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ORIGINAL RESEARCH

Impact of Estimated Glomerular Filtration Rate Equations on Vancomycin Dosing and Treatment Outcomes

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Background: Vancomycin has a narrow therapeutic window and is primarily renally excreted. This study explored whether varied estimated glomerular filtration rate (eGFR) equations lead to differences in chronic kidney disease (CKD) staging and vancomycin dosage, and their impact on treatment outcomes.

Methods: This cross-sectional study retrospectively included adult patients receiving vancomycin for therapeutic purposes (empirical or targeted therapy) at Nanjing Drum Tower Hospital (2019–2023). Consistency of each of the metrics (eGFR values, CKD staging, dose staging, and staging recommendations) derived from different equations was compared. Incidences of distinct clinical outcomes were compared among patients receiving doses recommended by different eGFR equations. Logistic regression analyzed associations between inconsistent status and patient characteristics as well as clinical outcomes.

Results: A total of 832 patients were identified. The Chinese population-adjusted creatinine (Cr)-based European Kidney Function Consortium equation (EKFC-eGFRCr[CN]) had the smallest impact on dosing adjustments (3.4%), whereas the cystatin(Cys)-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (CKD-EPI-eGFRCys) had the largest impact (16.0%) and exhibited favorable performance in target vancomycin trough concentration (C_{min}) attainment and other clinical outcomes (except for target 24 h area under the concentration-time curve [AUC_{0-24}]). Only staging discordance between the Xiangya equation and EKFC-eGFRCr+Cys was associated with a reduced C_{min} attainment rate. When dosing recommendations disagreed with those from the Cockcroft-Gault equation, all eGFR equations except the Xiangya equation were associated with higher C_{min} attainment rates.

Conclusion: Our study found that the CKD-EPI-eGFRCys equation required the most dosing adjustments, while the EKFC-eGFRCr(CN) equation required the fewest. Preferentially using the CKD-EPI-eGFRCys equation was optimal for target attainment of key clinical outcomes.

Keywords: vancomycin, estimated glomerular filtration rate, chronic kidney disease, Chinese population

Introduction

Accurate assessment of renal function is essential for individualized dosing of renally eliminated drugs, with glomerular filtration rate (GFR) being the most reliable measure and determinant of their clearance.[1] Although measured GFR (mGFR) is the gold standard, it is impractical for routine care due to its cost and complexity.[2] Consequently, estimated GFR (eGFR) equations are favorable choices for drug dosing decisions.[3] Cockcroft-Gault (CG) equation, which estimates creatinine clearance (Ccr), has long been used to guide drug dosing. However, Ccr is not an ideal substitute for GFR because creatinine (Cr) level is influenced by non-renal factors like muscle mass and tubular secretion.[4] Therefore, current guidelines suggest that eGFR not indexed for body surface area (BSA) should be used for pharmacokinetic studies and dosing regimen design instead of the CG equation.[5]

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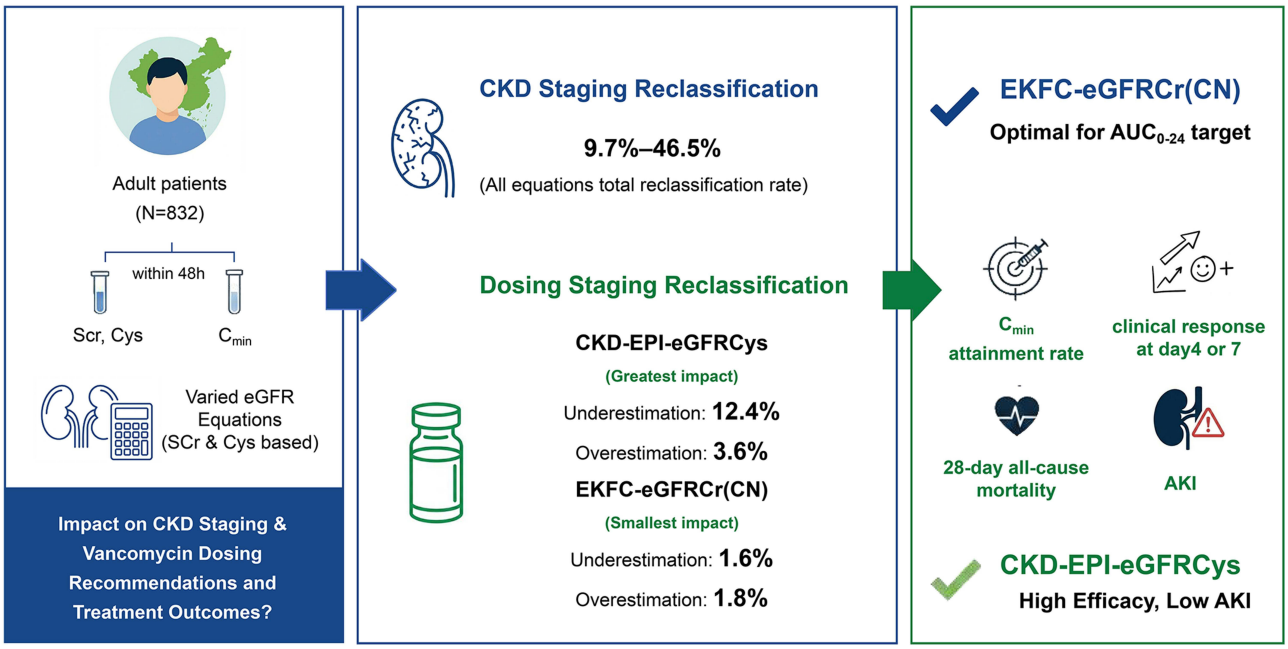
Graphical Abstract



Modern eGFR equations that incorporate serum Cr and/or cystatin (Cys) have continually evolved. Since Cr and Cys are affected by different non-GFR factors, combining them may yield more accurate estimates.[6] While the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is currently recommended by the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN),[7] the new European Kidney Function Consortium (EKFC) equation is preferred by the European Federation of Clinical Chemistry and Laboratory Medicine.[8] Furthermore, the EKFC-eGFRCr+Cys equation outperformed other EKFC and CKD-EPI equations in external validation cohorts of Chinese populations.[9]

