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Meta-Analysis of Urinary Tract Infections among Patients with Chronic Kidney Disease

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Abstract

This review aimed to estimate the incidence of UTIs among CKD patients with an emphasis on the incidence rate and antibiotic resistance profile of uropathogens. A systematic literature search was performed in nine electronic databases. The period of the search was from 1st January 2000 until 31st January 2020. Quality assessment and meta-analysis were performed. N=75 articles that met the inclusion criteria for this systematic review were identified after screening n=55,799 articles. Overall analysis revealed that there was about 80% of the resistance cases of UTI were reported among the CKD patients from the selected studies with an effect size of 0.80 CI [0.76 – 0.83]. From various countries like China (EF 0.90 CI [0.82 – 0.95]), Indonesia (EF 0.99 CI [0.96 – 1.00]), Iraq (EF 0.38 CI [0.28 – 0.48]), Malaysia (EF 0.94 CI [0.92 – 0.95]), Oman (EF 0.99 CI [0.98 – 1.00]), and Saudi Arabia (EF 0.43 CI [0.34 – 0.53]) there was only one study eligible for inclusion in the meta-analysis. However, for countries like Bangladesh, India, Iran, and Pakistan the number of studies was greater, and the pooled effect size of the number of resistance cases generated on the multiple studies. The prevalence of UTIs was 55.6% to 18% in kidney disease patients. Further studies are needed to identify the risk factors of urinary tract infections among CKD patients and to develop new antimicrobial agents for urinary tract infections.

Keywords: Chronic kidney disease, Urinary tract infections, Antimicrobial resistance, MDRO, Multi-drug resistant organisms, Kidney failure

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Introduction

In worldwide, chronic kidney disease (CKD) is the major cause of morbidity and mortality. An estimated 2.3–7.1 million people died with end-stage renal disease (ESRD) without access to chronic dialysis in 2010 [1]. In south Asian countries**,** CKD is liberally increasing, and multiple factors are cause of this spread. Most importantly, the increasing prevalence of risk factors for CKD such as diabetes and hypertension [2]. The total prevalence of

renal disease is 16.6% with 8.6% participants having mild renal disease and 8% having moderate renal disease. Age is considerably associated with renal disease [3]. Approximately 1.2 million people died due to CKD and 32% increase in renal failure since 2005. Every year around 1.7 million people are died due to acute renal failure [4].

CKD patients are prone to various kinds of infections especially urinary tract infections (UTIs) due to changes in host immune response [5]. Bacteremia, pneumonia and UTIs are most commonly present in patients having CKD as compared with patients who have no CKD. In CKD patients, greater susceptibility of UTIs may be elucidated, by a higher prevalence of urinary obstacles, which cause infections, frequently seen in patients with kidney stone, benign prostatic hypertrophy and cancers in urinary tract [6].

The prevalence of UTIs is high among CKD patients. Females are prone to have more bacteriuria and upper UTIs than male [7]. CKD patients have UTIs due to urinary stagnation, urine alkalization and absence of flushing action. Uropathogens target different parts of urinary tract [8]. Generally, urine is considered sterile and germ free. Different studies found that most Uropathogens responsible for UTIs colonize the colon and perianal region. Pathogens that arise with the primary part of urethra, towards the wall of urethra, multiply then move up towards bladder and cause signs and symptoms. Pathogenesis can be ascending route [9, 10]. Both Gram positive and Gram negative microorganisms are responsible for UTIs [11, 12]. Among Gram negative bacteria, *Escherichia coli* (*E. coli*) is the most frequent pathogen inducing acute renal failure. Moreover, urological complications are associated with UTIs and *E. coli* is the most common clinical isolate [13].

Most studies found on the treatment of CKD and there is currently no review which assesses the global prevalence of UTIs and antimicrobial susceptibility among CKD patients. This gap in the existing literature needs to be addressed particularly in CKD patients who pose a greater risk of infection than other patients. Understanding the extent of UTIs and antimicrobial susceptibility among CKD patients is important in highlighting the need to take appropriate action to reduce infection and mortality in this vulnerable population. This study aims to estimate the incidence of UTIs among CKD patients and investigate the resistance pattern for uropathogens. In the Asian region, to date, there is a scarcity of comprehensive evidence that elaborates on the prevalence of urinary tract infections and antimicrobial susceptibility among CKD patients. Understanding the extent of urinary tract infections and antimicrobial susceptibility among CKD patients is important in highlighting the need to take appropriate action to time recommend empirical/ direct therapy promptly to reduce infection and mortality in this vulnerable population. The current systematic review and meta-analysis will be estimating the incidence of UTIs urinary tract infections among CKD from the Southeast Asian Region (SEAR), Western Pacific Region (WPR), and Eastern Mediterranean Region (EMR) patients and document the resistance pattern for uropathogens. This information will help develop effective infection control protocols and guidelines to reduce urinary tract infections in these high-risk patients in the current healthcare setting.

Materials and Methods

A systematic review was performed to identify published research papers from the selected regions. The period of the search was from 1st January 2000 until 31st January 2020. Main health sciences-related scientific databases i.e., PubMed, Google Scholar, Ovid, Web of Science, and Cochrane Library were reviewed. In addition, Publisher databases i.e., Sage Journals, Taylor and Francis Online, Science Direct, and Wiley Online performed to identify the studies that assessed the prevalence of UTIs and antimicrobial susceptibility among CKD patients.

Search terms

The following search terms i.e., Prevalence AND Urinary Tract Infections OR UTIs AND Antimicrobial susceptibility AND Antimicrobial resistance AND Chronic kidney disease OR CKD to identify the research papers. The following MeSH terms were used in PubMed, connected with the Boolean operator AND "prevalence, CKD", "antimicrobial susceptibility, UTIs". A systematic review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. All titles and abstracts of retrieved articles were screened for relevance to the aim of the study and full texts were obtained for review if appropriate. The systematic review provides synthesized information on all available literature. Identified and reviewed, based on criteria, and follow a specific protocol i.e. pose a question, design a detailed strategy, search, identify, review, and synthesize. Meta-analysis uses statistical analysis to synthesize data for several studies and the result of meta-analysis may highlight the part of the literature.

Study selection

Articles were selected based on predefined inclusion and exclusion criteria. Studies which fulfilled the following criteria were eligible for inclusion:

Inclusion criteria

1. All experimental and observational studies from the Southeast Asian Region (SEAR), Western Pacific Region (WPR), and Eastern Mediterranean Region (EMR) were included in this study.

2. Studies were published between 1st January 2000 and 31st January 2020.
3. In a single population, it can be difficult to reach conclusions; if the question is too broad. We applied the acronym PICOT (Population, Intervention, Comparator, Outcome, and Time) for formulating the research question. PICOT is a very helpful technique to summarize the research question that discovers the outcome of therapy.

