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Original article

# Burden of cytomegalovirus disease in allogeneic hematopoietic cell transplant recipients: a national, matched cohort study in an inpatient setting

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ABSTRACT

*Purpose of the study.* – No studies have compared the risk of mortality or graft-versus-host disease, in an inpatient setting in France, in allogeneic hematopoietic cell transplant recipients who develop cytomegalovirus disease with those who do not. This study assessed the impact of cytomegalovirus disease on clinical outcomes and healthcare resource utilization in allogeneic hematopoietic cell transplant recipients using the French Programme de Médicalisation des Systèmes d'Information database.

*Patients and methods.* – Recipients who had undergone allogeneic hematopoietic cell transplant in French hospitals between 2008 and 2011 were included in this retrospective, matched cohort study. Those with cytomegalovirus disease were each matched with two allogeneic hematopoietic cell transplant recipients without cytomegalovirus disease according to demographic and clinical characteristics. Probabilities of in-hospital mortality, graft rejection and/or graft-versus-host disease, and healthcare resource utilization were compared up to 12 months after cytomegalovirus disease diagnosis.

*Results.* – Overall, 4884 transplant recipients were enrolled, of which 194 had cytomegalovirus disease. Of these, 165 recipients with cytomegalovirus disease were matched to 330 without cytomegalovirus disease (1:2 ratio). The development of cytomegalovirus disease was associated with a significantly higher risk of in-hospital mortality (relative risk = 1.7, p = 0.0005) and higher cumulative number of inpatient days ($p < 0.0001$), but was not associated with a significantly higher risk of graft rejection and/or graft-versus-host disease or healthcare costs.

*Conclusions.* – Due to the increased risk of in-hospital mortality and higher cumulative number of inpatient days in allogeneic hematopoietic cell transplant recipients with cytomegalovirus disease versus those without, new strategies to prevent and manage cytomegalovirus disease are warranted.


## Introduction

Cytomegalovirus (CMV) is a β-herpes virus that causes latent infections in 40–70% of healthy individuals in developed countries, and up to 80% of individuals in developing countries [1]. Active CMV infection occurs in 50–70% of allogeneic hematopoietic cell transplant (allo-HCT) recipients, either by reactivation of the latent virus in response to immunosuppression, as a primary infection due to exposure or blood transfusion, or from receiving an organ from a CMV-seropositive donor [2]. CMV reactivation after allo-HCT is predictive for developing CMV disease (CMV-D) [1], which has an incidence of less than 5% [3–6], and remains one of the most important infectious complications associated with allo-HCT owing to the long period of immunosuppression required by graft recipients [2,7]. Risk factors for post-transplant CMV-D after allo-HCT include the pre-transplantation CMV serostatus of the recipient, development of graft-versus-host disease (GVHD), T-

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cell depletion, the type of immunosuppressive therapy administered, and receiving a transplant from an unrelated donor [7–10].

Two main treatment strategies can be used to prevent CMV-D in allo-HCT recipients: administering antiviral therapies (AVTs) when there is laboratory evidence of an active, but asymptomatic, infection (pre-emptive strategy), or administering AVTs before there is evidence of CMV infection (prophylactic strategy) [11–14]. Despite these strategies, and the ongoing investigation of the potential benefit of T-cell therapies, CMV-D remains an important cause of morbidity and mortality in allo-HCT recipients [12,13]. Furthermore, the management and administration of AVTs is challenging, owing to toxicities and issues relating to other comorbidities associated with CMV-D, such as GVHD.

Many studies have investigated the risk of adverse clinical outcomes (i.e. death, graft rejection [GR], or GVHD) in allo-HCT recipients with CMV infection or CMV-D, including some that have assessed the use of AVTs in these patients [15–24]. However, few of these studies have compared the difference in the risk of mortality and/or GVHD between allo-HCT recipients with and without CMV-D [18]. Furthermore, few recent studies have assessed the hospital-related economic burden of CMV-D in allo-HCT recipients [25].

This study aimed to describe the burden of CMV-D in allo-HCT recipients in an inpatient setting in France by investigating the association between CMV-D and in-hospital mortality, GR and/or GVHD, and healthcare resource utilization up to 12 months after CMV-D diagnosis. This study was conducted using the Programme de Médicalisation des Systèmes d'Information (PMSI), a national hospitalization database in France.