Vancomycin is an antibiotic with a narrow therapeutic index and is primarily excreted by the kidneys.[10] Subtherapeutic exposure increases the risk of treatment failure and antimicrobial resistance, while supratherapeutic exposure elevates the risk of acute kidney injury (AKI). Thus, precise renal function assessment is critical for determining a safe and effective dose. Previous studies have shown that the choice of renal function estimation equation may substantially influence vancomycin dosing decisions. For example, a retrospective analysis reported a 38.3% discordance rate in dosing recommendations when CKD-EPI-eGFRCr+Cys was used instead of the CG equation.[11] Similarly, a prospective quality improvement study demonstrated improved initial trough target attainment (28% vs. 50%) with CKD-EPI eGFRCr+Cys-guided dosing; however, the study was underpowered to detect differences in short-term clinical outcomes such as mortality, AKI, or treatment failure.[12] In addition, recent studies reported that CKD-EPI-eGFRCys demonstrated the lowest bias in predicting renal vancomycin clearance in specific populations and that differences in GFR estimation were associated with up to 10-hour variations in predicted vancomycin half-life compared with the CG equation.[13,14] Currently, the Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends Cys-based eGFR for dosing narrow-therapeutic-index drugs, yet some reports suggest these equations may underestimate renal function during infection, leading to potential underdosing.[12] Although Cys-based equations may improve CKD staging, their effects on vancomycin clearance, dosing, key clinical outcomes, or microbial eradication remain unclear and warrant further investigation. The optimal eGFR equation to guide vancomycin dosing remains a clinical challenge.[15] Therefore, we investigated whether the choice of different eGFR equations influences CKD staging and dosing recommendations in patients treated with vancomycin. Importantly, by linking these discrepancies to real-world clinical

endpoints, we aimed to determine the most appropriate eGFR equation for guiding vancomycin dosing, thereby optimizing therapeutic efficacy and patient safety. This study may provide evidence to inform equation selection for vancomycin dosing and improve clinical decision-making in routine patient care.

Methods

Study Design and Population

This cross-sectional study retrospectively included adult patients who received vancomycin for therapeutic purposes (empirical or targeted therapy) at Nanjing Drum Tower Hospital from 2019 to 2023. Inclusion criteria: (1) at least one set of serum Cr and Cys measurements performed on the same day; (2) at least one steady-state vancomycin trough concentration (C_{min}) measured within 48 hours of the renal function tests; and (3) only the first eligible episode per patient during the study period. Exclusion criteria: (1) receipt of vancomycin for surgical prophylaxis; (2) pregnancy; and (3) receipt of renal replacement therapy during the treatment period. The study was approved by the Ethics Committee of Nanjing Drum Tower Hospital (Approval No. 2024-723-01) and conducted per the Declaration of Helsinki. Due to the retrospective design, the Ethics Committee waived the requirement for informed consent, ensuring patient data confidentiality and anonymity. This study follows the STROBE Statement (Table S1).

Exposures of Interest

Renal function was assessed using multiple eGFR equations based on Cr, Cys, or both (eGFRCr, eGFRCys, eGFRCr+Cys): CKD-EPI,[16–18] Asian modified CKD-EPI,[19] EKFC,[20] re-expressed Lund-Malmö Revised (r-LMR) equation,[21] Caucasian, Asian, pediatric, and adult cohorts (CAPA),[22] Xiangya,[23] Modification of Diet in Renal Disease (MDRD)[24] and CG.[25] For patients ≥70 years, the Berlin Initiative Study (BIS) equations[26] were also applied. BSA was calculated using the DuBois formula.[27] All equations are detailed in Table S2. Both Cr and Cys were measured using a Beckman Coulter AU5800 automatic biochemical analyzer at our hospital. Specifically, Cys was determined by enhanced immunoturbidimetry, and Cr was measured by the enzyme-coupled rate method.

CKD stages were defined per the KDIGO 2024 guideline[28] based on eGFR (mL/min/1.73m^2) as: G1 (≥90), G2 (60–89), G3a (45–59), G3b (30–44), G4 (15–29), and G5 (<15). Vancomycin dosing staging were based on the Sanford Guide[29] recommendations, defined by absolute (unadjusted) eGFR (mL/min) as: <10, 10–49, and ≥50 (Table S3). Augmented renal clearance (ARC) is defined as an estimated Ccr of ≥130 mL/min.[30]

For subsequent analyses, the EKFC-eGFRCr+Cys and CG equations were designated as the reference standards for CKD and dosing staging, respectively. Consistent with commonly applied definitions in the literature, ARC defined by CG-estimated Ccr ≥130 mL/min was used as the operational reference for ARC classification.

Outcomes

The primary outcome was goal C_{min} attainment rate.[31] Secondary outcomes included: (1) target 24 h area under the concentration-time curve ($AUC_{0\sim24}$) attainment rate;[31] (2) 28-day all-cause mortality; (3) incidence of AKI; (4) clinical response at day 4; (5) clinical response at day 7; and (6) outcome attainment in the ARC subgroup. Detailed definitions for all outcomes are provided in Appendix 1. As for $AUC_{0\sim24}$, its estimation was performed via Bayesian approach based on a population pharmacokinetic (PPK) model previously developed and validated at our institution.[32] Specifically, individual pharmacokinetic parameters were estimated using the Bayesian method, which combined the prior information from the PPK model with individual patient covariates and measured vancomycin concentrations to derive posterior estimates for $AUC_{0\sim24}$ calculation.

Statistical Analysis

The consistency of eGFR values across equations was evaluated using Lin's concordance correlation coefficient (CCC)[33] and by assessing differences with two thresholds: an absolute difference of 15 mL/min/1.73m^2 and a relative difference of 20%.[34] Concordance in CKD and dosing staging across equations was evaluated using overall percent agreement and the weighted

kappa (κ) coefficient.[35] Reclassification patterns were quantified using confusion matrices. Logistic regression was used to analyze associations of inconsistent status with patient characteristics and clinical outcomes (Details are in Appendix 2 and 3).

