Novel risk factors and outcomes in inflammatory bowel disease patients with *Clostridioides difficile* infection

Elida Voth, Dipesh Solanky, Edward V. Loftus Jr., Darrell S. Pardi and Sahil Khanna (iD)

Abstract

Background: Patients with inflammatory bowel disease (IBD) are at significantly increased risk for *Clostridioides difficile* infection (CDI) with an increased risk of adverse outcomes including increased in-hospital mortality, IBD treatment failure, re-hospitalization, and high CDI recurrence rates. The existing literature on predictors of these adverse outcomes is limited. We evaluated four potentially modifiable novel risk factors [body mass index (BMI), statin use, opioid use, and antidepressant use] on CDI risk and adverse outcomes in these patients.

Methods: Using a retrospective design, variables were abstracted from records for patients with IBD and CDI from 2008 to 2013. Statistical analysis comprised descriptive statistics and univariate and multivariate logistic regression analyses.

Results: There were 137 patients with IBD and CDI included in this study. On multivariate analysis controlling for age, 43% of patients in the overweight BMI category had severe or severe, complicated CDI, compared with 22% of patients in the underweight/normal BMI [odds ratio (OR) 2.85, $p = 0.02$] and 19% in the obese category (OR 3.95, $p = 0.04$). Statin use was associated with severe or severe, complicated CDI when controlling for age and BMI (OR 5.66, $p = 0.01$). There was no association between statin use and IBD exacerbations following CDI. Opioid and antidepressant use were not associated with disease severity or frequency of IBD exacerbations following CDI.

Conclusions: An overweight BMI and statin use were associated with severe or severe, complicated CDI in IBD patients. Further studies are needed to better understand how these factors impact management of patients with IBD to improve clinical outcomes and potentially reduce the risk of complications from CDI.

Keywords: *Clostridium difficile*, inflammatory bowel disease, obesity, treatment

Correspondence to:
Sahil Khanna
Division of Gastroenterology and Hepatology, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, USA
khanna.sahil@mayo.edu

Elida Voth
Department of Medicine, Mayo Clinic, Rochester, MN, USA

Dipesh Solanky
Department of Medicine, University of California San Diego, La Jolla, CA, USA

Edward V. Loftus Jr.
Darrell S. Pardi
Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Introduction

Over the past 3 decades, the incidence, severity, and recurrence rates of *Clostridioides difficile* infection (CDI) have dramatically increased in both the community and healthcare settings.[1] Inflammatory bowel disease (IBD) is an independent risk factor for CDI even without antibiotic exposure or recent hospitalization, likely due to microbial dysbiosis.[2,3] Patients with IBD are up to five times more likely to develop CDI compared with patients without IBD.[4,5] CDI in patients with IBD is associated with poor outcomes, including significantly higher mortality, longer length of hospitalization, and increased likelihood of dismissal to a care facility.[2,6,7] Additionally, CDI increases the risk of future IBD-related hospitalizations and surgery, including colectomy.[8] The existing literature on predictors of the aforementioned adverse outcomes of CDI in IBD is limited. Serum albumin level <3 g/dl, hemoglobin below 9 g/dl, and serum creatinine above

1.5 mg/dl are shown to be independent predictors of severe outcomes in hospitalized IBD patients with CDI.[8] In a recent study, the addition or escalation of corticosteroids to the treatment regimen during CDI in IBD was associated with significantly increased risk of colon surgery within 1 year.[9]

There is a need to identify additional risk factors that may be associated with adverse outcomes in IBD patients with CDI. To our knowledge, modifiable novel risk factors, including body mass index (BMI), statin use, opioid use, and use of antidepressants, have not been evaluated in IBD patients with CDI. Statins, opioids, and antidepressants are among the most commonly prescribed medications in the United States and may modify the risk of CDI. One meta-analysis showed a decreased risk of CDI in patients without IBD that were prescribed a statin, with up to 20% risk reduction.[10] Data suggest that moderate to high use of opioid analgesics is associated with increased risk of developing CDI in hospitalized patients.[11] Additionally, opioids were found to be an independent predictor of severe, complicated CDI in hospitalized patients without IBD.[12] Lastly, one study showed a relationship between depression and antidepressant use, with an increased risk of CDI.[13]

In this study, we aimed to determine if there was an association between these novel risk factors including BMI, statin use, opioid use, and antidepressants and: (a) the severity of CDI in patients with IBD; (b) the risk of adverse outcomes including colon surgery, CDI recurrence, CDI-related hospitalization, post-CDI IBD exacerbations, or mortality.

