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Predicting rifampicin interaction magnitude from strong CYP3A inhibitor interactions in clinical reports published from 2020 through 2025

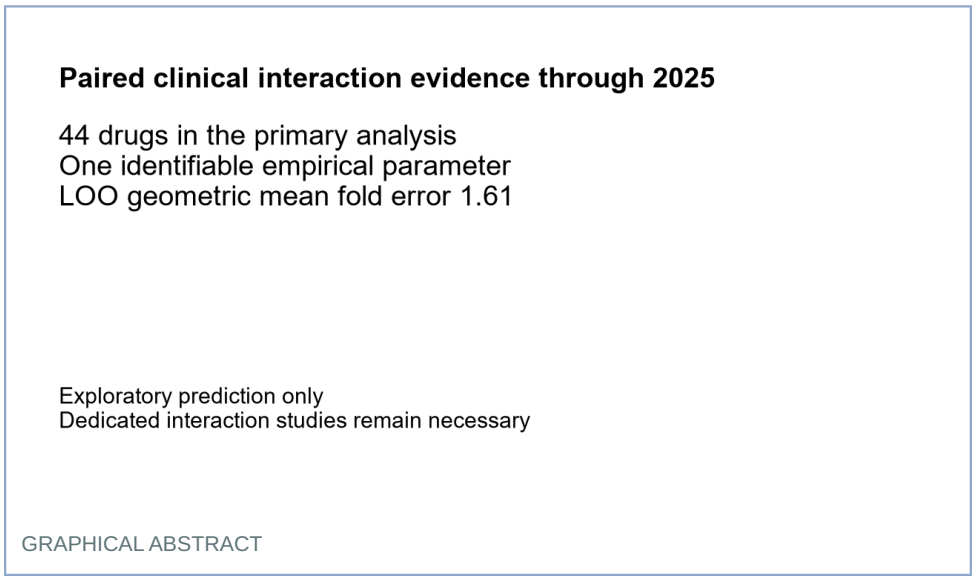
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ABSTRACT



Background: Dedicated clinical interaction studies with the index inducer rifampicin are costly and are often completed late in development. Whether the magnitude of the rifampicin interaction can be anticipated from a strong cytochrome P450 3A (CYP3A) inhibitor study already performed for the same victim drug has not been quantified in the contemporary clinical literature.

Methods: We retrospectively restricted a frozen PubMed search retrieved on 6 November 2026 to reports published by 31 December 2025. Paired inhibitor and rifampicin AUC ratios were available for 48 drugs, of which 44 formed the primary CYP3A analysis. An identifiable one-parameter empirical static model was fitted on the log scale, with 2,000 drug-level bootstrap resamples and leave-one-drug-out cross-validation against log–log regression and a no-covariate predictor. This date-restricted reanalysis does not establish completeness of the underlying single-database search.

Results: The fitted effective parameter K was 9.30 (95% bootstrap CI 7.41–11.65). Under an imposed complete-inhibition assumption, this corresponds to L = 10.30; inhibition completeness and induction strength cannot be estimated separately from these paired ratios. In-sample geometric mean fold error was 1.59 (95% CI 1.41–1.77). Leave-one-drug-out errors were 1.61 for the static model, 1.56 for log–log regression and 1.91 for the no-covariate predictor; 79.5% of static-model predictions were within two-fold and 93.2% within three-fold. The inhibitor AUC-ratio threshold of 2 identified a rifampicin ratio at or below 0.20 with sensitivity 81.8% (95% CI 61.5–92.7) and specificity 77.3% (56.6–89.9).

Conclusions: In this date-restricted exploratory synthesis, inhibitor interaction magnitude carried information about rifampicin exposure loss, but prediction error remained substantial. The effective fitted parameter is not an independently measured biological induction factor. The model does not replace dedicated interaction studies or establish dose-adjustment rules.

Keywords: drug–drug interaction; cytochrome P450 3A; rifampicin; enzyme induction; pharmacokinetics; systematic review; clinical pharmacology

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1. Introduction

Coadministration of a strong inducer of cytochrome P450 3A (CYP3A) with a drug cleared by that enzyme is one of the few pharmacokinetic interactions that routinely causes therapeutic failure rather than toxicity. Rifampicin, the index inducer used in regulatory interaction studies, increases hepatic and intestinal CYP3A activity through pregnane X receptor-mediated transcriptional activation and can reduce victim-drug exposure by more than 90%. The consequences are not hypothetical: loss of antiretroviral, antineoplastic or anticoagulant exposure during rifampicin-containing therapy translates directly into virological breakthrough, tumour progression or thrombosis.

