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Article

Risk Factors for Healthcare-Associated *Clostridioides difficile* Infection: A Systematic Review

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Abstract: Objectives: This systematic review sought to identify and synthesize the key patient-related, clinical and healthcare-associated risk factors for Clostridioides difficile infection (CDI), with a special interest in recurrent CDI. Methods: A systematic literature search identified studies investigating risk factors for CDI and recurrent CDI. The study consisted of twenty studies published from 2012 to 2025. Study characteristics, demographic factors, comorbidities, underlying diseases, healthcare exposures and CDI recurrence/recurrence were extracted and compared between different studies. Results: The study revealed that CDI is associated with several interdependent risk factors like older age, prior CDI, other hospitalization and intensive care unit admission (ICU), severe underlying disease and immunosuppression were the factors most commonly associated with an increased risk. Notable associations were also seen with malignancy, hematological malignancy, inflammatory bowel disease, chronic kidney disease, gastrointestinal disease, diabetes mellitus, cardiovascular disease, chronic pulmonary disease and chronic liver diseases. Recent surgery, chemotherapy, haematopoietic stem-cell transplantation, corticosteroid therapy, immunomodulatory treatment and renal replacement therapy were also identified as potential contributors. Previous CDI was most closely linked to recurrence, underscoring need for post-infection monitoring and preventive measures. Conclusions: The multifactorial etiology of CDI demonstrated in this systematic review reinforces the importance of patient susceptibility, disease, healthcare exposure, and prior infection. Advanced age, previous CDI, prolonged hospitalization, severe illness by the APACHE II score, immunosuppressive states malignancy and inflammatory bowel disease are relevant candidates for stratification of risk.

Keywords: Meta-Analysis, Risk Factors, Clostridioides difficile, CDI

Introduction

Clostridioides difficile infection (CDI) is a prominent healthcare-associated infection, which continues to be an important cause of morbidity, extended hospitalization, health care cost burden and mortality on global scale [1]. The clinical spectrum varies from mild diarrhea to fulminant colitis, toxic megacolon, sepsis and death. While CDI can occur in the community, healthcare exposure is particularly important since hospitalized patients often have other multiple predisposing factors,

notably antimicrobial exposure together with dysbiosis of the intestinal microbiota, advanced age, severe underlying disease and prolonged contact with contaminated healthcare environments [2]. Transmission in hospitals and other healthcare facilities is aided by the ability of C. difficile to form spores able to survive in the environment for long periods making prevention and early identification of high-risk patients an important part of infection-control programs [3].

Substantial evolutionary changes to the epidemiology of CDI occurred over the last few decades. The complexity of the continuing burden of disease is due to increased vulnerability among healthcare populations, environmental spread and use of antimicrobial agents, changes in diagnostic practices, and re-emergence and circulation of new virulence strains (Di Bella et al., 2024). Of particular concern is healthcare-associated CDI, which is associated with prolonged hospitalization, greater utilization of healthcare resources, and increased mortality. Moreover, CDI frequently occurs in patients with pre-existing comorbidities, making it challenging to disentangle the independent contribution of individual risk factors from the overall burden of underlying disease [4]. Therefore, identifying both modifiable and non-modifiable predictors of healthcare-associated CDI remains essential for improving risk stratification, informing targeted prevention strategies, and reducing the burden of infection [5].

Antimicrobial exposure remains a major modifiable risk factor for CDI (as well as other infections). Antibiotics alter the established intestinal microbiota, decreasing colonization resistance and permitting overgrowth of toxigenic C. difficile . However, the size of risk differs widely by class, spectrum, length, and cumulative exposure to antimicrobials [6]. Slimings and Riley performed a systematic review and meta-analysis to explore this association, illustrating significant associations between healthcare facility-associated CDI and multiple antibiotic classes; they recommended that antimicrobial stewardship be viewed as an integral part of CDI prevention. The importance of this evidence lies in the fact that antibiotic exposure is a potentially modifiable risk factor at the time of prescribing, with significant opportunity for reduction in risk through selection, dosing and duration of therapy [7].

