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ARTICLE

Scoring system for clinically significant CMV infection in seropositive recipients following allogenic hematopoietic cell transplant: an SFGM-TC study

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Abstract

In order to identify cytomegalovirus (CMV)-seropositive patients who are at risk of developing CMV infection following first allogeneic hematopoietic cell transplantation (allo-HCT), we built up a scoring system based on patient/donor characteristics and transplantation modalities. To this end, 3690 consecutive patients were chronologically divided into a derivation cohort (2010–2012, $n = 2180$) and a validation cohort (2013–2014, $n = 1490$). Haploidentical donors were excluded. The incidence of first clinically significant CMV infection (CMV disease or CMV viremia leading to preemptive treatment) at 1, 3, and 6 months in the derivation cohort was 13.8%, 38.5%, and 39.6%, respectively. CMV-seropositive donor, unrelated donor (HLA matched 10/10 or HLA mismatched 9/10), myeloablative conditioning, total body irradiation, antithymocyte globulin, and mycophenolate mofetil significantly and independently affected the incidence of 3-month infection. These six factors were selected to build up the prognostic model. Four risk groups were defined: low, intermediate-low, intermediate-high, and high-risk categories, with a 3-month predicted incidence of first clinically significant CMV infection in the derivation cohort of 22.2%, 31.1%, 45.4%, and 56.9%, respectively. This score represents a framework for the evaluation of patients who are at risk of developing clinically significant CMV infection following allo-HCT. Prospective studies using this score may be of benefit in assessing the value of anti-CMV prophylaxis in well-defined patient cohorts.

Introduction

Cytomegalovirus (CMV) infection is a major viral complication following allogeneic hematopoietic cell transplantation (allo-HCT) [1]. It is mostly observed in patients with a positive CMV serostatus and those with negative CMV serostatus receiving transplant from a positive CMV-serostatus donor [2]. Mainly occurring in the first 3 months, CMV infection is observed in over 60% of CMV-seropositive recipients, depending on the initial characteristics and posttransplant events [3]. CMV infection is associated with increased morbidity and mortality [4–7], especially in the case of CMV disease [8–11].

Preemptive therapy based on active monitoring of CMV in the blood long remained a standard of care [12–14]. The preemptive strategy improved the CMV-related outcome, mainly by decreasing the incidence of end-organ disease [15, 16], but did not fully prevent the emergence of breakthrough CMV disease. Until recently, no prophylactic strategy had been proven to be cost-effective, mainly because of the side effects of available drugs [17–22]. In a randomized phase 3 trial, prophylaxis with letermovir in CMV-seropositive adult allo-HCT patients was associated with a significantly lower risk of clinically significant CMV infection and improved survival, as compared to placebo, suggesting that universal prophylactic treatment could prove beneficial [23–26]. Many factors are known to be

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associated with a higher risk of developing CMV infection in CMV-seropositive patients, namely: CMV-seronegative donor, unrelated or HLA-mismatched donor, the use of immunosuppressive agents such as antithymocyte globulin (ATG) or calcineurin inhibitors, intensity and schedule of conditioning regimen, and development of GVHD [27, 28]. However, when considered separately, the predictive value of these factors is poor.

In order to estimate on an individual basis at the time of transplant the risk of developing clinically significant CMV infection, i.e., CMV disease or CMV viremia leading to preemptive treatment, we designed a scoring system considering and weighting the relevant baseline risk factors. This new score, based on large cohorts of CMV-seropositive patients, is designed to help evaluate the risk of CMV posttransplant infection in the era of primary CMV prophylaxis.

Material and methods

Study design and patients

Two distinct cohorts of patients were built up for the study, a derivation cohort and a validation cohort, both derived from the database of the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC), with matching inclusion and exclusion criteria. All consecutive CMV-seropositive adult patients undergoing a first allo-HCT between January 2010 and December 2014 were retrospectively included in the study. They were divided into two consecutive cohorts according to the date of transplant: a derivation cohort from January 2010 to December 2012 and a validation cohort from January 2013 to December 2014. Haploidentical allo-HCT was excluded as few patients had received haploidentical transplant in France before 2014 mainly for nonmalignant disease.

