Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

The burden of *Clostridioides difficile* infection in COVID-19 patients: A systematic review and meta-analysis

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ABSTRACT

Objectives: The main aim of this systematic review and meta-analysis was to assess the proportion of confirmed COVID-19 patients with *Clostridioides difficile* infection (CDI) and to describe risk factors and outcome of these patients.

Methods: MEDLINE and Cochrane Central Register of Controlled Trials databases were searched up to July 15, 2021. We included studies reporting data on CDI occurring in patients with a confirmed diagnosis of COVID-19. We pooled proportion of CDI patients using a random effects model (DerSimonian–Laird method) stabilising the variances using the Freeman-Tukey double arcsine transformation.

Results: Thirteen studies were included in the systematic review. All the studies retrospectively collected data between February 2020 and February 2021. The reported CDI incidence rates ranged from 1.4 to 4.4 CDI cases per 10,000 patient-days. Seven studies reported data on the number of COVID-19 patients who developed CDI and the total number of COVID-19 patients in the study period and were included in the meta-analysis, comprising 23,697 COVID-19 patients. The overall pooled proportion of COVID-19 patients who had CDI was 1% [95% confidence interval: 1–2]. Among studies reporting CDI occurrence in patients with and without COVID-19, the majority of them reported reduced or unchanged CDI rates compared to pre-COVID period.

Conclusions: CDI is a relevant issue for COVID-19 patients. Adherence to infection prevention and control measures and to the antimicrobial stewardship principles is crucial even during the COVID-19 pandemic.

1. Introduction

Since December 31, 2019, when the World Health Organization was informed of an outbreak of respiratory disease affecting the city of Wuhan, China, the world has been shaken by the most profound health crisis of the last several decades [1,2]. The infection caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) rapidly become pandemic, heavily testing the preparedness and resiliency of the health systems worldwide [3]. So far, more than two hundred million people are known to have been infected, and at least four million people died [3].

Especially in critical areas, health-care facilities suddenly faced high number of hospitalizations, shortage of staff, of essential supplies such as oxygen and of personal protective equipment (PPE). The novelty and rapid spread of COVID-19 entailed the lack of high-level evidence on COVID-19 management, leading to the adoption of heterogeneous approaches.

As an example, the first available recommendations on the management of COVID-19 patients considered the use of empirical antibiotic treatment for the fear of bacterial co-infections, resulting in a large use of antimicrobials [4-9]. Therefore, the compliance with antibiotic stewardship programs could have been challenged during the pandemic [4].

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At the same time, the epidemic spread of the SARS-COV-2 could have pushed the health care workers paying more attention to the measures aimed at preventing the transmission of the virus to themselves at the expense of the ordinary infection prevention and control (IPC) measures applied for protecting patients during hospital care.

These COVID-19 induced modifications in antimicrobial prescriptions and IPC measures could have had an impact on the spread of bacterial infection. On the other hand, some factors linked to the pandemic, for instance implementation of hand hygiene, extensive use of PPE and increased disinfection of the hospital environment, could have resulted in a decrease in the overall rate of bacterial infections.

The issue of bacterial co-infections in COVID-19 patients has received increasing attention among scientists and a considerable number of publications have been released in the last months.

Among bacterial infections, *Clostridioides difficile* infection (CDI) in COVID-19 patients had generated less resonance in the scientific community; yet CDI is commonly associated with the use of broad-spectrum antibiotics, hospital overcrowding [10], gut microbioma alterations, patient's ageing and frailty. Prior to the COVID-19 pandemic, *Clostridioides difficile* (CD) was among the commonest organism causing infections in hospitals and a raising incidence of CDI has been reported also in the community. Not surprisingly, CDI cases have been described in the course of COVID-19 [11, 12].

Currently, we do not yet have a clear picture of the prevalence of and of the risk factors for CDI in COVID-19 patients and importantly, there is a paucity of outcomes data in patients with these co-infections.

