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Cytomegalovirus-Related Hospitalization Is Associated With Adverse Outcomes and Increased Health-Care Resource Utilization in Inflammatory Bowel Disease

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OBJECTIVES: Impact of cytomegalovirus (CMV)-related hospitalization in inflammatory bowel disease (IBD) patients is unknown. The aim of this study was to determine hospital outcomes of CMV-related hospitalization in IBD patients in a large national in-patient administrative data set.

METHODS: This was a cross-sectional study using data from the Nationwide In-patient Sample database. IBD- and CMV-related hospitalizations between 2003 and 2011 were identified using appropriate ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) codes. Impact of CMV-related hospitalization on in-hospital mortality, length of stay (LOS), and hospital charges were quantified.

RESULTS: CMV-related hospitalization was associated with higher in-hospital mortality (odds ratio (OR) 7.09, 95% confidence interval (CI) 3.38–14.85), prolonged LOS (7.77 days, $P<0.0001$), and more hospital charge (US$66,495, $P<0.0001$) in IBD patients.

CONCLUSIONS: CMV-related hospitalization in IBD is associated with high in-hospital mortality, prolonged LOS, and hospital care costs.

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INTRODUCTION

The inflammatory bowel diseases (IBDs), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing conditions that frequently require hospitalization.[1] Patients with IBD, particularly those with severe, corticosteroid-refractory and -dependent states are often treated with immunosuppressive agents either alone or in combination. Therefore, patients with IBD are expected to be at an increased risk of infectious complications, such as cytomegalovirus (CMV)-related colitis.[2] CMV, a member of the herpesviridae family, is responsible for a common viral infection in humans, with 30–100% of adults exhibiting evidence of past infection.[3,4] The primary infection in immunocompetent subjects is usually asymptomatic or limited to fever, mononucleosis-like illness or mild hepatitis, and followed by either chronic infection or viral latency from which virus may be reactivated.[5] By contrast, CMV reactivation, which is common in situations favoring acquired defect of cellular immunity, including immunosuppressive therapy, malignancy, bone marrow or solid organ transplantation, and HIV/AIDS infection can induce high disease activity and mortality.[3,6]

However, the outcomes of CMV-related hospitalization in IBD patients who have coexistent CMV disease or infection are not clear. Whether CMV disease or infection, especially CMV colitis, is associated with increased mortality is still debated. There are no studies that address the association between CMV-related hospitalization and health-care resource utilization, such as length of hospital stay (LOS) and total hospital charge. Because CMV disease or infection is an uncommon disease in IBD patients,[7,8] exploring large administrative data sets will help to determine the strength of association of CMV exposure and health-care outcomes. While individual patient's data is usually not available, results from large population data sets can be used to generate hypothesis for future prospective clinic studies.

In our study, we investigated the impact of CMV-related hospitalization on hospital mortality and health-care resource utilization for IBD patients from 2003 to 2011 at national and population-based levels by using the Nationwide In-patient Sample (NIS).

METHODS

Data sources. All data were extracted from the NIS between 2003 and 2011. NIS is the largest all-payer in-patient care database in the United States.[9] The database represents a 20% sample of nonfederal, acute-care hospitals in the United States and is stratified on hospital characteristics, e.g., location (urban vs. rural), teaching vs. non-teaching status, ownership (nonfederal, private, or public), and bed size

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(tertiles). The sampling frame includes community and general hospitals and academic medical centers comprising ~90% of all-hospital discharges in the United States. Each data entry includes a unique identifier, demographic variables (defined as age, gender, and race/ethnicity), type of admission, source of admission, principal (DX1) and secondary diagnoses (from DX2 to DX25), primary insurance payers, total hospital charges, and LOS.[1] Comorbidity was assessed using Elixhauser score.[10] The comorbidity burden was stratified based on Elixhauser score <3 (as reference) and ≥ 3.

