Prognostic factors for severe and recurrent Clostridioides difficile infection: a systematic review.

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Abstract

Background
Clostridioides difficile infection (CDI), its subsequent recurrences (rCDI), and severe CDI (sCDI) provide a significant burden for both patients and the healthcare system. Identifying patients diagnosed with initial CDI who are at increased risk of developing sCDI/rCDI could lead to more cost-effective therapeutic choices.

Objectives
In this systematic review we aimed to identify clinical prognostic factors associated with an increased risk of developing sCDI or rCDI.

Methods
Data sources: PubMed, Embase, Emcare, Web of Science and COCHRANE Library databases were searched from database inception through March, 2021.
Study eligibility criteria: Cohort and case-control studies.
Participants: Patients ≥18 years diagnosed with CDI.
Exposure: Clinical or laboratory factors analyzed to predict sCDI/rCDI.
Assessment risk of bias: Quality in Prognostic Research (QUIPS) tool and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool modified for prognostic studies.
Methods of data synthesis: Study selection was performed by two independent reviewers. Overview tables of prognostic factors were constructed to assess the number of studies and the respective effect direction and statistical significance of an association.

Results
136 studies were included for final analysis. Higher age and the presence of multiple comorbidities were prognostic factors for sCDI. Identified risk factors for rCDI were higher age, healthcare-associated CDI, prior hospitalization, PPIs started during/after CDI diagnosis and previous rCDI.

Conclusions
Prognostic factors for sCDI and rCDI could aid clinicians to make treatment decisions based on risk stratification. We suggest that future studies use standardized definitions for sCDI/rCDI and systematically collect and report the risk factors assessed in this review, to allow for meaningful meta-analysis on risk factors using data of high-quality trials.
Introduction

*Clostridioides difficile* infection (CDI), its subsequent recurrences (rCDI), and severe CDI (sCDI) provide a significant burden for both patients and the healthcare system [1]. Antibiotic treatment with oral vancomycin and fidaxomicin are the cornerstone of CDI treatment [2-4]. Fidaxomicin reduces the number of recurrences compared to vancomycin [5]. Bezlotoxumab, a monoclonal anti-Toxin B antibody, can be added to oral anti-CDI antibiotic therapy and reduces the number or recurrences in patients at high risk for recurrence [6]. Fecal microbiota transplantation (FMT) is a highly efficacious ancillary treatment for multiple rCDI, and can lower mortality risk and disease burden of sCDI [7, 8].

The acquisition costs of fidaxomicin, bezlotoxumab and FMT are higher compared to those of vancomycin, which may limit widespread application. To this end the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) 2021 update on the treatment guidance for *C. difficile* infection suggest to apply a risk stratification strategy in case of economic restraints. Identifying patients at risk, however, is challenging. Several prediction models have been developed [9-30], yet none has been widely adopted in clinical practice. Here, we aim to identify clinical prognostic factors associated with an increased risk of developing sCDI or rCDI.

Methods

This systematic review was performed in the context of the ESCMID 2021 update of the CDI treatment guidance in adults. Preliminary results have been presented to the expert panel of the guideline committee of the European Study Group on *C. difficile* (ESGCD). As the review of prognostic factors for sCDI/rCDI yielded interesting findings that merited further discussion, it was decided to incorporate these results in a separate manuscript to allow in-depth discussion of results and methodology. The review is conducted according to the recommendations by the Cochrane Prognosis Methods Group following and following the structure of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [31-33].

Data sources

Two searches were performed to identify risk factors for (1) sCDI and (2) rCDI. The search terms and strategy were constructed by a trained librarian, see Supplementary data. PubMed, Embase, Emcare, Web of Science and COCHRANE Library databases were searched on October 4th, 2019 and updated on March 13th, 2021. Meeting abstracts were not considered. The search was not limited by year of publication. References of key papers were assessed for relevant papers.

Study eligibility criteria

Study eligibility was assessed in a two-step selection process. Two independent reviewers screened title and abstract for potentially eligible articles (TvR and RO); discrepancies were resolved by consensus. Full-text articles were retrieved for eligibility; data extraction and risk of bias assessment of included studies was performed by two researchers (TvR and RO).

