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IMPACT OF RENAL IMPAIRMENT SEVERITY ON HUMAN RENAL CLEARANCE OF XENOBIOTICS: A COMPARATIVE PHARMACOKINETIC ANALYSIS

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ABSTRACT-

Renal impairment may significantly affect the disposition of xenobiotics through a decrease in renal clearance and an increase in the systemic exposure. This work investigated renal clearance in humans in relation to the severity of renal impairment and the role of dose, route of administration and molecular properties in clearance variability. A secondary pharmacokinetic analysis of 1,706 curated observations of over 500 exogenous compounds was performed. The renal clearance was compared between healthy, mild, moderate and severe renal-impairment groups, and matched analysis was performed to control for differences in compound, study, route and dose. Median renal clearance showed a progressive decrease from healthy to mild, moderate and severe renal impairment (6.228, 2.768, 1.590 and 0.568 L/h respectively). In these categories, the reductions in the medians were 36.9%, 61.2% and 84.2% which were all statistically significant after adjustment in the matched comparisons. The between-compound variability was substantial, with compound identity accounting for a large proportion of clearance variation, but no consistent systematic effects were found for administered dose or route. There were weak inverse relationships between molecular weight, lipophilicity and renal clearance, and a weak positive relationship between hydrogen-bond donor count and renal clearance. But all the molecular descriptors together accounted for only a small fraction of the variability. These findings demonstrate a strong severity-dependent decline in renal clearance while highlighting considerable compound-specific heterogeneity. The combination of renal-function status and drug-specific pharmacokinetic properties could facilitate the adjustment of drug dose and personalized therapy.

Keywords – renal clearance; renal impairment; pharmacokinetics; xenobiotics; dose adjustment; drug disposition

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1. Introduction

Renal clearance is a major determinant of the systemic disposition of many pharmaceutical compounds and xenobiotics. The kidneys contribute to drug elimination through glomerular filtration, active tubular secretion, and tubular reabsorption, and alterations in any of these processes can substantially modify systemic exposure. Renal elimination is affected by several physiological and physicochemical factors such as plasma protein binding, membrane permeability, glomerular filtration rate (GFR), renal blood flow, and activity of transporters. This can therefore affect the pharmacokinetics of drugs and may lead to over-exposure, accumulation, and concentration dependent toxicity, especially for drugs that are mainly excreted via the kidneys (Lea-Henry et al., 2018).

There are significant alterations in drug disposition with progressive renal impairment. The elimination half-life of renally excreted drugs may also be prolonged and the total and renal clearance may be reduced with decreasing kidney function, leading to higher systemic exposure unless adequate adjustment of the dose regimen. Thus, rational dose adjustment necessitates knowledge of the relationship between renal function and drug clearance, not a "one-size fits all" approach. The doses needed for maintenance or the intervals between doses could be modified based on the severity of renal dysfunction and the therapeutic window of the compound and the relative importance of the renal pathways compared to the other pathways involved in its elimination (Roberts et al., 2018). The clinical implications of these adjustments are especially significant for medications that have narrow therapeutic windows, or strong renal clearance dependence (Stefani et al., 2019).

However, the impact of renal disease on pharmacokinetics goes beyond the fact that it decreases filtration. Renal impairment affects substantially active tubular secretion, and changes in transporter mediated elimination may not relate directly to the decrease in GFR. Organic cation drugs have been shown to be sensitive to changes in unbound drug concentration and altered transporter activity by simulation (Follman & Morris, 2018). Chronic kidney disease also can affect other routes of elimination (such as hepatic) by affecting hepatic enzymes and transport systems, suggesting that renal function could affect other physiological processes that impact drug disposition (Tan et al., 2018). Additional studies of organic anion transporters revealed that renal secretion may decrease in a different manner than filtration as chronic kidney disease becomes more severe and this information has significant implications for dose individualization and pharmacokinetic prediction (Tan et al., 2022).

Therefore, renal impairment is an important factor to take into account when assessing pharmacokinetic variations. GFR-based approaches have shown that changes in renal function can provide useful estimates of changes in clearance/exposure for renally eliminated compounds; however, there is some variability in the accuracy of prediction depending on the drug due to differences in elimination pathways (Mahmood, 2020). Therefore, renal impairment studies

typically categorize patients according to renal dysfunction (normal, mild, moderate, severe) to describe changes in systemic exposure and to make dosing recommendations (Ravenstijn et al., 2021). Clinical pharmacokinetic studies have still revealed a clear difference in drug exposure of these renal-function categories, highlighting the relevance of these renal categories in clinical drug evaluation (Katsube et al., 2024).