Study population and definition of variables

The definitions of UC-, CD-, and CMV-related hospitalization. Our study population consisted of all adult discharges aged 19 years or older of IBD-related hospitalizations with or without CMV disease or infection (Appendix 1). It is important to note that because we used an administration database, CMV-related hospitalization in our study likely included both CMV disease and CMV infection. CMV infection refers to the detection of CMV antigens or antibodies in blood, whereas CMV disease is the presence of CMV infection and the presence of clinical signs and symptoms such as fever, leukopenia, or end-organ involvement. Some also consider the presence of typical CMV inclusions within cell preparations or end-organ tissue or positive viral cultures, crucial for the diagnosis of CMV disease.[5,6] In IBD patients, because CMV disease or infection most commonly involves the colon[3,4,10,11] and CMV activates and replicates more often in inflamed colonic mucosa,[12] for the diagnosis of gastrointestinal CMV in IBD patients, detection of CMV inclusion bodies in biopsy specimens from the gastrointestinal mucosa either by hematoxylin and eosin or immunohistochemistry have been widely accepted.[13] Therefore, in our study, we only included patients with IBD who had undergone either sigmoidoscopy or colonoscopy during the hospitalizations.

The discharges were considered to be IBD- and CMV-related if they met one of the following criteria: (a) principal diagnosis was UC or CD with a secondary diagnosis of CMV and they underwent either sigmoidoscopy or colonoscopy during the hospitalizations; or (b) a principal diagnosis of CMV and a secondary diagnosis of UC or CD and they underwent either sigmoidoscopy or colonoscopy during the hospitalizations.

Definition of hospital IBD admission volume. We calculated the number of discharges with a principal diagnosis of IBD (CD or UC) from each hospital during the study years. The hospitals were divided into low-volume (1–50 hospitalizations), medium-volume (50–150 hospitalizations), and high volume (more than 150 hospitalizations) hospitals depending on their annual volume of IBD-related hospitalizations as described and validated in a previous study.[9]

Definition of disease-specific severity. Disease-specific severity scores for CD[14] and UC[15] are quantified based on the presence of certain complications such as anemia, malnu; trition, requirement for blood transfusion, or total parenteral nutrition (Appendix 2).[14,15] The scores ranged from 0 to 7 for UC and 0 to 12 for CD, with higher scores representing greater severity of disease, and thus a higher likelihood of bowel resection (for CD) or colectomy (for UC). The disease-specific severity score has been shown to predict the outcome of interest in derivation and validation cohorts from the NIS and could be used to stratify hospitalizations into low, intermediate, and high-severity strata.[14–16]

Outcomes. Our interested outcomes were in-hospital mortality, LOS, and total hospital charges (Appendix 1).

Statistical analysis. SAS 9.3 (SAS Institute, Cary, NC) was used to perform all analyses, using appropriate survey estimation commands and strata weights. Data with missing information was excluded from statistical analysis for outcome analysis. Differences between patients with CMV disease or infection and those without were analyzed using χ^2 tests or Student's *t*-tests, as appropriate. Multivariate linear regression was used to evaluate the effect of CMV disease or infection on LOS and total hospital charge and multivariate logistic regression was used to calculate adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for in-hospital mortality. Each multivariate model adjusted for variables significantly associated with CMV disease or infection at $P \leq 0.1$ on univariate analysis.

RESULTS

Demographic characteristics of CMV-related hospitalization among hospitalized IBD patients. After excluding patients (43,552) with missing data, a total of 145,282 IBD patients were identified from 2003 to 2011, among which there were a total of 144,484 hospitalizations with no CMV disease or infection (99.45%) and a total of 798 hospitalizations with CMV disease or infection (0.55%) (Table 1). A larger proportion of patients with CMV disease or infection, had more comorbidities (44.78% vs. 32.37%), and high disease-specific severity score (16.63% vs. 5.37%) were admitted to large hospitals (84.46% vs. 64.83%), hospitals with high IBD admission volume (23.36% vs. 8.47%), and urban teaching hospitals (71.47% vs. 44.97%) (Table 1).