Actual administered vancomycin doses were categorized as under-dosed, appropriate, or over-dosed relative to the theoretical dosing range derived from each equation. Target attainment rates were compared among patients whose doses were appropriate per each equation's recommendation. For each equation, attainment analyses were restricted to patients receiving doses consistent with that equation's dosing category, whereas under- or over-dosed patients were excluded from equation-specific comparisons. Subgroup analyses were performed by age (<40 vs. ≥40; <70 vs. ≥70 years), sex (Male vs. Female), body mass index (BMI) (<25 vs. ≥25 kg/m^2), and baseline renal function (EKFC-eGFRCr+Cys <60 vs. ≥60 mL/min/1.73m^2).

To evaluate the clinical impact of discordant dosing recommendations, we specifically analyzed patients in whom the administered dose aligned with one equation's guidance but diverged from that of another. Among these discordant pairs, we compared attainment rates for C_{min} and $AUC_{0\sim24}$, as well as 28-day all-cause mortality and AKI incidence. All p-values were adjusted for multiple comparisons using the Holm-Bonferroni method.

Normality of continuous variables was assessed by the Shapiro–Wilk test. Data conforming to a normal distribution were presented as mean ± standard deviation (SD), whereas non-normally distributed data were presented as median and interquartile range (IQR). Groups were compared using Student's t-tests or Mann–Whitney *U*-tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables. A two-sided p-value < 0.05 was considered statistically significant. All analyses were conducted with R (version 4.5.0). The sample size was calculated based on the result of a similar survey conducted in other regions, where the C_{min} target attainment rate of vancomycin was approximately 50%. With a preset margin of error of 5% and 95% confidence level (CI), the minimum sample size was determined to be 402 patients using PASS 15 software. Considering an anticipated 20% dropout rate of study participants, the required sample size was adjusted to 503 patients.

Results

Patient Characteristics

The study cohort comprised 832 patients, with a median age of 61.0 years (IQR: 51.0–70.3) and the median EKFC-eGFRCr+Cys was 78.44 mL/min/1.73 m^2 (IQR: 57.51–94.05). 554 patients (66.6%) were male, 231 patients (27.8%) were aged ≥70 years, 506 patients (60.8%) had a body mass index (BMI) in the range of 18.5–24.9 kg/m^2, 185 patients (22.2%) had a history of CKD. More details are provided in Table 1.

Table 1 Characteristics of The Study Population

Characteristics	Total (n = 832)
Age (years), median (IQR)	61.00 (51.00, 70.25)
Male, n (%)	554 (66.59)
BMI (kg/m^2), median (IQR)	23.88 (21.63, 26.30)
BSA (m^2), median (IQR)	1.74 (1.61, 1.90)
ALB (g/L), median (IQR)	36.00 (33.10, 38.80)
SCr (mg/dL), median (IQR)	0.77 (0.58, 1.09)
Cys (mg/L), median (IQR)	1.07 (0.85, 1.48)
EKFC-eGFRCr+Cys (mL/min/1.73 m^2), median (IQR)	78.44 (57.51, 94.05)
Evidence of Gram-positive bacteria, n (%)	369(44.30)
MV, n (%)	338 (40.62)
VA-ECMO, n (%)	12 (1.44)
ACCI, median (IQR)	3.00 (2.00, 5.00)

(*Continued*)

Table 1 (Continued).

Characteristics	Total (n = 832)
Comorbidities, n (%)	
CKD	185 (22.23)
Hypertension	402 (48.32)
Diabetes	157 (18.87)
Heart failure	204 (24.52)
Other cardiovascular diseases	291 (34.98)
Cerebrovascular diseases	268 (32.21)
Solid tumor	124 (14.90)
Hematological disease	39 (4.69)
Vancomycin daily dose, n(%)	
2.5~3.75 mg/kg/d	7(0.8%)
5~15 mg/kg/d	173(20.8%)
30~60 mg/kg/d	652(78.4%)
Department for prescription orders, n (%)	
Cardiology department	403 (48.44)
Critical care medicine department	186 (22.36)
Neurosurgery department	105 (12.62)
Other departments	138 (16.59)
Concomitant medications, n (%)	
Piperacillin	130 (15.62)
Carbapenem	252 (30.29)
Cephalosporin	184 (22.12)
Quinolone	46 (5.53)
Other nephrotoxic antibiotics	49 (5.89)
Outcome	
C_{min}(mg/L), median (IQR)	13.20 (9.00, 19.00)
28-day all-cause mortality, n (%)	48 (5.77)
AKI diagnosis, n (%)	89 (10.70)
$AUC_{0\sim24}$([mg/L] ·h), median (IQR)	510.63 (379.84, 681.57)

Notes: Continuous variables with a normal distribution are expressed as mean±standard deviation. Non-normally distributed continuous variables are presented as median (interquartile range). Categorical variables are summarized as number (percentage).

Abbreviations: BMI, body mass index; BSA, body surface area; C_{min}, trough concentration; $AUC_{0\sim24}$, 24 h area under the concentration-time curve; ALB, albumin; SCr, serum creatinine; Cys, cystatin; eGFR, estimated glomerular filtration; ACCI, age-adjusted charlson comorbidity index; MV, mechanical ventilation; VA-ECMO, venoarterial extracorporeal membrane oxygenation; CKD, chronic kidney disease.

Distribution Characteristics of eGFR

The MDRD and CG equations yielded eGFR values exceeding 200 mL/min/1.73 m^2 in some patients, a finding not observed with other equations (Figure 1). For CKD or dose staging, Cr-based equations tended to classify patients into higher stages, Cys-based equations into lower stages, and combined equations into intermediate stages (Figure 2). These trends remained consistent but more pronounced in patients aged ≥70 years (Figure S1 and S2).

