Post-Discharge Outcomes of Elderly Patients Hospitalized for Inflammatory Bowel Disease Flare Complicated by *Clostridioides difficile* Infection

Idan Goren*[1,2], Ortal Fallek Boldes*[3], Tomer Boldes[4], Oleg Knyazev[5,6], Anna Kagramanova[5,7], Jimmy K. Limdi[8,9], Eleanor Liu[9], Karishma Sethi-Arora[8], Tom Holvoet[10,11], Piotr Eder[12], Cristina Bezzio[13,14], Simone Saibeni[15], Marta Vernero[15,16], Eleonora Alimenti[15,17], María Chaparro[18], Javier P. Gisbert[18], Eleni Orfanoudaki[19], Ioannis E.Koutroubakis[19], Daniela Pugliese[20], Giuseppe Cuccia[21], Cristina Calviño Suarez[22], Davide Giuseppe Ribaldone[23], Ido Veisman[24], Kassem Sharif[24], Annalisa Aratari[25], Claudio Papi[25], Iordanis Mylonas[26], Gerassimos J. Mantzaris[26], Marie Truyens[27], Triana Lobaton[28] , Stéphane Nancey[29], Fabiana Castiglione[30], Olga Maria Nardone[31], Giulio Calabrese[31], Konstantinos Karmiris[32], Magdalini Velegraki[32], Angeliki Theodoropoulou[32], Ariella Bar-Gil Shitrit[33], Milan Lukas[34], Gabriela Vojtechová[34], Pierre Ellul[35], Luke Bugeja[35], Edoardo V. Savarino[36], Tali Sharar Fischler[1],Iris Dotan[1], Henit Yanai[1].

*Equal contribution

[1]Division of Gastroenterology, Rabin Medical Center, affiliated with the Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel; [2]Department of Gastroenterology, Hepatology and Nutrition, Cleveland Clinic, Cleveland, United States; [3]Department of Internal Medicine E, Rabin Medical Center, affiliated with the Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel; [4] Department of Otolaryngology, Meir Medical Center, affiliated with the Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel; [5]Moscow Clinical Scientific Center named after A. S. Loginov, Moscow, Russia; [6] State Scientific Centre of Coloproctology named after A.N. Ryzhyh, Moscow, Russia, Moscow, [7]Russia Research Institute of Health Organization and Medical Management, Moscow, Russia ; [8]Division of Gastroenterology, Northern Care Alliance Hospitals NHS Foundation Trust, Manchester, United Kingdom; [9] Faculty of Biology, Medicine & Health, University of Manchester, Manchester, United Kingdom; [10]VITAZ, Department of Gastroenterology, St Niklaas, Belgium; [11]University hospital Ghent, Department of Gastroenterology, Ghent, Belgium;[12]Poznan University of Medical Sciences, Department of Gastroenterology, Dietetics and Internal Medicine, Poznan, Poland; [13] IBD Center, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [14]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; [15]ASST Rhodense, Gastroenterology Unit, Rho, Italy; [16]University of Turin, Department of medical sciences, Turin, Italy; [17]University of Pavia, Gastroenterology Unit, Department of medical sciences, Pavia, Italy; [18]Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-Princesa), Universidad Autónoma de Madrid, and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Gastroenterology Unit, Madrid, Spain;[19]University Hospital of Heraklion, Gastroenterology, Heraklion, Greece; [20]Fondazione Policlinico Universitario "A. Gemelli" IRCCS,CEMAD – IBD UNIT - Unità Operativa Complessa di Medicina Interna e Gastroenterologia, Dipartimento di Scienze Mediche e Chirurgiche, Rome, Italy; [21]Università Cattolica del Sacro Cuore, Dipartimento Universitario di Medicina e Chirurgia Traslazionale,Rome, Italy; [22]University Hospital of Santiago de Compostela, Department of Gastroenterology and Hepatology, La Coruña, Spain; [23]University of Turin, Department of Medical

