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Original Article

The economic burden of *Clostridioides difficile* infection in patients with hematological malignancies in the United States: A case-control study

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Abstract

Objective: The primary study aim was to describe all direct healthcare costs associated with *Clostridioides difficile* infection (CDI), both in and out of the hospital, in patients with hematologic malignancies in the United States.

Design: A retrospective analysis was conducted utilizing data from US databases of Truven Health Analytics.

Patients: We analyzed health insurance claims between January 2014 and December 2017 of patients diagnosed with hematological cancer: acute myeloid leukemia (AML), acute lymphoblastic leukemia, Hodgkin's lymphoma, and non-Hodgkin's lymphoma (NHL).

Methods: Patients with CDI after cancer diagnosis (CDI+, cases) were matched with patients without CDI reported (CDI−, controls). Matched cases and controls were compared to identify the CDI-associated costs in the 90 days following the onset of CDI.

Results: We matched 622 CDI+ patients with 11,111 CDI− patients. NHL (41.7%) and AML (30.9%) were the predominant underlying diseases in the CDI+ groups. During study period, the average time in-hospital of CDI+ patients was 23.1 days longer than for CDI− patients ($P < 2\times10^{-16}$). Overall, CDI onset increased costs of care by an average of US$57,159 per patient ($P = 6\times10^{-12}$), mainly driven by hospital costs.

Conclusions: This study confirms the significant economic burden associated with CDI in the United States, especially in patients with hematological malignancies. These findings highlight the need for prevention of CDI in this specific patient population.

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Clostridioides (*Clostridium*) *difficile* is one of the most common pathogens found in healthcare-associated infections in the United States; it can lead to infections with symptoms ranging from mild diarrhea to life-threatening pseudomembranous colitis.[1] Antibiotic usage is the most common cause of CDI; antibiotics provoke a disruption of the intestinal microbiota, allowing the colonization of the intestine by *C. difficile*. The US Center for Disease Control and Prevention (CDC) has stated that advanced age, CDI history, recent hospitalizations, and a weakened immune system are the main risk factors for CDI.[2] Immunocompromised patients with hematologic malignancies, those who undergo chemotherapy and/or hematopoietic stem cell transplant (HSCT), and patients who develop neutropenia are at particularly high risk.[3–5]

Prior studies have assessed the high economic burden of CDI in the general population as well as in various high-risk subpopulations.[6,7] The disease is thought to incur significant additional costs borne by healthcare insurance, mostly in the hospital, as demonstrated in the United States[8,9] and Europe.[10–12] However, only a few studies have investigated the burden of CDI specifically in patients with hematologic malignancies,[13,14] and most of these focused on costs related to hospitalization.

CDI is diagnosed both in the hospital and outside the hospital, and it sometimes has long-lasting or late-occurring medical consequences such as CDI recurrence and increased utilization of healthcare resources in the weeks following the onset.[15] In the present study, we performed a longitudinal analysis of the burden of CDI for patients, looking at all uses of healthcare services in and outside the hospital. To our knowledge, this study is one of the first to assess both in- and out-of-hospital costs associated with CDI during the 90 days following the infection diagnosis in patients with hematologic malignancies in the United States.

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Methods

Data source

This study was performed retrospectively on data extracted from (1) Truven Health MarketScan Commercial Database and (2) Truven Health MarketScan Medicare Supplement Database.[16] Both MarketScan databases are administered by Truven Health Analytics, part of the IBM Watson Health business.[17] Data used for the analysis were derived from a subset of the MarketScan databases for the period January 2014–December 2017, covering the use of health services of ~1.9 million employees, dependents, and retirees in the United States with primary or Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated health plans. We collected all enrollment records, healthcare services encountered, and uses in and outside the hospital, along with drug prescriptions outside the hospital. The MarketScan databases contain anonymized patient-level data and were obtained through a license agreement with the data holder. The analyses using the MarketScan databases involved no risk to the subjects and did not meet the definition of human-subject research.

Study perspective

Following the definitions of the International Society for Pharmacoeconomics and Outcomes (ISPOR) Special Task Force,[18] the study was performed from the healthcare sector perspective. The healthcare sector perspective includes formal healthcare sector (medical) costs covered by third-party payers (eg, public or commercial insurances) and by patients as out-of-pocket costs (ie, the portion of the claims the patient was obligated to pay such as copayments or deductibles).