Concordance and Reclassification of Renal Function

Based on the CCC, EKFC-eGFRCr+Cys(CN) and rLMR-eGFRCr+Cys equations exhibited near-perfect concordance with EKFC-eGFRCr+Cys and the lowest reclassification rates (Figure S3–S5); MDRD and standardized CG equations had the lowest concordance. CKD-EPI-eGFRCr(AS) and Xiangya equations performed the poorest according to κ or agreement (Figure S6). The total CKD staging reclassification rate across all equations ranged from 9.7% to 46.5% (Table S4 and Figure S7). In patients aged ≥70 years, the total CKD staging reclassification rate ranged from 7.4% to 69.7% (Table S5 and Figure S8).

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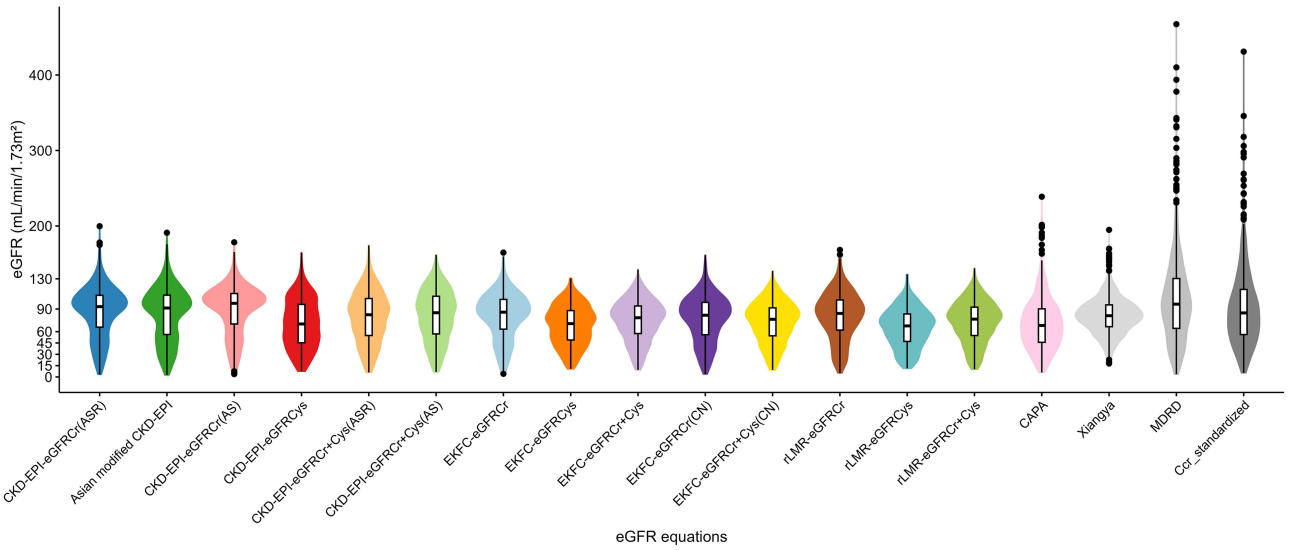

Figure 1 Distribution of eGFR in the Total Population. Ccr_standardized refers to the creatinine clearance calculated by the Cockcroft-Gault formula and standardized by body surface area. The eGFR values calculated by all formulas are expressed in mL/min/1.73 m^2.
Abbreviations: ASR, age, sex, and race; eGFR was adjusted for age, sex, and race; AS, Age and sex; eGFR was adjusted for age and sex; CN, Serum creatinine was adjusted based on the Q value for the Chinese population.

Concordance of Dosing Staging

With the exception of the Cys-based solely and Xiangya equations, most other formulas showed high agreement with the CG equation for dosing classification, with agreement ranging from 84.4% to 95.8% (Figure S9). Among the evaluated equations, the CKD-EPI-eGFRCys equation showed the lowest concordance and performed dose reclassification in 16.0% of patients, including recommending lower doses for 12.4% and higher doses for 3.6% of patients (Table S6 and Figure S10). In contrast, the EKFC-eGFRCr(CN) equation exhibited the highest concordance, with dose underestimation and overestimation rates of only 1.6% and 1.8%, respectively. The Xiangya equation had the highest dose overestimation rate (12.4%) (Table S6). 20.8% were classified as having ARC by CG equation. All other equations, except for MDRD (which caused a net increase of 5.4% in ARC diagnoses), reclassified 49.7% to 92.5% of these ARC patients as non-ARC (Table S6 and Figure S10). The largest reclassification was observed with rLMR-eGFRCys, which categorized 92.5% of the CG-defined ARC patients as non-ARC. In patients aged ≥70 years, only the EKFC-eGFRCr(CN) equation demonstrated excellent agreement with CG for dosing, altering dose recommendations in only 6.1% of patients (Figure S10 and S11). CKD-EPI-eGFRCys again exhibited the lowest agreement, reclassifying 25.5% of these patients and recommending lower doses in 20.3% of cases (Table S7).

Comparison of Target Attainment Rates

We evaluated the performance of different BSA-unadjusted eGFR equations in guiding drug dosage based on different outcomes. For the C_{min} target attainment rate, the four equations with the highest probabilities were CKD-EPI-eGFRCys (57.3%), CAPA (56.8%), EKFC-eGFRCr+Cys (CN) (56.3%), and rLMR-eGFRCys (56.3%) (Figure 3). In subgroup analyses, the C_{min} attainment rate for CKD-EPI-eGFRCys consistently ranked within the top three (Table S8). For the $AUC_{0\sim24}$ target attainment rate, the EKFC-eGFRCr (CN) equation yielded the highest rate. This equation's ranking remained within the top three across the total population and all subgroups (Table S9). Regarding other clinical outcomes, doses guided by Cys-based equations were associated with higher efficacy rates and a lower incidence of AKI compared to those guided by Cr-based or combined equations. Specifically, the CKD-EPI-eGFRCys equation performed consistently well; doses recommended by this equation led to high efficacy rates and a low incidence of AKI, ranking within the top three for these outcomes in both the total and all subgroup populations (Tables S10–S12). In the ARC patient, only Cys-based equations were associated with the highest incidence of subtherapeutic C_{min}; Cr-based equations showed the lowest incidence (Table S12).

