Prevalence of *Clostridium difficile* Infection in the Hematopoietic Transplantation Setting: Update of Systematic Review and Meta-Analysis

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Hematopoietic stem cell transplant (HSCT) recipients are vulnerable to *Clostridium difficile* infection (CDI) due to risk factors such as immunosuppression, antimicrobial use, and frequent hospitalization. We systematically searched PubMed and Embase to screen relevant studies from April 2014 to November 2021. A meta-analysis was performed to identify the association between CDI and hematopoietic transplantation based on the standard mean difference and 95% confidence intervals (CIs). Among the 431 retrieved citations, we obtained 43 eligible articles, which included 15,911 HSCT patients at risk. The overall estimated prevalence of CDI was 13.2%. The prevalence of CDI among the 10,685 allogeneic transplantation patients (15.3%) was significantly higher than that among the 3,840 autologous HSCT recipients (9.2%). Different incidence rates of CDI diagnosis over the last 7 years were found worldwide, of which North America (14.1%) was significantly higher than Europe (10.7%) but not significantly different from the prevalence among Asia (11.6%). Notably, we found that the estimated prevalence of CDI diagnosed by polymerase chain reaction (PCR) (17.7%) was significantly higher than that diagnosed by enzyme immunoassay (11.5%), indicating a significant discrepancy in the incidence rate of CDI owing to differences in the sensibility and specificity of the detection methods. Recurrence of CDI was found in approximately 15% of the initial patients with CDI. Furthermore, 20.3% of CDI cases were severe. CDI was found to be a common complication among HSCT recipients, displaying an evident increase in the morbidity of infection.

**Keywords:** *Clostridium difficile* infection, hematopoietic stem cell transplantation, meta-analysis, Asia, detection methods, allogeneic transplantation patients
INTRODUCTION

*Clostridium difficile* infections (CDI) remain the leading cause of infectious diarrhea among hospitalized patients across the world. The rates of CDI in industrialized countries have increased with the emergence of the NAP1/RT027 strain in 2002, which is responsible for the outbreaks of severe diseases in North America and Europe (Loo et al., 2005; Kuijper et al., 2006). Patients with hematologic malignancies—particularly those who undergo hematopoietic stem cell transplants (HSCT)—are at risk of developing CDI because of prolonged hospital stay, exposure to broad-spectrum antibiotics, and compromise of the gastrointestinal mucosal barrier (Alonso et al., 2013; Shah et al., 2017).

Given a set of important factors, such as the transplant population, follow-up period, and testing method, the incidence of confirmed CDI among autologous HSCT (auto-HSCT) recipients varies from 5% to 24% (Bruninhent et al., 2014; Pilcante et al., 2015), whereas the incidence among allogeneic HSCT (allo-HSCT) recipients varies from 9% to 34% (Lavallee et al., 2017; Dubberke et al., 2017). An earlier systematic review of published literature until 2014 showed that the pooled prevalence of CDI among 12,025 HSCT patients was 7.9%, and an increasing trend of CDI diagnosis was also found worldwide and across studies conducted in North America over the last 34 years (Zacharioudakis et al., 2014).

Recently, with the widely implemented antibiotic prophylaxis and progress in the diagnostic strategy of CDI, it is unknown how CDI trends change in HSCT recipients during the peri-transplantation and late post-transplantation periods. Therefore, this study evaluated and updated the epidemiology of CDI in the hematopoietic transplantation setting from April 2014 to November 2021.

METHODS

All procedures used in this meta-analysis were consistent with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (Stroup et al., 2000) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

Literature Search

We searched PubMed and Embase (April 1, 2014, to November 30, 2021) medical databases to identify publications reporting the prevalence of CDI among patients who received hematopoietic stem cell transplantation. The concise search term was transplant * AND [clostrid * OR difficile OR infect * OR diarrhea OR (clostridium difficile) OR (pseudomembranous colitis)] AND ([stem cell] OR marrow OR chord OR autologous or allogeneic) referring to previous systematic reviews (Zacharioudakis et al., 2014). We also manually searched the bibliographies of relevant papers to retrieve additional studies. Articles that were considered eligible following title and abstract reading were assessed in full text.

Selection Criteria

Studies were considered eligible if they reported the prevalence of CDI among HSCT patients during their hospitalization after stem cell transplantation. A restriction for English literature was imposed.

Outcomes of Interest

The prevalence of CDI among HSCT patients was the primary outcome of interest in this meta-analysis. CDI was defined as the presence of symptoms (usually diarrhea), and either a stool test positive for *C. difficile* toxins or the presence of toxigenic *C. difficile*, or colonoscopic, or histopathologic findings demonstrating pseudomembranous colitis (McDonald et al., 2018). The prevalence was calculated as the proportion of patients diagnosed with CDI among HSCT recipients. The subgroup analyses included the geographical region, study population, year of study implementation, transplantation type (i.e., autologous or allogeneic), study design, duration of follow-up, and detection methods used in the lab. The recurrence rate of CDI in infected patients was the secondary outcome of interest. Recurrent CDI was defined as a complete elimination of CDI and other symptoms with appropriate therapy, followed by the reappearance of diarrhea and positive result of toxigenic *C. difficile* after the cessation of treatment.

