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Research Article

Predictors and Temporal Trends of Mortality in Hematopoietic Stem Cell Transplant Patients with Clostridium Difficile Colitis: A Nationwide Analysis Over A Decade.

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Abstract

Clostridium Difficile infection (CDI) is the leading cause of healthcare-associated infections. Hematopoietic stem cell transplant (HSCT) recipients are highly vulnerable to the development of CDI, due to their immunocompromised status and antimicrobial resistance.

Patients and Methods: A retrospective review of the healthcare cost and utilization project: national inpatient sample was conducted between 2008-2018. International classification of disease (ICD) codes identified variables, including CDI and other comorbidities. The Chi-square test was used to assess statistical significance between groups. The data was propensity-matched, and then multivariate logistic regression was used to analyze independent predictors of mortality, and length of stay and to predict the odds of developing complications, including graft vs. host disease (GVHD).

Results: A total of 144,253 HSCT recipients are included, of which 33,470 were diagnosed with Clostridium Difficile Colitis (CDC). The mortality rate fluctuated from 9.2% in 2009 and 4.8% in 2017 ($p<0.05$). Patients with CDC had higher odds of mortality (1.70 $p<0.05$). HSCT recipients with CDC had higher rates of almost all complications. CDC increased the odds of developing GVHD (1.30 $p<0.05$), and GVHD increased the odds of developing CDC (1.20 $p<0.05$). HSCT patients with CDC who develop GVHD have significantly increased odds of mortality (2.33 $p<0.05$).

Conclusion: CDC remains a significant contributor to morbidity and mortality in HSCT recipients. Our study is the largest to date to evaluate trends and predictors of mortality in this population. We illustrate how CDC increases the incidence of several complications, increasing the odds of mortality. GVHD has a bidirectional relationship with CDC. We recommend further evaluating prophylactic strategies to decrease CDC and GVHD to reduce the burden of morbidity and mortality in this population.

1. Introduction

Clostridium Difficile (CD) is an anaerobic spore-forming gram-negative bacterium and is the leading cause of nosocomial diarrheal infections worldwide. It is responsible for >500,000 cases of infectious diarrhea and >14,000 deaths per annum in the United States CD is primarily a nosocomial infection that causes a broad spectrum of disease severity, ranging from mild diarrhea to fulminant colitis and death [1-6].

Due to the escalating rates of infection globally, coupled with an epidemic of hyper-toxigenic strains of CD, the burden of the disease as significantly increased. While the bacteria are commonly known to infect people with the recent use of broad-spectrum antibiotics, immunocompromised individuals also experience a high incidence of CDI. A large proportion of immunocompromised patients are those who undergo Hematopoietic Stem Cell Transplantation (HSCT). HSCT is therapeutically performed for many malignant and non-malignant diseases and, over time, has evolved into adoptive immunotherapy for multiple disorders While clinical outcomes of malignancies following HSCT have substantially revolutionized, HSCT recipients still represent one of the most immunologically vulnerable populations [7-10].

Nosocomial infections ranging from pneumonia to sepsis account for many deaths following HSCT, with CD being a significant contributor. The reported incidence of CDI in HSCT recipients is between 5.7% and 24.7%, and CDI rates in HSCT recipients are up to 9-fold higher than in other inpatients. There is an increased risk of CDI in HSCT patients, given their underlying immunodeficiencies, prolonged hospitalizations, frequent use of broad-spectrum antibiotics, and chemotherapy-related disruption of enteric mucosal barriers. These hospital-acquired infections are not the only challenges HSCT patients face. They are also prone. to developing graft failure, secondary malignancies, organ toxicity, and Graft-vs-host disease (GVHD) [7-9].