Several medication-related and patient-related factors beyond antibiotics have been proposed to be involved in CDI susceptibility. Acid-suppressive therapy, especially with proton pump inhibitors and histamine-2 receptor antagonists, may lower host defenses by interrupting acidic barriers to intestinal colonization. Also, among reported risk factors are previous hospitalization, extended healthcare exposure and older age as well as immunosuppression, malignant condition, renal disease, diabetes mellitus and severe underlying illness [8]. Even more importantly, they can also interact with one another rather than work independently. As an example, older inpatients often have multiple comorbidities and higher rates of exposure to antibiotics and invasive medical procedures which can create a synergistic risk that may not be adequately captured by assessing individual variables alone.

These associations have been further substantiated by recent evidence. Finally, a 2024 systematic literature review of risk factors for CDI in studies conducted in the United States identified a large number of patient-, treatment- and health care-related characteristics associated with CDI while describing considerable variability in timing to or definitions of exposures. In a similar vein, a recent meta-analysis of 40 studies examining approximately 3·9 million patients determined gastric acid suppression, recent hospitalization, antibiotic exposure and a number of comorbidities to be independent risk factors for healthcare-associated CDI. These findings emphasize the multifactorial nature of CDI risk and support the consideration of both modifiable exposures and patient-specific vulnerability during this stratification process [9].

Variability across individual studies in terms of study population, healthcare setting, definitions of healthcare-associated CDI, exposure window, adjustment for confounders and methods used to ascertain risk factors has led to inconsistent findings. Moreover, previous systematic reviews might be out of date due to several important changes in antimicrobial prescribing or diagnostic practices, infection-control strategies and health care populations since their respective publication dates. Thus, an updated synthesis of the evidence is needed to clarify which factors are consistently associated with healthcare-associated CDI and to differentiate potentially modifiable risk factors from markers of underlying disease.

Thus, this systematic review is to thoroughly assess the demographic Clinical and pharmacological and healthcare-associated risk factors for healthcare-associated C. difficile infection. This review could strengthen the evidence base for risk stratification, antimicrobial stewardship and targeted infection-prevention interventions and future research by synthesizing current evidence and identifying robust determinants that can be interpreted consistently across studies [10]. Furthermore, characterizing sufficiently homogeneous risk factors and effect estimates may enable quantitative meta-analysis and help assess the size and direction of individual associations with healthcare-associated CDI.

Materials and Methods

Search strategy and study selection

Systematic literature search systems such as PubMed/MEDLINE, Scopus, Web of Science, Embase and Cochrane Library for studies investigating some risk factors associated with Clostridioides difficile infection (CDI) and recurrent CDI. The search spanned studies published from the inception of each database to 2025 and utilized combinations of keywords like: Clostridioides difficile, CD, CDI, recurrent CDI, risk factors, comorbidities hospitalization and relevant clinical condition. We manually screened the reference lists of eligible studies and relevant reviews for other studies. The imported records are stored in a reference–management database, which also facilitates duplicates removal from the dataset.

Inclusion and Exclusion Criteria

Potentially eligible articles were assessed for eligibility by screening the titles and abstracts followed by full-text evaluation. Eligible studies were original human studies that examined one or more demographic, comorbid, clinical, or health care-related factors associated with CDI or recurrent CDI and contained adequate detail on study population and characteristics. We included studies from all geographical locations and health settings. The exclusion was for case reports, small case series, experimental or in-vitro studies, conference abstracts with inadequate data, reviews, editorials and letters to the editor as well as studies on factors not linked to CDI risk.

Data extraction and synthesis

Data extraction was performed with a pre-defined data-extraction form. Data extracted included first author, publication year, country, study design, sample size, age or mean/median age (years), gender distribution and recurrent CDI status. The information regarding possible risk factors was also extracted, such as: comorbid diseases (including underlying medical condition), immunosuppression, malignancy, inflammatory bowel disease (IBD), cardiovascular disease (CVD), renal disease, gastrointestinal illness, hospitalization within 90 days before the event or during the same day of the event occurrence and/or ICU admission at presentation; recent surgery or transplantation; chemotherapy; corticosteroid therapy for a month or paging line subsequent to outbreak initiation; use of other reported clinical or healthcare-related factors. The data were summarized in descriptive tables to find the most frequently reported as well as consistently linked predictors of both CDI as well as recurrent CDI.