Population: CKD patients

Intervention: Prevalence of UTIs due to E. coli to ciprofloxacin and nitrofurantoin, not all antibiotics, and Antimicrobial susceptibility

Comparator: None

Outcome: Resistance and susceptibility pattern

4. Studies published in the English language.

Exclusion criteria

1. All non-English studies were excluded from this review
2. All letters to the editors, case studies/reports, personal opinions, review papers, or any other type of study with unpredictable data or not reporting original data were excluded.

However, their reference lists were screened to identify any other article from grey literature that might not have appeared in the main search.

Data extraction and quality assessment

Abstracts and titles of studies were reviewed, and then Full-text articles were selected from retrieved studies for full-text review. Data extraction was performed through a data extraction form, which was made on a Microsoft Excel spreadsheet. Data extraction form comprised of first author`s name/ year, name of a country, study design, sample size, recruitment site, and the result obtained. The Newcastle-Ottawa scale (NOS) is a quality assessment tool for observational studies [15, 16], which was used for assessing the quality of each particular study.

Data analysis

A meta-analysis was performed using STATA version 14. The random effects model was utilized for the estimation of the effect size for the analysis of the proportion of the number of infections reported/ observed versus the total number of patients. The random Effect model is mostly recommended model. All p-values were set at <0.01 with 95% confidence intervals. The p-value <0.01 was considered significant. Subgroup analysis was performed to analyze data among the different countries. The I^2 statistic was used to interpret the heterogeneity at a confidence interval of 95% among the included studies.

Results and Discussion

Study selection

With the help of systematic literature search, 55,799 articles were found. 29,147 Records obtained after duplicates removed. After checking of title and abstract, 147 strongly relevant studies were selected for full text review for suitability. Of the 147 studies, 75 studies were included for qualitative study. The PRISMA flow chart of study selection is accessible in **Figure 1**.

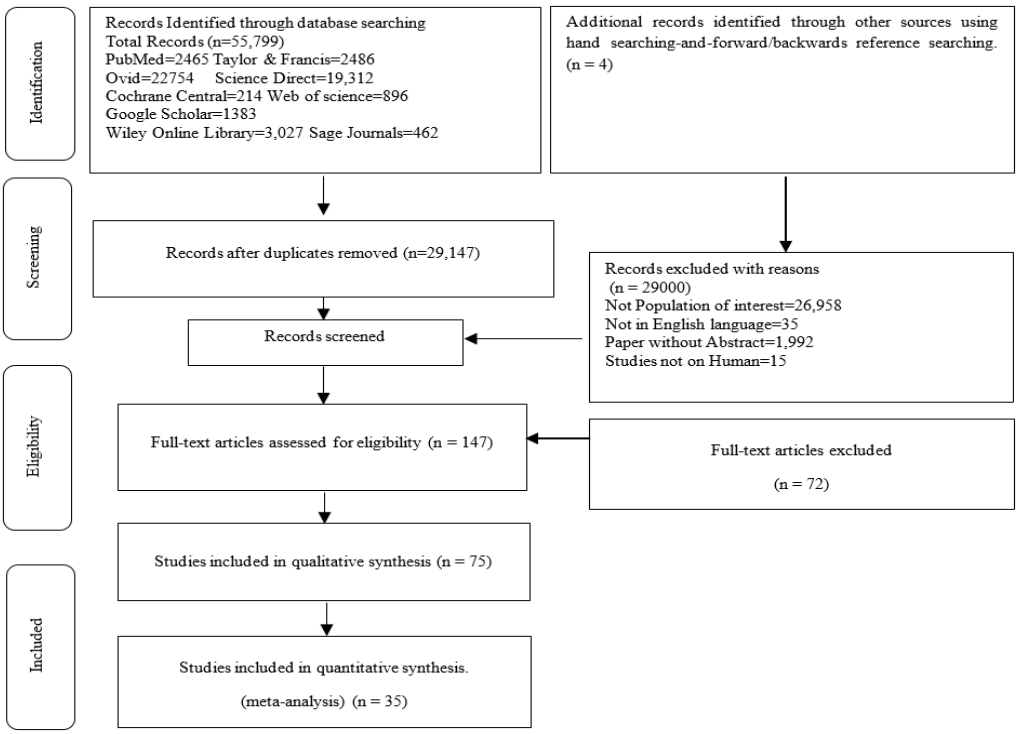

Figure 1. PRISMA Flow Diagram

Study characteristics

Of the 75 selected studies, 27 were cross sectional studies, 20 retrospective cohort ,1 descriptive retrospective, 20 prospective cohorts, 4 descriptive,1 case control and 1 experimental and 1 descriptive cross sectional. Studies were conducted in diverse geographical regions such as India (n=24), Iran (n=10), Bangladesh (n=9), China (n=8), Pakistan (n=7), Nepal (n=5), Iraq (n=3), Indonesia (n=2), Saudi Arabia (n=2), Australia (n=2), Egypt (n=1), Oman (n=1) and Malaysia (n=1). In most of the studies, prevalence of UTIs and antimicrobial susceptibility was found among CKD patients. A summary of study characteristics is shown in **Table 1**.

Table 1. General characteristics of included studies.

First Author/Year	Country	Study Design	Sample size (patients)	Recruitment site	Result Obtained		Quality Score
					Antibiotic Resistance	Antibiotic Susceptibility	
(White *et al*., 2005) [17]	Australia	Cross-sectional	N/A	Community	N/A	N/A	6
(Chadban *et al*., 2003) [18]	Australia	Cross-sectional	11,247	42 randomly selected urban and nonurban areas across Australia.	N/A	N/A	7
(Nazme *et al*., 2017) [19]	Bangladesh	Cross-sectional	180	Hospital	amoxicillin, co-trimoxazole, azithromycin, cefuroxime, ceftriaxone, cefixime, and ceftazidine.	ciprofloxacin, amikacin, nitrofurantoin levofloxacin	6
(Haque *et al*., 2015) [20]	Bangladesh	Retrospective cohort	443	Teaching Hospital	isolates showed 72.03 % to 91.53% resistance to co-trimoxazole, ciprofloxacin, cefuroxime, cephradin, amoxicillin, nalidixic acid, and gentamicin	*E. coli, Staph saprophyticus, Pseudomonas spp., and Enterococcus spp.* showed susceptibility to nitrofurantoin	6
(Siddiqua *et al*., 2017) [21]	Bangladesh	Retrospective cohort	2021	Teaching Hospital	cefuroxime (82%), nalidixic acid (74%), azithromycin (56%), cefotaxime (52%), ceftazidime (50%), cefixime (47%), cotrimoxazole (43%), ceftriaxone (41%)	gentamicin, meropenem, imipenem, amikacin and nitrofurantoin	5
(Begum *et al*., 2017) [22]	Bangladesh	Prospective cohort	102	Medical University (Teaching Hospital)	N/A	imipenem, meropenem, ceftriaxone, ceftazidime and gentamicin.	7
(Akhtar *et al*., 2016) [23]	Bangladesh	Prospective cohort	177	Hospital	cotrimoxazole, nalidixic acid and amoxicillin.	imipenem, meropenem, nitrofurantoin, and amikacin.	6
(Nahar *et al*., 2017) [24]	Bangladesh	Cross-sectional	303	Medical College	amoxicillin, cefradin, nalidixic acid, cefuroxime, ceftriaxone and cefixime.	N/A	5

