
Supplementary Material

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Table S1. The detailed search strategy in Embase

No.	Search terms
#1	vancomycin:ab,ti
#2	population /exp OR population AND (pharmacokinetics /exp OR pharmacokinetics)
#3	population /exp OR population AND (pharmacokinetic /exp OR pharmacokinetic)
#4	PPK
#5	bayes
#6	bayesian/exp OR bayesian
#7	monte AND carlo
#8	pharmacist/exp OR pharmacist

#9	TDM
#10	therapeutic AND (drug /exp OR drug) AND (monitoring /exp OR monitoring)
#11	patient specific
#12	patient tailored
#13	individualiz*
#14	individualis*
#15	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	#1 AND #15

Table S2. The detailed search strategy in PubMed

No	Search terms
#1	vancomycin:ab,ti
#2	Population pharmacokinetic
#3	Population pharmacokinetics
#4	PPK
#5	Monte Carlo
#6	bayes
#7	bayesian
#8	pharmacist
#9	TDM
#10	therapeutic drug monitoring
#11	patient-specific
#12	patient-tailored
#13	individualise*
#14	individualize*
#15	#1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)

Table S3. The detailed search strategy in The Cochrane Library

No.	Search terms
#1	VANCOMYCIN:ti,ab,kw in Trials
#2	Population pharmacokinetics
#3	population pharmacokinetic
#4	PPK
#5	bayes

#6	bayesian
#7	Monte Carlo
#8	pharmacist
#9	TDM
#10	therapeutic drug monitoring
#11	patient-specific
#12	patient-tailored
#13	individualized
#14	individualised
#15	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16	#1 and #15

Table S4 The list of excluded studies in the process of full text screening

No.	Author (year)	Title	Journal	Reason for exclusion	Note
1	2019	Optimizing individualized dosing regimen of vancomycin based on JPKD-vancomycin Population pharmacokinetic software and clinical application in patients of augmented renal clearance	Cochrane Central Register of Controlled Trials	insufficient clinical data	study protocol for registry
2	Bai 2015	Role of Clinical Pharmacist Intervention in Therapeutic Drug Monitoring of Vancomycin	Chinese Journal of Pharmacovigilance	insufficient clinical data	the details of pharmacists intervention was not reported
3	Berthaud 2018	Early Bayesian dose adjustment of vancomycin in children: a randomized controlled trial	Fundamental & clinical pharmacology Journal: Conference Abstract	insufficient clinical data	conference abstract without the detail of intervention
4	Bond 2005	Clinical and economic outcomes of pharmacist-managed aminoglycoside or vancomycin therapy	American Journal of Health-System Pharmacy	inappropriate interventions or comparisons	the intervention was not individualized dosing via pharmacokinetic tool
5	Broeker 2019	Towards precision dosing of vancomycin: a systematic evaluation of pharmacometric models for Bayesian forecasting	Clin Microbiol Infect	external validity of a nomogram or population PK model.	
6	Carreno 2017	Evaluation of a Bayesian Approach to Estimate Vancomycin Exposure in Obese Patients with Limited Pharmacokinetic Sampling: A Pilot Study	Antimicrob Agents Chemother	inappropriate interventions or comparisons	the comparison of different pharmacokinetic methods
7	Chen 2018	Analysis of clinical administration behavior of vancomycin under clinical pharmacy intervention	Chinese Journal of Drug Application and Monitoring	inappropriate interventions or comparisons	pharmacists intervention did not target at individualized vancomycin dosing

No.	Author (year)	Title	Journal	Reason for exclusion	Note
8	Drofenik 2012	Effect of pharmacy-guided TDM of vancomycin on achieving and maintaining recommended drug levels	International Journal of Clinical Pharmacy	single-arm study	
9	Duffy 2012	Vancomycin in newborns: Comparison of a standard dose to dosing adjusted for birth gestation and age	Archives of Disease in Childhood	inappropriate interventions or comparisons	the intervention was not individualized dosing via pharmacokinetic tool
10	Emoto 2017	Vancomycin dynamic PBPK modeling to assess pharmacokinetic profiles associated with changes in multiple physiological parameters	Clinical Pharmacology and Therapeutics	insufficient clinical data	conference abstract
11	Fang 2017	Study on the optimization of dosage regimen of vancomycin	Pharmaceutical Care and Research	single-arm study	
12	Foral 2017	A novel vancomycin standardized calculations method achieved therapeutic trough goals in obese and non-obese patients in a veterans affairs health care system	Open Forum Infectious Diseases	insufficient clinical data	conference abstract without the description of detailed calculation method
13	Giraud 2010	Vancomycin dose regimen adjustment in burn patients according to total burn surface area	Intensive Care Medicine	inappropriate interventions or comparisons	the intervention was not individualized dosing via pharmacokinetic tool
14	Hahn 2015	Validation of a pediatric population pharmacokinetic model for vancomycin	Ther Drug Monit	external validity of a nomogram or population PK model.	
15	Hanretty 2016	Assessing the impact of a pharmacist-managed vancomycin protocol on the duration of empiric therapy	Open Forum Infectious Diseases	inappropriate interventions or comparisons	pharmacists intervention did not target at individualized vancomycin dosing

No.	Author (year)	Title	Journal	Reason for exclusion	Note
16	Hong 2015	Individualized vancomycin dosing in obese patients: a two-sample measurement approach improves target attainment	Pharmacotherapy	inappropriate interventions or comparisons	both groups adopted pharmacokinetic tool, two sample measurement versus trough-only dosing
17	Igarashi 2000	Individualization of vancomycin therapy	Japanese Journal of Chemotherapy	single-arm study	
18	Imaura 2011	Effect of pharmacists intervention on the antibiotic therapy for the methicillin-resistant Staphylococcus aureus (MRSA) infectious diseases in the intensive care unit	Yakugaku Zasshi	neither English nor Chinese literature	
19	Janoly-Dumenil 2003	Interest of bayesian forecasting of vancomycin dosing regimens in a neonatal intensive care unit	Journal de Pharmacie Clinique	insufficient clinical data	the outcome of interest was not reported
20	Juan 2008	Design and validation of a dosing algorithm for vancomycin in premature neonates	An Pediatr (Barc)	external validity of a nomogram or population PK model.	
21	Kouroggi 2017	Establishment of a new initial dose plan for vancomycin using the generalized linear mixed model	Theor Biol Med Model	inappropriate interventions or comparisons	the comparison of different pharmacokinetic methods
22	Lee 2016	Evaluation of a pharmacy directed vancomycin and monitoring pilot program at an academic pediatric hospital	Open Forum Infectious Diseases	insufficient clinical data	conference abstract without the description of pharmacy driven vancomycin dosing
23	Lerous 2016	Clinical Utility and Safety of a Model-Based Patient-Tailored Dose of Vancomycin in Neonates	Antimicrob Agents Chemother	single-arm study	

