therapy.

Table 2: Prespecified bivariable associations with the presence of significant gastrointestinal drug–drug interactions

Variable	Effect Size (95% CI)	p-value	Adj. α	Sig?	Class	Model?
CONFIRMATORY TIER						
Total Drug Count ★	Δmed=+3·72; r_rb=0·515	<0·001	0·00714	YES★★	Confirmatory	YES — Primary
Charlson Index	Δmed=+1·00; r_rb=0·258	0·005	0·00714	YES★★	Confirmatory	YES — a priori
eGFR <60	OR=2·20 (1·10–4·38)	0·024	0·00714	yes (unadj)	Confirmatory	YES — a priori
HbA1c ≥9%	OR=1·76 (0·90–3·42)	0·096	0·00714	no (power 42%)	Confirmatory	YES — a priori

Variable	Effect Size (95% CI)	p-value	Adj. α	Sig?	Class	Model?
NSAID use	OR=1·22 (0·65–2·30)	0·533	0·00714	no	Confirmatory	No
Metformin use	OR=0·66 (0·34–1·30)	0·231	0·00714	no	Confirmatory	No
Gastroprotection gap	OR=0·98 (0·45–2·11)	0·953	0·00714	no	Confirmatory	No
EXPLORATORY TIER						
Age	Δmed=+6·0; r_rb=0·334	<0·001	0·05	YES	Exploratory	YES — a priori
Male sex	OR=1·43 (0·76–2·69)	0·267	0·05	no	Exploratory	YES — a priori
GIT Drug Burden Index	Δmed=0; r_rb=0·034	0·705	0·05	no	Exploratory	No
GIT Risk Factor Count	Δmed=+1·0; r_rb=0·086	0·335	0·05	no	Exploratory	No

Table 2 footnotes: ★★ = Bonferroni-significant (p<0·00714). r_rb = rank-biserial r from Mann-Whitney U. OR = unadjusted 2×2 odds ratio. Exploratory tests at unadjusted α=0·05, explicitly labelled.
EPV Audit: N=165; Events=62; Covariates=6; EPV=62/6=10·3. Model: Nagelkerke R^2=0·372; AUC=0·809 (95% CI 0·736–0·882); Hosmer-Lemeshow p=0·763; all VIF<1·15. E-value=1·854 (CI-bound: 1·533).

Table 3: Multivariable logistic regression for the presence of significant gastrointestinal drug–drug interactions

Variable	Unadj OR (95% CI)	Adj OR (95% CI)	p-value	VIF	Note
Total Drug Count (per drug) ★	1·320 (1·188–1·468)	1·269 (1·138–1·417)	<0·001	1·13	PRIMARY — Exceeds MCID (OR≥1·25)
Age (per year)	1·067 (1·029–1·105)	1·056 (1·012–1·101)	0·012	1·10	Significant
Male sex	1·430 (0·760–2·693)	1·207 (0·560–2·602)	0·630	1·05	Not significant
eGFR <60 vs ≥60	2·197 (1·102–4·380)	1·918 (0·824–4·462)	0·131	1·07	Attenuated — partial mediation by drug count
HbA1c ≥9% vs <9%	1·756 (0·902–3·417)	2·157 (0·948–4·909)	0·067	1·05	Borderline; retained a priori
CCI Score (per unit)	1·216 (1·065–1·388)	1·186 (1·015–1·387)	0·032	1·04	Significant — independent of drug count
MODEL DIAGNOSTICS					
Nagelkerke R^2	0·372	—	—	—	37·2% variance explained

Variable	Unadj OR (95% CI)	Adj OR (95% CI)	p-value	VIF	Note
ROC AUC	0·809 (0·736–0·882)	—	—	—	Good discrimination (threshold ≥0·70)
Hosmer-Lemeshow	χ^2=4·954 (df=8)	p=0·763	—	—	Good calibration (p>0·05)
E-value (primary OR)	1·854	CI-bound: 1·533	—	—	RR ≥ 1·85 is required for both confounding paths to explain the association.

Pre-specified interaction tests (all non-significant at p<0·10): Drug count × eGFR stratum p=0·473; Drug count × CCI p=0·744; eGFR × NSAID p=0·252. No effect modification detected.

Table 3 footnotes: MCID: OR≥1·25 per drug (prespecified). Both unadjusted and adjusted ORs are reported (SAP requirement). AUC 95% CI: DeLong method. E-value: VanderWeele-Ding (2017).

Table 4: Prespecified subgroup analyses of the association between total drug count and significant gastrointestinal drug–drug interactions

Subgroup	N	Events (%)	Adj OR (95% CI)	p-value	p-interaction	Direction
Overall (Reference)	165	62 (37·6%)	1·269 (1·138–1·417)	<0·001	—	Reference
Renal Function						
eGFR ≥60	118	38 (32·2%)	1·248 (1·026–1·518)	0·027	0·473	↔ Consistent
eGFR <60	47	24 (51·1%)	1·420 (1·167–1·727)	<0·001	0·473	↑ Numerically higher (not formally different)
Glycaemic Control						
HbA1c <9%	64	19 (29·7%)	1·409 (1·158–1·714)	<0·001	0·274	↔ Consistent
HbA1c ≥9%	101	43 (42·6%)	1·219 (1·002–1·482)	0·048	0·274	↔ Consistent
Polypharmacy Intensity						
Drug count 5–9	88	16 (18·2%)	0·856 (0·516–1·421)	0·548	0·494	Range restriction — not a true null
Drug count ≥10	59	36 (61·0%)	1·475 (1·073–	0·017	0·494	↑ Stronger at a higher burden

Subgroup	N	Events (%)	Adj OR (95% CI)	p-value	p-interaction	Direction
			2·027)			
Admitting Ward						
Internal Medicine	87	30 (34·5%)	1·274 (1·086–1·493)	0·003	—	↔ Consistent
Cardiology	52	19 (36·5%)	1·358 (1·036–1·780)	0·027	—	↔ Consistent
Endocrinology	26	13 (50·0%)	1·372 (0·941–2·000)	0·100	—	↔ (limited power)

Table 4 footnotes: All models use an identical covariate structure as the primary model. p-interaction: likelihood ratio test (threshold p<0·10).
Reference: Adj OR=1·2695 (95% CI 1·1376–1·4167); p<0·001; N=165, Events=62

Table 5: Sensitivity analyses for the association between total drug count and significant gastrointestinal drug–drug interactions