We performed a systematic review of the literature with the main aim to summarize available evidence on the proportion of patients with confirmed COVID-19 disease who presented CDI and to describe risk factors and outcome of these patients. In addition, we sought to summarize reported differences in the incidence of CDI comparing the pandemic period with the pre-COVID-19 period, contextually describing changes in the application of IPC measures and in the antibiotics' consumption.

2. Methods

2.1. Article identification

Published articles (from January 2020 to May 2021) reporting data on the occurrence of CDI in COVID-19 patients were identified through computerized literature searches using MEDLINE (National Library of Medicine Bethesda MD) and Cochrane Central Register of Controlled Trials (CENTRAL) databases and by reviewing the references of retrieved articles. Combinations of the following search terms were applied: [(COVID-19) OR (SARS-CoV-2) OR (coronavirus disease 2019)] AND [(clostridium difficile) OR (clostridoides difficile) OR (CDI)].

Publications written in languages other than English, studies published only in abstract form, reviews, case-reports, editorials, guidance articles or guidelines and clinical trial protocols were excluded from further assessment. No attempt was made to obtain information about unpublished studies. Reviewed articles were maintained in a master log and any reason for exclusion from analysis was documented in the rejected log.

2.2. Eligibility criteria

Studies of any design which reported data on CDI occurring in patients with a confirmed diagnosis of COVID-19 were eligible for inclusion in our systematic review.

2.3. Study selection and data extraction

Eligibility assessment and extraction of data were performed independently by two investigators (G.G. and M.A.C.). Each investigator was blinded to the other investigator's data extraction. In case of disagreement between the two reviewers, a third reviewer was consulted (N·P.). Data from each study were verified for consistency and accuracy, and then entered into a standardized computerized database. Abstracted information included: author, year of publication, country in which the study was conducted; study design, start and end date of study, health-care setting, sample size; CD testing methods and criteria for CDI diagnosis; proportion of patients receiving antibiotics; proportion of patients with a CDI diagnosis; site of CDI acquisition, i.e. community-acquired (CA), health-care associated (HCA), hospital onset (HO); patients' outcome data; antibiotic consumption during the study period and IPC measures applied.

2.4. Data synthesis

The main outcome of interest was the overall proportion of CDI in patients with COVID-19.

We pooled proportion of CDI patients using a random effects model (DerSimonian–Laird method) stabilising the variances using the Freeman-Tukey double arcsine transformation. Results were illustrated using forest plots.

Meta-analysis was done if more than two studies reporting data on the main outcome were available. The I^2 test was calculated to assess whether results varied no more than might have been expected by the play of chance (random sampling). A significant heterogeneity was considered for $P < 0.10$ and $I^2 > 50\%$.

Analysis was performed using the software program Intercooled Stata (Stata Statistical Software; release 15.0, College Station, Texas).

2.5. Assessment of bias

A formal assessment for risk of bias was deemed to have limited utility given the lack of an appropriate assessment tool. Although a risk-of-bias tool has been developed for meta-analyses of disease prevalence, many aspects of the tool are not directly relevant to our research question.

3. Results

3.1. Studies description

Fig. 1 shows the selection process of studies included in the systematic review. Thirteen studies were included in the systematic review [12–24]; summary description of the included studies is reported in Table 1.

All the included studies retrospectively collected data between February 2020 and February 2021. Four studies were multicenter [12,13,19,21], all but two [14,17] included COVID-19 patients admitted in all the hospital departments. One study reported the inclusion of both hospitalized and non hospitalized patients [23]. All included studies reported that the diagnosis of COVID-19 was laboratory confirmed.

Regarding CDI diagnosis, ten studies reported that CDI was defined by the presence of clinical symptoms and microbiological evidence of CD [12–17,19–22]; three studies did not specify if clinical symptoms were considered in the definition of CDI [18,23,24].

All but four studies [14,19,23,24] reported data on the epidemiological classification of included CDI; five studies included only HO cases [16–18,20,22].