Inclusion criteria: prospective and retrospective cohort and case-control studies including patients ≥18 years, diagnosed with CDI, and providing an analysis of clinical or laboratory data to predict severe/recurrent CDI.
Exclusion criteria: studies in specific patient populations with a distinct medical condition other than CDI (e.g. study population comprises only hemodialysis patients, since these results are not generalizable to the average C. difficile patient); and small studies (less than 30 patients with severe/recurrent CDI, since these increase the risk of false-positive results, and the risk overestimation of the magnitude of associations, and do not allow adjustment for important confounders). However, studies that assessed a particular medical condition as prognostic factor and compared this to a control group of patients without the condition, were included. Laboratory values that were studied as prognostic factors, but which are not part of the regular work-up in CDI (e.g. specific cytokine assays). Variables that are part of (some of) the definitions of sCDI (e.g. leukocytosis) were excluded as prognostic factor for sCDI to avoid circularity.

Studies on prognostic factors with conflicting results in uni- and multivariable analyses were scrutinized by weighing the results by the quality of evidence per study.

Outcomes of interest were:

1. Severe CDI:
   a. ESCMID 2014/2021 definition: an episode of CDI with (one or more specific signs and symptoms of) severe colitis or a complicated course of disease, with significant systemic toxin effects and shock, resulting in need for ICU admission, colectomy or death [3, 34, 35]; or:
   b. IDSA/SHEA definition: an episode of CDI with a white blood cell count of ≥15x10^9 cells/mL or a serum creatinine level >1.5 mg/dL or increase of 50% or greater from baseline [36]; or:
   c. Any other author-constructed definition of severe/complicated/fulminant/fatal CDI.

2. Recurrent CDI: Recurrence is a new episode of CDI within 2-12 weeks after a previous episode, provided the symptoms of the previous episode resolved after completion of initial treatment [37, 38].

Assessment of risk of bias
Risk of bias was assessed with the Quality in Prognostic Research (QUIPS) tool [32], which is recommended by the Cochrane Prognosis Methods Group. The QUIPS tool appraises six domains: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) study confounding and (6) statistical analysis and reporting. The overall risk of bias per study is scored as low, moderate, or high.

Quality assessment and data synthesis
The quality of evidence per study was assessed by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool, modified for prognostic studies (Supplementary figure 1) [33]. This tool is recommended by the Cochrane Prognosis Methods Group and consists of eight domains. The starting point for the quality of evidence is based on the phase of investigation. The quality can be up- or downgraded according to seven other domains. The QUIPS score is included in the second domain (‘Study limitations/risk of bias’) of the GRADE tool. The outcome of this assessment is the quality of evidence per study, which can be very low (+), low (++), moderate (+++) or high (++++).
Overview tables of prognostic factors were constructed to assess the number of studies and the respective direction of association, i.e. positive, negative, or no association, based on effect estimates, 95% CI intervals and p values, stratified by univariate and multivariate analyses. “Vote counting based on the direction of effect” was performed to assess the direction of effect regardless of statistical significance and to overcome some limitations of underpowered studies [39]. Similar prognostic factors (e.g. coronary artery disease and myocardial infarction) were combined to one factor for a more compact overview. No formal meta-analyses were performed since the definitions of the outcomes of interest (sCDI/rCDI), as well as the definitions of the prognostic factors used in the studies included in this review were highly heterogeneous, and due to incompletely reported effect estimates and different effect measures used across studies.

Results

The search for prognostic factors for sCDI yielded 1242 references; 126 studies were assessed in more detail and 76 were included for analysis [20, 24, 25, 29, 40-110]; twelve more studies retrieved from cross-references were also included [111-122] resulting in 88 studies for final analysis (Figure 1). The search for prognostic factors for rCDI yielded 1104 references; 105 studies were assessed in more detail and 36 were included for analysis [9, 10, 12-15, 103, 110, 123-150] as were seven studies from cross-references.) [112, 151-156]. This resulted in 43 studies for final analysis (Figure 1).

Additionally, data of the pivotal RCTs on fidaxomicin and bezlotoxumab were used to support findings [157-161].

Figure 1. Flow diagram of the selection process of studies on prognostic factors for severe/recurrent CDI

Prognostic factors for severe CDI

The overall quality of evidence ranged from very low to moderate, mainly due to the retrospective nature and small sample size of most studies. The prognostic factors studied in five or more articles are shown in Table 1. An overview of all included studies is provided in Supplementary table 1.