Methods

Patient selection
This was a retrospective cohort study. Patients seen at our institution in both the inpatient and outpatient setting with CDI and a diagnosis of IBD from 1 January 2008 through 31 December 2013 were identified from electronic health records (EHRs) using codes from the *International Classification of Diseases, Ninth Revision* (ICD-9) and confirmed manually after study protocol approval by the Mayo Clinic Institutional Review Board. This is a follow up to a previously published cohort study by Solanky *et al.*;[9] thus, the study period dates were selected to keep data and ICD-9 codes homogeneous. The criteria for the diagnosis of CDI included at least three loose or watery stools per day for ⩾2 days and a positive polymerase chain reaction (PCR)-based stool test at the time of symptoms. Exclusion criteria included patients who: (a) were younger than 18 years of age at the time of CDI; (b) were lost to follow up less than 1 year after CDI; (c) had a total colectomy before CDI diagnosis; (d) had other active infections at the time of CDI diagnosis; (e) were treated for CDI at another site; or (f) did not have sufficient documentation of CDI treatment duration.

Demographic and clinical variables
Patient demographic variables, including sex, race, ethnicity, smoking history, and age at diagnosis of CDI, were obtained from the EHR of patients who met inclusion criteria. IBD- and CDI-specific clinical factors of interest included IBD subtype, age of IBD onset, number of IBD-related exacerbations and colon surgery ⩽1 year after CDI. Additional clinical variables related to CDI included severity of CDI (non-severe, severe, and fulminant), number of subsequent CDI episodes, subsequent CDI-related hospitalizations, and mortality ⩽1 year following the CDI of interest. Four novel risk factors, including BMI, statin use, opioid use, and antidepressant use at the time of CDI diagnosis were also abstracted. BMI was included if documented within 30 days of CDI diagnosis. Underweight BMI was defined as BMI <18.5 kg/m², normal included BMI $>18.5-24.9$ kg/m², overweight included BMI $>25.0-29.9$ kg/m², and obese was BMI >30 kg/m². The underweight and normal categories were combined for statistical analysis.

Statin use was recorded if a statin medication was listed as a home medication at the time of CDI diagnosis. Opioid use was recorded if a drug of the opioid classification was listed as a home medication or a hospital administered medication at the time of CDI diagnosis. Tramadol was included among opioids; however, diphenoxylate-atropine, loperamide, and tincture of opium were excluded. Antidepressants, including serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, bupropion, and buspirone were included if listed as a home medication at the time of CDI diagnosis.

Variable definitions

Inflammatory-bowel-disease-related variables. IBD exacerbation was defined as: (a) increased diarrhea, rectal bleeding, or abdominal pain that was unexplained by a non-IBD pathology; (b) presence of symptoms despite medical or surgical management; (c) endoscopic evidence of active colitis; (d) IBD extra-intestinal manifestations; and (e) related IBD complications, such as fistula, abscess, bowel obstruction, or perforation. Signs and symptoms that met these criteria in the presence of positive CDI stool test were excluded. IBD-related hospitalization included any hospitalization for medical and/or surgical management of IBD.

Clostridioides difficile-related variables. As previously described, colon surgery after CDI was defined as any colonic resection within 1 year of diagnosis of CDI of interest.[9] CDI severity was defined per guidelines from the Infectious Diseases Society of America, with severe CDI being defined as leukocyte count >15,000 cells/ml and/or serum creatinine >1.5 mg/dl.[14] Laboratory data used to determine severity showed the highest values within 1 week of CDI diagnosis. Fulminant colitis was defined as CDI complicated by hypotension, shock, ileus, or toxic megacolon.[14] Future CDI episodes were defined as a positive repeat stool test with more than three loose stools per day for >2 days, along with initiation of antibiotics for CDI after symptom resolution, and completion of previous antibiotic therapy for CDI of interest within <365 days of CDI of interest, as previously described by Solanky *et al.*[9]

Statistical analyses

Statistical analysis consisted of descriptive statistics and univariate and multivariate logistic regression analyses using JMP software, version 13.0 (SAS Institute). Descriptive statistics were used for demographic and other clinical variables. Categorical variables were compared using Chi-squared analysis or the Fisher exact test for small cell counts. Multivariate logistic regression analyses for severity of CDI and clinical outcomes were used to correct for covariates including age and CDI severity. A *p* value of <0.05 was considered statistically significant.