GVHD is one of the most common and severe complications of HSCT and presents a distinctive syndrome of dermatitis, hepatitis, and enteritis following HSCT. Studies have shown that mortality rates, median hospital stay, and total hospital costs are significantly higher in HSCT patients who develop GVHD than in those who don't. Rates of GVHD are exceptionally high in this population due to an interplay between the donor's immunocompetent T cells and the recipient's weakened immune system because of the factors mentioned earlier. Prior studies have been done in HSCT patients to observe if there is any significant association between CDI and GVHD and have found that CDI causes an increased risk of developing GVHD, and most HSCT patients who developed GVHD following CDI had a more severe course of disease. However, the risk of developing CDI in HSCT patients with preexisting GVHD hasn't been observed in depth yet, which could potentially be an essential interplay between the diseases affecting morbidity and mortality of HSCT [10-16].

Resource utilization during hospital admissions for Clostridium Difficile colitis (CDC) in HSCT patients in the United States, and look at the relationship between CDC and GVHD over [8-13].

2. Methods

We retrospectively reviewed the Nationwide Inpatient Sample (NIS) database from 2008 through 2018. The NIS is the most extensive inpatient hospital database derived from hospitals' billing data to statewide data organizations across the United States (US). It contains a 20% stratified sample of all participating hospitals, which includes data from 48 states, covering around 97% of the US population. NIS includes patient and hospital-level discharge information. Each discharge is treated as a unique entity coded with one primary and multiple secondary diagnoses. These are collected and recorded using the International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-10-CM) coding system. The NIS is part of the Healthcare Cost and Utilization Project under the Agency for Healthcare Research and Quality.

To compare the degree of comorbid disease between study populations, we used the Charlson Comorbidity Index (CCI). The CCI is a validated, simple, and readily applicable method of estimating the risk of death from comorbid disease and has been widely used as a predictor of long-term prognosis and survival. Based on the CCI score, the severity of comorbidity exists in three grades: mild, with CCI scores of 0-1; moderate, with CCI scores of 2; and severe, with CCI scores of [17].

Table 1. Patient Characteristics

Characteristics	HSCT patients with Clostridium Difficile Colitis	HSCT patients without Clostridium Difficile Colitis	Total	P Value
	N=33,470	N=110,783	N=144,253	
Patient Age, mean (SD)	46	49		p<0.05
Sex				p=0.4739
Female	14,031 (42%)	45,886 (41%)	59,793 (41%)	
Male	19439 (58%)	64,897 (59%)	84,460 (59%)	
Race N(%)				p=0.2243
White	9375 (72%)	78,933 (71%)	102,838 (71%)	
Black	3397 (10%)	12,120 (11%)	15,709 (11%)	
Hispanic	3437 (10%)	11,787 (11%)	15,320 (11%)	
Asian or Pacific Islander	1,031 (3%)	3,279 (3%)	4,284 (3%)	
Native American	171 (1%)	399 (0.3%)	534 (0.04%)	
Other	1,335 (4%)	4,265 (4%)	5,568 (4%)	
Insurance, N(%)				p<0.05
Medicare	9,331 (28%)	37,522 (34%)	48,354 (34%)	
Medicaid	5,432 (16%)	15,133 (14%)	19,921 (13%)	
Private	18,345 (55%)	56,721 (51%)	74,160 (51%)	
Uninsured	361 (1%)	1,407 (1%)	1,817 (1%)	
Household Median Income, N(%)				p=0.2064
1-38,999	6,935 (21%)	26,023 (20%)	28,793 (20%)	
39,000-47,999	7,935 (24%)	26,023 (23%)	33,914 (24%)	
48,000-62,900	8,639 (26%)	29,845 (27%)	38,775 (26%)	
>63,000	9,961 (30%)	32,847 (30%)	42,785 (30%)	
Bed Size, N(%)				p=0.8524
Small	444 (13%)	14,080 (13%)	18,335 (13%)	
Medium	5164 (15%)	16,651 (15%)	21,725 (15%)	
Large	24,021 (72%)	80,052 (72%)	104,194 (72%)	
Hospital Region				p<0.05
Northeast	6871 (21%)	25,236 (23%)	32,673 (23%)	
Midwest	8973 (27%)	28,937 (26%)	37,737 (26%)	
South	9787 (29%)	4,243 (31%)	44,343 (31%)	
West	7839 (23%)	22,467 (20%)	29,514 (20%)	
Hospital Location				p<0.05
Rural	392 (1%)	2,149 (2%)	2,726 (2%)	
Urban	33,078 (98%)	108,634 (98%)	141,527 (98%)	
Hospital Teaching Status				p<0.05
Teaching	31,656 (95%)	98,705 (91%)	12,882 (9%)	
Non-Teaching	1,814 (5%)	10,126 (9%)	131,371 (91%)	
Charlson Comorbidity Index, mean (SD)				p<0.05
0	5,606 (17%)	18,157 (16%)	23,669 (16%)	
1	1,058 (3%)	4,564 (4%)	5,857 (4%)	
2	15,567 (47%)	48,091 (43%)	62,620 (43%)	
3	11,239 (34%)	39,971 (36%)	52,046 (36%)	