Data Analysis

Due to considerable heterogeneity between included studies in terms of study design, populations, clinical settings, definitions of CDI and reporting of risk factors the results were synthesized qualitatively rather than through quantitative pooling of effect estimates. Thus, it was not pooling or the main base for synthesis on odds ratios, risk ratios, hazard ratios and confidence intervals. Aggregated evidence was taken to interpret the direction and certainty of effect based on agreement and frequency of recognition (i.e., low, moderate, or high) for each risk factor across the included studies.

Results

This flow chart is based on the PRISMA-guided identification and selection of studies. Out of a total of 213 records that were identified initially (both from database and manual searches), duplicates removal left 142 individual records. After screening titles and abstracts, 28 articles were reviewed in full text, and ultimately, 20 studies were included in the meta-analysis (figure 1).

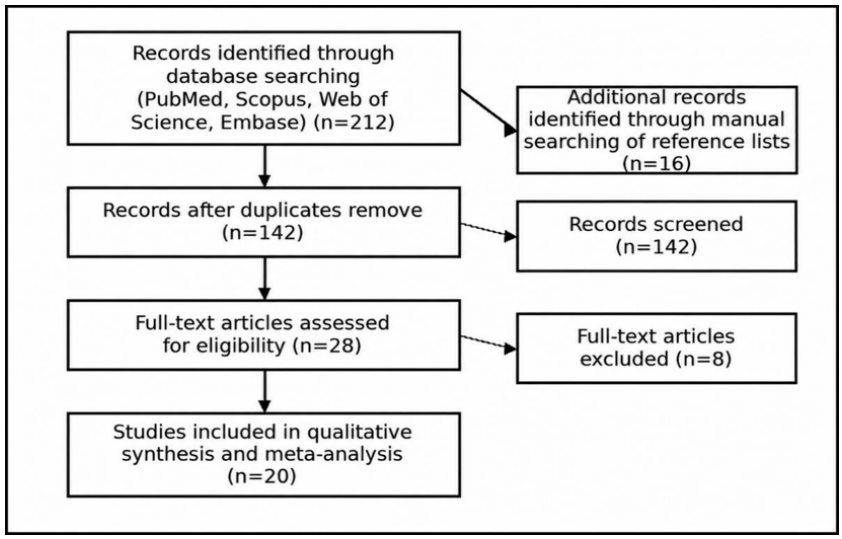

Figure 1. Flow chart for study search and selection methods

The primary characteristics of the 20 eligible studies included in the systematic review and showing high heterogeneity (in study populations, methodological designs, sample sizes and demographic characteristics) are summarized in Table 1. The majority of the studies adopted retrospective cohort/retrospective observational designs, while a small portion were prospective cohort/prospective observational and case-control [11]. The sample sizes varied considerably, from 114 to more than 13.8 million deliveries; the differences reflected unique study settings, populations and data sources. All the studies were multicentre and performed in varying countries (including USA, China, Saudi Arabia and a few European nations), thus ensuring evidence for different health systems/populations. Studies also differed greatly in the age distributions, but some examined only adults while others included upper limits of decades or specific populations such as pregnant women and hematopoietic stem cell transplant (HSCT) recipients with inflammatory bowel disease [12]. Where reported, sex distribution was generally quite balanced; however certain samples (particularly among studies including pregnant or other specialized clinical populations) were predominantly female. It is important to note that multiple studies specifically investigated recurrent CDI whereas others primarily assessed risk factors for initial or hospital-onset CDI.

Table 1. Main Characteristics of Eligible Studies indicating the antibiotic used in the studies, the sensitive bacteria and the resistance bacteria

First Author (Year)	Country	Study Design	Sample Size	Age Range (Years)	Male: Female Ratio	Recurrent CDI (Yes/No)
Enoch et al. (2020)	England	Retrospective observational	6862	19 81	NA	No
Falcone et al. (2019)	Italy	Multicenter retrospective cohort	505	19-88	53.8:46.2	Yes
Alrahmany et al. (2021)	USA	Retrospective cohort	204	≥18; median 66	46:54	Yes
Hsia et al. (2025)	Taiwan	Retrospective case-control	564	18-70	54:46	No/NR
Voth et al. (2021)	USA	Retrospective cohort	137	19–88	45:55	Yes
Nguyen et al. (2021)	USA	Retrospective cohort	98,463	≥18	NR	No
Zilberberg et al. (2014)	USA	Retrospective cohort	4,200	19–98	49:51	Yes