No.	Author (year)	Title	Journal	Reason for exclusion	Note
24	Li 2019	Study on Application of JPKD Population Pharmacokinetics Software in Individualized Administration of Vancomycin	Anti-Infection Pharmacy	single-arm study	
25	Liang 2015	A cohort study of vancomycin therapeutic drug monitoring	Chinese Journal of Infection and Chemotherapy	insufficient clinical data	the detail of TDM based dosed adjustment was not provided
26	Lin 2016	Population pharmacokinetics of vancomycin in adult Chinese patients with post-craniotomy meningitis and its application in individualised dosage regimens	Eur J Clin Pharmacol	external validity of a nomogram or population PK model.	
27	Mahmoud 2017	Optimization of therapeutic drug monitoring of vancomycin in patients with chronic hemodialysis	Clin Nephrol	inappropriate interventions or comparisons	the intervention was not individualized dosing via pharmacokinetic tool
28	Marquis 2015	Evaluation of a Pharmacist-Directed Vancomycin Dosing and Monitoring Pilot Program at a Tertiary Academic Medical Center	Ann Pharmacother	insufficient clinical data	the details of pharmacists intervention were not described
29	Masoumi 2017	Evaluation of pharmacist intervention on vancomycin dosing and nephrotoxicity prevention	European Journal of Hospital Pharmacy	inappropriate interventions or comparisons	the pharmacist intervention did not target at pharmacokinetic interpretation of serum concentration
30	Medellin-Garibay 2016	Pharmacokinetics of vancomycin and dosing recommendations for trauma patients	J Antimicrob Chemother	external validity of a nomogram or population PK	

No.	Author (year)	Title	Journal	Reason for exclusion	Note
				model.	
31	Mochizuki 2010	Efficacy and safety for vancomycin in uncomplicated catheter-related bloodstream infection by coagulase negative Staphylococcus	Japanese Journal of Chemotherapy	inappropriate interventions or comparisons	the intervention was not individualized dosing via pharmacokinetic tool
32	Moreno 2016	Impact of a bayesian pharmacokinetic dosing programme of vancomycin on clinical outcomes	European Journal of Hospital Pharmacy	single-arm study	
33	OBrien 2015	Evaluation of the safety of a vancomycin nomogram used to achieve target trough concentrations	Hospital Pharmacy	inappropriate interventions or comparisons	the intervention was not individualized dosing via pharmacokinetic tool
34	Okada 2016	Clinical Evaluation of Pharmacist Interventions in Patients Treated with Anti-methicillin-Resistant Staphylococcus aureus Agents in a Hematological Ward	Biol Pharm Bull	insufficient clinical data	the outcomes of vancomycin dosing could not be substracted
35	Olson 2019	Optimizing Vancomycin Dosing in Chronic Kidney Disease by Deriving and Implementing a Web-Based Tool Using a Population Pharmacokinetics Analysis	J Pediatric Infect Dis Soc	inappropriate interventions or comparisons	the intervention was not restricted to the pharmacokinetic intepretation of vancomycin, but also the timing of TDM
36	Radke 2016	Development of a Physiologically Based Pharmacokinetic Modelling Approach to Predict the Pharmacokinetics of Vancomycin in Critically Ill Septic Patients	Clin Pharmacokinet	external validity of a nomogram or population PK model.	

No.	Author (year)	Title	Journal	Reason for exclusion	Note
37	Robinson 2016	Effectiveness of a pharmacist to dose vancomycin consult service in attaining therapeutic trough levels in a teaching hospital	Pharmacotherapy	insufficient clinical data	the details of pharmacist to dose vancomycin consult service was not reported
38	Romero 2017	Comparison of area under the curve estimated between a prediction mathematical method versus Bayesian bicompartimental model	International Journal of Clinical Pharmacy	inappropriate interventions or comparisons	the comparison of different pharmacokinetic methods
39	Romero 2018	Could a Bayesian bicompartimental model be equivalent to a prediction mathematical method to estimate trough values for vancomycin monitoring?	International Journal of Clinical Pharmacy	inappropriate interventions or comparisons	the comparison of different pharmacokinetic methods
40	Roux 1992	Vancomycin drug monitoring: Computerized Bayesian method	Journal de Pharmacie Clinique	external validity of a nomogram or population PK model.	
41	Sanchez 2016	Clinical impact of pharmacist intervention in therapeutic vancomycin monitoring	European Journal of Hospital Pharmacy	insufficient clinical data	the pathway of intervention was not provided
42	Sato 2007	Evaluation of the usefulness of vancomycin dosage design based on pharmacokinetics/pharmacodynamics theory	Japanese Journal of Chemotherapy	inappropriate interventions or comparisons	the intervention was not individualized dosing via pharmacokinetic tool
43	Shankar 2009	Pharmacist managed vancomycin serum level monitoring leads to improved achievement of therapeutic target levels in children in pediatric intensive care unit (PICU)		insufficient clinical data	the details of pharmacokinetic modeling process were not reported
44	Shao 2014	Influence of Effect of Vancomycin by Pharmaceutical Care in Patients with Severe Pneumonia Complicated with Acute	Chin J Pharmacoepidemiol	insufficient clinical data	the details of individualized dosing were not reported

No.	Author (year)	Title	Journal	Reason for exclusion	Note
		Renal Injury			
45	Shi 2018	Relationship between vancomycins blood concentration monitoring and clinical outcomes in critically ill patients	Practical Pharmacy and Clinical Remedies	inappropriate interventions or comparisons	the intervention group targeted at TDM, rather than the pharmacokinetic interpretation to serum concentration
46	Smith 2016	Impact of a Pharmacist-Initiated Vancomycin Monitoring Program	Consult Pharm	inappropriate interventions or comparisons	pharmacists intervention did not target at pharmacokinetic interpretation to serum concentrations
47	Stockmann 2015	Predictive Performance of a Vancomycin Population Pharmacokinetic Model in Neonates	Infect Dis Ther	external validity of a nomogram or population PK model.	
48	Suardi 2016	Individualized dose of Vancomycin for Patients with Chronic Kidney Disease at a Government Hospital in Padang, West Sumatra, Indonesia	Der Pharmacia Lettre	insufficient clinical data	the detail of the intervention was not provided
49	Sussman 2013	Evaluation of a pharmacist managed vancomycin therapy compared to physician managed dosing in establishing timely and therapeutic vancomycin serum concentrations at a community hospital	Journal of Pharmacy Practice	insufficient clinical data	the detail of pharmacist managed vancomycin therapy was not provided

No.	Author (year)	Title	Journal	Reason for exclusion	Note
50	Taghizadeh-Ghehi 2015	Predictive performance of Vancomycin population pharmacokinetic models in Iranian patients underwent hematopoietic stem cell transplantation	J Res Pharm Pract	external validity of a nomogram or population PK model.	
51	Takahashi 1998	Clinical evaluation of vancomycin dosage regimens based on the Bayesian method	Japanese Journal of Chemotherapy	single-arm study	
52	Takahashi 2018	The effects of intervention by a ward pharmacist on vancomycin blood level control in the emergency medical center	Intensive Care Medicine Experimental	inappropriate interventions or comparisons	the detailed intervention by pharmacists were not mentioned
53	Xu 2018	Research of optimal dosing regimens and therapeutic drug monitoring for vancomycin by clinical pharmacists: analysis of 7-year data	Chin Crit Care Med	inappropriate interventions or comparisons	the intervention of pharmacokinetic dosing was not mentioned
54	Xu 2018	Research of optimal dosing regimens and therapeutic drug monitoring for vancomycin by clinical pharmacists: analysis of 7-year data	Zhonghua Wei Zhong Bing Ji Jiu Yi Xue	repeptitive data	the study was included in the second round of study selection for two times and was excluded