The baseline parameters assessed included those of the recipient (age, sex, diagnosis, disease status), those of the donor (age, sex, CMV serostatus, type of donor), and transplantation modalities (stem cell source, intensity of the conditioning regimen, use of total body irradiation [TBI], ATG, GVHD prophylaxis). HLA-matched (10/10) and HLA-mismatched (9/10) donors were defined using high-resolution four-digit 10/10. Given that subhazard ratios (SHRs) were very similar in univariate analyses (Table 2 and Fig. S1, Supplementary Material), all unrelated donors were merged into one category named “unrelated” in multivariate analysis. Cord blood transplants were regarded as CMV seronegative [29]. Conditioning intensity was defined according to standard criteria [30]. Thus, TBI–cyclophosphamide, busulfan–cyclophosphamide, thiotepa–busulfan–fludarabine, fludarabine–busulfan ≥ 8 mg/kg days were considered myeloablative conditioning (MAC) regimens, whereas other conditioning regimens were classified as reduced intensity conditioning regimens. Only the first clinically significant CMV infection was considered [14, 31, 32].

This study was conducted according to the Declaration of Helsinki and was approved by the SFGM-TC scientific board. All patients gave consent for data recovery.

CMV monitoring and treatment

All patients were placed on a surveillance and treatment protocol based on the guidelines issued by SFGM-TC and periodically updated [33]. No CMV prophylactic treatment was given during the study period. According to risk factors and local policy, weekly or biweekly monitoring for CMV was performed from day 0 to at least day 100, using a real-time polymerase chain reaction. The threshold for the initiation of anti-CMV treatment followed local criteria based on the national SFGM-TC guidelines cited above. Treatment was mainly based on ganciclovir or foscarnet at recommended doses, according to the patient profile.

Statistical analysis

The median time from transplantation to last follow-up was estimated using the reverse Kaplan–Meier method [34]. Predictions of the first episode of clinically significant CMV infection were based on Fine–Gray models for survival, considering death as a competing event [35]. The cumulative incidence of the first episode of clinically significant CMV infection was estimated using the approach of Kalbfleisch and Prentice [36].

Firstly, candidate predictors were analyzed using bivariate Fine–Gray regression models; SHRs were reported as effect size with their 95% confidence intervals (CIs). For each continuous predictor (recipient and donor age), the log-linearity assumption was assessed using the restricted cubic spline functions [37]. Since we found no evidence of non-log-linear relationship, continuous predictors were introduced as linear terms in analyses. For each candidate predictor, we assessed proportional hazards assumption by plotting the Schoenfeld residuals against the rank of event time [38]. To develop the prognostic model, all candidate predictors were considered for entrance into the multivariable Fine–Gray regression model irrespective of the bivariate analyses. The full model was then simplified with a backward selection procedure by using a removal criterion of 0.05. The proportional hazards assumption for the prognostic index of the selected model was also assessed by plotting the Schoenfeld residuals against the rank of event time.

To avoid case deletion in univariate and multivariate analyses, missing data for candidate predictors (ranged from