The peri-transplantation period for HSCT patients was divided into four periods: pre-transplantation (pre-T, hospitalization before transplantation), pre-engraftment (pre-E, approximately 0 to 30 days after transplantation), post-engraftment (post-E, approximately 30 to 100 days after transplantation), and late post-transplantation (Lpost-T, generally the day after +100 day of transplantation). Furthermore, to understand the effect of follow-up duration on the estimated prevalence of CDI, we distinguished the duration of follow-up as early- (pre-T + pre-E), middle- (pre-T + pre-E + post-E), and long-term (pre-T + pre-E + post-E + Lpost-T).

Data Extraction

Two reviewers (YL and QW) independently assessed the studies that were considered for inclusion in the meta-analysis. A spreadsheet was used to summarize the relevant information from the figures, tables, and text of the eligible articles. The trial data published in duplicate were included only once, and the maximum relevant information was extracted. Any disagreements or uncertainties regarding data extraction were resolved in consensus with a third reviewer (BZ). The extracted data included the region of source; study period; patient population; HSCT types (autologous or allogeneic); study design (prospective versus retrospective); laboratory detection methods; source of stem cells; duration of follow-up; the total number of patients who underwent HSCT during the study period; the total number of CDI cases among such patients; the number of NAP1/027 strains; the severity of CDI; and the number of recurrent episodes. If CDI recurred more than once, only the data of the first one were used in the analysis and assessed for the incidence. The severity of CDI in each patient was assessed as severe by the following clinical features: evidence of sepsis, gastrointestinal perforation, pseudomembranous colitis, toxic megacolon, ileus, intensive care unit admission, surgery for colitis, or death because of colitis (Kaltsas et al., 2012). Only studies that
mentioned the outcome and severity of CDI were coverage initiated in the analysis.

Quality Assessment
Two reviewers (YL and QW) independently evaluated the methodological quality of the eligible studies using the Newcastle–Ottawa Quality Assessment Scale, which was a “star-based” rating system. The parameters used to assess the quality of each eligible study were as follows: representative of the exposed cohort, ascertainment of exposure, demonstration that the outcome of interest was not present at the start of the study, assessment of outcome, duration of follow-up for outcomes to occur, and adequacy of follow-up cohorts (Zacharioudakis et al., 2014). Two parameters, selection of the non-exposed cohort and comparability between cohorts, were not applicable to our analysis. Therefore, each study could obtain up to six stars. As representative of the study population in the exposed cohort, we considered the occurrence of CDI among all available transplantation patients rather than a specific subpopulation. We assessed the outcome by presenting the symptoms and laboratory diagnosis of CDI. The follow-up time was viewed as adequate for outcomes to occur, if it was at least 100 days or it included the entire period of hospitalization. Studies that received at least 4 stars were considered adequate quality to extract relevant information.

Data Analysis
A random-effects model, estimating the pooled prevalence and 95% confidence intervals (CIs), was performed in the meta-analysis (DerSimonian and Laird, 1986). The Freeman–Tukey arcsine methodology was used to remove an excessively large weight for studies with extremely low (close to 0) or extremely high (close to 100%) prevalence (Ziakas et al., 2015). Egger’s test was used to assess the publication bias (Egger et al., 1997). Between-study variance $\tau^2$ estimation was used to assess statistical heterogeneity (Rucker et al., 2008). Subgroup analyses were used to account for possible sources of heterogeneity. Statistical analysis was implemented by R language software and SPSS software (version 18.0, IBM, New York, USA). The statistical significance threshold was set at 0.05.

RESULTS
Our search generated 431 publications by accessing the databases between April 1, 2014, and November 30, 2021. After scrutinizing the titles and abstracts of the retrieved articles, 431 studies were excluded from our analysis, and 92 studies were retrieved in full text for more detailed evaluation. Among these, 49 articles were excluded because of the absence of extractable data on the prevalence of CDI among HSCT patients. Of the remaining 43 articles considered suitable for our meta-analysis, two contained partially overlapping data (Schuster et al., 2017; Dubberke et al., 2018), and the maximum available data were extracted from each article. Finally, 44 analyses were included in the final analysis coded from 43 articles (Table 1). We presented the details for selecting eligible articles in a flowchart presented in Figure 1.

The 44 analyses (coded from 43 articles) included in our analysis were published from April 2014 to November 2021, and data on 15,911 HSCT patients were reported from 1998 to 2019. The characteristics of each study are presented in Table 1. In the study containing intervention or prophylaxis that could affect the incidence of CDI among HSCT patients, only the data from the un-intervened cohort were used in the analysis. All studies were considered to possess the adequate quality to be included in the analysis based on the Newcastle–Ottawa Scale (Supplementary Table 1).

Among the 44 included analyses, 13 were prospective and 31 were retrospective, and one contained both prospectively and retrospectively collected data. The included studies varied by location, of which 32 were conducted in North America, 6 in Europe, 4 in Asia, and 2 in South America.

The laboratory detection methods of CDI used in each included study are displayed in Table 1. The pooled prevalence of CDI among the 15,911 HSCT recipients was 13.2% [95% CI, 11.6% to 15.0%], $\tau^2 = 0.0054$ according to the random-effects model (Figure 2). No evidence of publication bias was found for the overall estimated prevalence according to Egger’s test (bias: 1.654, p value = 0.176).