Clinical interaction studies remain the reference standard for characterising strong inhibition and induction. Biomarker-informed evaluation and physiologically based pharmacokinetic modelling provide complementary approaches, but require additional data and context-specific qualification [2, 3]. A simple prediction from an available inhibitor study may aid research prioritisation, provided its error and assumptions are made explicit.

Under a static clearance model, an inhibitor AUC ratio may contain information about susceptibility to induction. Related relationships have been used for non-oral CYP3A substrates and CYP2B6 [4, 5]. Paired ratios alone, however, do not separately identify inhibition completeness and induction strength: without saturation the prediction depends only on $K = (L - 1)/I$.

The question is relevant to medication-safety research in Saudi Arabia, where health-system reform includes better pharmaceutical care [6]. This review does not contain Saudi patient-level validation. It therefore addresses a general pharmacokinetic prediction question rather than demonstrating local clinical effectiveness.

We reanalysed paired clinical AUC ratios from reports published from 2020 through 2025, estimated a single effective static-model parameter, assessed drug-level cross-validated predictive accuracy and described a screening threshold for large exposure loss.

2. Methods

2.1 Design and reporting

This is a date-restricted reanalysis of an existing single-database systematic search, with model-based synthesis of aggregate pharmacokinetic ratios. PRISMA 2020 guided reporting [1], but the original review was not prospectively registered and extraction was not performed independently in duplicate. The revised publication cutoff and identifiable model were introduced during editorial review, after the original results were known.

2.2 Data source and search

The supplied PubMed search was executed on 6 November 2026 using inhibitor, rifampicin, phase 1 and pharmacokinetic terms, restricted to English-language records from 2020. We reviewed the frozen PubMed XML publication dates and excluded records first published after 31 December 2025. Of 107 retrieved records, 99 had a publication date no later than 2025. This is retrospective date filtering of the supplied search, not a search performed in 2025 or a newly validated comprehensive search. Search restrictions and reliance on one database may omit eligible studies.

2.3 Eligibility

Eligible reports described a clinical pharmacokinetic study in adults in which a victim drug was administered alone and with multiple-dose rifampicin, and in which the same victim drug was also studied with a strong CYP3A inhibitor within the same development programme, with a geometric mean or geometric least-squares mean AUC ratio reported for both perpetrators. Reports presenting only model-predicted ratios, reviews, population pharmacokinetic analyses, case reports and in vitro-only reports were excluded, as were reports in which a usable paired ratio could not be obtained.

The primary analysis set comprised victim drugs whose interaction the source investigators attributed to hepatic or intestinal CYP3A. Drugs for which the source investigators identified a different dominant pathway — P-glycoprotein or CYP2C8 — and drugs studied in patients rather than healthy participants were held out of the primary set and analysed separately, because for these the inhibitor AUC ratio does not carry information about CYP3A-mediated clearance.

2.4 Variables and outcomes

For each victim drug the following were extracted: the AUC ratio with the strong CYP3A inhibitor (AUC extrapolated to infinity preferred, otherwise AUC to the last quantifiable concentration), the identity of that inhibitor, the AUC ratio with multiple-dose rifampicin, the study population, the dominant elimination pathway as described by the source investigators, and the PubMed identifier. The primary outcome was the agreement between the rifampicin AUC ratio predicted from the inhibitor AUC ratio and the observed rifampicin AUC ratio.

2.5 Statistical analysis

Let $f^* = \max(0, 1 - 1/\mathrm{AUCRinh})$, the apparent CYP3A fraction under an assumed complete-inhibition model. The revised empirical prediction is

$$\mathrm{AUCRrif} = 1 / (1 + K \cdot f^*),$$

where K is a single effective parameter. In the unsaturated original parameterisation,

$K = (L - 1) / I$. Therefore I and L are not separately identifiable from these observations.

K was estimated by minimising squared log prediction errors over $K > 0$. Uncertainty used 2,000 nonparametric drug-level bootstrap resamples and percentile 95% intervals. If I is fixed to 1, L equals 1 + K by assumption; it must not be interpreted as an independently identified induction estimate. This reparameterisation and publication-date restriction are editorial corrections rather than prespecified analyses.

Each drug was omitted in turn, the parameter was re-estimated, and the omitted ratio was predicted. Reference predictors were log–log linear regression and the geometric mean rifampicin ratio. Performance was

summarised with geometric mean fold error, directional average fold error, log RMSE, and proportions within two-fold and three-fold. Prior paired significance tests from the 48-drug analysis were withdrawn and were not carried over to this 44-drug analysis.

The threshold AUCRinh ≥ 2 was assessed against AUCRrif ≤ 0.20, with Wilson 95% confidence intervals. Revised sensitivity analyses included all 48 date-eligible drugs, an itraconazole-only subset and exclusion of midazolam. The obsolete free-I sensitivity analysis was removed because the revised model estimates only K. Spearman correlation described the relation between paired ratios.