First Author (Year)	Country	Study Design	Sample Size	Age Range (Years)	Male: Female Ratio	Recurrent CDI (Yes/No)
Watson et al. (2018)	USA	Retrospective cohort	4587	NA	NA	Yes
Cui et al. (2019)	China	Prospective observational cohort	800	54.15±20.89	22:78	No
Xu et al. (2019)	China	Retrospective cohort	NR	NR	NR	Yes
Ran-Castillo et al. (2019)	USA	Retrospective database study	114,249	≥18	54:46	No
Aldhaif et al. (2025)	Saudi Arabia	Retrospective cohort	114	<18–>60; median 37	59:55	Yes
Carvour et al. (2019)	USA	Retrospective cohort	1092	≥18	NR	No/NR
Benitez et al. (2022)	USA	Retrospective cohort	1,253	≥18	63:37	Yes
Kwon et al. (2023)	USA	Retrospective cohort	220,444	≥18	49.5:50.5	No
Ruiter-Ligeti et al. (2018)	USA	Retrospective cohort	13,881,592 deliveries	< 25 - > 35	Female only	No
Bouza et al. (2017)	Spain	Prospective cohort	115	median 76	NR	Yes
Willems et al. (2012)	France	Retrospective cohort	407	4-59	34-66	Yes
Althaqafi et al. (2022)	Saudi Arabia	Retrospective cohort	NR	NR	NR	No
Stefansson et al. (2025)	Sweden	Retrospective cohort	231	18-84	48:52	No

Table 2 provides a summary of all potential risk factors identified across the eligible studies as comorbid diseases and clinical conditions associated with CDI. Our results show that CDI occurs in the setting of a large variety of underlying medical conditions, with immunosuppression, diabetes mellitus, and end-stage renal disease being the most commonly described other conditions, with >5 studies each assessing these comorbidities [13]. Cardiovascular disease, chronic kidney disease, and malignancy were also recurrently detected, suggesting that chronic diseases may largely account for the increased susceptibility to CDI. The biologic plausibility of a link of immunosuppression with CDI can be related to impaired host immune response to C. difficile to control colonization and direct intestinal injury caused by C. difficile toxins. Gastrointestinal disorders (in particular, inflammatory bowel disease (IBD)) may similarly render individuals more susceptible by compromising the functioning of the intestinal mucosal barrier layer and changing the composition of intestinal microbiome. The co-morbidity of malignancy and hematological malignancies might enhance CDI susceptibility due to a combination of immune system compromise, exposure to chemotherapy, increased rates of hospitalization and antibiotic use [14]. Chronic kidney disease, cardiovascular disease, heart failure and chronic pulmonary disease may also be markers for higher burden of comorbidity, since they are most likely to have more healthcare exposure. For some conditions, such as neurological disease/dementia, the evidence was more limited and these conditions were classified as possible risk factors, with fewer studies analyzing that particular risk factor or less consistent evidence across the literature included. In one of the studies this should also be interpreted with caution as the evidence is limited and could

reflect the effects of hospitalization, antibiotic exposure, corticosteroid treatment or other pandemic-associated healthcare factors, rather than a biological effect of SARS-CoV-2 infection [15].

Table 2. Summary of Comorbid Diseases or Conditions as Potential Risk Factors for Clostridioides difficile Infection

Comorbid diseases or conditions	Number of studies	Possible risk factor for CDI
Diabetes mellitus	5	Yes
Cardiovascular disease	4	Yes
Chronic kidney disease	4	Yes
Malignancy	4	Yes
Immunosuppression	5	Yes
Inflammatory bowel disease	3	Yes
Chronic liver disease	3	Yes
Chronic pulmonary disease/COPD	3	Yes
Gastrointestinal disease	5	Yes
Hematological malignancy	3	Yes
Heart failure	3	Yes
Autoimmune/inflammatory disease	3	Yes
COVID	1	Yes
Neurological disease/dementia	2	Possible
Obesity	2	Possible
Hypertension	3	Possible
HIV/AIDS	1	Possible
Pregnancy/obstetric conditions	1	Possible

