Poster 421

Economic Consequences of Cytomegalovirus Disease Among Stem Cell Transplant Recipients

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ABSTRACT

Background: Cytomegalovirus (CMV), a common opportunistic infection among stem cell transplant recipients, is associated with substantial morbidity and mortality. Limited information is available regarding the economic consequences of CMV disease among these patients. The current study evaluated the incremental healthcare costs associated with CMV disease among stem cell transplant recipients.

Methods: Adults with stem cell transplant were identified in the Truven Health MarketScan® database (Q1 2002–Q4 2011). Patients were required to have ≥ 2 years of continuous enrollment following the transplantation. They were classified into the CMV cohort if they had ≥ 1 observed CMV diagnosis within the 2-year period after transplantation (post-transplant period), or the No CMV cohort if they did not have any CMV diagnosis during the entire observation period in the database. Patients in the CMV cohort were matched 1:1 to patients in the No CMV cohort in two steps. The first step was exact matching based on age strata, gender, relevant comorbidities, year of transplantation, type of stem cell transplant, and donor status. The second step was a propensity score match based on region of residence, health plan type, relevant comorbidities, and baseline healthcare resource utilization and costs. The costs in the post-transplant period were compared between the two matched cohorts using Wilcoxon signed-rank tests.

Results: Among 189 stem cell transplant recipients with CMV and 2,539 recipients without CMV, a total of 113 matched pairs were identified. The baseline characteristics were comparable between the matched CMV and No CMV cohorts. During the 2-year post-transplant period, the CMV cohort was associated with significantly higher costs across all cost categories. The total costs were $586,416 in the CMV cohort vs. $305,462 in the No CMV cohort (incremental cost of $280,954, $p < 0.0001$). The majority of the differences were attributable to the incremental medical costs, accounting for ~95% of the total incremental costs.

Conclusions: Stem cell transplant recipients with CMV disease incurred significantly higher healthcare costs, including costs for CMV lab tests and antiviral drugs, than those without CMV disease.

BACKGROUND

- Cytomegalovirus (CMV) is one of the most common opportunistic infections among stem cell transplant (SCT) recipients
  - After myeloablative conditioning or post-transplant immunosuppression, CMV disease can occur from reactivation of latent infection in previously exposed patients or from a newly acquired infection in unexposed patients
  - The risk of infection is higher for recipients who are CMV seropositive than those who are seronegative and is also higher for recipients with allogeneic transplantation than those with autologous transplantation[1]
- CMV is associated with high clinical burden
  - Direct clinical manifestations of CMV disease include viremia, systemic illness, and tissue-invasive disease[2,3]
  - CMV infection is also associated with bacterial or fungal superinfections,[4] graft rejection,[5] and graft-versus-host disease[6]
- Studies are needed to measure the economic burden of CMV disease among SCT recipients
  - Previous research has primarily focused on the economic burden of CMV among solid organ transplant (SOT) recipients at a small number of specific institutions;[7–9] however, CMV can impact SCT differently from SOT

OBJECTIVE

- To evaluate the economic burden of CMV among SCT recipients using real-world data

METHODS

Data source

- Large administrative claims database (Truven Health Analytics MarketScan® database, 2002–2011)

Patient selection criteria

- Patients with SCTs (patients with solid organ transplantations were excluded)
- Patients ≥ 18 years of age on the date of their first transplant (index date)
- Patients continuously enrolled in their healthcare plan in the 6-month period before transplantation (baseline period) and the 2-year period following transplantation (post-transplant period)

METHODS (CONT.)

Matching

- Selected patients were further included into the CMV cohort if they had more than one CMV diagnosis code (ICD-9: 078.5), and into the No CMV cohort if there was no CMV diagnosis at any time during their healthcare enrollment period
- Within each group, CMV patients and No CMV patients with similar propensity for a CMV diagnosis were paired 1:1 using propensity score matching. The propensity score was calculated for each patient based on the patient's region of residence, health plan type, comorbidities, and baseline healthcare resource utilization and costs