The revised calculation used Python, NumPy, pandas and SciPy, with seed 20261108. The original input file was preserved; a separate date-eligibility table and revised numerical results were saved. All evidence included in the revised analysis was published by 31 December 2025; retrieval and reanalysis occurred in 2026.

3. Results

3.1 Study selection and characteristics

Of 107 records in the supplied search, 99 had publication dates no later than 2025. The extracted 52-drug set contained four drugs with source reports first published in 2026: aildenafil, vebreltinib, DA-8010 and tinlarebant; these were excluded. Forty-eight date-eligible drugs remained, of which four retained the original pathway or patient-population exclusions, leaving 44 in the primary analysis. Records, reports and drugs are distinct units and should not be treated as an interchangeable PRISMA flow.

Twenty-two of 44 drugs had a rifampicin AUC ratio at or below 0.20. The complete date-restricted paired ratios and revised predictions are shown in Table 1. Four additional date-eligible drugs were retained outside the primary set for the original pathway or patient-population reasons, as described in Table 4.

3.2 Relationship between the inhibitor and inducer interactions

The paired AUC ratios were inversely related (Spearman rho −0.759; P = 2.36 × 10−9). This is an association across drug programmes and does not establish a within-patient causal exposure relationship.

3.3 Mechanistic model

The effective parameter K was 9.30 (95% bootstrap CI 7.41–11.65). The equivalent value L = 10.30 assumes complete inhibition. No separate estimate or confidence interval for inhibition completeness is identifiable. The former claims of I = 0.98 and an independently estimated biological L were withdrawn.

In-sample geometric mean fold error was 1.59 (95% bootstrap CI 1.41–1.77), directional average fold error 0.998 and log RMSE 0.569. Predictions were within two-fold for 79.5% and within three-fold for 95.5% of drugs. Average agreement does not imply absence of error for an individual drug.

3.4 Cross-validated predictive performance

Leave-one-drug-out cross-validation gave geometric mean fold errors of 1.61 for the one-parameter static model, 1.56 for log–log regression and 1.91 for the no-covariate predictor. Static-model predictions were within two-fold for 79.5% and three-fold for 93.2%. These are internal drug-level resampling results, not independent prospective validation (Table 2).

The largest exposure losses were not fully explained by the inhibitor ratio. Unmodelled intestinal first-pass effects, transporter activity, study design and extraction error may contribute. Aildenafil was excluded on publication date and no longer contributes to the fitted curve or its reported errors.

3.5 Screening rule

The screening threshold gave 18 true positives, 5 false positives, 4 false negatives and 17 true negatives. Sensitivity was 81.8% (95% CI 61.5–92.7), specificity 77.3% (56.6–89.9), positive predictive value 78.3%

(58.1–90.3) and negative predictive value 81.0% (60.0–92.3). Four drugs with an inhibitor ratio below 2 still lost at least 80% of exposure; a negative result does not exclude a major interaction.

3.6 Sensitivity analyses

The revised sensitivity analyses are shown in Table 3. They vary the eligible drug set while retaining the identifiable one-parameter model. Numerical results from the former 48-drug primary analysis are superseded. None of these sensitivity analyses separates inhibition completeness from induction strength.

Additional post hoc scope sensitivity omitted six programmes with active-moiety, ritonavir-boosting or prominent non-CYP3A pathway concerns (mobocertinib, simnotrelvir, tucatinib, ozanimod, vericiguat and manogepix). In the remaining 38 drugs, K was 9.16 and in-sample GMFE 1.57. This addresses heterogeneity of the model context; it is not an independent validation or a prespecified analysis.

Table 1. Paired AUC ratios and revised one-parameter predictions for 44 drugs with reports published through 2025.

