Supplementary material

Method

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Data extraction: We extracted the following data from each paper: authors, publication year, study setting and country, study design and population, age (mean ± standard deviation (SD) or median (interquartile range (IQR)), sex ratio, the type of polymyxins administered (PMB or colistin), daily dosage (mean ± SD or median (IQR)), information on loading dose, dosing interval, AKI criteria, sample size, number of AKI events, AKI events based on Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification scheme, Kidney Disease: Improving Global Outcomes (KDIGO) classification scheme or Acute Kidney Injury Network (AKIN) classification scheme, the need for renal replacement therapy (RRT), Acute Physiology and Chronic Health Evaluation (APACHE) II score for disease severity scoring (mean or median), and potential predictors of nephrotoxicity.

Subgroup analysis: We performed several subgroup analyses according to age (< 65 *vs.* ≥ 65 years), sex proportion, geographical location, definition of AKI, study design, the type of polymyxins (PMB or colistin), daily dosage, giving loading dose or not, dosing interval, APACHE II score, sample size, publication year and risk of bias.

Supplementary Table 1 Search strategy for the study

A．Search strategy for PubMed

Search	Query	Number
#1	Search: "critical care" OR critically ill OR critical illness OR "intensive care" OR "intensive care unit" OR "critically ill" OR "critical illness"	523,382
#2	Search: "Colistin"[MeSH] OR colistin[ALL] OR Colisticin[ALL] OR "Polymyxin E"[ALL] OR "Polymyxin-E"[ALL] OR "Polymyxin E"[ALL] OR "Polymyxin-E"[ALL] OR Colimycin[ALL] OR "Coly-Mycin"[ALL] OR Totazina[ALL] OR "Colistin Sulfate"[ALL] OR "Colistin Sulphate"[ALL] OR "sodium colistimethate"[ALL] OR "colistimethate sodium"[ALL] OR "Polymyxin B"[MeSH] OR "polymyxin B"[ALL] OR "polymyxin-B"[ALL] OR "Polymixin B"[ALL] OR "Polymixin-B"[ALL] OR Aerosporin[ALL] OR "Polymyxins"[MeSH] OR polymyxin[ALL] OR polymyxins[ALL] OR polymyxin[ALL] OR polymyxins[ALL] OR "colistinmethanesulfonic acid" [Supplementary Concept] OR colistimethate[ALL]	18,926
#3	Search: ("Kidney/adverse effects"[MeSH] OR "Kidney/drug effects"[MeSH] OR "Kidney/injuries"[MeSH] OR "Kidney/metabolism"[MeSH] OR "Kidney/pathology"[MeSH] OR "Kidney/toxicity"[MeSH]) OR ("Kidney Diseases/chemically induced"[MeSH] OR "Kidney Diseases/diagnosis"[MeSH] OR "Kidney Diseases/drug effects"[MeSH] OR "Kidney Diseases/injuries"[MeSH]	435,268

	OR "Kidney Diseases/metabolism"[MeSH] OR "Kidney Diseases/pathology"[MeSH] OR "Kidney Diseases/pharmacology"[MeSH] OR "Kidney Diseases/prevention and control"[MeSH]) OR ("Acute Kidney Injury/chemically induced"[MeSH] OR "Acute Kidney Injury/drug effects"[MeSH] OR "Acute Kidney Injury/epidemiology"[MeSH] OR "Acute Kidney Injury/metabolism"[MeSH] OR "Acute Kidney Injury/pathology"[MeSH] OR "Acute Kidney Injury/pharmacology"[MeSH] OR "Acute Kidney Injury/prevention and control"[MeSH])	
#4	Search: nephrotoxic*[ALL] OR "Renal toxicity"[ALL] OR "renal toxicities"[ALL] OR "kidney toxicity"[ALL] OR "kidney toxicities"[ALL] OR "renal failure"[ALL] OR "renal failures"[ALL] OR "kidney disease"[ALL] OR "kidney diseases"[ALL] OR "kidney failure"[ALL] OR "kidney failures"[ALL] OR "renal disease"[ALL] OR "renal diseases"[ALL] OR "kidney injury"[ALL] OR "kidney injuries"[ALL] OR "renal injury"[ALL] OR "renal injuries"[ALL] OR "renal function"[ALL] OR "renal dysfunction"[ALL] OR "renal functions"[ALL] OR "renal dysfunctions"[ALL]	495,953
#5	Search: #3 OR #4	741,114
#6	Search: #1 AND #2	1,851
#7	Search: #5 AND #6	317
#8	Search: animals[MeSH] NOT humans[MeSH]	4,955,293
#9	Search: #7 NOT #8	314
#10	Search: #9 AND English[Filter]	301

B. Search strategy for Ovid Embase

Search	Query	Number
#1	'intensive care'/exp OR 'critical care':ab,ti OR 'intensive care':ab,ti OR 'intensive care unit'/exp OR 'critical* ill*':ab,ti OR 'critical illness'/exp OR 'intensive care nursing'/exp	1,086,856
#2	'colistin'/exp OR colistin OR colisticin OR 'polymyxin e' OR 'polymyxin-e' OR 'polymyxin e' OR 'polymyxin-e' OR 'neomycin'/exp OR 'coly-mycin' OR totazina OR 'colistin sulfate' OR 'colistin sulphate' OR 'colistimethate'/exp OR 'sodium colistimethate' OR 'colistimethate sodium' OR colistimethate OR 'polymyxin b'/exp OR 'polymyxin b' OR 'polymyxin-b' OR 'polymyxin b' OR 'polymyxin-b' OR aerosporin OR 'polymyxin'/exp OR polymyxin OR polymyxins OR polymyxin OR polymyxins	64,392
#3	'kidney/adverse effects' OR 'kidney/drug effects' OR 'kidney/injuries' OR 'kidney/metabolism' OR 'kidney/pathology' OR 'kidney/toxicity' OR 'kidney diseases/chemically induced' OR 'kidney diseases/diagnosis' OR 'kidney diseases/drug effects' OR 'kidney diseases/injuries' OR 'kidney diseases/metabolism' OR 'kidney diseases/pathology' OR 'kidney diseases/pharmacology' OR 'kidney diseases/prevention and control' OR 'acute kidney injury/chemically induced' OR 'acute kidney injury/drug effects' OR 'acute kidney injury/epidemiology' OR 'acute kidney injury/metabolism' OR 'acute kidney injury/pathology' OR 'acute kidney injury/pharmacology' OR 'acute kidney	73,720

	injury/prevention and control' OR 'nephrotoxicity'/exp	
#4	nephrotoxic* OR 'renal toxicity' OR 'renal toxicities' OR 'kidney toxicity' OR 'kidney toxicities' OR 'renal failure' OR 'renal failures' OR 'kidney disease' OR 'kidney diseases' OR 'kidney failure' OR 'kidney failures' OR 'renal disease' OR 'renal diseases' OR 'kidney injury' OR 'kidney injuries' OR 'renal injury' OR 'renal injuries' OR 'renal function' OR 'renal functions' OR 'renal dysfunction' OR 'renal dysfunctions'	895,669
#5	#3 OR #4	897,426
#6	#2 AND #5	4,135
#7	#1 AND #6	1,154
#8	('animal'/exp OR [animal cell]/lim OR [animal experiment]/lim OR [animal model]/lim OR [animal tissue]/lim OR [animals]/lim) NOT ('human'/exp OR [humans]/lim)	6,207,929
#9	#7 NOT #8 AND [english]/lim AND [embase]/lim	1,090

C. Search strategy for Cochrane Library

Search	**Query**	**Number**
#1	MeSH descriptor: [Critical Care] explode all trees	2,165
#2	MeSH descriptor: [Intensive Care Units] explode all trees	3,952
#3	MeSH descriptor: [Critical Illness] explode all trees	2,531
#4	MeSH descriptor: [Critical Care Nursing] explode all	44

	trees	
#5	(critical care):ti,ab,kw OR (intensive care):ti,ab,kw OR (critical* ill*):ti,ab,kw	44,040
#6	#1 OR #2 OR #3 OR #4 OR #5	44,284
#7	MeSH descriptor: [Colistin] explode all trees	186
#8	(colistin OR colisticin OR 'polymyxin e' OR 'polymyxin-e' OR 'polymixin e' OR 'polymixin-e' OR 'neomycin' OR sodium colistimethate' OR 'colistimethate sodium' OR colistimethate OR 'polymyxin b' OR polymyxin OR polymyxins OR polymyxin OR polymyxins):ti,ab,kw (Word variations have been searched)	1,421
#9	#7 OR #8	1,421
#10	MeSH descriptor: [Kidney Diseases] explode all trees	17,295
#11	("Kidney Diseases" OR "Kidney" OR "acute kidney injury") (Word variations have been searched)	60,753
#12	(nephrotoxic* OR 'renal toxicity' OR 'renal toxicities' OR 'kidney toxicity' OR 'kidney toxicities' OR 'renal failure' OR 'renal failures' OR 'kidney disease' OR 'kidney diseases' OR 'kidney failure' OR 'kidney failures' OR 'renal disease' OR 'renal diseases' OR 'kidney injury' OR 'kidney injuries' OR 'renal injury' OR 'renal injuries' OR 'renal function' OR 'renal functions' OR 'renal dysfunction' OR 'renal dysfunctions') (Word variations have been searched)	72,563
#13	#10 OR #11 OR #12	85,680
#14	#6 AND #9 AND #13	46

Supplementary Table 2 Characteristics of primary studies included

Study	Study design	Location and sites	Study period	Total patients	AKI patients	Patient population	Key exclusion criteria	Age [Mean (±SD) or Median (IQR)] (years)	APACHE II score (Mean ± SD)	Sex (M/F)	Style of Polymyxins	Regimen		Nephrotoxicity criteria
												Dose [Mean (±SD) or Median (IQR)]	Duration(days) [Mean (±SD) or Median (IQR)]	
Abdellatif, et al., 2016 [1]	RCT	Tunisia (single centre)	Apr 2013 to Apr 2015	76	30	Adults (> 18 y)	Septic shock; pregancy	53 ± 17	NR	49/27	CMS	4.5 MIU Q48 - 12H	> 14	1.5-fold increase in baseline SCr

Abdelsalam, et al., 2018 [2]	RCT	Egypt (single centre)	May 2016 to Oct 2016	60	14	Adults (> 18 y)	Colistin <72 h; Glasgow Coma Scale < 9; APACHE II > 34, SOFA> 15; risk of mortality> 80%	56.1 ± 6.8	18.5 ± 6.3	28/32	CMS	1.25 - 5 mg/kg/day	> 15	1.5-fold increase in baseline SCr to > 1.3 mg/dL or RRT

Aggarwal, et al., 2018 [3]	Prospective cohort	India (single centre)	Jul 2016 to Jun 2017	112	30	Adults (> 18 y)	Polymyxin <72 h; CKD patients on haemodialysis or CrCL <10 ml/min; concomitant any other nephrotoxic drug (contrast, aminoglycosides, vancomycin, amphotericin B, NSAIDs, cyclosporine, diuretics, etc.)	63.9 ± 15.2	21.4 ± 4.4	75/37	Colistin PMB	Colistin, 2.5 mg/kg Q12H; PMB, 1.5 mg/kg Q12H	Colistin, 7 (5 - 7); PMB, 7 (7 - 9)	RIFLE*

Aitullina, et al., 2019 [4]	Retrospective cohort	Latvia (single centre)	2015 to 2017	97 (100 cases)	18	Adults (> 18 y)	Colistin < 72 h	63.0 (51.0 - 73.5)	NR	65/32	Colistin	1 - 9 MU/day	Normal renal function, 9 (7 - 17); ARC, 16 (7 - 27); Renal impairment, 10 (4 - 15); CRRT, 11.5 (7 - 24)	AKIN
Aitullina, et al., 2021 [5]	Retrospective cohort	Latvia (single centre)	2015 to 2018	87	24	Adults (> 18 y)	RRT at baseline; colistin < 72 hours	64 (52–75)	NR	58/29	Colistin	NR	11 (7 - 20)	RIFLE