## Patients and methods

### *Study design and data source*

This was a retrospective, multicenter, matched cohort study using data from the PMSI database, a comprehensive French hospital database containing records of all hospitalizations (public and private) across the country. Three related datasets were used: the Medicine, Surgery, Obstetrics and Odontology database (Médecine, Chirurgie, Obstétrique et Odontologie) for short-stay hospitalizations, the Follow-up and Rehabilitation Care database (Soins de Suite ou de Réadaptation), and Complementary Files (FICHCOMP) for drugs taken during hospital stays.

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. allo-HCT recipients were identified via an anonymized code assigned by data holders, and the authors did not have access to the original data containing personal information. This study was authorized by the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés). As the PMSI database is de-identified, it was neither possible nor required to identify individual allo-HCT recipients to obtain consent for this study.

### *Target population*

Eligible recipients had undergone allo-HCT in public or private French hospitals between January 2008 and December 2011, been diagnosed with CMV-D, and been followed for at least 12 months after the date of CMV-D diagnosis. No exclusion criteria were applied.

The indication for allo-HCT was identified based on the principal diagnosis that resulted in hospitalization for transplantation using International Statistical Classification of Diseases and Related Health Problems (ICD-10) diagnosis codes. Indications were classified into five categories: myeloid neoplasms (acute myeloid leukemia, chronic myeloid leukemia, myelodysplastic syndrome, and other myeloid neoplasms); lymphoid neoplasms (acute lymphocytic leukemia, chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, and other lymphoid neoplasms); aplastic anemia; plasma cell disorders (multiple myeloma); and other.

For each allo-HCT recipient, information was collected on whether total body irradiation (TBI) or anti-thymocyte globulin (ATG) infusion was used as part of the transplant preparatory regimen. The use of TBI was identified using procedure codes, and the use of ATG infusion was identified using Unité Commune de Dispensation codes in patient medication records.

ICD-10 codes were used to identify cases of CMV-D based on primary and secondary diagnoses provided in the PMSI database. allo-HCT recipients were considered to have CMV-D if they had a primary or secondary diagnosis of a specified CMV-D (CMV pneumonia [B25.0], colitis [K93.820], hepatitis [B25.1], cholangitis [K87.00], mononucleosis [B27.1], pancreatitis [B25.2], or retinitis [H32.00]), or if they were hospitalized with a primary diagnosis of an unspecified CMV-D (B25.8, B25.9) and remained in the hospital for at least 7 days. The list of ICD-10 codes used to identify CMV-D cases is provided in Table 1.

### *Patient matching*

Each allo-HCT recipient with a CMV-D diagnosis (referred to as an exposed recipient) was matched to two allo-HCT recipients without CMV-D (referred to as non-exposed recipients), selected randomly with replacement. Matching criteria were: age at the time of transplantation (±5 years), gender, indication for disease at transplantation, whether the pre-transplant conditioning regimen contained ATG infusion and/or TBI, and previous or simultaneous occurrence of GR and/or GVHD. Each exposed allo-HCT recipient with GR and/or GVHD before the date of admission for the first hospital stay with a diagnosis of CMV-D (index date) were matched to two non-exposed allo-HCT recipients with GR and/or GVHD before the index date; exposed allo-HCT recipients with a record of GR and/or GVHD in the same hospital stay in which CMV-D was recorded were matched to non-exposed allo-HCT recipients with a record of GR and/or GVHD 15 days before to 15 days after the index date.

### *Index date and patient observation*

For the exposed cohort, the index date was defined as the date the allo-HCT recipient was diagnosed with CMV-D. For the non-exposed allo-HCT recipient cohort, the index date was defined as the date of initial admission for transplantation, plus the time from transplantation to CMV-D diagnosis of the corresponding exposed allo-HCT recipient. Therefore, non-exposed allo-HCT recipients were followed after transplantation for a period of time that was at least equal to the time from initial admission to CMV-D diagnosis of the corresponding exposed allo-HCT recipient. Those in the non-exposed cohort could have a diagnosis of CMV-D after the index date, but not at the index date or before. Occurrence of CMV-D was assessed for up to 24 months after hospitalization for allo-HCT.