Table S5 Risk of bias assessment for RCTs included

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Fernandez 1996	Low risk	Low risk	High risk	High risk	Low risk	Unclear	Unclear
Pea 2002	Unclear	Unclear	High risk	Low risk	Low risk	Unclear	Unclear
Shahrami 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear

Irikura (2011)	☆	☆	☆	☆	☆	☆	☆	☆	8
Miller (2018)	☆	☆	☆	☆	☆	☆	☆	☆	8
Welty (1994)	☆	☆	☆	☆	☆	☆	☆	☆	8
Komoto (2018)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Abulfathi (2018)	☆	☆	☆	☆	☆	☆	☆	☆	8
Neely (2018)	☆	☆	☆	☆	☆	☆	☆	☆	8
Dorajoo (2019)	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Truong (2018)	☆	☆	☆	☆	☆	☆	☆	☆	8
Finch (2017)	☆	☆	☆	☆	☆☆	☆	☆	☆	9

Table S7. Definitions and attainment of target trough serum concentrations

Study	Definition	Intervention group		Control group	
		Number of events	Total	Number of events	Total
Brinkman (2015)	Initial (< 48 hours) trough levels of > 15 mg/l	9	15	4	14
Cardile (2015)	National guideline targets of 10–15 or 15–20 mg/L according to treatment indication.	53	66	33	79
Crumby (2009)	Steady-state trough concentrations were within 5-15 mg/L	32	39	54	108
Grimsley (1999)	A first therapeutic drug monitoring serum vancomycin concentration within 5-12 mg/L	18	25	40	122
Hirano (2016)	Steady state serum concentration within 10-20 mg/L	43	51	11	28
Irikura (2011)	Serum trough concentration of vancomycin at steady state within 5–15 mg/L	18	22	20	41
Leu (2012)	Trough target was at 5–15 mg/L and 15–20 mg/L according to indications	28	43	18	56
Masuda (2015)	10 – 20 µg/mL therapeutic trough concentration range	64	102	212	508
Miller (2018)	10–15 mg/L or 15–20 mg/L specified by physicians (at 7 days)	16	16	20	35
Momattin (2015)	Therapeutic trough levels were within 10–20 mg/L	227	286	137	278
Pea (2002)	Average vancomycin C _{min} within 5-10 mg/L	16	16	9	16
Shahrami, B.(2016)	Trough serum concentrations not less than 15 mg/L at steady state	9	10	3	8
Zhao (2013)	Serum vancomycin concentrations within the therapeutic range of 15–25 mg/l	41	58	48	116
Abulfathi 2018	Trough concentration; 10–20 mg/L for intermittent infusion, and average steady-state concentration; 17–29 mg/L for continuous infusion	118	217	130	292
Komoto 2018	The target VCM trough concentration was set at 10–20 µg/mL (first trough)	18	28	20	49
Truong 2018	achieving a goal trough concentration (10 to 20 mg/L) at any point during vancomycin therapy	42	50	28	50

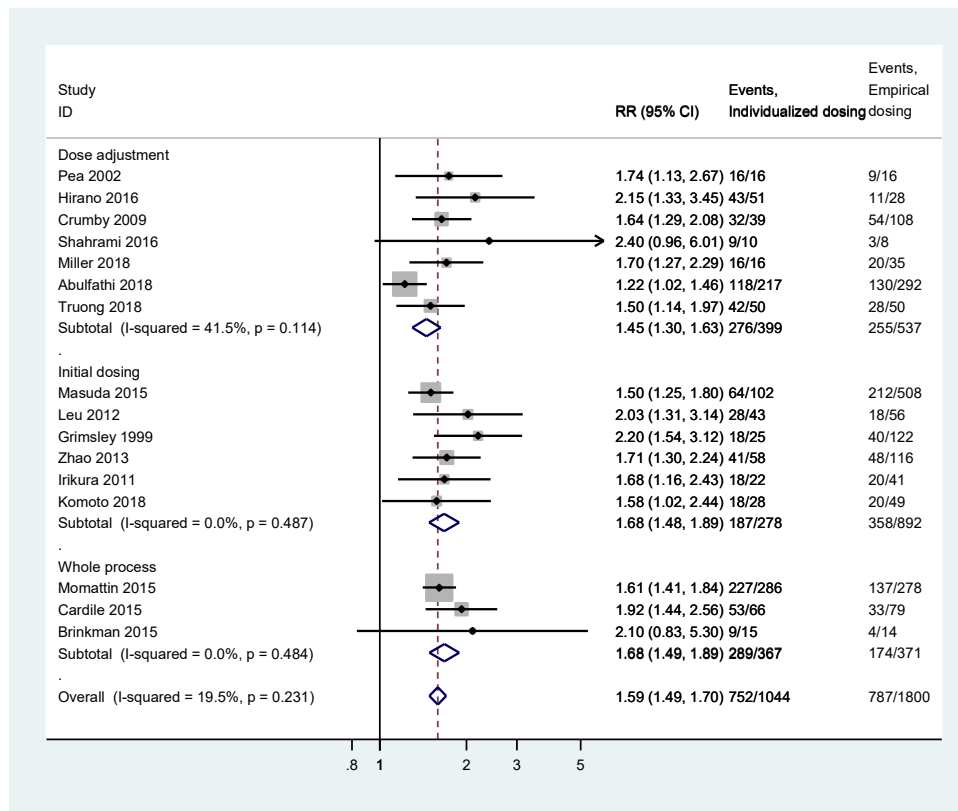
Table S8. Definitions and occurrence of nephrotoxicity

Study	Definition	Intervention group		Control group	
		Number of events	Total	Number of events	Total
Cardile (2015)	Defined and graded as acute kidney injury (AKI) via the RIFLE Criteria	23	173	20	79
Fernandez (1996)	Mild if the increase in creatinine levels was 0.5 to 0.9 mg/dl, moderate if the increase was 1.0 to 2.4 mg/dl, and severe if the increase was 2.5 mg/dl or more	5	37	14	33
Hirano (2016)	Vancomycin induced AKI was evaluated based on RIFLE criteria	7	51	6	28
Irikura (2011)	The dosing was discontinued because of increase in serum creatinine level	1	21	2	33
Leu (2012)	An increase in serum creatinine of 0.5 mg/dl at any time during vancomycin treatment, or a decrease in creatinine clearance over 50% compared to baseline	4	28	11	48
Momattin (2015)	0.5 mg/dl elevation in serum creatinine (SCr) if the initial value was <3 mg/dl, or a rise of >1 mg/dl if the initial value was >3 mg/dl	16	286	29	278
Welty (1994)	A rise in serum creatinine concentration of greater than 44 µmol/l (0.5 mg/dL) during vancomycin therapy	4	61	13	55
Neely (2018)	an increase in serum creatinine of ≥ 0.5 mg/dl or ≥ 50% from baseline	0	88	6	75
Truong (2018)	AKI was defined as an increase in serum creatinine by ≥ 50% or 0.5 mg/dL, whichever was greater, from baseline for 2 or more consecutive occurrences in accordance with the RIFLE criteria	4	50	7	50
Dorajoo (2019)	50% or greater increase in serum creatinine	2	22	1	21
Finch (2017)	SCr increase of ≥ 0.5 mg/dl and ≥ 50% the baseline SCr for > 2 consecutive measurements	54	734	54	546
Masuda (2015)	The incidence of nephrotoxicity was defined as a 50% or higher increase from the baseline Scr level during the period from Initiation of VAN therapy to 72 – 96 hours after administration	OR 0.548 (0.189, 1.59)			