Summary of comorbid diseases, clinical conditions, and treatment-related factors assessed in studies that investigated risk factors of Clostridioides difficile infection (CDI). The characteristics of CDI susceptibility are multivariable and some characteristics are associated with CDI susceptibility in a consistent direction across studies. Older age, prior CDI, length of stay, severe underlying disease, immune suppression, malignancy, inflammatory bowel disease, and ICU admission were identified as particularly critical. Older age was one of the most common factors evaluated, with a positive association documented in 11 of 13 studies, corroborating the known associations of age-related immunologic-quality and microbial-altered intestinal microbiota and susceptibility to infection with increasing exposure to healthcare [16]. These findings reinforce the implication of incomplete restoration of the gut microbiome and autochthonous immunity after a first episode, the persistence of C. difficile spores, and previous CDI as a prime indicator for clinically relevant recurrence. Consistent positive associations were observed for prolonged hospitalization and prior admission to the ICU which likely represent greater exposure to healthcare facilities, antimicrobial therapy, invasive manipulations, and colonization with MRSA. Serious underlying condition may also increase the risk of CDI through increasing physiologic susceptibility and cumulative healthcare exposure. A variety of underlying diseases had also been explored, with malignancy, hematological malignancy, immunosuppression, inflammatory bowel disease, and gastrointestinal disease showing relatively consistent positive associations [17]. Impaired host immunity, disruption of intestinal mucosal integrity, changes in gut microbial composition, and repeated exposure to antibiotics or immunosuppressive treatments could lead to these relationships. Chronic kidney disease and those undergoing renal replacement therapy had increased risk, perhaps because of increased comorbidity, multiple hospitalisation and healthcare contact. Additional factors of importance included those related to treatment and procedure. Most commonly, chemotherapy, corticosteroid therapy, immunomodulatory therapy, recent surgery, and hematopoietic stem-cell transplantation were associated with increased CDI risk. Designing drugs directed on the basis of how these exposures may directly or indirectly affect the integrity of the intestinal microbiota and host immune defences may

mitigate CDI susceptibility [18]. All studies examining the effect of chemotherapy and hematopoietic stem-cell transplantation on CDI showed an association, although the number of studies was small.

Table 3. Comorbid Diseases and Clinical Conditions Associated With the Risk of Clostridioides difficile Infection

Comorbid disease/condition	No. of studies	Positive association	Population/context	Direction of association	Overall interpretation
Advanced age (≥65 years)	13	11	Hospitalized/older adults	↑ Risk	Strong potential risk factor
Previous CDI	7	6	Patients with previous CDI	↑ Recurrence	Strong risk factor for recurrence
Malignancy	5	4	Oncology patients	↑ Risk	Important risk factor
Hematological malignancy	3	3	Hematology/oncology patients	↑ Risk	Strong risk factor
Immunosuppression	6	5	Immunocompromised patients	↑ Risk	Important risk factor
Inflammatory bowel disease	3	3	IBD patients	↑ Risk	Strong potential risk factor
Chronic kidney disease	5	4	Hospitalized patients	↑ Risk	Moderate–strong risk factor
Chronic liver disease	4	3	Hospitalized patients	↑ Risk	Potential risk factor
Cardiovascular disease	5	3	Hospitalized adults	↑ Risk	Potential risk factor
Diabetes mellitus	6	4	Hospitalized patients	↑ Risk	Potential risk factor
Chronic pulmonary disease	4	3	Hospitalized/older adults	↑ Risk	Potential risk factor
Gastrointestinal disease	5	4	GI/IBD populations	↑ Risk	Important potential risk factor
Autoimmune/inflammatory disease	3	2	Immunosuppressed patients	↑ Risk	Potential risk factor
Severe underlying illness	7	6	Hospitalized/critically ill patients	↑ Risk	Strong potential risk factor
Prolonged hospitalization	10	9	Hospitalized patients	↑ Risk	Strong risk factor
ICU admission	4	4	Critically ill patients	↑ Risk	Strong risk factor
Hematopoietic stem-cell transplantation	2	2	Transplant recipients	↑ Risk	Strong risk factor