Results

Patient demographic variables

The study included 137 patients with IBD and CDI. A total of 70 IBD patients (51%) had

Table 1. Patient demographics.

Variable	n (%)
Age, years	
Median (range)	46 (19–88)
Sex	
Women	75 (55)
Men	62 (45)
IBD subtype	
Ulcerative colitis	70 (51)
Crohn's disease	63 (46)
Indeterminate colitis	4 (3)
CDI severity	
Moderate	95 (69)
Severe	20 (15)
Severe, complicated	22 (16)
BMI	
Mean, all patients	26.2
Underweight (<18.5 kg/m²)	7 (5%)
Normal (>18.5–24.9 kg/m²)	58 (42%)
Overweight (>25.0–29.9 kg/m²)	51 (37%)
Obese (>30 kg/m²)	21 (15%)
Patients on a statin	14 (10%)
Patients on an opioid	36 (26%)
Patients on an antidepressant	43 (31%)

BMI, body mass index; CDI, *Clostridioides difficile* infection; IBD, inflammatory bowel disease.

ulcerative colitis, 63 (46%) had Crohn's disease, and 4 (3%) had indeterminate colitis. The median age at CDI diagnosis was 46 years, and 55% were female. A sum of 95 (69%) patients had moderate CDI, 20 (15%) had severe CDI, and 22 (16%) had severe, complicated CDI. The demographics are summarized in Table 1. The mean BMI of all patients at the time of CDI was 26.2 kg/m². The distribution of patients by BMI category was: 7 (5%) underweight, 58 (42%) normal, 51 (37%) overweight, and 21 (15%) obese. At the time of CDI, 14 patients (10%)

Table 2. Distribution of CDI severity by risk factor.

	Moderate CDI (%)	Severe or severe complicated CDI (%)	n	p Value
BMI Category				0.02
Underweight/normal	51 (78)	14 (22)	65	
Overweight	29 (57)	22 (43)	51	
Obese	17 (81)	4 (19)	21	
Patients on statin	6 (43)	8 (57)	14	0.02
Patients on opioid(s)	25 (69)	11 (31)	36	0.83
Patients on antidepressant(s)	31 (72)	12 (28)	43	0.82

Data presented as number (%) of total *n*.
BMI, body mass index; CDI, *Clostridioides difficile* infection.

Table 3. Adjusted odds ratio for severe or severe complicated CDI compared with moderate CDI by risk factor in patients with IBD.[a]

Risk factor	Odds ratio	95% CI	p value
BMI			
Overweight BMI *versus* underweight/normal BMI	2.85	1.22–6.64	0.02
Overweight BMI *versus* obese BMI	3.95	1.06–14.66	0.04
Overweight and obese BMI *versus* normal BMI	1.99	0.94–4.37	0.09
Statin use	5.66	1.46–21.96	0.01
Opioid use	1.56	0.63–3.90	0.34
Antidepressant use	0.65	0.26–1.62	0.36

[a]Multivariate analysis adjusted for age and BMI.
BMI, body mass index; CDI, *Clostridium difficile* infection; CI, confidence interval; IBD, inflammatory bowel disease.

were on a statin, 36 (26%) were prescribed at least one opioid(s), and 43 (31%) were prescribed at least one antidepressant(s).