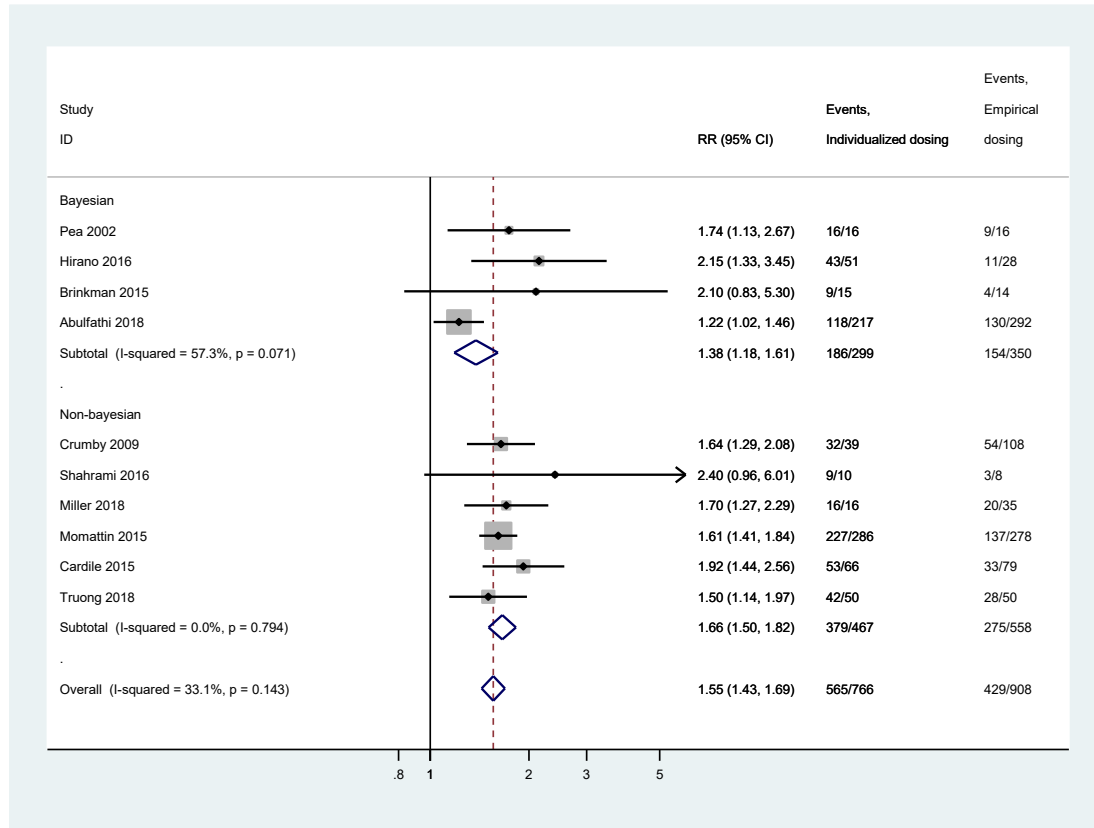
RIFLE: Risk, Injury, Failure, Loss, ESRD (End Stage Renal Disease)

Figure S1 Subgroup analysis for individualized dosing via PK tool and attainment of target trough concentration

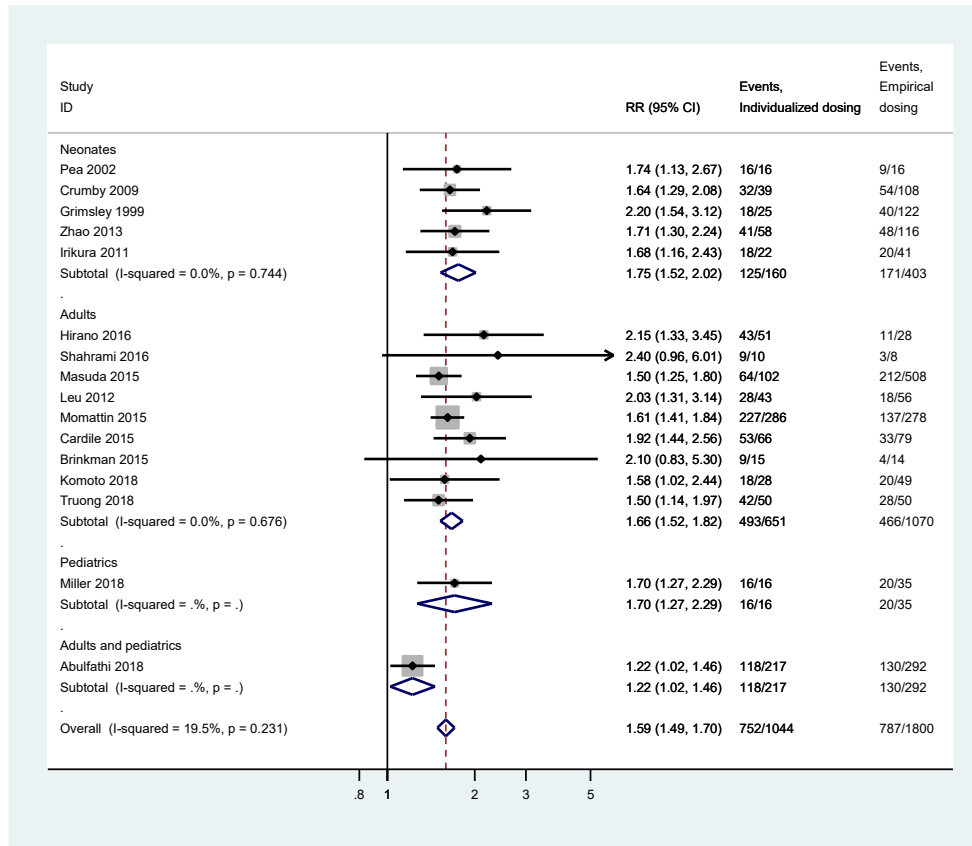
A, Subgroup analysis by mode of individualization