Akajagbor, et al., 2013 [6]	Retrospective cohort	USA (single centre)	Jan 2008 to Jun 2010	154	79	Adults (> 18 y)	Dialysis at baseline	NR	NR	NR	Colistin PMB	Colistin, 5 mg/kg/day (IBW) PMB, 15 000 - 25 000 units/kg/day	colistin, 11.7 ± 11.4 PMB, 12.5 ± 11.9	RIFLE
Almutairy, et al., 2020 [7]	Retrospective cohort	Saudi Arabia (single centre)	Jan 2014 to Dec 2015	131	65	Adults (> 18 y)	AKI at the time of initiation of colistin therapy; RRT at baseline	55.7 ± 19.4	NR	NR	Colistin	NR	NR	KDIGO

Alp, et al., 2017 [8]	Retrospective cohort	Turkey (single centre)	March 2014 to May 2015	52	21	Adults (> 16 y)	Renal impairment at baseline; concomitant inhaled colistin	61 (16 - 87)	NR	27/25	CMS	150 mg Q12H	NR	RIFLE
Asan, et al., 2020 [9]	Retrospective cohort	Bursa (single centre)	NR	85	35	Adults (> 18 y)	Acute renal failure; chronic renal failure	67.8 ± 16.6	23.2 ± 5.2	45/40	Colistin	NR	NR	RIFLE
Aydoğan, et al., 2018 [10]	Retrospective cohort	Turkey (single centre)	Jan 2010 to Jun 2014	76	36	Adults (> 18 y)	Colistin < 72 h; dialysis or RRT at baseline	61.8 ± 16.3	21.9 ± 7.2	50/26	Colistin	2.5-5 mg/kg/day	11.8 ± 7.6	RIFLE

Bassetti, et al., 2008 [11]	Prospective cohort	Italy (2 centres)	Jan 2006 to Jul 2007	29	3	Adults (> 18 y)	Colistin < 72 h	47 ± 14	17.0 ± 3.7	NR	Colistin	2 MU Q8H	17.7 ± 10.4	SCr > 2 mg/ml (1.5-fold increase in baseline SCr for patients with pre-existing renal impairment) or CrCL 50% of baseline
Betrosian, et al., 2008 [12]	RCT	Greece (2 centres)	NR	15	5	Adults (> 18 y)	Combination therapy	67 ± 9	14 ± 2	7/8	Colistin	5.83 ± 2.3 MIU/day	9.2 ± 1.5	1.5-fold increase in baseline SCr or need for RRT

Bilgili, et al., 2016 [13]	Retrospective cohort	Turkey (single centre)	Jan 2013 to Jan 2015	102	79	Adults (> 18 y)	Colistin < 72 h; pre-existing AKI or AKI developed within 2 days of colistin initiation	56.5 (18 - 90)	NR	49/53	Colistin	5 mg/kg/day	9 (3-40)	RIFLE
Binh, et al., 2015 [14]	Retrospective cohort	Vietnam (single centre)	Aug 15th, 2013 to Jan 15th, 2014	28	6	Adults (> 18 y)	Colistin treatment < 5 days; RRT at baseline	60.0 ± 20.4	13.6 ± 5.5	18/10	Colistin	4.1 ± 1.6 MIU/Kg/day	12.5 ± 5.2	RIFLE
Choe, et al., 2019 [15]	Retrospective cohort	Korea (single centre)	Jan 1st, 2008 to Dec 31th, 2016	138	66	Adults (> 18 y)	Colistin < 72 h; patients on RRT at the time of IV colistin initiation	65.8 ± 14.1	NR	NR	Colistin	NR	NR	RIFLE*

Chuang, et al., 2014 [16]	Retrospective cohort	Taiwan (single centre)	Jan 2009 to Dec 2010	119	12	Adults (> 18 y)	Concomitant infection (e.g. methicillin resistant Staphylococcus aureus or Pseudomonas aeruginosa)	63.7 ± 19.5	22.8 ± 9.3	86/33	Colistin	2.5 - 5 mg CBA /kg/day	14.6 ± 13.7	1.5-fold increase in baseline SCr or 20% decrease in baseline CrCL or need for RRT
Çiftçi, et al., 2017 [17]	Retrospective cohort	Turkey (single centre)	2010 to 2012	91	64	Adults (> 18 y)	Colistin < 48 h; baseline SCr > 2mg/dL or RRT at baseline	66.6 ± 14.3	20.4 ± 4.5	46/45	CMS	75 mg TID or 150 mg BID	NR	KDIGO
Dalfino, et al., 2012 [18]	Prospective cohort	Italy (single centre)	Aug 2010 to Jun 2011	25 (28 cases)	5	Adults (> 18 y)	Pregnant; Colistin < 72 h	62 ± 18	18 ± 6	19/6	CMS	8.02 ± 1.98 MU/day	12.33 ± 6.84	AKIN

Dalfino, et al., 2015 [19]	Prospective cohort	Italy (single centre)	Nov 2012 to Oct 2014	70	31	Adults (> 18 y)	Colistin < 72 h; AKI with 48 h; RRT at baseline	64 (48.5-75.2)	20.2 ± 8.4	44/26	CMS	105919 ± 93369 IU/kg/day (IBW)	14.3 ± 6.1	AKIN
De Leon-Borras, et al., 2019 [20]	Prospective cohort	Puerto Rico (single centre)	Jan 1st, 2012 to Jun 30th, 2013	20	3	Adults (> 18 y)	NR	58.5 (37 - 71.5)	NR	11/9	PMB	1076000 Units/day	NR	2-fold increase in baseline SCr to ≥ 2.0 mg/dL
Demirdal, et al., 2016 [21]	Case control	Turkey (single centre)	Jan 2013 to Dec 2014	123	64	Adults (> 18 y)	ICU stay < 48 h	64.2 ± 17.8	NR	83/40	Colistin	150 mg CBA Q12H	11.2 ± 6.7	RIFLE

Dewan, et al., 2014 [22]	Prospective cohort	India (single centre)	Mar 2013 to sep 2013	31	5	Adults (> 18 y)	Pregnant or breast-feeding patients; hemodialysis therapy at baseline	65 ± 15	20 ± 4	24/7	CMS	4.5 MU Q12H	14 (12 - 16)	RIFLE, other
Doshi, et al., 2011 [23]	Retrospective cohort	USA (single centre)	Jul 2007 to Jul 2009	49	15	Adults (> 18 y)	RRT or end-stage renal disease at baseline	55.6 ± 17.4	23.7 ± 6.2	25/24	Colistin	3 - 5 mg/kg/day	9.0 ± 8.1	RIFLE

Durante-Mangoni, et al., 2013 [24]	RCT	Italy (5 centres)	Nov 7th, 2008 to Jul 29th, 2011	209	53	Adults (> 18 y)	Treatment with colistin or rifampicin before microbiologic culture during the index hospitalization; significant liver dysfunction; hypersensitivity fo either study drug	63 ± 15.4	NR	137/72	CMS	2 MU Q8H	NR	RIFLE
Durante-Mangoni, et al., 2016 [25]	RCT	Italy (multicentre)	NR	166	84	Adults (> 18 y)	End-stage kidney disease on RRT	61.3 ± 16.0	NR	104/62	Colistin	2 MU Q8H	13	AKIN

Elefritz, et al., 2017 [26]	Retrospective cohort	USA (single centre)	Apr 1st, 2009 to Feb 28th, 2014	49	26	Adults (> 18 y)	Colistin < 48h; pregnancy; colistin therapy initiated >72h after respiratory culture collection	59.8 ± 13.4	23.8 ± 7.9	NR	Colistin	5.0 ± 2.9 mg/kg/d	9.2 ± 6.2	RIFLE
Garnacho-Montero, et al., 2013 [27]	Retrospective cohort	Spain (single centre)	Jan 2008 to Jul 2011	57	24	Adults (> 18 y)	RRT at baseline	58.4 ± 14.1	17.5 ± 6.4	35/22	Colistin	6.75 ± 2.8 MU/day	13.3 ± 7.5	AKIN

Garnacho-Montero, et al., 2003 [28]	Prospective cohort	Spain (single centre)	Jan 1997 to Jun 2001	21	5	Adults (> 18 y)	NR	56.9 ± 13.1	19.6 ± 7.2	14/7	Colistin	0.75 - 5.0 mg /kg/day	14.7 ± 4.1	SCr > 2 mg/dL (or 1.5-fold increase in baseline for patients with pre-existing renal impairment), CrCL 50% of baseline, or RRT

Gounden, et al., 2009 [29]	Retrospective cohort	South Africa (single centre)	Jan 2003 to Dec 2005	21	2	Adults (> 18 y)	Combination therapy	43.5 ± 15.6	14.4 ± 5.1	NR	Colistin	3 MU Q8H	8 (5 - 13)	SCr > 50% above upper limit of normal
Gregoire, et al., 2014 [30]	Prospective cohort	France (9 centres)	May 2009 to Dec 2011	73	5	Adults (> 18 y)	RRT at baseline	62 (range 18 - 91)	NR	43/30	CMS	6.0 (range 0.9 - 9) MIU/day	NR	RIFLE
Gunay, et al., 2020 [31]	Retrospective cohort	Turkey (single centre)	Apr 2011 to Dec 2017	149	96	Adults (> 18 y)	Colistin < 48 hours e-GFR value < 60 mL/min/1.73 m^2	58.7 ± 20.3	30.4 ± 9.5	91/58	Colistin	300 mg/day	12.5 ± 5.4	KDIGO

Heybeli, et al., 2020 [32]	Case control	Turkey (single centre)	Oct 2012 to Apr 2019	133	92	Adults (> 18 y)	RRT at baseline, colistin < 72 hours	71 (60 - 80)	24.4 ± 6.7	74/59	CMS	300 (250 - 325) mg/day	10 (6 - 14)	KDIGO
Holloway, et al., 2006 [33]	Retrospective cohort	USA (single centre)	Mar 2002 to May 2005	31	7	Adults (> 15 y)	< 2 doses antibiotic	41 (15 - 77)	19.0 ± 6.3	NR	PMB	1300000 IU (range 186000 - 3000000)/day	NR	0.5 mg/dL increase or 1.5-fold increase in baseline SCr or 50% decrease in baseline CrCL

Inci, et al., 2018 [34]	Retrospective cohort	Turkey (single centre)	Jan 1st to Dec 31th, 2016	48	26	Adults (> 18 y)	Colistin < 72 h	58.9 ± 22.4	NR	24/24	Colistin	NR	14.2 ± 7.2	RIFLE
Jang, et al., 2017 [35]	Retrospective cohort	Korea (single centre)	Mar 2013 to Jan 2016	44	26	Adults (> 18 y)	Colistin <5 days; concomitant IV and inhaled colistin	60.0 ± 15.2	16.3 ± 5.2	35/9	Colistin	4.5 MU Q12H	10.9 ± 4.5	RIFLE
John, et al., 2018 [36]	Retrospective cohort	Brazil (2 centres)	Jan 2013 to Dec 2015	54	14	Adults (> 18 y)	PMB <48h; hemodialysis at baseline	58 ± 17	NR	NR	PMB	3.41 ± 0.75 mg/kg/day	7 (4 - 12)	RIFLE

Jung, et al., 2019 [37]	Retrospective cohort	Korea (single centre)	Jan 2013 to Dec 2014	153	84	Adults (> 20 y)	Colistin treatment course was interrupted for more than a week	66 (range 21 - 91)	23.8 ± 7.6	109/44	Colistin	312 (84 - 1004) mg/day	14 (3 - 156)	increase in SCr by 0.3 mg/dL or 1.5- to 2-fold increase in SCr from baseline
Kalin, et al., 2012 [38]	Retrospective cohort	Turkey (single centre)	Jan to Aug 2011	45	15	Adults (> 18 y)	NR	50.1 ± 20.7	22 (median)	32/13	CMS	2.5 mg/kg Q12-6H	NR	RIFLE
Kalin, et al., 2014 [39]	Retrospective cohort	Turkey (single centre)	Jan to Dec 2011	82	22	Adults (> 19 y)	Colistin <5 days	56.3 ± 17.2	24.3 ± 5.0	NR	Colistin	2.5 mg/kg Q12-6H	14 (range 2 - 22)	RIFLE