Although the pharmacokinetic principles governing renal clearance are well established, variability in the degree of reduction can be seen from compound to compound. This may be due to variability in filtration, tubular secretion, reabsorption, physicochemical properties, dosage, and other study level factors. Furthermore, analytical strategy can affect the quantification of renal-impairment effects, as categorical comparisons as well as regression-based strategies can provide complementary information for examining pharmacokinetic changes across renal-function levels (So et al., 2025). Large cross-compound analyses might thus yield a wider perspective on the uniformity and heterogeneity of renal-clearance changes as renal function declines. The objectives of the present analysis were to:

1. Characterize the distribution and between-compound variability of experimentally determined human renal clearance across a broad range of xenobiotics.
2. Quantify changes in renal clearance across healthy, mild, moderate, and severe renal impairment groups using within-compound and within-study comparisons.
3. Examine whether drug-, dose-, administration-route-, and molecular-level characteristics contribute to variability in human renal clearance.

2. Methodology

2.1. Data Source and Study Design

A secondary pharmacokinetic analysis was conducted using experimentally determined human renal-clearance records compiled from published scientific studies (Łapińska & Polak, 2025). Over 500 exogenous compounds were reported from studies from 1947 to 2025 and included in the source compilation. The variables that were available were compound identity, study reference, year of publication, Structural information represented by Simplified Molecular Input Line Entry System (SMILES) notation, Body weight, Route of administration, Analytical method, Number of participants, Health status, Administered dose and renal clearance (CLren, L/h).

There were 1,714 observations in the data set. The records were standardized prior to the analysis, and eight duplicate observations were excluded from the analysis based on the matching of the compound, study, molecular structure, body weight, mode of administration, analytical method, number of participants, health status, dosage and renal-clearance values. The final analytical dataset therefore contained 1,706 observations.

2.2. Classification and Data Processing

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Kidney function categories were uniformly defined by using health-status terminology. Those records that were determined healthy were kept as the reference category. The terms "slight" and "mild" renal impairment were grouped together as "mild" renal impairment, and those with "moderate" and "severe" renal impairment were placed in each of those categories. The four categories for severity indicated above do not include end-stage renal disease or hemodialysis records. Renal-severity comparisons excluded records with renal impairment that did not fit into the healthy, mild, moderate or severe renal-function categories, but included where applicable, in overall descriptive analyses. Administration-route terminology was also standardized, including equivalent intramuscular and inhalation labels.

The main outcome was renal clearance (L/h). Since its distribution was skewed to the right, for this reason the clearance was reported mainly in terms of medians and interquartile ranges (IQR), but means and standard deviations were also computed for descriptive analysis. Renal clearance was log transformed and analyzed in a random-intercept, mixed-effects model; variability between compounds was assessed for healthy observations with positive renal clearance values. The random intercept was specified as compound identity and the intraclass correlation coefficient (ICC) was determined from between-compound and residual variance components.

2.3. Renal Impairment Analysis

The effect of renal impairment was explored by conducting matched comparisons in order to reduce the heterogeneity that could be due to inter-compound and inter-study differences. The observations were matched by compound, study, route of administration and dosages administered. If there were multiple records for the same matched condition, the median renal clearance was employed.

Renal clearance for each category of renal impairment was normalized by the matched value in the healthy group. This ratio was then used to calculate the percentage reduction in clearance. The values of the ratios of mild, moderate, and severe impairment were tested separately against a null ratio of 1 by applying two-sided Wilcoxon signed-rank tests to the log-transformed ratio. The 5000 bootstrapped resamples were clustered at the compound level to estimate 95% confidence intervals for median ratios. The P values of the three severity comparisons were adjusted by Holm.

All four renal-function categories (healthy, mild renal impairment, moderate renal impairment, and severe renal impairment) were present within a given compound, study, route and dose group for each matched set and a repeated measures analysis was performed for each of these groups. The Friedman test was used to compare the differences between the four categories. The proportion of matched sets showing a gradual decrease in clearance from healthy to severe impairment was also calculated.

