Microbiology

High Mortality Risk in Chronic Kidney Disease and End Stage Kidney Disease Patients with Clostridium Difficile Infection: A Systematic Review and Meta-analysis

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Background: The objective of this systematic review and meta-analysis was to evaluate the mortality risk in patients with chronic kidney diseases (CKD) and end stage renal disease (ESRD) requiring dialysis with *Clostridium difficile* infection (CDI). Methods: A literature search was performed from inception through February 2015. Studies that reported relative risks, odds ratios, or hazard ratios comparing the mortality risk of CKD or ESRD patients with CDI versus those without CDI were included. Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using a random-effect, generic inverse variance method. Results: Four cohort studies with 8,214,676 patients were included in the meta-analysis. Pooled RR of mortality in CKD patients with CDI was 1.73 (95% CI 1.39–2.15). When meta-analysis was limited only to included studies with ESRD patients, the pooled RR of mortality in patients with ESRD was 2.15 (95% CI, 2.07-2.23). Conclusion: This meta-analysis demonstrates significantly increased risks of mortality in CKD and ESRD patients with CDI. The magnitudes of mortality risk are high. *Journal of Nature and Science, 1(4):e85, 2015*

clostridium difficile | clostridium difficile-associated colitis | Clostridium Difficile Infection | chronic kidney disease | end stage kidney disease | Meta-analysis

Introduction

Clostridium difficile infection (CDI), caused by a gram-positive, spore-forming anaerobic bacillus, is the leading cause of health care–associated diarrhea [1-3]. Over North America and Europe, there has been a marked increase in CDI incidence during the last decade [4-8]. Moreover, CDI is also independently associated with increased mortality, morbidity, resource utilization. During 2007 to 2008, the reported age-adjusted mortality rate for CDI in the United States increased from 2.0 deaths per 100 000 population to 2.3 deaths per 100 000 population, expressing a 15% increase [4,9]. Known risk factors for CDI include antibiotic use, advanced age, hospitalization, severe illness, gastric acid suppression, and immunosuppression[10].

Chronic kidney disease (CKD) is a prevalent problem worldwide estimated at 8-16% [11-13]. In addition, the prevalence of patients with end-stage renal disease (ESRD) is also increasing [14]. As of 2011, the number of patients registered in the ESRD Medicare-funded program in the United States has increased from nearly 10,000 beneficiaries in 1973 to 615,899 [15]. Studies have demonstrated the associations between both CDI/recurrent CDI and CKD[10]. Recently, studies have demonstrated a high incidence of CDI in CKD and ESRD patients with approximately 2-fold and 2.5-fold increased risks compared to patients without CKD or ESRD [16,17]. Moreover, when patients with CKD or ESRD develop CDI, they encounter high in-hospital mortality, approximately 6.62% and 13.2% in CKD and ESRD, respectively [17,18]. In order to identify the effective interventions to reduce the incidence of CDI, the data regarding the magnitude of increased mortality risk in CKD and ESRD patients with CDI are needed. These reported risks, however, are still conflicting. Thus, we conducted this systematic review and meta-analysis to assess the mortality risk of CKD and ESRD patients with CDI.

Materials and methods

Search Strategy

Two investigators (WC and CT) independently searched published studies and conference abstracts indexed in EMBASE, MEDLINE and the Cochrane database from inception to February, 2015 using the search strategy described in Table 1. A manual search for additional relevant studies using references from retrieved articles was also performed.

Inclusion Criteria

The inclusion criteria were as follows: (1) randomized controlled trials (RCTs) or observational studies (case-control, cross-sectional or cohort studies) published as original studies or conference abstracts that evaluated the risk of mortality in CKD or ESRD patients with CDI, (2) studies that provided data to calculate odds ratios (ORs), relative risks, hazard ratios or standardized incidence ratios with 95% confidence intervals (CIs), and (3) a reference group composed of patients without CDI.

Study eligibility was independently determined by the 2 investigators noted previously. Differing decisions were resolved by mutual consensus. The quality of each study was evaluated by using the Jadad quality-assessment scale [19] for RCTs and the Newcastle-Ottawa quality assessment scale [20] for observational studies.