Age was the most studied prognostic factor, and was investigated in 53 of 88 included studies [20, 24, 25, 29, 40-44, 46, 48-51, 54, 56, 57, 59, 61, 63-66, 68, 72, 73, 76, 78, 79, 81, 82, 84, 86-89, 92-95, 97, 98, 101, 105, 107, 110-112, 114, 115, 117-119]. Fifty-one studies performed a univariate analysis and 40 studies (also) a multivariable analysis; 37/51 studies reported higher age as risk factor for sCDI in univariate analysis, and 26/40 studies in multivariable analysis (overall moderate quality of evidence).

Thirty-two studies assessed the presence of multiple comorbidities as risk factor for sCDI [25, 40-44, 48-51, 54, 64, 68, 70, 72, 74, 75, 81, 82, 86, 88, 89, 92-95, 97, 98, 110, 115, 117, 118]; 20/30 studies found an association between the presence of multiple comorbidities and sCDI in univariate analysis and 11/23 studies in multivariable analysis (moderate quality of evidence).

For both higher age and the presence of multiple comorbidities a dose effect was observed: the higher the age or the more concurrent disorders, the higher the risk of severe disease. No specific
medical condition was associated with sCDI, although a positive effect direction (regardless of statistical significance) was observed for cardiovascular-, pulmonary-, neurological-, infectious-, renal- and hepatic comorbidity and for malignancy. For clinical decision making, a specific cut-off value for age and number of comorbidities would be convenient. However, in many studies age was used as a continuous variable (31/53 studies) or varying cut-off values are used. The majority of studies found a higher risk for sCDI in patients older than 65-70 years. For comorbidity, different established or self-constructed comorbidity scores were reported, the Charlson Comorbidity Index (CCI) most frequently [162]. Again, most studies used CCI as continuous variable. Of the studies that identified more comorbidities as risk factor for sCDI, only three used a cut-off value: one study reported a higher risk in patients with a CCI of ≥3, and two found a higher risk in patients with ≥2 comorbidities [89, 94, 97]. Thus, no statement can be made on the association between exact numbers of comorbidities and severe CDI. Twenty articles studied the association between the presence of NAP1/RT027 strain and sCDI [46-48, 58, 62, 63, 74, 75, 82, 85, 86, 89, 90, 92, 95, 97, 101, 102, 109, 112]; 9/19 studies reported a higher risk of sCDI in patients with NAP1/027 strain in univariate analysis, and 7/10 in multivariate analysis. One study found that NAP1/027 was more prevalent in patients with mild disease compared to patients with sCDI [46]. Furthermore, seven studies assessed C. difficile binary toxin as risk factor for sCDI [47, 83, 92, 95, 118, 120, 122]. Of these, three identified C. difficile binary toxin as a risk factor for sCDI in univariate analysis, and only 1/1 study in multivariate analysis. The overall quality of evidence of these studies was low. We scrutinized the separate studies on the presence of NAP1/RT027 strain and/or binary toxin by weighing the results by the quality of evidence per study, but this did not alter the conclusion. However, when we considered the direction of effect regardless of statistical significance, we observed a positive effect direction for both NAP1/RT027 strain and binary toxin. Another interesting finding was that the majority of studies did not find an association between the use of PPIs, H2 receptor antagonists or antibiotics and the occurrence of sCDI in uni- and multivariate analyses. Also for these factors, we found a positive effect direction. However, the quality of evidence was low. In conclusion, only the factors higher age (>65-70 years old) and the presence of multiple comorbidities were consistently associated with sCDI (Table 3).
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<th>Potential prognostic factor</th>
<th>Number of participants</th>
<th>Number of studies</th>
<th>Univariate</th>
<th>Multivariable</th>
<th>Direction of effect$^*$</th>
<th>Phase</th>
<th>Study limitations</th>
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<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Moderate/large effect size</th>
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### CDI factors

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<th>Healthcare facility associated</th>
<th>Community associated</th>
<th>NAP1/027 strain</th>
<th>Binary toxin</th>
<th>Positive toxin EIA</th>
<th>Prior CDI (&gt;3 months)</th>
<th>Recurrent CDI (&lt;3 months)</th>
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**Table 1.** Potential prognostic factors for severe CDI. Phase, phase of investigation. For uni- and multivariate analyses: +, number of significant effects with a positive value; 0, number of non-significant effects; -, number of significant effects with a negative value. For GRADE factors: ✓, no serious limitations; X, serious limitations (or not present for moderate/large effect size, dose effect); unclear, unable to rate item based on available information. For overall quality of evidence: +, very low; ++, low; ++++, moderate; +++++, high.