Patient selection

Female and male patients, regardless of age, with diagnosed acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), Hodgkin's lymphoma (HL), and non-Hodgkin's lymphoma (NHL) between January 2014 and December 2017 and no diagnosis of any other malignancy in the 6 months before that were included for analysis. In brief, we limited our study population to these hematologic malignancies because they are often treated with intensive chemotherapy and/or HSCT with a concomitant antibiotics support, increasing the odds of developing a CDI.[19] We used the detailed *International Classification of Diseases-9* and *-10* (ICD-9-CM and ICD-10-CM) codes to detect diagnoses of AML, ALL, HL, and NHL in the database (the codes for diagnosis of each condition are detailed in supplementary Table 1 (online)).

The following exclusion criteria were used to reduce the study population:

- Patients with a hematologic malignancy in remission at study entry, if the information was available in the diagnosis codes
- Patients with <6 months of continuous enrollment in the databases prior to the hematological diagnosis, to have sufficient data of medical history
- Patients with <5 diagnoses reported on 5 distinct days for the hematologic malignancy, to avoid including patients with only a suspicion of cancer or with an erroneously reported diagnosis code
- Patients with a CDI in the 6 months prior to the cancer diagnosis
- Patients with partially or fully capitated insurance plans or with a disenrollment period between their cancer diagnosis and their first CDI episode, to avoid bias when reporting costs.

Study groups

CDI was detected using the corresponding 008.45 (ICD-9-CM) or A04.7 (ICD-10-CM) codes in the diagnoses reported either in admissions records or out-of-hospital services. To analyze the burden of CDI in hematological patients, we divided our study population into 2 groups: (1) a case group (CDI+) comprising patients with a CDI diagnosed up to 3 years after cancer diagnosis and (2) a control group (CDI−) comprising patients without any CDI diagnosis recorded after their cancer diagnosis. Comprehensive data related to hospital stays, out-of-hospital services, and out-of-hospital drug prescriptions of patients were analyzed separately for both groups and compared.

Definition of index date and study period

For CDI+ patients, the index date was chosen as the date of the first CDI diagnosis recorded after the cancer diagnosis. For CDI− patients, the index date was randomly assigned so that the delay between the patients' cancer diagnosis and index date follows the same distribution than for CDI+ patients. The study period was defined as the period from the index date to 90 days later. For patients who were lost to follow-up (eg, due to death, change of healthcare insurance), the study period might be <90 days.

Comorbidities and major medical procedures

The non–age-adjusted weighted Charlson comorbidity index was computed for each patient using all diagnoses recorded in the database during the 90 days prior to the index date with an algorithm derived from Quan et al[20] and the R package comorbidity.[21]

Patients who underwent allogeneic or autologous HSCT during the study period were also identified using admissions diagnosis-related groups (MS-DRG v34) and procedures codes indicating the transplant. Supplementary Table 2 (online) lists all medico-administrative codes used for HSCT detection.

Economic outcomes

All costs reported in insurance claims in the databases for the study period were collected, adjusted to 2017 US dollars using the consumer price index for all urban consumers of medical care services,[22] then analyzed. Costs associated with CDI were further analyzed by splitting them based on their origin: costs associated with out-of-hospital services, with out-of-hospital drug uses, or with in-hospital stays and procedures. Drug use was further analyzing according to the drug type: drugs indicated for CDI treatment [fidaxomicin, bezlotoxumab and metronidazole (oral or intravenous), and oral vancomycin], other antibiotics, and other drugs. The Truven dataset structure does not allow a robust identification of CDI recurrences. However, a fixed 90-day study period permitted us to assess the costs associated to a CDI and possible short-term recurrences.