Characteristics and management of inflammatory bowel disease

The mean duration of IBD was 11.5 years. Prior to the diagnosis of CDI, 16 (12%) patients had a previous colon surgery, 6 (4%) had small bowel resection, 54 (39%) patients had an IBD-related hospitalization in the previous year, and 91 (66%) had an IBD exacerbation within the past year.[9] Medication management of IBD at the time of CDI diagnosis included 68 (50%) patients on a corticosteroid, 55 (40%) patients on a 5-aminosalicylic acid derivative, 34 (25%) patients on an immunomodulator (6-mercaptopurine, azathioprine, or methotrexate), 26 (19%) patients on a biologic, and 16 (12%) patients on tacrolimus. Changes to the IBD medication regimen during the episode of CDI are previously described by Solanky *et al.*[9]

Severity of C. difficile infection

BMI patterns and statin use were associated with severe or severe, complicated CDI on univariate analysis (Table 2). Statin use was associated with a fivefold increased risk of severe or severe, complicated CDI on multivariate regression analysis controlling for age and BMI (Table 3). The risk

Table 4. Distribution of 1-year adverse outcomes by risk factor.

	Colon surgery		CDI recurrence		CDI-related hospitalization		Post-CDI IBD exacerbation		Mortality	
	n (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value	*n* (%)	*p* value
BMI	37, 31, 11 (58%)	0.80	12, 4, 3 (14%)	0.26	4, 3, 3 (7%)	0.41	32, 22, 11 (5%)	0.58	7, 1, 1 (7%)	0.14
Patients on a statin	4 (29%)	0.27	2 (14%)	0.11	1 (7%)	0.27	2 (14%)	0.01	2 (14%)	0.22
Patients on opioid(s)	14 (39%)	0.63	4 (11%)	0.57	4 (11%)	0.31	19 (53%)	0.59	3 (8%)	0.64
Patients on antidepressant(s)	19 (44%)	0.77	6 (14%)	0.98	2 (5%)	0.42	17 (40%)	0.14	5 (12%)	0.11

BMI *n* recorded as number of underweight/normal, overweight, obese, followed by (%) of total patients.
BMI, body mass index; CDI, *Clostridium difficile* infection; IBD, inflammatory bowel disease.

Table 5. Adjusted odds ratio for 1 year adverse outcomes by risk factor.[a]

	Colon surgery	CDI recurrence	CDI-related hospitalization	Post-CDI IBD exacerbations	Mortality
Overweight BMI *versus* underweight/normal BMI	1.42 (0.62–3.24), $p=0.40$	0.38 (0.11–1.33), $p=0.13$	1.39 (0.27–7.05), $p=0.69$	0.82 (0.36–1.86), $p=0.64$	7.61 (0.77–75.58), $p=0.08$
Overweight BMI *versus* obese BMI	1.24 (0.42–3.67), $p=0.70$	0.51 (0.10–2.67), $p=0.10$	0.49 (0.08–2.91), $p=0.43$	0.90 (0.29–2.76), $p=0.85$	3.51 (0.16–75.04), $p=0.42$
Statin use	1.02 (0.23–4.59), $p=0.70$	0.98 (0.04–4.65), $p=0.11$	1.18 (0.34–2.16) $p=0.27$	0.35 (0.07–1.85) $p=0.12$	1.47 (0.13–16.94) $p=0.22$
Opioid use	1.03 (0.43–2.43), $p=0.95$	0.62 (0.18–2.13), $p=0.57$	2.13 (0.52–8.68), $p=0.31$	1.60 (0.67–3.83) $p=0.59$	1.39 (0.24–8.21) $p=0.64$
Antidepressant use	1.36 (0.61–3.04), $p=0.46$	1.31 (0.44–3.89), $p=0.98$	0.48 (0.09–2.56), $p=0.42$	0.60 (0.27–1.35), $p=0.14$	0.28 (0.05–1.43) $p=0.11$

[a]Multivariate analysis adjusted for age and CDI severity. Data are presented as Odds ratio (95% confidence intervals), *p*-value.
BMI, body mass index; CDI, *Clostridium difficile* Infection; IBD, inflammatory bowel disease.

of severe or severe, complicated CDI was three- and fourfold higher in overweight individuals compared with underweight/normal or obese individuals on multivariate regression analysis, respectively (Table 3). An overweight or obese BMI (combined) was associated with a twofold increased risk of severe or severe complicated CDI; however, this was not statistically significant (Table 3). Opioid use and antidepressant use were not associated with severe or severe, complicated CDI (Table 3).