2.4. Dose and Administration-Route Analyses

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Healthy observations of positive dose and clearance were used for the evaluation of potential dose related changes in renal clearance. Studies were only analysed for compound–study–route combinations with a minimum of 3 distinct dose levels. Median clearance values were calculated for each dose level and log transformed renal clearance was then regressed against log transformed dose in each set of data. The slope of the curve obtained was a measure of the direction and magnitude of dose dependence. The Wilcoxon signed rank test was used to determine if the distribution of slopes was different from zero.

The administration-route effects were assessed by exact matched comparisons in healthy volunteers for compounds reported within the same study at the same dose through both oral and intravenous administration. We calculated the clearance ratios of oral to intravenous, and compared the deviation from unity by using a two-sided Wilcoxon signed-rank test of log-transformed clearance ratios.

2.5. Molecular Descriptor Analysis

Molecular structures encoded as SMILES were used to calculate physicochemical descriptors. If there are two or more valid structural strings for a compound, the one that occurs most was chosen. The following cheminformatics procedures were used to calculate molecular weight, partition coefficient between octanol–water (LogP), topological polar surface area (TPSA), number of hydrogen-bond donors, hydrogen-bond acceptors, and number of rotatable bonds.

To minimize the confounding effect of renal disease, only compound-level median renal-clearance values from healthy subjects were used. Spearman's rank correlations were used to determine the relationship between each descriptor and renal clearance. The 95% CI was calculated with 2,500 bootstrap resample and the probability values for the six descriptor analyses were adjusted by the Holm procedure. The log-clearance of compounds were modelled by a multi-variable linear regression model with the predictors molecular weight, LogP, TPSA, and rotatable-bond count. The coefficient of determination (R 2) and the adjusted R 2 were used to summarize the performance of the model; and heteroscedasticity-consistent standard errors were used.

Statistically significant p values were defined as < 0.05 for all statistical tests. Data preparation and statistical analyses were programmed with the use of standard data-analysis, statistical-modelling and cheminformatics software libraries.

3. Results

3.1. Variability in Human Renal Clearance

Renal clearance showed substantial variability across xenobiotics, with an overall median of 5.082 L/h (IQR: 1.133–10.517 L/h) and values ranging from 0 to 76.080 L/h. Among observations obtained from healthy participants, the median renal clearance was 6.228 L/h (IQR: 1.877–11.741 L/h). At the compound level, the median clearance across 448 xenobiotics represented in healthy

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participants was 5.329 L/h (IQR: 1.473–10.838 L/h), demonstrating pronounced between-compound heterogeneity.

A random-intercept analysis of positive renal-clearance observations from healthy participants produced an intraclass correlation coefficient of 0.945, indicating that most variation in log-transformed renal clearance occurred between compounds rather than among repeated observations of the same compound. Renal clearance also declined progressively with increasing severity of renal impairment. As presented in Table 1, the median decreased from 6.228 L/h in healthy participants to 2.768 L/h in mild renal impairment, 1.590 L/h in moderate impairment, and 0.568 L/h in severe impairment. The progressive reduction is illustrated in Figure 1.

Table 1. Renal clearance according to renal function category

Renal function	Observations (n)	Compounds (n)	Median CLren (L/h)	IQR (L/h)	Mean ± SD (L/h)
Healthy	1,240	448	6.228	1.877–11.741	8.373 ± 8.275
Mild impairment	58	55	2.768	0.902–6.797	4.589 ± 5.430
Moderate impairment	87	74	1.590	0.464–3.551	2.394 ± 2.534
Severe impairment	85	75	0.568	0.185–1.140	0.976 ± 1.420

CLren, renal clearance; IQR, interquartile range.