Case-control matching

Stringent and granular case-control matching was performed to evaluate the impact of CDI on overall costs of healthcare to ensure a maximimum resemblance between cases and controls. CDI cases were matched with as many CDI controls as possible with the following matching criteria using an exact matching algorithm:

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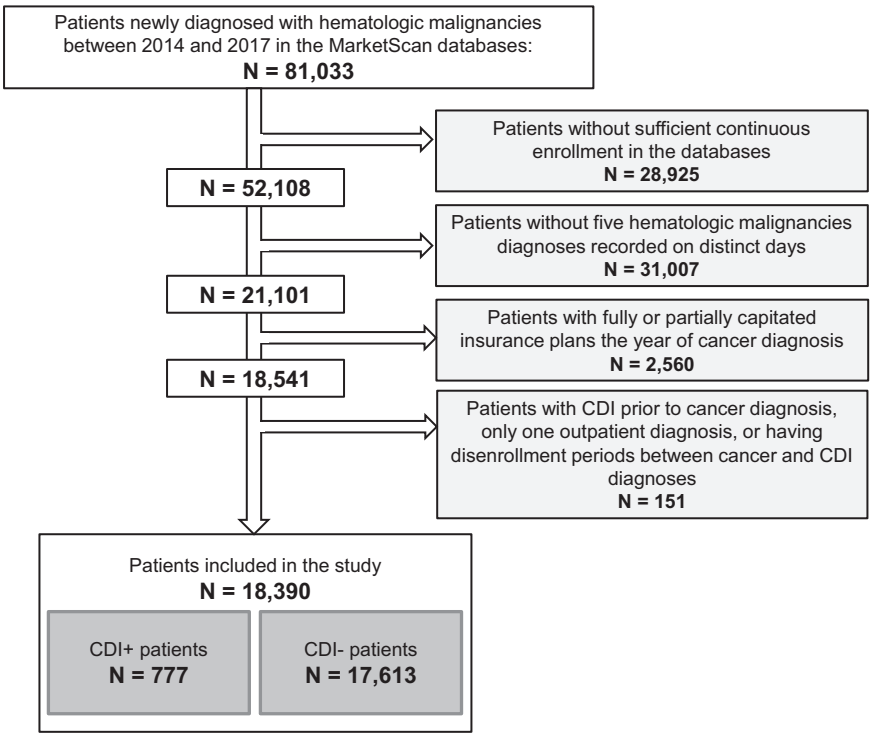

Figure 1. Patients' selection

- Same sex
- Similar age, coarsened in groups of 6 consecutive years (eg, 18–23 years old)
- Same underlying disease, either AML, ALL, NHL or HL
- Same HSCT status during the study period, either none, allo-HSCT, or auto-HSCT
- Similar Charlson comorbidity score, coarsened in groups of 3 points to ensure that 2 patients in the same group had no more than a 2-point difference in Charlson comorbidity index
- Same hospitalization status at index date, whether the patient was hospitalized on the index date

The CDI-associated costs were calculated as the differences of means in costs between cases and controls.

Statistical analysis

All analyses were performed using R version 3.6.1 software,[23] data.table version 1.12.0 software,[24] and the matching process was performed by using the "MatchIt" package.[25] Percentages were used to describe categorical variables; medians, means and 95% confidence intervals (95% CI) were used to describe continuous variables. The Fisher exact test and the Welch *t* test were used to compare quantitative data. A *P* value of .05 was the threshold for statistical significance.

Results

Patients selection

Of the 81,033 patients diagnosed with hematological underlying cancer between 2014 and 2017 found in the database, the selection was narrowed to 18,390 patients who fulfilled the inclusion and exclusion criteria. A flow diagram of patients' selection is presented in Figure 1.

Characteristics of patients

Overall, the patients' mean age was 53 years (95% CI, 53.1–53.6; min, 1; max, 106) with 46% of female patients. The CDI+ group comprised 777 patients, with a mean age of 45 years (95% CI, 43.3–46.7) and 47% of whom were women. The CDI− group comprised 17,613 patients with a mean age of 54 years (95% CI, 53.4–54.0) and 46% of whom were women. The Charlson comorbidity score ranged from 0 to 15, with a mean of 3.0 points (95% CI, 2.96–3.02; min, 0; max, 15) and a median of 2. The score was significantly higher in the CDI+ group compared with the CDI− group (mean 3.6 vs 3.0, $P < 2\times10^{-16}$). Further patient characteristics are presented in Table 1.

The overall incidence of CDI after cancer diagnosis was 4.2%, with a higher incidence in leukemia patients (15.5% for ALL and 13.7% for AML) compared with lymphoma patients (1.2% for HL and 2.5% for NHL).

Matching

Overall, 692 CDI+ cases were successfully matched with 11,111 CDI− control cases. The 692 CDI+ cases were allocated into 306 groups of patients with similar characteristics by the matching algorithm. On average, each group consisted of 2.3 CDI+ cases and 36.3 controls.