Kallel, et al., 2006 [40]	Prospective cohort	Tunisia (single centre)	Jul 2003 to Oct 2004	52	7	Adults (> 18 y)	Renal failure at baseline	48 ± 20	NR	NR	Colistin	5.5 ± 1.1 MU/day	9.3 ± 3.8	SCr > 150 µmol/L or BUN > 10 mmol/L
Kallel, et al., 2007 [41]	Case control	Tunisia (single centre)	Jul 2003 to Jun 2005	60	0	Adults (> 18 y)	Renal failure at the onset of colistin therapy	43.4 ± 18.8	NR	52/8	Colistin	6 MU/day	9.5 ± 3.8	SCr > 150 µmol/L or BUN > 10 mmol/L
Kara, et al., 2015 [42]	Retrospective cohort	Greece (single centre)	Jan 2009 to Sep 2014	134	26	Adults (> 18 y)	Colistin < 72 h	68 (58.0 - 76.3)	23.0 ± 6.0	72/62	Colistin	150 (150.0-300.0) mg/day	9 (4-17)	RIFLE

Katip, et al., 2020 [43]	Retrospective cohort	Thailand (single centre)	Jan 2015 to Aug 2017	248	96	Adults (> 18 y)	Patients with CRAB cultures assessed to be colonisers or contaminants or who had incomplete records	65.4 ± 17.5	17.4 ± 4.5	158/90	Colistin	150 mg Q12H	NR	RIFLE
Katip, et al., 2021 [44]	Retrospective cohort	Thailand (single centre)	Jan 2010 to Aug 2017	365	179	Adults (> 18 y)	Patients with CRAB cultures assessed to be colonisers or contaminants or who had incomplete records	65.2 ± 17.4	12.0 ± 5.1	141/124	colistin	150 mg Q12H	NR	RIFLE

Khalili, et al., 2018 [45]	RCT	Iran (single centre)	Oct 2015 to Oct 2017	24	3	Adults (> 18 y)	NR	60.6 ± 13.0	NR	16/8	Colistin	4.5 MU Q12H	NR	KDIGO
Kim, et al., 2016 [46]	Retrospective cohort	Korea (single centre)	Jan 2009 to Dec 2010	40	8	Adults (> 20 y)	Concomitant use of tigecycline and colistin, inadequate treatment (<3 days), or combined infection without appropriate antibiotic therapy	67(57 - 75)	NR	30/10	Colistin	150 mg Q12H	12 (9 - 19)	SCr > 2.0 mg/dL (1.5-fold increase in patients with pre-existing renal dysfunction), CrCL 50% baseline or need for RRT

Kim, et al., 2017 [47]	Retrospective cohort	Korea (2 centres)	Mar 2010 to Nov 2015	93	35	Adults (> 18 y)	Nebulized and intravenous colistin simultaneously	65(52 - 74)	20.6 ± 6.8	63/30	Colistin (CBA)	1 - 5mg/kg/day	10 (7 - 16)	SCr > 2.0 mg/dL (1.5-fold increase in patients with pre-existing renal dysfunction), CrCL 50% baseline need for RRT
Kofteridis, et al., 2010 [48]	Case control	Greece (single centre)	Jan 2005 to Dec 2008	86	16	Adults (> 18 y)	Colistin < 72 h	62.2 ± 15.0	17.4 ± 7.1	58/28	Colistin	9 MIU/d	10 (range 4 - 36)	Increase of > 50% of the baseline creatinine level

Kwon, et al., 2014 [49]	Retrospective cohort	Korea (single centre)	Feb 2010 to Aug 2010	39	17	Adults (> 18 y)	Treatment < 5 days	59.0 ± 19.2	NR	33/22	CMS	75 - 300 mg/day	15.0 (9 - 24)	SCr > 2.0 mg/dL (1.5-fold increase in patients with pre-existing renal dysfunction)

Lambiase, et al., 2012 [50]	Prospective cohort	Italy (single centre)	Jan 2007 to Oct 2010	46	1	Adults (> 18 y)	NR	55.4 ± 18.0	NR	24/22	Colistin	50000 IU/kg/day	10	3.0-fold increase SCr and decreased GFR < 75% in patients with baseline SCr, or SCr > 4.0 mg/dL and urine output < 0.3ml/kg/h in 24h or anuria for the previous

Li, et al., 2020 [51]	Retrospective cohort	Philippine (single centre)	Jan 2015 to May 2018	123	38	Adults (> 18 y)	RRT at baseline	NR	NR	NR	CMS	NR	NR	KDIGO
Lodise, et al., 2018 [52]	Retrospective cohort	USA (multicentre)	Jan 1st, 2010 to Dec 31th, 2015	4910	1153	Adults (> 18 y)	Patients with cystic fibrosis; hemodialysis during prior month	61.36 ± 16.0	NR	2848/2062	Colistin	NR	10.05 ± 8.35	ICD-9 codes of 584.XX or ICD-10 codes of N17.XX
Makris, et al., 2018 [53]	RCT	Greece (2 centres)	NR	39	8	Adults (> 18 y)	Intubated <48h	56.8 ± 16.7	15.5 ± 4.1	12/27	Colistin	3 MU Q8H	>10	Need for Continuous venovenous haemofiltration

Markou, et al., 2003 [54]	Prospective cohort	Greece (single centre)	NR	21	3	Adults (> 18 y)	Death within 48 h	44.3 (mean)	20.6 ± 4.6	17/7	Colistin	3 MU Q8H	13.5 (range 4 - 24)	Increase in SCr >1 mg/dL
Michalopoulos, et al., 2005 [55]	Retrospective cohort	Greece (single centre)	Jul 1st, 2001 to Dec 1st, 2003	43	8	Adults (> 18 y)	NR	56.5 ± 16.2	25.8 ± 3.7	37/6	CMS	3 MU Q36-8H	18.6 ± 5.8	Increase in SCr of 2 mg/dL in patients with previously normal renal function
Moghadam, et al., 2018 [56]	Retrospective cohort	Iran (single centre)	2011 to 2016	102	50	Adults (> 18 y)	History of renal failure; dialysis at baseline	NR	NR	64/38	Colistin	3 MU Q8H	NR	RIFLE

Mosaed, et al., 2018 [57]	RCT	Iran (single centre)	Sep 2017 to May 2018	11	6	Adults (> 18 y)	GFR <60 mL/min at baseline	66.9 ± 9.9	19.9 ± 3.4	7/4	Colistin	4.5 MU Q12H	8 (range 7 - 9)	30% increase in SCr
Nandha, et al., 2013 [58]	Retrospective cohort	India (single centre)	Mar 2009 to Oct 2010	32	6	Adults (> 18 y)	PMB <3 days; SCr ≥ 4 mg/dL; concomitant nephrotoxins	48.5 ± 13.9	11.8 ± 4.3	17/15	PMB	11.09 ± 4.01 lakh units	7.44 ± 4.94	RIFLE
Nazer, et al., 2015 [59]	Retrospective cohort	Jordan (single centre)	Jan 2010 to Dec 2013	89	35	Adults (> 18 y)	Colistin <48 h	57.3 ± 15.4	24.8 ± 8.3	64/25	CMS	3 MU Q24-8H	15.8 ± 11	RIFLE

Ozel, et al., 2019 [60]	Prospective cohort	Turkey (single centre)	Dec 1st, 2012 to Jan 1st, 2014	59	31	Adults (> 18 y)	RRT at baseline colistin < 48 hours	58.1 ± 19.1	20.4 ± 7.4	35/24	CMS	5.49 ± 1.90 mg (CBA)/kg/day	11.41 ± 4.33	RIFLE
Özkaraakaş, et al., 2017 [61]	Retrospective cohort	Turkey (single centre)	Jan 1st, 2013 to Apr 1st, 2014	56	39	Adults (> 18 y)	Colistin <72 h; CKD at baseline	64.1 ± 20.9	NR	29/27	Colistin	5 mg/kg/day (Maximum 300mg/day)	11.5 ± 5.58	RIFLE

Papadimitriou-Olivgeris, et al., 2019 [62]	Retrospective cohort	Greece (single centre)	2012 to 2016	228	64	Adults (> 18 y)	RRT at baseline	NR	NR	NR	Colistin	1 - 4.5 MIU Q12H	NR	AKIN
Petrosillo, et al., 2014 [63]	Retrospective cohort	Unclear location (3 centres)	Jan 2010 to Jan 2011	166	21	Adults (> 18 y)	Death within 5 days	62 (46 - 73.2)	20.4 ± 5.2	103 /63	Colistin	6 (4 - 8) MU/day	NR	RIFLE
Porwal, et al., 2014 [64]	Retrospective cohort	India (single centre)	May 2011 to May 2012	50	6	Adults (> 18 y)	NR	52.3 ± 15.4	19.6 ± 3.8	32/ 18	Colistin	5.18 MU/day	NR	Need for RRT

Pourheida, et al., 2019 [65]	RCT	Iran (single centre)	Sep to Jan 2018	16	8	Adults (> 18 y)	Pneumonia before intubation, dialysis, history of receiving appropriate antibiotics for this episode of VAP for more than 96 h before recruitment	60 ± 19	15 ± 4	10/6	Colistin	4.5 MU Q12H	8 ± 3 (range 3 - 14)	AKIN
Quintanilha, et al., 2019 [66]	Retrospective cohort	Brazil (single centre)	Aug 2010 to Jul 2013	102	50	Adults (> 18 y)	No undergo an antimicrobial susceptibility test	51.4 ± 16.8	15.6 ± 5.5	77/25	Colistin PMB	Colistin, 3.3 ± 1.5 MU/day PMB, 1.5 ± 0.4 MU/day	Colistin, 9.9 ± 4.8; PMB, 11.5 ± 4.9	AKIN

Ramasubban, et al., 2008 [67]	Retrospective cohort	India (single centre)	Mar 2006 to 2007	45	2	Adults (> 18 y)	PMB < 2 doses	53 (range 19 - 82)	NR	25/20	PMB	1.2 (range 1 - 1.5) MU/day	7.6 (range2 - 32)	Increase in SCr by 0.5 mg/dL over 24 h
Rashizal, et al., 2017 [68]	Retrospective cohort	Malaysia (2 centres)	2010 to 2012	100	23	Adults (> 18 y)	NR	45.5 ± 19.6	NR	71/29	Colistin	3.8 ± 2.1 MIU/day	6 ± 4	RIFLE
Reina, et al., 2005 [69]	Prospective cohort	Argentina (single centre)	Jan 2000 to Jan 2004	55	0	Adults (> 18 y)	NR	40 ± 16	21 ± 7	19/36	Colistin	1.5 - 5.0 mg/kg/day (maximum 300mg/day)	13 ± 5	SCr > 2.0 mg/dL, 50% decrease in baseline CrCL or need for RRT

Rigatto, et al., 2015 [70]	Prospective cohort	Brazil (3 centres)	Feb 1st, 2013 to Jan 31th, 2014	222	111	Adults (> 18 y)	SCr < 10 mL/min, RRT at baseline; did not have serum creatinine collected after the beginning of polymyxin B therapy	NR	NR	NR	PMB	NR	NR	RIFLE
Rigatto ,et et al., 2016 [71]	Prospective cohort	Brazil (6 centres)	Feb 1st, 2013 to Jan 31th, 2014	281	62	Adults (> 18 y)	Treatment for < 48 h; SCr <10 mL/min; RRT at baseline	NR	NR	NR	CMS PMB	CMS, 300 (300 - 450) mg CBA/day PMB, 1.5 - 3 mg/kg/day	CMS, 13 (10 - 15); PMB, 10 (7 - 14)	RIFLE

Rocco, et al., 2013 [72]	Retrospective cohort	Italy (2 centres)	Apr 2009 to Jun 2011	147	57	Adults (> 18 y)	Abnormal renal function	55.6 ± 6.1	NR	95/37	CMS	130,000 IU/Kg/day (IBW)	11	RIFLE