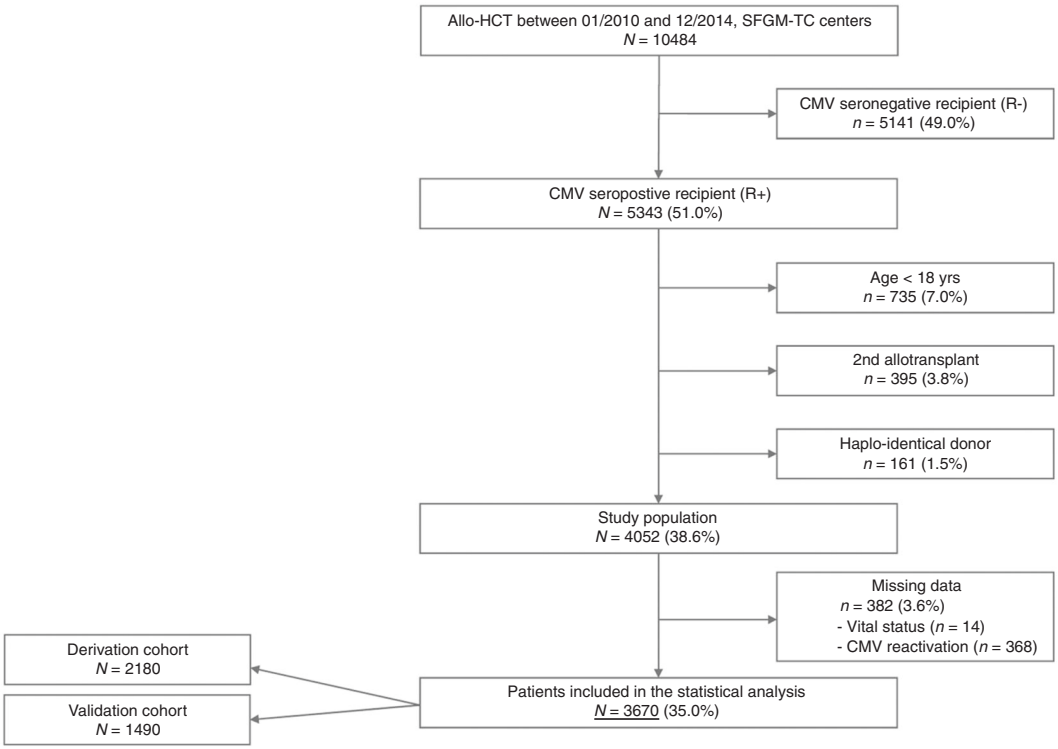

Fig. 1 Flowchart of the patient selection process for the derivation and validation cohorts. Allo-CHT allogeneic hematopoietic cell transplantation, CMV cytomegalovirus, SFGM-TC Société Francophone de Greffe de Moelle et de Thérapie Cellulaire.

0 to 4.7%) were imputed by simple imputation using the regression-switching approach [39], with the predictive mean-matching method for continuous variables and logistic regression (binary, ordinal, or multinomial) models for categorical variables.

The performance of the selected model was examined by assessing discrimination and calibration. Discrimination was assessed using the c-statistic adapted to the presence of competing risks [40], which indicates to what extent the model distinguishes between patients who will reactivate the CMV from those who will not. To address the overestimation issues in developing prognostic model [37], we performed an internal validation by using bootstrap resampling method (200 resamples) to correct the c-statistic for overoptimism and to calculate the shrinkage factor. Calibration (i.e., the predicted-to-observed incidence function agreement) was evaluated by comparing the predicted mean cumulative incidences (predicted from selected model) to the Kalbfleisch and Prentice cumulative incidences (observed) in four risk groups determined as the 16th, 50th, and 84th percentiles of the prognostic index's distribution [41].

For clinical purpose, a point-scoring system was determined using regression coefficients of the selected Fine–Gray model; the number of points was determined by multiplying the regression coefficient by 10 and rounding to the nearest integer [42].

For the external validation, calibration and discrimination performances were assessed for continuous and discreet point score models in the validation dataset. The predicted survival probabilities calculated within the validation dataset were issued from the coefficient estimates (after applying the shrinkage factor) and the baseline survival estimate from the derivation dataset.

Statistical testing was performed at the two-tailed α level of 0.05. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the patients

Between January 2010 and December 2014, 10,484 patients received an allo-HCT in any of the SFGM-TC centers, 5343 (51.0%) of them being seropositive for CMV. A total of 1673 patients (16.0% of the entire population) were excluded from the analysis because of age < 18 years ($n = 735$; 7.0%), second allo-HCT ($n = 395$; 3.8%), haploidentical allo-HCT ($n = 161$; 1.5%), and missing data on survival status, CMV infection status or time of CMV infection ($n = 382$; 3.6%) (Fig. 1).

The analysis included the data from 3670 patients, chronologically divided according to the date of transplant

Table 1 Patient and donor characteristics in the derivation and validation cohorts.