Clinical outcomes within 1 year following *C. difficile* diagnosis

The number of patients on a statin with at least one post-CDI IBD exacerbation during the study period was significantly lower than patients not on a statin on univariate analysis (14% *versus* 52%, $p=0.01$; Table 4). However, on multivariate analysis, this relationship was not seen (Table 5). There were no significant associations between post-CDI IBD exacerbations and BMI category, opioid use, or antidepressant use on univariate analysis (Table 4). There was no significant association between colon surgery, CDI recurrence, CDI-related hospitalization, or death and any of the variables assessed on univariate or multivariate analysis (Tables 4–5).

Discussion

CDI is a significant public health concern, particularly in patients with comorbid conditions

such as IBD. CDI is a leading cause of health-care-associated infection in the United States and an important precipitant of disease exacerbation in patients with IBD.[1] Patients with IBD affected by CDI not only have increased IBD-related hospitalizations and risk of colon surgery, but also increased hospital mortality, increased length of stay, and increased likelihood of discharge to a care facility.[2] We analyzed BMI, statin use, opioid use, and antidepressants in patients with CDI and IBD to determine if there is an association between these four novel risk factors and the severity of CDI or various clinical outcomes. Our retrospective cohort study demonstrated that overweight BMI and statin use were associated with an increased risk of severe or severe complicated CDI. BMI patterns, opioid use, statin use, and antidepressants were not associated with increased risk of colon surgery, CDI recurrence, CDI-related hospitalization, post-CDI IBD exacerbations, or mortality in the present study. Specific patient characteristics related to IBD history and IBD medication management in our cohort of patients are previously described by Solanky *et al.*[9] Approximately 50% of patients in our study were on a corticosteroid at the time of CDI diagnosis. This study found patients with more severe CDI were significantly more likely to have corticosteroids initiated or dose escalated, but immunomodulators were more likely to be de-escalated or discontinued. The previous study highlighted a need to better understand the optimal management of immunosuppressant medications in patients with severe CDI. Additionally, this study demonstrated that antibiotic choice for treatment of CDI was not associated with adverse events in our patients, including CDI recurrence, CDI-related hospitalization, IBD exacerbation, or colon surgery within 1 year of CDI diagnosis.[9]

Patients with a BMI in the overweight category had significantly increased risk of severe or severe complicated CDI in comparison with patients with underweight or normal BMI. Obesity is shown to be associated with poor outcomes in IBD, including an increased risk of colectomy.[15,16] The mechanism(s) of the detrimental effects from being overweight in this patient population are likely multifactorial, including, but not limited to, increased inflammation and further derangements in the gut microbiome. Obesity has been associated with increased inflammation as measured by C-reactive protein in patients with Crohn's disease[17] and increased levels of resistin, a pro-inflammatory adipokine.[18] In addition, a BMI greater than 35 kg/m² is an independent risk factor for severe CDI in patients without IBD.[19] Obesity is a major contributor to loss of gut microbiome diversity;[20] more specifically, the relative proportion of *Bacteroides* species is decreased in obese compared with lean individuals.[21] Despite the association of increased risk of CDI in obese individuals and increased risk of CDI with IBD, a recent study showed no association between increased risk of CDI in obese patients with ulcerative colitis, highlighting an obesity paradox.[22] A recent nationwide retrospective study showed that CDI patients with obesity had a significantly decreased risk of mortality compared to non-obese patients. This association was preserved in those patients classified as 'morbidly' obese.[23] An obesity paradox in other gastrointestinal pathologies, such as colorectal cancer, has been observed, where a recent meta-analysis showed that underweight and obese patients had increased mortality compared with patients with normal weight.[24]

Interestingly, in our study, overweight BMI was also associated with severe or severe complicated CDI in comparison with obese BMI. However, when combining overweight and obese BMI in comparison with normal BMI, the association with severe or severe complicated CDI was no longer significant [odds ratio (OR) 1.99, 95% confidence interval (CI) 0.91–4.37]. Although not statistically significant, the twofold increased OR suggests a potential association with obesity and severity of CDI in patients with IBD with the non-significant confidence ratio potentially be explained by an inadequate sample size in our study. Alternatively, an obesity paradox, where overweight BMI is associated but obese BMI is not, has been observed in previous studies of CDI.[23] The relationship between obesity and CDI, particularly in IBD, is complex; thus, further investigation is warranted.