The HSCT patients included in the study were stratified based on age (pediatric or adult) and the type of HSCT (autologous or allogeneic). The included 15,911 HSCT patients included 1,095 pediatric patients extracted from six studies, 10,515 adult patients from 31 studies, and 4,301 patients unidentifiable by age. No significant difference was found in the pooled prevalence of CDI between the pediatric patients [14.8% (95% CI, 10.8% to 19.2%), $\tau^2 = 0.0037$] and adult patients [13.7% (95% CI, 11.5% to 16.1%), $\tau^2 = 0.613$] (Supplementary Figure 1). Seventeen studies reported relevant data on 3,840 auto-HSCT patients, whereas 34 studies provided extractable data on 10,685 allo-HSCT patients. The prevalence of patients with CDI who underwent allogeneic transplantation was 15.3% [95% CI (13.2% to 17.5%), $\tau^2 = 0.0061$], which was significantly higher than the corresponding prevalence among auto-HSCT recipients [9.2% (95% CI, 7.5% to 11.2%), $\tau^2 = 0.0026$, p < 0.01] (Supplementary Figure 2).

Among the 43 studies, the estimated prevalence of CDI in North America [14.1% (95% CI, 12.1% to 16.4%), $\tau^2 = 0.0063$] was higher than the estimated prevalence among European studies [10.7% (95% CI, 7.6% to 14.3%), $\tau^2 = 0.0034$, p = 0.001] but not significantly different from the prevalence among Asian studies [11.6% (95% CI, 8.6% to 14.8%), $\tau^2 = 0.0005$, p = 0.231] (Supplementary Figure 3). We also conducted a subgroup analysis on the basis of the population and found that the estimated prevalence of 16 studies with <200 patients [15.8% (95% CI, 12.5% to 19.4%), $\tau^2 = 0.0064$] was statistically significantly higher than that of 28 studies with ≥200 patients [12.3% (95% CI, 10.5% to 14.2%), $\tau^2 = 0.0049$, p < 0.01] (Supplementary Figure 4).