(Mahbub *et al*., 2011) [25]	Bangladesh	Prospective cohort	12	Hospital	oxacillin, cefsulodine	methicillin. polymyxin B and imipenem were 100% sensitive to *E. coli.*	6
(Saha *et al*., 2015) [26]	Bangladesh	Cross-sectional	74	Hospital	Most of the strains were highly resistant to amoxicillin (85.14%), and cotrimoxazole (81.08%).	Strains showed significant sensitivity to amikacin (94.59%), azithromycin (93.24%), doxycycline (90.54%) and ceftriaxone (89.18%) respectively showed significant sensitivity.	5
(Mia *et al*., 2017) [27]	Bangladesh	Retrospective cohort	910	Hospital	N/A	A high level of sensitivity was found to imipenem, amikacin, and nitrofurantoin for most of the isolates.	7
(Wang *et al*., 2019) [28]	China	Retrospective cohort	2092	Hospital	A high level of resistance showed with amoxicillin and ampicillin.	N/A	6
(Shan *et al*., 2010) [29]	China	Cross-sectional	4156	Community	N/A	N/A	7
(Wei *et al*., 2012) [30]	China	Cross-sectional	1187	Hospital	N/A	N/A	6
(Qian *et al*., 2014) [31]	China	Cross-sectional	530	Hospital	N/A	N/A	6
(Zhang *et al*., 2008) [32]	China	Cross-sectional	13925	Community	N/A	N/A	7
(Chen *et al*., 2010) [33]	China	Cross-sectional	1289	Community	N/A	N/A	6
(Zhang *et al*., 2007) [34]	China	Cross-sectional	2353	Hospital	N/A	N/A	7
(Yuan *et al*., 2018) [35]	China	Retrospective cohort	1569	Hospital	Almost all multidrug resistant Gram-negative bacteria were resistant to a first and second generation of cephalosporin. and monocyclic beta-lactam.	They were sensitive to meropenem, amikacin and tigecycline.	7
(Ghonemy *et al*., 2016) [36]	Egypt	Cross-sectional	1004	Hospital	N/A	N/A	6
(Simon *et al*., 2018) [37]	India	Retrospective cohort	129	Hospital	*Bacteria* were highly (>90%) resistant to ampicillin.	80% Amikacin, cefoperazone and piperacillin-tazobactam while >70% were sensitive to gentamicin and nitrofurantoin. *Klebsiella* also showed more than 80% sensitivity to ciprofloxacin and norfloxacin.	5

(Semwal *et al*., 2017) [38]	India	Prospective cohort	205	Hospital	ciprofloxacin (20.15%), co-trimoxazole (19.37%), cefotaxime (18.60%), amoxicillin-clavulanic acid (16.27%), gentamycin (15.50%), cefazolin (14.72%), ampicillin (13.95%), ticarcillin-clavulanic acid (13.95%), cefuroxime (13.17%), aztreonam (11.62%) and cefepime (77.51%).	amikacin (25.58%), nitrofurantoin (18.60%), piperacillin-tazobactam (15.50%), gentamicin (15.50%), cefoperazone-sulbactum (14.72%), amoxicillin clavulanic acid (13.95%), meropenem (13.95%), ciprofloxacin (11.62%), co-trimoxazole (9.30%), and aztreonam (7.75%).	6
(George and Prasad, 2014) [39]	India	Prospective cohort	138	Hospital	A high level of resistance was seen to ciprofloxacin (75%), gatifloxacin (68%), ceftazidime (62%), meropenem (51%), and imipenem (39%).	nitrofurantoin showed sensitivity.	6
(Singh and Haque, 2019) [40]	India	Cross-sectional	180	Hospital	N/A	The highest sensitivity to amikacin is 100% followed by gentamicin at 96% and nitrofurantoin at 98%.	7
(Shanavas *et al*., 2015) [41]	India	Retrospective cohort	150	Hospital	ampicillin (92%) and cefazolin (80%)	fosfomycin (99%). nitrofurantoin (92%, gentamicin (92%) and amikacin (92%)	5
(Nath *et al*., 2018) [42]	India	Retrospective cohort	40	Hospital	High resistance to ampicillin, cefotaxime, and tetracycline has caused considerable alarm.	*E. coli* was sensitive to amikacin (90.5%), cefotaxime (89.6%), ciprofloxacin (85.3%), and kanamycin (76.1%). amikacin was more effective against *Pseudomonas* (77.5%). *Klebsiella* was more sensitive to amikacin.	7
(Singhal *et al*., 2014) [43]	India	Prospective cohort	2653	Hospital	High level of resistance to fluoroquinolones 70.3% and cephalosporins 75.1% whereas resistance to Nitrofurantoin 19.8%, Amikacin 32.4%, and cephoperazone-sulbactam 22% was low.	N/A	6
(Gupta *et al*., 2007) [44]	India	Retrospective cohort	4674	Institute of medical sciences	resistance co-trimoxazole, ampicillin, and ciprofloxacin were 90 to 96%, 92 to 98%, and 55 to 65%, respectively.	More susceptible to amikacin, followed by cefotaxime, gentamicin, ciprofloxacin, norfloxacin, ampicillin, and co-trimoxazole.	5

(Manikandan *et al*., 2011) [45]	India	Prospective cohort	10	Hospital	trimethoprim/sulfamethoxazole 83.3%, Nalidixic acid 80.6%, amoxicillin 67.3%, cotrimoxazole 61%, gentamycin 48.8%, ciprofloxacin 46% and cephalexin 43%.	N/A	5
(Sujatha and Pal, 2015) [46]	India	Prospective cohort	297	Hospital	*Proteus* was resistant to all the quinolones antibiotics. All the isolated uropathogens were highly resistant to aminoglycosides and carbapenem.	Better sensitivity against Nitrofurantoin.	5
(Prakash and Saxena, 2013) [47]	India	Prospective cohort	288	Hospital	nalidixic acid (78.71%), ceftazidime (71.61%), cefotaxime (67.74%).	meropenem (92.26%), imipenem (84.52%), levofloxacin, and netillin each were showing 74.84% sensitivity.	5
(Malhotra *et al*., 2016) [48]	India	Prospective cohort	500	Department of microbiology, SGT University.	Maximum resistance to ampicillin and co-trimoxazole and least resistance to nitrofurantoin, amikacin, imipenem, and vancomycin.	N/A	6
(Venkatesh *et al*., 2016) [49]	India	Prospective cohort	106	Hospital	aztreonam, ticarcillin-clavulanic acid, cefodroxil and ciprofloxacin or levofloxacin were resistant.	amikacin, netilmicin and imipenem were 100% sensitive, cefoperazone-sulbactam (95%) and piperacillin-tazobactam (77.2%).	6
(Saha *et al*., 2014) [50]	India	Retrospective cohort	Unknown	Hospital	penicillin was least effective against UTI-causing E. coli and	Maximum susceptibility was recorded for the drugs belonging to fourth-generation cephalosporins.	5
(Nigam *et al*., 2017) [51]	India	Descriptive	100	Hospital	N/A	Susceptibility to imipenem (96%), followed by nitrofurantoin 90%, amikacin 88%, piperacillin/tazobactam 82%, netilmicin 78%, cefoperazone/sulbactam 71%, lower susceptibility ciprofloxacin 40%, norfloxacin 44% and amoxicillin-clavulanic acid 23%.	5
(Pratap *et al*., 2016) [52]	India	Cross-sectional	175	Hospital	*E. coli* exhibited the highest resistance to nalidixic acid. amoxicillin, cefixime, cotrimoxazole, ceftriaxone, and ofloxacin also showed high resistance.	N/A	6