Some patients (85 CDI+ and 6,502 CDI−) were not matched because of the stringent criteria adopted in the exact matching. Notably, matched CDI+ patients were not significantly different from the whole CDI+ group in terms of costs ($P = .08$). However, costs for unmatched CDI+ patients were significantly

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higher than the matched CDI+ costs ($P = 2\times10^{-6}$) or the whole CDI+ group ($P = 2\times10^{-5}$). Further comparisons are available in Supplementary Table 3 (online).

Costs associated with CDI

On average, the total costs incurred during the 90-day study period were US$196,524 for patients in the CDI+ group and US$136,365 for patients in the CDI− group. The excess costs associated with CDI were +US$57,159 ($P = 6\times10^{-12}$; 95% CI, US$41,870–US$89,117), which represents a 42% increase in healthcare costs. All results of the costs comparison are available in Table 2.

To assess sensitivity to the randomness introduced by the computation of index dates in the CDI− group, a sensitivity analysis was run 100 times. It yielded a mean difference in total healthcare costs of US$60,856 (95% CI, US$60,059–US$61,653; min, US$48,451; max, US$69,515), showing that the reported results are not overly sensitive to the random attribution of the index date.

The excess costs associated with CDI were mainly related to hospitalization costs. Indeed, although out-of-hospital services related costs were not different between the 2 groups ($37,612 for CDI+ patients vs $34,850 for CDI− patients; $P = .15$), in-hospital costs were significantly higher in the CDI+ group ($151,208 vs $98,552; $P = 6\times10^{-12}$). Treatment with drugs outside the hospital also contributed to the excess costs of CDI in the CDI+ group, but to a lesser extent ($4,704 vs $2,963; $P = 3\times10^{-6}$).

The CDI+ patients were more frequently hospitalized during the study period: the average number of hospitalizations was higher by 1.6 stays ($P < 2\times10^{-16}$; 95% CI, 1.50–1.71) and the average length of stay was 23.1 days longer ($P < 2\times10^{-16}$; 95% CI, 21.5–24.5) in this group. CDI+ patients also had a higher probability of being admitted to ICU or emergencies: 47.0% of CDI+ patients were admitted to ICU at least once during the study period (vs 10.3% in the CDI− group, $P < 2\times10^{-16}$), and 54.9% visited an emergency room at least once (vs 15.2% in the CDI− group, $P < 2\times10^{-16}$). Also, regarding out-of-hospital drug use, the costs for CDI-specific drugs and other drugs were significantly higher for CDI+ patients, but no significant difference was seen for other antibiotics. These results are detailed in Table 3.

Table 1. Patient Characteristics

Participants	Total, No. (%)	CDI+, No. (%)	CDI−, No. (%)
Total	18,390 (100)	777 (100)	17,613 (100)
AML patients	1,758 (9.6)	241 (31.0)	1,518 (8.6)
ALL patients	1,195 (6.5)	186 (23.9)	1,009 (5.7)
NHL patients	13,203 (71.8)	324 (41.7)	12,879 (73.1)
HL patients	2,234 (12.1)	27 (3.5)	2,207 (12.5)
Age strata			
0–9 y	613 (3.3)	87 (11.2)	526 (3.0)
10–19 y	789 (4.9)	94 (12.1)	695 (3.9)
20–29 y	1,165 (6.3)	57 (7.3)	1,108 (6.3)
30–39 y	1,358 (7.4)	46 (5.9)	1,312 (7.4)
40–49 y	2,206 (12.0)	75 (9.6)	2,131 (12.1)
50–59 y	4,471 (24.3)	159 (20.4)	4,312 (24.5)
60–69 y	4,439 (24.1)	153 (19.7)	4,286 (24.3)
70–79 y	1,983 (10.8)	58 (7.5)	1,925 (10.9)
80–89 y	1,143 (6.2)	43 (5.5)	1,100 (6.2)
>89 y	223 (1.2)	5 (0.6)	218 (1.2)
Sex			
Female	8,474 (46.1)	368 (47.4)	8,106 (46.0)
Male	9,916 (53.9)	409 (52.6)	9,507 (54.0)
Charlson comorbidity index			
0–2	10,336 (56.2)	320 (41.2)	10,016 (56.7)
3–5	5,827 (31.7)	308 (39.6)	5,519 (31.3)
6–8	1,925 (10.5)	119 (15.3)	1,806 (10.3)
9–11	247 (1.3)	23 (3.0)	224 (1.3)
12–14	49 (0.3)	7 (0.9)	42 (0.2)
15	6 (0.03)	0 (0)	6 (0.03)
Hospitalized at index date			
No	16,687 (90.7)	283 (36.4)	16,404 (93.1)
Yes	1,713 (9.3)	494 (63.6)	1,209 (6.9)
HSCT received during the study period			
Allo-HSCT	240 (1.3)	83 (10.7)	157 (0.9)
Auto-HSCT	101 (0.6)	31 (4.0)	70 (0.4)
No HSCT	18,049 (98.1)	663 (85.3)	17,386 (98.7)