Comorbid disease/condition	No. of studies	Positive association	Population/context	Direction of association	Overall interpretation
Recent surgery	5	4	Surgical patients	↑ Risk	Important risk factor
Pregnancy/obstetric conditions	1	1	Obstetric population	↑ Risk	Population-specific risk factor
Chemotherapy	3	3	Cancer patients	↑ Risk	Strong potential risk factor
Corticosteroid therapy	5	3	Hospitalized/immunosuppressed patients	↑ Risk	Potential risk factor
Immunomodulatory therapy	4	3	IBD/immune-mediated diseases	↑ Risk	Potential risk factor
Renal replacement therapy	2	2	Severe renal disease	↑ Risk	Potential risk factor

Forest plot showing all published risk factors with reported odds ratios (ORs) for Clostridioides difficile infection (CDI) and relapse from the 22 included studies. These results demonstrate that many of the patient-related and healthcare-associated factors were consistently associated with increased risk of CDI. Older age, history of CDI, longer hospital stay, ICU admission, high burden of underlying disease, immunocompromised state, malignancy, inflammatory bowel disease, recent surgery and use of immunosuppressive or anticancer therapies were identified as especially relevant risk factors [19]. Most results for the estimates of associations were in the direction of increased risk, but they vary widely in terms of magnitude and precision. Variability between the neighbouring studies in terms of study populations, healthcare settings, definitions of CDI and recurrent CDI, sample sizes, follow-up periods and adjustment for confounders is likely to be responsible for a part of this observed variability. In particular, studies in hospitalized, critically ill, oncological, transplant, or immunocompromised populations were more likely to report stronger associations than studies in broader community or general inpatient populations. Thus, the forest plot is consistent with the interpretation that CDI is multifactorial, resulting from the synergy of host susceptibility (eg. underlying comorbidities), healthcare exposure, and treatment-related factors, rather than a standalone independent risk factor [20].