Drug / الدواء	PMID	Inhibitor / المثبط	AUCR inh	AUCR rif	f*	Predicted	Fold error
Youkenafil	35605912	itraconazole	12.000	0.0200	0.917	0.1050	5.25
Lemborexant	33455055	itraconazole	3.702	0.0340	0.730	0.1284	3.78
Mobocertinib	34145979	itraconazole	6.270	0.0500	0.841	0.1134	2.27
Balovaptan	32935287	itraconazole	5.570	0.0700	0.820	0.1159	1.66
Almonertinib	34267345	itraconazole	3.380	0.0740	0.704	0.1325	1.79
Zanubrutinib	31875923	itraconazole	3.800	0.0740	0.737	0.1273	1.72
Avacopan	38423992	itraconazole	2.190	0.0741	0.543	0.1652	2.23
Iclepertin	34716565	itraconazole	5.970	0.0980	0.832	0.1144	1.17
TPN171	40640049	itraconazole	2.857	0.0986	0.650	0.1419	1.44
Limertinib	37811634	itraconazole	3.898	0.1214	0.743	0.1263	1.04
Pemigatinib	34282472	itraconazole	1.880	0.1500	0.468	0.1868	1.25
Ocedurenone	37357226	itraconazole	2.040	0.1600	0.510	0.1742	1.09
Soticlestat	38123352	itraconazole	1.240	0.1640	0.194	0.3571	2.18
FHND9041	40336126	itraconazole	1.683	0.1651	0.406	0.2095	1.27
Naldemedine	32323104	itraconazole	2.910	0.1700	0.656	0.1408	1.21
Senaparib	36458825	itraconazole	2.800	0.1700	0.643	0.1433	1.19
Iberdomide	32965548	itraconazole	2.400	0.1800	0.583	0.1556	1.16
Midazolam	39073244	itraconazole	11.220	0.1800	0.911	0.1056	1.70
Simnotrelvir	39299559	itraconazole	1.250	0.1850	0.200	0.3496	1.89
Rimegepant	39364583	itraconazole	4.140	0.1900	0.758	0.1242	1.53
Laquinimod	32237115	ketoconazole	3.100	0.2000	0.677	0.1370	1.46
Brigatinib	31287236	itraconazole	2.010	0.2000	0.502	0.1763	1.13

Drug / الدواء	PMID	Inhibitor / المثبط	AUCR inh	AUCR rif	f*	Predicted	Fold error
Zilurgisertib	40462754	itraconazole	2.130	0.2100	0.531	0.1685	1.25
Tropifexor	35962468	itraconazole	1.470	0.2300	0.320	0.2517	1.09
Parsaclisib	32515832	itraconazole	2.070	0.2300	0.517	0.1722	1.34
Entrectinib	34417912	itraconazole	6.040	0.2300	0.834	0.1141	2.01
Olverembatinib	39228016	itraconazole	2.587	0.2481	0.613	0.1491	1.66
Bictegravir	40518723	voriconazole	1.610	0.2500	0.379	0.2211	1.13
Gilteritinib	32304015	itraconazole	2.214	0.2850	0.548	0.1639	1.74
Esaxerenone	32250463	itraconazole	1.530	0.3120	0.346	0.2369	1.32
Capmatinib	36087217	itraconazole	1.420	0.3350	0.296	0.2666	1.26
Fruquintinib	40366223	itraconazole	1.100	0.3500	0.091	0.5419	1.55
Futibatinib	37132707	itraconazole	1.410	0.3600	0.291	0.2699	1.33
Pexidartinib	36264536	itraconazole	1.730	0.3700	0.422	0.2031	1.82
Savolitinib	34322894	itraconazole	1.084	0.3850	0.077	0.5812	1.51
Sotorasib	38421129	itraconazole	1.260	0.4900	0.206	0.3426	1.43
SHR0302	37005376	itraconazole	1.480	0.5100	0.324	0.2490	2.05
Tucatinib	35931943	itraconazole	1.300	0.5200	0.231	0.3178	1.64
Manogepix	38757982	itraconazole	1.000	0.5470	0.000	1.0000	1.83
Ritlecitinib	40331456	itraconazole	1.150	0.5500	0.130	0.4518	1.22
SKLB1028	39533673	itraconazole	1.280	0.7000	0.219	0.3295	2.12
Vericiguat	32458378	ketoconazole	1.130	0.7100	0.115	0.4831	1.47
Ozanimod	32857315	itraconazole	1.130	0.7600	0.115	0.4831	1.57
Asciminib	35616006	clarithromycin	1.350	0.8700	0.259	0.2931	2.97

AUC, area under the concentration–time curve. Predictions are 1/[1 + K(1 − 1/AUCRinh)] with K = 9.30; values below zero for the apparent fraction are set to zero. Fold error is the larger of observed/predicted and predicted/observed. Source identifiers are PubMed IDs.

Table 2. Leave-one-drug-out predictive performance in 44 date-eligible drugs.

Model / النموذج	GMFE	AFE	log RMSE	Within 2-fold %	Within 3-fold %
Static K / الساكن	1.611	0.997	0.583	79.5	93.2
Log–log / اللوغاريتمي	1.557	1.005	0.586	81.8	93.2
No covariate / بلا متغير	1.907	1.000	0.843	59.1	81.8

RMSE = root mean squared error. The average fold error measures systematic bias, with 1.00 indicating no bias; the geometric mean fold error measures average magnitude of error irrespective of direction. Each model was re-estimated with each drug omitted in turn and used to predict the omitted drug.

Table 3. Revised one-parameter sensitivity analyses using reports published through 2025.