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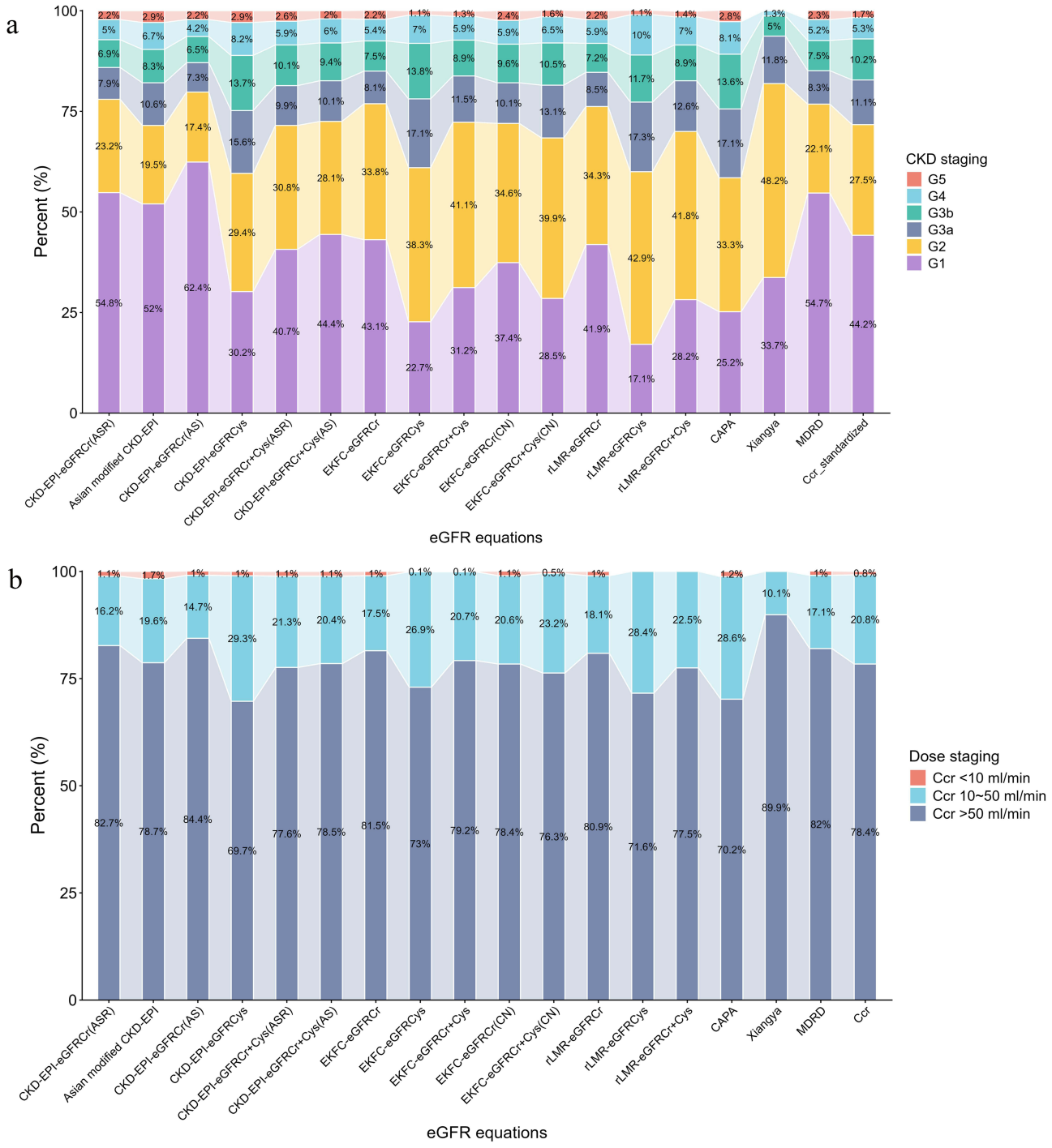

Figure 2 Percentages of CKD Staging and Dosing Staging Across Equations in the Total Population. (**a**) Distribution of CKD Stages (BSA-adjusted eGFR, mL/min/1.73m^2); (**b**) Distribution of Dosing Stages (BSA-unadjusted eGFR, mL/min).

Comparison of Outcomes Between CG and eGFR-Based Dosing Groups

When dosing recommendations were inconsistent with the CG equation, other eGFR equations demonstrated higher rates of C_{min} target attainment, whereas the Xiangya equation showed lower rates of C_{min} target attainment (Figure 4). Specifically, the CKD-EPI-eGFRCr+Cys(ASR), CKD-EPI-eGFRCr+Cys(AS), EKFC-eGFRCr+Cys(CN), rLMR-eGFRCr+Cys, and Xiangya groups each showed statistically significant differences in attainment rates compared with the CG group (Figure 4). The target $AUC_{0\sim24}$ attainment rates for EKFC-eGFRCr(CN), EKFC-eGFRCr+Cys(CN), and