Sciences, Turin, Italy; [24]Sheba Medical Center, affiliated to Faculty of Medicine, Tel Aviv University, Israel, Department of Gastroenterology, Ramat Gan, Israel; [25]S Filippo Neri Hospital, Rome Italy; [26]S. Filippo Neri Hospital, Gastroenterology, Rome, Italy; [27]Evangelismos-Polycliniki 'General Hospital, Department of Gastroenterology, Athens, Greece; [28]Ghent University, Department of Internal Medicine and Pediatrics, Ghent, Belgium; [29]South Lyon university hospital, Hospices Civils de Lyon, Dept. de Gastroenterologie, Lyon, France; [30]Federico II University ,Gastroenterology, Department of Clinical Medicine and Surgery, Naples, Italy; [31]University of Naples Federico II, Gastroenterology ,Department of Public Health, Naples, Italy; [32]Venizeleio General Hospital Department of Gastroenterology, Heraklion, Greece; [33]IBD MOM unit, Digestive diseases institute , Shaare Zedek Medical center, Hebrew university, Jerusalem, Israel,[34]Charles University, Clinical and Research Center for Inflammatory Bowel Disease ISCARE and First Faculty of Medicine, Prague, Czech Republic; [35]Mater Dei Hospital ,Division of Gastroenterology, Birkirkara, Malta; [36]University of Padua, Division of Gastroenterology, Department Of Surgery, Oncology And Gastroenterology, Padua, Italy.

Correspondence:

Idan Goren, MD, Section of Inflammatory Bowel Diseases, Department of Gastroenterology, Hepatology and Nutrition, Cleveland Clinic, Cleveland, Ohio, USA, Email: goreni@ccf.org

Henit Yanai, MD MBA; Division of Gastroenterology, Rabin Medical Center 39 Ze'ev Jabotinsky St. Petah Tikva, 4941492, Israel; Email: henityanai@gmail.com

Guarantor of the article:

Prof. Henit Yanai

Specific author contribution:

I.G. and H.Y., conceived and designed the study. I.G., O.F.B., T.B., O.K., A.K., J.K.L., E.L., T.H., P.E., C.B., S.S., M.V., E.A., M.C., J.G., E.O., I.E.K., D.P., G.C., C.C.S., D.G.R., I.V., K.S., A.A., C.P., I.M., G.J.M., M.T., T.L, S.N., F.C., O.M.N., G.C., K.K., M.V., A.T., A.B.S., M.L., G.V., P.E., L.B., E.V.S., I.D., H.Y., participated in data acquisition. I.G, and H.Y. performed data analysis and interpretation. I.G, O.F.B., T.S.F and H.Y. drafted and revised the manuscript with input from all authors. All authors critically revised the manuscript for important intellectual property and approved submitting this manuscript.

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Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Abbreviations

IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, Ulcerative colitis; CDI, *Clostridioides difficile* infection; 5-ASA, 5-aminosalicylic acid; anti-TNFα, Tumor necrosis factor-alpha; ED, Emergency department; ELISA, Enzyme-linked immunosorbent assay; PCR, Polymerase chain reaction.

ABSTRACT

Objectives

Elderly hospitalized patients with inflammatory bowel disease (IBD) flare and concurrent *Clostridioides difficile* infection (CDI) are considered at high risk of IBD-related complications. We aimed to evaluate the short, intermediate, and long-term post-discharge complications among these patients.

Methods

A retrospective multicenter cohort study assessing outcomes of elderly individuals (≥60 years) hospitalized for an IBD flare who were tested for CDI (either positive or negative) and discharged. The primary outcome was the 3-months post-discharge IBD-related complication rates defined as: steroid dependency, re-admissions (emergency department or hospitalization), IBD-related surgery, or mortality. We assessed post-discharge IBD-related complications within 6-months and mortality at 12-months among secondary outcomes. Risk factors for complication were assessed by multivariable logistic regression.

Results

In a cohort of 654 patients hospitalized for IBD (age 68.9 [interquartile range {IQR}]:63.9-75.2) years, 60.9% ulcerative colitis), 23.4% were CDI-positive. Post-discharge complication rates at 3 and 6-months, and 12-months mortality, did not differ significantly between CDI-positive and CDI-negative patients (32% vs. 33.1%, p=0.8; 40.5% vs. 42.5%, p=0.66; and 4.6% vs. 8%, p=0.153, respectively). The Charlson comorbidity index was the only significant risk factor for complications within 3-months (aOR 1.1), whereas mesalamine (5-aminosalicylic acid [5-ASA]) use was protective (aOR 0.6). An ulcerative colitis diagnosis was the sole risk factor for complication at 6-months (aOR 1.5). CDI did not significantly impact outcomes or interact with IBD type.

Conclusions

In elderly IBD patients hospitalized for IBD flare and subsequently discharged, a concurrent CDI infection was not associated with post-discharge IBD-related complications or mortality up to 1-year.