### *Study outcomes*

All outcomes were assessed over 3, 6, and 12 months from the index date. The clinical outcomes assessed were all-cause in-hospital mortality (death is not recorded in the PMSI database if it occurs outside of the hospital, and thus was not taken into account in the analyses), and GR and/or GVHD, which were detected based on primary and secondary diagnoses provided in the PMSI database using ICD-10 codes (Table 1).

Healthcare resource utilization was also assessed. Healthcare costs were defined as total hospitalization costs, which included costs of inpatient stays in short stay (médecine chirurgie

**Table 1**
Demographic and clinical characteristics.

| | Exposed allo-HCT recipients (before matching) (n = 194) | Exposed allo-HCT recipients (n = 165) | Non-exposed allo-HCT recipients (n = 330) | P-value (matched cohort) |
|---|---|---|---|---|
| Female, n (%)* | 87 (44.8) | 72 (43.6) | 144 (43.6) | 1.00 |
| Mean age at transplantation, years (SD)* | 40.7 (19.8) | 41.2 (19.7) | 41.0 (19.7) | 0.92 |
| Year of transplantation, n (%) | | | | <0.0001 |
| 2008 | 4 (2.1) | 56 (33.9) | 117 (35.5) | |
| 2009 | 61 (31.4) | 43 (26.1) | 148 (44.9) | |
| 2010 | 53 (27.3) | 34 (20.6) | 65 (19.7) | |
| 2011 | 45 (23.2) | 32 (19.4) | 0 | |
| Indication for transplantation, n (%)* | | | | 1.00 |
| Myeloid neoplasm (AML/CML/MDS/other MN) | 95 (49.0) | 86 (52.1) | 172 (52.1) | |
| Lymphoid neoplasm (ALL/CLL/HD/NHL/other LN) | 62 (32.0) | 50 (30.3) | 100 (30.3) | |
| Aplastic anemia | 25 (12.9) | 21 (12.7) | 42 (12.7) | |
| Plasma cell disorder (MM) | 9 (4.6) | 5 (3.0) | 10 (3.0) | |
| Other | 3 (1.5) | 3 (1.8) | 6 (1.8) | |
| Preparative regimen, n (%)* | | | | |
| TBI | 60 (30.9) | 50 (30.3) | 100 (30.3) | 1.00 |
| ATG | 100 (51.5) | 79 (47.9) | 158 (47.9) | 1.00 |
| Mean length of initial hospital stay, days (SD) | 49.5 (30.9) | 49.0 (26.9) | 45.3 (28.7) | 0.17 |
| Discharge status after initial stay, n (%) | | | | 0.02 |
| Transfer to another MU | 46 (23.7) | 38 (23.0) | 46 (13.9) | |
| Went home | 138 (71.1) | 118 (71.5) | 272 (82.4) | |
| Died | 10 (5.2) | 9 (5.5) | 12 (3.6) | |
| GR and/or GVHD, n (%) | 92 (47.4) | 82 (49.7) | 164 (49.7) | 1.00 |
| Before the index date | 39 (20.1) | 21 (12.7) | 42 (12.7) | |
| Around the time of the index date (±15 days) | 63 (32.5) | 62 (37.6) | 124 (37.6) | |
| Without GR and/or GVHD before the index date | 92 (47.4) | 82 (49.7) | 164 (49.7) | |

*Matching criterion.
ALL = acute lymphocytic leukemia; allo-HCT = allogeneic hematopoietic cell transplantation; AML = acute myeloid leukemia; ATG = anti-thymocyte globulin; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; GR = graft rejection; GVHD = graft-versus-host disease; HD = Hodgkin's disease; LN = lymphoid neoplasm; MDS = myelodysplastic syndrome; MM = multiple myeloma; MN = myeloid neoplasm; MU = medical unit; NHL = non-Hodgkin's lymphoma; SD, standard deviation; TBI = total body irradiation.

obstétrique) and rehabilitation (soins de suite et de réadaptation) medical units (including any additional costs of medication incurred during these stays). Additional measures of healthcare resource utilization were total inpatient days and the number of hospital admissions (stays lasting for at least 1 day).

### *Statistical analyses*

Descriptive statistics were performed on recipient characteristics at transplantation, and on study outcomes for exposed and non-exposed allo-HCT recipients. Categorical variables were compared using the Chi-square test or Fisher's exact test, and continuous variables were compared using the Student's *t*-test or Wilcoxon test.