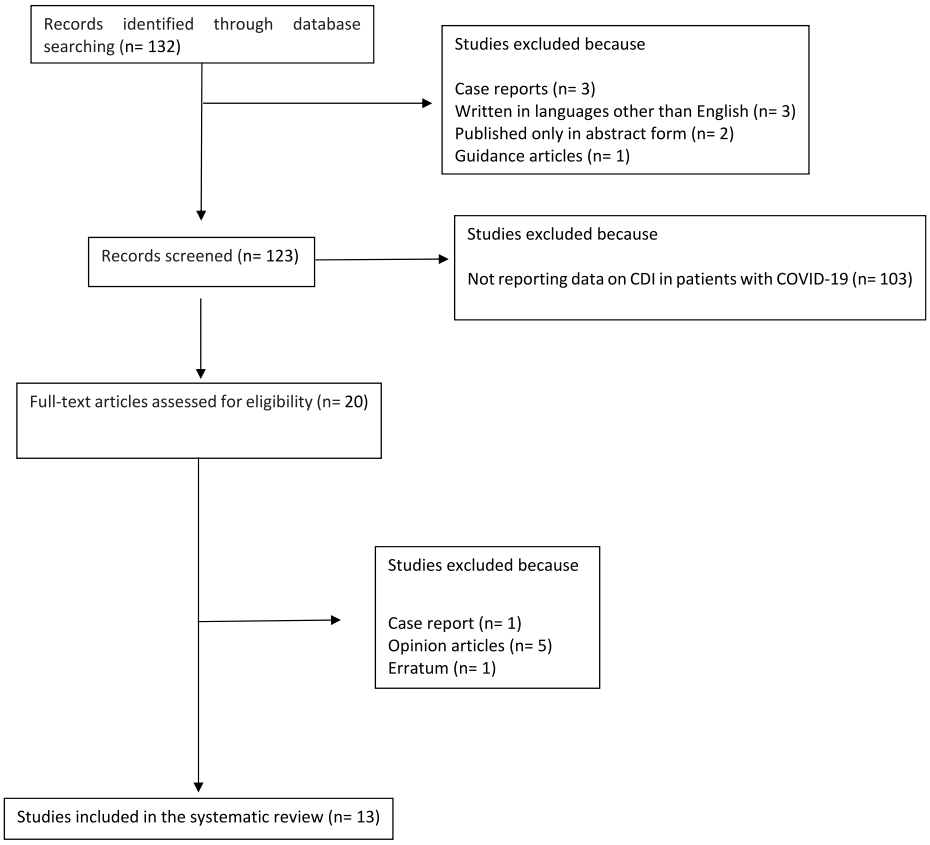

Fig. 1. Flowchart depicting the selection process of studies included in the systematic review.

3.2. Proportion of COVID-19 patients with CDI: meta-analyses

Seven studies reported data on the number of COVID-19 patients who developed CDI and the total number of COVID-19 patients in the study period and were included in the meta-analysis [13–15,17,19,21,22], comprising 23,697 COVID-19 patients.

The overall pooled proportion of COVID-19 patients who had CDI was 1% [95% confidence interval (CI) 1–2] (Fig. 2). There was high statistical heterogeneity between studies ($I^2 = 95.8\%$). The overall pooled proportion of COVID-19 patients who had HO-CDI was 1% [95% CI 0–1; $I^2 = 81\%$] (Fig. 3).

The causes of heterogeneity were not explored due to the low number of included studies.

3.3. Comparison of occurrence of CDI in COVID-19 and non COVID-19 patients, antibiotic use and infection control measures

Eleven studies reported CDI occurrence in patients with and without COVID-19, by comparing data of patients hospitalized in the same hospital in the pre-pandemic period [12,14–18,20–22,24] or data of patients without a COVID-19 diagnosis hospitalized in the same hospital and in the same period [19].

It should be emphasised that studies reported results of comparison in a heterogeneous way and in some cases without detailing specific data on number of CDI in the two groups.

Four studies found a decrease in CDI occurrence in COVID-19 patients [15–17,20].