(Sharma *et al*., 2016) [53]	India	Retrospective cohort	2107	Hospital	resistance to imipenem decreased from 11.86 % to 11.36 %. nitrofurantoin from 36.1 % to 18.15 %. resistance to ceftriaxone increased from 53.39 % to 73.33 %.	N/A	6
(Vij *et al*., 2014) [54]	India	Retrospective cohort	365	Punjab institute of medical sciences	resistance to norfloxacin was 90.6%, ciprofloxacin 89.4%, cefotaxime 87.1%, ceftriaxone 84.7%, meropenem 62.7% and gentamicin 59.6%.	The effective drugs for *E. coli* were nitrofurantoin, amikacin, piperacillin/tazobactam , and imipenem.	6
(Sood and Gupta, 2012) [55]	India	Retrospective cohort	346	Hospital	ampicillin (>80%), amoxicillin-clavulanic acid (>80%), co-trimethoprim-sulfamethoxazole (>67%), nalidixic acid (>95%), norfloxacin (>77%), and ciprofloxacin (>74%).	nitrofurantoin is the drug with the least resistance (>5-6%) to *E. coli* throughout the 2½ years study period.	5
(Saha and Kulkarni, 2018) [56]	India	Cross-sectional	140	Hospital	N/A	nitrofurantoin's sensitivity *to E. coli* was significantly higher than the other two uropathogens.	5
(Prakash *et al*., 2006) [57]	India	Prospective cohort	200	Hospital	N/A	N/A	5
(Niranjan and Malini, 2014) [58]	India	Cross-sectional	119	Hospital	The isolates showed high levels of resistance to ampicillin (88.4%), amoxicillin-clavulanic acid (74.4%), norfloxacin (74.2%), cefuroxime (72.2%), ceftriaxone (71.4%) and co-trimoxazole (64.2%)	The isolates were sensitive to amikacin (82.6%), piperacillin-tazobactum (78.2%), nitrofurantoin (82.1%), and imipenem (98.9%).	5
(Vali *et al*., 2018) [59]	India	Retrospective cohort	94	Hospital	N/A	N/A	4
(Reddy *et al*., 2016) [60]	India	Prospective cohort	100	Hospital	N/A	N/A	7
(Gunawan and Umboh, 2016) [61]	Indonesia	Retrospective cohort	74	Hospital	N/A	N/A	6
(Herdiyanti *et al*., 2019) [62]	Indonesia	Descriptive Retrospective	163	Hospital	*Escherichia coli* resistance pattern against ceftazidime (75.6%), nitrofurantoin (12.6%) and meropenem (2.4%). meanwhile, *Klebsiella pneumonia* against ceftazidime (72.2%), Nitrofurantoin (55.6%), meropenem (11.1%), and amikacin (2.8%).	N/A	7

(Amin *et al*., 2009) [63]	Iran	Prospective Cohort	553	Hospital	N/A	The most effective antimicrobial agents were amikacin, tobramycin, and ciprofloxacin against *Gram-negative bacilli* and the most effective antibiotics against *Gram-positive cocci* were kanamycin, tobramycin, and ciprofloxacin.	6
(Ali *et al*., 2014) [64]	Iran	Descriptive	371	Hospital	N/A	ciprofloxacin (95.3%), amikacin (93.9%), and nalidixic acid (92.2%), gentamicin (89.2%) and nitrofurantoin (83.8%).	6
(Mirsoleymani *et al*., 2014) [65]	Iran	Retrospective cohort	1513	Hospital	N/A	antimicrobial susceptibility analysis for E. coli to commonly used antibiotics are as follows: amikacin (79.7%), ofloxacin (78.3%), gentamicin (71.6%), ceftriaxone (41.8), cefotaxime (41.4%), and cefixime (27.8%).	5
(Pouladfar *et al*., 2017) [66]	Iran	Cross-sectional	202	Shiraz university of medical sciences.	Highest resistance to ampicillin (81.2%) and cotrimoxazole (79.2%).	highest susceptibility to imipenem (90.1%) and gentamicin (65.3%).	7
(Naghibi *et al*., 2015) [67]	Iran	Cross sectional	1285	Community	N/A	N/A	6
(Fallah *et al*., 2008) [68]	Iran	Descriptive	34	Hospital	The lowest resistance rate of microorganisms was against amikacin (3.7%) and the highest resistance rate was against amoxicillin (70.4%).	N/A	6
(Mihan khah *et al*., 2017) [69]	Iran	Cross sectional s	3798	Hospital	The highest antibiotic resistance to methicillin (76.06%) and ampicillin (89.29%).	The most sensitivity to imipenem (99.1%) and amikacin (91.57%).	7
(Mirzarazi *et al*., 2013) [70]	Iran	Cross-sectional descriptive	702	Hospital	nalidixic acid, trimethoprim sulphamethoxazole,	nitrofurantoin, cotrimoxazole and ciprofloxacin	6
(Salarzaei *et al*., 2017) [71]	Iran	Descriptive	124	Hospital	N/A	N/A	6