Data Extraction

A standardized data collection form was used to extract the following information: last name of first author, country of origin, study design, year of publication, sample size, definition of CDI, method used to diagnose CDI, definition of CKD and ESRD, confounder adjustment, and adjusted effect estimate with 95% CI.

Statistical Analysis

Review Manager 5.2 software (The Cochrane Collaboration, Oxford, UK) was used for data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird [21]. Given the high likelihood of between study variances, a random-effect model was used rather than a fixed-effect model. Statistical heterogeneity was assessed using Cochran's Q test. This statistic was complemented with the I^2 statistic, which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. An I^2 of 0%–25% represents insignificant heterogeneity, 26%–50% low heterogeneity, 51%–75% moderate heterogeneity and >75% high heterogeneity [22,23]. The presence of publication bias was assessed by funnel plots of the logarithm of odds ratios vs their standard errors [24].

Conflict of interest: No conflicts declared.

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Table 1. Search Strategy

Database: Embase (1988 to February 2015), MEDLINE (1946 to February 2015), Cochrane Database of Systematic Reviews (2005 to February 2015), Cochrane Central Register of Controlled Trials (2005 to February 2015)
1. exp clostridium/ 2. clostridium$.mp. 3. exp clostridium difficile/ 4. clostridium$.mp. 5. difficile$.mp. 6. exp clostridium difficile/ 7. clostridium difficile$.mp. 8. c difficile$.mp. 9. Or/1-8 10. exp Kidney Disease/ 11. exp Kidney Failure/ 12. exp Chronic Kidney Failure/ 13. exp hemodialysis/ 14. (hemodialysis or haemodialysis).tw. 15. dialysis.tw. 16. (CAPD or CCPD or APD).tw. 17. predialysis.tw. 18. (chronic renal or chronic kidney).tw. 19. exp kidney function tests/ or exp glomerular filtration rate/ 20. exp creatinine/ 21. or/10-20 22. 9 and 21 23. limit 22 to "all adult (19 plus years)" 24. limit 23 to humans