Ponce-Alonso M et al. reported that the healthcare facility associated CDI incidence density was around 3 times lower for the COVID-19 period than for the non-COVID-19 period (2.68 per 10,000 patient days versus 8.54 per 10,000 patient days; incidence rate ratio, 0.31; 95% CI, 0.16–0.61; P = 0.000257) [15].

Regarding IPC measures, an infection prevention bundle was implemented during the COVID-19 period, including extensive use of PPE when caring for patients with COVID-19 and of mask, gloves, and gowns when treating patients without COVID-19. Environmental cleaning was reinforced and visits were prohibited [15]. The consumption of antibiotics measured by DDD per 100 bed days was higher during the COVID-19 period (89.73) than during the control period (79.16) [15].

Ochoa E et al. identified 1.4 and 9.3 HO-CDI per 10,000 patient-days during the pandemic and the pre-pandemic period, respectively [16]. Mean adherence to hand hygiene before and after the pandemic was 66.1% and 94.7%, respectively. In the COVID-19 period, contact precautions were applied to all patients, but only 52.3% of 976 questionnaire respondents reported full compliance with contact precautions all the time; 66.3% used gloves and 58.9% used gowns in every patient encounter. Noteworthy, during the pandemic, adherence to hand hygiene and to contact precautions were assessed by self-reporting with the use of a standardized electronic questionnaire. Cleaning and disinfection procedures were unchanged [16].

Bentivegna E et al. reported that during the pandemic HCA-CDI incidence was significantly lower with respect to 2017 (odds ratio [OR] = 2.98; P = .002), 2018 (OR = 2.27; P = .023) and 2019 (OR = 2.07; P = .047). Interestingly, during 2020, COVID-19 departments showed higher, but not significant, HCA-CDI incidence with respect to COVID-19 free wards [17]. Regarding IPC measures, authors did not detail differences in their application during the different periods however, they stated that from the beginning of the pandemic, PPE were employed by health care workers and a greater attention has been paid to frequent handwashing and

Table 1
Characteristics of the studies on CDI occurrence during COVID-19 pandemic.

Author	Country	Study design	Setting	COVID-19 pandemic study period	Number of CDI cases/ COVID-19 patients enrolled in the study	Non COVID-19 study period	CDI incidence(10,000 patients/day) during COVID-19	CDI incidence (10,000 patients/day) before the COVID-19 pandemic
Granata G et al. [13]	Italy	Retrospective, observational, 3:1 matching case-control	8 tertiary hospitals	From February to July 2020	38/8402	–	4.4	–
Lewandoski K et al. [14]	Poland	Retrospective, observational	Hospital department of internal medicine and gastroenterology	From March 15th to June 15th, 2020	48/441	From January 2019 to December 2019	–	–
Ponce-Alonso M et al. [15]	Spain	Retrospective, observational	Tertiary care hospital	From March 11 to May 11, 2020	12/2337	From March 11, 2019, to May 11, 2019	2.68	8.54
Bentivegna E et al. [17]	Italy	Retrospective, observational	Single tertiary hospital. Intensive care units and paediatric wards were excluded	From March 1 to June 30, 2020	7/150	from March 1, 2019 to June 30, 2019	–	–
Laszkowska L et al. [19]	US	Retrospective, observational	Two tertiary care hospitals	From March 11 to April 28, 2020	9/2870	From March 11, 2020 to April 28, 2020	–	–
Allegretti J et al. [21]	US	Retrospective, cohort	Nine hospitals (two tertiary, seven community hospitals)	From November 3 to February 4, 2020	5/390	2019	–	–
Manea E et al. [22]	Romania	retrospective, cohort	Tertiary care hospital	From March 2020 to February 2021	51/9107	From March 2017 to February 2018	–	–
Sandhu A et al. [12]	US	Retrospective, observational	Eight hospitals belonging to the Detroit Medical Center	March–April 2020	9 CDI cases	–	3.6	3.3
Ochoa E et al. [16]	Mexico	Retrospective, observational, before-after	Tertiary care hospital	From April to July 2020	2 CDI cases	From January 1, 2019 to February 29, 2020	1.4	9.3
Luo Y et al. [18]	US	Retrospective, observational	Tertiary care hospital	February –June 2020	–	February –June 2019	–	–
Hazel K et al. [20]	Ireland	Retrospective, observational	Tertiary care hospital	From March 1 to May 31, 2020	4 CDI cases	March 1 to May 31, 2019	2.15	4.24
Sehgal et al. [23]	US	Retrospective, observational	Tertiary care hospital	from March 1 to November 17, 2020	–	–	–	–
Hawes AM et al. [24]	US	Retrospective, observational	Tertiary care hospital	March–June 2020	–	from January to February 2020	–	–