Baseline variables and study outcomes

- Demographics and comorbidities measured during the baseline period
- Information on the first transplant received (date and type)
- Healthcare resource utilization (inpatient admissions, emergency department visits, outpatient visits, and antiviral drugs) and costs (medical and pharmacy costs) incurred during the 2-year post-transplant period due to any cause
  - Inpatient admissions were classified into different periods (baseline or post-transplant period) based on the admission date. If a hospitalization spanned both baseline and post-transplant periods, respective costs were allocated to periods in which the costs occurred
  - Antiviral drugs considered included foscarnet, ganciclovir, valacyclovir, valganciclovir, CMV immunoglobulin, and cidofovir. For foscarnet, ganciclovir, and cidofovir, both oral form and intravenous form were considered. Valacyclovir was only considered if initiated within 1 month of the transplantation date
  - CMV-related lab/diagnostic tests were identified by CPT codes and/or associated CMV diagnosis codes

Statistical Analyses

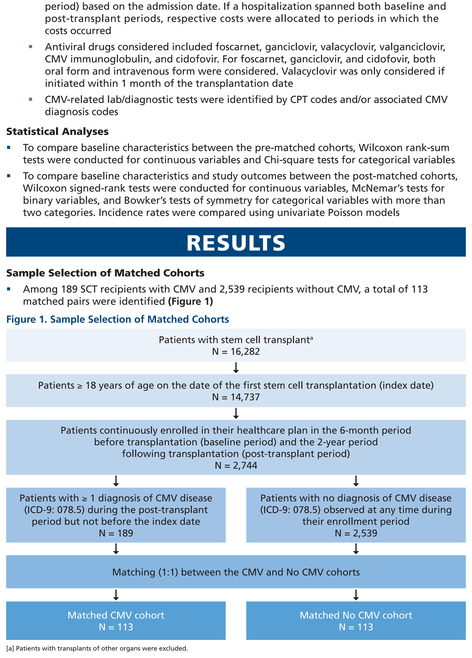
- To compare baseline characteristics between the pre-matched cohorts, Wilcoxon rank-sum tests were conducted for continuous variables and Chi-square tests for categorical variables
- To compare baseline characteristics and study outcomes between the post-matched cohorts, Wilcoxon signed-rank tests were conducted for continuous variables, McNemar's tests for binary variables, and Bowker's tests of symmetry for categorical variables with more than two categories. Incidence rates were compared using univariate Poisson models

RESULTS

Sample Selection of Matched Cohorts

- Among 189 SCT recipients with CMV and 2,539 recipients without CMV, a total of 113 matched pairs were identified **(Figure 1)**

Figure 1. Sample Selection of Matched Cohorts



[a] Patients with transplants of other organs were excluded.

RESULTS (CONT.)

Pre-Matched and Post-Matched Baseline Characteristics

- In the pre-matched cohort, there were significant differences between CMV and No CMV cohorts in multiple baseline characteristics
  - The CMV cohort was younger and had a smaller proportion of men compared with the No CMV cohort.
  - The CMV cohort had a greater proportion of patients with acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myelodysplastic syndrome, and aplastic anemia, and a smaller proportion of patients with metastatic solid tumors and multiple myeloma or plasma cell neoplasms, compared with the No CMV cohort
  - The CMV cohort had a greater proportion of patients receiving allogeneic SCT and a smaller proportion receiving autologous SCT than the No CMV cohort
  - The CMV cohort used healthcare resources more frequently and incurred higher healthcare costs during the baseline period compared with the No CMV cohort
- All of the significant differences in baseline characteristics between the cohorts that were observed in the pre-matched cohort were eliminated in the post-matched cohort **(Table 1)**