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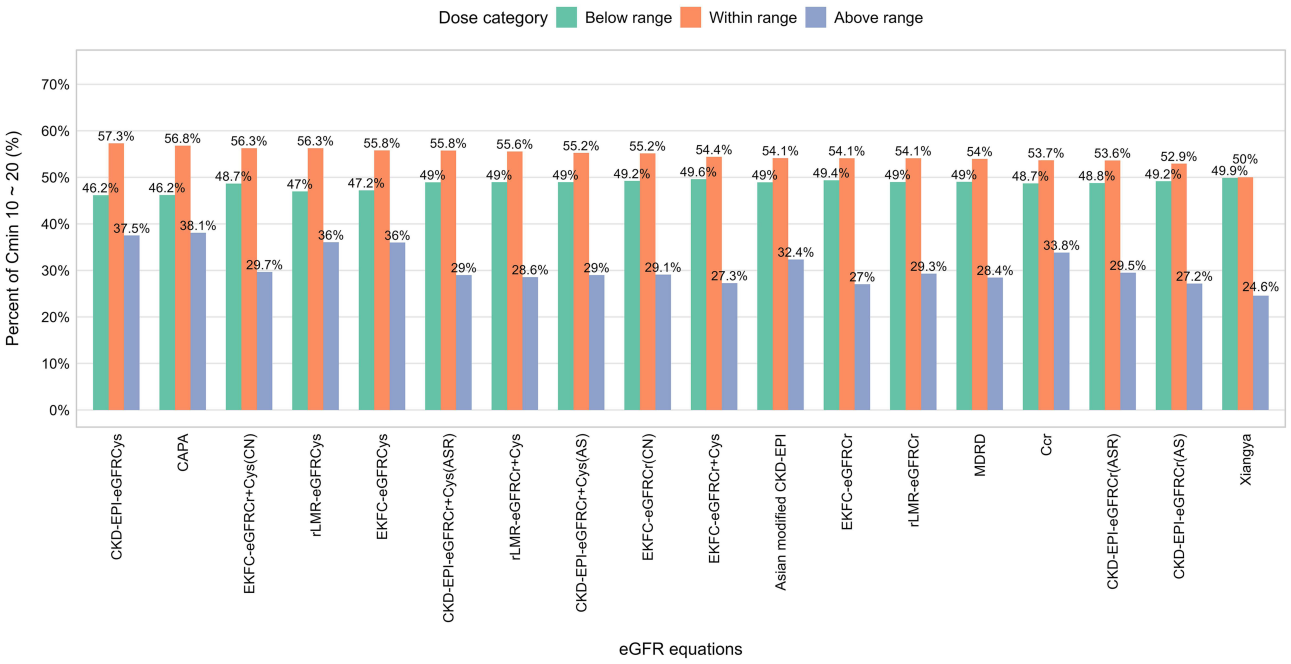

Figure 3 Target C_{min} Attainment Rate in Patients Receiving Formula-Recommended Appropriate Dose. Ccr calculated by the Cockcroft-Gault formula refers to the creatinine clearance used in this study. The eGFR values calculated by all formulas are BSA-unadjusted and expressed in mL/min.

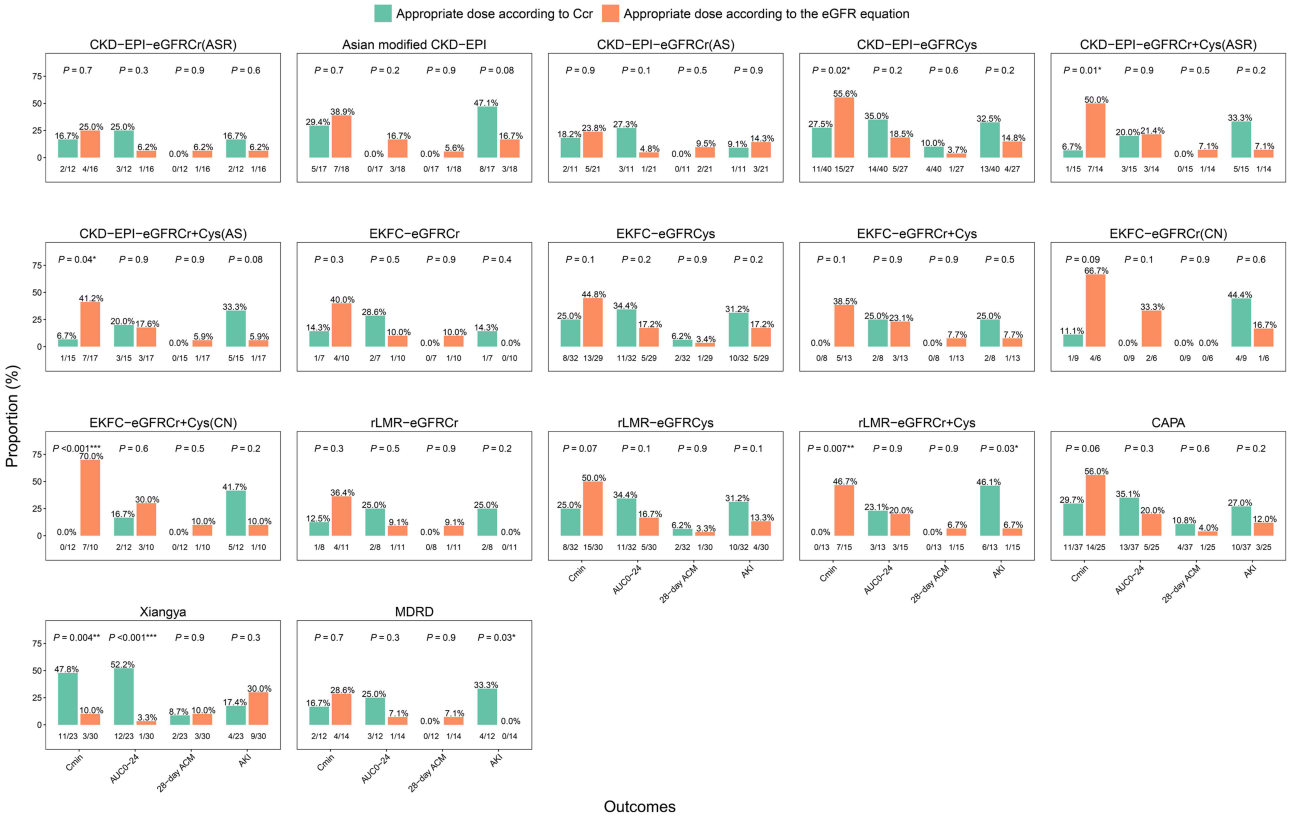

Figure 4 Differences in Efficacy Endpoint Incidence Between Patients with Discrepant Dosing Statuses: Comparison of Cockcroft-Gault Equation and eGFR Equation. *p < 0.05, **p < 0.01, ***p < 0.001, indicating statistical significance at different levels, respectively. The eGFR values calculated by all formulas are expressed in mL/min.
Abbreviations: 28-ACM, 28-day all-cause mortality; AKI, acute kidney injury.