‡ Direction of effect regardless of statistical significance. NB Many studies did not report the direction of effect, particularly when no effect was found, so it is likely that these results are biased in favor of a positive effect direction; upward arrow ▲, positive direction of effect (prognostic factor for sCDI); downward arrow ▼, negative direction of effect (protective factor for sCDI); sideways arrow ◄►, mixed effects/conflicting findings.

* M = male; F = female. In 5 studies male gender and in 2 studies female gender was identified as prognostic factor for severe CDI in univariate analysis. In multivariate analysis, 3 studies reported male gender and 2 studies reported female gender as risk factor of sCDI.

~ One study analyzed both under- and overweight as prognostic factors for sCDI; this study identified underweight but not overweight as risk factor for sCDI in uni- and multivariate analyses.

¶ Besides from antibiotic use (yes/no) prior to CDI diagnosis, none of the following separate antibiotic class was found to be predictive of sCDI: cephalosporins (n=7 studies), penicillins (n=4), macrolides (n=4), glycopeptides (n=3). Results for carbapenems were inconsistent with a tendency towards 'no effect' (n=8).

^ Publication bias is probable since most prognostic studies for sCDI are performed in hospitalized patients.
Seven studies assessed the presence of C. difficile binary toxin as prognostic factor for sCDI. Of these, one study contained two cohorts: in univariate analysis, binary toxin was associated with sCDI in one cohort, but not in the other cohort [122]. Both results are reported in the results columns of the univariate analyses. Therefore, in this table the number of studies on binary toxin is 7, but the total number of univariate analyses is 8.

† 7 studies, of which one study describes 2 independent cohorts. Therefore, the total number of reported univariate results is 8 instead of 7.

§ One large prospective study (Berry et al) and one small prospective study (López-Cárdenas) found binary toxin as risk factor for severe CDI and/or mortality; one large retrospective study (Carlson et al) found that the combination of binary toxin and eosinopenia was associated with mortality; two smaller prospective studies and two retrospective studies did not identify binary toxin as risk factor for sCDI.
Prognostic factors for recurrent CDI

The overall quality of evidence for the prognosis of recurrent CDI (rCDI) was low to moderate (Table 2). The majority of studies was retrospective, with a high to moderate risk of bias. An overview of all included studies is provided in Supplementary table 2.

Higher age (>65 years old) is the most studied factor and was investigated in 35/43 included studies [9, 10, 12-15, 110, 112, 123, 124, 126, 127, 129, 131-135, 137-142, 144-154], 15/30 studies identified higher age as risk factor for rCDI in univariate analysis, and 16/31 studies in multivariable analysis. Moreover, higher age was the only factor for which we found a moderate to large effect size and a dose-dependent effect.

Eight studies assessed whether a previous CDI recurrence in the preceding 3 months was a risk factor for a subsequent rCDI, and showed inconsistent results [9, 10, 15, 112, 126, 134, 141, 146]. Two prospective studies of higher quality found a clear association of previous recurrence with the risk of a subsequent rCDI [112, 141]. Also, data of the pivotal trials on fidaxomicin and bezlotoxumab indicate that recurrence rates are higher in patients with any previous CDI episode or patients that fulfill criteria for rCDI [157-161]. Since these trials are considered high quality studies, we have upgraded the level of evidence from low to moderate (Table 3). Finally, we consider two or more episodes of CDI as risk factor for a subsequent rCDI.

Healthcare-acquired CDI was associated with rCDI in univariate analyses of 4/10 studies, and in multivariable analyses of 1/4 studies [9, 14, 112, 126, 129, 142, 145, 146, 150, 151]. This is also reflected by the correlation of prior hospitalization (<3 months) with a recurrent episode of CDI [13, 15, 126, 129, 134, 139, 144, 150]. The two largest cohort studies showed a significant association between prior hospitalization and rCDI in uni- and multivariable analysis [129, 150]. Of note, one large cohort study reported a protective effect of community-acquired CDI for the development of rCDI [129], and one study found a protective effect of hospital acquired CDI which they could not explain [146].