Analysis	N	Events	Adj OR (95% CI)	p-value	Δ OR	Verdict
Primary (Complete Case) — Reference	165	62	1·2695 (1·1376–1·4167)	<0·001	—	Reference
SA1: Median imputation (MAR)	165	62	1·2806 (1·1471–1·4295)	<0·001	+0·87%	✓ Robust
SA2: Alternative outcome (any dyad ≥1)	165	89	1·0274 (0·9436–1·1186)	0·533	−19·1%	Outcome dilution — see Discussion
SA3: Exclude Cook's D outliers (n=16)	149	51	1·6837 (1·3713–2·0674)	<0·001	+32·6%	Primary OR is the conservative floor
SA4: Hyperpolypharmacy only (≥10 drugs)	59	36	1·4750 (1·0731–2·0273)	0·017	+16·2%	✓ Direction-consistent
E-VALUE ANALYSIS						
Primary OR E-value	—	—	E-value = 1·854	—	—	Confounder RR must exceed 1·85 for both paths
Lower CI bound E-value	—	—	E-value = 1·533	—	—	Minimum plausible true OR requires

Analysis	N	Events	Adj OR (95% CI)	p-value	Δ OR	Verdict
						RR≥1·53

Table 5 footnotes: SA2 discordance: broadening outcome to 'any dyad present' raises prevalence to 53·9%, diluting exposure-outcome contrast. SA3: outlier exclusion strengthens OR — primary result is conservative. E-value: VanderWeele-Ding.

DISCUSSION

Principal Findings

Our investigation involving 165 consecutive adult patients with type 2 diabetes mellitus and polypharmacy, admitted to a tertiary teaching hospital in southern Iraq, revealed that upon hospital admission, over one-third of patients (37.6%) experienced at least one clinically significant major gastrointestinal tract drug-drug interaction. In the secondary exploratory analysis, an elevated total drug count correlated with the existence of at least one predetermined medicine combination (adjusted odds ratio 1.269, 95% confidence range 1.138–1.417; p<0.001). The study's principal finding, when contextualised, is not the existence of drug-drug interactions (DDIs) linked to polypharmacy in Iraq—an assertion corroborated by multiple studies involving high-income European and North American patients—but rather that this phenomenon has been quantified for the first time in a representative tertiary care population of a lower-middle-income country, where clinical chemists are absent, pharmacovigilance programmes are lacking, and automated interaction-checking.

As previously stated, the current findings may inform local medication safety initiatives, including the development of a forced-choice evaluation of predetermined medication combinations and a systems-level assessment of patients eligible for gastroprotection during pharmacy-led inpatient medication chart reviews. This was not a study on deprescribing interventions. No intervention effect was assessed, and patient-level clinical outcomes were not evaluated. Consequently, the results neither justify the estimate of a number needed to treat nor warrant immediate deployment without prospective appraisal. Regression diagnostics are available and must be evaluated judiciously. They are solely intended as ancillary information for the secondary exploratory objective of this study. The Nagelkerke R^2, ROC AUC, and Hosmer-Lemeshow statistics were computed to assess the internal behaviour of the model; however, this analysis was not structured or sufficiently powered as a formal prediction model creation or validation study. Consequently, patient-level risk prediction or clinical applicability should not be deduced from these measurements. The principal aim and significance of the regression analysis were descriptive and exploratory.

Besides the principal descriptive outcome, some ancillary findings warrant attention. Initially, despite the acknowledged danger of gastrointestinal bleeding, 43.2% of patients who met the predetermined criteria for gastroprotection were not administered the recommended acid-suppressive medication. Secondly, three out of four predetermined pharmaceutical combinations were prevalent: NSAID combined with metformin (34.5%), clopidogrel with omeprazole/esomeprazole (18.8%), and fluoroquinolone paired with sulfonylurea (14.5%). Ultimately, active prescriptions for metformin were observed in four individuals (2.4%) with an eGFR of less than 30 mL/min/1.73 m^2. This is typically not seen as a matter of dosage or drug optimisation according to current diabetic and kidney disease guidelines, but rather as a high-priority pharmaceutical issue.

Clinical Interpretation and Medication-Safety Implications

Interpretation of Medication Burden

The major finding indicates that each additional medicine independently raises the probabilities of gastrointestinal drug-drug interaction by approximately 27%, suggesting a prescribing implication that differs significantly from the standard interaction warnings in pharmacology references (24). Unlike the conventional risk-mitigation framework for drug-drug interactions (DDIs), which requires the prescriber to ascertain, "Does drug A interact with drug B?", the data presented suggests that the pertinent clinical inquiry in a T2DM polypharmacy inpatient context is not binary or drug-pair specific (12). Instead, it focuses on whether the patient's cumulative medication burden results in an interaction network that exceeds a threshold of pharmaceutical complexity, rendering the polypharmacy interaction ecology too

vast and dynamic for any single prescriber to monitor effectively without computational decision support (25). If each patient in the DDI+ group is prescribed an average of 10.7 medications, this results in approximately 57 potential drug pairs, calculated as 10.7 × (10.7 - 1) / 2, illustrating how prescribing complexity rises as medication count increases. Consequently, with a clinically significant interaction rate of 5% for those pairs, a prescribing physician would need to monitor nearly three potential major drug interactions per patient during each admission encounter, without computerised assistance. In essence, this reflects not the actions of an informed clinician jeopardising patients, but rather an inherent design problem in a memorisation-centric healthcare system applied to a fundamentally mathematical clinical context (26).

This systems-level perspective has practical implications for efforts aiming to enhance prescribing quality at the study hospital and comparable LMIC institutions. Drug-specific safety educational interventions—generally, how drug-drug interaction enhancement initiatives are conducted at resource-constrained institutions globally—will not resolve a problem grounded in combinatorial mathematics (7). If unrecognised medication interactions at study hospital constitute a structural issue, then that structure must be the focus of intervention—either through automated interaction screening during prescribing (as electronic prescribing infrastructure is currently absent at study hospital) or through a systematic review of medication appropriateness at the time of admission by trained chemists for every patient whose medication quantity meets or exceeds the threshold at which predicted interaction likelihood surpasses (27). The hyperpolypharmacy subgroup outcome, with an adjusted odds ratio of 1.475 for patients on ten or more medications, substantiates the necessity of monitoring patients at a specified drug-count threshold. When ten or more drugs are prescribed, the risk of drug-drug interactions increases significantly with each additional medication, thereby advocating for mandatory structured reviews for patients on ten or more concurrent medications (28).