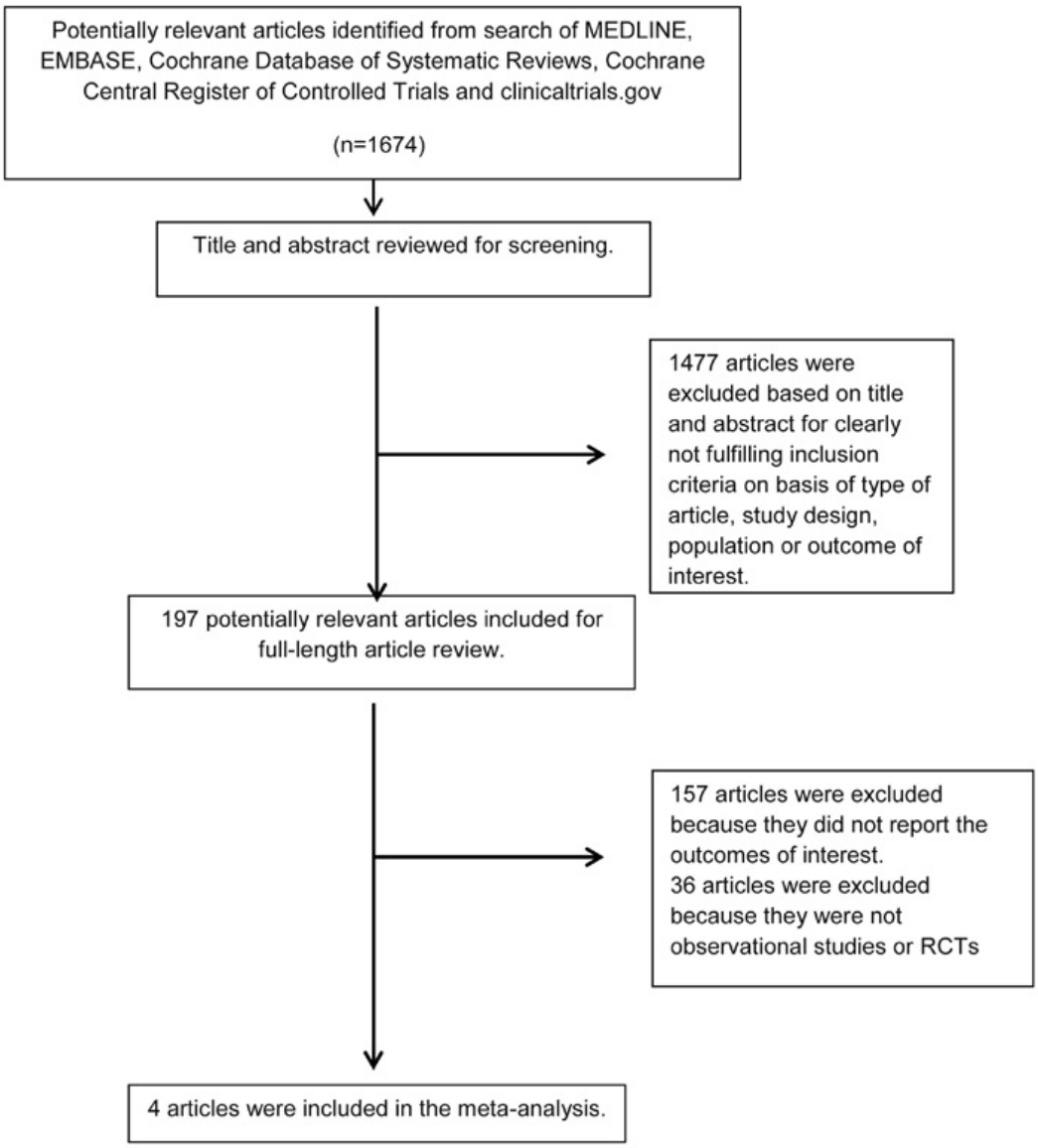

Figure 1. Outline of our search methodology.

Table 2: Main characteristics of the studies included in this meta-analysis

	Barany et al [25]	Sheth et al[26]	Pant et al [18]	Keddis et al [17]
Country	Sweden	USA	USA	USA
Study design	Cohort study	Cohort study	Cohort study	Cohort study
Year	1992	2010	2012	2012
Total number	210	327	184139	8.03 million
Patient sample	Patient in nephrology ward at a single center; 89% were on dialysis (HD or PD)	Outpatient dialysis patients (HD or PD)	Hospitalized patients with a discharge diagnosis of ESRD (ICD-9-CM 585.6) from the US Nationwide Inpatient Sample database	Hospitalized patients with a ICD-9-CM of chronic kidney disease (585.1-585.6 and 585.9) from the National Hospital Discharge Survey database with
CDI definition	Positive stool culture and /or cytotoxin assay for C. difficile	Medical record review of patients with positive toxin for C. difficile	ICD-9-CM 008.45	ICD-9-CM 008.45
Outcome definition	5-year mortality	Mortality	In-hospital mortality	In-hospital mortality
Adjusted OR or relative risk	1.38 (1.17-1.62)	1.97 (1.22-3.19)	2.15 (2.07-2.24)	1.61 (1.58-1.65)
Confounder adjusted	Age-matched control of dialysis patients during the same study period	None	Age, sex, race, insurance status, geographic location, pneumonia, UTI, BSI and Charlson comorbidity index	Sex, diagnosis of cardiovascular disease, peripheral vascular disease, diabetes and its complications, hypotension-associated complication, liver disease, and obesity
Quality assessment (Newcastle-Ottawa scale)	Selection:3 Comparability: 1 Outcome: 2	Selection:3 Comparability: 0 Outcome: 2	Selection:4 Comparability: 2 Outcome: 3	Selection:4 Comparability: 2 Outcome: 3

Abbreviations: CDI, *Clostridium difficile* infection; HD, hemodialysis; ICD-9-CM, the International Classification of Disease, Ninth Revision, Clinical modification; PD, peritoneal dialysis.