In this study, we included 144,253 patients from 2008 to 2018 who underwent HSCT. The incidence of CDC in HSCT patients was 23.2% (N=33,470). Table 1 represents the baseline patient characteristics between HSCT patients admitted with and without CDC. Patients who developed CDC were younger, with a mean age of 46 compared to 49. The two groups are similar in gender, race, household median income, and bed size. The majority of patients in both groups of patients with and without CDC were admitted to urban hospitals (98% vs. 98%, p<0.05), which were teaching hospitals (95% vs. 91%, p<0.05). Patients with CDC have higher rates of coverage with private insurance (55% vs. 51%, p<0.05) and lower rates of insurance coverage for Medicare (28% vs. 34%, p<0.05).

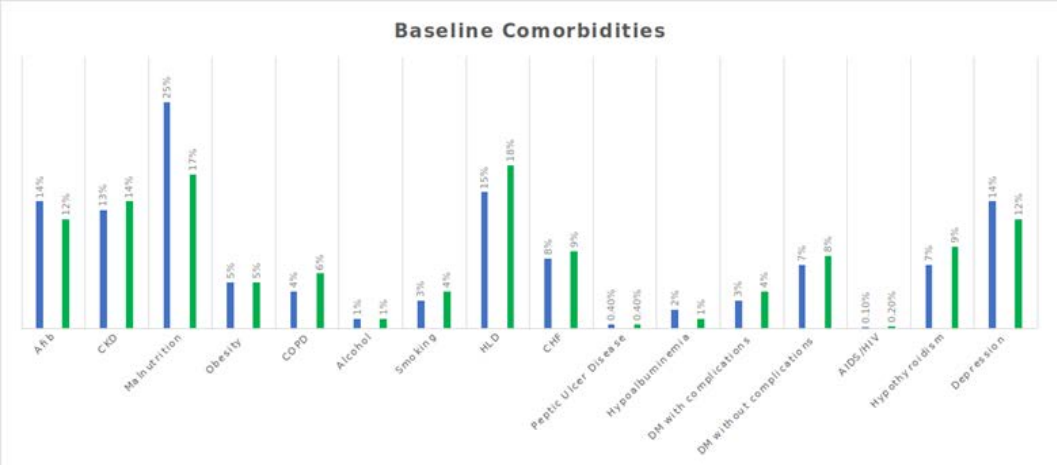

Figure 1: Baseline Comorbidities of HScott Patients with And Without CDCs

Figure 1. depicts the baseline comorbidities of HSCT patients with and without CDC. CDC patients have higher mild to moderate baseline comorbidities reflected by a greater CCI score than patients without CDC (47% vs. 43%, p<0.05) but interestingly, severe baseline comorbidities were higher in patients without CDC as shown by CCI score (34% vs. 36%, p<0.05). Patients with CDC had higher rates of Afib (14% vs. 12%, p<0.05), malnutrition (25% vs. 17%, p<0.05), hypoalbuminemia (2% vs. 1%, p<0.05), and depression (14% vs. 12%, p<0.05).