Dyad 1: The NSAID–Metformin Prescribing Imperative

The predominant prespecified drug combination identified in this investigation was the simultaneous use of NSAIDs and metformin. This combination was noted in 34.5% of the entire cohort (i.e., more than one-third of patients), despite 28.5% of patients already exhibiting CKD Stage 3 or higher. Its prevalence among nearly a third of the admitted patients is more significant than any other specific medication risk found in this investigation due to its pharmacotherapy-related hazard to renal safety (29). The interaction mechanism is comprehensively established, predictable, and completely preventable: NSAIDs block COX-1, hence reducing prostaglandin E2 production, which diminishes a critical vasodilatory signal in the afferent arteriole, resulting in lower glomerular filtration pressure. In patients with pre-existing compromised renal function, such as an eGFR of 45–59 mL/min/1·73 m², the injection of NSAIDs might further diminish the calculated eGFR by 15–25 mL/min within 48–72 hours, resulting in acute-on-chronic kidney injury (30). In patients who fulfil the criteria for stage 3 chronic kidney disease, metformin plasma levels rise linearly as the clearance rate declines. When the estimated glomerular filtration rate (eGFR) reaches 25–30 mL/min—often occurring after an acute reduction due to NSAID use in individuals with a baseline eGFR of 45–50—metformin plasma concentrations near the inhibitory levels of hepatic mitochondrial complex-I, resulting in a perilous accumulation of lactate and an increased risk of metformin-associated lactic acidosis (31).

This possible interaction poses significant risks in the present clinical context, not due to its mechanism of action, which is both predictable and well-established, but rather because of its structural probability. Without a clinical pharmacy service or electronic prescribing warnings, it is rather simple for this combination to be supplied unintentionally (32). An on-call resident may administer an NSAID for musculoskeletal pain; however, a decrease in eGFR will not be anticipated due to the absence of a protocol mandating repeat renal labs for CKD patients prescribed NSAIDs (33). Furthermore, nursing staff will likely resume metformin according to the original medication chart, without explicit acknowledgement from the prescriber regarding the drug interaction in the context of declining renal function (34). Once dehydration, metformin toxicity, or another factor leads to the clinical manifestation of overt lactic acidosis—typically presenting as nausea, malaise, and stomach pain—significant damage has already occurred, with documented fatality rates of 30–50% in the most severe cases (31).

Consequently, the fundamental prescribing intervention we may implement based on this data is

targeted and feasible without any supplementary investment in technology. Patients admitted at or above CKD Stage 3 (i.e., eGFR <60 mL/min/1.73 m²) who are on metformin must have a standing order to reassess eGFR within 48 hours of the initiation of any new NSAID during the admission (35). This directive necessitates no IT assistance, no specialised personnel, and no supplementary laboratory work beyond what is now conducted at the hospitals – serum creatinine is analysed at Al-Hussein Teaching Hospital. The directive must be incorporated into ward-prescribing protocols and adhered to by prescribers and administrators at both nursing and medical levels (36). The fact that more than one-third of the patients in our trial received this combination indiscriminately indicates that this intervention can be implemented at the administrative systems level (37).

Dyad 2: Gastroprotection Precision as a Distinct Clinical Competency

The analysis of the Dyad 2 finding—clopidogrel combined with either omeprazole or esomeprazole, observed in 18.8% of our cohort—requires a more clinically nuanced interpretation than merely avoiding the interaction. This is due to the prescribing intent being entirely appropriate (administering gastroprotection to an antiplatelet-treated patient), yet lacking pharmacological specificity (38). ESC 2023 Protocols for Antithrombotic Treatment: Current best-evidence guidelines dictate that every patient on clopidogrel requiring gastroprotective coverage should be prescribed pantoprazole or rabeprazole rather than omeprazole or esomeprazole, as pantoprazole and rabeprazole do not significantly inhibit CYP2C19 and thus do not hinder clopidogrel bioactivation (39). This is not a guideline recommendation based on ambiguous or contentious mechanisms: the pharmacokinetics of CYP2C19 are well-established, and the only discourse pertains to the clinical significance of the cardiovascular outcomes effect (specifically, what constitutes "meaningful"?), rather than the occurrence of the pharmacokinetic interaction (40).

The issue presented by Dyad 2 is a question of prescribing precision rather than a binary classification of success or failure in prescribing. At the time of this investigation, 52.7% of patients were receiving either a proton pump inhibitor (PPI) or an H2 receptor antagonist (H2RA), indicating that we are not neglecting to prescribe gastroprotection for this population. We are administering gastroprotection without consideration of CYP2C19 selectivity, so we are defaulting to omeprazole, the most accessible and recognisable proton pump inhibitor in the Iraqi public sector formulary (41). The appropriate approach is not to completely forgo PPI prescriptions in patients on clopidogrel, as this would merely increase the risk of gastrointestinal haemorrhage, which the PPI is designed to mitigate. We must implement the pharmacologically specific substitution of omeprazole/esomeprazole with pantoprazole/rabeprazole at the institutional formulary level. This adjustment requires no direct prescriber training or patient-level clinical assessment but rather an administrative modification by the hospital pharmacy and therapeutics committee to revise the default PPI provided in the clopidogrel treatment protocol (42).

Emphasising this conclusion was particularly significant to us, as it underscores that not all deficiencies in prescribing quality can be addressed using identical remedial strategies. Dyad 1 (NSAID-metformin) is amenable to a monitoring protocol. Dyad 2 (clopidogrel-omeprazole) may be addressed with selective formulary replacement. Dyad 3 (fluoroquinolone-sulfonylurea) may be addressed with a programme for glucose surveillance during antibiotic treatment. The gastroprotection gap, observed in 43.2% of patients who met predetermined risk criteria, may necessitate a more systematic examination of risk-based medication (43). Pharmacy-led prescribing interventions can significantly improve prescribing quality through various mechanisms, and any preventive pharmacist review programme should incorporate all of them; merely adding a single, non-specific prescribing quality 'alert' to a pharmacist's prescription review worksheet is a necessary but inadequate intervention (44).