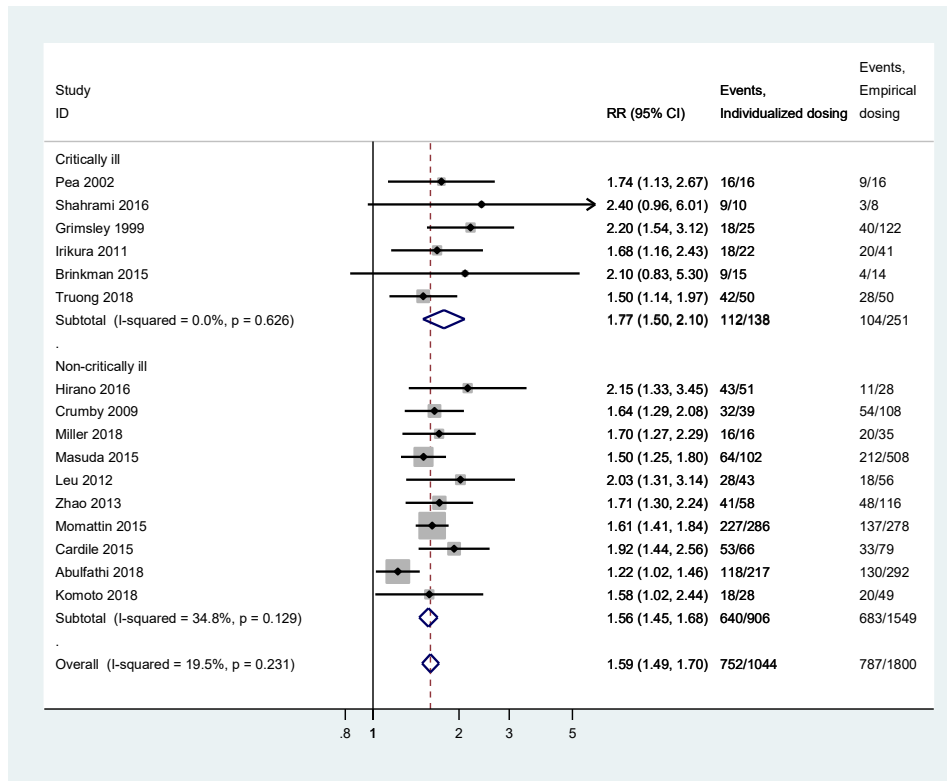
B, Subgroup analysis by utility of Bayesian forecasting method in dose adjustment



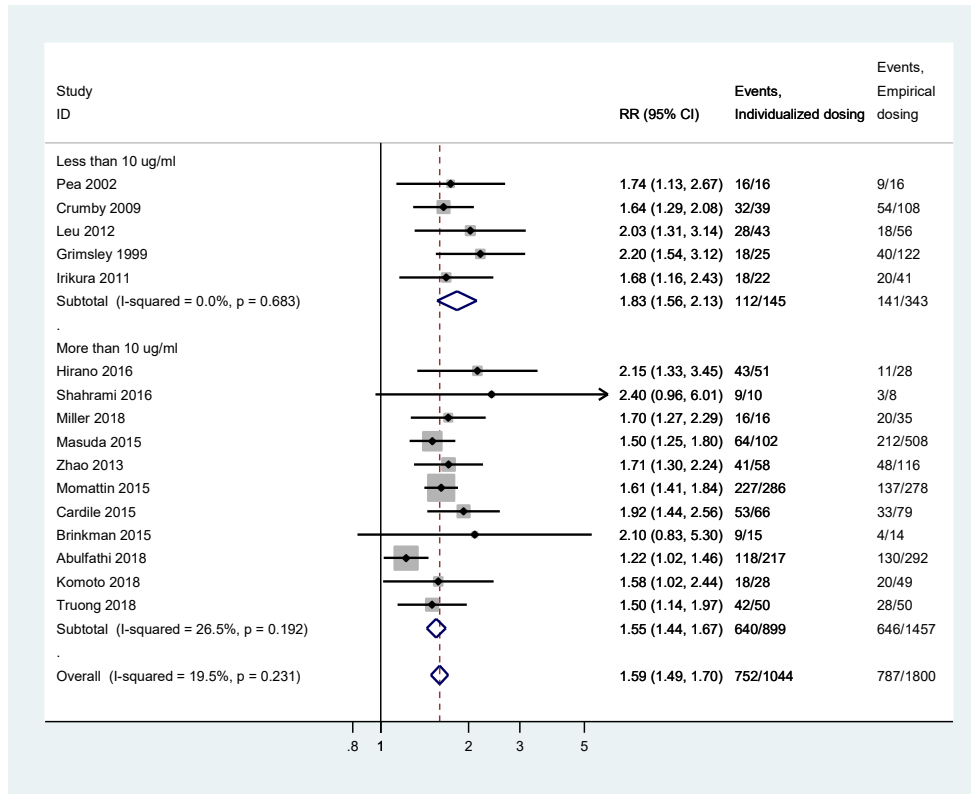
C, Subgroup analysis by age



D, Subgroup analysis by whether patients were critically ill



E, Subgroup analysis by target trough concentration



F, Subgroup analysis by study design

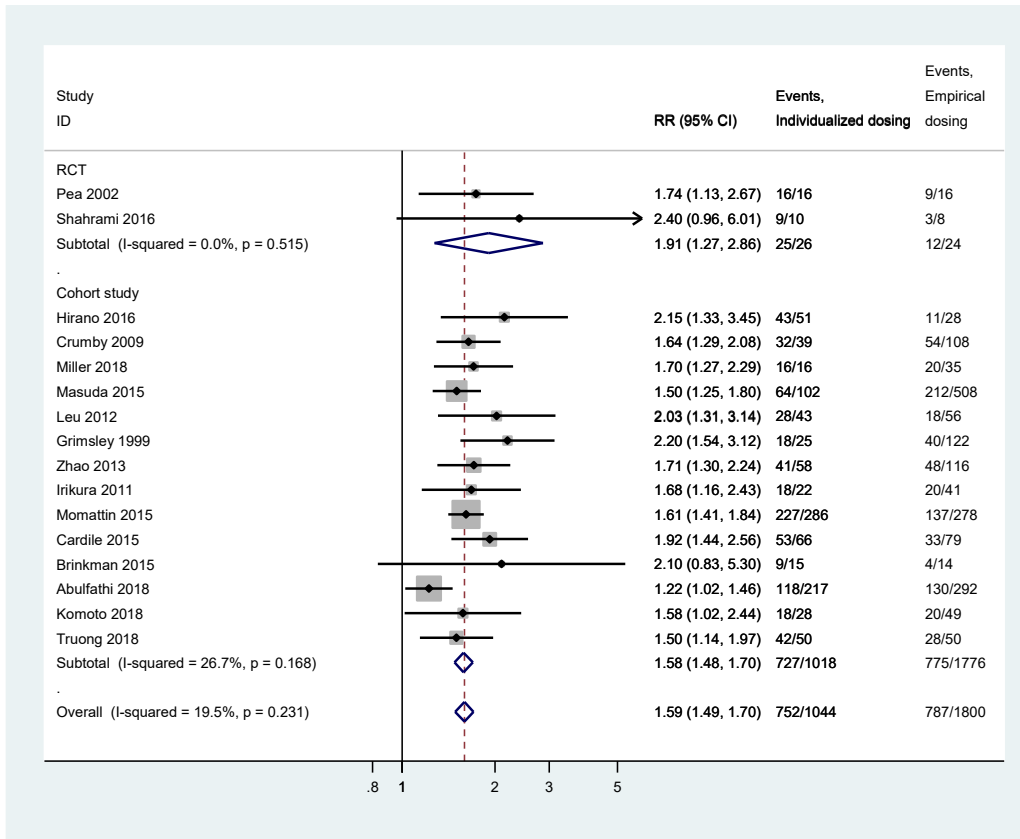


Figure. S2. Sub-analysis of target trough concentration in accordance with guidelines