We stratified our data based on the study design (prospective or retrospective) and found that the estimated prevalence of CDI in 13 prospective studies was 16.5% (95% CI, 11.9% to 21.7%), which was significantly higher than that of the 31 retrospective studies [12.0%...
| Study Citation          | Date Source         | Study Period | Patient Population | HSCT Types | Study Design     | Detection Methods                           | Follow-up          | Source of Stem Cells | N         | N-AU | N-AL | n-CDI (AU) | n-CDI (AL) | Recurrence Score |
|------------------------|---------------------|--------------|--------------------|------------|------------------|---------------------------------------------|-------------------|---------------------|-----------|------|------|------------|------------|------------------|
| Willis et al., 2021    | St. Louis Children's Hospital, USA | 07/2009–02/2018 | Ped AU, AL | Retrospective study | Toxin EIA (2009–2010), GDH EIA, confirmed by a PCR for toxin B (2011–05/2017) and toxin A/B EIA (06/2017–2018) | NR | NR | 159 | 81 | 78 | 29 | 14 | 15 | NR | 5 |
| Jabr et al., 2021      | University of Kansas Medical Center, USA | 01/01/2010–12/31/2016 | Adult AL | Retrospective study | Toxin A/B EIA (01/2010–05/2010), and a PCR for toxin B (06/2010–12/2016) | 100 days after | PB, BM, UC | 656 | NR | 656 | 111 | NR | 111 | 8 | 5 |
| Cioeix et al., 2021    | The University of Minnesota, USA | 03/2010–06/2015 | Adult AL | Retrospective study | PCR test for toxin B | 30 days after | NR | 466 | NR | 466 | 48 | NR | 48 | 12 | 5 |
| Weber et al., 2020     | University Hospital Frankfurt, Germany | 01/2007–12/2015 | Adult AU, AL | Retrospective study | CD toxin by EIA | 30 days before–100 days after | NR | 467 | 191 | (lymphoma) | 276 | 61 | 14 | 47 | NR | 5 |
| Majeed et al., 2020    | Banner University Medical Center, USA | 11/2013–05/2016 | Adult AU, AL | Retrospective study | GDH, toxin EIA, and a PCR for toxin B (Cepheid), supplement by a cytotoxicity assay | Six months after | BM, UC | 42 | 16 | 26 | 5 | NR | NR | NR | 6 |
| Austin et al., 2020    | West Virginia University Hospitals, USA | 10/2015–06/2017 | Adult AU, AL | Retrospective study | GDH and toxin EIA, supplement by a PCR for toxin B | NR | BM, UC | 180 | 125 | 55 | 17 | 6 | 11 | 2 | 6 |
| Ford et al., 2020      | LDS Hospital, Salt Lake City, USA | 06/2015–12/2017 | Adult AU, AL | Retrospective study | GDH and toxin EIA, supplement by a PCR for toxin B (Cepheid) | NR | BM, UC | 223 | 122 | 101 | 20 | 11 | 9 | NR | 6 |
| Rosignoli et al., 2020 | The Transplant Center of Udine, Italy | 01/2015–12/31/2019 | Adult AU, AL | Retrospective study | GDH and toxin EIA (2015–2017), GDH and toxin EIA supplement by a PCR for toxin B (2018–2019, Cepheid) | 100 days after | BM, UC | 481 | 220 | 261 | 26 | 11 | 15 | 0 | 5 |
| Spruit et al., 2020    | Children’s Hospital of Michigan, USA | 01/2007–10/31/2017 | Adult AU, AL | Retrospective study | CD toxin by EIA (BD), later by PCR targeting toxin genes (OH) | Whole study period | PB, BM, UC | 142 | 63 | 79 | 28 | 15 | 13 | 6/7 | 5 |
| Mardani et al., 2020   | Ayatollah Taleghani University Hospital, Tehran, Iran | 05/2017–05/2018 | Adult NR | Prospective study | ELISA A + B kits (Abnova) | NR | BM | 43 | NR | NR | 5 | NR | NR | NR | 6 |
| Makaaron et al., 2020  | The Ohio State University, Columbus, USA | 07/2015–07/2018 | Adult (age, 21–79 years), MM or lymphoma | Retrospective study | CD toxin EIA (Meridian) until 2013, GDH, and toxin EIA (bioMinieux) after 2013 | NR | BM | 514 | 514 | 0 | 51 | 51 | 0 | NR | 5 |
| Amherger et al., 2020  | University Hospital Carl Gustav Carus, | 01/01/2004–3/31/2015 | Adult, AML, MDS | Retrospective study | CD toxin EIA (Meridian) until 2013, GDH, and toxin EIA (bioMinieux) after 2013 | 33 months (median) | NR | 727 | 0 | 727 | 96 | 0 | 96 | NR | 6 |
| Study Citation | Date Source | Study Period | Patient Population | HSCT Types | Study Design | Detection Methods | Follow-up | Source of Stem Cells | N | N-AU | N-AL | n-CDI (AU) | n-CDI (AL) | Recurrence | Quality Score |
|----------------|-------------|--------------|--------------------|------------|--------------|-------------------|-----------|---------------------|---|------|------|-----------|-----------|------------|---------------|
| Rahman et al., 2019 | | 2007–2016 | Adult (age, 22–76 years), MM | AU | Retrospective cohort study | CD toxin EIA before 2010, and PCR test after 2011 | 100 days after | PB | 413 | NR | NR | 23 | NR | NR | 5 |
| Mullaney et al., 2019 | | NR | Adult (age ≥ 18 years) | AL | Prospective study | Toxin EIA or NAAT (Cepheid Xpert) | 60 days after the end of treatment | NR | 299 | 176 | 123 | 32 | 14 | 18 | 6 |
| Ganetsky et al., 2019 | | 04/2015–11/2016 | Adult (age, 17–75 years) | AL | Retrospective cohort study | GDH and toxin EIA, supplement by PCR for toxin genes | 30 days before~30 days after | NR | 55 | 0 | 55 | 11 | 0 | 11 | 6 |
| Clemmons et al., 2019 | | 2011–2015 | Adult (age, 17–75 years) | AU, AL | Retrospective, single-center study | NR | NR | 171 | 55 | 0 | 55 | 11 | 0 | 11 | 5 |
| Bhutani et al., 2019 | | 04/2009–12/2013 | Adult (age, 19–62 years) | AL | Retrospective study | qPCR for CD toxin genes | 2.43 years (median) | BM, PB | 310 | 0 | 310 | 74 | 0 | 74 | 6 |
| Salamonowicz et al., 2018 | | 01/01/2010–12/31/2015 | Ped | AU, AL | Retrospective study | EIA, PCR, or culture for toxigenic CD | At least 6 months after | NR | 342 | 75 | 267 | 29 | 5 | 24 | 6 |
| Dubberke et al., 2018 | | 04/2007–03/2010 | NR | AL | Prospective multicenter study | EIA for toxins A/B or cytotoxicity assay or antigen detection; PCR or GDH plus toxin EIA | 365 days after | NR | 385 | 0 | 385 | 120 | 0 | 120 | 6 |
| Apewokin et al., 2018 | | 03/1998–09/2010 | MM | AU | Prospective study | CD toxin by EIA (3 samples) | 0–21 days after | NR | 646 | 0 | 646 | 57 | 57 | 0 | 6 |
| Schuster et al., 2017 | | 2006–2011 | Adult (age, 18–75 years) | AL | Prospective multicenter cohort study | NR | BM, PB, UC, T-cell depleted | 30 months after | NR | 444 | 0 | 444 | 148 | 0 | 148 | 38 |
| Scardina et al., 2017 | | 12/01/2009–12/31/2014 | NR | AU, AL | Retrospective case-control study | CD toxin EIA (Meridian) until 07/2011, Xpert (Cepheid) after 07/2011 | NR | NR | 550 | NR | NR | 44 | NR | NR | 6 |
| Lee et al., 2017 | | 12/01/2010–11/30/2014 | Adult | AL | Prospective study | GeneXpert C. difficile toxin assay (Cepheid) | 1 year after | NR | 234 | 0 | 234 | 53 | 0 | 53 | 15 |
| Lavallee et al., 2017 | | 01/01/2002–12/31/2011 | Adult | AL | Retrospective case-control study | 2002–2005: cytotoxicity assay; 06/2005–01/2010: toxin EIA; 01/2010–2011: GDH and toxin EIA, | 1 year after | BM, PB, UC | 760 | 0 | 760 | 65 | 0 | 65 | 6 |