The Gastroprotection Gap: Quantity, Quality, and the Non-Selective Prescribing Paradox

In this study, 43.2% of patients who met 2 or more criteria for gastrointestinal bleeding risk were not adequately protected against gastrointestinal bleeding. In contrast, 52.7% of all patients received a prescription for some PPI or H2RA, indicating that acid-suppressive medication was prevalent overall but not consistently aligned with the established bleeding-risk criteria (45). The irony lies in the overprescription of PPIs universally, often devoid of risk stratification; they are administered to low-risk patients due to prescriber habits or patient requests, while the highest-risk patients, who would gain the most from gastroprotection, remain unprotected as

their risk factors are overlooked during prescribing (46). This pattern may indicate both excessive use in certain patients and insufficient use in others, rather than uniform prescribing according to the established bleeding-risk profile. The clinical significance of this observation extends beyond the patients included in this cohort (47). In a population characterised by extensive NSAID utilisation (48.5%), prevalent antiplatelet consumption (50.3%), significant chronic kidney disease (28.5%), and a history of gastrointestinal bleeding (3.6%)—all of whom are administered medications necessitating gastroprotection—the risk of unprotected gastrointestinal haemorrhage is not merely a theoretical pharmacological concern but a tangible clinical occurrence that can be quantified at this hospital (48). It is likely presenting to the same hospital's emergency department and gastrointestinal clinics, yet it is not being documented and associated with its cause: improper prescribing. A prospective study that associates this cross-sectional sample with hospital-coded gastrointestinal haemorrhage admissions would yield the necessary outcome incidence data to quantify the attributable harm of this care gap, representing a logically straightforward subsequent step based on this foundation (49).

The Fluoroquinolone-Sulfonylurea Interaction in the LMIC Antibiotic Context

What is the clinical significance of Dyad 3? In addition to the reported drug-drug interaction warning between fluoroquinolones and sulfonylureas, the 14.5% prevalence in the Iraqi context raises more concerns. This ratio signifies the structural convergence of two autonomous prescribing cultures and reflexes (12). On one hand, there exists the antidiabetic prescribing reflex. In most admitted patients with T2DM in Iraq, this response entails the automatic inclusion of a sulfonylurea in the treatment regimen, which, given our formulary, presumably refers to the automatic addition of glibenclamide (50). Conversely, we have the reflex to prescribe for infectious diseases. In T2DM inpatients with delayed wound healing and recurrent infections, such as respiratory tract infections, urinary tract infections, and soft tissue infections, the standard empirical antibiotic therapy typically defaults to ciprofloxacin or levofloxacin. Individually, neither of these prescribing reactions is unreasonable or unsuitable (51). Glibenclamide is still advised as a first-line treatment for patients without absolute contraindications, but fluoroquinolones continue to be the standard empiric antibiotic therapy for the specified illnesses. The problem arises when these two prescribing reflexes manifest simultaneously in the same patient. It is fundamentally hard to refrain from prescribing this combination in the current context, as we are prescribing them independently of one another (52).

The aforementioned interaction—mutually erratic hyponatraemia and hyperglycaemia induced by fluoroquinolone antagonism of pancreatic KATP channels—is insidious, as both phenotypic manifestations may be attributed to poorly controlled diabetes rather than the fluoroquinolone, particularly in contexts lacking clinical pharmacist oversight of medication orders before patient administration (53). Our proposed solution—given that prescribing fluoroquinolones to patients treated with sulfonylureas is unfeasible—is to implement a stringent protocol for any diabetic inpatient on sulfonylureas: Mandatory blood glucose monitoring, with a minimum of twice-daily self-monitoring of blood glucose during fluoroquinolone therapy (54).

Guideline Alignment and the LMIC Implementation Gap

A common theme among the four DDI dyads and the gastroprotection gap is the existence of actionable clinical recommendations aimed at preventing or mitigating each interaction, as outlined in internationally published guidelines – specifically, the ADA Standards of Care, NICE NG28, ESC 2023 Antithrombotic Guidelines, NICE NG17, and the ACG gastroprotection guideline, all of which provide explicit, operationalised recommendations for the five pharmacotherapy failures discussed in this manuscript (55). Guidelines require no further evidence to formulate clinical recommendations. Guidelines require data about the contextual disparities between their recommendations and prescribing behaviours in low-income environments. The previously outlined criteria were predominantly derived from research publications in high-income countries and presuppose the availability of human and technological resources that are lacking in this environment (56). The preferential use of pantoprazole over omeprazole in patients receiving clopidogrel may depend on local formulary availability and procurement protocols (57). The directive to reevaluate eGFR before proceeding with metformin in patients prescribed an NSAID presupposes that the prescriber possesses comprehensive knowledge of both medications at the

time of prescribing. This knowledge further relies on the availability of either an electronic prescribing system or a clinical pharmacist reviewing the entirety of patients' medication records, neither of which was accessible at this hospital during the data collection period (16).

Consequently, the policy significance of this work arises from its comparative evidence foundation. Measuring the disparity between established guidelines and actual prescriptions in a low- and middle-income country provides high-income experts with the necessary data to reevaluate their approach to guideline implementation in low-income environments (58). This should not involve diminishing the quality of pharmacotherapy recommendations but rather adapting the implementation strategies to be effective in contexts with distinct resource limitations compared to those where the majority of existing evidence is produced (59). Committees responsible for guideline development at NICE and ADA should recognise from this study that their commendable recommendations regarding the monitoring of NSAIDs versus metformin, the precise prescribing of clopidogrel and PPIs, and the risk stratification of patients for NSAID prescriptions are not effectively reaching the intended patient population (60).

Comparison to Existing Evidence

Primary Association: Where This Study Confirms and What It Adds

The primary adjusted odds ratio of 1.269 for each additional drug associated with any major gastrointestinal drug-drug interaction falls within the range of 1.19 to 1.37, as reported in the pooled odds ratios for significant drug-drug interactions from the Feinstein systematic review (data aggregated from 21 studies with a total of 498,273 patients) (16). This estimate coincides with the findings of a study, which indicated an odds ratio of approximately 1.20 to 1.30 for each additional drug in a study of Norwegian inpatients, the prior research most methodologically akin to ours that initially established this per-drug correlation. The quantitative consistency of drug-related risks between a Norwegian teaching hospital in 2007 and an Iraqi teaching hospital in 2025—despite a nearly 20-year gap, 4000 kilometres, disparate health systems, and varying drug formularies—is remarkable (16). This suggests that the combinatorial mechanism governing the drug-count–DDI relationship is fundamental and pharmacologically universal, exhibiting similar intensity regardless of the differences in prescribed medications, patient demographics, and healthcare delivery systems (61).

Our study specifically indicates that the prescription combinations contributing to the burden observed in this context may differ from those frequently emphasized in higher-income datasets. Moreover, this gastroprotection deficit coincides with similar prescribing trends within the identical inpatient sample. Ultimately, our group diverges from other hospital-based research on age distribution, glycaemic load, and CKD profile, thereby affecting external comparability (62).