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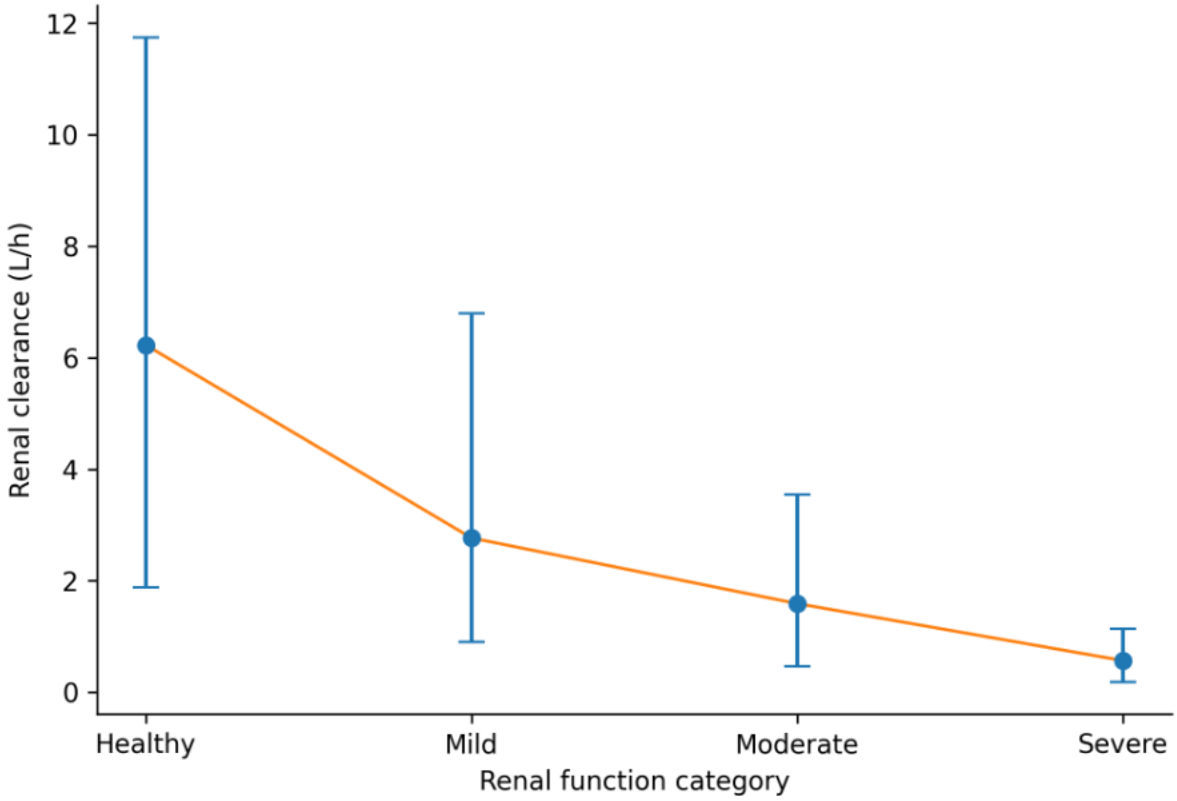


Figure 1. Renal clearance across renal function categories.

Points represent median renal clearance and error bars represent the interquartile range.

3.2. Reduction in Renal Clearance with Increasing Renal Impairment

The progressive reduction in clearance remained evident when comparisons were restricted to the same compound, study, administration route, and dose. Relative to the corresponding healthy group, mild renal impairment was associated with a median renal-clearance ratio of 0.631 (95% CI: 0.582–0.697), corresponding to a median reduction of 36.9%. The ratio decreased further to 0.388 (95% CI: 0.319–0.437) in moderate renal impairment and 0.158 (95% CI: 0.123–0.208) in severe impairment, equivalent to median reductions of 61.2% and 84.2%, respectively. As shown in Table 2, all three paired reductions remained statistically significant after adjustment for multiple comparisons (adjusted $p < 0.001$).

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Table 2. Matched within-study changes in renal clearance according to renal impairment severity

Renal impairment	Matched comparisons (n)	Compounds (n)	Median CLren ratio vs healthy	IQR	95% CI	Median reduction	Adjusted p
Mild	52	49	0.631	0.550 – 0.768	0.582 – 0.697	36.9%	<0.001
Moderate	59	54	0.388	0.255 – 0.514	0.319 – 0.437	61.2%	<0.001
Severe	61	58	0.158	0.100 – 0.244	0.123 – 0.208	84.2%	<0.001

The renal-clearance ratio represents clearance in the renal-impairment group divided by clearance in the matched healthy group. Comparisons were matched by compound, study, administration route, and dose. Confidence intervals were obtained using compound-level clustered bootstrap resampling.

The dose- and study-matched analysis therefore demonstrated a clear severity-dependent gradient, as shown in Figure 2. Among the 42 matched sets that contained healthy, mild, moderate, and severe renal-function categories simultaneously, median renal clearance declined from 5.194 L/h in healthy participants to 2.926, 1.390, and 0.606 L/h in the mild, moderate, and severe groups, respectively. The overall difference across the four categories was highly significant (Friedman $\chi^2(3) = 117.20$, $p < 0.001$). A strictly progressive decline from healthy through severe impairment occurred in 36 of 42 matched sets (85.7%), while 37 sets (88.1%) showed a non-increasing pattern when ties were permitted.