3.1 Trends in Mortality

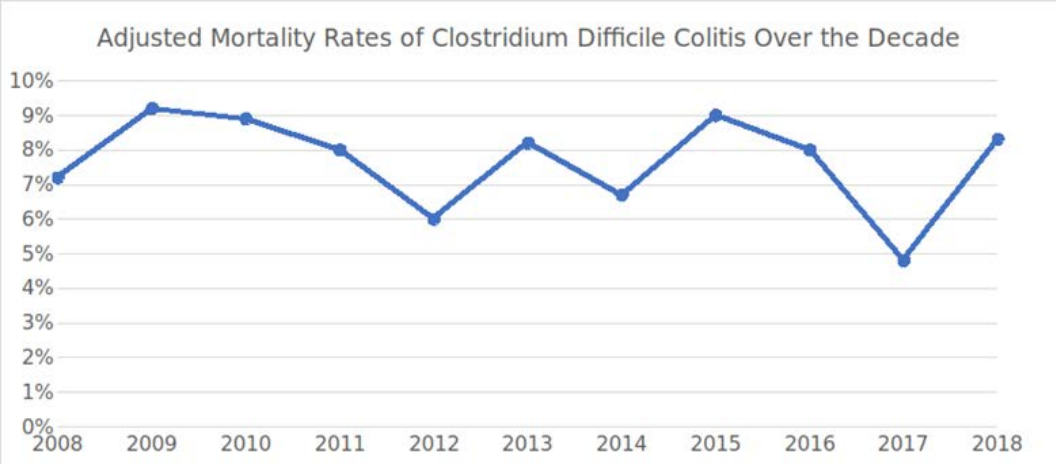

Figure 2: Adjusted Mortality Rates of Patients with CDC After HScott Over the Decade

Figure 2. reflects the adjusted mortality rates of patients with CDC after HSCT over the decade. Although the mortality rates fluctuate over the decade, there has been an overall decline in mortality from 2008 through 2018 (p<0.05). Compared with patients without CDC, patients with CDC after HSCT had higher odds of mortality compared to those without CDC.

3.2 In Hospital Outcomes

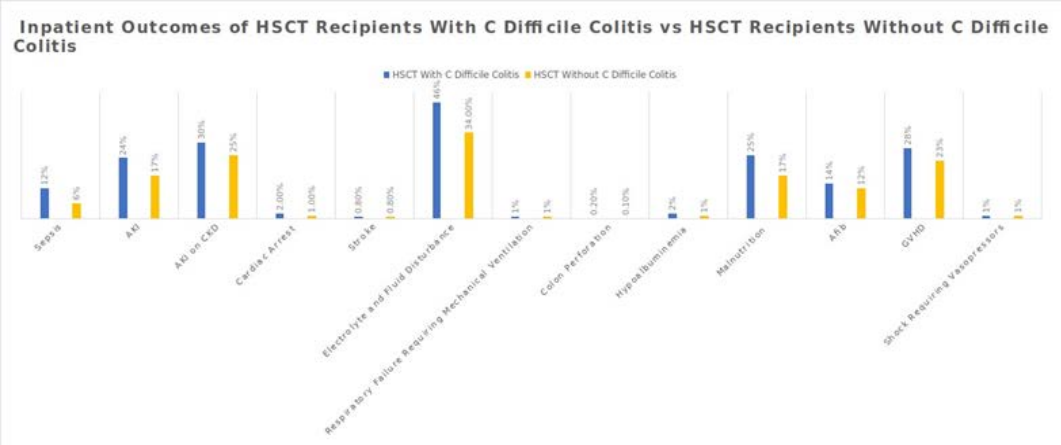

Figure 3: Inpatient Outcomes of HScott Recipients with And Without CDC

Figure 3. represents the inpatient outcomes of HSCT recipients with and without CDC. Patients with CDC had higher rates of cardiac arrest (2% vs. 1%, p<0.05), sepsis (12% vs. 6%, p<0.05), acute kidney injury (24% vs. 17%, p<0.05), stroke (0.8% vs. 0.8%, p<0.05), malnutrition (25% vs. 17%, p<0.05), atrial fibrillation (14% vs. 12%, p<0.05), and most importantly GVHD (28% vs. 23%, p<0.05) compared to those without CDC.