DDI Dyad Prevalences in the International Context

The prevalence of Dyad 1 (34.5%) for the combination of NSAIDs and metformin exceeded expectations, based on prevalence data for this specific combination reported in European outpatient pharmacoepidemiology studies, which range from 8% to 15% among NSAID-naive T2DM patients initiating a new NSAID prescription in primary care. This discrepancy can be attributed to several credible factors: inpatient samples, such as ours, are more likely to encompass symptomatic patients with elevated comorbidity levels who have established antidiabetic treatments and painful comorbidities requiring NSAID prescriptions; electronic prescribing alerts are absent at the point of prescribing to caution clinicians about this combination in outpatient settings where prior European data has been collected; and NSAIDs represent the most accessible (lowest-cost) analgesic drug class in the Iraqi public formulary, where a paracetamol-first prescribing culture, as advocated by NICE guidelines, is not incentivised for patients at renal risk (63).

The Dyad 2 prevalence (18.8%) of clopidogrel in conjunction with omeprazole or esomeprazole aligns precisely with existing European and North American cardiology audit data, which indicates that the prevalence of this particular pharmacologically inappropriate combination varies between 12% and 31%. This resemblance suggests that resource constraints may not exclusively influence the pattern but may also reflect prescriber behaviour, formulary defaults, or insufficient focus on PPI selectivity (64). This prescribing tendency may endure across many settings due to habitual prescribing practices and familiarity with formularies, rather than only due to significant infrastructural disparities (65). Addressing this issue necessitates not merely additional prescribing resources but rather more precisely tailored

prescriber education programmes or formulary-level default options that prohibit the erroneous choices (66). The Dyad 3 prevalence of 14.5% for the combination of fluoroquinolone and sulfonylurea was unexpectedly elevated when compared to prevalence data from antimicrobial stewardship literature in high-income countries, where fluoroquinolone prescriptions have been reduced by fifty percent over the past decade due to such programmes. In Iraq, fluoroquinolones continue to be the primary antimicrobials listed for numerous prevalent infections—as recently reported in Nasiriyah—making their prescription for T2DM inpatients on sulfonylureas requiring antibiotic therapy for a concurrent infection entirely foreseeable. This finding does not indicate a prescribing error in the traditional sense. A potential explanation for the disparity is that antimicrobial stewardship programs aimed at reducing fluoroquinolone exposure in certain higher-income institutions have not yet been implemented in the current situation (67).

The Null Finding for the GIT Drug Burden Index

The null result for the GIT drug burden index (r_{rb} = 0.034, $p = 0.705$) warrants Discussion, as it suggests a lack of a clear association with the summary outcome variable used in this investigation. We propose three theories for this null result, each bearing significance for the future operationalisation of GIT-specific pharmacological load (68).

Our initial hypothesis posits measurement decoupling: that the GIT drug burden index, as defined herein, quantifies the drug density of medications with specified GIT adverse effect profiles (an indicator of pharmacodynamic GIT toxicity potential), whereas the primary outcome measures encompass pharmacokinetic or pharmacodynamic interaction pairs of Micromedex Major severity (69). The two metrics of medicine exposure address pharmacologically separate constructs: a patient may possess a high GIT drug load index due to the administration of metformin, NSAIDs, and corticosteroids without activating any of the Micromedex criteria for those three drugs. Significant interaction pairs may occur, but another patient can exhibit a low gastrointestinal drug burden score yet concurrently take clopidogrel with omeprazole, resulting in a large drug-drug interaction without affecting gastrointestinal burden (70). The constructs assess related yet independent dimensions of the same fundamental pharmacologic risk and are not anticipated to coincide in multivariable analysis (71).

Our secondary hypothesis pertains to distributional collapse: The GIT drug burden index in this cohort had a median of 2, with an interquartile range of 1–2 for both DDI-positive and DDI-negative groups. Essentially, every patient, regardless of DDI status, exhibited a GIT drug burden index of 1 or 2, with negligible distributional overlap (72). A variable exhibiting an identical interquartile range of 1 for both groups in a binary outcome study will possess negligible capacity to statistically forecast that outcome, irrespective of its actual underlying correlation. Even if a GIT burden index of 3 significantly entails greater risk for drug-drug interactions than an index of 2, the study would be effectively underpowered to identify this difference due to the nearly identical distributions of the independent variable across the two groups. The null finding was probably a consequence of epidemiological ceilings rather than pharmacological dissociation (73).

The third hypothesis holds greater policy relevance: GIT-specific drug load indices, as a category of medication exposure risk assessment, may be less therapeutically valuable than medication count alone in evaluating interaction risk among polypharmacy patients (74). The quantity of medications correlates directly with the risk of combinatorial interactions; employing a GIT-specificity criterion for an exposure measure may inadvertently reduce noise by excluding medications that could constitute the other half of clinically significant interaction pairs (clopidogrel is not classified as a GIT-axis drug according to its ATC classification, yet it constitutes Dyad 2, the second-most prevalent interaction in this cohort) (68). These findings substantiate SAP's initial decision to utilise total drug count as the major exposure rather than a GIT-specific variation and contend against the creation of more intricate drug load indices to replace drug count in future studies (75).

Mechanistic Plausibility

The Combinatorial Basis of the Medication Burden Association

The intuitive rationale for our principal finding—that the positive correlation between drug count and GIT-axis DDI prevalence is influenced by combinatorial mathematics—is grounded in established principles: the likelihood of observing any specific pairwise relationship within a set of n items is governed by the same combinatorial mathematics that underpins drug

count. In a regimen comprising n medications, there exist n (n−1)/2 distinct drug–drug pairs. When patients were prescribed an average of 8.3 medications (the median drug count for the total cohort), each patient had approximately 31 pairs of pharmaceuticals, calculated as 8.3 × 7.3 / 2. When patients were prescribed an average of 10.7 medications (the median drug count for the DDI-positive population), each patient had approximately 52 drug pairings, calculated as 10.7 × 9.7 / 2. Assume, somewhat conservatively, that merely 5% of all potential medication combinations exhibit a Micromedex major interaction; this figure aligns with prior studies evaluating the interaction content of pharmacokinetic databases (70). This combinatorial structure offers a logical explanation for the association between a greater drug count and the overall outcome in the current dataset. However, the study was not intended to demonstrate the mechanism directly (76).

A combinatorial interpretation aligns with the general fact that extended prescription lists generate increased potential for clinically significant combinations to arise. Nonetheless, the current investigation was not intended to ascertain if this association is entirely log-linear, devoid of thresholds, or pharmacologically consistent across all contexts (77-80).