(Rezaee and Abdinia, 2015) [72]	Iran	Prospective cohort	25,811	Health care center	*E. coli* resistance level was 11% for Nitrofurantoin, 15% for ciprofloxacin, 25% for nalidixic acid, and 30% to 75% for amikacin, gentamicin, ceftriaxone, ceftizoxime, cefotaxime, and co-trimoxazole.	ciprofloxacin showed the highest activity against *Klebsiella spp.* and amikacin, gentamicin, and nalidixic acid showed activity against *Pseudomonas aeruginosa.*	6
(Abdulraham *et al.*, 2018) [57]	Iraq	Retrospective cohort	1003	Hospital	The maximum resistance was seen against cefazolin (79.7%) and amoxicillin/clavulanic acid (77.5%).	maximum sensitivity was seen for meropenem (94.9%), followed by imipenem (89.7%) and ertapenem (88.7%).	5
(AL-Jebouri and Al-Alwani, 2015) [73]	Iraq	Prospective cohort	100	Teaching Hospital	Complete resistance to ampicillin and amoxicillin.	The most effective antibiotic was imipenem (100%) susceptibility	5
(Majeed and Aljanaby, 2019) [74]	Iraq	Case-Control	120	Teaching Hospital	Most bacterial isolates were highly resistant to most antibiotics, especially against amoxicillin and third generation cephalosporins.	imipenem provided the best antibacterial effect against most isolates.	6
(Nor *et al*., 2015) [75]	Malaysia	Retrospective cohort	721	Hospital	resistance to ampicillin, cefuroxime and gentamicin as was 67.7%, 15.3%, and 7.3% respectively.	N/A	6
(Shah *et al*., 2016) [76]	Nepal	Cross-sectional	88	Hospital	The resistance of *E. Coli* to ampicillin, ofloxacin, cefotaxime, gentamicin, and amikacin was (85%), (82%), (75%), (28%) and (3%) respectively. The resistance to ampicillin was *Klebsiella species* (87%), *Proteus* (86%), and *Enterococcus* (60%).	N/A	6
(Yadav *et al*., 2016) [77]	Nepal	Prospective cohort	206	Hospital	N/A	N/A	6
(Ganesh *et al*., 2019) [78]	Nepal	Cross-sectional	1599	Hospital	Most of the isolates were resistant to ampicillin and co-trimoxazole, while the least were resistant to amikacin and nitrofurantoin.	N/A	5
(Sah *et al*., 2016) [79]	Nepal	Prospective cohort	200	Hospital	Drug resistance with amikacin, gentamycin, and Nitrofurantoin was found to be lower than other antibiotics which were subjected to sensitivity tests.	N/A	6
(Shakya *et al*., 2014) [80]	Nepal	Cross-sectional	300	Hospital	multidrug resistance was observed in 68.82% of the total bacterial isolates.	N/A	5

(Khalid *et al*., 2018) [81]	Oman	Retrospective cohort	846	Hospital	The highest (34.3%) antibiotic resistance was noticed in *E. coli* against nalidixic acid.	Susceptibility was found against ceftriaxone, ceftazidime, ciprofloxacin, and nitrofurantoin.	5
(Muntaha *et al*., 2016) [82]	Pakistan	Cross-sectional	155	Hospital	N/A	These bacterial pathogens were sensitive to amoxicillin-clavulanic acid and trimethoprim-sulfamethoxazole.	6
(Anjum *et al*., 2016) [83]	Pakistan	Experimental	113	Medical College	More resistant to amoxicillin/clavulanic acid and gentamicin.	*E. coli* was sensitive to imipenem and ciprofloxacin.	6
(Ullah *et al*., 2018) [2]	Pakistan	Cross-sectional	500	Hospital	N/A	Most *Gram-Ve bacteria* were sensitive to cefepime and all gram-positive isolates were sensitive to meropenem.	7
(Afridi *et al*., 2014) [84]	Pakistan	Cross-sectional	100	Hayatabad Medical Complex	N/A	The sensitivity of different urinary isolated to amikacin was highest (82%) followed by meropenem (75%), and tazocin (61%).	5
(Zareef *et al*., 2009) [85]	Pakistan	Cross-sectional	524	Hospital	sulphamethoxazole trimethoprim had shown resistant patterns with only 34.11% sensitivity.	third generation cephalosporin, imipenem, and fluoroquinolones show high sensitivity against the uropathogens studied.	6
(Naz *et al*., 2018) [86]	Pakistan	Cross-sectional	1370	Hospital	Pathogens were resistant to cefixime (83%), ceftriaxone (81%), and amoxicillin-clavulanic acid (69%). *Acinetobacter baumannii* were found most resistant.	meropenem, amikacin and piperacillin-tazobactam were most effective.	6
(Sohail *et al*., 2015) [87]	Pakistan	Retrospective cohort	1429	Chagatai's Lab Lahore.	*E. coli* was highly resistant to cephalexin (95%), cephradine (95%), pipemidic acid (92%), amikacin (91%), and nalidixic acid (91%). amoxicillin/clavulanic acid, ampicillin, and aztreonam were resistant to *E. coli*, 84%, 84%, and 72%, respectively.	Maximum susceptibility (97%) against three drugs, namely imipenem, meropenem, and cefoperazone. piperacillin and fosfomycin also provided significant results against *E. coli* with respective susceptibility rates of 96% and 90%.	6

(Al-Mijalli, 2017) [88]	Saudi Arabia	Prospective cohort	116	Hospital	N/A	All isolates of *E. coli and K. pneumonia* were highly susceptible to meropenem, imipenem, colistin, ertapenem, and amikacin.	5
(El-Mongy and Reyad, 2013) [89]	Saudi Arabia	Prospective cohort	100	Hospital	Among these E. coli, K. pneumonia, and P. aeruginosa were highly resistant to the antibiotics.	*Staphylococcus* and *Serratia marcescens* exhibited high sensitivity to cefoxitin, cefepime, and aztreonam.	5

Quality assessment

For the quality assessment of included studies, 2 distinct Newcastle-Ottawa Scale were used. 50 selected studies were of good quality with scores ranging from 6 to 7; 24 studies had average quality with score of 5 and 1 study had poor quality with score of 4. The quality assessment of selected studies is shown in **Table 1**.

Data analysis

In Bangladesh, one study had large effect size 0.81[95% CI 0.69-0.90] [19] following by one, which showed medium effect size 0.61[95% CI 0.51-0.70] [22]. One study conducted in China showed large effect size 0.90[95% CI 0.80-0.95 [35]. In India, the magnitude of effect size was large as 1.00[95% CI 0.98-1.00] [55] followed by small effect size 0.37[95% CI 0.32- 0.43] [46]. In Indonesia, effect size was large 0.99[95% CI 0.96-1.00] [61]. In Iran, one study with large effect size 0.97[95% CI 0.93-0.99] [66]. followed by one study, which represented medium effect size 0.50[95% CI 0.47-0.53] [72]. One study conducted in Iraq with medium effect size 0.38[95% CI 0.28-0.48] [73]. Study conducted in Malaysia with large effect size 0.94[95% CI 0.5-0.92] [75]. In Oman, one study showed large effect size 0.99[95% CI 0.98-1.00] [81]. In Pakistan, one study was with large effect size 0.79[95% CI 0.70-0.86] [83] followed by study with medium effect size 0.50[95% CI 0.40-0.60] [84]. In Saudi Arabia, study represented medium effect size 0.43[95% CI 0.3- 0.53] [81]. Overall random pooled effect size in studies conducted in Iran was large 0.84[95% CI 0.75-0.93] followed by studies conducted in Pakistan with medium overall random effect size 0.66[95% CI 0.53-0.78]. Results revealed that antimicrobial resistance is increasing in the treatment of UTIs alarmingly. Antibiotic resistance monitoring is necessary to develop the most effective empirical treatment of UTIs in CKD patients. Antibiotic resistance among different countries is shown in **Table 2**.

Table 2. Meta-Analysis of Proportion of Resistance Cases Using Random Effect Model.