Şahin, et al., 2019 [73]	Retrospective cohort	Turkey (single centre)	Jun 2016 to Sep 2018	37	17	Adults (> 18 y)	NR	61.0 ± 19.3	20.7±5.6	26/11	Colistin	2.5 mg/kg Q12H	NR	Increase in serum creatinine by ≥ 0.3 mg/dL within 48 h, Increase in serum creatinine to ≥ 1.5 times baseline, Urine volume < 0.5 mL/kg/h for 6 h

Salahuddin, et al., 2017 [74]	Prospective cohort	Saudi Arabia (single centre)	Aug 2013 to Dec 2013	97	48	Adults (> 18 y)	ICU stay < 72 h, patients with AKI at ICU admission and end-stage renal disease patients treated by chronic dialysis	NR	NR	NR	Colistin	NR	NR	RIFLE
Sekhri, et al., 2013 [75]	Retrospective cohort	India (single centre)	Mar 2008-2010	48	15	Adults (> 18 y)	SCr > 4 mg/dL; dialysis; AKI with loss or end-stage kidney disease at baseline; concomitant nephrotoxins	58.4 ± 18.2	11.9 ± 4.9	29/19	PMB Colistin	PMB, 11.46 ± 3.08 lakhs units/day ; polymyxin E, 5.3 ± 5.64 MU/day	8.0 ± 4.1	RIFLE

Soares, et al., 2017 [76]	Retrospective cohort	Brazil (single centre)	Jan 2012 to Dec 2014	115	53	Adults (> 18 y)	Treatment < 3 days; AKI or RRT at baseline	59.2 ± 16.1	14.0 ± 6.6	60/55	PMB	2.5 MU/kg/day	14.5 ± 6.5	RIFLE
Tanita, et al., 2013 [77]	Retrospective cohort	Brazil (single centre)	Jan to Dec 2008	80	21	Adults (> 18 y)	Colistin < 48 h; death within 48 h	66 (48-75)	25.7 ± 9.0	NR	CMS	1 - 5 mg/kg/day	10 (5 - 15)	KDIGO

Tigen, et al., 2013 [78]	Retrospective cohort	Turkey (single centre)	Sep 2010 to Mar 2012	46	21	Adults (> 18 y)	Patients who had been administered colistin but were not confirmed as having ColsA infections were excluded	52.5 ± 19.5	15.9 ± 12.1	31/15	Colistin	4.5 MIU Q8H	13 ± 5.8	RIFLE
Tigen, et al., 2016 [79]	Prospective cohort	Turkey (single centre)	Sep 2010 to Apr 2012	55	22	Adults (> 18 y)	Colistin < 72 h; RRT at baseline	51 (median)	19.3 ± 6.8	37/18	CMS	2.5 - 5 mg/kg/day	11.9 ± 7.0	RIFLE

Tumbarello, et al., 2013 [80]	Retrospective cohort	Italy (single centre)	Jan 1st, 2005 to Dec 31th, 2012	208	49	Adults (> 18 y)	Colistin < 72 h	63.5 ± 21.1	NR	132/76	CMS	7.2 ± 2.5 MIU/day	9.5 ± 7.0	2-fold increase in SCr, 50% decrease in GFR or urine output < 0.5 mL/kg/h for ≥ 12h

Turkoglu, et al., 2012 [81]	Case control	Turkey (single centre)	Dec 2008 to Jun 2010	55	13	Adults (> 18 y)	Colistin < 1 day; CRF at baseline	63.7 ± 17.6	22.9 ± 6.0	23/32	Colistin	2.5 - 7.5 mg/kg/day	NR	SCr ≥ 2 mg/dL (1.5-fold increase SCr in patients with baseline SCr ≥ 1.2 mg/dL), 50% decrease in CrCL or RRT
Vazin, et al., 2020 [82]	Prospective cohort	Iran (2 centres)	Nov 2016 to Dec 2017	33	6	Adults (> 18 y)	Colistin < one week	51.8 ± 20.9	22.0 ± 5.6	27/6	Colistin	5.69 ± 2.69 MIU/day	7.3 3 ± 3.68	RIFLE

Zalts, et al., 2016 [83]	Retrospective cohort	Israel (single centre)	Jan 1st, 2008 to Dec 31th, 2009	66	1	Adults(>18 y)	Treatment <3 days	56.7 ± 20.4	17.8 ± 7.2	45/21	Colistin	2 MU CBA Q8H	NR	Need for haemodialysis
Katip, et al., 2021 [84]	Retrospective cohort	Thailand (single centre)	Jan 2012 to Aug 2017	383	187	Adults (>18 y)	Incomplete records	66.15 ± 16.08	Non-LD CMS: 13.57± 4.03 LD CMS: 12.69 ± 4.22	144/239	CMS	150 mg CBA Q12H	NR	RIFLE

Feng, et al, 2021 [85]	Retrospective cohort	Taiwan (single centre)	Jan 2016 to Oct 2018	195	97	Adults (> 20 y)	End-stage renal disease; dialysis	73.8 ± 13.5	24 (19–30)	138/57	CMS	8 MIU (4–10)/day	7 (4–12)	KDIGO
Ye, et al, 2022 [86]	Retrospective cohort	China (single centre)	May 2019 to Jan 2021	62	28	Adults (> 18 y)	Severe renal dysfunction	65.2 ± 13.8	24.2 ± 7.1	34/28	PMB	NR	11 (6–17.3)	RIFLE

Gulen, et al, 2022 [87]	Retrospective cohort	Turkey (single centre)	Jan 1st, 2012 to Dec 31th, 2019	170	106	Adults (> 18 y)	Treatment <72 h; Acute and chronic renal failure	73 (range, 18-95)	Nephrotoxicity : 25.17± 6.8 Non-nephrotoxicity:21.94±7.85	98/72	CMS	NR	NR	RIFLE
Chang, et al, 2022 [88]	Retrospective cohort	China (14 centres)	Jan 2018 to May 2020	220	80	Adults (> 18 y)	Died within 48 h of polymyxin B	NR	NR	NR	PMB	NR	NR	KDIGO

Wang, et al, 2022 [89]	Retrospective cohort	Taiwan (five centres)	Jan 2016 to Dec 2016	110	58	Adults (> 20 y)	age < 20 years, community-acquired pneumonia or healthcare-associated pneumonia, concomitant lung cancer with obstructive pneumonitis, CRGNB that were resistant to colistin, and no intravenous colistin prescribed within 7 days of the index date for pneumonia	NR	NR	NR	CMS	NR	NR	KDIGO

Note: ABW, actual body weight; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; APACHE II, Acute Physiology and Chronic Health Evaluation II; BID, twice daily; CBA, Colistin base activity; CKD, Chronic kidney disease; CMS, Colistin methane sulfonate; CrCL, Creatinine clearance; CRF, Chronic renal failure; CRGNB: Carbapenem-resistant gram-negative bacteria; IBW, Ideal body weight; ICU, intensive care unit; KIDGO, Kidney Disease Improving Global Outcomes; LD: Loading dose; MIU, Million international units; NR, Not reported; PMB, Polymyxin B; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; RRT, renal replacement therapy; Scr, Serum creatinine; TID, Three times daily.

Supplementary Table 3 Risk of bias for studies

A. Risk of bias for cohort studies using Newcastle Ottawa Scale assessment for cohort studies

Study	**Selection**				**Comparability**	**Outcome**			**Total score**	**Comments (High/ Fair/Low)**
	1. Representative of the exposed cohort:	2. Selection of the non-exposed cohort	3. Ascertainment of exposure	4. Demonstration that outcome of interest was not present at the start of study	1. Comparability of cohorts on the basis of the design or analysis	1. Assessment of the outcome:	2. Was follow-up long enough for outcomes to occur?	3. Adequacy of follow up of cohorts		
	a) Truly representative*	a) Drawn from the same community as the exposed cohort*	a) Secure record*	a) Yes*	a) Study controls for the most important factor*	a) Independent blind assessment*	a) Yes*	a) Complete follow up		
	b) Somewhat representativ	b) Drawn from a	b) Structured	b) No	b) Study controls for any	b) Record	b) No	b) Subjects		

	e of the average in the community*	different source	interview*		additional factor*	linkage*		lost to follow up unlikely to introduce bias*		
	c) Selected group of users	c) No description of the derivation of the non-exposed cohort	c) Written self-report		c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders	c) Self report		c) Follow up rate < 80% and no description		
	d) No description of the derivation of the cohort		d) No description			d) No description		d) No statement		
Aggarwal, et al.,	*	*	*	*	*	*	Unclear	No statement	6	Fair

2018 [3]										
Aitullina, et al., 2019 [4]	*	*	*	No	No	*	Unclear	No statement	4	Low
Aitullina, et al., 2021 [5]	*	*	*	*	*	*	*	*	8	High
Akajagbor, et al., 2013 [6]	*	*	*	*	*	*	unclear	No statement	6	Fair
Almutairy, et al., 2020 [7]	*	*	*	*	*	*	*	*	8	High
Alp, et al., 2017 [8]	*	*	*	*	*	*	*	No statement	7	Fair
Asan, et al., 2020 [9]	*	*	*	*	*	*	Unclear	No statement	6	Fair
Aydoğa	*	*	*	No	**	*	Unclear	No	6	Fair

n, et al., 2018 [10]								statement		
Bassetti, et al., 2008 [11]	*	*	*	No	*	*	Unclear	No statement	5	Fair
Bilgili, et al., 2016 [13]	*	*	*	*	**	*	*	No statement	8	High
Binh, et al., 2015 [14]	*	*	*	No	**	*	*	*	8	High
Choe, et al., 2019 [15]	*	*	*	*	*	*	Unclear	No statement	6	Fair
Chuang, et al., 2014	*	*	*	*	**	*	Unclear	No statement	7	Fair

[16]										
Çiftçi, et al., 2017 [17]	*	*	*	*	No	*	Unclear	No statement	5	Fair
Dalfino, et al., 2012 [18]	*	*	*	No	**	*	*	*	8	High
Dalfino, et al., 2015 [19]	*	*	*	*	**	*	*	*	9	High
De Leon-Borras, et al., 2019 [20]	*	*	*	No	No	*	Unclear	No statement	4	Low
Dewan, et al., 2014	*	*	*	*	No	*	*	*	7	Fair

[18]										
Doshi, et al., 2011 [19]	*	*	*	*	**	*	*	No statement	8	High
Elefritz, et al., 2017 [26]	*	*	*	*	*	*	*	No statement	7	Fair
Garnacho-Montero, et al., 2003 [27]	*	*	*	No	**	*	*	*	8	High
Garnacho-Montero, et al., 2013 [28]	*	*	*	*	*	*	*	*	8	High
Gounde	*	*	*	*	No	*	Unclear	No	5	Fair

n, et al., 2009 [29]								statement		
Gregoire, et al., 2014 [30]	*	*	*	*	No	*	*	*	7	Fair
Gunay, et al., 2020 [31]	*	*	*	*	*	*	*	No statement	7	Fair
Holloway, et al., 2006 [33]	*	*	*	No	No	*	unclear	No statement	4	Low
Inci, et al., 2018 [34]	*	*	*	*	*	*	*	No statement	7	Fair
Jang, et al., 2017	*	*	*	No	No	*	*	*	6	Fair

[35]										
John, et al., 2018 [36]	*	*	*	*	*	*	*	*	8	High
Jung, et al., 2019 [37]	*	*	*	*	*	*	Unclear	No statement	6	Fair
Kalin, et al., 2012 [38]	*	*	*	No	**	*	*	*	8	High
Kalin, et al., 2014 [39]	*	*	*	No	*	*	*	*	7	Fair
Kallel, et al., 2006 [40]	*	*	*	*	No	*	Unclear	No statement	5	Fair
Kara, et al., 2015 [42]	*	*	*	No	*	*	*	*	7	Fair

Katip, et al., 2020 [43]	*	*	*	No	**	*	Unclear	No statement	6	Fair
Katip, et al., 2021 [44]	*	*	*	No	**	*	Unclear	No statement	6	Fair
Kim, et al., 2016 [46]	*	*	*	No	*	*	Unclear	No statement	5	Fair
Kim, et al., 2017 [47]	*	*	*	No	**	*	Unclear	No statement	6	Fair
Kwon, et al., 2014 [49]	*	*	*	No	*	*	*	*	7	Fair
Lambiase, et al., 2012 [50]	*	*	*	No	No	*	Unclear	No statement	4	Low