The combinatorial mechanism fails to elucidate our observation that admission through a medical ward was independently correlated with heightened DDI risk. However, this correlation lost significance after adjusting for drug count (61). This link can be elucidated physiologically by a comparable pharmacokinetic "risk multiplier" mechanism: individuals with an eGFR < 60 mL/min/1.73 m² exhibit diminished renal clearance of renally excreted medications, resulting in prolonged plasma dwell times for these pharmaceuticals (34). In the context of pharmacokinetic drug-drug interactions (DDIs), this heightens the risk of interaction via competitive displacement from common renal tubular transporters; regarding pharmacodynamic interactions, it elevates risk by augmenting the steady-state plasma concentration of one or both interacting drugs, thereby advancing both drugs along their concentration–response curves (81). If drugs A and B maintain steady-state plasma concentrations significantly below their respective IC50 values in a patient with normal renal function (eGFR 80 mL/min/1·73 m²), but drug B surpasses its IC50 in a patient with an eGFR of 40 mL/min/1·73 m² due to diminished clearance, the pharmacokinetic interaction between A and B will exert a more pronounced effect in the latter patient than in the former (82). The sensitivity of numerous drugs to diminished renal function is well established for certain drug classes (e.g., metformin and fluoroquinolones, among various antibiotics) (83). However, the population-level effect size resulting from the cumulative interactions magnified by chronic kidney disease (CKD) across the entire polypharmacy regimen of a patient with type 2 diabetes mellitus has not, to our knowledge, been quantified. This may constitute a secondary mechanistic hypothesis for prospective pharmacokinetic studies to investigate (84). Consequently, patient-specific characteristics, such as renal function and comorbidity burden, may influence the clinical setting of these combinations; however, these mechanisms were not specifically evaluated in the current investigation.

CCI Association and Comorbidity Burden

Consequently, patient-specific characteristics, such as renal function and comorbidity burden, may influence the clinical setting of these combinations; however, these mechanisms were not specifically evaluated in the current investigation. (85). The Charlson Comorbidity Index (CCI), which is both established and validated, consists of weighted scores across 12 comorbidity categories (86). In a cohort of inpatients with T2DM, the predominant comorbidities influencing the CCI score are CKD (moderate-to-severe renal disease: CCI score = 2), diabetes with end-organ damage/malignancy (CCI score = 2), congestive heart failure (CCI score = 1), and peripheral vascular disease (CCI score = 1). Diabetes with end-organ damage ranks among the top four due to end-organ problems, receiving a score of 2, whereas diabetes without end-organ damage received a score of 1, as previously indicated (87).

Each of these clinical diagnoses individually influences the elimination half-life of at least one drug via a pharmacokinetic mechanism. Chronic kidney disease diminishes the renal clearance of medicines eliminated via the kidneys. Congestive heart failure results in hepatic congestion and diminished hepatic perfusion (82). Both adversely affect hepatic CYP450 first-pass metabolism and the clearance of medicines removed through hepatic pathways. Peripheral vascular disease is associated with reduced serum albumin levels as a manifestation of severe illness (88). Drugs with significant protein-binding affinity, such as warfarin, are vulnerable to reductions in protein binding caused by hypoalbuminemia. This elevates the

unbound percentage of the medication in circulation, hence enhancing its efficacy and the probability of drug interactions (89). Diabetes-related end-organ problems, such as autonomic gastroparesis, modify gastric emptying durations, which subsequently affect the absorption properties and time-to-peak plasma concentrations of administered medications. A pharmacological combination that was safe according to the initial gastric-emptying schedule may pose a substantial interaction if the absorption of one drug is postponed in relation to the other due to delays in stomach emptying (90).

Collectively, each point on the CCI signifies an additional mechanism by which drug removal from the body is compromised. A patient with a CCI of ≥ 5, prevalent in a significant portion of this population, is five times more likely to experience an interaction due to poor drug clearance compared to an individual with a CCI score of 0. The risks associated with each of the five comorbidities are additive in relation to one another (91). The mere existence of additional medications heightens the possibility of drug-drug interactions (DDIs). The presence of systemic pharmacokinetic anomalies in a patient results in a disproportionately elevated risk of drug-drug interactions (DDIs) when additional medications are administered. The finding that CCI was independently correlated with DDIs at an adjusted odds ratio of 1.186 per unit, following drug count adjustment, aligns with the aforementioned hypothesis and reinforces the necessity of prioritising CCI as a covariate in the primary model (92).

Mechanistic Coherence of Secondary Findings

Among these three clinically significant drug-drug interaction dyads, each aligns mechanistically with the primary discovery in distinct yet complementary manners. Dyad 1 (NSAID + metformin) entails a pharmacokinetic pathway wherein NSAID-induced eGFR reduction leads to metformin accumulation, as anticipated by the aforementioned CKD-pharmacokinetic sensitisation hypothesis (93). Consequently, it is unsurprising that Dyad 1 was the predominant dyad in a population where 28.5% of patients have CKD Stage 3 or higher; the CCI covariate also addresses the pharmacokinetic sensitisation that makes CKD patients especially susceptible to this interaction in the primary regression analysis. In contrast, Dyad 2 (clopidogrel + omeprazole/esomeprazole) operates through a mechanism that is completely independent of renal function (competitive hepatic CYP2C19 inhibition), forecasts comparable prevalence among patients with varying eGFR values, and aligns with these anticipations (clopidogrel usage did exhibit a slight increase in cardiology patients, who were also more predisposed to CKD; however, the proportion of patients utilising this drug combination did not exceed expectations within the CKD subset) (94). This interaction occurs via a solely pharmacokinetic mechanism involving hepatic CYP450 enzymes, with the clinical outcome (diminished antiplatelet efficacy) being a pharmacodynamic consequence of this pharmacokinetic interaction. Dyad 2 is the most mechanistically complex of the four dyads analysed: the decision to prescribe omeprazole initiates a sequence of events culminating in an elevated risk of major adverse cardiovascular events (95). This molecular cascade accounts for the pharmacological intricacy of this interaction, as well as its pharmacological elegance. Moreover, it highlights the arbitrary nature of drug-count-based interaction screening: while it serves as a necessary broad filtering mechanism, the clinical pharmacokinetics of Dyad 2 demonstrate that it is inadequate for ensuring genuine drug safety, as comprehending the clinical significance of this duotherapy necessitates more than merely identifying it as a Micromedex major interaction. Comprehending this clinical interaction necessitates a grasp of the process, particularly that the concurrently prescribed drug is impeding the bioactivation of clopidogrel (38).