In-hospital mortality and health-care utilization of CMV-related hospitalization in IBD patients. On multivariate logistic regression analysis for in-hospital mortality, adjusting for patients' race, comorbidities, and disease-specific severity, hospital's size and type, and IBD admission volume, the odds of in-hospital mortality for an IBD patient with CMV disease or infection was 7.09 times higher (95% CI: 3.38–14.85) compared with an IBD patient without CMV (Table 2). Similarly, after adjusting for the above covariates, LOS, and the total hospital charge of an IBD patient with CMV disease or infection were 7.77 days longer (95% CI: 5.98–9.55, $P<0.0001$) and US$66,495 more (95% CI: 45,486–87,505, $P<0.0001$), respectively (Table 3).

Other factors associated with increased mortality, prolonged LOS and more hospital charge (Tables 2 and 3) included more comorbidities and high disease-specific severity. Patients' race, hospital's size and type were associated with LOS and

Table 1 Univariate analysis of baseline characteristics among patients with IBD

	No CMV disease or infection ($n=144,484$)		CMV disease or infection ($n=798$)		*P*-value
Age (mean, CI)	48.45 (48.14, 48.77)		50.59 (47.72, 53.45)		0.1442
Sex					0.1339
Male	62,122	43.00%	388	48.65%	
Female	82,362	57.00%	410	51.35%	
Race					0.0008
White	107,732	74.56%	567	71.00%	
Black	17,661	12.22%	73	9.17%	
Hispanic	12,492	8.65%	70	8.82%	
Other	6,599	4.57%	88	11.01%	
Hospital bed size					<0.0001
Small	15,692	10.86%	47	5.93%	
Medium	35,127	24.31%	77	9.61%	
Large	93,664	64.83%	674	84.46%	
Hospital type					<0.0001
Rural	11,849	8.20%	14	1.75%	
Urban non-teaching	67,665	46.83%	214	26.78%	
Urban teaching	64,970	44.97%	570	71.47%	
Insurance					0.1038
Medicare	40,832	28.26%	240	30.12%	
Medicaid	16,733	11.58%	84	10.54%	
Private[a]	67,493	46.71%	418	52.43%	
Other[b]	19,426	13.45%	55	6.91%	
Elixhauser score					0.0010
<3	97,721	67.63%	441	55.22%	
≥3	46,762	32.37%	357	44.78%	
IBD admission volume					<0.0001
Low (0–50)	90,705	62.78%	289	36.19%	
Medium (51–150)	41,535	28.75%	323	40.45%	
High (>150)	12,244	8.47%	186	23.36%	
Admission day					0.1765
Weekday	112,318	77.74%	655	82.05%	
Weekend	32,165	22.26%	143	17.95%	
Severity score					<0.0001
Low	93,877	64.97%	330	41.39%	
Intermediate	42,846	29.65%	335	41.98%	
High	7,760	5.37%	133	16.63%	

CI, confidence interval; CMV, cytomegalovirus; HMO, Health Maintenance Organization; IBD, inflammatory bowel disease.
[a]Private insurance includes HMO.
[b]"Other" includes self-pay and with "no-charge".

hospital charge (Table 3). High IBD admission volume was only associated with more hospital charge (Table 3).

DISCUSSION

Our nationwide analysis of hospital discharges showed that CMV-related hospitalization in IBD patients who have coexistent CMV disease or infection was associated with significant mortality, prolonged LOS, and higher cost. To our knowledge, this is the first study to investigate in-hospital mortality and health-care resource utilization of CMV-related hospitalization among IBD patients in a large administrative data set.

Table 2 Multivariate logistic regression analysis of CMV disease or infection's impacts on hospital mortality in IBD patients

	Odds ratio	95% CI	*P*-value
CMV disease or infection			<0.0001
No	Reference		
Yes	7.09	(3.38, 14.85)	
Race			0.4162
White	Reference		
Black	0.61	(0.33, 1.12)	
Hispanic	1.06	(0.61, 1.83)	
Other	0.79	(0.35, 1.80)	
Hospital bed size			0.7313
Small	0.81	(0.47, 1.41)	
Medium	1.01	(0.69, 1.49)	
Large	Reference		
Hospital type			0.7391
Rural	1.24	(0.67, 2.30)	
Urban non-teaching	1.13	(0.78, 1.62)	
Urban teaching	Reference		
Elixhauser score			<0.0001
<3	Reference		
≥3	3.37	(2.39, 4.77)	
IBD admission volume			0.0785
Low (0–50)	2.71	(1.13, 6.50)	
Medium (51–150)	2.20	(0.95, 5.11)	
High (>150)	Reference		
Severity score			<0.0001
Low	Reference		
Intermediate	2.84	(1.95, 4.12)	
High	6.44	(4.05, 10.25)	

CI, confidence interval; CMV, cytomegalovirus; IBD, inflammatory bowel disease.