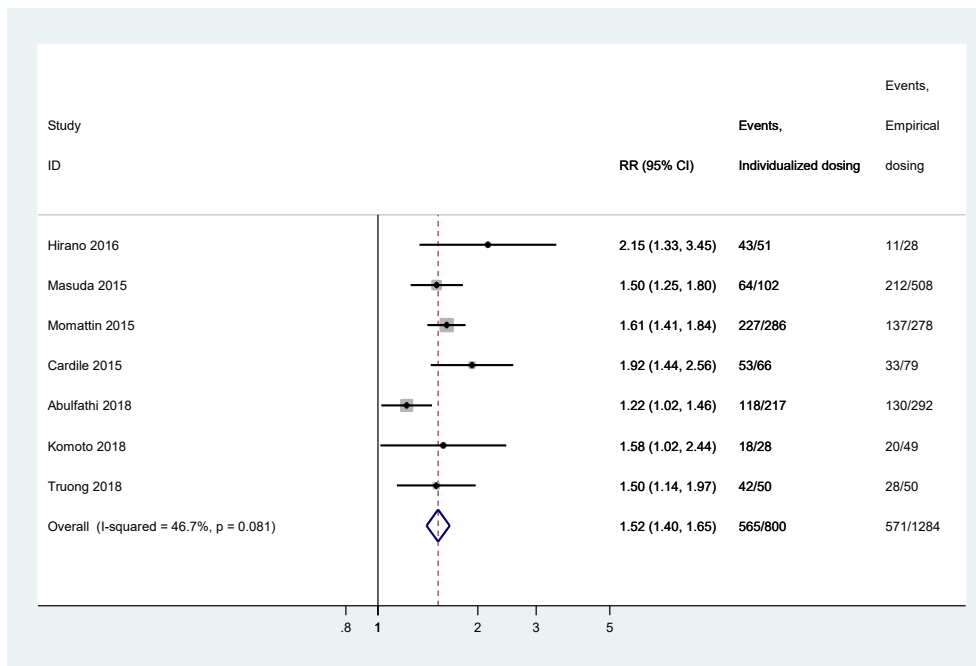


Figure. S3. Sub-analysis of nephrotoxicity's definition in accordance with guidelines