Statins, or HMG-CoA reductase inhibitors, have pleiotropic effects independent of their role in lipid lowering, including anti-inflammatory, immunomodulatory, and anti-apoptotic properties.[25] Our study showed patients prescribed a statin had significantly increased risk of severe or severe complicated CDI on multivariate analysis controlling for age and BMI. This finding could theoretically be supported by multimodal statin effects on immunomodulatory pathways, including T-cell proliferation and leukocyte migration

to sites of inflammation.[26] Statins have been found to inhibit the L-mevalonate pathway, which is critical in multiple steps of the immune response, resulting in some degree of immuno-suppression.[25] Additionally, one preliminary report suggested statins might have an increased risk of CDI due to an unfavorable interaction between the drug and *C. difficile* toxins A and B, perhaps by potentiating the toxins' effects on colonic epithelium through Rho, a small guanosine triphosphate (GTP)-binding protein involved in multiple cellular signaling pathways.[27] In addition, statin use may serve as an indirect marker of significant medical comorbidities.

We found that patients on a statin were less likely to have an IBD exacerbation in the year following CDI; however, this effect was not seen on multivariate analysis. In patients without a diagnosis of IBD, one meta-analysis suggested statins may be have a role in prevention of CDI, with up to 20% risk reduction; however, this effect was not seen after adjusting for confounders.[10] Literature suggests statins may have a beneficial role in some infections, as one study demonstrated decreased mortality after pneumonia and a possible benefit in acute bacterial infections due to decreased level of inflammatory cytokines in patients on statin therapy.[28] Statin exposure has also been associated with decreased risk of new onset ulcerative colitis and Crohn's disease.[29] In general, the immunomodulatory role of statins is currently ill defined, and will require future prospective studies to better understand the role of statin therapy in the setting of active infection and inflammatory disease processes.

There was no significant association between opioids and the severity of CDI or adverse clinical outcomes within 1 year following CDI. Medications that inhibit peristalsis, such as opioids, are typically avoided during active CDI, as it was traditionally assumed that intestinal motility would be necessary to eradicate enteric pathogens such as *C. difficile* or decrease contact time between toxins and the colonic mucosa. Indeed, one retrospective cohort study showed that the incidence of CDI increased significantly with use of opioids in a dose-dependent manner.[11] Additionally, in a retrospective study of 1446 hospitalized patients with CDI, narcotic use was an independent predictor of severe, complicated CDI.[12] Overall, evidence on the safety of anti-motility agents in CDI is equivocal.[30] Current

guidelines state 'the use of anti-peristaltic agents to control diarrhea should be limited or avoided, as they may obscure symptoms and precipitate complicated disease,'[31] although our results did not support this concern.

Our study found that antidepressants were not associated with severity of CDI or adverse clinical outcomes. The association between antidepressant use and clinical outcomes in CDI has not previously been studied to the best of our knowledge.

A number of strengths are present in this study. This is the first study to our knowledge to evaluate BMI, statin use, opioid use, and antidepressants on CDI severity and a number of important clinical outcomes of CDI in patients with IBD. Although we cannot draw causal relationships from the results of this study because of the retrospective cohort design, our results can help guide future prospective studies. Certainly, statins should be continued in patients with IBD if indicated. This study reinforces the importance of patient education and support in maintaining a healthy BMI to reduce the risk of health complications. Our study has several limitations, including a limited sample size, absence of information on confounding variables in some patients, and the fact that our data come from a tertiary care center, so the results may not be generalizable to other settings. Our institution does not have enzyme immunoassay testing available for *C. difficile* toxins A and B. However, current guidelines state nucleic acid amplification testing alone, such as PCR, is appropriate when there are established institutional criteria for patient stool submission based on clinical symptoms.[14] Another limitation is the assumption that the patient was taking the statin, opioid, or antidepressant as prescribed if they were listed on the home medication list in the EMR.

In conclusion, an overweight BMI and statin use were associated with development of severe or severe, complicated CDI. We found no association between statin use and IBD exacerbations following CDI. Opioid and antidepressant use were not associated with CDI severity or frequency of IBD exacerbations following CDI. Future prospective studies are needed to better understand the effects of statin use in CDI and IBD; particularly, investigating differences among dose, drug, and duration of statin therapy may be beneficial.

ORCID iD

Sahil Khanna [iD] https://orcid.org/0000-0002-7619-8338

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