In IBD patients, CMV is able to induce at least three types of disorders: (i) CMV infection without intestinal involvement; (ii) CMV infection involving the gastrointestinal tract, which most commonly presents as CMV colitis; and (iii) intestinal CMV infection limited to histologic stigmata of local CMV reactivation without systemic or local signs of disease.[3] As the ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) code of CMV disease or infection has only one code, encompassing all types of CMV disease or infection, it was likely that we have included patients with CMV disease or infection without gastrointestinal involvement, such as CMV pneumonia, CMV retinitis, or hemophagocytic lymphohistiocytosis. However, in IBD patients, the colon is the most common site for CMV-related disease or infection.[3,4,8,11] Extracolonic manifestations of CMV disease or infection, such as CMV pneumonia or hemophagocytic lymphohistiocytosis, are exceedingly rare and only reported in case reports in IBD patients even if in the presence of immunosuppressant therapy.[8,17,18] Furthermore, CMV disease or infection in active IBD patients seems to be a peculiar local process that could be facilitated by the tropism of CMV for granulation tissue, and triggered by local (proinflammatory cytokines) and systemic (medical-induced immunosuppression) conditions.[8] In our study, we only included patients with IBD discharge codes

Table 3 Multivariate linear regression analysis of CMV disease or infection's impacts on LOS and total hospital charges in IBD patients

	LOS			Total charges		
	Days	**95% CI**	***P*-value**	**Dollars**	**95% CI**	***P*-value**
CMV disease or infection			<0.0001			<0.0001
No	Reference			Reference		
Yes	7.77	(5.98, 9.55)		66,495	(45,486, 87,505)	
Race			<0.0001			<0.0001
White	Reference			Reference		
Black	−0.47	(−0.70, −0.24)		−1,802	(−3,516, −88)	
Hispanic	−0.40	(−0.61, −0.20)		5,334	(3,485, 7,184)	
Other	−0.14	(−0.50, 0.23)		5,606	(2,774, 8,439)	
Hospital bed size			<0.0001			<0.0001
Small	−0.83	(−1.12, −0.54)		−8,336	(−10,683, −5,988)	
Medium	−0.53	(−0.73, −0.32)		−4,157	(−5,902, −2,412)	
Large	Reference			Reference		
Hospital type			0.0018			<0.0001
Rural	−0.51	(−0.80, −0.21)		−10,613	(−12,735, −8,490)	
Urban non-teaching	−0.13	(−0.34, 0.07)		2,506	(724, 4,289)	
Urban teaching	Reference			Reference		
Elixhauser score			<0.0001			<0.0001
<3	Reference			Reference		
≥3	1.74	(1.56, 1.92)		11,588	(10,354, 12,822)	
IBD admission volume			0.7647			0.0138
Low (0–50)	−0.18	(−0.68, 0.32)		−6,096	(−11,180, −1,011)	
Medium (51–150)	−0.13	(−0.62, 0.36)		−7,569	(−12,747, −2,391)	
High (>150)	Reference			Reference		
Severity score			<0.0001			<0.0001
Low	Reference			Reference		
Intermediate	2.48	(2.31, 2.66)		14,157	(12,954, 15,359)	
High	9.63	(9.01, 10.26)		56,657	(51,817, 61,496)	

CI, confidence interval; CMV, cytomegalovirus; IBD, inflammatory bowel disease; LOS, length of stay.

who have received either sigmoidoscopy or colonoscopy during the hospitalization. Therefore, the CMV disease or infection in our study most likely represented CMV colitis in the majority of hospitalized IBD patients.

In our study, a significantly larger proportion of IBD patients with CMV disease or infection were admitted to urban teaching, large hospitals, and hospitals with high IBD admission volume, suggesting that more CMV disease or infection were managed in more specialized or experienced hospitals.