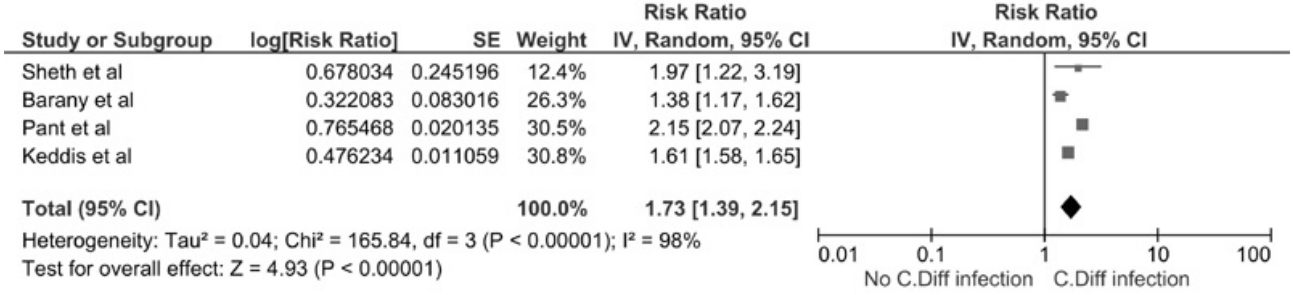

Figure 2. Forest plot of the all included studies comparing the mortality risk in CKD patients with CDI vs. without CDI; square data markers represent risk ratios (RRs); horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest; IV = inverse variance.

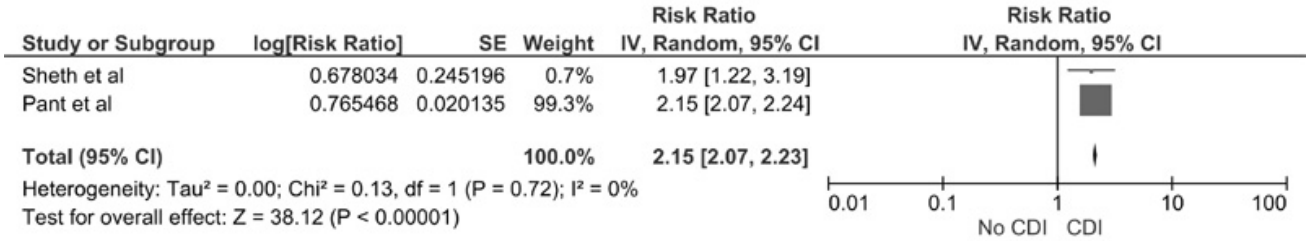

Figure 3. Forest plot of the all included studies comparing the mortality risk in ESRD patients with CDI vs. without CDI; square data markers represent risk ratios (RRs); horizontal lines, the 95% CIs with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest. IV = inverse variance.

Results

The search strategy yielded 1674 potentially relevant articles: 1477 were excluded based on the title and abstract indicating that they clearly did not fulfill inclusion criteria on the basis of article type, study design, population, or outcome of interest (Figure 1). The remaining 197 articles underwent full-length review, with 193 excluded because they did not report outcomes of interest (n=157) or were not RCTs or observational studies (n=36). Four cohort studies met our inclusion criteria [17,18,25,26] with a total of 8,214,676 patients were included in this analysis regarding the mortality risk of CKD or ESRD patients with CDI. Table 2 contains detailed characteristics and quality assessment of all included studies.

The Risk of Mortality in Chronic Kidney Disease and End Stage Kidney Disease Patients with *Clostridium Difficile* Infection

The pooled risk ratio (RR) of mortality in CKD patients with CDI was 1.73 (95% CI 1.39–2.15, I^2 =98%) (Figure 2). The mortality risk of CKD patients with CDI remained significant in a sensitivity analysis that included only studies that adjusted for potential confounders [17,18,25] with a pooled RR of 1.70 (95% CI, 1.34-2.15, I^2 =99%). The pooled risk ratio (RR) of mortality in ESRD patients with CDI was 2.15 (95% CI, 2.07–2.23) (Figure 3). There was no significant statistical heterogeneity with an I^2 of 0%.