Note. CDI+, Patients with *Clostridioides difficile* infection after cancer diagnosis; CDI−, patients without *Clostridioides difficile* infection reported; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma; HSCT, hematopoietic stem cell transplant.

Discussion

In the present study, we analyzed insurance claims data for 18,390 patients diagnosed with a hematologic malignancy in the United States. The observed overall CDI incidence rate was 4.2%, which is in line with incidences retrieved from recently published US studies.[13,26,27] As expected, AML and ALL patients were the most at-risk patients, but CDI incidences observed in these subpopulations were higher than in previously published literature. This discrepancy may be explained by the difference in the CDI observation window. In the present study, the CDI could be recorded within the 3 years after cancer diagnosis, whereas Ford et al[26] limited the analysis of CDI to the 49 days following a hospitalization and Luo et al[13] and Duhalde et al[27] only observed CDI during the hospital stay.

The results highlight the significant economic burden of CDI in this specific population (US$57,159 of excess costs associated with CDI) mainly driven by in-hospital costs. This finding is consistent with earlier published studies that unveiled important hospital costs associated with CDI in patients with hematologic malignancies in the United States. Luo et al analyzed the outcomes of CDI among >1.2 million hospitalizations of leukemia patients and showed a CDI-associated increase in hospital charges of US $43,553 per patient.[13] In a recently published study in which 2,611 patients with hematologic malignancies undergoing intensive chemotherapy were analyzed, an increase in hospitalization costs of US$36,113 per patients with CDI on average could be demonstrated.[27] The slightly lower CDI-associated costs observed in these 2 studies may be due to the exclusion of hospitalization costs incurred after the index CDI hospitalization.

In our study, out-of-hospital costs were not the main source of economic burden in patients with hematological malignancies. Indeed, we detected no significant additional costs for out-of-hospital services, and the excess cost of out-of-hospital drugs contributed only weakly (US$1,740 of US$57,159).

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Table 2. Healthcare Costs Per Patient (2017 US$)

2017 US$ Healthcare Costs Over Study Period	CDI+ (Cases)	CDI− (Controls)	Difference	*P* Value[a]
In-hospital				
Mean	151,208	98,552	52,657	6×10^{-12}
(95% CI)	(136,679–165,738)	(95,896–101,207)	(37,887–67,427)	
Median	90,343	47,027		
Min–Max	0 – 2,001,739	0–1,478,769		
IQR	184,243	141,042		
Out-of-hospital services				
Mean	37,612	34,850	2,762	.15
(95% CI)	(34,083–41,141)	(33,691–36,010)	(−952 to 6,476)	
Median	23,452	20,355		
Min–Max	0 – 490,757	0 – 1,279,671		
IQR	39,581	37,594		
Out-of-hospital drugs				
Mean	4,704	2,963	1,740	3×10^{-6}
(95% CI)	(4,003–5,404)	(2,802–3,125)	(1,021–2,460)	
Median	1,059	359		
Min–Max	0–83,964	0–300,086		
IQR	4,147	2,003		
Total				
Mean	193,524	136,365	57,159	6×10^{-13}
(95% CI)	(178,527–208,521)	(133,390–139,340)	(41,870–72,448)	
Median	146,745	89,117		
Min–Max	0–2,004,094	0–1,706,303		
IQR	196,676	153,855		

Note. CDI+, Patients with *Clostridioides difficile* infection after cancer diagnosis; CDI−, patients without *Clostridioides difficile* infection reported.
[a]Welch *t* test.