Analysis / التحليل	n	K	L if I=1	GMFE	Within 2-fold %
All eligible / جميع المؤهلة	48	8.678	9.678	1.626	81.2
Itraconazole / إيتراكونازول	40	9.843	10.843	1.595	80.0
Without midazolam / دون ميدازولام	43	9.473	10.473	1.594	79.1

K is an effective empirical parameter. L = 1 + K only if complete inhibition is imposed. These parameters do not separately measure biological inhibition and induction.

Table 4. Victim drugs held out of the primary analysis set, with the reason for exclusion.

Victim drug	CYP3A inhibitor	AUC ratio with inhibitor	AUC ratio with rifampicin	Reported dominant pathway	Population	PMID
Pamiparib	itraconazole	0.99	0.57	CYP3A and CYP2C8	Patients with solid tumours	33772633
Trilaciclib	itraconazole	0.86	0.83	Not CYP3A-dominant	Healthy participants	35842567
Filgotinib	itraconazole	1.45	0.73	P-glycoprotein-mediated	Healthy participants	34498807
Talazoparib	itraconazole	1.56	1.02	P-glycoprotein, not CYP3A	Patients with solid tumours	31770456

AUC = area under the plasma concentration–time curve; CYP3A = cytochrome P450 3A; PMID = PubMed identifier. For these drugs the inhibitor AUC ratio reflects transporter modulation or a non-CYP3A enzymatic pathway, so it does not carry information about CYP3A-mediated clearance; they were analysed only in the combined sensitivity analysis.

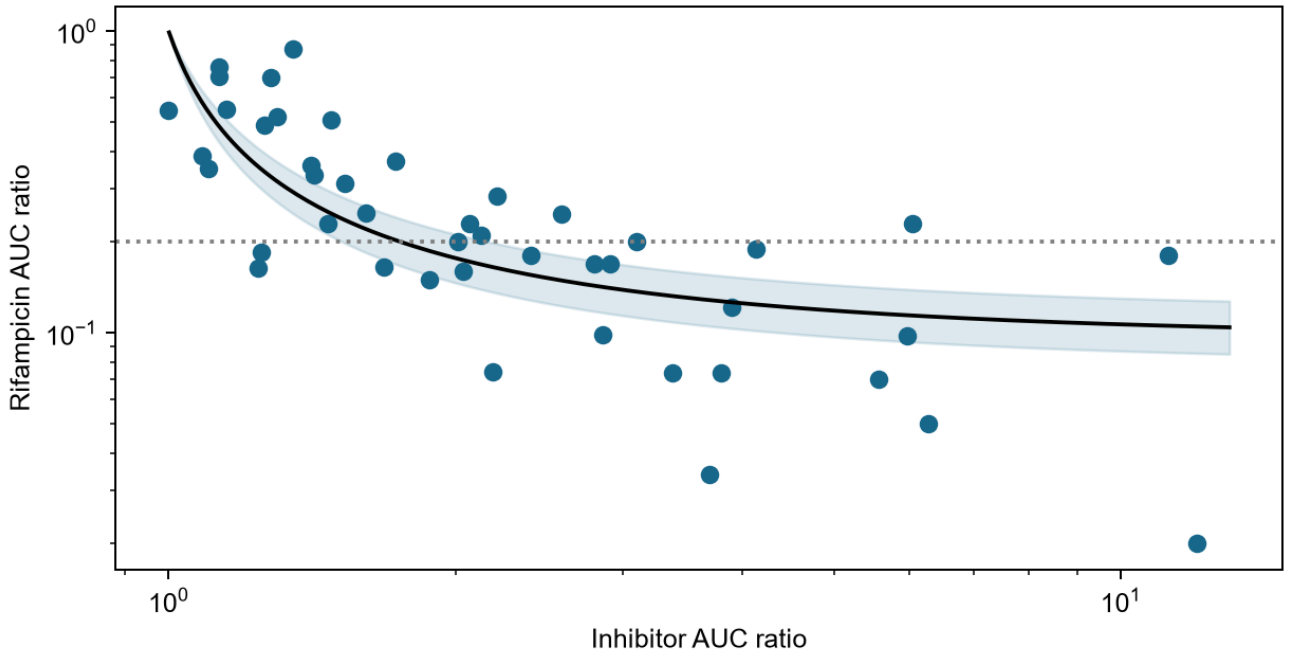


Figure 1. Paired inhibitor and rifampicin AUC ratios for 44 drugs and the revised one-parameter curve. The band represents the percentile bootstrap interval for the fitted curve; it is not an individual prediction interval. Both axes are logarithmic.