Li, et al., 2020 [51]	*	*	*	*	**	*	*	*	9	High
Lodise, et al., 2018 [52]	*	*	*	*	No	No description	unclear	No statement	4	Low
Markou, et al., 2003 [54]	*	*	No description	No	No	No description	*	*	4	Low
Michalopoulos, et al., 2005 [55]	*	*	*	No	*	*	Unclear	No statement	5	Fair
Moghadam, et al., 2018 [56]	*	*	*	*	*	*	Unclear	No statement	6	Fair

Nandha, et al., 2013 [58]	*	*	*	*	*	*	Unclear	No statement	6	Fair
Nazer, et al., 2015 [59]	*	*	*	No	*	*	*	*	7	Fair
Ozel, et al., 2019 [60]	*	*	*	*	**	*	*	*	9	High
Özkarakaş, et al., 2017 [61]	*	*	*	*	**	*	*	No statement	8	High
Papadimitriou-Olivgeris, et al., 2019	*	*	*	*	**	*	Unclear	No statement	7	Fair

[62]										
Petrosillo, et al., 2014 [63]	*	*	*	No	*	*	unclear	No statement	5	Fair
Porwal, et al., 2014 [64]	*	*	*	No	No	No description	Unclear	No statement	3	Low
Quintanilha, et al., 2019 [66]	*	*	*	No	*	*	*	*	7	Fair
Ramasubban, et al., 2008 [67]	*	*	*	No	No	*	Unclear	No statement	4	Low
Rashizal, et al., 2017	*	*	*	No	No	*	*	No statement	5	Fair

[68]										
Reina, et al., 2005 [69]	*	*	*	*	*	*	Unclear	No statement	6	Fair
Rigatto, et al., 2015 [70]	*	*	*	*	**	*	*	*	9	High
Rigatto et al., 2016 [71]	*	*	*	*	**	*	*	*	9	High
Rocco, et al., 2013 [72]	*	*	*	*	**	*	Unclear	no statement	7	Fair
Şahin, et al., 2019 [73]	*	*	*	No	*	*	Unclear	No statement	5	Fair
Salahud	*	*	*	*	*	*	*	No	7	Fair

din, et al., 2017 [74]								statement		
Sekhri, et al., 2013 [75]	*	*	*	*	No	*	*	*	7	Fair
Soares, et al., 2017 [76]	*	*	*	*	No	*	Unclear	No statement	5	Fair
Tanita, et al., 2013 [77]	*	*	*	*	**	*	Unclear	No statement	7	Fair
Tigen, et al., 2013 [78]	*	*	*	No	No	*	Unclear	No statement	4	Low
Tigen, et al., 2016	*	*	*	*	*	*	*	No statement	7	Fair

[79]										
Tumbarello, et al., 2013 [80]	*	*	*	No	*	*	Unclear	No statement	5	Fair
Vazin, et al., 2020 [82]	No	*	*	*	*	*	Unclear	No statement	5	Fair
Zalts, et al., 2016 [83]	*	*	*	No	No	*	Unclear	No statement	4	Low
Katip, et al., 2021 [84]	*	*	*	No	No	*	Unclear	No statement	4	Low
Feng, et al, 2021 [85]	*	*	*	*	**	*	*	No statement	8	High
Ye, et al, 2022	*	*	*	*	*	*	*	No statement	7	Fair

[86]										
Gulen, et al, 2022 [87]	*	*	*	*	*	*	Unclear	No statement	6	Fair
Chang, et al, 2022 [88]	*	*	*	*	*	*	*	No statement	7	Fair
Wang, et al, 2022 [89]	*	*	*	No	*	*	Unclear	No statement	5	Fair

Note: Articles that scored ≤ 4 were classified as low methodological quality, articles with score between 5 and 7 were classified as fair quality, and those with score ≥ 8 were classified as high quality.

B. Risk of bias for case control studies using Newcastle Ottawa Scale assessment

Study	**Selection**				**Comparability**	**Exposure**			**Total score**	**Comments (High/Fair/ Low)**
	1. Is the case definition adequate ?	2. Representativeness of the cases	3. Selection of controls	4. Definition of controls	1. Comparability of cohorts on the basis of the design or analysis	1. Ascertainment of exposure	2. Same method of ascertainment for cases and controls	3. Non-Response rate		
	a) yes, with independent validation*	a) consecutive or obviously representative series of cases*	a) community controls*	a) no history of disease (endpoint)*	a) Study controls for the most important factor (select one)*	a) secure record (eg surgical records)*	a) yes*	a) same rate for both groups*		

	b) yes, e.g., record linkage or based on self reports	b) potential for selection biases or not stated	b) hospital controls	b) no description of source	b) Study controls for any additional factor*	b) structured interview where blind to case/control status*	b) no	b) non respondents described		
	c) no description		c) no description		c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders	c) interview not blinded to case/control status		c) rate different and no designation		
						d) written self report				

						or medical record only				
						e) no description				
Demirdal, et al., 2016 [21]	*	*	*	No	**	*	*	Unclear	7	Fair
Heybeli, et al., 2020 [32]	*	*	*	*	*	*	*	Unclear	7	Fair
Kallel, et al., 2007 [41]	*	*	*	*	*	*	*	*	8	High
Kofteri	*	*	*	No	*	*	*	*	7	Fair

dis, et al., 2010 [48]										
Turkoglu, et al., 2012 [81]	*	*	*	No	*	*	*	Unclear	6	Fair

Note: Articles that scored ≤ 4 were classified as low methodological quality, articles with score between 5 and 7 were classified as fair quality, and those with score ≥ 8 were classified as high quality.

C. Risk of bias for randomized controlled trials using Cochrane risk of bias tool assessment

Study	Was the allocation sequence adequately generated?	Was the concealment of treatment allocation adequate?	Was knowledge of the allocated interventions adequately prevented from	Was knowledge of the allocated interventions adequately prevented from	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study apparently free of other problems that could put it at a high risk of	**Comments (High/Fair/Low)**

			participants and personnel?	outcome assessors?			bias?	
Abdellatif, et al., 2016 [1]	*	Unclear	Unclear	*	*	*	*	Unclear
Abdelsalam, et al., 2018 [2]	Unclear	Unclear	Unclear	*	*	*	*	Unclear
Betrosian, et al., 2008 [11]	High	Unclear	*	*	*	*	*	High
Durante-Mangoni, et al., 2013 [24]	*	*	*	*	*	*	*	Low
Durante-Mangoni, et al., 2016 [25]	Unclear	Unclear	Unclear	*	*	*	Unclear	Unclear
Khalili, et al., 2018 [45]	*	Unclear	Unclear	*	*	*	*	Unclear
Makris, et al., 2018 [53]	Unclear	Unclear	Unclear	*	*	*	*	Unclear
Mosaed, et al.,	*	Unclear	Unclear	*	*	*	*	Unclear

2018 [57]								
Pourheida, et al., 2019 [65]	*	Unclear	Unclear	*	*	*	*	Unclear

Note: The overall risk of bias for each study was classified as high methodological quality if the risk of bias was low in all domains, unclear if the risk of bias was unclear in one or more domains and with no judgment of high risk of bias, or low quality if the risk of bias was high in one or more domains.

Supplementary Table 4 Details of potential predictors of polymyxin-induced nephrotoxicity

A. Univariate analysis for predictors of acute kidney injury (AKI)

Study	**Variables**	**OR/HR/RR**	**Effect (95% CI)**
Abdellatif, et al., 2016 [1]	Concoamitant nephrotoxic agents (aminoglycosides, glycopeptides and iodinated contrast agents)	OR	2.79 (1.23-6.32)
Aggarwal, et al., 2018 [3]	Age≥65 years	OR	1.64 (0.58-4.65)
	APACHE II ≥ 20	OR	0.39 (0.13-1.11)
	Baseline creatinine clearance < 50 ml/min	OR	0.16 (0.05-0.53)
	BMI≥ 30	OR	0.92 (0.31-2.73)
	Daily dose ≥300 mg/day	OR	6.56 (2.1-20.52)
	Diabetes mellitus (yes)	OR	0.8 (0.29-2.24)
Bilgili, et al., 2016 [13]	Septic shock	OR	8.580 (1.868-39.417)
Choe, et al., 2019 [15]	Aerosolized colistin	OR	1.775 (0.756-4.168)
	Age (year)	OR	1.023 (0.995-1.051)
	Colistin dose (mg/kg/day)	OR	0.996 (0.992-1.001)
	Colistin duration (days)	OR	1.065 (1.004-1.129)
	Concomitant vancomycin	OR	2.631 (1.241-5.576)
	Gender (male)	OR	1.675 (0.76-3.691)
Heybeli, et al., 2020 [32]	Age (per 10 years)	OR	1.41 (1.11-1.79)
	Baseline eGFR (per 10ml/min)	OR	0.89 (0.82-0.97)
	Furosemide treatment	OR	2.29 (1.08-4.84)

	Gender (female)	OR	1.85 (0.86-3.96)
	Glucocorticoid treatment	OR	0.23 (0.1-0.53)
	Proton-pump inhibitor use	OR	3.21 (1.37-7.54)
Ozel, et al., 2019 [60]	30 day mortality	OR	1.598 (0.57-4.474)
	Age (years)	OR	1.036 (1.005-1.067)
	APACHE II score	OR	0.988 (0.921-1.06)
	Baseline creatinine (mg/dL)	OR	0.448 (0.201-0.998)
	Chronic kidney disease	OR	1.375 (0.457-4.137)
	Colistin dose (CBA, mg/kg/day)	OR	0.948 (0.721-1.246)
	Colistin treatment duration (days)	OR	1.001 (0.888-1.129)
	Comorbidities ≥ 2	OR	3.245 (1.115-9.45)
	Concomitant daptomycin	OR	1.393 (0.215-9.011)
	Concomitant diuretic and vasopressor	OR	2.293 (1.006-8.494)
	Concomitant imipenem	OR	1.104 (0.296-4.112)
	Concomitant linezolid	OR	0.893 (0.165-4.833)
	Concomitant meropenem	OR	0.521 (0.183-1.482)
	Concomitant sulbactam	OR	1.882 (0.545-6.501)
	Diabetes	OR	1.603 (0.346-7.423)
	Gender (male)	OR	1.482 (0.52-4.227)
	Hypertension	OR	4.941 (1.383-17.649)
	ICU stay during colistin administration (days)	OR	1.019 (0.96-1.083)
	Receipt of > 2 concomitant nephrotoxins	OR	0.763 (0.409-3.384)
	Sepsis or septic shock	OR	1.176 (0.409-3.384)

	Serum albumin ≤ 2 mg/dL	OR	1.882 (0.545-6.501)
	The number of days that estimated target plasma concentrations of colistin were ≥ 3.5 mg/L during therapy	OR	1.577 (1.138-2.187)
	The number of days that estimated target plasma concentrations of colistin were ≥ 3.5 mg/L in the first week of therapy	OR	1.788 (1.137-2.811)
	Total iv and inhaled colistin dose (CBA, mg/day)	OR	1 (1-1)
	Total iv colistin dose (CBA, mg/day)	OR	1 (1-1)
Özkarakaş, et al., 2017 [61]	Age (old age, 61-78)	OR	7.78 (1.91-31.73)
	Albumin (hypoalbuminemia)	OR	4.76 (1.41-16.13)
	Concomitant vasopressors	OR	6.43 (1.29-2.11)
Papadimitriou-Olivgeris, et al., 2019 [62]	Concomitant voriconazole	OR	6.8 (1-46.1)
	eGFR upon BSI onset < 60 mL/min/1.73 m^2	OR	4.6 (1.9-11.2)
	Maximum noradrenaline dose	OR	1.1 (1-1.1)
	Obesity	OR	3.2 (1.4-7.6)
	Septic shock	OR	3.9 (1.1-14.3)
Rashizal, et al., 2017 [68]	Age (years)	OR	1.01 (0.99-1.03)
	Cumulative dose (MIU)	OR	0.99 (0.98-1.02)