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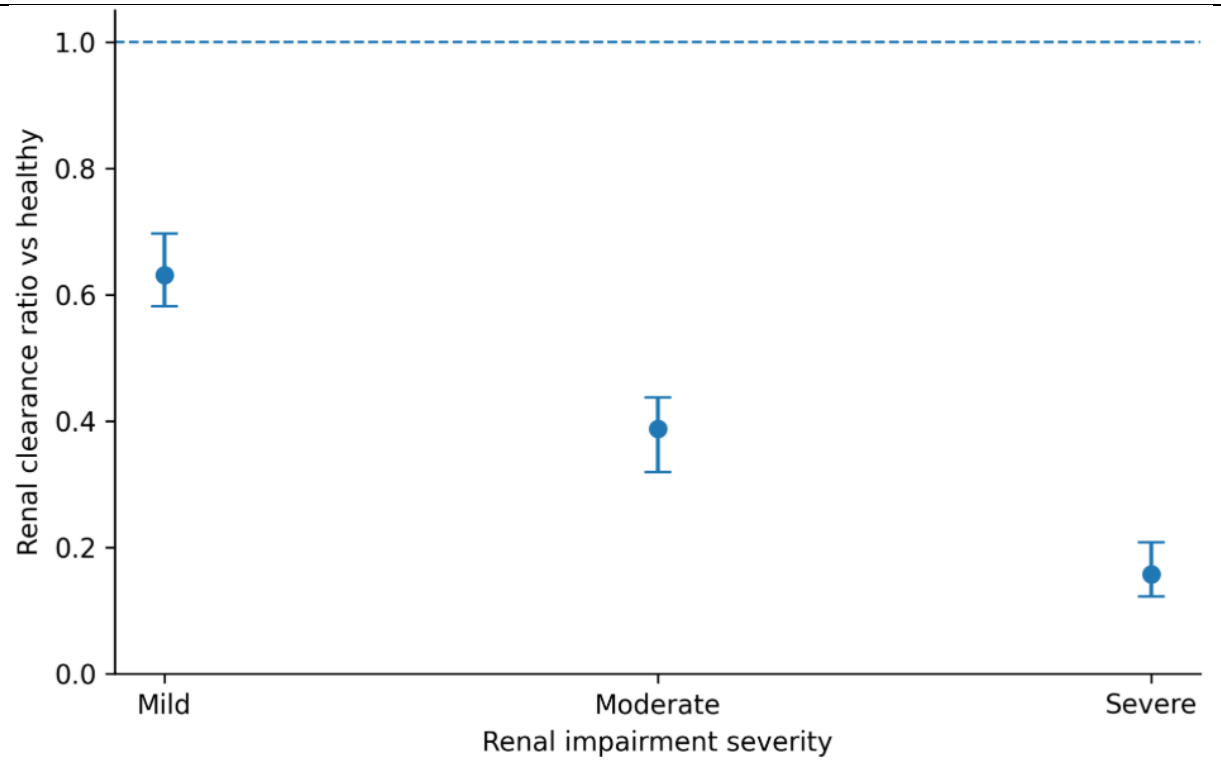


Figure 2. Matched renal-clearance ratios across increasing renal impairment severity.

Points represent median within-study ratios relative to healthy participants; error bars represent 95% compound-clustered bootstrap confidence intervals. The dashed reference line represents no change from healthy renal clearance.

3.3. Influence of Dose, Administration Route, and Molecular Characteristics

Drug identity accounted for a substantial proportion of renal-clearance variability, whereas dose and administration route showed comparatively limited systematic effects. Among 117 within-compound, within-study, and within-route dose series involving 101 compounds and at least three dose levels, the median log–log slope relating dose to renal clearance was 0.003 (IQR: −0.073 to 0.076). The distribution of slopes did not differ significantly from zero ($p = 0.731$), indicating no consistent dose-related change in renal clearance across the examined compounds.

Similarly, 33 exact oral–intravenous comparisons involving 26 compounds yielded a median oral-to-intravenous renal-clearance ratio of 1.069 (IQR: 0.972–1.194). The difference was not statistically significant ($p = 0.117$), suggesting that administration route did not produce a consistent shift in measured renal clearance when compound, study, and dose were held constant.