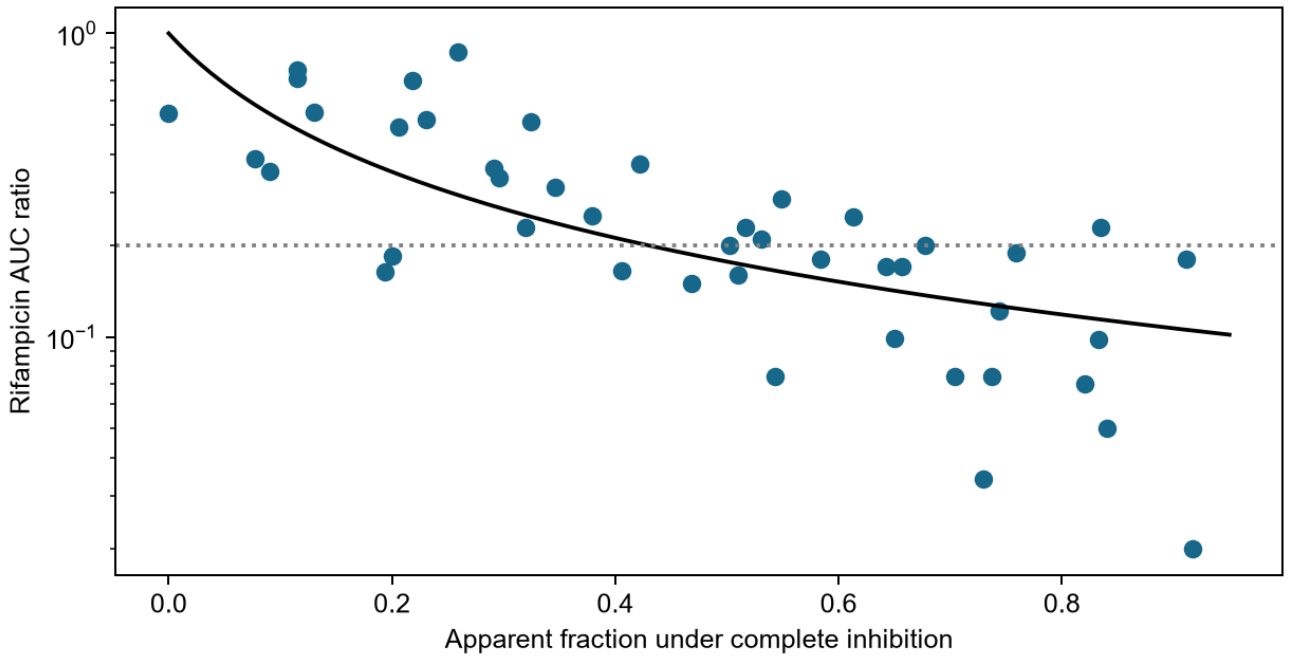


Figure 2. Rifampicin AUC ratio against f* = 1 − 1/AUCRinh under the assumed complete-inhibition parameterisation. The curve uses K = 9.30. f* is an apparent model quantity, not an independently measured clearance fraction.