Keywords: inflammatory bowel disease, *Clostridioides difficile*, elderly, hospitalization, outcomes, mortality.

Introduction

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), can affect individuals of any age group. The rising incidence and prevalence of older persons with IBD has enabled appropriate emphasis on the unique and complex considerations involved in caring for elderly patients with IBD[1]. *Clostridioides difficile* infection (CDI) has been identified as a potential environmental trigger for a flare-up of preexisting IBD[2], and patients with IBD are at a higher risk of developing CDI than the general population[3]. Several risk factors associated with CDI in IBD patients include using immunosuppressive agents[4], prolonged hospitalization[5], prior exposure to antibiotics[6], colonic disease location[7], and an altered gut micobiome[8]. Notably, age over 65 has been identified as an independent risk factor for CDI[9,10].

Post-discharge outcomes of hospitalized patients with IBD flare and a concurrent CDI compared to those of patients with hospitalized for an IBD flare who were found negative for without CDI have been a subject of debate. While some data propose that concurrent CDI in hospitalized IBD patients with a flare is associated with higher risk of post-discharge hospital re-admissions and colectomy, treatment optimization, and mortality[11-14], contrasting data indicate a low hospital re-admission rate and comparable short-term clinical outcomes to patients discharged after an IBD flare that was not complicated with CDI[15-18]. The impact of CDI on IBD course and mortality in elderly patients hospitalized for IBD exacerbation remains elusive.

Our study aimed to evaluate short- and long-term outcomes in elderly IBD patients who were admitted for a flare and tested positive for CDI (CDI-positive), compared to those who tested negative (CDI-negative).

1. Methods

2.1 Study design

This was an observational, multicenter, retrospective study which included elderly patients with IBD flare and CDI - the ENTRIT study group. In May 2022, we initiated a call to multiple IBD centers throughout Israel and Europe, inviting collaborators to collect data on eligible patients through the utilization of a standardized criteria and case reporting form.

2.2 Patients and procedures

The study population consisted of elderly patients with an established diagnosis of IBD (CD, UC, or IBD unclassified) documented in hospital or clinic records, aged 60 years or older at the time of the index hospital admission for a working diagnosis of an IBD flare who were tested for CDI during the hospitalization and eventually discharged from the hospital. Inclusion criteria included: 1. having ≥1 stool analysis taken within 72 hours of the index hospital admission for CDI assays. We allowed variable testing based on institutional standards at admission, including both antigen and toxins A/B-based or genetic-based assays. 2. a post-discharge follow-up of 1 year. Only the first hospitalization data was included in cases of multiple hospitalizations during the study period. Patients with established non-CD bacterial or cytomegalovirus (CMV) infection were excluded. The Charlson Comorbidity Index, a weighted index designed to predict the risk of death within one year of hospitalization, was used to stratify elderly hospitalized patients with IBD, as described by Charlson et al. [19] and previously employed to assess post-discharge outcomes in patients with IBD. [20]

2.3 Endpoints

The primary endpoint was the 3 months post-discharge IBD-related complication rates defined as a composite of either steroid dependency, any IBD-related re-admissions (emergency department (ED) or hospitalization), IBD-related surgery, or mortality. The secondary endpoints

were the following: the 6 months post-discharge IBD-related complication rates (as defined for the primary endpoint), early emergency department re-admissions within 2 and 4 weeks, IBD therapy optimization at 6 and 12 months, and mortality at 12 months. Details on the definitions of all these outcomes are provided in Supplementary Table 1. We compared the characteristics and outcomes of the CDI-positive group with those of the CDI-negative group.

2.4 Statistical analysis

Descriptive statistics, including median with interquartile range (IQR) and mean with standard deviation (SD), were used to summarize quantitative variables and their distributions. The Mann-Whitney U test was used to assess continuous variables and compare medians between groups, while Pearson's $\chi 2$ test, and the Fisher's exact test were used to assess associations between categorical variables. Multivariable logistic regression was utilized to assess risk factors for major endpoints. To confirm that the CDI-positive/negative status is included in the analysis we forced this variable into the model. Next we used a backward stepwise method for variable selection (p-value>0.1 on Wald test was used for variable removal) while adjusting for age at the index hospitalization, sex, disease type (CD vs. UC), smoking status, IBD-related medications at the index hospitalization, and the Charlson comorbidity index. The adjusted odds ratio (aOR) and 95% confidence interval (CI) were calculated for each predictor variable. The level of statistical significance was set at $\alpha < 0.05$, and all tests were two-sided. Statistical analysis was performed using SPSS version 27 (IBM SPSS Statistics, IBM Corporation).