surfaces disinfection [17].

Hazel K et al. found that HCA-CDI decreased during the first wave of the COVID-19 pandemic period compared with the same periods in 2018 ($P = .0013$) and 2019 ($P < 0.0001$). Of note, authors also included cases of CDI which occurred in non COVID-19 patients during the pandemic period [20]. IPC measures implemented during the pandemic included a hospital-wide transmission-based–precautions educational program, increased focus on hand hygiene compliance and audit, social distancing, and reduced ward occupancy. Hand hygiene audit scores showed a significant improvement during the first COVID-19 wave compared with 2018 ($P = .0015$) and 2019 ($P = .045$). No changes in antimicrobial consumption were reported [20].

Only one study found a significant increase in the rate of CDI during the COVID-19 pandemic compared to the pre-pandemic period (10.9% versus 2.6%, $p < 0.0001$). This study included only patients hospitalized in the Department of Internal Medicine and Gastroenterology and excluded from the analysis patients with inflammatory bowel disease [14]. Of note, authors reported an increase in antibiotic use, expressed as daily antibiotic intake per 100 person-day of hospitalisation, from 57.2 before the pandemic to 105 during the COVID-19 period. No data on IPC measures were reported [14].

The remaining studies reported no statistically significant differences in the incidence or in the proportion of CDI during the two periods [18,22,24] or did not report data on statistical comparison [12,21].

Regarding IPC measures and antibiotic use, in the study by Luo Y et al. an increased rate of high-risk antibiotic prescriptions predisposing to CDI, including clindamycin, fluoroquinolones, and third generation cephalosporins was detected [18]. In the study by Hawes et al. guidance on optimisation use for secondary bacterial pneumonia was added to the institutional COVID-19 treatment guidelines; moreover, authors reported an increased use of cephalosporins, quinolones and clindamycin in the second month of the post-pandemic period [24].

Finally, Laszkowska L et al. reported a CDI rate of 5.1% in COVID-19 positive patients versus 8.2% in negative patients hospitalized during the same period [19]. No data on IPC measures and antibiotic consumption were reported.

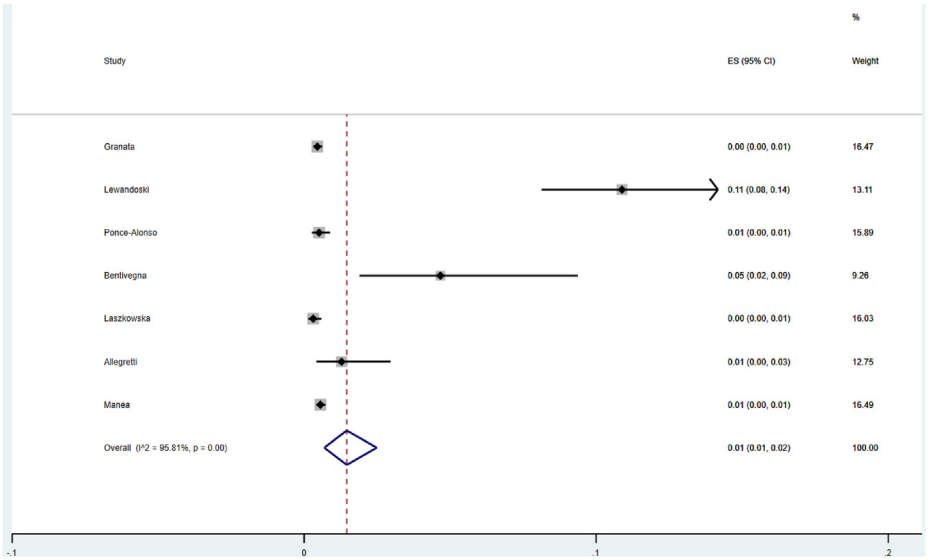

Fig. 2. Pooled proportion of COVID-19 patients who had CDI
Legend: ES, Estimated proportion.