(Continued)
| Study Citation                  | Date Source                     | Study Period          | Patient Population | HSCT Types | Study Design          | Detection Methods | Follow-up | Source of Stem Cells | N  | N-AU | N-AL | n-CDI (AU) | n-CDI (AL) | Recurrence Quality Score |
|--------------------------------|---------------------------------|-----------------------|--------------------|------------|-----------------------|------------------|-----------|----------------------|----|-----|------|-----------|-----------|-------------------------|
| (Duberberke et al., 2017)      | Siteman Cancer Center, St. Louis, MO, USA | 04/2007–03/2010       | Adult AL           | AL         | Prospective cohort study | Remeli Xpect C. difficile Toxin A/B | 30 months after | NR 187 | 0 187 63| 0 63 5 5  |
| (Cannon et al., 2017)          | University of Wisconsin School of Medicine and Public Health, Madison, USA | 05/12/2015–09/24/2015 | Adult AL           | AL         | Prospective cohort study | Culture and in-house PCR to detect toxin gene | NR BM 59 | NR | NR 5 | NR 6 |
| (Adinete et al., 2017)         | Emory University Hospital, Atlanta, USA | 11/01/2010–3/31/2013 | Adult AU, AL       | AL         | Retrospective, case-control study | GeneXpert C. difficile toxin assay (Cepheid) | 30 days before~90 days after | NR 650 | 507 143 86| 61 25 6 5  |
| (Mani et al., 2016)            | Cleveland Clinic, Cleveland, USA | 2005–2012             | Age range (2–73 years) | AL         | Retrospective, single-center study | Toxin EIA before 2010, and PCR test after 2011 | 6 months before~2 years after | BM PB 499 | 0 499 61| 0 61 20 5 |
| (Lee et al., 2016)             | San Antonio Military Medical Center, San Antonio, USA | 07/2011–04/2014       | Adult (age, 19–72 years) | AL         | Retrospective, single-center study | Cytotoxin assay or PCR assay | 100 days after | NR 77 | 50 27 8 5| 3 3 5 |
| (Kamboj et al., 2016)          | Karmanos Cancer Institute and Wayne State University, Detroit, MI, USA | 12/01/2010–06/31/2012 | Adult AL           | AL         | Prospective study | GeneXpert C. difficile toxin assay (Cepheid) | 10 days before~40 days after | NR 264 | 0 264 52| 0 52 8 6 |
| (Jain et al., 2016)            | Karmanos Cancer Institute and Wayne State University, Detroit, MI, USA | 12/01/2010–06/31/2012 | Adult AL           | AL         | Prospective study | Culture and PCR to detect toxin gene | 90 days after | BM 150 | 7 143 25| NR | NR 7 6 |
| (Akihoshi et al., 2016)        | Saitama Medical Center, Jichi Medical University, Japan | 11/2007–05/2014       | Adult AL           | AL         | Retrospective study | GDH and toxin since 07/2012 (QUIK CHEK COMPLETE, Techlab), and toxin A/B (TOX A/B QUIK CHEK, Techlab) | 100 days after | BM PB 206 | 0 206 29| 0 29 1 5 |
| (Aghi et al., 2016)            | University of Pittsburgh Medical Center, Pittsburgh, USA | 01/2011–12/2014       | Adult (age, 22–73 years) | AL         | Retrospective cohort study | CD toxin A/B or PCR | 28 days after | NR 147 | 0 147 16| 0 16 6 NR |
| (Picante et al., 2015)         | Hospital Clinico Universidad Católica, Santiago, Chile | 01/2000–06/2013       | Adult (age, 17–69 years) | AL         | Retrospective study | Toxin EIA from 01/2000 to 02/2012; GeneXpert (Cepheid) at the end of the study | 7 days before~365 days after | NR 250 | 103 147 25 | 5 20 NR |
| (Gu et al., 2015)              | The First Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang, China | 08/01/2009–08/31/2013 | Age range (19–77 years) | AL         | Retrospective study | Culture and identified by MS (Bruker), then PCR to detect toxin A and B genes | NR | NR 103 | NR | NR 14 NR | NR |