2.5 Ethical considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki and received approval from the local institutional review boards of the participating centers when required by local regulations. Due to the retrospective and anonymized nature of the data, the requirement for informed consent was waived. The privacy and confidentiality of the study

participants were protected at all times. Personal information and data related to the study were kept confidential by the investigators and the participating sites. Access to the data was limited to research team members, and any disclosed information was strictly used for the purposes of the study and not for any other reasons. All data were stored securely in accordance with local regulations. All identifying information was removed from the dataset before data sharing and analysis.

2. Results

We identified 720 IBD patients from 29 centers in 11 countries, of whom 654 patients met the eligibility criteria and were included in the analysis (Supplementary Figure 1). Of these, 335 were males (51.2%), with a median age of 68.9 (IQR 63.9-75.2) years at the time of hospital admission and the mean disease duration time was 13.3±13.0 years. UC was the most common type of IBD (398 [60.9%]) and most patients were on 5-ASA maintenance therapy (451 [69%]). Baseline characteristics of the patients are presented in Table 1.

3.1 Characteristics of patients with concurrent *Clostridioides difficile* infection (CDI-positive)

Overall, 153 (23.4%) patients were tested positive for CDI (CDI-positive). CDI severity and treatment are depicted in Supplementary table 2. Patients in the CDI-positive group were slightly younger and more likely to receive antibiotics prior to hospital admission compared to the CDI-negative group (median age 67.4 [IQR 62.9-72.3] vs. 69.9 [IQR 64.3-76.0] years, p=0.002, and 24.2% vs. 7.8%, p<0.001). CDI was more common among patients with UC than those with CD (69.3% vs. 28.8%, p=0.009) and among never-smokers (77.8% vs. 54.3%, p<0.001). The CDI-positive group more commonly used anti-TNFα and 5-ASA therapy compared to the CDI-negative group, whereas the use of acid suppressants (including proton pump inhibitors or H2 blockers) was similar between the groups. As expected, IBD-related treatment modification during the index hospitalization was significantly different between the groups; corticosteroids and therapy

optimization were less common interventions in CDI-positive vs. CDI-negative patients (32.7%, vs. 67.1%, p<0.001, and 16.5% vs. 36.8%, p<0.001, respectively). See detailed comparison between groups in Table 2.

2.2 Post-discharge outcomes

The primary endpoint, the 3-month post-discharge complication rates, were 32% vs. 33.1%, p=0.8; and the 6-month post-discharge complication rates were 40.5% vs. 42.5%, p=0.66, in CDI-positive vs. CDI-negative, respectively. ED readmissions, corticosteroid dependency, IBD-related hospital readmissions, IBD-related surgery, and therapy optimization did not differ between the groups in the specified time points; see Table 3 for detailed outcome rates between groups. A sensitivity analysis was conducted comparing the primary endpoint among different subgroups of patients with CDI. The subgroups analyzed were: patients diagnosed with CDI using immunoassay alone versus those diagnosed using both immunoassay and PCR; patients with fulminant CDI (i.e. characterized by hypotension, shock, ileus or megacolon) versus those with non-fulminant CDI; and patients with a white blood cell count over 15×10^9/L (a prognostic marker for severe CDI) versus those with a count below 15×10^9/L. No significant differences were observed in achieving the primary outcomes across these subgroups (p=0.099, p=0.35, and p=0.72, respectively).

The overall 6-month mortality rate was 4.4%, which was relatively higher among the CDI-negative vs. the CDI-positive groups (5.4% vs. 1.3%, p=0.032, respectively). The mortality rate increased to 7.2% by 12 months post-discharge, and the original trend for disadvantage in the CDI-negative vs. CDI-positive groups was held. However, the difference was not significant anymore (8.0% vs. 4.6%, p=0.153, respectively). Notably, one patient from the CDI-positive group died of complicated CDI during the post-discharge period; for detailed causes of mortality, see Supplementary Table 3.