Table 3. Healthcare Utilization Per Patient

Healthcare Utilization Over Study Period		CDI+ (Cases)	CDI− (Controls)	*P* Value[a]
Patients with at least 1 ICU use during hospitalization	No. (%)	365 (47)	1,810 (10.3)	$<2\times10^{-16}$[b]
Patients with at least 1 visit to an emergency room during hospitalization	No. (%)	427 (54.9)	2,687 (15.2)	$<2\times10^{-16}$[b]
Out-of-hospital CDI drugs costs (US$)[c]	Mean	704.4	305.7	.001
	Median	134.6	19.2	
	IQR	761.1	39.8	
Out-of-hospital non-CDI antibiotics costs (US$)[c]	Mean	82.1	105.4	.15
	Median	18.8	16.6	
	IQR	49.5	43.2	
Out-of-hospital other drugs (US$)[c]	Mean	5,149	3,834	.002
	Median	1,122	731.1	
	IQR	5,227	2,969	

Note. CDI+, patients with *Clostridioides difficile* infection after cancer diagnosis; CDI−, patients without *Clostridioides difficile* infection reported.
[a]Welch *t* test.
[b]Fisher exact test.
[c]CDI drugs are defined as vancomycin oral, metronidazole, fidaxomicin, and bezlotoxumab.

To our knowledge, this study is one of the first to assess the cost associated with CDI in patients with hematologic malignancies considering both costs from in- and out-of-hospital settings for a predetermined period of time after the index CDI diagnosis. *Clostridioides difficile* infection is a pathology known for its high rate of recurrence; it can reach up to 40% in some populations.[15] The Center for Diseases Control and Prevention defined a CDI recurrence as any CDI episode occurring within 8 weeks (56 days) after the index episode.[28] By covering the 90-day period after the index CDI diagnosis, we considered costs corresponding to the index episode and its potential recurrences. Therefore, unlike most previous studies that might underestimate the CDI economic burden, the results presented here could be more representative of the real cost associated with a CDI episode and its

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consequences for patients. Nevertheless, our study results are in line with a recent cost-of-illness study that focused on the impact of CDI recurrence, demonstrating additional hospitalization costs per patient within a 12-week follow-up period of ~US$64,079 (€59,000).[29]

Another strength of the present study is the use of an exact matching algorithm to ensure the most unbiased comparison of patients with and without CDI. Patients were matched with very stringent and granular criteria; thus, the differences observed are likely associated with the occurrence of CDI. Also, our conservative approach with stringent matching criteria led to the exclusion of some CDI+ patients that would not match with any control without releasing the constraints of matching. Notably, significantly higher costs were reported for these patients in insurance claims, and their exclusion from the analysis may have avoided a distortion of the cost comparison if they had very specific comorbidities or needed very special medical care, which explained the nonmatching.

One potential weakness of this study could be the random choice of the index date for CDI− patients. However, our sensitivity analysis showed that the reported results were not overly sensitive to the random attribution of the index date. Another major limitation of this work relates to the strength of the CDI diagnosis as reported in the insurance claims database. We may not have captured the correct CDI diagnosis because the CDI cases were identified using insurance-claim diagnosis codes and we were not able to ensure that the diagnosis was performed according to published guidelines and had been medically validated (especially in the United States, where the use of PCR-based detection without further confirmation is more prevalent). However, as mentioned in Scheurer et al,[30] some studies have reported a correlation between diagnosis codes in insurance claims databases and *C. difficile* toxin assay results, increasing confidence in the true CDI status of patients. Also, with imperfect insurance claims data, it is often difficult to differentiate an initial CDI episode from a recurrence. Consequently, we did not assess the number of recurrences per patient, nor did we compare costs associated with an index CDI episode or due to a recurrence.

This study demonstrated a significant economic burden of CDI in hematological patients, mostly driven by hospitalization and readmission-associated costs. Since more detailed potential CDI cost sources (eg, isolation measures, inpatients medications or mechanical ventilation) were not recorded in the present analysis' data source, further studies are needed to strengthen the understanding of CDI cost drivers. These findings highlight the important need for swift treatment and appropriate prevention of CDI in this specific high-risk patient population.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2020.153

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Conflicts of interest. Pierre-Alain Bandinelli, Lise Lurienne, Renaud Buffet, Lucien Guillou, and Lola Duhalde are employees of Da Volterra and may own or hold stock in the company.

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