(Continued)
| Study Citation | Date Source | Study Period | Patient Population | HSCT Types | Study Design | Detection Methods | Follow-up | Source of Stem Cells | N | N-AU | N-AL | n-CDI (AU) | n-CDI (AL) | Recurrence | Quality Score |
|----------------|-------------|--------------|--------------------|------------|--------------|-------------------|-----------|----------------------|---|-----|-----|-----------|-----------|------------|--------------|
| Boyle et al., 2015 | Fred Hutchinson Cancer Research Center, Seattle, USA | 01/01/2008–12/31/2012 | Ped, Adult | AL | Prospective study | GDH and toxin EIA (TechLab), supplement by real-time PCR or cytotoxin assay before 2010; GeneXpert (Cepheid) after 2010 | 56 days before–100 days after | BM, PB, UC | 1,182 | 0 | 1182 | 140 | 0 | 140 | NR | 6 |
| Vehreschild et al., 2014 | University Hospital of Cologne, Cologne, Germany | 01/2007–08/2010 | Adult | AL | Prospective cohort study | CD toxin A/B EIA (R-Biopharm) | NR | NR | 229 | 0 | 229 | 30 | 0 | 30 | NR | 6 |
| Spadao et al., 2014 | Hospital das Clinicas of University of Sào Paulo, Sào Paulo, Brazil | 01/2007–06/2011 | Age range (12–66 years) | AU, AL | Retrospective study | CD toxin A/B EIA (bioMerieux) | 100 days after | NR | 52 | 0 | 52 | 8 | 0 | 8 | NR | 5 |
| Kroenewehr et al., 2014 | Memorial Sloan-Kettering Cancer Center, New York, USA | 09/04/2009–08/04/2011 | Adult | AL | Prospective study | Real-time PCR for toxin B gene | 15 days before–35 days after | NR | 94 | 0 | 94 | 16 | 0 | 16 | 5 |
| Kamboj et al., 2014 | Memorial Sloan-Kettering Cancer Center, New York, USA | 01/01/1999–03/29/2012 | NR | AL | Retrospective study | Cytotoxicity assay before 08/29/2008; GDH, and cytotoxin assay from 08/29/2008 to 09/10/2010; Xpert (Cepheid) after 2010 | NR | NR | 1,144 | 0 | 1144 | 138 | 0 | 138 | 5 |
| Huang et al., 2014 | University of Michigan Health System (UMHS), Ann Arbor, MI, USA | 01/2010–03/29/2012 | NR (mean age, 45 years) | AU, AL | Retrospective case-control study | GDH and toxin EIA, supplement by real-time PCR for toxin genes | 7 days before–1 year after | NR | 711 | 381 | 330 | 95 | 35 | 60 | 22 | 5 |
| Hosokawa et al., 2014 | Toranomon Hospital, Tokyo, Japan | 01/2007–12/2008 | Adult | AL | Retrospective study | CD toxin A EIA | 100 days after | BM, PB, UC | 201 | 0 | 201 | 17 | 0 | 17 | NR | 5 |
| Brunnimht et al., 2014 | Thomas Jefferson University Hospital, Philadelphia, PA, USA | 01/2011–12/2012 | Adult | AU, AL | Retrospective study | GDH and toxin A/B EIA, supplement by tissue culture cytotoxin assay or molecular assay (Illumigene) | 100 days after | BM, PB, UC | 150 | 58 | 92 | 37 | 14 | 23 | 3 | 6 |

CD, Clostridium difficile; CDI, Clostridium difficile infection; HSCT, hematopoietic stem cell transplantation; Ped, pediatric; MM, multiple myeloma; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; AU, autologous; AL, allogeneic; EIA, enzyme immunoassay; PCR, polymerase chain reaction; NAAT, nucleic acid amplification tests; NR, unreported; PB, peripheral blood; BM, bone marrow; UC, umbilical cord.
(95% CI, 10.6% to 13.5%), p < 0.01] (Supplementary Figure 5). Based on the duration of follow-up, the estimated prevalence of CDI surveyed in the middle term [12.7% (95% CI, 10.5% to 15.2%)] was significantly higher than that in the early term [10.5% (95% CI, 7.9% to 13.4%), p = 0.014] and lower than that in the long term [16.5% (95% CI, 12.0% to 21.5%), p < 0.01] (Supplementary Figure 6).

We also stratified the studies on the detection methods. Forty-one studies expounded on the laboratory detection methods of CDI. The laboratory detection methods of CDI used in each included study are displayed in Table 1. Approximately half of the included studies used two or more detection methods to test the C. difficile toxin; thereinto, twelve studies altered the detection methods of CDI with time. One or more of the following methods were used in the laboratory detection of CDI: enzyme immunoassay (EIA), tissue culture cytotoxin assay (CC), and polymerase chain reaction (PCR). Ten studies used GDH and/or toxin EIA, supplemented by a PCR for toxin B or culture cytotoxin assay, abbreviated as EIA + PCR/CC. The estimated prevalence of CDI in studies that used EIA + PCR/CC was 14.4% (95% CI, 11.2% to 18%), which was significantly higher than studies that used EIA only [11.5% (95% CI, 9.9% to 13.1%), p = 0.02] as well as significantly lower than that in studies that used PCR only [17.7% (95% CI, 13.4% to 22.4%), p < 0.01] (Supplementary Figure 7 and Table 2).
Eighteen studies reported data on recurrence of CDI among 990 infected patients, among which 11 studies included the definition of recurrence. The reported recurrence rate was estimated to be 14.9% [95% CI (9.8% to 20.7%), \( \chi^2 = 0.0193 \)] (Supplementary Figure 8). The individual study data of the first recurrent case are presented in Table 1. Further analyses were performed for the estimated prevalence of CDI patients from 1998 to 2010 and from 2011 to 2021; the results showed that the estimated prevalence of CDI in 1998–2010 patients was 10.1% (95% CI, 8.7% to 11.7%), which was significantly lower than that of the 2011–2021 patients [13.0% (95% CI, 10.9% to 15.3%), \( p < 0.01 \)] (Supplementary Figure 9).