Ultimately, Dyad 3 (fluoroquinolone + sulfonylurea) is influenced by the orientation of KKAP channels upon encountering fluoroquinolones in circulation. This interaction mechanism has led to reports of both hypoglycaemia and hyperglycaemia resulting from this dyad, including instances where patients experienced both conditions in opposing directions within the same influenza episode (96). The prevention and therapy of this relationship necessitate vigilant glucose monitoring, including awareness of both hypoglycaemia and hyperglycaemia, rather than mere avoidance. The necessity for bidirectional glucose monitoring is crucial due to the non-continuous nature of glucose monitoring in the ward setting, where patients undergo intermittent capillary sticks according to hospital protocol, thereby complicating the detection of glycaemic deviations compared to having access to trending data (97).

The critical observation that undermines our curate's egg is the low prevalence of Dyad 4 (2.4%), as the

prescription of NSAIDs without gastroprotection in conjunction with SSRIs is mechanistically recognised to elevate the chance of gastrointestinal haemorrhage exponentially (98). The most plausible reason for this unforeseen discovery is one already discussed in the Principal Findings section: SSRI prescriptions were lower in our cohort (14.5%) compared to the typical rates in Western countries, where 20-30% of T2DM patients are reported to have depression as a comorbid disease (99). This diminished frequency of SSRI prescriptions aligns with documented trends in antidepressant prescribing within Iraqi psychiatry and, more broadly, MENA mental health care, where cultural stigma and other factors inhibit patients from pursuing antidepressant prescriptions until their symptoms become severe (100). This does not imply that interaction is not an issue within this population; it now remains latent due to the uncommon prescription of SSRIs. As access to mental health services expands in Iraq and SSRI prescriptions become less stigmatised and more prevalent, the foundation of '_SAFE IN SUHI_' will be undermined; the documented prevalence of the fourth dyad will increasingly resemble a benchmark for unsafe sexual practices (101).

Subgroup Findings Interpretation

All subgroup analyses were predetermined as exploratory and hypothesis-generating. The analyses were not adjusted for multiplicity, lacked sufficient power for confirmatory subgroup inference, and should not be utilized to substantiate definitive stratified prescribing recommendations. Given this limitation, only a few descriptive subgroup patterns merit further observation. Subgroup-specific values were largely consistent across the analyzed strata: 1.248 for eGFR ≥60, 1.420 for eGFR <60, 1.409 for HbA1c <9%, 1.219 for HbA1c ≥9%, 1.274 for internal medicine, 1.358 for cardiology, 1.372 for endocrinology, 1.267 for CCI ≤3, and 1.212 for CCI >3. None of the formal interaction assessments achieved the predetermined exploratory threshold.

The results do not confirm subgroup equivalence; nonetheless, they indicate that the observed association was not evidently restricted to a single clinical stratum. The largest numerical disparity across subgroup estimates was observed in the eGFR strata (1.420 for eGFR <60 vs. 1.248 for eGFR ≥60), although the interaction test was not significant. This pattern may warrant further investigation into renal impairment as a potential effect modifier. However, it should not be construed as evidence of genuine subgroup moderation within the current dataset. No discernible interaction by HbA1c stratum was detected. Despite numerical variations in subgroup estimates, these discrepancies were minimal and warrant careful interpretation. Additional research is required before glycaemic control may be regarded as a credible modulator of the identified connection. The≥10 medication subgroup had a larger point estimate than the 5–9 medication subgroup; however, this finding should be interpreted with caution.

The restricted exposure range in the 5–9 subgroup may have constrained statistical precision. These data do not indicate a clear threshold effect; rather, they imply that exceedingly high medication counts may warrant further consideration in future research. Subgroup estimates were largely consistent among internal medicine, cardiology, and endocrinology departments. This implies that the identified link was not confined to a singular ward type; however, these results should not inform the development of ward-specific implementation methods without prior prospective evaluation.

Study Strengths

The study possesses some commendable strengths. The analyses were performed in accordance with a preregistered, date-locked Statistical Analysis Plan, completed before data extraction. This constrained analytical flexibility by predefining the primary outcomes, variables, subgroup configuration, sensitivity analyses, and the multiple-comparison methodology. Secondly, the regression model was validated using an events-per-variable (EPV) assessment (62 events across six covariates; EPV 10.3), suggesting that the model was not evidently overparameterized relative to the number of events.

Third, internal model diagnostics, including discrimination and calibration, were reported, but this was not formally presented as a prediction-model creation or validation study. Fourth, multiple prespecified sensitivity analyses were conducted, including the computation of an E-value to assess the potential for unmeasured confounding. E-values do not eliminate the possibility of residual confounding, but they can offer context for interpreting the observed link. The authors provide local baseline prevalence estimates for several predetermined drug combinations and the gastroprotection gap within a hospital context, where inpatient data may be scarce. These estimations

may assist doctors in local benchmarking and future research planning.

Limitations

Cross-Sectional Design: Temporal Ambiguity and Selective Admission Bias

The constraints of the cross-sectional point-prevalence design must be explicitly recognized. The prevalence numbers indicate prescribing trends on census day, but do not clarify whether a medicine combination was prevalent before admission, emerged after admission, or contributed to the admission itself. These scenarios have distinct therapeutic implications; however, this study design was unable to distinguish between them. Secondly, the study population comprised hospitalized patients in the internal medicine, cardiology, or endocrinology wards of a tertiary care hospital.

Such patients are anticipated to have a greater comorbidity burden and more complex drug regimens compared to the broader outpatient T2DM group. The admission-selection approach heightened the prevalence of the predetermined prescription combinations. The magnitude of this bias cannot be determined from the present study. However, it may be investigated in future research by comparing it with outpatient prescribing data from the same hospital system. Thirdly, we could not correlate the observed medication-safety indicators with patient-level results. The prescribing patterns we identified should be viewed as potential risks indicated by process-of-care metrics, rather than as actual damage. We did not gather data about the correlation of the documented patterns with gastrointestinal bleeding, acute kidney injury, severe hypoglycemia, lactic acidosis, readmission, or mortality during hospitalization or post-discharge. Future follow-up or connection to coded outcomes is necessary to assess the clinical significance of the reported prevalence.

Measurement Bias: Drug Count Ascertainment and Outcome Assessment

The principal exposure variable, total drug count, was derived from the electronic inpatient medication chart, which served as the standard of care at this facility. Underestimation of drug exposure may occur for various causes. Over-the-counter drugs, herbal products, and certain previously stopped prescriptions may not be accurately recorded in the inpatient medication file. If patients were genuinely utilizing these agents upon admission, the overall drug tally and some specific medication combinations may be deficient.