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CKD-EPI-eGFRCr+Cys(ASR) were all higher than those in the CG group, but the differences were not statistically significant. Compared with the CG group, Cys-only equation groups had lower 28-day all-cause mortality, whereas other equations had higher 28-day all-cause mortality. In terms of AKI incidence, only the CKD-EPI-eGFRCr(AS) and Xiangya groups had higher rates than the CG group.

Factors Associated with Staging Discordance and Clinical Outcomes

Multivariate analysis indicated that older age was a shared independent risk factor contributing to discordance in both eGFR staging (EKFC-eGFRCr+Cys vs. CKD-EPI-eGFRCr+Cys) and dosing classification (BSA-adjusted EKFC-eGFRCr+Cys vs. CG). Additionally, concomitant use of carbapenems or cephalosporins, BMI, and a history of autoimmune disease or CKD were identified as significant factors influencing discordance (Table S13 and S14). Such staging discordance was significantly associated with adverse clinical outcomes. Specifically, discordance between equations based solely on Cr (e.g., Xiangya, EKFC-eGFRCr) and EKFC-eGFRCr+Cys was consistently accompanied by a significantly increased incidence of AKI and significant alterations in vancomycin PK target (C_{min} and $AUC_{0\sim24}$) attainment rates (Table S15–S17). Details are provided in Appendix 3.

Discussion

In the clinical application of eGFR equations for vancomycin therapy in Chinese population, our study found that the CKD-EPI-eGFRCys equation had the highest proportion of patients (16.0%) for whom dosing recommendation adjustments were made based on the CG equation's dose. Additionally, the doses recommended by the CKD-EPI-eGFRCys equation were associated with the highest target C_{min} attainment rate and demonstrated good, stable performance across other clinical endpoints (except $AUC_{0\sim24}$). Moreover, when the dosing recommendations of Cr+Cys-based eGFR equations were inconsistent with those of the CG equation, the former had a significantly higher target C_{min} attainment rate. In contrast, the EKFC-eGFRCr(CN) equation had the smallest influence on dosing recommendation adjustments (3.4%), but was associated with the highest target $AUC_{0\sim24}$ attainment rate. Thus, this highlights that choosing the best equation depends on the target outcome.

Similar to our results, previous investigations have documented the potential for Cr-based equations to overestimate and Cys-based equations to underestimate CKD stage.[9,36,37] This is attributable to the fact that Cys is eliminated solely through glomerular filtration, with being less affected by demographic factors.[38] Moreover, reclassification by other equations had a more pronounced effect at higher renal function levels. There are two main reasons: the hyperbolic relationship between eGFR equations and biomarkers means that low biomarker concentrations cause minor changes to induce significant eGFR fluctuations;[4] the proportion of Cr eliminated via tubular secretion and extrarenal pathways increases with declining renal function.[39]

Except for the Xiangya, Cys-only based equations underestimated the dose for a substantial 9.4%–12.4% of patients. This may be partly because the CG equation itself has poor accuracy in predicting true GFR.[40] A study indicated that CG and CKD-EPI-eGFRCys performed the worst, with tendencies toward dose overestimation and underestimation, respectively.[40]

The inconsistencies in staging and dose recommendations did not translate into apparent differences in most clinical outcomes. The main explanations are as follows: firstly, clinical outcomes are multifactorial, and subtle differences in GFR estimation may not be the primary driver; secondly, in clinical practice, doses are often adjusted according to the patient's overall condition rather than strictly adhering to the output of a single equation;[5] lastly, clinical outcomes may be relatively insensitive to reclassification near dose thresholds. An interventional study found that a nomogram based on the CKD-EPI-eGFRCr+Cys equation, despite improving target C_{min} attainment, did not enhance clinical efficacy or safety compared to the CG equation.[12] In contrast, another study suggested a Cys-based pharmacokinetic model could improve treatment success in MRSA patients.[41] For other studies, the clinical relevance of different eGFR equations for dosing is also controversial.[36,40]

Nevertheless, the outcome attainment rates differed slightly depending on the equation used. The EKFC-eGFRCr(CN) equation was associated with the highest $AUC_{0\sim24}$ target attainment rate, which may be plausibly linked to the fact that the PPK model was developed based on Cr. Although the CKD-EPI-eGFRCys equation underestimated doses, it demonstrated the best overall performance in achieving the target C_{min} and other endpoints. A previous study suggested that it might lead to

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significant under-dosing.[42] Critically ill patients with highly variable pharmacokinetics were not recommended to use Cys-based eGFR equations for guiding dose recommendations.[43] However, our results seem to suggest that Cys may more accurately reflect the actual vancomycin clearance and pharmacodynamic responses. This hypothesis is supported by several lines of evidence: studies have shown that eGFRCys has a superior predictive effect compared to eGFRCr for both vancomycin clearance and C_{min};[13,43] when making dose adjustments or therapeutic decisions for drugs with a narrow therapeutic window, using Cys to obtain a more accurate estimation of GFR is recommended.[4,38] Inflammation represents a non-GFR determinant of Cys,[44] and a study has indicated a positive correlation between C-reactive protein and Cys levels.[45] Consequently, Cys levels may reflect both the severity of infection and GFR levels, which could ultimately impact the efficacy of vancomycin. Our findings align with the 2024 KDIGO guidelines, particularly regarding the impact of non-GFR determinants. Although muscle status was not directly measured, our cohort's high proportion of elderly (median age, 61 years) and critically ill patients (40.62% on mechanical ventilation) suggests potential interference from age-related atrophy or protein catabolism on serum creatinine. The 2024 guidelines note that eGFRCys may be more reasonable when creatinine's non-GFR determinants are significantly altered.[28]