	Daily dose (MIU)	OR	0.87 (0.68-1.11)
	Dosing interval (BD)	OR	0.75 (0.22-2.52)
	Dosing interval (TDS)	OR	0.77 (0.26-2.32)
	Duration (days)	OR	1.03 (0.93-1.15)
	Gender (female)	OR	0.829 (0.29-2.37)
	Race (Chinese)	OR	0.30 (0.04-2.55)
	Race (Indian)	OR	0.64 (0.19-2.16)
Rocco, et al., 2013 [72]	Age (year)	OR	1.02 (1.01-1.04)
	Albumin serum levels < 2g/dL	OR	2.66 (1.32-5.37)
	Cardiovascular disease	OR	1.61 (0.89-2.9)
	Concomitant ACEI	OR	1.83 (0.89-3.78)
	Concomitant iodate contrast	OR	1.27 (0.76-2.1)
	Concomitant NSAIDs	OR	0.62 (0.35-1.1)
	Congestive heart failure	OR	1 (0.35-2.92)
	CVC related-BSI	OR	0.86 (0.48-1.55)
	Diabetes mellitus	OR	1.79 (0.58-5.47)
	Gender (female)	OR	0.63 (0.37-1.06)
	Hypertension	OR	1.68 (0.92-3.05)
	Immunocompromised status	OR	1.14 (0.63-2.05)
	Neurological disease	OR	0.47 (0.18-1.24)
	SAPS II score	OR	1.04 (1.03-1.06)
	Sepsis	OR	1.9 (1.17-3.1)
	Septic shock at infection onset	OR	7.5 (4.36-12.9)
	Total bilirubin serum	OR	2.2 (0.85-5.65)

	levels > 5 mg/dL		
	Trauma	OR	0.4 (0.22-0.7)
	Two or more comorbidities	OR	2.06 (0.9-4.72)
	VAP	OR	1.19 (0.7-2.05)
Tanita, et al., 2013 [77]	Age (years)	OR	1.003 (0.977-1.029)
	APACHE II score	OR	1.017 (0.945-1.094)
	Colistin treatment duration (days)	OR	0.94 (0.867-1.02)
	Concomitant aminoglycoside	OR	1.425 (0.122-16.579)
	Concomitant amphotericin B	OR	0.933 (0.092-9.498)
	Concomitant diuretics	OR	0.425 (0.137-1.315)
	Concomitant vancomycin	OR	1.529 (0.559-4.181)
	Concomitant vasopressors	OR	4.727 (1.255-17.802)
	Creatinine at ICU admission (mg/dl)	OR	1.071 (0.63-1.823)
	Creatinine at the beginning of treatment (mg/dl)	OR	1.949 (1.124-3.38)
	Gender (male)	OR	1.654 (0.578-4.732)
	Length of stay in the hospital (days)	OR	0.975 (0.951-0.999)
	Length of stay in the ICU (days)	OR	0.956 (0.911-1.002)
	Mechanical ventilation	OR	3.486 (0.18-67.546)
	SOFA score at ICU admission	OR	1.082 (0.93-1.258)
	SOFA score at the beginning	OR	1.467 (1.202-1.789)

	of colistin treatment		
Vazin, et al., 2020 [82]	Age (years)	OR	1.057 (0.999-1.119)
	APACHE II score	OR	0.965 (0.729-1.49)
	Baseline GFR (mL/min/1.73 m^2)	OR	0.858 (0.729-1.010)
	Colistin cumulative dose (MIU)	OR	0.985 (0.941-1.032)
	Colistin indication (%)	OR	0.88 (0.083-9.28)
	Colistin treatment duration (day)	OR	1 (0.782-1.279)
	Concomitant loop diuretics (furosemide) (%)	OR	0.07 (0.007-0.707)
	Concomitant vancomycin (%)	OR	1.6 (0.249-10.27)
	Daily dose (MIU)	OR	0.906 (0.637-1.28)
	Gender (%)-Male	OR	0.880 (0.083-9.280)
	Loading dose (%)	OR	4.4 (0.68-28.6)
	Trauma	OR	0.69 (0.12-4.05)
Gulen, et al., 2022 [87]	Age	OR	1.052 (1.030-1.075)
	Sex (female)	OR	0.422 (0.219-0.815)
	APACHE II score	OR	1.064 (1.017-1.112)
	COPD (+)	OR	0.473 (0.251-0.890)
	Initial serum creatinine (mg/dl)	OR	40.320 (6.389-254.465)
	Concomitant nephrotoxic agent use	OR	3.057 (1.598-5.849)

Note: ACEI, angiotensin converting enzyme inhibitors; APACHE II, Acute physiology and chronic health evaluation II; BD, twice daily; BMI, Body mass index; BSI,

Bloodstream infection; CBA, Colistin base activity; CI, Confidence interval; CVC, central venous catheter; GFR, Glomerular filtration rate; HR, hazard ratio; ICU, intensive care unit; MIU, million international units; NSAIDs, Non-steroidal anti-inflammatory drugs; OR, Odds ratio; RR, risk ratio; SAPS II, Simplified acute physiology score II; SOFA, Sequential organ failure assessment; TDS, Three times daily; VAP, Ventilator associated pneumonia.

B. Multivariate analysis for predictors of acute kidney injury (AKI)

Study	**Variables**	**OR/HR/RR**	**Effect (95% CI)**
Aitullina, et al., 2021 [5]	Carbapenem protective role	OR	0.34 (0.1-1.11)
	Colistin loading dose of 9 MIU	OR	9.57 (1.85-49.6)
Aydoğan, et al., 2018 [10]	Colistin (mg/kg/day)	RR	0.41 (0.19-0.89)
	Concomitant vasopressor	RR	13.54 (2.21-83.09)
Choe, et al., 2019 [15]	Age (years)	OR	1.031 (1.001-1.063)
	Concomitant vancomycin	OR	2.623 (1.146-6.004)
Çiftçi, et al., 2017 [17]	APACHE II score at admission	OR	1.179 (1.033-1.346)
	N-acetylcysteine dosage	OR	1.005 (0.999-1.01)
	Need for vasopressors	OR	5.486 (1.522-19.769)
Dalfino, et al., 2015 [19]	Adjuvant ascorbic acid	HR	0.27 (0.13-0.57)
	Age (years)	HR	1.03 (1-1.05)
	Baseline renal impairment	HR	4.15 (1.9-9.2)
	SOFA score	HR	1.09 (0.9-1.3)
Doshi, et al., 2011 [23]	Concomitant nephrotoxins (= 2)	OR	6.5 (1.16-36.6)
	Concomitant nephrotoxins (=1)	OR	1.77 (0.25-12.6)
Heybeli, et al., 2020 [32]	Age (per 10 years)	OR	1.41 (1.05-1.91)
	Baseline eGFR (per 10ml/min)	OR	0.96 (0.87-1.06)
	Concomitant furosemide treatment	OR	2.66 (1.01-6.98)
	Concomitant glucocorticoid	OR	0.17 (0.06-0.49)
	Concomitant proton-pump inhibitor	OR	3.3 (1.18-9.23)
John, et al., 2018 [36]	Baseline creatinine clearance (ml/min)	HR	1.01 (1.00-1.01)
	Concomitant another nephrotoxic drug	HR	2.50 (1.02-6.14)
	Concomitant vasopressor	HR	2.75 (1.17-6.43)

	Daily dose (mg/kg/day)	HR	0.78 (0.49-1.27)
Jung, et al., 2019 [37]	Use of inhaled colistin immediately prior to the initiation or after the end of systemic colistin treatment	OR	0.331 (0.119-0.925)
Ozel, et al., 2019 [60]	Age (years)	OR	1.039 (1.001-1.077)
	Creatinine at start	OR	0.197 (0.065-0.598)
	The number of days that estimated target plasma concentrations of colistin were ≥ 3.5 mg/L in the first week of therapy	OR	2.362 (1.249-4.47)
Rocco, et al., 2013 [72]	Gender (female)	OR	0.62 (0.34-1.14)
	SAPS II score	OR	1.03 (1.01-1.05)
	Sepsis	OR	1.74 (0.99-3.05)
	Septic shock at infection onset	OR	5.89 (3.35-10.35)
Soares, et al., 2017 [76]	Polymyxin B dose > 10 MIU	OR	2.72 (1.13-6.51)
Tanita, et al., 2013 [77]	SOFA score at the beginning of colistin treatment	OR	1.467 (1.202-1.789)
Vazin, et al., 2020 [82]	Age (years)	OR	0.97 (0.83-1.14)
	Baseline GFR (mL/min/1.73 m^2)	OR	0.86 (0.74-1.01)
	Co-administration of loop diuretics (furosemide)	OR	0.087 (0-118.47)
Katip, et al., 2022 [84]	Loading dose colistin methanesulfonate	HR	1.70 (1.07-2.70)
	Age > 60 years	HR	2.06 (1.96-2.17)
	Male	HR	1.45 (1.29-1.63)

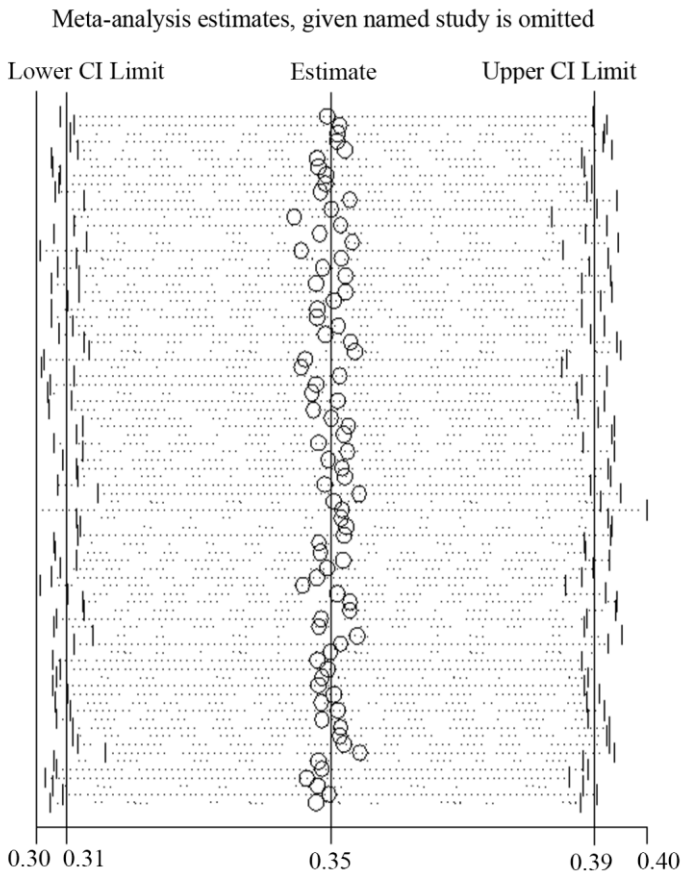
	Vasopressor	HR	1.22 (1.11-1.34)
	Amphotericin B	HR	1.08 (1.02-1.16)
	APACHE II score	HR	1.03 (1.01-1.04)
	Baseline GFR	HR	1.00 (1.00-1.01)
Ye, et al., 2022 [86]	Charlson comorbidity index score	OR	0.97 (0.71-1.32)
	Loop diuretic	OR	5.93 (1.03-34.07)
	Baseline creatinine clearance	OR	0.96 (0.93-0.99)
	Polymyxin B daily dose (mg/kg/day)	OR	0.99 (0.94-1.04)
Gulen, et al, 2022 [87]	Age	OR	1.043 (1.018-1.068)
	APACHE II score	OR	1.022 (0.967-1.080)
	Initial serum creatinine (mg/dl)	OR	23.122 (3.123-171.217)
	Concomitant nephrotoxic agent use	OR	2.398 (1.147-5.012)

Note: APACHE II, Acute physiology and chronic health evaluation II; CI, Confidence interval; GFR, Glomerular filtration rate; HR, hazard ratio; ICU, intensive care unit; MIU, million international units; OR, Odds ratio; RR, risk ratio; SAPS II, Simplified acute physiology score II; SOFA, Sequential organ failure assessment.