3.3 Risk factors for post-discharge IBD-related complications

Upon conducting a multivariable regression analysis, the sole risk factor significantly correlated with IBD-related complications within the 3-month post-discharge period was the Charlson comorbidity index yielding an aOR of 1.1 (95% CI: 1.0-1.2, p=0.032). Conversely, administration of 5-ASA before the index hospitalization was protective, yielding an aOR of 0.6 (95% CI: 0.4-0.9, p=0.023). In the context of the 6-monthly post-discharge interval, the sole risk factor was a diagnosis of UC, which was associated with an aOR of 1.5 (95% CI: 1.1-2.1, p=0.007). There was no statistically significant association of CDI with any outcomes, nor was there any evidence of an interaction between CDI and the type of IBD (CD vs UC). Subsequent analyses by IBD type revealed that, within the CD group for the 3-monthly post-discharge period, 5-ASA had a protective effect, with an aOR of 0.6 (95% CI: 0.3-0.9, p=0.033). In the UC group, two independent risk factors were identified: female gender, with an aOR of 1.6 (95% CI: 1.0-2.5, p=0.041), and the Charlson comorbidity index, with an aOR of 1.1 (95% CI: 1.0-1.3, p=0.026). For the 6-monthly post-discharge complication, female gender persisted as a risk factor within the UC group, with an aOR of 1.6 (95% CI: 1.0-2.4, p=0.034). See Table 4 for the risk factors for main outcomes.

3. Discussion

In this international European multicenter cohort, we report on the post-discharge outcomes of elderly IBD patients hospitalized for a flare with concurrent CDI. The challenges posed by advancing age, clinical comorbidities, polypharmacy and a myriad of complex issues around IBD, not implausibly present a scenario wherein CDI could exacerbate adverse outcomes or indeed be a marker for a complicated disease course (similar to concomitant CMV infection in IBD[21]). Interestingly, our findings indicate that CDI did not aggravate the IBD post-discharge, either in the short or the intermediate terms (i.e., at 3- and 6-months post-discharge), and did not increase

mortality rates within 12 months. In this cohort of elderly patients with a flare of IBD that necessitated hospitalization, an increased Charlson comorbidity index (surrogate marker for sicker patients) was a risk factor for IBD-related complications within 3-months post-discharge, while the *a-priori* administration of 5-ASA therapies (suggesting a milder IBD) was protective against complications. In the intermediate period (6 months post-discharge), a diagnosis of UC was a risk factor for complications.

Our cohort had a relatively high incidence of CDI, with almost one-fourth of cases testing CDI-positive. Previous studies on unselected cohorts of IBD patients presenting with a flare demonstrated a CDI incidence ranging from 7 to 20%[22–25]. The variable incidence rates of CDI may be due to differences in baseline carriage rates[26], testing methods, the different prevalence of CDI-related risk factors in the studied population, and potentially a selection bias (cases were identified by the investigators, not regional/national registries). Additionally, in our cohort of elderly patients with IBD, the relatively high CDI-positive rate may reflect the intrinsic susceptibility of elderly patients to CDI, attributed, among other causes, to age-related immune system impairment, increasing antibiotic usage, and frequent healthcare exposures[27,28].

As in previous studies[6,21,29], we noted a higher prevalence of CDI in patients with UC compared to patients with CD. This difference may be attributable to greater colonic involvement in the UC compared to the CD subgroup and the inherent affinity of *Clostridioides difficile* toxins to the colonic epithelial cells[30]. It may also be due to the more common use of antibiotics (such as metronidazole) in patients with CD relative to UC[31].

We also confirmed other previously reported risk factors for CDI among patients with IBD, including pre-admission antibiotic usage, and 5-ASA maintenance, all of which exhibited an association with CDI[31,32]. While the association between anti-TNFα therapy and the risk for CDI in IBD has shown conflicting results[23,33, 34], we noted a significant association between anti-TNFα use and CDI-positivity. This therapy may potentially increase the risk in elderly patients more than in the general

IBD population. While the initial utilization of non-TNF biologics, primarily vedolizumab, exhibited similar rates between the CDI-negative and positive groups, it is important to note that the absolute number of patients within these groups might be relatively small. Additionally, our cohort was not specifically structured to investigate pre-admission risk factors; rather, its primary focus lies in assessing post-discharge outcomes.

Somewhat surprisingly, we found no correlation between CDI and IBD-related complications documented up to 12-month follow-up. This finding likely indicates that the clinical presentation of the patients who were CDI-positive during the hospitalization was primarily driven by CDI and less so by the IBD per se. Conversely, patients in the CDI-negative subgroup, hospitalized for an IBD flare, were more likely to require therapy optimization during their initial hospital stay. However, in the post-discharge period, this group exhibited similar rates of all IBD-related outcomes compared to those in the CDI-positive group.