Regarding ARC, equations showed marked discordance with the CG-based definition. Critically, despite these large reclassification effects, the choice of equation had only a minor impact on subtherapeutic C_{min} rates in the ARC cohort. This highlights a key clinical issue: in the absence of a consensus definition for ARC, the choice of diagnostic equation may cause diagnostic confusion and fail to identify true ARC patients, which ultimately does not improve therapeutic outcomes.[46]

In terms of CKD staging, older age and lower BMI were associated with discordance, likely because the EKFC equation specifically models that age-related muscle mass decline.[20] Concomitant use of carbapenem or cephalosporin was associated with better consistency, possibly because they can slightly inhibit tubular Cr secretion,[47] which may have offset the decrease in serum Cr from malnutrition and muscle wasting in this critically ill population. For dose stratification, older age and comorbid autoimmune diseases or CKD increased discordance between the CG and EKFC equations. This may be because autoimmune diseases and their treatments (e.g., glucocorticoids), as well as the inflammatory status and malnutrition commonly associated with CKD, affect the levels of serum Cr and Cys.[43,45,48,49]

The Xiangya equation showed considerable divergence from other Cr-based equations in our results. External validation studies have reported its suboptimal performance in Chinese populations.[23,50]

The study has certain limitations. First, as a single-center retrospective cross-sectional study, it cannot establish definitive causality. Due to the nature of retrospective data collection, the asynchrony in sampling Cr, Cys, and C_{min} may prevent precise capture of instantaneous renal function, while the absence of mGFR precluded a direct assessment of absolute accuracy. Since Cys is not yet universally tested at our center, the selection bias in sample screening and the clinical heterogeneity between ICU and general ward populations may affect the generalizability of the results. Second, in terms of statistical analysis, the sample size for some secondary outcome measures was limited, which may have constrained the statistical power. Specifically, for the exploratory analysis regarding the correlation between the inconsistency group and clinical outcomes, the model only performed preliminary adjustments for age and sex due to the Events Per Variable (EPV) principle, and residual confounding may still exist. Finally, with respect to equation application, we used the widely applied CG equation as a reference for dose comparisons, although many PPK models exist. Additionally, we did not apply the China-specific Q-value to the rLMR equation because its local validation was not completed. This Q-value was developed using a non-ideal mGFR measurement method, which likely explains why the improvement in accuracy for the EKFC (CN) equation was limited.[51] In addition, most international eGFR equations were originally developed and validated in cohorts with stable renal function.[43] This study aimed to further evaluate the practical reliability of these stable-derived equations for vancomycin therapy in acutely ill patients with potential renal fluctuations. Therefore, while our results highlight the performance differences among various equations in a real-world setting, further large-scale prospective studies are warranted to validate these findings.

Considering the accessibility of Cr and the evolving role of Cys, we propose a pragmatic clinical workflow aligned with the 2024 KDIGO rationale: new Cr-based equations (such as EKFC-eGFRCr) have shown good performance, even outperforming CKD-EPI-eGFRCr+Cys equation.[20] When considering that the use of different equations results in differences in outcomes for Chinese patients on vancomycin, priority can be given to the EKFC-eGFRCr(CN) equation, which has higher target attainment rates for both C_{min} and $AUC_{0\sim24}$. The eGFRCys or eGFRCr+Cys equations can be

used for confirmatory testing in patients with renal insufficiency or when important decisions need to be made.[52] When Cys values are available, the use of the CKD-EPI-eGFRCys equation is recommended. By integrating these refined GFR estimates into clinical protocols, healthcare providers can enhance the precision of vancomycin therapy, thereby optimizing efficacy and patient safety.

Conclusion

The study found that the CKD-EPI-eGFRCys equation had the greatest effect on dosing recommendation adjustments, while the EKFC-eGFRCr(CN) equation had the least effect. And our findings support a targeted strategy: EKFC-eGFRCr (CN) equation is favored for maximizing $AUC_{0\sim24}$ target achievement; CKD-EPI-eGFRCys equation is preferred for optimizing C_{min} target attainment and other key clinical outcomes. Guiding vancomycin dosing regimens with these equations may improve therapeutic efficacy and safety. Furthermore, future large-scale prospective studies are needed to validate these findings.

Abbreviations

eGFR, Estimated Glomerular Filtration Rate; CKD, Chronic Kidney Disease; Cr, Creatinine; Cys, Cystatin; C_{min}, Trough Concentration; $AUC_{0\sim24}$, 24 h Area Under The Concentration-time Curve; EKFC, European Kidney Function Consortium; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CG, Cockcroft-Gault; mGFR, Measured GFR; Ccr, Creatinine Clearance; BSA, Body Surface Area; NKF/ASN, The National Kidney Foundation And The American Society Of Nephrology; AKI, Acute Kidney Injury; KDIGO, Kidney Disease: Improving Global Outcomes; r-LMR, Re-Expressed Lund-Malmö Revised; CAPA, Caucasian, Asian, Pediatric, And Adult Cohorts; MDRD, Modification Of Diet In Renal Disease; BIS, Berlin Initiative Study; ARC, Augmented Renal Clearance; PPK, Population Pharmacokinetic; CCC, Lin's Concordance Correlation Coefficient; κ, Kappa; BMI, Body Mass Index; SD, Standard Deviation; IQR, Interquartile Range; OR, Odds Ratio.

Data Sharing Statement

The datasets generated and/or analysed during the current study are not publicly available, but are available from the corresponding author (Dayu Chen) on reasonable request.

Ethical Approval

The study was approved by the Ethics Committee of Nanjing Drum Tower Hospital (Approval No. 2024-723-01). As this was a retrospective study and the data were analyzed anonymously, the requirement for informed consent was waived by the Ethics Committee of Nanjing Drum Tower Hospital. This study was conducted in accordance with the Declaration of Helsinki and ensured the confidentiality of patient data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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