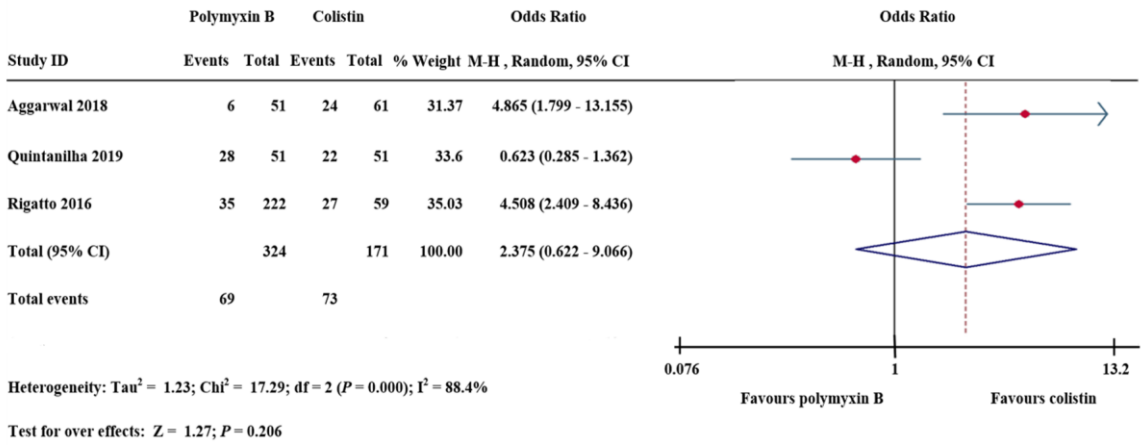
Supplementary Table 5 Stratification of the degree of nephrotoxicity from all patients who developed AKI during therapy

Category	Severity of AKI	No. of studies	No. of patients	Events rate (95% CI)	Model	Heterogeneity (I^2)
Degree of nephrotoxicity *	Overall	56	5, 163	0.389 (0.340 - 0.438)	random	97.70%
	Severe nephrotoxicity	47		0.127 (0.103-0.150)	random	89.60%
	Mild-moderate nephrotoxicity	49		0.258 (0.216-0.299)	random	96.80%
Degree of nephrotoxicity based on RIFLE criteria	Overall	25	2, 425	0.409 (0.335 - 0.482)	random	93.60%
	Risk	25		0.127 (0.096 - 0.158)	random	84.80%
	Injury	24		0.126 (0.100 - 0.152)	random	75.10%
	Failure	22		0.149 (0.111 - 0.186)	random	87.70%
	Loss of function	7		0.008 (0.003-0.013)	fixed	0
	End-stage	4		0.004 (0.000-0.009)	fixed	0

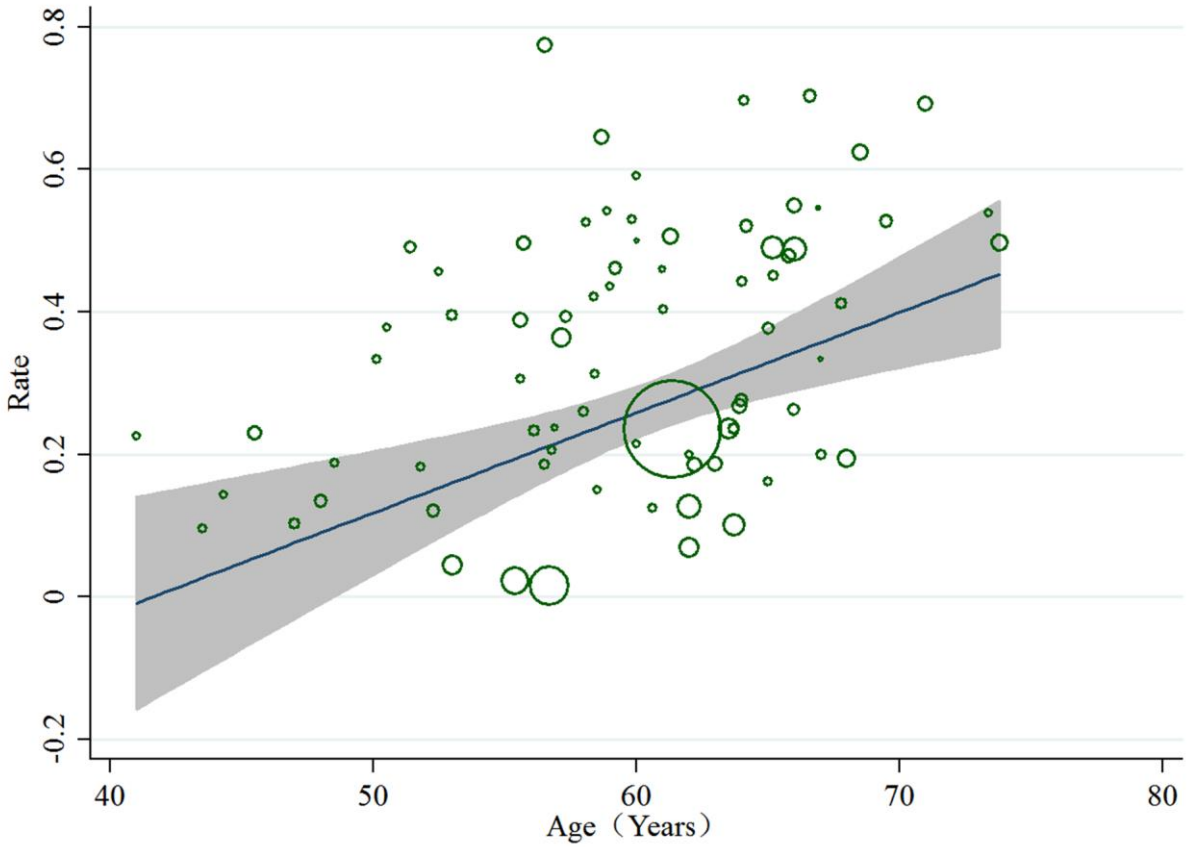
Note: * Severe nephrotoxicity defined as RIFLE grade of ' failure ' or above, AKIN grade of 3 or KDIGO grade of 3 or required renal replacement therapy.



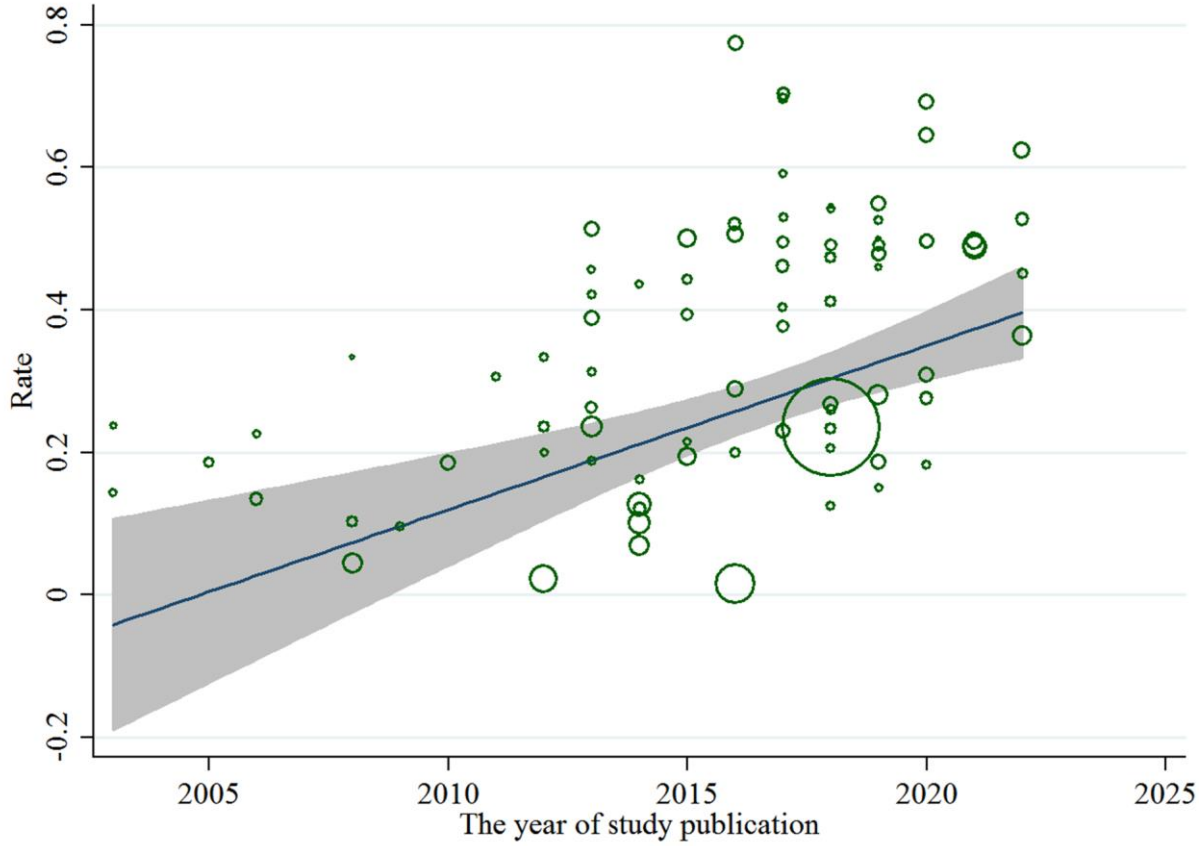
Supplementary Figure 1 Sensitivity analysis for pooled incidence of polymyxin-induced nephrotoxicity using a random-effects model by omitting one study at a time and pooling the rest of the included studies.



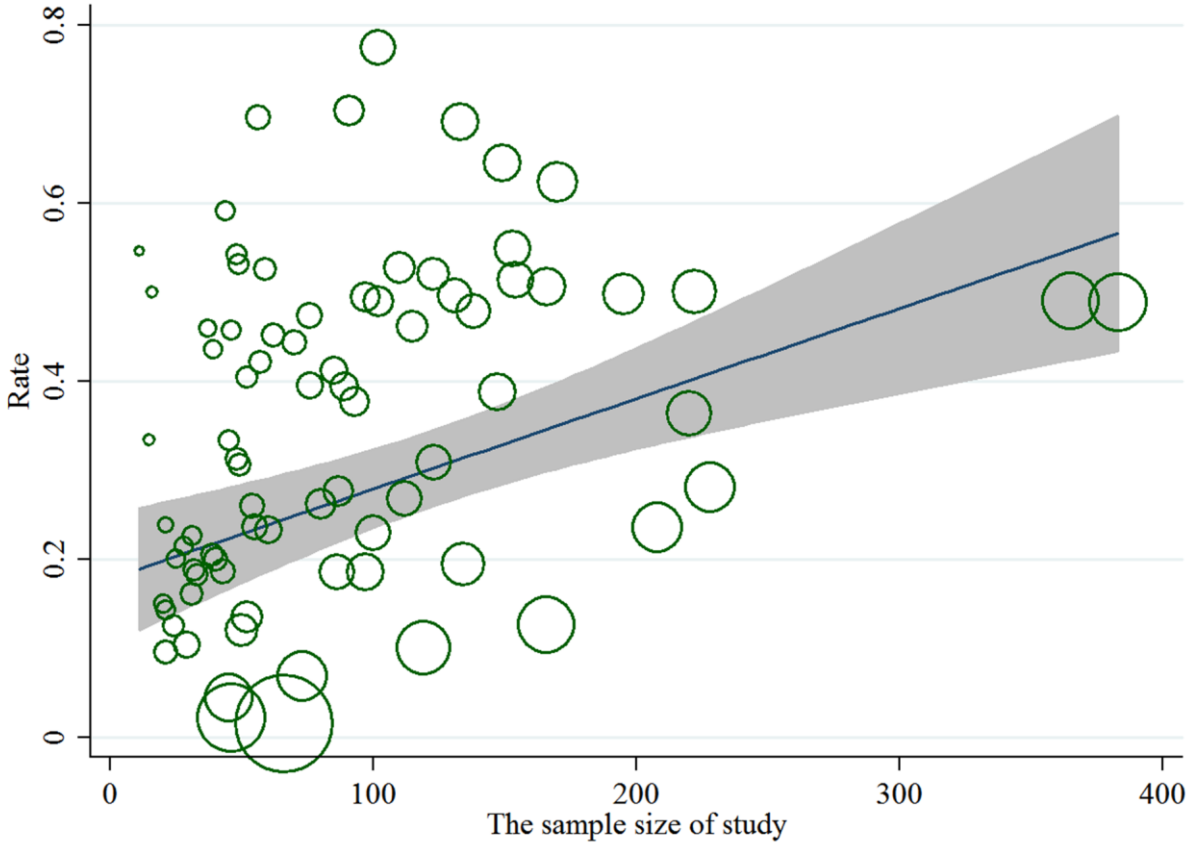
Supplementary Figure 2 Forest plot of nephrotoxicity rates in patients receiving colistin compared to patients receiving polymyxin B