Characteristics	Derivation cohort, $n = 2180$	Validation cohort, $n = 1490$
Recipient age (years), mean (SD)	49.9 (13.2)	51.2 (13.3)
Missing data	0	0
Sex, *n* (%)		
Female	996 (45.7)	622 (41.8)
Male	1183 (54.3)	822 (55.2)
Missing data	1	2
Diagnosis, *n* (%)		
Acute myeloid leukemia	935 (43.0)	664 (44.5)
Acute lymphoblastic leukemia	196 (9.0)	144 (9.7)
MDS and MPN	415 (19.1)	329 (22.1)
Bone marrow failure	63 (2.9)	37 (2.5)
Hodgkin and non-Hodgkin lymphoma	417 (19.1)	241 (16.2)
Plasma cell disorders	131 (6.0)	65 (4.3)
Others	20 (0.9)	10 (0.7)
Missing data	3	0
Disease status at transplant, *n* (%)		
Complete remission	1405 (67.6)	925 (66.5)
Partial remission/Stable disease	374 (18.0)	238 (17.1)
Progressive disease	298 (14.4)	229 (16.4)
Missing data	103	98
Donor age (year), mean (SD)	37.2 (18.1)	37.5 (16.6)
Missing data	68	28
Donor sex, *n* (%)		
Female	873 (40.3)	622 (42.2)
Male	1292 (59.7)	853 (57.8)
Missing data	15	15
Donor CMV serostatus, *n* (%)		
Positive	1033 (47.5)	789 (53.2)
Negative	1141 (52.5)	694 (46.8)
Missing data	6	7
Donor type, *n* (%)		
Identical sibling	942 (43.3)	613 (41.1)
Unrelated	1235 (56.7)	877 (58.9)
Matched 10/10	599 (27.5)	489 (32.8)
Mismatched 9/10	398 (18.3)	264 (17.7)
No HLA-match precision	238 (10.9)	124 (8.3)
Missing data	3	0
Stem cell source, *n* (%)		
Bone marrow	434 (19.9)	229 (15.4)
Peripheral blood	1532 (70.4)	1157 (77.8)
Cord blood	212 (9.7)	102 (6.8)
Missing data	2	2
Conditioning regimen, *n* (%)		
Reduced intensity	1400 (64.3)	957 (64.4)
Myeloablative	777 (35.7)	529 (35.6)
Missing data	3	4
Total body irradiation, *n* (%)	700 (32.2)	288 (19.4)
Missing data	6	4
Antithymocyte globulin, *n* (%)	1306 (60.0)	1096 (73.7)
Missing data	3	3
GVHD prophylaxis		
CNI, *n* (%)	2119 (97.7)	1418 (96.1)
MTX, *n* (%)	881 (40.6)	566 (38.4)
MMF, *n* (%)	835 (38.5)	561 (38.0)
Others, *n* (%)	35 (1.6)	44 (3.0)
Missing data	12	15

CNI calcineurin inhibitor, *GVHD* graft-versus-host disease, *MTX* methotrexate, *MMF* mycophenolate mofetil, *MDS* myelodysplastic syndrome, *MPN* myeloproliferative neoplasm, *SD* standard deviation.

into a derivation cohort (2010–2012, $n = 2180$) and a validation cohort (2013–2014, $n = 1490$). The baseline characteristics of the two cohorts are presented in Table 1. The mean age (standard derivation) was respectively 49.9 (13.2) and 51.2 (13.3) years, with 54.3 and 55.2% males. The median time from transplantation to last follow-up was 42.4 months (interquartile range [IQR], 26.6–53.3) in the derivation cohort, 18.8 months (11.8–25.7) in the validation cohort. Acute myeloid leukemia was the most frequent diagnosis (43.0 and 44.5%) and most patients were in complete remission (67.6 and 66.5%) in the derivation and validation cohorts, respectively. The donor was an identical sibling in 43.3 and 41.1% and unrelated in 56.7 and 58.9% of patients (including matched 10/10 in 27.5% and 32.8%, mismatched 9/10 in 18.3 and 17.7% and without precision in 10.9 and 8.3%) in the derivation and validation cohorts, respectively. Half of the donors were seronegative for CMV (52.5 and 46.8%). Source of stem cells was peripheral blood in 73.1% (70.4 and 77.8%), bone marrow in 18.1% (19.9 and 15.4%), and cord blood in 8.3% of transplantations (9.7 and 6.8%). A MAC was used in 35.7% of patients (35.7 and 35.6%), including TBI in 27.0% (32.2 and 19.4%) of the cases and in vivo T-cell depletion with ATG in 64.1% (60.0 and 73.7%). GVHD prophylaxis was mainly based on a combination of calcineurin inhibitor and methotrexate (40.6 and 38.4%) or mycophenolate mofetil (MMF) (38.5 and 38.0%). The other characteristics of each cohort are given in Table 1.

CMV infection

In the derivation cohort, 864 episodes of clinically significant CMV infection requiring first-line treatment occurred, within 1–180 days (median 36 days; IQR 26–49), leading to an incidence of 13.8% (95% CI, 12.4–15.2) at 1 month, 38.5% (95% CI, 36.5–40.5) at 3 months, and 39.7% (95% CI, 37.6–41.7) at 6 months. In the validation cohort, 625 first clinically significant CMV infection events occurred during the follow-up, within 1 day to 13.5 months (median 36 days; IQR 27–49), leading to an incidence of 15.5% (95% CI, 13.7–17.3) at 1 month, 41.1% (95% CI, 38.6–43.6) at 3 months, and 42.8% (95% CI, 40.2–45.3) at 6 months.