CMV disease or infection leads to high morbidity and mortality in patients with immunosuppressive drugs or corticosteroid, as well as in organ transplant and AIDS patients.[19] CMV may cause severe colitis with significant morbidity and mortality in the immunocompetent host as well.[20] However, the outcomes of CMV disease or infection, especially CMV colitis, in IBD patients are still debated. Coexistent CMV colitis in severe and refractory IBD patients has been associated with high rates of toxic megacolon, colectomy rates, and mortality.[2,5,21] Anti-viral therapy can induce remission in IBD patients with concomitant CMV colitis.[5,6,20,22–24] Therefore, the American College of Gastroenterology guideline,[25] European Crohn's and Colitis Organization consensus,[26] and Canada consensus statements[27] have stressed the importance of ruling out CMV disease or infection in all cases of severe colitis, especially in steroid-refractory patients. On the other hand, CMV was probably just an "innocent bystander" without an actual impact on remission rate, mortality, or requirement for surgery.[7,21,23,28–31] A few case series studies found no benefit of anti-viral therapy with regard to the need for surgery,[21,27,31,32] which may support the role of CMV as an innocent bystander of intestinal inflammation, with no pathogenic activity by itself. Despite the above controversy, our study found that CMV-related hospitalization has been associated with significant mortality, prolonged LOS, and higher hospital costs among hospitalized IBD patients. However, we could not determine whether CMV disease or infection was a causative factor as this would require a prospective study. Based on these results, we suggest that the health provider should be vigilant about the coexistent CMV disease or infection in hospitalized IBD patients. In addition, the results also support that coexistent CMV disease or infection might be an indicator of severe inflammation in hospitalized IBD patients.[6]

There are some inherent limitations to our study. Although the current American College of Gastroenterology and European Crohn's and Colitis Organization guidelines emphasize the importance of awareness of coexistent CMV disease or infection in severe colitis patients, not every hospitalized IBD patient in our study has been tested for CMV. In addition, although the main target of CMV disease or infection is the gastrointestinal tract and CMV colitis is the most common type of CMV disease or infection in IBD patients,[4] the single

ICD-9-CM code of CMV might include all types of CMV disease or infection. Furthermore, the diagnostic modalities of CMV disease of infection in our study were unknown. There is a wide range of normal values for CMV diagnostic tests that are institution dependent. Several methods are currently used for detecting CMV disease or infection. For the diagnosis of gastrointestinal CMV, combined CMV antigenemia assay and detection of CMV inclusion bodies in biopsy specimens from the gastrointestinal mucosa either by hematoxylin and eosin or immunohistochemistry have been proposed. The real-time tissue PCR assay that allows more sensitive and rapid detection of CMV-DNA in clinical samples has also been widely used in clinical practice.[13] This data type is not available in the NIS database. In our study, by only including the IBD patients who have received either sigmoidoscopy or colonoscopy, the patients with CMV disease or infection more likely had CMV colitis. Another limitation of the NIS database in our study was that the IBD severity could not be assessed based on patient's symptoms, signs, and test results. CMV colitis, however, is found to be more prevalent in severe or steroid-refractory IBD patients.[7,23,24] The association between CMV disease or infection and adverse hospital outcomes may only reflect the IBD severity.[6] In our study, we controlled for the disease-specific severity that is determeind by using the variables available in the NIS database, which has been validated by previous studies.[14–16] In addition, NIS database analysis did not allow us to distinguish between CMV infection and disease. Therefore, the association between CMV-related hospitalization and adverse outcomes might be because of either CMV disease or CMV infection. Also, given the structure of the NIS, we could not determine the impact of CMV treatment on outcomes. The significance of CMV inclusions on colon biopsies in the absence of systemic features as well as anti-viral treatment in this context remains controversial. Some authors, including the current American College of Gastroenterology guideline along with consensus statements from European Crohn's and Colitis Organization and Canada, advocate the treatment of CMV disease or infection in IBD patients.[22,25–27] Other authors reported remission or improvement of IBD patients with coexistent CMV disease or infection without anti-viral therapy.[21,28,29] To address this question, a randomized clinical trial is warranted.