At the molecular level, several statistically detectable but weak associations were observed (Table 3). Higher lipophilicity was associated with lower compound-level renal clearance (Spearman $\rho = -0.218$, 95% CI: −0.303 to −0.124; adjusted $p < 0.001$). Molecular weight also showed a weak

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inverse relationship (ρ = −0.174, 95% CI: −0.262 to −0.084; adjusted p = 0.001), whereas hydrogen-bond donor count showed a weak positive association (ρ = 0.120, 95% CI: 0.028–0.210; adjusted p = 0.045). Topological polar surface area, hydrogen-bond acceptor count, and rotatable bond count were not significantly associated with renal clearance after correction for multiple testing.

Table 3. Drug-, dose-, route-, and molecular-level associations with renal clearance

Factor	Analysis/effect measure	Estimate	Statistical result
Compound identity	Random-intercept ICC	0.945	—
Dose	Median log–log slope	0.003 (IQR: −0.073 to 0.076)	p = 0.731
Oral vs intravenous route	Median oral/IV CLren ratio	1.069 (IQR: 0.972–1.194)	p = 0.117
Molecular weight	Spearman ρ	−0.174 (95% CI: −0.262 to −0.084)	adjusted p = 0.001
LogP	Spearman ρ	−0.218 (95% CI: −0.303 to −0.124)	adjusted p < 0.001
TPSA	Spearman ρ	0.068 (95% CI: −0.024 to 0.162)	adjusted p = 0.459
H-bond donors	Spearman ρ	0.120 (95% CI: 0.028 to 0.210)	adjusted p = 0.045
H-bond acceptors	Spearman ρ	−0.032 (95% CI: −0.128 to 0.058)	adjusted p = 0.495
Rotatable bonds	Spearman ρ	−0.059 (95% CI: −0.155 to 0.036)	adjusted p = 0.459

ICC, intraclass correlation coefficient; LogP, octanol–water partition coefficient; TPSA, topological polar surface area. Molecular associations were calculated from compound-level median renal clearance in healthy participants. P values for the six molecular descriptors were adjusted using the Holm procedure.

Although molecular weight and lipophilicity were significantly associated with renal clearance, their effect sizes were small. A multivariable model incorporating molecular weight, LogP, TPSA, and rotatable bond count explained only 5.1% of the between-compound variation in log-

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transformed median renal clearance (R^2 = 0.051; adjusted R^2 = 0.042). Thus, simple structural descriptors accounted for only a limited fraction of the large compound-to-compound variability. The magnitude and direction of the individual molecular associations are presented in Figure 3.