Prognostic model

Univariate analyses of potential predictors of first CMV infection at transplant are presented in Table 2. Multivariable model screening (using backward-stepwise selection procedure including all potential predictors) selected six predictors of first clinically significant CMV infection: CMV serostatus of the donor, type of donor, intensity of the conditioning regimen, TBI, ATG, and MMF (Table 3). There was no deviation from proportional hazard assumptions for the prognostic index of selected prognostic continuous model. One-, three-, and six-month risk predictions computed by the prognostic continuous model (after shrinking the regression coefficients to improve the prediction in future patients) are available in Appendix. After correcting for overoptimism, the c-index of the prognostic continuous model was 0.610 (95% CI, 0.591–0.628). As shown in Table 4 and Fig. 2, the prediction of first clinically significant CMV infection incidence rate at 1, 3, and 6 months were close to the observed incidences, which indicated a good calibration of the prognostic continuous model. In the validation cohort, the c-index was 0.583 (95% CI, 0.560–0.606); after the shrinkage of the coefficients, the calibration remained satisfactory despite a slight underestimation observed (Table 4).

A point-scoring system was built from the prognostic continuous model (Table 3), the total number of points ranging from 0 to 20. The bounds of low, intermediate-low, intermediate-high, and high-risk categories were 0–4, 5–10, 11–14, and 15–20 respectively. At 3 months, the predicted incidence of first clinically significant CMV infection for the four categories in the derivation cohort was 22.2, 31.1, 45.4, and 56.9%. The predicted 1-, 3-, and 6-month incidence by classes of risk are reported in Table 5.

Table 2 Univariate analysis of potential predictors of first clinically significant CMV infection in the derivation cohort after handling missing data.

Potential predictors	SHR (95% CI)	*p* value
Recipient age, per 10-year increase	1.01 (0.96–1.06)	0.68
Sex (male vs female)	0.87 (0.76–0.99)	**0.042**
Diagnosis		0.40
Acute myeloid leukemia	1.00 (ref.)	–
Acute lymphoblastic leukemia	1.09 (0.86–1.38)	0.49
MDS and MPN	0.99 (0.83–1.19)	0.93
Bone marrow failure	1.44 (1.01–2.03)	0.043
Hodgkin and non-Hodgkin lymphoma	1.07 (0.89–1.28)	0.50
Plasma cell disorders	1.16 (0.88–1.54)	0.29
Others	0.74 (0.33–1.66)	0.47
Disease status at transplant		0.15
Complete remission	1.00 (ref.)	–
Partial remission/stable disease	0.85 (0.71–1.02)	0.080
Progressive disease	1.05 (0.87–1.27)	0.63
Donor age, per 10-year increase	0.89 (0.86–0.92)	**<0.001**
Donor sex (male vs female)	1.06 (0.93–1.22)	0.37
CMV-seronegative donor	1.63 (1.42–1.86)	**<0.001**
Donor type	2.00 (1.73–2.31)	**<0.001**
Identical sibling	1.00 (ref.)	
Unrelated[a]	2.00 (1.73–2.31)	**<0.001**
Unrelated matched 10/10	1.96 (1.66–2.31)	**<0.001**
Unrelated mismatched 9/10	2.12 (1.77–2.55)	**<0.001**
No HLA-match precision	1.91 (1.53–2.38)	**<0.001**
Stem cell source		<0.001
Bone marrow	1.00 (ref.)	–
Peripheral blood	1.09 (0.92–1.29)	0.32
Cord blood	1.55 (1.22–1.97)	**<0.001**
Myeloablative conditioning regimen	0.99 (0.87–1.14)	0.93
Total body irradiation	1.22 (1.06–1.40)	**0.005**
Antithymocyte globulin	1.30 (1.13–1.49)	**<0.001**
GVHD prophylaxis		
CNI	1.02 (0.65–1.60)	0.94
MTX	0.82 (0.72–0.94)	**0.005**
MMF	1.49 (1.30–1.70)	**<0.001**
Others	0.80 (0.46–1.39)	0.44

CI confidence interval, *CNI* calcineurin inhibitor, *GVHD* graft-versus-host disease, *MDS* myelodysplastic syndrome, *MMF* mycophenolate mofetil, *MPN* myeloproliferative neoplasm, *MTX* methotrexate, *SHR* subhazard ratio.