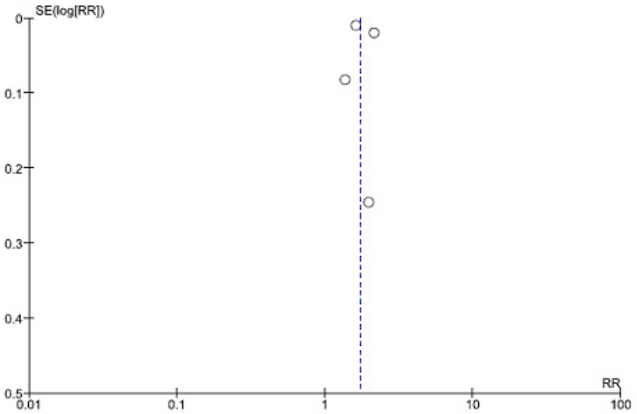

Figure 4: Funnel plot of studies included in the meta-analysis for the mortality risk in CKD patients with CDI vs. without CDI. The graph is slight asymmetric and suggests the presence of publication in favor of positive studies. RR = risk ratio, SE = standard error.

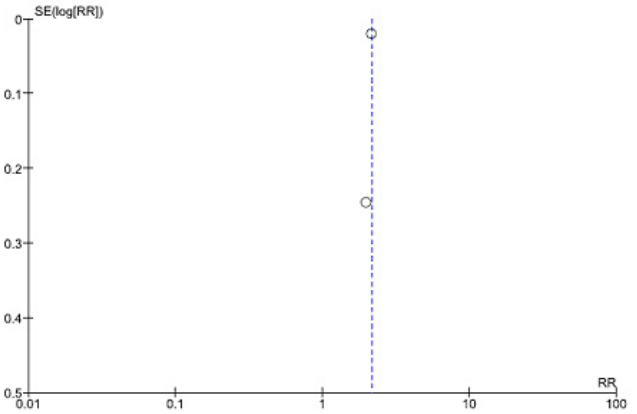

Figure 5: Funnel plot of studies included in the meta-analysis for the mortality risk in ESRD patients with CDI vs. without CDI. The graph is slight asymmetric and suggests the presence of publication in favor of positive studies. RR = risk ratio, SE = standard error.

Evaluation for Publication Bias

Funnel plots to evaluate publication bias for the risk of mortality in CKD and ESRD patients with CDI are summarized in Figure 4 and Figure 5, respectively. The graphs for assessing publication bias are asymmetric and suggest no significant publication bias.

Discussions

Our meta-analysis demonstrated significant increased risks of mortality in both CKD and ESRD patients with CDI, with 1.73-fold and 2.15-fold increased risks, respectively. These findings suggest high magnitude of mortality in both CKD and ESRD patients with CDI compared to those without CDI.

The underlying explanation for the increased mortality risk in CKD and ESRD patients with CDI is likely due to impaired immune system function to fight against infection in these patient populations [27,28]. Moreover, when these CKD and ESRD patients have encountered CDI, they have higher risk of developing adverse outcomes and complications from CDI such as the need for colectomy [17]. In CKD patients, CDI is also a risk factor for acute kidney injury [16]. Moreover the studies have shown higher morbidities and lengths of hospital stay in CKD and ESRD patients with CDI [17,18,25,26], which may result in subsequent long-term mortality [29].

Although all included studies were of moderate to high quality, there are some limitations. First, although the meta-analysis of cohort studies with confounder adjusted analysis helps limit potential bias; all included studies were observational studies. Thus, our meta-analysis can demonstrate an association but not a causal relationship. Second, there are statistical heterogeneities in the complete analysis in CKD patients with CDI. The potential sources of these heterogeneities include the differences in the diagnosis methodology of CDI, definitions of CKD, and the differences in confounder adjusted methods. Unfortunately, the available data were limited and prevented us from further investigation for potential sources of heterogeneities. Lastly, although most included studies defined mortality as in-hospital mortality, the data on specific cause were limited.

In summary, this study shows a statistically significant increase in the mortality risk of CKD and ESRD patients with CDI. The mortality risk is higher in ESRD patients with CDI. Clinicians should raise awareness of this significant mortality and these patients with CKD and ESRD need careful monitoring to lower the mortality risk. We should emphasize the measures to control and prevent CDI as part of the infection control programs, including monitor CDI rates and antibiotic stewardship especially in hemodialysis units. In addition, future studies are needed to reduce the incidence of CDI especially in these patient populations.

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Conflict of interest statement for all authors

We do not have any financial or non-financial potential conflicts of interest.

Authors' contributions

All authors had access to the data and a role in writing the manuscript.

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