Study	Sample Size (N)	Resistance Cases	Prevalence (n)	[95% CI]	Weight	I^2 (%) / P-value
Bangladesh						0.01
Nazme *et al*. (2017)	58	47	0.81	[0.69-0.90]	3.11	
Begum *et al*. (2017)	102	62	0.61	[0.51-0.70]	3.11	
Akhtar *et al*. (2016)	177	134	0.76	[0.69-0.82]	3.12	
Saha *et al*. (2015)	74	60	0.81	[0.70-0.89]	3.12	
Mia *et al*. (2017)	238	172	0.72	[0.66-0.78]	3.13	
Random pooled ES			**0.74**	**[0.68-0.80]**	**15.59**	**67.73**
China						0.00
Yuan *et al*. (2018)	98	88	0.90	[0.82 – 0.95]	3.13	0
India						0.00
Simon *et al*. (2018)	129	105	0.81	[0.74 – 0.88]	3.12	
Semwal *et al*. (2017)	101	89	0.88	[0.80 – 0.94]	3.12	
Shanavas *et al*. (2015)	150	148	0.99	[0.95 – 1.00]	3.13	
Sujatha and Pal (2015)	297	110	0.37	[0.32 – 0.43]	3.13	
Prakash and Saxena (2013)	155	150	0.97	[0.93– 0.99]	3.13	
Malhotra *et al*. (2016)	95	82	0.86	[0.78– 0.93]	3.12	
Venkatesh *et al*. (2016)	83	47	0.57	[0.45 – 0.67]	3.11	

Pratap *et al*. (2016)	175	113	0.65	[0.57 – 0.72]	3.12	
Sharma *et al*. (2016)	2464	2107	0.86	[0.84 – 0.87]	3.13	
Vij *et al*. (2014)	365	319	0.87	[0.84 – 0.91]	3.13	
Sood and Gupta (2012)	346	345	1.00	[0.98 – 1.00]	3.13	
Saha *et al.* (2018)	140	113	0.81	[0.73 – 0.87]	3.12	
Niranjan and Malini (2014)	119	91	0.76	[0.68 – 0.84]	3.12	
Random pooled ES			**0.80**	**[0.74-0.87]**	**40.63**	**98.87**
Indonesia						0.00
Herdiyanti *et al*. (2019)	163	161	0.99	[0.96 – 1.00]	3.13	0
Iran						0.00
Amin *et al*. (2009)	553	527	0.95	[0.93 – 0.97]	3.13	
Ali *et al*. (2014)	379	353	0.93	[0.90– 0.95]	3.13	
Mirsoleymani *et al*. (2014)	1209	1125	0.93	[0.91 – 0.94]	3.13	
Pouladfar *et al*. (2017)	202	195	0.97	[0.93– 0.99]	3.13	
Fallah *et al*. (2008)	50	34	0.68	[0.53 – 0.80]	3.10	
Mihankhah *et al*. (2017)	3798	497	0.13	[0.12-0.14]	3.13	
Mirzarazi *et al*. (2013)	702	203	0.29	[0.26 – 0.32]	3.13	
Rezaee and Abdinia (2015)	19223	47	0	[0.001 – 0.003]	3.13	
Random pooled ES			**0.61**	**[0.27-0.95]**	**25.02**	**99.98**
Iraq						0.00
Al- Jebouri and Al- Alwani (2015)	100	38	0.38	[0.28 – 0.48]	3.11	0
Oman						0.00
Khalid *et al*. (2018)	4480	846	0.43	[0.40 – 0.47]	3.13	0
Pakistan						0.00
Zareef *et al*. (2014)	2374	524	0.22	[0.20-0.24]	3.13	0
Saudi Arabia						0.00
Al- Mijall *et al* (2017)	116	92	0.79	[0.71 – 0.86]	3.12	0
Overall Random Pooled ES			**0.71**	**[0.50 – 0.92]**	**100**	**99.98**

The focus of this review lies in the antimicrobial profile of the organism isolated. Different populations were selected for this review because we observed that antibiotic resistance for organism isolated from UTIs in CKD patients was present. Antimicrobial resistance in UTIs is becoming more common globally, increases morbidity and double healthcare costs. In most of the studies, Gram-ve organisms accounted for over 90% of the isolates, with *E.coli* predominating. Among isolates of E.coli from patients with renal problems, resistance was more common compared to community isolates. Based on the results of our findings, most of the uropathogens were showing resistance to antibiotics up to some extent. Overall, there were significantly more resistant to most antibiotics in Southeast Asian Region, Western Pacific Region, East Mediterranean Region. Based on the results of our study, Nitrofurantoin, Imipenem, Meropenem, Ertapenem, Aztreonam and Amikacin should be considered for first line empiric treatment of UTIs in CKD patients. Details are shown in **Table 3**.

Table 3. Antibiotic resistance among different countries.

Antibiotic	Bangladesh	China	India	Iran	Iraq	Nepal	Pakistan	Saudi Arabia
Amoxicillin	79.83% - 95.41% [22, 24, 27]	N/A	91.1% [52]	71.4% [68]	100% [73]	N/A	N/A	98.90% [88]
Ampicillin	N/A	N/A	>80-92% [41, 55]	81.20%-96.49% [64, 66]	100% [73]	71.90%-85% [78, 79]	84% [87]	98.90% [88]
Cefuroxime	70.39%-100% [20, 24]	96.6% [35]	13.17% [38]	N/A	N/A	N/A	N/A	N/A