Proton pump inhibitor use was studied in 23 included studies [9, 13, 14, 110, 123, 124, 131-136, 138, 140, 142, 146, 148-152, 154, 156]. The results show no clear association between PPIs and rCDI in univariate analyses, while in multivariable analyses there appears to be an association. Of note, some studies made a distinction between the moment PPI was started, i.e. prior to initial CDI episode or during/shortly after the initial episode [12, 13, 15, 124, 126, 147, 150, 156]; PPI prescribed during or shortly after initial CDI appears to be associated with an increased risk of rCDI (effect found in 6/7 studies in univariate analysis, and in 2/4 studies in multivariable analysis; low quality of evidence).

Eight studies reported on non-CDI antibiotic use after initial CDI diagnosis as a risk factor, but results were inconsistent [12, 124, 130, 137, 142, 146, 147, 149]; 4/6 studies found an association between non-CDI antibiotic use and rCDI in univariate analysis, and 2/5 studies in multivariable analysis. A high-quality prospective study showed no significant association between antibiotic use and rCDI in both uni- and multivariate analysis [137]. Several other studies investigated whether specific antibiotics that incited the primary CDI episode, were associated with recurrence; none of these antibiotic drugs was associated with rCDI. In conclusion, nor non-CDI antibiotic use prior to the primary CDI, nor concomitant non-CDI antibiotics used during the primary CDI episode, appeared to be convincing predictors for rCDI.
Although various definitions of sCDI are used in prognostic studies, most studies did not find severity of CDI to be a prognostic factor for rCDI [9, 124, 127, 132, 135, 141-143, 148, 151]; 2/7 studies identified sCDI as risk factor for rCDI in univariate analysis, and 2/4 in multivariable analysis. In the MODIFY trials, sCDI was a prespecified risk factor for recurrence, but in the placebo arm the recurrence rate was lower in the sCDI subgroup (22.4%) than in the non-CDI subgroup (27.5%) [159]. In conclusion, we found insufficient evidence to consider sCDI a risk factor for rCDI.

Several studies investigated specific comorbidities, including chronic renal failure, diabetes mellitus, and cardiovascular disease as risk factors for rCDI [9, 12-15, 112, 123, 124, 126, 127, 129, 131-135, 137, 139-155]. Our review did not find any of these comorbidities to be clearly associated with an increased risk for rCDI. Even when combined into a robust score such as the Charlson Comorbidity Index, we did not identify a clear association [13, 67, 123, 131, 133-135, 141, 146, 147, 149, 151, 153]. Immunocompromised status was a prespecified risk factor in the MODIFY trials; though in the placebo arm the recurrence rate in immunocompromised patients did not differ from that in immunocompetent patients (27.5% vs 26.6%) [159]. A post-hoc analysis of the pivotal fidaxomicin trials investigated fever, leukocytosis and renal failure as prognostic markers, and identified renal failure as the only significant predictor for recurrence (RR, 1.45; 95% CI, 1.05–2.02). Overall, we found insufficient evidence to consider other comorbidities a risk factor for rCDI.

The ribotype 027 strain was not clearly associated with recurrence. However, only five studies reported on this ribotype as a possible risk factor [112, 124, 130, 146, 149]; 2/5 studies found that the presence of a RT027 strain was associated with sCDI in univariate analysis, and only 1/3 studies in multivariable analysis. Since these results were inconsistent when compared to a previous systematic review, results were re-assessed by a third researcher [163]. This reassessment did not result in different conclusions.

Laboratory parameters studied include white blood cell counts, and levels albumin, creatinine and C-reactive protein. None of these parameters was clearly associated with rCDI [10, 12-15, 112, 135, 142, 145-148, 150].

Our findings show the use of probiotics as prophylaxis for CDI seemed to be associated with rCDI [13, 14, 124, 134]. However, this association is based on a small number of studies (n=4) and might be confounded by the fact that probiotics are started in patients with a high risk of rCDI and/or concomitant antibiotic use.
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<th>Multivariate +</th>
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<th>Study limitations</th>
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<th>Moderate/ large effect size</th>
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<td>✓</td>
<td>✓</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Increased length of stay (&gt;10 days)</td>
<td>2,464</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Potential prognostic factors for recurrent CDI. Phase, phase of investigation. For uni- and multivariate analyses: +, number of significant effects with a positive value; 0, number of non-significant effects; -, number of significant effects with a negative value. For GRADE factors: ✓, no serious limitations; X, serious limitations (or not present for moderate/large effect size, dose effect); unclear, unable to rate item based on available information. For overall quality of evidence: +, very low; ++, low; ++++, moderate; ++++, high.