3.3 Predictors of Mortality

Figure. 4 represents the predictors of mortality in HSCT patients with CDC. After adjusting for confounders, the inpatient hospital outcomes that significantly increased the greatest odds of mortality in CDC patients were sepsis (OR=7.48, [5.69-9.83] p<0.05), AKI (OR=2.48, [1.26-4.52] p<0.05), cardiac arrest (OR=12.2, [3.99- 37.35] p<0.05), malnutrition (OR=1.79, [1.41-2.27] p<0.05), Afib (OR=1.78, [1.61-2.27] p<0.05), respiratory failure requiring mechanical ventilation (OR=5.92, [2.45-14.31] p<0.05), and stroke (OR=3.94, [1.64- 9.49] p<0.05). Most importantly, from this data, we find that HSCT patients with CDC who develop GVHD have significantly increased odds of mortality (OR=2.33, [1.83-2.96] p<0.05).

3.4 Odds of Developing CDCs And Gvhd

One of the most impactful findings observed in our analysis is that CDC independently increases the odds of developing GVHD (OR=1.30, [1.21- 1.39] p<0.05), and GVHD also independently increases the odds of developing CDC (OR=1.20, [1.12- 1.30] p<0.05) [18-25].

4. Discussion

We compare patients who underwent HSCTs and developed CDC to those who did not develop this infection. To our knowledge, this is the largest sample size comparing the outcomes of mortality in HSCT patients with and without CDI and finds its association with GVHD and other predictors of morbidity and mortality. Prior studies have been single-center studies or had smaller sample sizes. Our study is among the pioneer studies depicting GVHD's bidirectional relationship with CDC. GVHD increases the risk of developing CDC, and CDC independently increases the risk of GVHD: a very significant interplay between two phenomena primarily associated with high morbidity and mortality in HSCT patients. One explanation for this phenomenon is the dysbiosis of the gut microbiota and subsequent inflammation that, in turn, leaves these patients vulnerable to infection and immune dysregulation. It could also be explained by the fact that HSCT patients are treated with immunosuppressants, thereby increasing the likelihood of procuring infections such as CDC [17-34].

This shared mechanism likely explains how GVHD and CDC significantly increase mortality in HSCT recipients. GVHD is one of the most typical and most challenging complications following HSCT. GVHD results from a complex interplay between recipient and donor immunological process, which can result in a range of stigmata of the disease from a rash to arthritis, conjunctivitis, and enteritis [32,33].

Previous studies on the association between GVHD and CDI were smaller in sample size and ranged over shorter periods. A review published by Alonso et al. included four papers concluding the presence of CDC leads to the development of severe onset and new-onset GVHD. A retrospective review by Willems et al. showed a 30-fold increase in the risk of developing GVHD with CDC. These studies support that alteration in the microbiome of gut results from both HSCT and CDC increases the likelihood of developing GVHD. Interestingly, Kinnebrew et al. did not find an association between the two in their prospective cohort. They analyzed CDI as a time-dependent predictor for GVHD with an endpoint of 30 days to obtain an unbiased estimate using only CDI occurring before the onset of GVHD. Our study is the first to show an independent bidirectional relationship between CDC and GVHD. Our analysis also finds that GVHD independently increases the risk of inpatient mortality. Our finding further emphasizes the essential need for the prevention and treatment of both CDC and GVHD [6-34].