The time from CMV-D diagnosis to in-hospital death and GR and/or GVHD over 12 months from the index date was described using Kaplan–Meier survival curves for exposed and non-exposed allo-HCT recipients. For a non-exposed allo-HCT recipient, the survival curves demonstrated the probability of survival without occurrence of the event of interest over time, starting from the index date of the corresponding matched exposed allo-HCT recipient. Differences between survival curves were compared using the log-rank test. A p-value of 0.05 was considered to be statistically significant. Analyses were performed using SAS v9.3.

## Results

### *Incidence of CMV-D and allo-HCT recipient matching*

Between January 2008 and December 2011, a total of 4884 allo-HCTs were recorded in public and private French hospitals. During initial hospitalization, or at any time during the 24 months post transplant, CMV infection or CMV-D was recorded as a primary or secondary diagnosis in 825/4884 allo-HCT recipients (16.9%). Of these, 159 allo-HCT recipients (19.3%) were readmitted to hospital due to a primary diagnosis of CMV infection or CMV-D; CMV-D was recorded for 194/4884 allo-HCT recipients (4.0%). CMV pneumonia (n = 43/194 [22.2%]) and CMV colitis (n = 34/194 [17.5%]) were the most common manifestations of CMV-D, but 86/194 allo-HCT recipients (44.3%) had unspecified CMV-D. Of the 194 exposed allo-HCT recipients, 165 could be matched to two non-exposed allo-HCT recipients. There was a total of 330 matched, non-exposed allo-HCT recipients; therefore, the matched cohort consisted of 495 allo-HCT recipients (Fig. 1).

### *Patient characteristics at transplantation*

In the matched cohort, fewer allo-HCT recipients were female (43.6% in exposed [n = 72/165] and non-exposed allo-HCT recipients [n = 144/330]) compared with male, the most common indications for transplantation were myeloid neoplasm (52.1% in exposed [n = 86/165] and non-exposed [n = 172/330] allo-HCT recipients) and lymphoid neoplasm (30.3% in exposed [n = 50/165] and non-exposed [n = 100/330] allo-HCT recipients), and 78.2% of exposed [n = 129/165] and non-exposed [n = 258/330] allo-HCT recipients had received TBI (n = 150/495 [30.3%]) or ATG (n = 237/495 [47.9%]) as part of their conditioning regimen (Table 1).

In the matched cohort, 49.7% of allo-HCT recipients had GR and/or GVHD before the index date, 12.7% of allo-HCT recipients had GR and/or GVHD around the time of the index date (±15 days), and 37.6% of allo-HCT recipients did not have GR and/or GVHD before the index date.

### *Impact of CMV-D on in-hospital mortality*

Over the 12 months after the index date, the incidence of in-hospital mortality was significantly higher in exposed allo-HCT recipients than in non-exposed allo-HCT recipients (37.0% vs 22.1%, p = 0.0005) (Table 2). CMV-D was also significantly

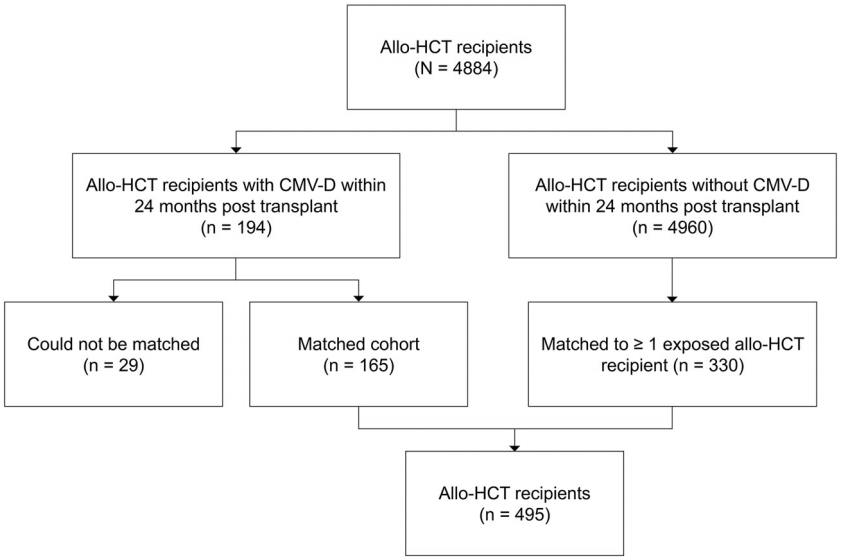


**Fig. 1.** Disposition of allo-HCT recipients.
allo-HCT = allogeneic hematopoietic cell transplantation; CMV-D = cytomegalovirus disease.

associated with an increased risk of in-hospital mortality at all time points after the index date (3 months: relative risk [RR] 2.7, $p < 0.0001$; 6 months: RR 2.1, $p < 0.0001$; 12 months: RR 1.7, $p = 0.0005$) (Table 2).