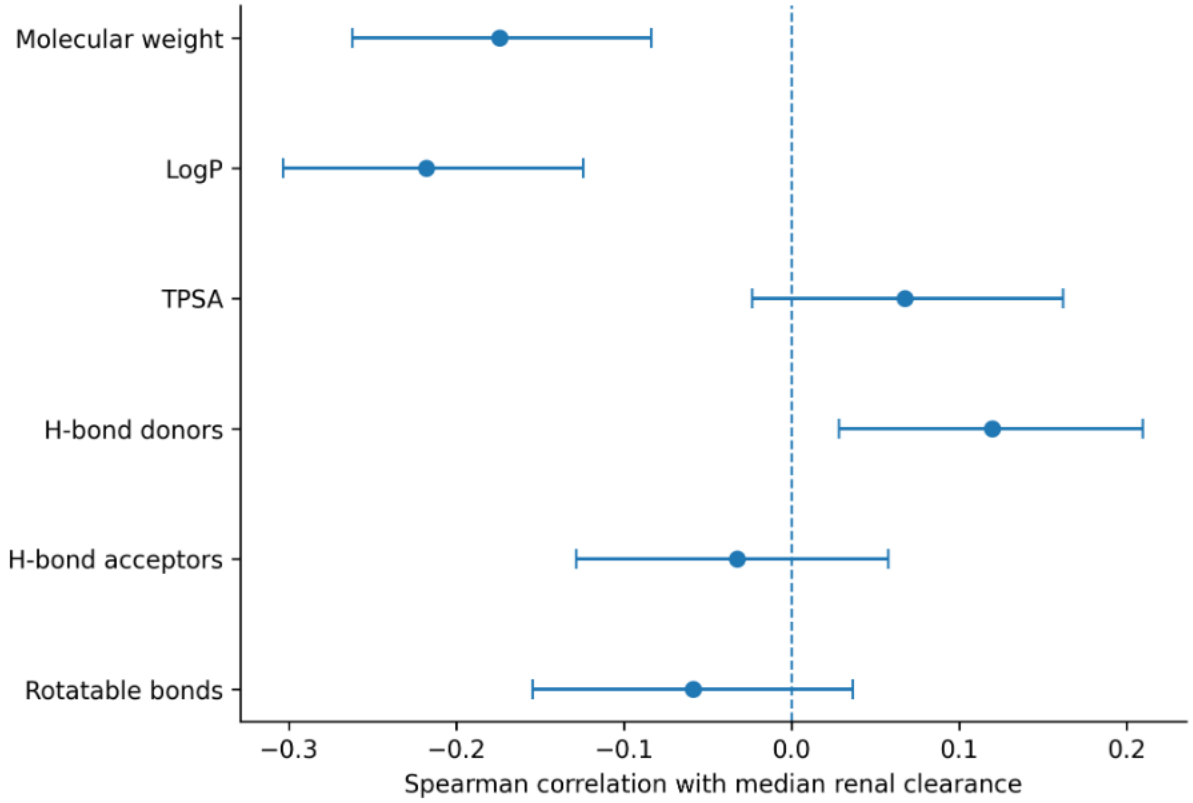


Figure 3. Associations between molecular descriptors and compound-level median renal clearance in healthy participants.

Points represent Spearman correlation coefficients and error bars represent 95% bootstrap confidence intervals. The dashed vertical line indicates no association.

4. Discussion

In the present analysis, substantial interxenobiotic variability in human renal clearance was found and a good progressive decrease in renal clearance was observed with increasing renal impairment severity. The overall median renal clearance was 5.082 L/h with the median of healthy participants being higher at 6.228 L/h. Most importantly, the intraclass correlation coefficient for the random-intercept analysis was 0.945, meaning that most of the variability was due to differences between the compounds, and not repeated measurements within the compound. This variability among compounds is pharmacologically reasonable since renal elimination is mediated by several compound-specific processes such as glomerular filtration, active tubular secretion, tubular reabsorption, protein binding and affinity of transporters. Renal drug transporters may significantly

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change the transport of xenobiotics across tubular epithelial cells and therefore affect systemic clearance and level of renal exposure (Łapczuk-Romańska et al., 2023).

One of the most striking constant observations was a progressive decrease in renal clearance with worsening renal impairment. The healthy participants had a median of 6.228 L/h, while the mild, moderate and severe impairments had medians of 2.768 L/h, 1.590 L/h and 0.568 L/h respectively. This gradient remained when only comparisons that were matched for compound, study, administration and dose were used, thus minimizing the impact of the significant between-study and between-treatment differences. Median renal clearance was about 36.9% and 61.2% lower in mild and moderate impairment, respectively, and 84.2% lower in severe impairment when compared with healthy participants. It is consistent with the mechanistic pharmacokinetic models, which indicate that impaired renal function can impact passive reabsorption, tubular handling, and filtration in a progressive manner, leading to greater decrements in drug clearance as chronic kidney disease progresses (Huang & Isoherranen, 2020).

This association was further supported by the matched repeated measures analysis. In 42 sets of healthy, mild, moderate and severe renal-function categories under the same compound, study, route and dose conditions, 85.7% had a strictly progressive decrease in clearance. Because of the highly significant Friedman test, the observed renal-function gradient appears not to have been due to merely aggregating disparate drugs or studies. However, the magnitude of the decrease varied among compounds, indicating that renal clearance did not decline proportionally across all xenobiotics as renal function decreased. This could be especially important in the case of compounds that are dependent on an active secretion. Some other evidence of organic anion transporter substrates suggests that perhaps renal secretory clearance may change differently from glomerular filtration in chronic kidney disease, particularly in severe cases, because the activity of these transporters and uremic conditions can alter its tubular handling independent of changes in GFR only (Tan et al., 2022).