Finally, seven studies which included the definition of CDI severity, and 11 studies which reported data on the severity of CDI among infected patients, were included in the analysis. Among 524 CDI patients, 107 (20.3%, 107/524) severe cases, 26 (5.0%, 26/524) ICU admissions, 9 (1.7%, 9/524) CDI-related colectomies, 7 (1.3%, 7/524) gastrointestinal perforations, 13 (2.5%, 13/524) pseudomembranous colitis cases, and 13 (2.5%, 13/524) deaths were reported in the remaining 11 studies.
studies reported high-virulent NAP1/027 strains, in one of which NAP1/027 strains account for 24.5% (23/94), in the other one only 2.7% (1/37) (Supplementary Table 2).

**DISCUSSION**

CDI has been increasingly discerned among HSCT recipients because of the fragility of the immune system, graft-versus-host disease (GVHD), and antibiotic usage or prophylaxis (Lillet et al., 2019; Rosignoli et al., 2020; Jabr et al., 2021). Along with the growing cognition on CDI for clinical physicians and improving diagnostic capacity of laboratories on CDI, the relevant data on the prevalence of reported CDI have gradually increased in recent years. This study aimed to update the previous analysis on the prevalence of CDI among HSCT patients. The risk factors for CDI in allo-HSCT patients included receipt of chemotherapy before conditioning for HSCT, broad-spectrum antimicrobial use, acute GVHD, and greater immunosuppression caused by allo-HSCT conditioning regimens (Alonso et al., 2012). A greater deviation in the prevalence of CDI compared to the overall estimated prevalence (13.2%) was found for smaller studies (<200 patients, 12.3%), highlighting that a reasonable and large sample size was necessary for reducing the random error and being representative.

In our analysis, we observed that most of the studies (72.1%, 31/43) were obtained from North America, and the estimated prevalence of CDI among HSCT patients in North America was 14.1%, which was significantly higher than that in Europe (10.7%) but did not reach statistical significance than that in Asia (11.6%). It revealed the regional epidemic characteristics of CDI over the last 7 years. Another national discharge data also indicated that the USA had a 10-fold higher CDI rate than England among overall inpatients (King et al., 2017). The regional difference might be associated with the national

### TABLE 2 | Summary estimates.

| CDI Studies (Articles) | N   | Combined Effect (95% CI) | $\chi^2$ | Bias | $p$-value |
|------------------------|-----|--------------------------|---------|------|-----------|
| All studies            | 44 (43) | 15,911                    | 13.2% (11.6–15.0%) | 0.054 | 1.654     | 0.256 | 0.613 |
| Age                    |     |                          |         |      |           |
| Ped                    | 6   | 1,095                    | 14.8% (10.8–19.2%) | 0.037 | 4.536     |       |      |
| Adult                  | 31  | 10,515                   | 13.7% (11.5–16.1%) | 0.076 | 1.919     |       |      |
| Graft type             |     |                          |         |      |           |
| Autologous             | 17  | 3,840                    | 9.2% (7.5–11.2%)  | 0.026 | 1.168     | 70.990 | 0.000 |
| Allogeneic             | 34 (33) | 10,685                   | 15.3% (13.2–17.5%) | 0.061 | 1.806     |       |      |
| Population             |     |                          |         |      |           |
| ≥200 patients          | 28  | 14,100                   | 12.3% (10.5–14.2%) | 0.049 | 1.546     |       |      |
| <200 patients          | 16  | 1,811                    | 15.8% (12.5–19.4%) | 0.064 | -2.203    |       |      |
| Geographical region    |     |                          |         |      |           |
| North America          | 32 (31) | 12,371                   | 14.1% (12.1–16.4%) | 0.063 | 2.352     |       |      |
| Europe                 | 6   | 2,298                    | 10.7% (7.6–14.3%)  | 0.034 | 0.762     | 11.966 | 0.001 |
| Asia                   | 4   | 553                      | 11.6% (8.6–14.8)   | 0.005 | 0.762     | 1.436  | 0.231 |
| Study design           |     |                          |         |      |           |
| Prospective            | 13  | 3,873                    | 16.5% (11.9–21.7%) | 0.012 | 1.806     | 50.827 | 0.000 |
| Retrospective          | 31  | 12,038                   | 12.0% (10.6–13.5%) | 0.029 | 1.335     |       |      |
| Duration of follow-up  |     |                          |         |      |           |
| Early term             | 3   | 1,314                    | 10.5% (7.9–13.4%)  | 0.010 | 2.876     | 6.002  | 0.014 |
| Middle term            | 16  | 6,135                    | 12.7% (10.5–15.2%) | 0.039 | 1.409     |       |      |
| Long term              | 11  | 4,786                    | 16.5% (12.0–21.5%) | 0.016 | 5.737     | 24.227 | 0.000 |
| Detection method       |     |                          |         |      |           |
| EIA                    | 9   | 3,010                    | 11.5% (9.9–13.1%)  | 0.005  | 0.713     | 5.449  | 0.020 |
| EIA+PCR/CC             | 10  | 3,078                    | 14.4% (11.2–18.0%) | 0.044 | 1.984     |       |      |
| PCR                    | 10  | 2,517                    | 17.7% (13.4–22.4%) | 0.074 | 2.146     | 14.991 | 0.000 |
| Detection years        |     |                          |         |      |           |
| Before 2010s           | 7   | 3,120                    | 10.1% (8.7–11.7%)  | 0.004  | 1.393     | 15.531 | 0.000 |
| After 2010s            | 21  | 14,100                   | 12.3% (10.5–14.2%) | 0.049 | 0.952     |       |      |

CDI, Clostridium difficile infection; Ped, pediatric; EIA, enzyme immunoassay; PCR, polymerase chain reaction; CC, culture cytotoxin assay; Ref, reference.
infection control policy or epidemic of a hypervirulent strain. Therefore, continuous regional surveillance was necessary to investigate the presumed association between vulnerability and CDI in the different ethnic groups and regions.