| Concomitant non-CDI AB | 7,980 | 8 | 2 | 4 | 0 | 2 | 3 | 0 | ▲► | 1 | x | x | ✓ | ✓ | ✓ | ✓ | X | X | + |
| Proton pump inhibitor | 43,653 | 23 | 6 | 14 | 1 | 8 | 3 | 1 | ▲► | 1 | x | x | ✓ | ✓ | ✓ | ✓ | X | X | ++ |
| PPI prior to CDI | 14,308 | 5 | 2 | 3 | 0 | 0 | 0 | 0 | ▲► | 1 | x | x | ✓ | ✓ | ✓ | ✓ | X | X | + |
| PPI during/after CDI | 11,785 | 7 | 6 | 1 | 0 | 2 | 2 | 0 | ▲ | 1 | x | x | ✓ | ✓ | ✓ | ✓ | X | X | ++ |
| H2 receptor antagonist | 29,998 | 5 | 2 | 2 | 0 | 2 | 1 | 0 | ▲► | 1 | x | x | ✓ | ✓ | ✓ | ✓ | X | X | ++ |
| Steroids / immunosuppression | 11,429 | 10 | 3 | 6 | 0 | 2 | 3 | 0 | ▲ | 1 | x | ✓ | ✓ | ✓ | ✓ | ✓ | X | X | ++ |
| Probiotics | 29,847 | 4 | 3 | 0 | 0 | 2 | 1 | 0 | ▲► | 1 | x | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | X | X | ++ |
| Chemotherapy | 20,494 | 8 | 0 | 7 | 0 | 1 | 1 | 0 | ▲► | 1 | x | x | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | X | X | ++ |
| Parenteral feeding | 2,988 | 7 | 1 | 6 | 0 | 0 | 0 | 0 | ▲► | 1 | x | x | ✓ | ✓ | ✓ | ✓ | X | X | + |
| Laboratory values | | | | | | | | | | | | | | | | | | | | |
| Leukocytes (mean/peak) | 22,954 | 17 | 6 | 10 | 0 | 1 | 3 | 0 | ▲► | 1 | x | ✓ | ✓ | ✓ | ✓ | ✓ | X | X | ++ |
| Albumin (mean/low) | 18,737 | 12 | 4 | 8 | 0 | 1 | 2 | 0 | ▲► | 1 | x | ✓ | ✓ | ✓ | ✓ | ✓ | X | X | ++ |
| Creatinine (mean/peak) | 19,651 | 14 | 1 | 12 | 0 | 1 | 2 | 0 | ▲► | 1 | x | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | X | X | +++ |
| C-reactive protein | 9,805 | 5 | 2 | 2 | 0 | 0 | 0 | 0 | ▲► | 1 | x | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | X | X | + |
| Symptoms | | | | | | | | | | | | | | | | | | | | |
| Fever | 3,740 | 9 | 3 | 6 | 0 | 2 | 0 | 0 | ▲► | 1 | x | x | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | X | X | ++ |
| Abdominal pain | 5,756 | 5 | 2 | 3 | 0 | 0 | 0 | 0 | ▲► | 1 | x | x | ✓ | ✓ | ✓ | ✓ | ✓ | X | X | + |

‡ Direction of effect regardless of statistical significance. NB Many studies did not report the direction of effect, particularly when no effect was found, so it is likely that these results are biased in favor of a positive effect direction; upward arrow ▲, positive direction of effect (prognostic factor for sCDI); downward arrow ▼, negative direction of effect (protective factor for sCDI); sideways arrow ▲►, mixed effects/conflicting findings.
Table 3. Summary of findings

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe CDI</strong></td>
<td></td>
</tr>
<tr>
<td>Higher age (&gt;65-70 years old)</td>
<td>moderate</td>
</tr>
<tr>
<td>Presence of multiple comorbidities</td>
<td>moderate</td>
</tr>
<tr>
<td><strong>Recurrent CDI</strong></td>
<td></td>
</tr>
<tr>
<td>Higher age (&gt;65-70 years old)</td>
<td>moderate</td>
</tr>
<tr>
<td>Previous recurrence of CDI (&lt;3 months)</td>
<td>moderate</td>
</tr>
<tr>
<td>Healthcare-associated CDI</td>
<td>low</td>
</tr>
<tr>
<td>Prior hospitalization (&lt;3 months)</td>
<td>low</td>
</tr>
<tr>
<td>Proton pump inhibitors started during/after CDI diagnosis</td>
<td>low</td>
</tr>
</tbody>
</table>