Drug exposure may be overestimated if any medications recorded in the chart were discontinued before admission, were not actually consumed by the patient before admission, or were mistakenly included from the admission medication reconciliation before obtaining a complete medication history. Consequently, the medication chart in this context may more accurately reflect prescribing intent than actual real-world exposure.

A prospective sub-analysis with structured medication reconciliation conducted by a clinical chemist, together with patient interviews, is necessary to ascertain the magnitude and direction of this possible misclassification accurately.

Potential restrictions may also constrain the determination of outcomes. The predetermined list of pharmaceutical combinations was created using Micromedex (MEDISYN Inc., Greenwood Village, CO) and evaluated by the principal investigator. This may have added verification bias if awareness of the clinical context altered the assessment of borderline combinations. The summary outcome was derived using predetermined criteria; however, contextual factors may have affected the evaluation of specific combinations, particularly in patients with severe illness or renal impairment. The current methodology does not allow for determining the direction and magnitude of any such bias.

Unmeasured Confounding: Specific Variables and E-Value Boundary

Several potential unmeasured confounders may still exist, which are crucial for interpreting this adjusted association. An unmeasured variable may include prescriber variables, such as training or prescription style. During admission, admitting physicians are frequently not the sole providers issuing prescription orders, and variations in training may influence prescribing intensity and recognition of problematic medication combinations. The E-value assesses the strength of association an unmeasured confounder would have with both exposure and outcome, although it does not establish the nonexistence of such a confounder.

Acute disease severity may serve as an unmeasured confounder, not accounted for by chronic comorbidity indices such as the CCI. Patients with greater illness severity may receive a higher number of prescriptions and exhibit increased vulnerability to medication-

related complications, necessitating more oversight by healthcare professionals. Formal severity assessments were unavailable for these wards; residual confounding by the severity of acute illness cannot be excluded.

Hospital-specific factors influencing overall prescribing patterns and formulary preferences are significant unmeasured variables in a single-center study. These factors may affect the total medication count and the observed prescribing combinations, thereby restricting the generalisability of the adjusted correlation identified herein. The E-value offers insight into the robustness of our findings against unmeasured confounding; it does not eliminate the possibility of such confounding.

Generalisability: Who This Study Does and Does Not Apply To

The results are primarily applicable to other adult hospital populations with Type 2 Diabetes Mellitus receiving polypharmacy at the examined tertiary institution. Exercise caution when extrapolating results to the subsequent populations, which were not directly included in this study:

Outpatients and primary care individuals diagnosed with Type 2 Diabetes Mellitus. Outpatients and primary care patients may exhibit distinct distributions of medication counts, monitoring contexts, and prescribing practices compared to our inpatient group. The prevalence numbers from this study should not be assumed to apply to patients in community settings.

Patients receiving care at hospitals with greater resources. Patients treated in institutions with established clinical pharmacy services, electronic prescription decision support, and/or formulary constraints may differ significantly from those in our study. The extent to which observed prevalences and adjusted relationships can be generalized across situations remains unclear.

Patients with diabetes types other than Type 2 Diabetes Mellitus (T2DM). Type 1 diabetic mellitus, gestational diabetes, and secondary diabetes were omitted from the studies due to their differing treatment protocols and the likelihood of unique medication combinations.

Geriatric patients. Individuals aged 80 or older were underrepresented in this cohort, which had a mean age of 54.2 years. Considering that the risk associated with medicine may fluctuate due to age-related deterioration in renal and hepatic function, the results of this study should be interpreted with caution for elderly inpatients.

Implications for Research

This analysis highlights key areas that should be prioritised in future research endeavours. The subsequent stage should ideally involve a prospective multicenter (preferably interventional) study to ascertain whether medication review can mitigate patient-level damage associated with these prescribing trends.

The study does not allow for the determination of incidence rates. This study was not longitudinal; hence, we cannot evaluate whether the identified pharmaceutical safety indicators led to further gastrointestinal bleeding, acute renal damage, dysglycemia, or other unfavourable patient outcomes.

The study cannot demonstrate that reducing these prescribing behaviours mitigates patient-level harm. This study's non-interventional nature precludes us from demonstrating the efficacy of an intervention and from eliminating the potential for residual confounding.

The applicability of these results to other hospitals or locations globally remains uncertain. This investigation was performed at a single center; hence, the prevalence estimates, adjusted relationships, and potential intervention effects may lack generalisability to different environments or implementation scenarios. A suitable subsequent step would be a prospective multicenter study that examines patient-level outcomes and assesses the impact of a systematic medication review intervention, when feasible.

CONCLUSION

Our study revealed a significant prevalence of predetermined high-risk medication combinations and deficiencies in gastroprotection among hospitalized persons with type 2 diabetes mellitus undergoing polypharmacy, as observed in this single-center, 30-day cross-sectional investigation at a tertiary hospital in Nasiriyah, Iraq. The total number of drugs correlated with the administration of at least one predefined medication combination in the secondary exploratory analysis (adjusted OR 1.269; 95% CI 1.138–1.417; $p<0.001$). This result should be viewed as exploratory and hypothesis-generating rather than confirming; it is statistically significant but does not demonstrate an independent predictive or causal influence.

The constraints associated with interpreting the primary findings include the following: we did not ascertain whether any of these prescribing behaviours resulted in patient harm. This cross-sectional study lacks long-term outcomes data, preventing it from

determining if the observed pharmaceutical safety indicators correlate with patient-level gastrointestinal bleeding episodes, acute renal damage, dysglycemia, or other unfavourable clinical outcomes. This study identifies the risks associated with pharmacologic drugs and prescribing practices, rather than measured clinical injuries.

The findings of this study inform medication safety evaluations at the local hospital and future prospective research in analogous inpatient environments. This data should not be utilized to provide adequate evidence for regional implementation or to draw guideline-level conclusions. A prospective multicenter study assessing patient-level outcomes and evaluating a structured medication review intervention might yield more useful results, if practicable.

DECLARATIONS

Author Contributions

Author contributions according to the CRediT taxonomy are reported by author initials: Conceptualisation, Methodology, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing, and Supervision.

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Ethics approval

Ethics approval was obtained from the National University Research Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki (2013 revision). The approving ethics committees waived the requirement for written informed consent.

Consent for publication

Not applicable. No personally identifiable information is included in this manuscript.

Data availability

De-identified study data, the data dictionary, statistical analysis plan, and analysis syntax files are available from the corresponding author upon reasonable request, subject to institutional and ethical restrictions.

Conflicts of interest

The authors declare no competing interests.

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