*Impact of CMV-D on GR and/or GVHD*

In the matched cohort, the proportion of allo-HCT recipients who had GR and/or GVHD over 12 months after the index date was similar between exposed and non-exposed allo-HCT recipients (21.2% vs 19.4%) (Table 2). The Kaplan–Meier estimate of the probability of GR and/or GVHD over 12 months from the index date was not significantly different between exposed and non-exposed allo-HCT recipients (23.1% vs 20.4%, $p = 0.38$) (Fig. 2). Additionally, CMV-D did not appear to have an impact on the risk of GR and/or GVHD over 3, 6, or 12 months after the index date (3 months: RR 1.3; 6 months: RR 1.2; 12 months: RR 1.1; all $p > 0.05$) (Table 2).

*Impact of CMV-D on healthcare resource utilization*

Over the 12 months from the index date, the mean total hospitalization costs were higher in exposed allo-HCT recipients than in non-exposed allo-HCT recipients, but the difference was not statistically significant (€52,747 vs €46,396, $p = 0.18$). Exposed allo-HCT recipients had significantly higher cumulative number of inpatient days ($p < 0.0001$), but there were no statistically significant differences in the mean number of hospital

**Table 2**
Impact of CMV-D on clinical outcomes and resource use after the index date.

| | Exposed allo-HCT recipients (n = 165) | Non-exposed allo-HCT recipients (n = 330) | Relative risk (95% CI) | P-value |
|---|---|---|---|---|
| In-hospital mortality, n (%) | | | | |
| Over 3 months after the index date | 34 (20.6) | 25 (7.6) | 2.7 (1.7–4.4) | <0.0001 |
| Over 6 months after the index date | 53 (32.1) | 51 (15.5) | 2.1 (1.5–2.9) | <0.0001 |
| Over 12 months after the index date | 61 (37.0) | 73 (22.1) | 1.7 (1.3–2.2) | 0.0005 |
| GR and/or GVHD, n (%) | | | | |
| Over 3 months after the index date | 30 (18.2) | 45 (13.6) | 1.3 (0.9–2.0) | 0.18 |
| Over 6 months after the index date | 35 (21.2) | 57 (17.3) | 1.2 (0.8–1.8) | 0.29 |
| Over 12 months after the index date | 35 (21.2) | 64 (19.4) | 1.1 (0.8–1.6) | 0.63 |
| Cumulative length of hospital stay (days), mean (SD) | | | | |
| Over 3 months after the index date | 42.5 (36.8) | 23.3 (35.1) | NA | <0.0001 |
| Over 6 months after the index date | 58.5 (46.3) | 33.4 (47.0) | NA | <0.0001 |
| Over 12 months after the index date | 70.1 (60.9) | 42.7 (58.8) | NA | <0.0001 |
| Cumulative hospitalization costs (€), mean (SD) | | | | |
| Over 3 months after the index date | 32,641 (28,280) | 28,526 (36,049) | NA | <0.0001 |
| Over 6 months after the index date | 44,645 (34,639) | 37,405 (42,115) | NA | <0.0001 |
| Over 12 months after the index date | 52,747 (44,098) | 46,396 (51,561) | NA | 0.18 |
| Hospital readmissions, mean (SD) | | | | |
| Over 3 months after the index date | 2.5 (2.6) | 1.5 (2.6) | NA | 0.0001 |
| Over 6 months after the index date | 3.2 (3.3) | 2.4 (4.1) | NA | 0.02 |
| Over 12 months after the index date | 4.0 (4.3) | 3.4 (5.9) | NA | 0.30 |

allo-HCT = allogeneic hematopoietic cell transplantation; CI = confidence interval; CMV-D = cytomegalovirus disease; GR = graft rejection; GVHD = graft-versus-host disease; NA = not applicable; SD = standard deviation.