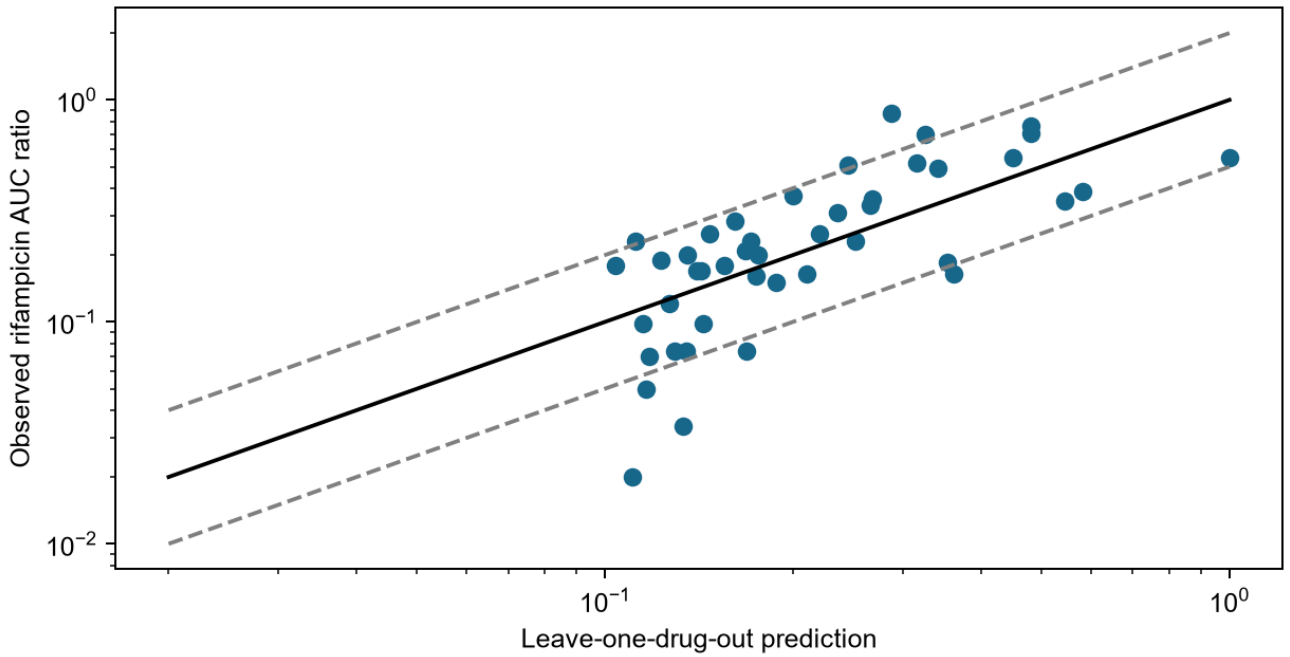


Figure 3. Observed versus leave-one-drug-out predicted rifampicin ratios for 44 drugs. Solid line is identity; dashed lines mark two-fold error.

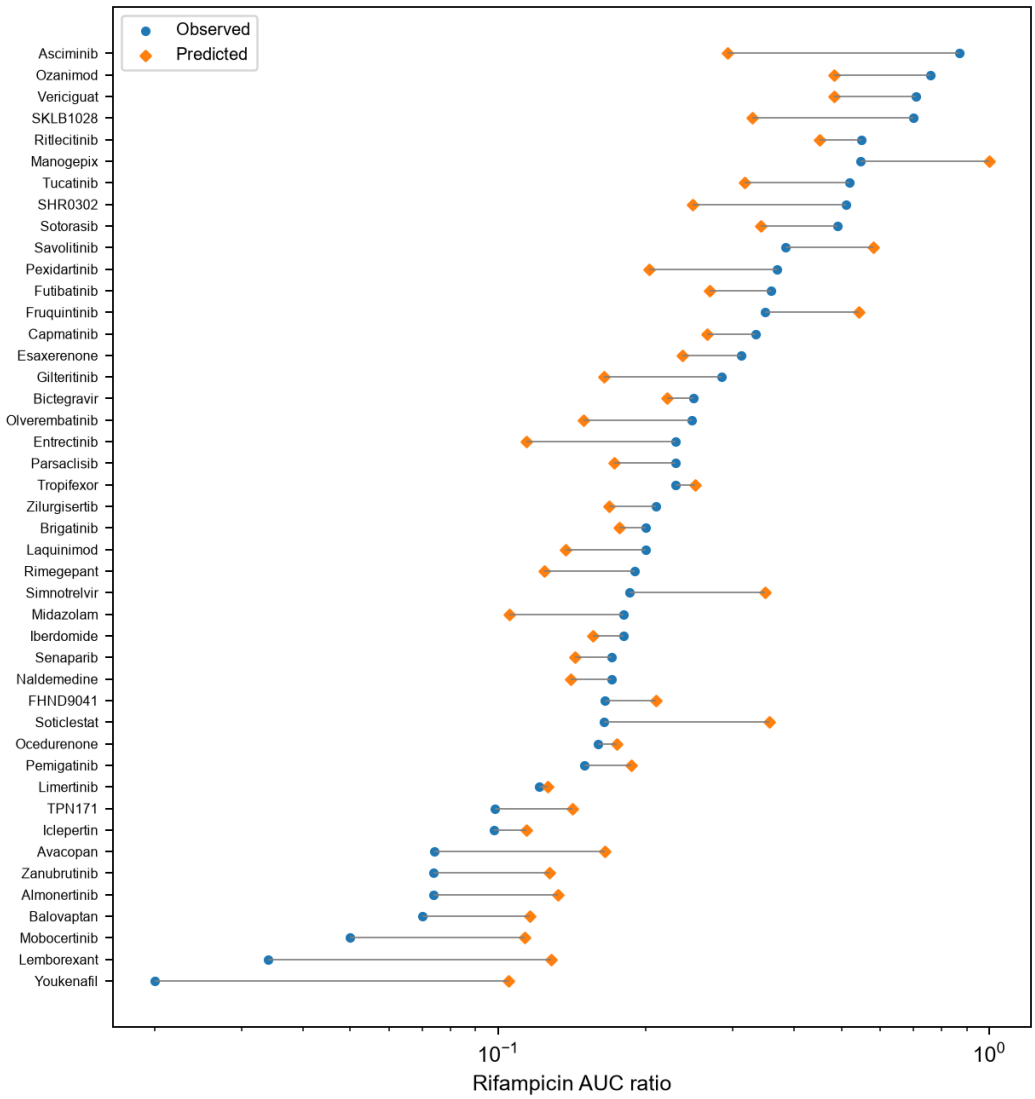


Figure 4. Observed and revised predicted rifampicin AUC ratios for each of the 44 date-eligible primary drugs.