It has been well established that CDC increases mortality risk in immunologically vulnerable patients such as those who have undergone HSCT. Patients undergoing HSCT are among the highest risk groups to develop infections, partic-

ularly with CD, with an incidence ranging from 5-24.7% Our study shows a decreasing trend in adjusted mortality rates of patients who developed CDC after a HSCT over the decade from 2008 to 2018. This finding can be attributed to better healthcare, advances in treatment options, and a better understanding of post-transplant infections and how to prevent them. Other reasons include being more judicious in antibiotic use, especially those prone to causing CDC. Although there have been fluctuations in the mortality trend over the years, as shown in Figure 1, there has been a spike in mortality in 2018. Previous studies have shown an increase in 30-day mortality of patients with CDC patients with baseline [7].

comorbidities like AKI, malnutrition, and hypoalbuminemia, among others. We looked at independent baseline comorbid conditions in patients with and without CDC. We found that Afib, CKD, malnutrition, and hypoalbuminemia were present in greater frequencies in patients. with CDC than in those without CDC. Although unclear why the mortality rate increased in 2018, given the trajectory is decreasing over time, the rate will likely continue to fall over the coming years [18-19].

We also explored reasons for higher mortality rates in HSCT patients with CDC; We observed that HSCT patients with CDC developed higher inpatient rates of sepsis, AKI, cardiac arrest, stroke, electrolyte and fluid disturbances, malnutrition, A-fib, and GVHD, as shown in figure 4. Out of these, sepsis, AKI, cardiac arrest, stroke, respiratory failure requiring mechanical ventilation, malnutrition, Afib, and GVHD were all independent predictors of mortality. Prior studies have shown that sepsis in CDC patients may result from a derangement of gastrointestinal barrier function, which could lead to the translocation of microbes, endotoxins, and activation of inflammatory cascades resulting in bacteremia. HSCT disrupts the equilibrium of intestinal microbiota that is engaged in a complex relationship with the mucosal epithelium and underlying immune tissues, resulting in an invasion of bacteria into the bloodstream and leading to sepsis. Studies have also shown that patients with underlying CKD are more vulnerable to infections by Clostridium species. The National Hospital Discharge Survey (NHDS) database showed a significantly higher rate of CDI in both dialysis and non-dialysis CKD patients than in patients without CKD. Because CKD and CDI are both associated with increased morbidity and mortality, the association of increased mortality in CKD patients with CDI appears consistent [20-27].

Not surprisingly, CKD patients with CDI who had concomitant AKI had significantly higher mortality rates, which is consistent with the known adverse impact of AKI in hospitalized patients with or without CKD Interestingly, however, AKI on CKD was not an independent predictor of mortality. A review by Tanovic et al. showed that HSCT is also associated with excess cardiovascular risk partially due to exposure to cardiotoxic chemotherapy and radiation, as well as indirect and direct detrimental effects on cardiovascular reserve, which is an indicator of cardiac well-being [23-32].

Life-threatening cardiotoxicity can present during HSCT as acute heart failure, arrhythmias, pericardial tamponade, or cardiac arrest. Our study shows cardiac arrest as one of the highest predictors of mortality in HSCT patients with CDC [33].

Despite significant findings in this study, our study has its limitations, most significantly by the propensity-matched, it cannot still be compared to a randomized clinical trial or another prospective study. Second, this data is a finding of a national administrative database. This between different transplants and when the patient presented to the hospital with CDC from the hospital charges. Fifth, NIS only depicts inpatient mortality rates. It cannot report mortality for pate ients who passed away at home, en route to the hospital, in the ER, or within a given period post-discharge. Again, the large sample size will unlikely impact the overall results, but it reflects that the results are likely underestimated [34].

Our study, however, has many strengths as well. It is the largest and longest study yet on CDC in HSCT patients. The NIS database can provide a large sample size covering a national sample of patients, reducing beta error. The database can provide data on all types of hospitals, large, small, urban, rural, community, or teaching across 48 states encompassing 97% of the United States Population. This impressive sample size is the ideal dataset to assess for significant associations and ascertain the role of specific factors in inpatient mortality, disease development.

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