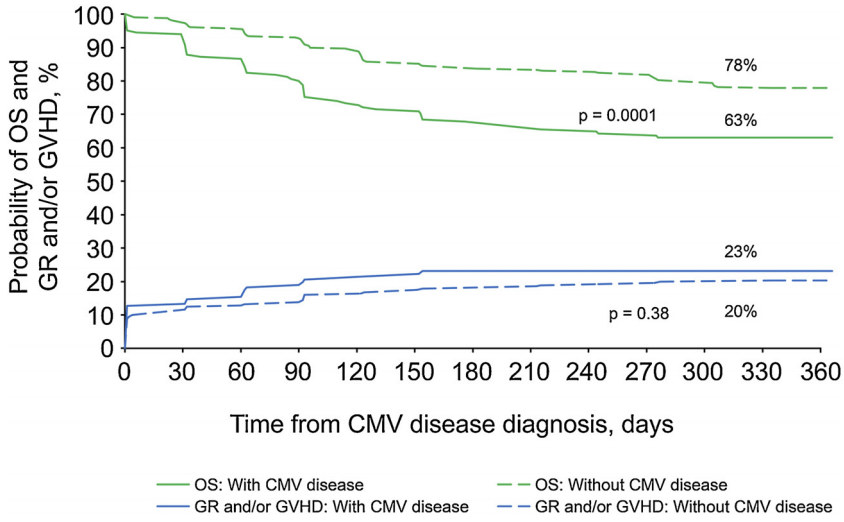


**Fig. 2.** Probability of OS and GR and/or GVHD after CMV-D diagnosis.
CMV-D = cytomegalovirus disease; GR = graft rejection; GVHD = graft-versus-host disease; OS = overall survival.

readmissions between exposed and non-exposed allo-HCT recipients (p = 0.30).

## Discussion

This retrospective analysis of data for 4884 allo-HCT recipients in France between 2008 and 2011 allowed the impact of CMV-D on clinical outcomes and healthcare resource utilization to be investigated. These data demonstrate that exposed allo-HCT recipients have a higher probability of mortality and higher cumulative number of inpatient days than non-exposed allo-HCT recipients over the 12 months after CMV-D diagnosis. CMV-D was not associated with significantly higher healthcare costs or number of hospital readmissions.

In this national hospitalization database study, 16.9% of allo-HCT recipients had a reported primary or secondary diagnosis of CMV infection or CMV-D. Based on the strict pre-defined criteria, the incidence of CMV-D in this study was 4.0%, which may not reflect the true incidence owing to the way that CMV infection and CMV-D are recorded in the PMSI database. Most cases of CMV reactivation were recorded under two ICD-10 codes (B25.8: other CMV-D [46.4%] and B25.9: CMV-D, unspecified [45.2%]). As asymptomatic CMV infections could have been misreported as CMV-D under these ICD-10 codes, allo-HCT recipients with CMV-D recorded under these codes were only assumed to have true CMV-D if it was the primary cause of admission and if they stayed in the hospital for at least 7 days. Therefore, it is likely that some cases of CMV-D were excluded. As the patients included in this study were allo-HCT recipients who received their transplant between 2008 and 2011, the 2017 French national recommendations for the management of CMV infection were not used [26]. Additionally, some exposed allo-HCT recipients may have been excluded due to receiving treatment outside of the hospital because the PMSI database only contains inpatient records. Furthermore, the PMSI database was primarily developed for administrative purposes, which means that some secondary diagnostics may not have been reported if they did not lead to any additional payment to the hospital.

Most published estimates of the incidence of CMV-D are based on specific populations (e.g. For writer - CMV-seropositive patients [9,27,28], pediatric patients [24,29], and those treated using specific treatment strategies [30–32] that are not comparable with this population, which included allo-HCT recipients of all ages, CMV-seronegative donors, and recipients who underwent different treatment strategies.