[a]Given that the SHRs were very similar, all unrelated donors were merged into one category named "unrelated" in the multivariate analysis.

Bold values are the selected predictors with a p-value < 0.05.

Discussion

Implementation of strategies to prevent CMV infection and disease after allo-HCT entails substantial commitment of resources, especially laboratory tests and drugs. Tailoring the strategy to the recipient risk profile appears to be justified. For this purpose, we studied in a large population of

Table 3 Selected multivariable prognostic model of first clinically significant CMV infection and point scoring attributed to each variable.

Predictors	SHR (95% CI)[a]	*p* value[a]	Points[b]
Donor CMV serostatus			
Positive	1.00 (ref.)	–	0
Negative	1.31 (1.13–1.52)	<0.001	3
Donor type			
Identical sibling	1.00 (ref.)	–	0
Unrelated	1.57 (1.34–1.85)	<0.001	5
Conditioning regimen			
Reduced intensity	1.00 (ref.)	–	0
Myeloablative	1.22 (1.05–1.43)	0.011	2
Total body irradiation			
No	1.00 (ref.)	–	0
Yes	1.35 (1.14–1.59)	<0.001	3
Antithymocyte globulin			
No	1.00 (ref.)	–	0
Yes	1.52 (1.27–1.81)	<0.001	4
MMF			
No	1.00 (ref.)	–	0
Yes	1.34 (1.15–1.56)	<0.001	3

CI confidence interval, *MMF* mycophenolate mofetil, *SHR* subhazard ratio.

[a]Estimated using a backward-stepwise Fine and Gray model using a removal criteria $p > 0.05$ (after handling missing values by simple imputation).

[b]Point-scoring system determined using regression coefficients.

patients the correlation between baseline risk factors and the incidence of CMV infection.

Clinically significant CMV infection in our population of CMV-seropositive recipients of a first allo-HCT occurred mainly within the first 3 months post transplant, and the global incidence at 3 months in the total population was 39.6%, consistent with published data [43, 44]. Using multivariate analysis, we found six independent predictors of new-onset clinically significant CMV infection: CMV-seronegative donor, unrelated donor, MAC regimen, TBI, ATG, and MMF. These risk factors were previously described to be associated with CMV infection, but their respective prognostic importance had not yet been fully determined [45–50]. In transplant preparation, use of ATG (SHR 1.52; 1.27–1.81), TBI (SHR 1.35; 1.14–1.59), and MAC regimen (SHR 1.22; 1.05–1.43) was associated with a significant increase of the risk of CMV infection [51–56]. Regarding the GVHD prophylaxis, the use of MMF was associated in our study, as previously described [57], with a significant increase of the risk of CMV infection (SHR 1.34; 1.15–1.56). Contrary to many published data [58–60], cord blood transplant in our study was associated to CMV infection only in univariate, but not in multivariate analysis, most likely because of confounding factors correlated with this stem cell source (CMV-seronegative status of cord

Table 4 Calibration and discrimination of the selected continuous prognostic model.

	Derivation cohort			Validation cohort[a]		
	Event/*n*	Observed	Predicted	Event/*n*	Observed	Predicted
	Incidence of first CMV infection at 1 month					
Risk group [PI]						
Very low [0.00–0.42]	28/382	0.073	0.071	26/231	0.113	0.070
Low [0.42–0.99]	66/726	0.091	0.104	60/480	0.125	0.098
High [0.99–1.44]	115/704	0.163	0.164	94/523	0.180	0.145
Very high [1.44–1.94]	91/368	0.247	0.220	47/224	0.210	0.189
	Incidence of first CMV infection at 3 months					
Risk group [PI]						
Very low [0.00–0.42]	83/382	0.217	0.222	61/231	0.265	0.217
Low [0.42–0.99]	235/726	0.324	0.311	171/480	0.359	0.295
High [0.99–1.44]	315/704	0.448	0.454	248/523	0.475	0.412
Very high [1.44–1.94]	206/368	0.561	0.569	122/224	0.545	0.507
	Incidence of first CMV infection at 6 months					
Risk group [PI]						
Very low [0.00–0.42]	88/382	0.231	0.230	64/231	0.279	0.225
Low [0.42–0.99]	236/726	0.325	0.321	181/480	0.383	0.305
High [0.99–1.44]	326/704	0.463	0.467	256/532	0.492	0.425
Very high [1.44–1.94]	214/368	0.583	0.583	124/224	0.555	0.521
C-statistics (95% CI)	0.610 (0.591–0.628)[b]	0.583 (0.560–0.606)				