Ceftriaxone	10.78%-83.3% [24, 26]	N/A	68%-84.7% [41, 54]	9.50%-87% [63, 72]	25%-40% [73, 74]	26.3% [79]	51%-81% [84, 86]	N/A
Cefixime	47%-100% [21, 24]	N/A	22%-77.9% [40, 52]	72.2% [65]	N/A	40% [79]	55%-83% [84, 86]	N/A
Ceftazidime	50%-87% [19, 21]	81.8% [35]	62%-71.61% [39, 90]	N/A	N/A	25% [74]	65%-78.8% [84, 91]	N/A
Cefepime	30% [21]	84.1% [35]	68% [41, 42]	N/A	N/A	N/A	8.3% [2]	96.70% [88]
Cefotaxime	52% [21]	N/A	10.4%-87.1% [42, 54]	58.6%-89% [65, 72]	33.40% [74]	75% [79]	N/A	N/A
Cephalexin	89.22% [20]	N/A	47%-58% [45, 56]	50.88% [64]	N/A	59.3% [79]	95% [87]	N/A
Cefradine	67.22%-90.45% [24, 27]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Cefazolin	N/A	96.6% [35]	14.72%-100% [38, 49]	53.6% [68]	79.7% [57]	N/A	N/A	N/A
Nalidixic acid	65.67%-91.53% [20, 27]	N/A	78%->95% [41, 42, 55]	7.6%-63% [64, 65]	N/A	N/A	37.50%-91% [85, 87]	N/A
Sparfloxacin	N/A	N/A	11%-75% [53, 56]	N/A	N/A	N/A	N/A	N/A
Ofloxacin	N/A	N/A	16%-75% [53, 56]	21.7% [65]	N/A	82% [79]	N/A	N/A
Norfloxacin	N/A	N/A	20%-90.6% [37, 54]	N/A	N/A	25.9% [79]	12.39% [85]	N/A
Levofloxacin	28.3%-59% [19, 21, 23]	N/A	25.16%-100% [49, 57]	N/A	33.40% [74]	N/A	12.39% [85]	63.23% [88]
Ciprofloxacin	38%-85.78% [20, 21]	N/A	14%-100% [40, 49]	0%-58% [63, 70]	33.40%-65% [73, 74]	25% [79]	12.39%-87.5% [2, 85]	62.64% [88]
Amikacin	1%-69% [19-21]	28.4% [35]	0%-41.7% [40, 54]	6.1%-55% [64, 72]	16.60%-23.30% [73, 74]	3%-8% [76, 79]	12%-91% [86, 87]	1.10% [88]
Gentamicin	9%-79% [19, 21]	N/A	4%-59.6% [40, 54]	8.43%-62% [69]	51.40%-66.40% [73, 74]	9.4%-28% [79]	19.28%-44% [83, 85]	N/A
Tobramycin	N/A	N/A	29.2% [52]	0% [63, 65]	16.60% [73, 74]	N/A	N/A	N/A
Kanamycin	N/A	N/A	13.9% [42]	0% [63]	50% [73]	N/A	N/A	N/A
Azithromycin	6.76%-77% [19, 26]	N/A	36.3% [52]	N/A	N/A	N/A	N/A	N/A
Erythromycin	83.33% [24]	N/A	N/A	N/A	N/A	N/A	70% [85]	N/A
Doxycycline	9.46% [26]	N/A	N/A	73.8% [63]	N/A	N/A	70% [85]	N/A
Fosfomycin	N/A	N/A	1% [41]	N/A	N/A	N/A	10% [87]	N/A
Polymyxin-B	0% [25]	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Nitrofurantoin	2%-53% [19, 21]	N/A	2%-25% [40, 54]	11%-24.5% [70, 72]	54% [73]	5.9%-24.5% [78, 79]	N/A	N/A

Vancomycin	N/A	N/A	0% [54]	N/A	N/A	N/A	0% [85]	N/A
Chloramphenicol	N/A	N/A	6% [56]	N/A	N/A	N/A	N/A	N/A
Imipenem	1.14%-38.5% [22, 24]	N/A	0%-39% [39, 49]	0.9%-9.9% [66, 69]	0%-10.3% [57]	N/A	3%-24% [83, 87]	1.10% [88]
Meropenem	2%-40% [21, 22]	28.4% [35]	7.84%-62.7% [54, 57]	N/A	5.1% [57]	N/A	0%-25% [84, 86]	1.10% [88]
Ertapenem	N/A	N/A	N/A	N/A	11.3% [57]	N/A	N/A	1.10% [88]
Aztreonam	N/A	N/A	11%-100% [38, 49]	N/A	N/A	N/A	54%-72% [86, 87]	98.90% [88]
Amoxicillin-clavulanic acid	31% [21]	N/A	74.4%->80% [55, 58]	N/A	66.40%-77.5% [57, 74]	N/A	38%-84% [82, 87]	N/A
Piperacillin-tazobactam	N/A	N/A	12.80%-50% [49, 54]	N/A	N/A	N/A	6.70% [86]	N/A
Cefoperazone-sulbactam	N/A	N/A	5%-22% [43, 49]	N/A	N/A	N/A	3%-8.6% [85, 86]	N/A
Co-trimoxazole	58%-98% [19, 25]	70.5% [35]	19.37%-100% [38, 51]	36.84%-83.3% [64, 68]	N/A	45.20%-48.9% [78, 79]	44%-66% [82, 85]	N/A

This systematic review is perhaps the first systematic assessment to assess the incidence of urinary tract infections (UTIs) among kidney failure patients. UTIs are considered a risk factor in chronic kidney disease, hypertensive, and kidney failure patients. Kidney parenchyma involves symptomatic Urinary tract infections which lead to kidney scarring [19]. Results of this study have shown that the prevalence of urinary tract infections (was 55.6% to 18% in kidney failure patients. Among chronic kidney disease patients, 82% were confirmed to have upper urinary tract infections, and 18% were found to have lower urinary tract infections [60]. It is found that the most common microorganism in infected urinary tract patients was E. coli 24% [62].

Hsiao *et al*. discovered that regardless of sex, Escherichia coli was the bacterium that had infected half of the patients [7]. Escherichia coli is the most contagious bacteria found in UTI patients; thus, it is not surprising that it infected 50% of CKD patients. Muntaha *et al*. found that the incidence of urinary tract infections due to E. coli was 72.26% in children [82]. If it is not treated in childhood may cause kidneys carrying to kidney failure. Urinary tract infections are common bacterial infections found in kidney disease patients and the prevalence of Urinary tract infections was higher in females (40.40%) than in males (27.52%) [80]. UTIs were seen in 21.3% of cases i.e., 1.2% of chronic kidney disease patients [77]. In 8.8% of kidney failure patients, urinary tract infections were found [36]. The kidney, ureters, and bladder are infected with urinary tract infections by a pathogenic attack on the urinary tract. Antibiotic resistance among urinary tract pathogens is increasing at an alarming rate [25, 39]. *E. coli* was the most common bacteria in infected urinary tract patients [39]. Based on our findings, Imipenem, Meropenem, Amikacin, Gentamicin, Nitrofurantoin, Polymyxin B, Ceftriaxone, Levofloxacin, And Ciprofloxacin remain the drug of choice for the treatment of urinary tract infections in 9 studies, which were conducted in Bangladesh [19-25].

Meropenem, amikacin, and tigecycline consider effective in urinary tract infections in 1 study in China [35]. Amikacin, Kanamycin, Gentamicin, Nitrofurantoin, Piperacillin-Tazobactam, Cefoperazone-Sulbactam, Imipenem, Netilmicin, Tobramycin, Vancomycin, Chloramphenicol, Ciprofloxacin, Sparfloxacin, Ofloxacin, Norfloxacin, and Fosfomycin are suitable for the treatment of urinary tract infections Indian studies [1, 38, 40, 42-44, 47-50, 52, 54, 55, 57, 58, 62, 90]. Amikacin, meropenem, and nitrofurantoin consider more susceptible to uropathogens, which was conducted in Indonesia [62]. Amikacin, Kanamycin, Gentamicin, Imipenem, Nitrofurantoin, Tobramycin, Ciprofloxacin, Ceftriaxone, Co-Trimoxazole, and Ceftazidime are used as empirical treatments of urinary tract infections in seven studies of Iran [67]. Meropenem, Imipenem, and Ertapenem are more susceptible to uropathogens and consider good empirical therapy for UTIs, which were described in 3 studies in Iraq [57, 73, 74]. Amikacin, Gentamicin, and nitrofurantoin are more effective against pathogenic bacteria, which were involved in UTIs in 2 studies in Nepal [78, 79]. Amoxicillin-clavulanic acid, Trimethoprim-sulfamethoxazole, Imipenem,

Ciprofloxacin, Meropenem, Amikacin, Tazocin, Erythromycin, Cefoperazone-sulbactam, Vancomycin, Piperacillin-tazobactam, Fosfomycin, and Cefepime are more susceptible to uropathogens and consider as good for the treatment of urinary tract infection in 7 studies, which were conducted in Pakistan [2, 3, 85-87, 91, 92]. meropenem, imipenem, ertapenem, amikacin, cefoxitin, cefepime, and aztreonam were more susceptible to uropathogens [88, 89].