Notably, in this study, we did not assess mortality rates associated with CDI-related hospitalization among elderly with IBD. Rather, we excluded cases of in-hospital mortality at the index hospitalization. As the majority of CDI-positive patients recover and are discharged, we focused on IBD-related post-discharge complications and mortality potentially related to CDI in this population. We showed that within 6 and 12 months, mortality rates were 4.4% and 7.2%, respectively. Mortality rates within 6 months of discharge were numerically higher among the CDI-negative compared with the CDI-positive (5.4% vs 1.3%, p=0.032, respectively), and this difference was maintained through 12 months, although not statistically significant (8% vs. 4.6%, p=0.153, respectively). Although we do not have data for all the causes of mortality, from available data, a predominant cause of mortality was a non-CD infection (such as pneumonia, urinary tract infections and SARS-CoV-2 infection) among the IBD patients who were CDI-negative during the index hospitalization. Notably, most cases with an unknown cause of death were reported during the SARS-CoV-2 pandemic. Our findings suggest that the CDI was not the reason for death within the

following 12 months**.** Our findings are in contrasts with a previous study from the UK that reported an increased risk for post-discharge all-cause mortality in patients with CDI relative to those without [35]. This difference may be attributed to our specific cohort of elderly patients with an inherently higher mortality risk (with or without CDI), or the association of CDI in the general population with more severe comorbidities and risk factors, compared to patients with IBD. Additionally, as mentioned above, we excluded cases with in-hospital mortality at the index hospitalization, which is probably a major contributor to CDI-associated all-cause mortality[36]. Our findings are, however, in keeping with a report from The Nationwide Inpatient Sample database in the United States that demonstrated a 54% decrease in the mortality of IBD patients who were concurrently CDI-positive and a 38% decrease in the rate of colectomy in patients hospitalized with UC and CDI, between 2007 to 2013[37]. Considering that our cohort consists of patients hospitalized between 2013 and 2022, it is not implausible that advancements in CDI and IBD care, have reduced CDI-related mortality.

In addition, access to health care and IBD specialist care through different pathways can significantly impact post-hospitalization outcomes in elderly patients, particularly when multidisciplinary team care and post-acute services are involved. Data have shown that post-discharge multidisciplinary team care can lead to better disease management and improved health outcomes by providing comprehensive and coordinated care [38].

It is essential to acknowledge the inherent limitations of this study. These include the retrospective methodology employed for data acquisition. We did not have data on treatment success rates, or rates of recurrent CDI. We also acknowledge a potential selection bias when collecting patients from multiple centers. Furthermore, it is important to note that CDI diagnostic assays and other enteric pathogens testing may vary across centers and change over time. This variation could have resulted in misclassifying patients as infected, not infected, or even misclassifying carriers as infected. However, previous data have shown similar IBD outcomes in inpatients with CDI detected by either

ELISA or PCR Assay[39], and our subgroup analysis comparing patients who were diagnosed based on immunoassay alone versus those diagnosed using immunoassay and confirmatory molecular testing with PCR had comparable rates of the primary endpoint. While variations in treatment approaches across different centers prevented a comprehensive assessment of the impact of specific CDI treatment on outcomes, our data suggest that the primary driver of outcomes was the nature of the underlying disease.

In conclusion, in this international multicenter study focusing on post-discharge IBD outcomes of elderly patients hospitalized with a flare and a concurrent CDI, we found that among patients who survived the hospitalization, the CDI was not associated with adverse IBD-related outcomes or mortality within 12 months, suggesting that the CDI per se is not a marker of more complicated IBD course in this population. Further studies and prospective data on risk factors for morbidity and mortality in elderly patients with IBD with CDI infection are needed to characterize and mitigate against risk in this otherwise potentially vulnerable group.

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Table 1. Characteristics of patients (N=654).