As the objective of this analysis was not to estimate the incidence of CMV-D, but to describe the impact of CMV-D reactivation on clinical and economic outcomes after allo-HCT, the fact that some cases of CMV-D may not have been identified should not be a major limitation. However, it should be noted that the group of allo-HCT recipients classified as not having CMV-D may have included allo-HCT recipients for whom CMV-D was not recorded. This could mean that differences between exposed and non-exposed allo-HCT recipients were underestimated; however, CMV-D is unlikely to have been present in over 10% of non-exposed allo-HCT recipients, based on previous estimates of CMV-D incidence. This study was limited by the lack of stratification by CMV serostatus of the allo-HCT recipient; therefore, no conclusions could be drawn regarding the clinical and economic impact of the serostatus of the allo-HCT recipient, which is a risk factor for the development of CMV-D [10]. Another limitation was the inability to distinguish between whether each allo-HCT recipient had GR or GVHD as they were both recorded using the T86.00 ICD-10 code.

This study demonstrated that CMV pneumonia and colitis were frequent manifestations of CMV-D, which is consistent with previous studies of the epidemiology of CMV-D in the post-pre-emptive therapy era [33]. Also consistent with previous studies, allo-HCT recipients were more likely to develop CMV-D later than 3 months after allo-HCT, possibly confirming previous observations that the incidence of CMV-D during the first 100 days after allo-HCT has decreased due to pre-emptive treatment strategies [33–35].

Regarding mortality after CMV-D diagnosis, the mortality rate over 12 months in this study was 37.0%, which is similar to the rates of 30–50% in adults [23,36,37] and 15–33% in children [15,17] reported in the literature. However, relatively few studies have compared the risk of death for exposed allo-HCT recipients with non-exposed allo-HCT recipients. A study that has made this comparison demonstrated a clear association between CMV-D and an increased risk of death [23].

An association between CMV-D and GVHD has been previously shown [38], however it is not known whether CMV-D is the specific cause of GVHD. Quantifying the relationship between CMV-D and GVHD in practice is challenging because acute rejection or GVHD may increase the probability of CMV infection or CMV-D due to the need for stronger immunosuppressive treatment. Thus, many studies have demonstrated that developing GVHD is a risk factor

for subsequent CMV infection or CMV-D [18,28,39], but no data directly linking CMV-D with the development of GVHD are available. However, one of the few studies to have examined the association between CMV-D and the development of GVHD concluded that, although GVHD induces CMV replication, patients are at increased risk of acute GVHD during CMV replication [38]. This study examined this association and did not show any significant increase in the risk of GVHD in allo-HCT recipients who had developed CMV-D. It should be noted that because GVHD may increase the risk of CMV-D, and could be a confounding factor when evaluating the consequences of CMV-D, GVHD diagnoses that were recorded before or around the index date as part of the allo-HCT recipient matching criteria were taken into account in this study. However, this may have underestimated the effect of CMV-D on GVHD because GVHD occurring during the same hospital stay as the diagnosis of CMV-D was not considered to be attributable to CMV-D. This limitation is particularly notable because the number of cases with CMV-D and GVHD during the same hospital stay was relatively high.

The key strength of this study is that the data are based on a national patient population and may be more relevant to real-life clinical practice than data from clinical trials or single-center studies. Furthermore, this study not only describes the clinical burden of CMV-D after allo-HCT, but also describes the hospital-related economic burden for allo-HCT recipients which, to the best of our knowledge, has not been studied before. The study was limited by the absence of information on whether an active CMV infection (but not CMV-D) developed. Consequently, it was not possible to analyze the epidemiologic or resource use burden associated with reactivated CMV infection. Furthermore, the study was limited by the absence of data on AVT use, deaths occurring outside the hospital, and the exact date of diagnosis and procedures used.

## Conclusions

Based on a national hospitalization database in France, this study demonstrated that CMV-D is associated with increases in mortality and healthcare resource utilization in allo-HCT recipients in an inpatient setting in France. These analyses reinforce the clinical significance of CMV-D in the modern era and encourage the development of new strategies to prevent and manage CMV-D in allo-HCT recipients.

## Disclosure of conflicts of interest

Z.H. was an employee of Astellas Pharma Europe B.V. during the conduct of this study. M.E. is an employee of Astellas Pharma Global Development, Inc. S.F., S.A., and M.T. are employees of Creativ-Ceutical, who were contracted by Astellas Pharma Inc. to provide support for this study. I.O. was employed by Astellas Pharma Europe, Ltd. during the conduct of this study and is now employed by Manchester Metropolitan University. I.Y-A. received honorarium from Astellas Pharma Inc., Merck & Co. Inc., and Biotest Pharmaceuticals Corporation.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.retram.2018.08.004.

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