Table 1. Pre-Matched and Post-Matched Baseline Characteristics

	Pre-Matched			Post-Matched		
	CMV Cohort [A] N = 189	No CMV Cohort [B] N = 2,539	*p* [A] vs. [B]	CMV Cohort [A] N = 113	No CMV Cohort [B] N = 113	*p* [A] vs. [B]
Demographics						
Age, mean ± SD	52.5 ± 12.6	55.4 ± 11.8	0.0053 *	54.7 ± 10.3	55.0 ± 10.4	0.3145
Male, n (%)	91 (48.1)	1,441 (56.8)	0.0214 *	59 (52.2)	59 (52.2)	1.0000
Charlson Comorbidity Index (CCI), mean	3.0	3.4	0.5206	3.0	3.0	0.7631
Comorbidities, n(%)						
Lymphoma	77 (40.7)	1,070 (42.1)	0.7064	47 (41.6)	42 (37.2)	0.4561
Multiple myeloma and plasma cell neoplasms	38 (20.1)	1,089 (42.9)	<0.0001 *	26 (23.0)	31 (27.4)	0.3173
Acute myeloid leukemia	83 (43.9)	389 (15.3)	<0.0001 *	48 (42.5)	42 (37.2)	0.2888
Acute lymphoblastic leukemia	54 (28.6)	183 (7.2)	<0.0001 *	30 (26.5)	18 (15.9)	0.0578
Chronic lymphocytic leukemia	31 (16.4)	116 (4.6)	<0.0001 *	24 (21.2)	17 (15.0)	0.1936
Metastatic solid tumor	13 (6.9)	393 (15.5)	0.0014 *	5 (4.4)	5 (4.4)	1.0000
Amyloidosis	1 (0.5)	65 (2.6)	0.0857	1 (0.9)	1 (0.9)	1.0000
Myelodysplastic syndrome	31 (16.4)	148 (5.8)	<0.0001 *	13 (11.5)	13 (11.5)	1.0000
Aplastic anemia	73 (38.6)	498 (19.6)	<0.0001 *	34 (30.1)	34 (30.1)	1.0000
First Stem Cell Transplant Type, n (%)						
Allo-SCT	128 (67.7)	633 (24.9)	<0.0001 *	71 (62.8)	65 (57.5)	0.1088
Auto-SCT	47 (24.9)	1,701 (67.0)	<0.0001 *	33 (29.2)	36 (31.9)	0.2568
Unspecified SCT	14 (7.4)	205 (8.1)	0.7449	9 (8.0)	12 (10.6)	0.5127
Year of Index Date (First Transplantation), n (%)						
2005 and before	7 (3.7)	154 (6.1)	0.1838	2 (1.8)	2 (1.8)	1.0000
2006	29 (15.3)	340 (13.4)	0.4489	19 (16.8)	19 (16.8)	1.0000
2007	39 (20.6)	433 (17.1)	0.2093	27 (23.9)	27 (23.9)	1.0000
2008	33 (17.5)	506 (19.9)	0.4109	20 (17.7)	20 (17.7)	1.0000
2009	47 (24.9)	640 (25.2)	0.9175	26 (23.0)	26 (23.0)	1.0000
2010	34 (18.0)	466 (18.4)	0.9006	19 (16.8)	19 (16.8)	1.0000
Baseline resource utilization						
Number of events per patient						
Inpatient admissions	1.7	1.3	0.0006 *	1.7	1.5	0.5339
Inpatient length of stay (days)	20.6	11.0	<0.0001 *	20.1	16.4	0.1387
Emergency department visits	1.1	0.9	0.0301 *	1.1	1.5	0.6808
Outpatient visits	38.6	36.7	0.2338	39.8	37.1	0.1674
Baseline healthcare costs (2013 USD)						
Total costs	175,190.5	124,733.4	<0.0001 *	181,893.6	163,810.4	0.0698
Medical costs	167,180.8	114,040.7	<0.0001 *	172,647.0	155,228.1	0.0654
Inpatient admissions	88,310.4	45,031.4	<0.0001 *	88,540.4	76,477.4	0.2419
Emergency department visits	1,301.0	977.3	0.1371	1,669.0	1,590.0	0.1202
Outpatient visits	77,569.4	68,032.1	0.0662	82,437.6	77,160.7	0.2726
Pharmacy costs	8,009.7	10,692.6	0.0574	9,246.6	8,582.3	0.8342

SD = standard deviation
* Significant at the 5% level

RESULTS (CONT.)

Healthcare Resource Utilization by CMV vs. No CMV Patients during the Post-transplant Period

- The CMV cohort had higher healthcare resource utilization during the two-year post-transplant period compared with the No CMV cohort
  - The annual incidence rate of inpatient admissions and outpatient visits were higher in the CMV cohort than the No CMV cohort
  - The CMV cohort had more days in the hospital over the 2-year post-transplant period than the No CMV cohort
  - 76.1% of CMV cohort had at least one antiviral therapy, compared with 19.5% in the No CMV cohort ($p < 0.0001$)
  - The number of CMV-related lab/diagnostic tests per patient was also higher in the CMV cohort than in No CMV cohort **(Tables 2a and 2b)**

Table 2a: Healthcare Resource Utilization by CMV vs. No CMV Patients during the Post-transplant Period