Characteristics	n (%)
Demographics	
Sex, male	335 (51.2)
Age at hospitalization*, median (IQR), years	68.9 (63.9-75.2)
Age at IBD diagnosis, median (IQR), years	59.45 (49.9- 66.3)
Family history of IBD	41 (6.3)
Charlson comorbidity index score	
≤2	119 (18.2)
3-4	312 (47.7)
≥5	223 (34.1)
Smoking status	
Never	391 (59.8)
Current	80 (12.2)
Past	183 (28.0)
IBD type	
Crohn's' Disease (CD)	248 (37.9)
Location, n (%)	
Ileal (L1)	88 (35.5)
Colonic (L2)	60 (24.2)
Ileocolonic (L3)	100 (40.3)
Proximal disease (L4)	27 (10.9)
Behavior, n (%)	
Inflammatory (B1)	113 (45.6)
Stricturing (B2)	78 (31.5)
Penetrating (B3)	36 (14.5)
Stricturing + Penetrating (B2+B3)	21 (8.5)
Perianal	49 (19.8)
Ulcerative colitis (UC)	398 (60.9)
Extent, n (%)	
Proctitis (E1)	22 (5.5)
Left-sided colitis (E2)	165 (41.5)
Extensive colitis (E3)	211 (53.0)
IBD-Unclassified	8 (1.2)
Baseline IBD medications	
Mesalamine (5-ASA)	451 (69.0)
Immunomodulator	86 (13.1)
Anti-TNFα	108 (16.5)
non-anti-TNFα biologic	53 (8.1)
JAK inhibitor	1 (0.2)
Corticosteroids	133 (20.3)
Pre-admission antibiotics	76 (11.6)
Pre-admission acid suppressants**	222 (33.9)
CDI-positive at index hospitalization	153 (23.4)
CD (% of CDI)	44 (28.8)
UC (% of CDI)	106 (69.3)

IBD-Unclassified (% of CDI)	3 (1.9)

Inflammatory bowel disease (IBD), Clostridioides difficile infection (CDI), Standard deviation (SD), 5-aminosalicylic acid (5-ASA), Tumor necrosis factor-alpha (TNFα), Janus kinase (JAK). *Analyzed at first hospitalization per individual

** Proton pump inhibitors (PPI) or Histamine Type-2 blockers (H2b)

Table 2. Clinical features of the CDI-positive vs. CDI-negative groups (univariate analysis).

Characteristics	CDI-positive (n=153)	CDI-negative (n=501)	p-value
Demographics			
Sex, male, n (%)	69 (45.1)	266 (53.1)	0.084
Age at hospitalization*, median (IQR), years	69.9 (64.3-76.0)	67.4 (62.9-72.3)	0.002
Age at IBD diagnosis, median (IQR), years	59.6 (49.7-66.8)	58.7 (51.3-64.8)	0.3
Family history of IBD, n (%)	5 (3.3)	36 (7.2)	0.08
The Charlson comorbidity index score, mean (SD)	4.41 (1.82)	4.03 (1.84)	0.006
≤2 , n (%) 3-4 , n (%) ≥5 , n (%)	19 (12.4) 69 (45.1) 65 (42.5)	100 (20) 243 (48.5) 158 (31.5)	0.017
Smoking status, n (%)			
Never	119 (77.8)	272 (54.3)	<0.001
Current	13 (8.5)	67 (13.4)	
Past	21 (13.7)	162 (32.3)	
IBD type			
Crohn's' Disease (CD)	44 (28.8)	204 (40.7)	0.006
Location, n (%)			
Ileal (L1)	9 (20.5)	79 (38.7)	0.091
Colonic (L2)	15 (34.1)	45 (22.1)	
Ileocolonic (L3)	20 (45.5)	80 (39.2)	
Proximal disease (L4)	1 (2.3)	26 (12.7)	0.058
Behavior, n (%)			
Inflammatory (B1)	16 (36.4)	97 (47.5)	0.367
Stricturing (B2)	16 (36.4)	62 (30.4)	
Penetrating (B3)	9 (20.5)	27 (13.2)	
Stricturing + Penetrating (B2+B3)	3 (6.8)	18 (8.8)	
Perianal	9 (20.5)	40 (19.6)	0.898
Ulcerative colitis (UC)	106 (69.3)	292 (58.3)	0.014
Extent, n (%)			
Proctitis (E1)	5 (4.7)	17 (5.8)	0.314
Left-sided colitis (E2)	51 (48.1)	114 (39.0)	
Extensive colitis (E3)	50 (47.2)	161 (55.1)	
IBD-Unclassified, n (%)	3 (2.0)	5 (1.0)	
Past IBD-related surgery, n (%)	18 (11.7)	95 (18.9)	0.039
Baseline IBD medications, n (%)			
Mesalamine (5-ASA)	126 (82.4)	325 (64.9)	<0.001
Immunomodulator	23 (15.0)	63 (12.6)	0.431
Anti-TNFα	41 (26.8)	67 (13.4)	<0.001
non-anti-TNFα biologic	10 (6.5)	43 (8.6)	0.417
JAK inhibitor	0 (0)	1 (0.2)	0.99
Corticosteroids	26 (17.0)	107 (21.4)	0.241
Pre-admission antibiotics	37 (24.2)	39 (7.8)	<0.001
Pre-admission acid suppressants**	56 (36.6)	166 (33.1)	0.428
Presenting symptoms, n (%)			
Diarrhea	150 (98.7)	449 (89.6)	<0.001