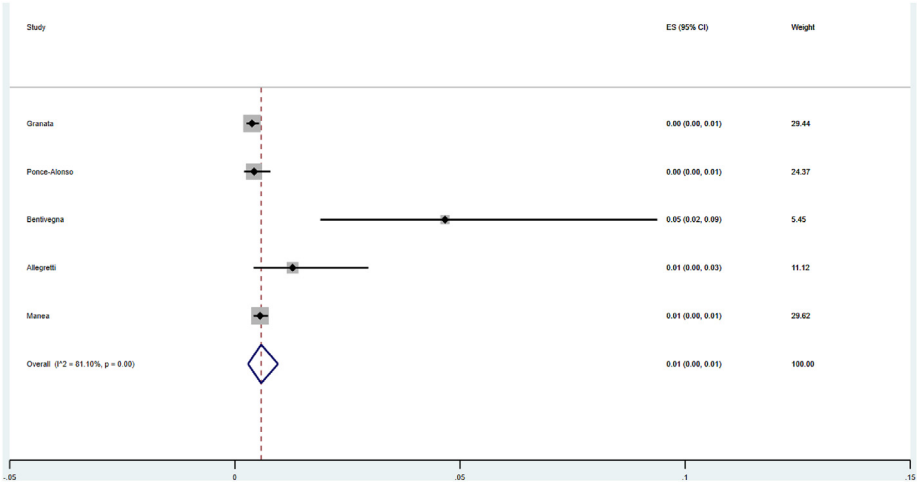

Fig. 3. Pooled proportion of COVID-19 patients who had hospital-onset CDI
Legend: ES, Estimated proportion.

3.4. Risk factors for CDI in COVID-19 patients

Out of the 13 articles included in this review, only 3 articles assessed risk factors for CDI in COVID-19 patients [13,14,21] and one study examined differences between COVID-19 positive and negative patients with CDI [22].

In a multicenter, 3:1 matching case-control study including 32 HO- and 6 community-onset HCA-CDI, logistic regression analysis identified a previous hospitalisation ($p = 0.001$), previous steroid administration ($p = 0.008$) and the administration of antibiotics during the hospital stay ($p = 0.004$) as independent risk factors associated with CDI in COVID-19 patients [13].

In the retrospective, single center observational study performed by Lewandoski K. et al., a multivariable logistic regression model found that duration of hospitalisation ($p = 0.010$), stay in the intensive care unit (ICU) ($p = 0.006$), and onset of abdominal symptoms during hospitalisation ($p = 0.001$) were significant factors associated with the occurrence of CDI in COVID-19 patients [14].

The retrospective multicenter cohort study by Allegretti et al. reported that all COVID-19 patients with CDI were exposed to at least two antibiotics prior to CDI diagnosis, however no significant difference between CDI and non-CDI patients were found regarding the median number of antibiotics used. Moreover, proton pump inhibitor use during hospitalisation was more common among CDI patients, although statistical significance was not reached [21].

The retrospective study by Manea et al. compared CDI patients hospitalized during the pandemic with those previously hospitalized [22]. Patients with HO-CDI in the COVID-19 group were older, with a higher rate of cardiovascular disease and less immunosuppression, moreover they had a higher use of proton pump inhibitors but similar previous use of antimicrobials [22]. Differences in antibiotic classes were noted, with a higher use of cephalosporin and macrolides and a lower exposure to quinolones and glycopeptides [22].

3.5. Outcome of COVID-19 patients with CDI

Only six of the 13 studies reported data on outcome of COVID-19 patients with CDI [12,13,16,21–23].