In our study, we only included data on the first post-transplant hospitalization, which may have resulted in the higher overall estimated prevalence. Most studies were followed up from pre-transplantation to 100 days post-transplantation, and the estimated prevalence of CDI with the middle term of follow-up was 12.7%, which was significantly higher than the early term (p = 0.014) and significantly lower than the long term (p < 0.01).

However, most cases of CDI among HSCT recipients were diagnosed in the early term of transplantation because of more intense antimicrobial exposure, high immunosuppression, accelerated antimicrobial exposure, and increased transmission in the hospital environment (Schuster et al., 2017). Our study indicated that the risk of CDI among the middle and late periods cannot be ignored.

The diagnosis of CDI is a complicated process, incorporating clinical diagnosis, defined by the presence of symptoms (usually diarrhea), with laboratory diagnosis, assured by either a stool test positive for C. difficile toxin or detection of toxigenic C. difficile or colonoscopic or histopathologic findings revealing pseudomembranous colitis (McDonald et al., 2018). In our studies, the estimated prevalence of CDI diagnosed by EIA (11.5%) was significantly lower than that diagnosed by EIA+PCR/CC (14.4%, p = 0.02), and the CDI diagnosed by EIA+PCR/CC was significantly lower than that diagnosed by PCR (17.7%, p < 0.01), indicating that a significant discrepancy in the incidence rate of CDI was observed because of the different sensitivity and specificity of the detection methods of CDI. The related laboratory indices of CDI diagnosis detected by EIA were glutamate dehydrogenase (GDH) and C. difficile toxin A and/or B (CDAB). One of our previous studies revealed that the sensitivity of the detection method combining GDH and CDAB for the diagnosis of CDI was only 54.2% (39/72), and with further addition of PCR to the scheme, the sensitivity for the diagnosis of CDI could be increased to 100% (Luo et al., 2018). This mate analysis showed that a PCR for CD toxin was the most sensitive detection method for CDI. A conventional PCR for CD toxin needs to be combined with time-consuming and demanding anaerobic culture, increasing the difficulty of its universal use.

In recent years, some commercially nucleic acid amplification test (NAAT) products were approved by the FDA, such as the Gene Xpert CD assay (Cepheid, Sunnyvale, USA) directly detecting the tcdB gene in feces by RT-PCR, and widely used in the national rapid and simple (Bai et al., 2017). The Gene Xpert was notable because of its high sensitivity and specificity in diagnosing toxigenic CDI both rapidly and simply (Bai et al., 2017).

The recurrence of CD infection occurred in approximately 15% of the initial patients with CDI, with a large variation from 3% to 46% in our analysis. Antecedent antibiotic usage and neutropenia were considered independent predictors of recurrent CDI (Huang et al., 2014; Mani et al., 2016). Notably, 20.3% of CDI cases were severe. However, because of failing raw data on each risk factor, further statistical statements could not be implemented in our analysis. Infection control measures and regional epidemiology possess a significant role in the prevalence of CDI among individual medical centers, and our pooled estimation does not reduce the need for local centers to understand local prevalence. The meta-analysis showed that fecal microbiota transplantation, as an innovative strategy to reduce CDI occurrence, was recommended in patients with recurrent CDI in whom appropriate antibiotic treatments failed (Pession et al., 2021).

Our study estimated the pooled prevalence of CDI among HSCT recipients to be almost 2-fold higher than that in the previous analysis (Zacharioudakis et al., 2014). The increased prevalence of CDI with the high rate of severe cases highlighted the necessity for prophylactic policies, such as antimicrobial stewardship programs, strict hand hygiene procedures, and environmental decontamination that is specifically aimed at this patient population. Furthermore, future studies were required to recognize immunosuppressive and preventive antimicrobial regimens that were presumably associated with a lower risk of CDI.

DATA AVAILABILITY STATEMENT
The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS
Conceptualization: QW. Data curation: YL, BZ, SZ, and HS. Software: YL and WC. Writing—original draft: YL, BZ, and QW. Writing—review and editing: YL, SZ, and HS. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcimb.2022.801475/full#supplementary-material

Supplementary Table 1 | Newcastle Ottawa Quality assessment of individual studies.

Supplementary Table 2 | Recurrence and outcomes of CDI in HSCT recipients.

Supplementary Figure 1 | Prevalence of CDI among adult (A) and pediatric (B) HSCT patients.
**Supplementary Figure 2** | Prevalence of CDI among allogeneic (A) and autologous (B) HSCT recipients.

**Supplementary Figure 3** | Prevalence of CDI among studies in North America (A), Asia (B), and Europe (C).

**Supplementary Figure 4** | Prevalence of CDI among studies with < 200 patients (A) and studies with ≥ 200 patients (B).

**Supplementary Figure 5** | Prevalence of CDI in prospective studies (A) and retrospective studies (B).

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