Discussion

In this systematic review, we applied the GRADE methodology to weight the evidence on prognostic factors for sCDI and rCDI [33]. We found that the most important risk factors for sCDI were higher age (>65-70 years old) and presence of multiple comorbidities. Higher age was also a prognostic factor for rCDI. Other factors associated with an increased risk of rCDI were a previous recurrence of CDI, the acquisition of CDI as a healthcare-associated infection, prior hospitalization and the start of PPIs during/after CDI diagnosis.

Our review has several strengths. First, we used a broad search strategy and included a large number of studies, minimizing the risk of missing data. Second, articles were selected based on strict predefined criteria by two independent researchers (TvR and RO). Third, the quality of the studies was judged by the structured prognostic GRADE approach. To our knowledge this approach has not been previously used for prognostic factors for sCDI and rCDI. Also, we report results of both univariate and multivariable analyses, providing a complete overview of available data. Including only data from multivariate analysis would introduce a major selection bias, since many studies only included significant univariate prognostic factors in the multivariate models.

A limitation is the generally low quality of available studies. Most studies have not performed a sample size calculation, allowing for possible type I and type II statistical errors. As many studies were retrospective, it was not always clear whether certain factors were already present before the occurrence of sCDI/rCDI (i.e. truly prognostic factors) or whether they co-existed. A second important limitation is the subjectivity how to weight different quality studies, which also resulted in stimulating discussions in our working group. Due to incompletely reported effect estimates and different effect measures used across studies, a meta-analysis and most “Acceptable synthesis methods” recommended by the Cochrane group were not feasible [39]. The first proposed acceptable synthesis method, “Summarizing effect estimates” could not be performed since in the majority of included studies effect estimates were not available and could not be calculated from the reported data. Especially for univariate analyses, most studies provided only p values and not relative measures (such as odds ratios) or absolute measures (such as mean differences). Furthermore, “Combining p values” – the next recommended synthesis method – was not applicable because many studies reported only binary p values such as “<0.05” or “>0.05”. For the final recommended
approach, “Vote counting based on the direction of effect”, a direction of effect should be reported. Unfortunately, this data was only available for most multivariate- but not many univariate results. Nevertheless, we performed “Vote counting based on the direction of effect” on the available results of included studies, in order to provide more information on the direction of effect regardless of statistical significance (see Supplementary). This overcomes some limitations of underpowered studies.

Identifying prognostic factors for sCDI and rCDI could aid clinicians to make an optimal treatment decision to reduce the risk of recurrent disease and decrease CDI complications. The findings of this review are especially relevant for rCDI: a risk stratification strategy may allow for selective use of more expensive novel treatments with less risk of recurrence. To implement risk stratification of in clinical practice, simple risk tools are needed. Several prediction models or risk scores for scDI and rCDI have been developed [9-30]. However, none has gained widespread clinical implementation. Based on the low quality of the studies and small effects of identified prognostic factors, it is not surprising that external validation of prediction tools show disappointing results [164-166]. Additional explanations are the heterogeneity and multimorbidity of the CDI population and variation in study setting, diagnostic criteria and CDI treatment regiments. The current review may be used as starting point for the development of a risk tool with a better performance in the overall CDI population.

In conclusion, our approach identified higher age and the presence of multiple comorbidities as prognostic factors for sCDI. The only identified risk factors for rCDI were higher age, healthcare-associated CDI, prior hospitalization (<3 months), PPIs started during/after CDI diagnosis and rCDI. We suggest that future clinical trials on CDI treatment use standardized (ESCMID/ECDC) definitions for recurrence and severity and systematically collect and report the risk factors that we have discussed in this review, to allow for meaningful meta-analysis on risk factors using data of high-quality trials.

Transparency declaration

Conflict of interest disclosures, funding
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Contribution
JP and EK conceived the study on behalf of the ESGCD. JP designed the search strategy. TvR and RO selected the studies and acquired the data. TvR, RO, CV-G and JK graded selected studies. TvR, RO and OD analyzed the data. TvR and RO drafted the manuscript. All authors critically revised the manuscript and approved the final version.

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