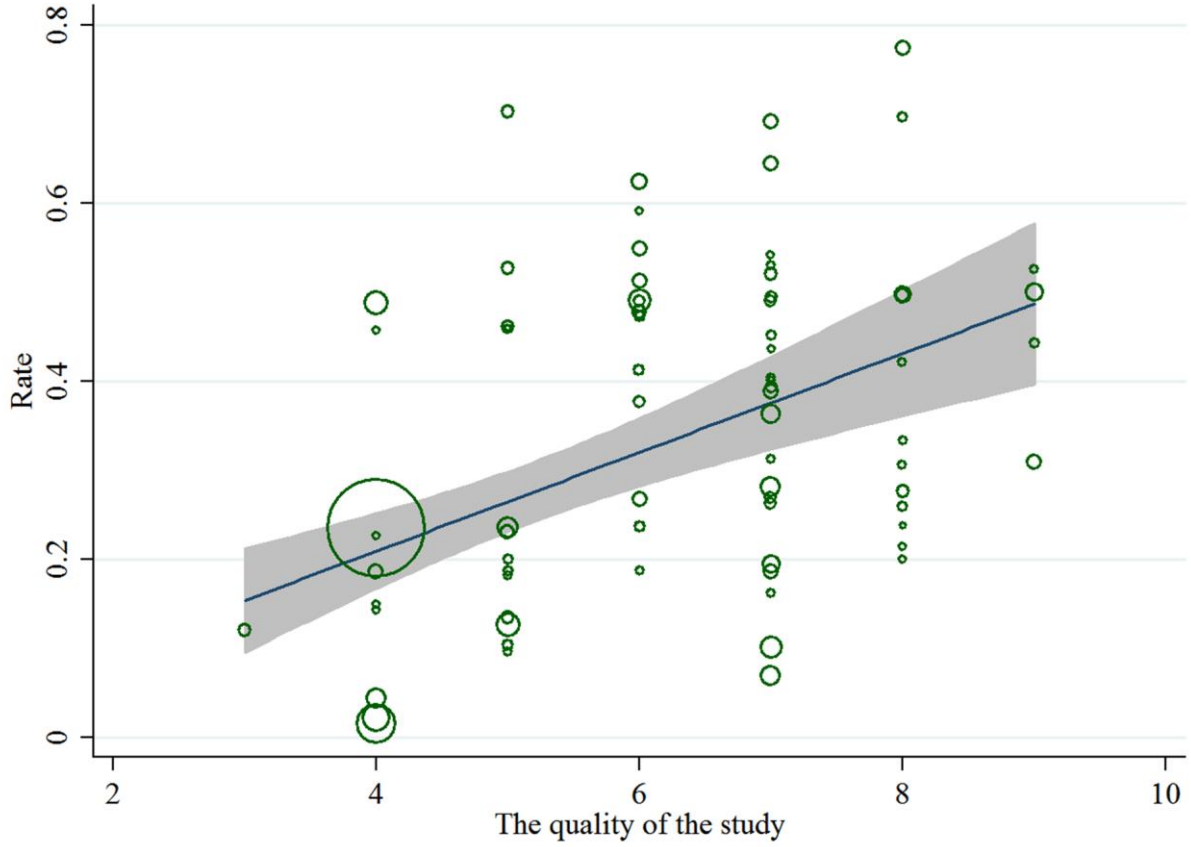
Supplementary Figure 3 Univariate meta-regression analysis for polymyxin-induced nephrotoxicity rate according to mean or medium age



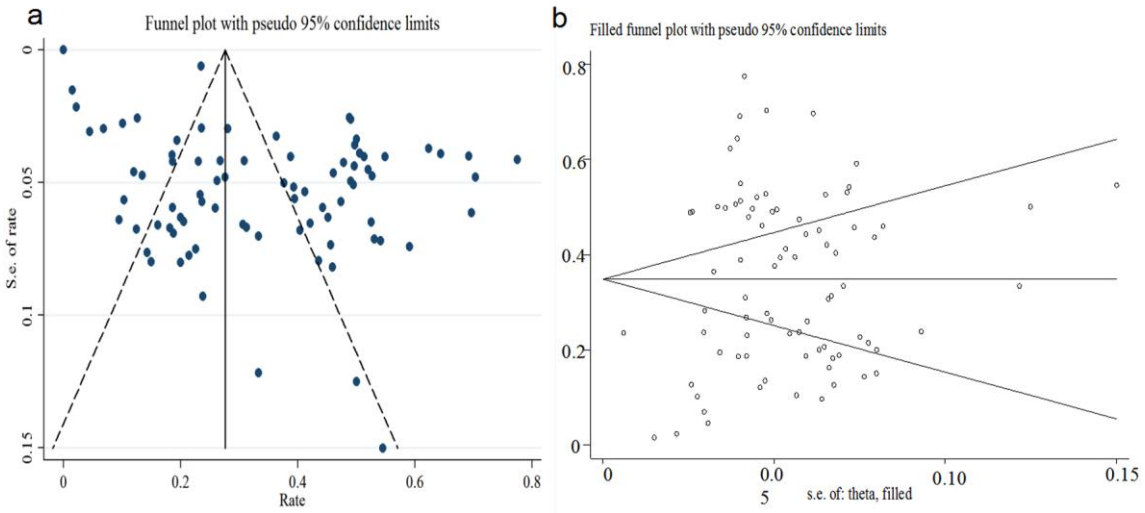
Supplementary Figure 4 Univariate meta-regression analysis for polymyxin-induced nephrotoxicity rate according to the year of study publication



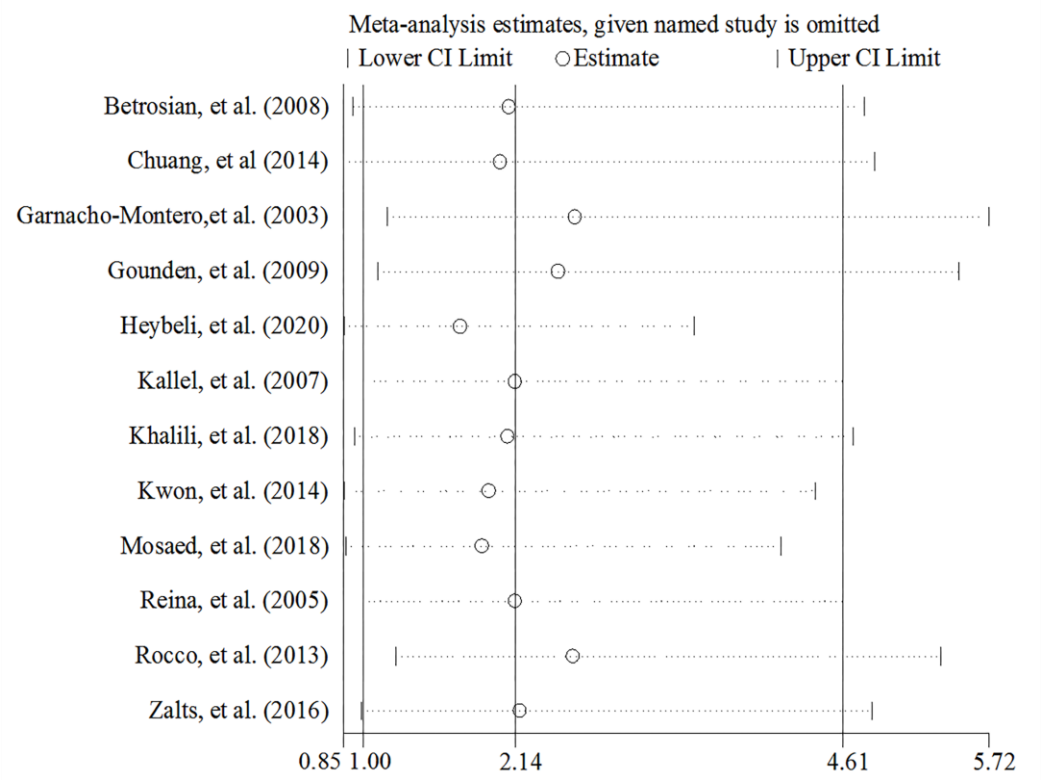
Supplementary Figure 5 Univariate meta-regression analysis for polymyxin-induced nephrotoxicity rate according to the sample size of study



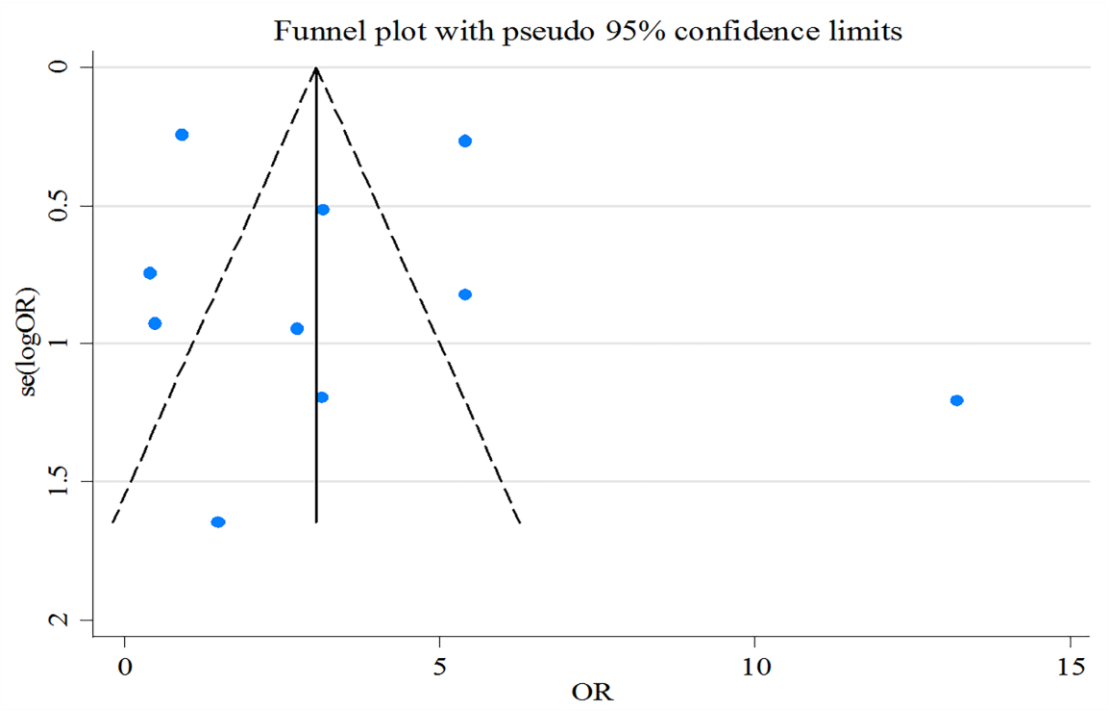
Supplementary Figure 6 Univariate meta-regression analysis for polymyxin-induced nephrotoxicity rate according to the quality of study



Supplementary Figure 7 Publication biases in polymyxin-induced nephrotoxicity incidence



Supplementary Figure 8 Meta-influence analysis of polymyxin-induced nephrotoxicity rates in patients treated with polymyxins compared to patients treated with other regimens



Supplementary Figure 9 Funnel plots depicting publication biases in odd ratio of patients treated with polymyxins versus patients treated with other regimens

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