	Matched SCT Patients					
	CMV Cohort N = 113		No CMV Cohort N = 113		Incidence Rate Ratios[b]	
Outcome Measures	Number of Events	Annual Rate[a]	Number of Events	Annual Rate[a]	IRR (95% CI)	*p*
Inpatient admissions	400	1.77	249	1.10	1.61 (1.37 , 1.88)	<0.0001 *
Emergency department visits	311	1.38	324	1.43	0.96 (0.82 , 1.12)	0.6060
Outpatient visits	13,458	59.55	10,180	45.04	1.32 (1.29 , 1.36)	<0.0001 *

[a] Annual rate reflected the annual incidence of each outcome measure.
[b] IRR was defined as the ratio of the incidence rates in CMV patients and No CMV patients
* Significant at the 5% level

Table 2b. Healthcare Resource Utilization by CMV vs. No CMV Patients during the Post-transplant Period (cont'd)

	Matched SCT Patients		
Outcome Measures	CMV Cohort [A] N = 113	No CMV Cohort [B] N = 113	*p* [A] vs. [B]
Number of days in hospital	56.1	30.4	<0.0001 *
N (%) of antiviral therapy utilization			
Patients who have used ≥ 1 antiviral therapy	86 (76.1)	22 (19.5)	<0.0001 *
Number of CMV-related lab/diagnostic tests	23.4	12.3	0.0002 *

* Significant at the 5% level

Healthcare Costs for CMV vs. No CMV Patients during the Post-transplant Period

- During the two-year post-transplant period, the CMV cohort was associated with significantly higher costs across all cost categories
  - The total costs were $586,416 in the CMV cohort vs. $305,462 in the No CMV cohort (incremental cost of $280,954, $p < 0.0001$)
  - The majority of the incremental cost was attributable to the incremental medical costs of $267,220, which accounted for 95% of the total incremental cost
  - The incremental medical cost burden mainly came from incremental inpatient admission costs (66% of the total incremental costs) and incremental outpatient visit costs (29% of the total incremental costs)
- The CMV cohort was associated with significantly higher average antiviral costs and higher costs for CMV-related lab and diagnostic tests compared with the No CMV cohort **(Table 3)**

RESULTS (CONT.)

Table 3. Healthcare Costs for CMV vs. No CMV Patients during the Post-transplant Period

	Matched SCT Patients			
Outcome Measures[a]	CMV Cohort [A] N = 113	No CMV Cohort [B] N = 113	Cost Difference [A] – [B]	*p* [A] vs. [B]
Total costs	586,416.0	305,462.1	280,953.9	<0.0001 *
Medical costs	543,813.1	276,593.3	267,219.7	<0.0001 *
Inpatient admissions	343,691.6	157,995.6	185,696.0	<0.0001 *
Emergency department visits	4,555.3	5,404.2	-848.9	0.2860
Outpatient visits	195,566.2	113,193.6	82,372.6	<0.0001 *
Pharmacy costs	42,602.9	28,868.7	13,734.2	0.0079 *
Other cost categories				
Antiviral therapy costs	6,920.6	449.7	6,470.9	<0.0001 *
Costs of CMV-related lab/diagnostic tests	3,357.1	1,473.3	1,883.7	0.0002 *

[a] Costs were adjusted to 2013 US dollars using the medical care component of the Consumer Price Index (CPI).
* Significant at the 5% level

LIMITATIONS

- The study relied on retrospective data with limited clinical information. There were no data on the CMV serostatus of donors and recipients
- Mortality information was not taken into account since patients had to be alive and followed for two years
  - SCT recipients who died within two years after transplantation were excluded from the analysis to ensure a fair comparison with equal follow-up time for both cohorts
- Indirect costs from CMV, such as work loss, were not considered
- As with all databases, the data are subject to coding errors
  - Although CMV was identified based on the presence of particular ICD-9 codes, these codes might have also been used for patients with CMV viremia but no disease

CONCLUSIONS

- SCT recipients with CMV were associated with greater healthcare resource utilization and incurred significantly higher healthcare costs than those without CMV over a 2-year period following transplantation
  - The majority of the cost difference was attributable to the increased medical costs in the CMV cohort compared with the No CMV cohort
- Despite recent improvements in the prevention and management of CMV, this study suggests there is still considerable economic burden due to CMV disease among SCT recipients

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