The risk groups were defined by the 16th, 50th, and 84th centiles of the prognostic index (PI) of selected prognostic model; minimum and maximum values of PI by risk group are shown. *n* and event denote the number of patients and first clinically significant CMV infection events in each risk group. Observed and predicted probabilities of cumulative incidence of first clinically significant CMV infection at 1, 3, and 6 months are shown; values labeled "observed" were calculated using Kalbfleisch and Prentice estimates and values labeled "predicted" were calculated as the predicted probabilities by the Fine and Gray regression model within each risk group.

[a]Calculated in 1458 patients due to missing values on variables included in the prognostic index (PI).

[b]C-statistics corrected for overoptimism.

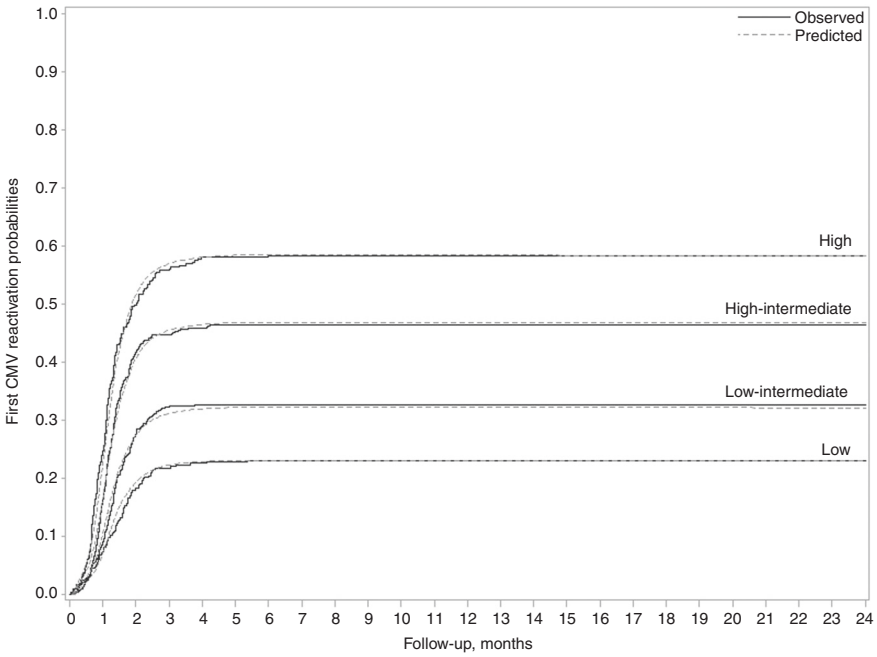

Fig. 2 Observed and predicted cumulative incidence curves for the first clinically significant CMV infection in the derivation cohort. CMV cytomegalovirus.

Table 5 Estimated cumulative incidence of the first clinically significant CMV infection in the derivation cohort according to point-scoring system.

		Incidence of first CMV infection, %		
Points	*n*	1 month	3 months	6 months
0	28	5.2	16.7	17.3
2	97	6.2	19.5	20.2
3	62	6.7	21.0	21.8
4	195	7.3	22.6	23.4
5	145	7.9	24.3	25.2
6	115	8.6	26.2	27.1
7	175	9.3	28.1	29.1
8	77	10.1	30.2	31.2
9	153	10.9	32.4	33.5
10	101	11.8	34.7	35.8
11	105	12.8	37.1	38.3
12	269	13.8	39.6	40.8
13	58	14.9	42.2	43.5
14	232	16.1	44.9	46.3
15	213	17.4	47.8	49.1
16	34	18.8	50.7	52.1
17	90	20.3	53.7	55.1
18	25	21.9	56.7	58.2
20	6	25.3	62.9	64.4
Total	2180			

n indicates the distribution of total score in the derivation cohort. Probabilities of cumulative incidence of first clinically significant CMV infection estimated from point-scoring system were calculated using Fine and Gray regression model with total score as a single covariable.

blood graft, unrelated transplant and frequent use of ATG and of MMF). To allow for the development of a risk score based on pretransplant characteristics of patient/donor and transplantation modalities, GVHD was deliberately excluded from the analysis.