The article by Sandhu A et al., including nine COVID-19 patients with CDI, reported that four of them (44.4%) died during hospitalisation [12].

The study by Granata reported that 19/38 (50%) COVID-19 patients with CDI recovered and were discharged without complications; 8/38 (21.1%) developed complications at discharge; 11/38 (28.9%) patients died in the hospital. CDI was the main cause of death in one of these patients. Mortality rate did not differ significantly in CDI patients as compared to COVID-19 patients without CDI; in-hospital stays was longer among CDI cases (35 versus 19.4 days, $p = 0.0007$). Among the twenty-one patients who were followed up to 30 days from the hospital discharge, three developed a recurrence of CDI and one of them died due to the recurrence [13].

In the study by Ocho-Hein, both COVID-19 patients who acquired CDI were discharged without complications [16].

The retrospective cohort study by Allegretti et al. found a significantly higher mortality rate among the five CDI patients compared to COVID-19 patients without CDI (80% versus 12.2%, $p < 0.0001$) [21].

Manea et al. reported no significantly different mortality rate in CDI patients with COVID-19 and in those who acquired CDI in the pre-COVID-19 period (7.8% versus 10.1%, $p = 0.07$) [22].

Among 21 COVID-19 patients with CDI included in the study by Sehgal, 2 required ICU admission and 4 died within 30 days; authors reported that neither ICU admission nor death were related to CDI [23].

4. Discussion

During the COVID-19 pandemic, some risk factors for CDI, including older age, comorbidities and overuse of antimicrobials were well represented in the population of hospitalized patients with SARS-CoV-2 infection.

In our systematic review, we included 13 studies dealing with the issue of CDI in the pandemic period, the reported CDI incidence rates were not negligible, ranging from 1.4 to 4.4 CDI cases per 10,000 patient-days.

We were able to include seven studies in the meta-analysis, comprising 23,697 COVID-19 patients.

According to our results, the estimated pooled proportion of COVID-19 patients who presented CDI was 1%. When we included in the meta-analysis only HO-CDI cases the pooled proportion did not change.

As reported by the Center for Diseases Control and Prevention, 2,281,115 COVID-19 patients have been hospitalized in the United States from the August 1, 2020 to the June 28, 2021 [25]. Therefore, according to our findings, the estimated CDI cases among hospitalized COVID-19 patients in the United States since August 2020 could reach the impressive figure of 22,811 cases.

It should be emphasised that the included studies were extremely heterogeneous, being studies performed in different epidemiological settings, with different adherence to IPC measures and to antimicrobial stewardship principles. Additionally, the way patients who acquired CDI were identified differed widely, with some studies reporting little data on the methods used. Certainly, a major limitation is represented by the retrospective inclusion of CDI cases in all studies.

Regrettably, due to few studies reporting data on patient-days, we could not calculate a pooled incidence rate.

Importantly, we systematically reviewed available data on comparison of CDI occurrence in the pre- and in the post-COVID-19 period. Among ten studies reporting data on this comparison, four found a decrease in CDI occurrence in COVID-19 patients [15–17,20] and three reported no statistically significant differences [18,22,24]. It should be highlighted those studies reported results of comparison in a heterogeneous way and in some cases without detailing specific data on number of CDI in the two groups.

Furthermore, the available data on the implementation of IPC measures and adherence to them and the data on antibiotic consumption were scarce and not systematically collected.

Of concern, data on CDI occurrence in COVID-19 patients may represent an underestimate of the real CDI burden, as COVID-19 may cause CDI underdiagnosis due to the misleading interpretation of gastrointestinal symptoms in COVID-19 patients. Indeed, Luo Y et al. detected a trend toward decreased CD testing volume during the COVID-19 period, but a higher percentage of tests returned positive [18]. Therefore, patients who presented with diarrhea during the pandemic may have had their gastrointestinal symptoms attributed to COVID-19, and CD testing may have been not performed.