These findings also have direct implications for the interpretation of renal-impairment pharmacokinetic studies. Conventional categorical comparisons are still useful as they serve to indicate clinically meaningful differences between normal, mild, moderate and severe renal dysfunction. However, categorical classification can simplify what is biologically a continuous deterioration in kidney function. There recent methodological studies comparing categorical and regression-based approaches have highlighted that the two approaches offer complementary information and that continuous modelling can help to better characterize the relationships between exposure and kidney function when individual kidney-function measurements are available (So et al., 2025). The health status categories used in the present analysis were appropriate, given that the health status information in the records for whom it was available was mostly categorical. However, the results here suggest that future analyses based on standardized eGFR and/or creatinine clearance values might further clarify these relationships.

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While renal function was a significant factor in renal clearance, there was little systematic effect on renal clearance for administered dose or route. The median log–log slope was near zero and not significantly different from zero across the dose series that contained at least three different dose levels. Similarly, matched oral and intravenous observations produced a median oral-to-intravenous clearance ratio close to unity. Overall, renal clearance appeared to be a relatively constant elimination parameter for this large group of compounds studied, across the dose range and route of administration. This should not be taken as a rule that dose or route can never affect renal elimination, however, as saturation of transporters, nonlinear protein binding or formulation-specific effects may be significant for individual drugs.

The molecular analysis data also indicated that very little of the variation between the compounds could be explained by simple physicochemical descriptors. Renal clearance showed weak inverse relationships with lipophilicity and molecular weight and a weak positive relationship with the number of hydrogen-bond donors. However, the multivariable molecular model explained only 5.1% of the variability in clearance. This limited explanatory performance is similar to the previous structure-based modelling work, which revealed that the inclusion of pharmacokinetic data (e.g., fraction unbound in plasma) in addition to chemical descriptors significantly improves human renal excretion prediction (Watanabe et al., 2019). Thus, renal clearance seems to rely not only on the physicochemical characteristics of the molecule, but also on biological factors that cannot be adequately represented by simple physicochemical properties alone.

The results are of great significance for drug development and dose individualization in clinical settings. The steep decrease in clearance with increasing renal impairment emphasizes the importance of considering renal function when making recommendations for the dose of renally eliminated drugs. Concurrently, the high inter-compound variation suggests that renal dose adjustment cannot be determined exclusively on general renal function classification or renal function assumptions based only on filtration. Newer methods have begun to take a more comprehensive view of the changes in kidney function, transporter activity, protein binding, and renal-specific elimination pathways when predicting changes in pharmacokinetics in renal disease (Sharma et al., 2022).

There are a few limitations to be noted. The analysis was based on study-level pharmacokinetic records rather than individual-participant data, and detailed measures such as eGFR, creatinine clearance, plasma protein binding, age, sex, transporter phenotype, and urinary characteristics were not consistently available. Residual heterogeneity may also be caused by differences in analytical methods and historical study practices. However, matched within-study comparison greatly minimized the confounding of compound, dose, route and study conditions. Overall, the results indicate a strong severity-dependent reduction in human renal clearance, while the magnitude of this reduction varies considerably among compounds and is only weakly explained by basic molecular properties.

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5. Conclusion

There is large interxenobiotic variability in human renal clearance, which is also strongly influenced by the severity of renal impairment. This analysis in the present study showed a gradual decrease in renal clearance as renal dysfunction progressed from normal to mild, moderate, or severe. This trend was also apparent when there was matching on compound, study, administration route and dose, which suggests that the decrease was not simply due to variations in study design and treatment conditions. The magnitude of this reduction increased as renal impairment increased, further highlighting the need for renal-function stratification in pharmacokinetic analysis and dose individualization.

There was also large inter-compound variability, with the identity of the compound explaining a significant proportion of the clearance variability. Neither administered dose nor route of administration showed a consistent systematic effect across the compounds analyzed. Only weak relationships were found between renal clearance and molecular descriptors such as lipophilicity and molecular weight, and the overall contribution of these descriptors to explaining variability was modest. It suggests that renal elimination is not just a matter of simple structural properties but also a complex interaction of the different characteristics of a drug and physiological processes.

The significant decrease in clearance in the presence of worsening renal dysfunction further highlights the importance of closely monitoring renal function when prescribing doses of renally excreted drugs. This significant variation among the xenobiotics also implies that some drugs might require individual dose adjustment strategies. Future studies combining standardized renal-function variables with protein binding, transporter activity, and other mechanistic pharmacokinetic variables may enhance the prediction of renal clearance and support more personalized and clinically sound dosing strategies.

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