The present study was based on a very large population of patients undergoing a first allo-HCT, with numbers of 2180 in the derivation cohort and 1490 in the validation cohort, which strengthen the validity of our results. George et al. previously described a three-class risk score for early CMV infection after allogeneic HCT. However, their study was based on 335 patients only, and more than half of them were CMV-seronegative recipients, whose risk and pathogenesis of CMV infection are distinct [50]. Our point-scoring system was calculated from the derivation cohort and confirmed in a validation cohort of CMV-seropositive patients with similar characteristics. It allowed the classification of patients into four risk groups, namely low, intermediate low, intermediate high, and high risk, with scores 0–4, 5–10, 11–14, and 15–20, respectively. These four classes were associated with clearly distinct predicted rates of infection at every point of time. In particular, the 3-month infection predicted risk was 22.2%, 31.1%, 45.4%, and 56.9%, respectively.

Our point-scoring system is very simple to implement in routine practice and will help clinicians to more accurately predict the probability of CMV infection in a CMV-seropositive patient who is not on anti-CMV prophylaxis. However, recent years have seen the more widespread use of letermovir prophylaxis following randomized trial evidence of clinical benefit. In this context, it should be noted

that although the prevention of clinically significant CMV infection by letermovir was consistent in both high-risk and low-risk patients, the lower mortality seen in letermovir recipients was more pronounced in high-risk patients. This latter group was defined by the presence of one or more of the following criteria: HLA-mismatched related or unrelated donors, haploidentical donors, cord blood, ex vivo T-cell-depleted grafts, and GVHD requiring systemic immunosuppression. This high-risk cohort made up 31% of trial participants [24]. Many of these patients would have been classified as either high or very high risk by our score. Given the lesser benefit seen with the use of letermovir in the 69% of patients classified as low risk in the trial, and the greater discrimination of very low-risk patients allowed by the four subcategories in our study, this scoring system could potentially allow for the identification of a very low-risk group in whom there is no significant benefit to letermovir prophylaxis. However, this remains to be shown and, at present, our score offers a potential structure to allow this hypothesis to be formally tested in trials.

The avoidance of unnecessary prophylactic drugs and any associated drug interactions is clearly preferable in stem cell transplant recipients and letermovir is a substrate of OATP1B1/3 transporters and a moderate inhibitor of CYP3A. Possible future dynamic prophylactic strategies meriting investigation would include, for example, the prescribing of letermovir when patients develop GVHD requiring systemic corticosteroids, a complication which is known to greatly increase the risk of CMV infection [61, 62]. Obviously, these more nuanced approaches would need to be evaluated in prospective studies.

One of the potential limitations to the implementation of our score is the exclusion of haploidentical transplants. The inclusion of these patients was not possible because of the limited numbers and the heterogeneity of GVHD prophylaxis in those patients. Indeed, some patients had received ex vivo T-cell depletion plus ATG, while others received posttransplant cyclophosphamide with or without ATG. In addition, many of these patients received haploidentical transplants for nonmalignant diseases. Given the increasing use of this type of transplant, validation of our scoring system in this context would be desirable. Another limitation of our study is that all unrelated donors are four-digit HLA-matched (10/10) or mismatched (9/10). Therefore, a potential effect of another degree of HLA-matching could not be investigated. However, given that the SHR was as high as 2, such an effect would probably be insignificant.

In conclusion, this new score may help in evaluating the risk of clinically significant CMV infection in CMV-seropositive recipient who are being managed with a pre-emptive anti-CMV strategy. Although there is more use of letermovir, this remains a widely used strategy. In the coming years, the score could be used in prospective clinical trials to allow for the further refining of patient populations most likely to benefit from prophylactic anti-CMV treatment.

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Author contributions DB, ED, AD, and IY-A designed the study, reviewed the data, analyzed results, and made the figures. All authors wrote and approved the manuscript.

Compliance with ethical standards

Conflict of interest IY-A received honorarium from MSD and Biotest, both are selling anti-CMV drugs. The other authors have no conflicts of interest to declare.

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