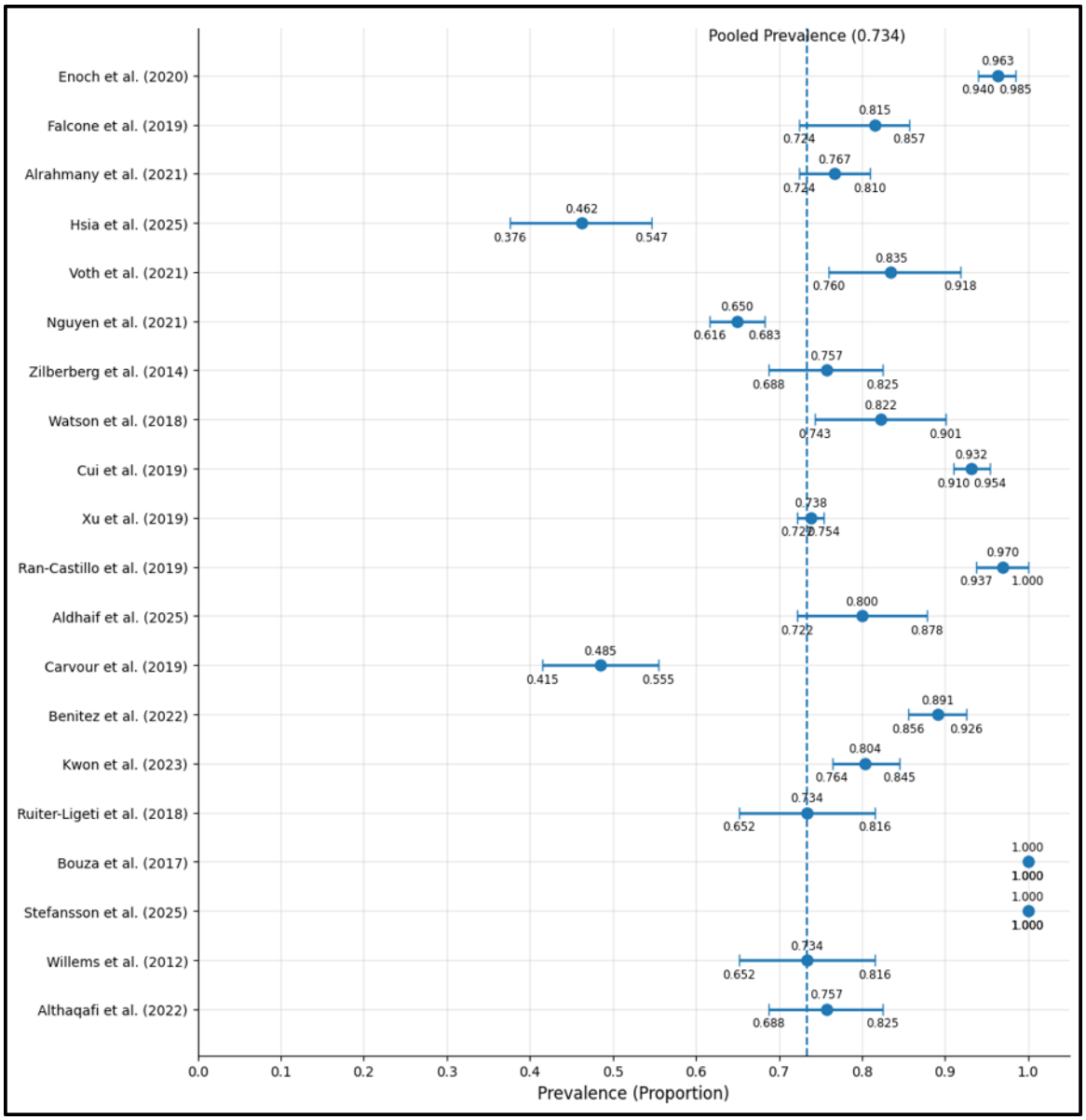

Figure 2. Forest plot of the prevalence of Clostridioides difficile Infection across the included studies

Discussion

This systematic review includes 20 studies describing the association between demographic, clinical or health care–related factors and Clostridioides difficile infection (CDI) and recurrent CDI [21]. These associations, seen in geographically diverse populations, reinforce the idea that CDI occurs as a result of the interaction of the disturbance of the intestinal microbial community, host susceptibility, exposure to healthcare, and repeated antimicrobial or immunosuppressive pressures.

In the applicability assessment, advanced age was one of the most frequently identified risk factors, shown in a positive direction in 11 of 13 studies. These results are in line with previous data indicating that older individuals have particularly high risk of CDI and recurrent disease. This association may be attributed to age-related changes of intestinal microbiota, increased healthcare exposure, increased burden of frequent antibiotic exposure, and immunosenescence among the older person [22]. While the 2021 IDSA/SHEA guideline additionally recognizes age ≥65 years as a major risk factor for CDI recurrence, it considers older age to be among the characteristics that might support the implementation of preventive strategies in high-risk patients. Likewise, older age was significantly associated with recurrent CDI (OR 1.62, 95% CI 1.11-2.36) in a prior meta-analysis. These findings

bolster the argument for considering advanced age as a clinically relevant predictor as opposed to a mere surrogate for increased healthcare utilization.

An older history of CDI was also a potent predictor of recurrence. The current review abstracted data on prior CDI from studies published between April 2019 and October 2021; six of the seven studies assessed a link with prior CDI and reported a positive association [23]. This finding is biologically plausible given that recurrence may be representative of incomplete restitution of the gut microbiome, incomplete colonization resistance, impaired toxin-specific immunity, or even re-disruption of protective intestinal flora. Falcone et al. Zilberberg et al. Alrahmany et al, and Stefansson et al. also showed that a history of CDI has a major impact on a future recurrence. The recent clinical guidelines also recognize a history of CDI, especially within the last six months, as one of the strongest predictors of recurrence [24]. For this reason, historical CDI should be assessed as a distinct entity from conventional comorbidities since it is a measure of host susceptibility as well as an index of a disrupted intestinal microbial ecosystem.

A strong association between healthcare-associated factors and CDI was also demonstrated in the review. In 9 out of 10 studies, prolonged hospitalization was associated with CDI and all four studies assessing admission to intensive care unit showed an association with increased risk [25]. These results are consistent with the previously known epidemiology of CDI. Additional exposure to C. difficile spores occurs with hospitalization (which facilitates antimicrobial therapy, procedures that disturb the bowel and increasing numbers of contaminated patients and healthcare environments). Furthermore, critically ill patients are also exposed to multiple antibiotics, invasive procedures, enteral nutrition, acid-suppressive medications and immunosuppressive treatment. Cui et al. For instance, describe significant associations between CDI/colonization and clinical factors in patients in the ICU. Similarly, Watson et al. reported several healthcare-related factors associated with hospital-onset CDI were identified in a large healthcare system. Therefore, these current data highlights that infection prevention does not focus only on patient factors but also on health care-associated exposure [26].