Abdominal pain	121 (79.1)	285 (56.9)	<0.001
Fever	25 (16.4)	93 (18.6)	0.553
Length of hospitalization, mean (SD), d	10.8 (7)	11 (16.2)	0.62
Treatment during hospitalization, n (%)			
Corticosteroids	50 (32.7)	336 (67.1)	<0.001
IBD therapy optimization	25 (16.3)	192 (38.3)	<0.001

Years (y), Inflammatory bowel disease (IBD), Clostridioides difficile infection (CDI), Standard deviation (SD), number (n), 5-aminosalicylic acid (5-ASA), Tumor necrosis factor-alpha (TNFα), Janus kinase (JAK), Days (d), Emergency department (ED)

*Analyzed at first hospitalization per individual
** Proton pump inhibitors (PPI or Histamine Type-2 blockers (H2b)

Table 3. Post-discharge outcomes of CDI-positive vs. CDI-negative groups.

Endpoints n (%)	CDI-positive (n=153)	CDI-negative (n=501)	p-value
3 months post-discharge IBD-related complications [#]	**49 (32.0)**	**166 (33.1)**	**0.8**
6 months post-discharge IBD-related complications [##]	**62 (40.5)**	**213 (42.5)**	**0.66**
ED readmission			
2 weeks	8 (5.2)	37 (7.4)	0.357
4 weeks	10 (6.5)	49 (9.8)	0.221
3 months	32 (20.9)	101 (20.2)	0.839
6 months	49 (32.0)	154 (30.7)	0.763
Corticosteroids dependence			
3 months	22 (14.4)	76 (15.2)	0.811
6 months	23 (15.0)	96 (19.2)	0.247
IBD-related hospital readmissions			
3 months	25 (16.3)	68 (13.6)	0.391
6 months	42 (27.5)	106 (21.2)	0.104
IBD-related surgery			
3 months	3 (2.0)	18 (3.6)	0.435
6 months	6 (3.9)	31 (6.2)	0.289
IBD therapy optimization			
6 months	41 (26.8)	150 (29.9)	0.455
12 months	46 (30.1)	179 (35.7)	0.197
Mortality			
6 months	2 (1.3)	27 (5.4)	**0.032**
12 months	7 (4.6)	40 (8.0)	0.153

[#] **3 months post-discharge IBD-related complications** - a composite of either steroid dependency, any readmissions (emergency department or hospitalization), IBD-related surgery, or mortality.
[##] **6 months post-discharge IBD-related complications** - a composite of either steroid dependency, any readmissions (emergency department or hospitalization), IBD-related surgery, or mortality.

Table 4. Risk factors for post discharge IBD-related complications.

Outcome	Variables	aOR	95% CI	p-value
3-months post-discharge IBD-related complications [#]	CDI-positive	1.021	0.683-1.526	0.920
	Diagnosis of UC	4.629	0.550-1.145	0.793
	The Charlson comorbidity index	1.101	1.008-1.203	0.032
	Administration of mesalamine (5-ASA)	0.642	0.437-0.941	0.023
6-months post-discharge IBD-related complications [#]	CDI-positive	0.975	0.670-1.419	0.896
	Diagnosis of UC	1.555	1.126-2.145	0.007

Clostridioides difficile infection (CDI), Inflammatory bowel disease (IBD), ulcerative colitis (UC), adjusted odd ratio (aOR), confidence interval (CI)

[#] **3 months post-discharge IBD-related complications -** a composite of either steroid dependency, any readmissions (emergency department or hospitalization), IBD-related surgery, or mortality.
[##] **6 months post-discharge IBD-related complications -** a composite of either steroid dependency, any readmissions (emergency department or hospitalization), IBD-related surgery, or mortality.

Multivariable regression analysis, adjusting for: age at the index hospitalization, sex, disease type (CD vs. UC), smoking status, IBD-related medications at the index hospitalization, and the Charlson comorbidity index.