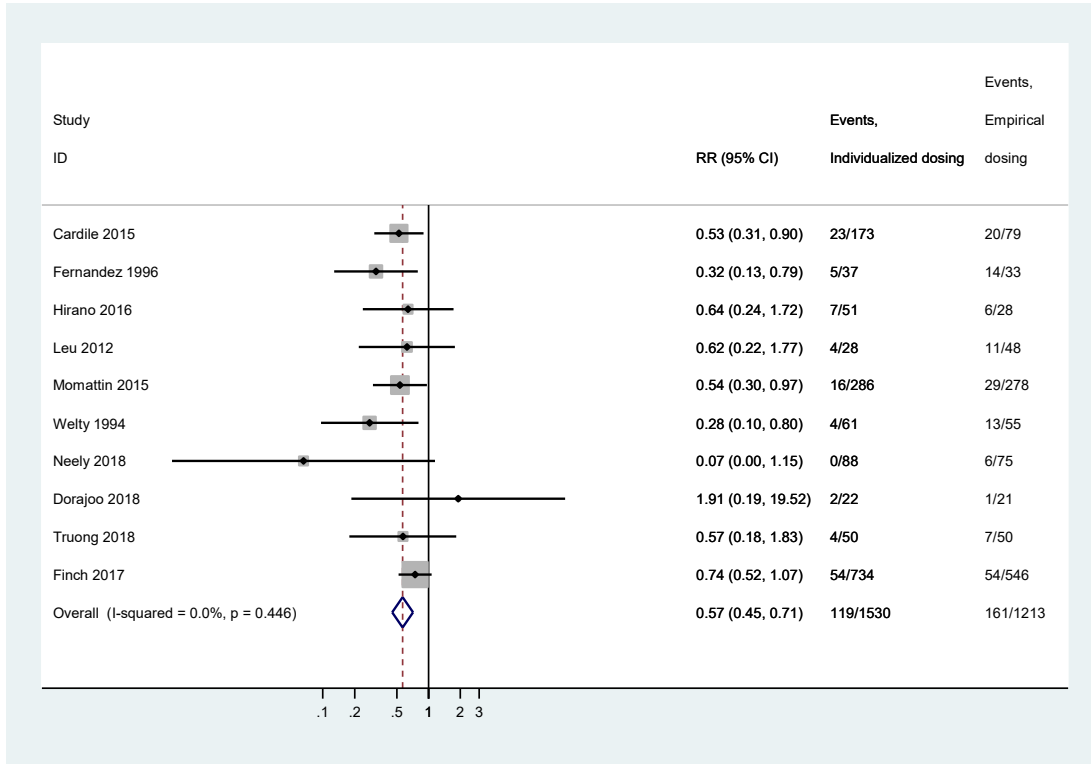


Figure S4 Meta-analysis for all-cause mortality

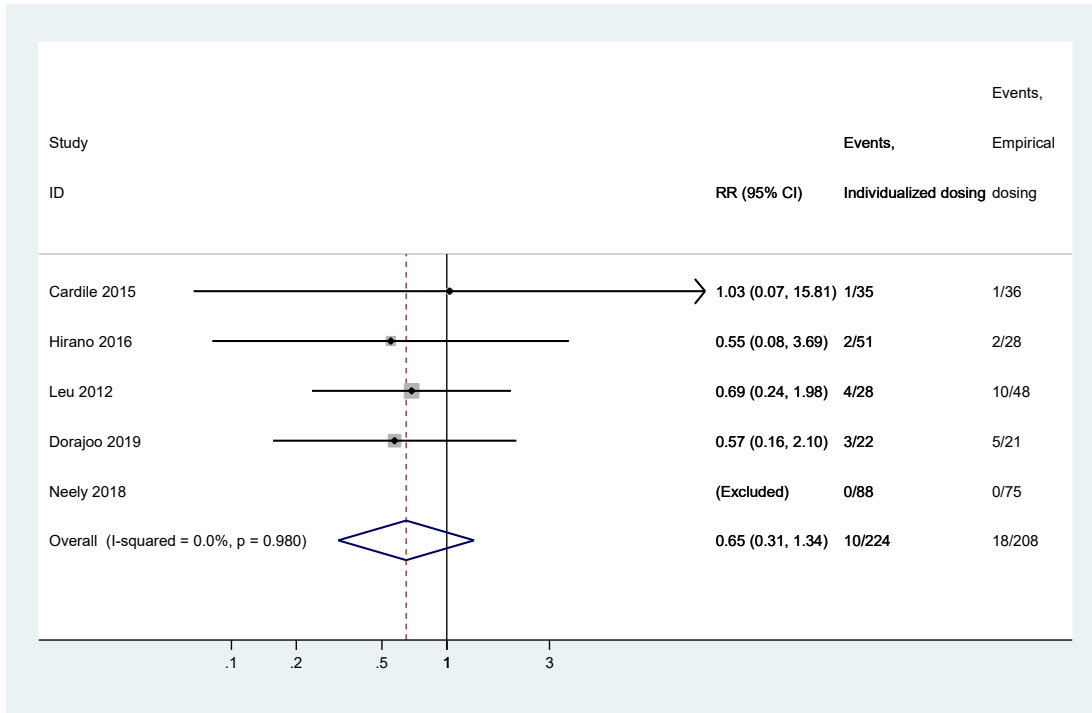


Figure S5 Meta-analysis for length of hospital-stay

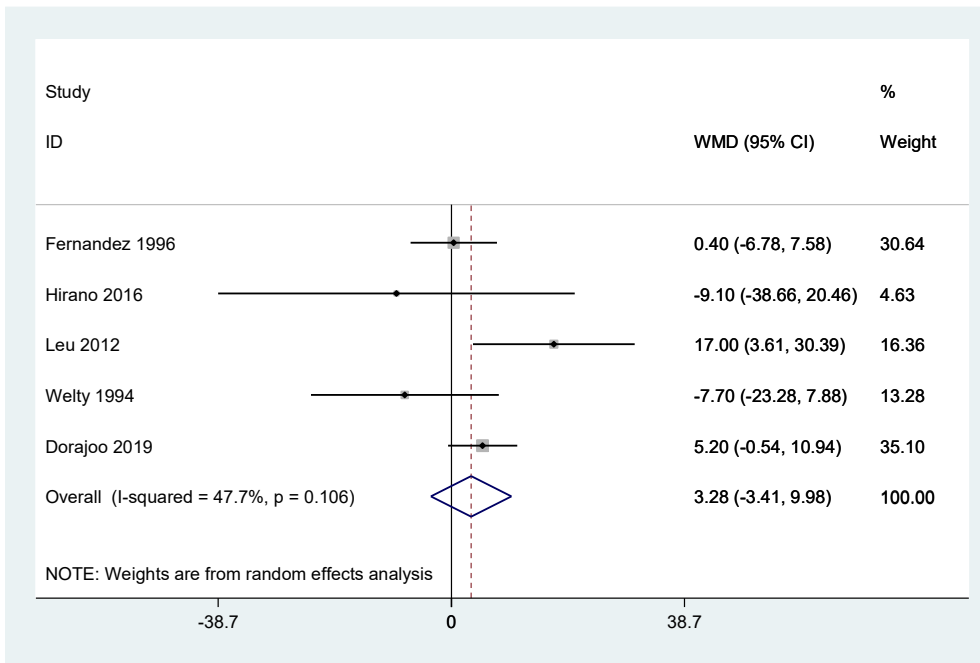
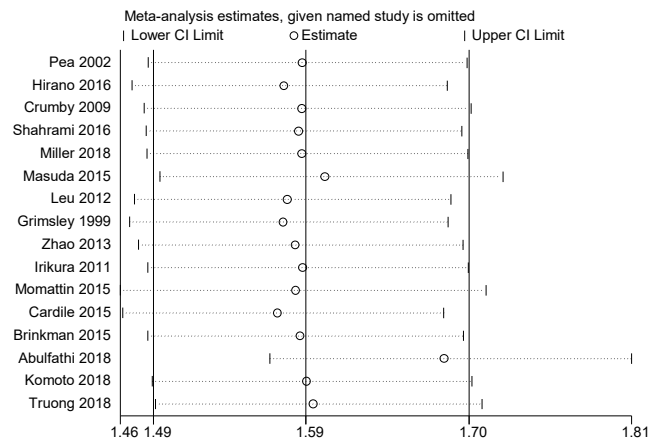
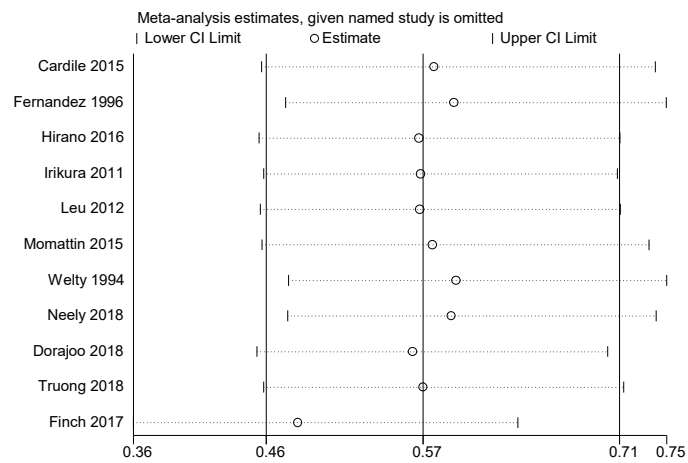


Figure. S6. Sensitivity analysis using function “metaninf”

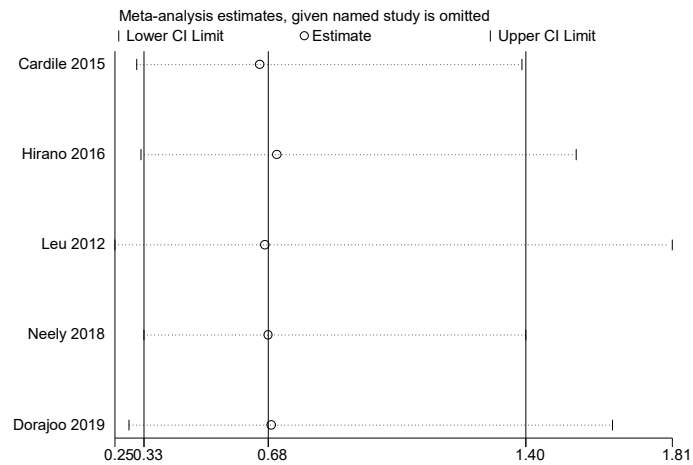
(A). Attainment of target trough concentration



(B). Nephrotoxicity



(C). Mortality



(D).Length of hospital-stay

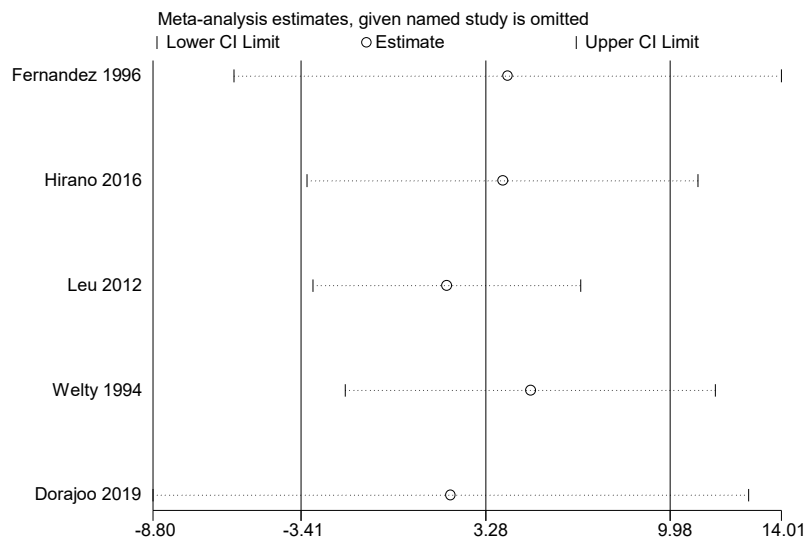
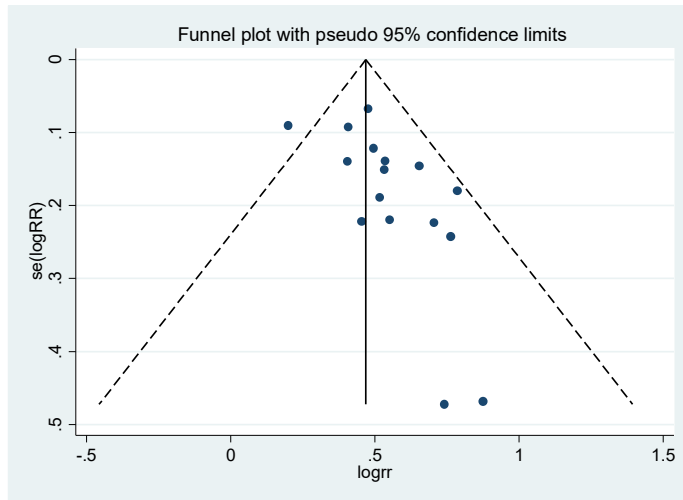