Despite above limitations, our study also has strengths. The NIS database provides a large number of patients with discharge diagnosis of CMV disease or infection and IBD, which otherwise would not be possible from smaller single-center or multicenter studies because of the relatively uncommon CMV disease or infection in IBD patients.[7,8] In addition, by only focusing on patients with IBD who received either sigmoidoscopy or colonoscopy during the hospitalization, CMV disease or infection in our cohort is enriched to capture those patients more likely having CMV colitis. The benefit of using the NIS database is that the results represent the current national in-patient health-care utilization of IBD patients with CMV disease or infection.

In conclusion, IBD patients who have coexistent CMV disease or infection had significant in-hospital mortality, prolonged LOS, and higher total hospital charge. This strong association warrants prospective trials to determine the impact of anti-viral therapy in IBD patients with isolated colonic CMV disease or infection and/or systemic disease.

CONFLICT OF INTEREST

Guarantor of the article: Cheng Zhang, MD, PhD.
Specific author contributions: Dr. Cheng Zhang had designed and conducted the research and written the manuscript. Dr. Alice Hinton had performed the statistical analysis. Dr. Somashekar Krishna, Razvan Arsenescu, Edward Levine and Darwin Conwell had participated in discussion the research project, interpretation of the results, and written the manuscript.
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Study Highlights

WHAT IS CURRENT KNOWLEDGE

✓ Inflammatory bowel disease (IBD) patients are predisposed to have cytomegalovirus (CMV) disease or infection, especially CMV colitis.

✓ The impact of CMV-associated hospitalization on hospital outcomes in IBD patients was unknown.

WHAT IS NEW HERE

✓ CMV-associated hospitalization was associated with increased health resource utilizations, including length of stay (LOS) and total hospital charge, in IBD patients.

✓ CMV-associated hospitalization was associated with significant in-hospital mortality in IBD patients.

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APPENDIX

Appendix 1. International Classification of Diseases, Ninth revision, Clinical modification code (ICD-9-CM) codes

Crohn's disease (CD) 555, 555.1, 555.2, and 555.9
Ulcerative colitis (UC) 556, 556.0, 556.1, 556.2, 556.3, 556.4, 556.5, 556.6, 556.8, and 556.9
CMV disease or infection 078.5
Procedures:
Flexible sigmoidoscopy 45.24
Rigid sigmoidoscopy 48.23
Colonoscopy 45.21, 45.22, 45.23, and 45.25
Severity score variables:
Anemia: 280, 280.1, 280.9, 285.1, and 285.9
Blood transfusion 99.0, 99.00, 99.03, and 99.04
Malnutrition: 263, 263.0, 263.1, 263.2, 263.8, and 263.9
Parental nutrition: 99.15
Obstructing: 560, 560.0, 560.1, 560.2, 560.3, 560.8, 560.9, 568.0, and 537.3
Fistulizing: 537.4, 567.2, 567.21, 567.22, 569.5, 569.8, 569.81, 569.82, 569.83, 569.89, 593.3, 593.82, 596.1, and 619.1
Volume depletion: 276.5
Clostridium difficile infection 008.45.

Appendix 2

CD		*UC*	
Characteristic	*Points*	*Characteristic*	*Points*
Inflammatory*	0	Anemia	1
Obstructing*	2	Requirement for blood transfusion	1
Fistulizing*	4	Malnutrition	2
No anemia	0	Total parental nutrition (TPN)	2
Anemia	1	Admission to teaching hospital	1
Requirement for blood transfusion	1		
No malnutrition/TPN	0		
Malnutrition	2		
TPN	1		
Volume depletion	1		
Admission to teaching hospital	1		
Clostridium diffcile Infection	1		
Risk stratification for severity	*CD*		*UC*
Low severity	0–1	Low severity	0–1
Intermediate severity	2–4	Intermediate severity	2–3
Severe severity	≥5	Severity	≥4

*Only one disease behavior is assigned per hospitalization.
Risk score to predict sever hospitalization course among patients with either ulcerative colitis (UC) or Crohn' disease (CD).