This increased resistance of bacteria further limits the availability of therapeutic options for the treatment of urinary tract infections in CKD patients. Antimicrobials for urinary tract infections should be selected based on culture and sensitivity tests and must consider the latest antibiogram of a specific geographic area [20]. In addition, the implementation of antibiotic stewardship programs should be considered to promote the appropriate selection of empirical antibiotic therapy regimen, dose, duration of therapy, and route of administration to optimize therapy, reduce the cost of treatment, improve clinical outcomes, and reduce the development of microbial resistance [93].

In developing countries, chronic kidney disease (CKD) is a major public health problem that needs to be addressed. Weakened immunity, anemia, malnutrition, inflammation, vitamin deficiencies, and poor quality of life are the consequences of chronic kidney disease. Patients undergoing long-term hemodialysis have weakened immune systems and are more susceptible to infections such as urinary tract infections. (UTIs). Research on urinary tract infections in people with chronic kidney disease is quite rare. Due to persistent inflammation, the immune system of people with CKD is weakened, making them more susceptible to infection. The fact that these germs were at least resistant to two maybe more categories of antibiotics is concerning. This highlights the urgent need to develop a consistent empirical antibiotic strategy for improved clinical care and outcomes for people with UTI in the CKD group.

The increased rates of antimicrobial resistance among patients with CKD are due to COVID-19. The rates of bacterial co-infection and death have been greatly surpassed by COVID-19 infections [94, 95]. In COVID-19 patients who were admitted to healthcare settings and intensive care units, bacterial co-infections appear to be uncommon in this group of patients, a rise in the usage of empirical antibiotics has been noted. Unfortunately, their broad usage may result in the evolution of organisms that are resistant to many drugs, which would diminish the effectiveness of the most powerful antibiotics. Limitations of this review include the exclusion of publications, which were not in English because of the lack of funding, and the fact that only observational studies were included in this review. Our reliance was on pre-public data. Therefore, we are not able to judge the clinical situation, improvement, and follow-up data. Unreported comorbidities among patients in the study could have contributed to the higher risk of infections among CKD patients. High heterogeneity among the studies can be another issue, which should be kept into consideration while interpreting the results. Research is recommended to focus on evaluating and monitoring antibiotic resistance profiles to develop new antibiotics and prevent infections and epidemics in this high-risk population.

Conclusion

The incidence of UTIs was 55.6% to 18% of kidney disease patients. Regular monitoring and routine surveillance studies should be conducted to provide perfect knowledge about the empirical treatment of urinary tract infections due to E. coli pathogen and in CKD patients.

Suggestion

Hence, further research is encouraged to focus on assessing and monitoring resistance profile of antibiotics for development of new antibiotics to prevent infection and outbreaks in this high-risk population.

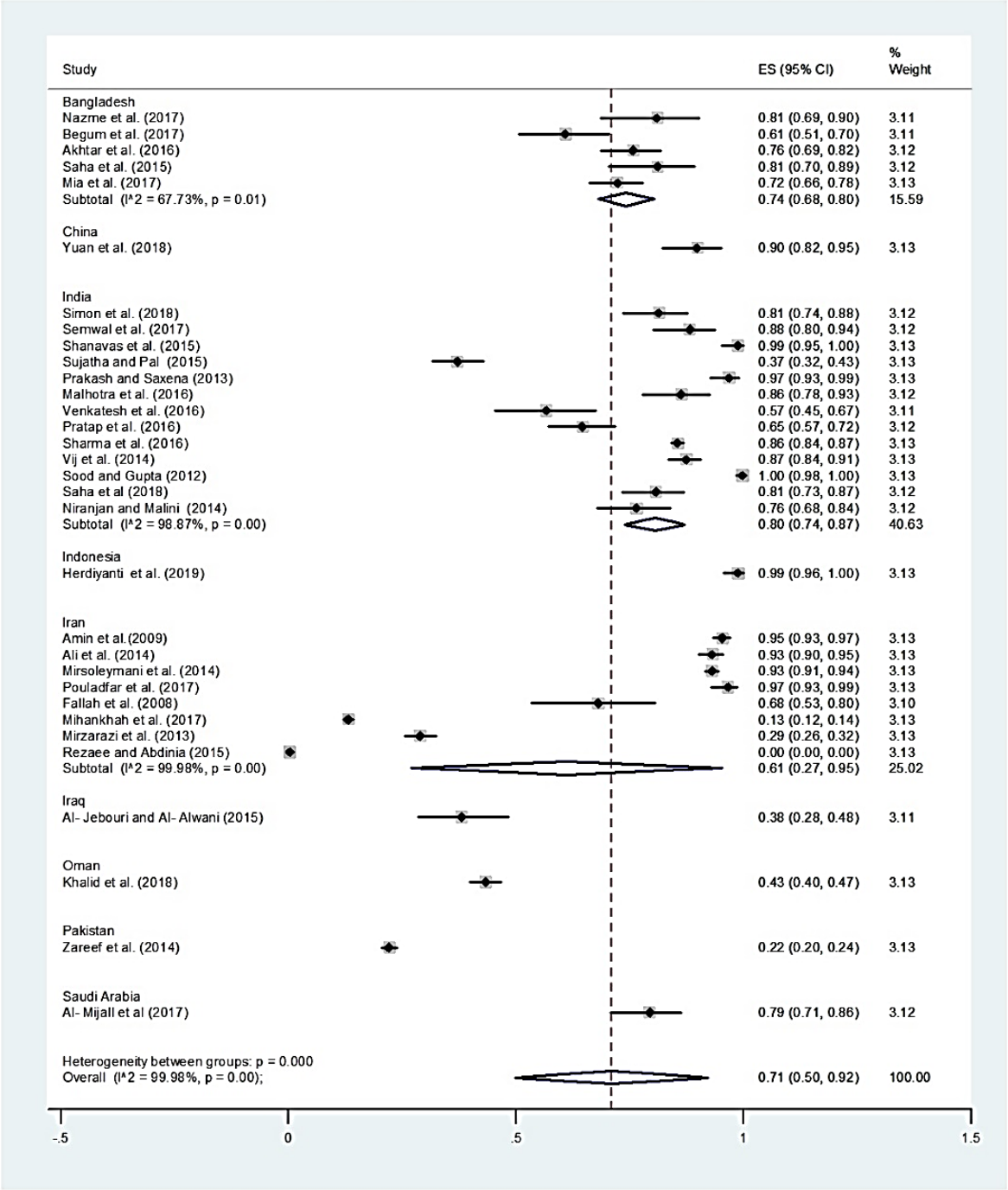

Figure 2. Forest Plot of the Included Studies for Meta-analysis.

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