Figure S7 Funnel plot for publication bias assessment

(A). Attainment of target trough concentration



(B) Nephrotoxicity

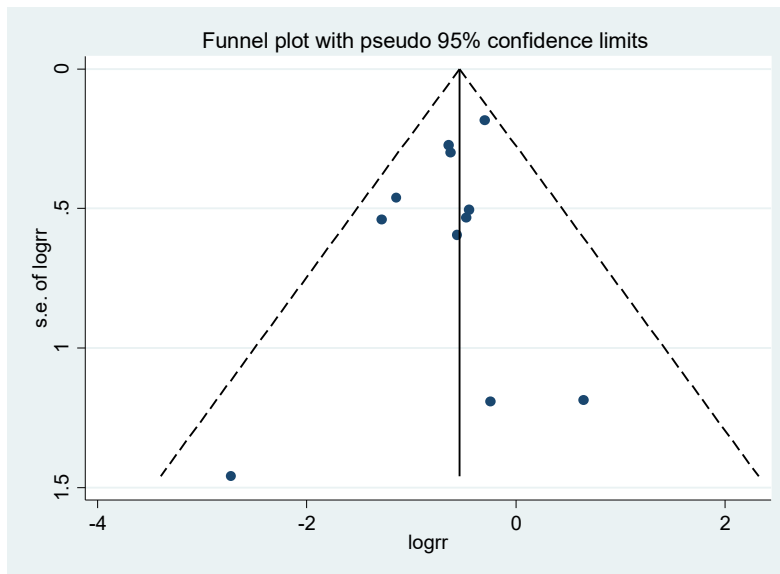
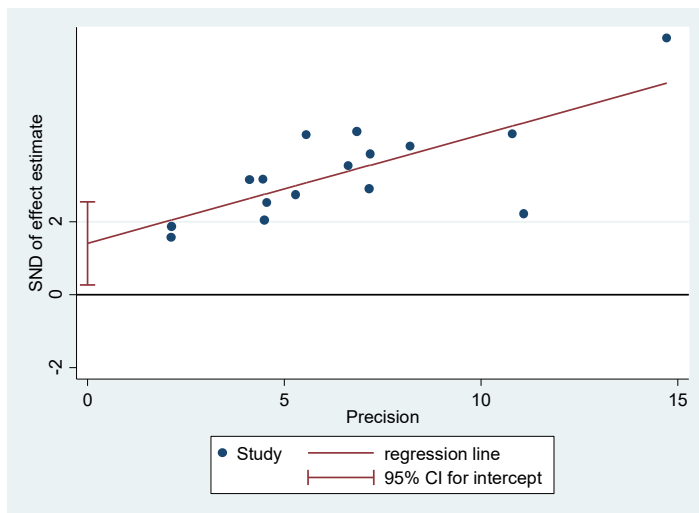


Figure S8 Egger's test for publication bias assessment

(A). Attainment of target trough concentration



Number of studies = 16

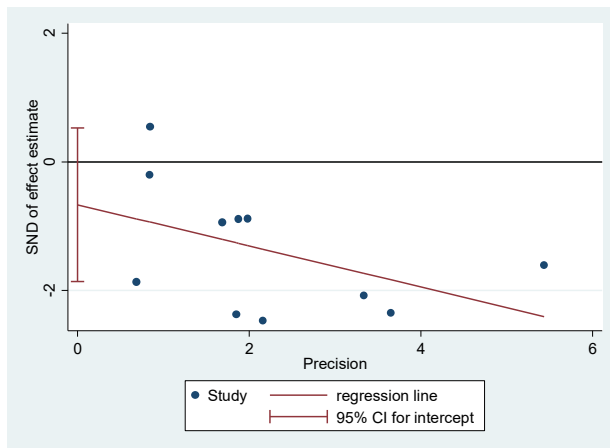
Root MSE = .941

Std_Eff	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
slope	.297409	.0723315	4.11	0.001	.1422734	.4525446
bias	1.407992	.5312744	2.65	0.019	.2685222	2.547463

Test of H0: no small-study effects

P = 0.019

(B). Nephrotoxicity



Eggers test for small -study effects:

Regress standard normal deviate of intervention effect estimate against its standard error

Number of studies = 11

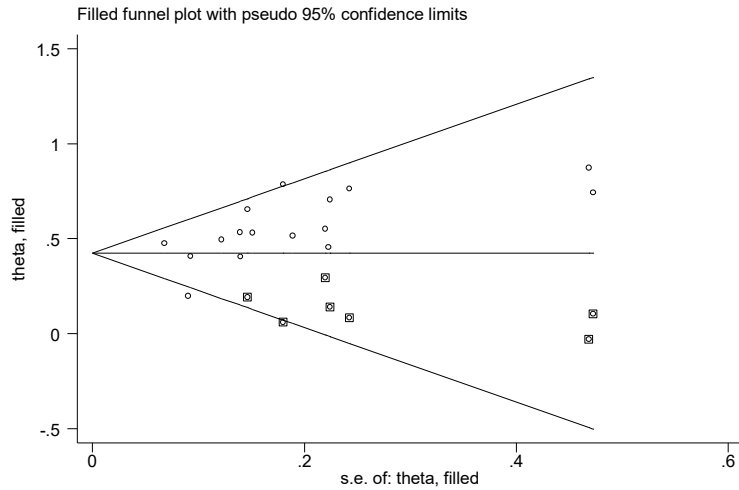
Root MSE = .9179

Std_Eff	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
slope	-.3199546	.2032505	-1.57	0.150	-.7797392	.1398301
bias	-.6662212	.528091	-1.26	0.239	-1.860846	.5284037

Test of H0: no small-study effects P = 0.239

Figure S9 Trim and fill analysis for attainment of target trough concentration

Filled funnel plot



Meta-analysis

Method	Pooled Est	95% CI		Asymptotic z_value	Asymptotic p_value	No. of studies
		Lower	Upper			
Fixed	0.469	0.403	0.536	13.788	0.000	16
Random	0.484	0.404	0.565	11.851	0.000	

Test for heterogeneity: $Q = 18.616$ on 15 degrees of freedom ($p = 0.232$)
 Moment-based estimate of between studies variance = 0.005

Trimming estimator: Linear

Meta-analysis type: Fixed-effects model

iteration	estimate	Tn	# to trim	diff
1	0.469	111	6	136
2	0.427	122	7	22
3	0.423	123	7	2
4	0.423	123	7	0

Filled

Meta-analysis (exponential form)

Method	Pooled Est	95% CI		Asymptotic z_value	Asymptotic p_value	No. of studies
		Lower	Upper			
Fixed	1.527	1.436	1.624	13.441	0.000	23
Random	1.534	1.412	1.668	10.080	0.000	

Test for heterogeneity: $Q= 32.273$ on 22 degrees of freedom ($p= 0.073$)

Moment-based estimate of between studies variance = 0.011