4. Discussion

4.1 Principal findings

The date-restricted analysis retained an inverse relation between inhibitor and rifampicin AUC ratios. A one-parameter static predictor gave a leave-one-drug-out geometric mean fold error of 1.61; log–log regression gave 1.56. The screening threshold had sensitivity 81.8% and specificity 77.3%, with wide intervals. These findings support further prediction research and do not validate a bedside dosing algorithm.

The principal methodological correction is identifiability. The original unsaturated prediction depends on (L − 1)/I, so reporting independent estimates of I and L was not justified. K should be treated as an empirical predictor fitted across heterogeneous drug programmes. Its apparent stability cannot establish a conserved biological induction effect. Internal cross-validation still leaves roughly one fifth of predictions outside two-fold.

4.2 Comparison with prior work

Earlier work used static relationships for non-oral CYP3A substrates and CYP2B6 [4, 5]. The present analysis examines prediction across paired inhibitor–inducer programmes, using the inhibitor ratio as the predictor and drug-level internal cross-validation to estimate error. The effective parameter does not resolve hepatic and intestinal contributions.

The strong-inhibitor classification does not prove complete inhibition in every study or identify I from these data. Biomarker-informed evaluation [2] and PBPK models [3] remain complementary. Model predictions depend on the doses, durations, routes and competing elimination processes represented in the source reports.

Extreme prediction errors may reflect intestinal and hepatic first-pass effects, transporter modulation or measurement and extraction uncertainty. The available paired point estimates cannot distinguish these explanations. Biological explanations for individual outliers remain hypotheses requiring confirmation from their full study reports.

4.3 Implications for clinical practice in Saudi Arabia

Saudi relevance is indirect. The synthesis contains published aggregate drug-interaction measurements rather than a local patient cohort. Translation would require independent prospective validation in the target population and explicit assessment of interacting drugs, comorbidities and exposure–response relationships.

A possible research use is prioritisation of dedicated interaction studies. The model should not direct dose escalation or be embedded as a validated clinical decision rule. Four false-negative drugs in the present sample show that a modest inhibitor ratio cannot be used to reassure clinicians about rifampicin coadministration.

4.4 Strengths and limitations

Strengths are traceable published source identifiers, preservation of the frozen input data, an explicit publication cutoff and revised drug-level resampling. Reproducibility of the calculation does not establish validity or completeness of the extracted evidence.

Important limitations remain: the single English-language PubMed search and phase 1 filter may miss eligible studies; extraction was not independently duplicated; published point estimates were treated as error-free; inhibitor and rifampicin regimens and AUC definitions varied; no formal validated study-quality assessment was supplied; and no independent prospective validation was performed. The date cutoff and model revision were introduced after the original results were known. Source-level full-text verification and a reproducible report-to-drug screening flow are required before final acceptance. Most underlying trials were conducted outside Arab populations; as an aggregate evidence synthesis this is not an original Arab clinical cohort and provides no local validation.

Source verification during correction checked the paired ratios against all 44 deposited source abstracts, with targeted full-text checks where accessible. Abstracts do not fully verify every numerical precision or study-quality item. Mobocertinib measures combined parent-plus-active-metabolite AUC, simnotrelvir is ritonavir-boosted, and several drugs have important alternative pathways; these are not interchangeable mechanistic CYP3A clearance measurements. The original 44-drug set is retained transparently as an empirical synthesis, with the additional 38-drug sensitivity above.

4.5 Future research

Future work should independently verify every extracted ratio and eligibility decision, expand and validate the search, account for study-level uncertainty, and evaluate performance in drug programmes not used for model construction. Separately identifying inhibition and induction would require additional information or constraints, not simply a larger set of the same paired ratios.

5. Conclusions

For reports published from 2020 through 2025, the strong-inhibitor AUC ratio predicted part of the variation in rifampicin exposure loss. The corrected one-parameter model had a leave-one-drug-out geometric mean fold error of 1.61. Its error and false negatives preclude replacement of dedicated interaction studies. The effective parameter is an empirical association rather than an independently identified biological induction factor.

Declarations

Funding: NA

Conflicts of Interest: NA

Institutional Review Board Statement: This study used only publicly available, de-identified, aggregate pharmacokinetic parameters published in the peer-reviewed literature. No human participants were enrolled and no individual-level data were accessed; no institutional review board approval was sought or is claimed.

Informed Consent Statement: Not applicable. The study used published aggregate data only.

Data availability: Source PubMed identifiers are listed in the tables. The supplied search was retrieved on 6 November 2026. Date-eligible paired ratios, the date audit, corrected one-parameter calculation and numerical results accompany this editorial reanalysis. Underlying sources were published by 31 December 2025. Publication dates and retrieval dates have not been backdated.

Author Contributions: NA

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