Finally, a question should be raised whether the available studies on CDI performed before and after the COVID-19 pandemic were comparing the same patient population. This is a key question in order to evaluate the impact of COVID-19 on CDI incidence, considering that patients hospitalized during the COVID-19 pandemic were probably different in terms of comorbidities, age and type of health care needed to those in the pre-COVID-19 period.

Even if acknowledging these pitfalls, our finding could be comforting as, at least in part, it mitigates fears that the pandemic could cause an alarming increase in the incidence of CDI. Certainly, further studies carried out with more reliable and homogeneous methods are needed to confirm this preliminary finding.

Interestingly, renowned risk factors associated with CDI were confirmed also in COVID-19 patients. In fact, studies included in our systematic review, reported antimicrobial exposure, previous hospitalisation and ICU stay as risk factors associated with CDI in COVID-19 patients.

An alarming finding is represented by the extremely high percentage of COVID-19 patients who received broad-spectrum antibiotics during their hospital stay, even though there is no evidence of any benefit of empirical antimicrobial administration for pneumonia during SARS-CoV-2 infection. Interestingly, a study that described national antibacterial use in England between January and October 2020 reported that the rate of prescribing measured in DDDs/1000 admissions increased in April 2020 and returned in July 2020 to similar levels seen in previous years [26]. An international web-based survey that investigated the pattern of antibiotic use by physicians involved in treatment of COVID-19 during April 2020, reported a widespread use of broad-spectrum antibiotic [9]. In fact, only 29% of respondents chose not to prescribe an antibiotic to patients hospitalized for COVID-19. Importantly, the length of empirical antibiotic treatment ranged from 5 to 8 days. Many factors could have influenced the antibiotic prescribing pattern, especially during the first wave of the pandemic, among them the uncertainties about bacterial co-infection, the greater disease severity of patients admitted to hospitals, the difficulties in obtaining microbiological results. As a consequence, many prescriptions may have been driven by the fear of facing an unknown disease and COVID-19 patients have been unnecessarily and for longer time than required exposed to antibiotics. This placed them at risk for serious adverse events, including CDI, with no clinical benefit.

Regarding the outcome of COVID-19 patients who acquired CDI, data are contrasting with one study reporting that the mortality rate did not differ significantly [13] and one study that found a significantly higher mortality rate in CDI patients as compared to COVID-19 patients without CDI (80% versus 12.2%) [21].

It should be borne in mind that the available data refer mainly to the crude hospital mortality rate. In the study by Granata et al., it has been specified that CDI was the main cause of death for one of the 11 patients died during hospitalisation [13]. In another study authors stated that neither ICU admission nor death were related to CDI in their cohort of patients [23].

Comparing CDI patients with COVID-19 with those who acquired CDI in the pre-COVID-19 period, no significantly different mortality rate was found (7.8% versus 10.1%) [22].

It is anyway alarming the finding of a high mortality rate, up to 80% of patients with COVID-19 and CDI.

In conclusion, our systematic review highlighted that CDI is a relevant issue for COVID-19 patients. The infection by SARS-CoV-2 may alter the onset and the clinical course of CDI through different mechanisms, including the derangement of the innate and the adaptive immune response [27] and the damage to the host gastrointestinal barrier exerted by the virus [28,29], the detrimental effect to the gut microbiome exerted by hospitalisation and antimicrobials administration during the treatment of COVID-19 patients. Moreover, the long-term impact of COVID-19 and CDI coinfection is still unknown. Gastrointestinal tract express SARS-CoV-2 receptors angiotensin converting enzyme 2 and transmembrane Serine Protease 2 and may be directly damaged by the virus [30]; also, the elderly patients surviving COVID-19 might be exposed to more hospitalizations and antibiotics, with a higher risk of gut microbiota disequilibrium and subsequent exposure to CD [31].

Consequently, adherence to IPC measures and to the antimicrobial stewardship principles is more important than ever during the COVID-19 pandemic.

Further studies are needed to better assess the impact of infection control procedures reinforcement during the COVID-19 pandemic on CDI incidence and to clarify the interplay between COVID-19 and CDI.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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