Severe illness was also strongly related to CDI (six of 7 studies). Several comorbidities demonstrated similar patterns. Out of five studies, four found a positive association with malignancy and of the three beryllium-induced cancers, hematological malignancy was reported by all three studies evaluated. Immunosuppression was linked to risk in five studies, while one had a risk factor of <1. These data corroborate previous observations from cancer- and hematology-confirmed populations [27]. Patients with malignancy are at risk for multiple exposures to antibiotics, chemotherapy-induced mucosal injury, extended hospitalization, neutropenia, and diminished microbiota-driven immunity, all of which can predispose to CDI. Willems et al. for example, were aware of the significant burden of CDI among patients with multiple myeloma.

Another significant risk factor however was IBD, which stands for inflammatory bowel disease. There was a consistent positive association between CDI and IBD in all three studies [28]. This relationship has clinical importance in that IBD can be associated with intestinal inflammation and disruption of the mucosal barrier, and corticosteroids, immunomodulators, biologic therapies, hospitalization and antibiotic exposure may all contribute to increased risk individually [29]. Voth et al. have evidenced the significant clinical and treatment-related contributions of patients with IBD with CDI [30]. Similarly, Xu et al. reported the presence of CDI in patients with ulcerative colitis. Because CDI can also aggravate preexisting intestinal inflammation and confound diagnosis of an IBD flare versus active infection, the association may be bidirectional [31], [32].

Renal illness, coronary artery illness, diabetes mellitus, chronic pulmonary illness, liver illness, and different gastrointestinal diseases have been frequently recognized as potential chance factors. Positive associations were identified between chronic kidney disease (4 studies), diabetes mellitus (4 studies), and cardiovascular disease (3 studies). These associations might be partly attributable to the greater comorbidity burden, high frequency of hospitalization, antimicrobial exposure, and impaired immune responses these populations experience [33]. Importantly, such conditions may also operate as confounders, as they are highly correlated with advanced age and healthcare utilization.

The treatment and procedure-related factors wound up serving to underwrite the multifactorial nature of CDI. History of recent surgery, chemotherapy, corticosteroid therapy, immunomodulatory therapy, renal replacement therapy, and hematopoietic stem-cell transplantation

were generally associated with increased risk [34]. These exposures can modify gut microbial composition, mucosal barrier function, or host immunity. However, the observational nature of the majority of the included studies means that causal inference should be made with caution. Because patients receiving these therapies are often the very sickest patients, excluding residual confounding by disease severity is challenging [35], [36], [37], [38].

In general, findings support the existing literature and current guidelines in the clinical practice. The 2021 IDSA/SHEA guideline identified advanced age, immunocompromised status, severe CDI, and history of CDI as key recurrence-associated factors, and acknowledged the increased likelihood of recurrence as risk factors accumulate. This review corroborates these findings by highlighting how the risk factors act through different domains, namely demographic factors, comorbid conditions, health care exposure, and treatment-related immunological or microbiological disruption [39], [40]. Availability of large randomized trials, however, is an outbreak in population characteristics, CDI definitions, follow-up duration, and confounders adjusted in the analysis has limited the direct quantitative comparison between studies. Future multicenter studies with standardized definitions and appropriately adjusted multivariable models are therefore required [41], [42]. Clinically, the early identification of patients with multiple risk factors may promote selective antimicrobial stewardship, infection-control interventions, appropriate surveillance, and preventive strategies for reducing both primary and recurrent CDI.

Conclusion

This systematic review shows that Clostridioides difficile infection (CDI) is associated with multifactorial patient, disease and health care risk factors. Advanced age, a history of CDI, long hospitalization, ICU admission, severe comorbid illness and recent health care exposure were some of the most consistent predictors. Increased risk of CDI was also frequently associated with malignancy, immunosuppression, inflammatory bowel disease, chronic kidney disease and other major comorbidities. Certain treatment-related factors, such as chemotherapy, corticosteroids, immunomodulatory therapy and surgery recently performed may have clear risk of increasing susceptibility to infection. The results emphasize early identification of high-risk patients, antibiotic stewardship and the need for effective infection-prevention strategies.

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