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Seasonal Human Coronavirus Respiratory Tract Infection in Recipients of Allogeneic Hematopoietic Stem Cell Transplantation

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Background. Little is known about characteristics of seasonal human coronaviruses (HCoVs) (NL63, 229E, OC43, and HKU1) after allogeneic stem cell transplantation (allo-HSCT).

Methods. This was a collaborative Spanish and European bone marrow transplantation retrospective multicenter study, which included allo-HSCT recipients (adults and children) with upper respiratory tract disease (URTD) and/or lower respiratory tract disease (LRTD) caused by seasonal HCoV diagnosed through multiplex polymerase chain reaction assays from January 2012 to January 2019.

Results. We included 402 allo-HSCT recipients who developed 449 HCoV URTD/LRTD episodes. Median age of recipients was 46 years (range, 0.3–73.8 years). HCoV episodes were diagnosed at a median of 222 days after transplantation. The most common HCoV subtype was OC43 (n = 170 [38%]). LRTD involvement occurred in 121 episodes (27%). HCoV infection frequently required hospitalization (18%), oxygen administration (13%), and intensive care unit (ICU) admission (3%). Three-month overall mortality after HCoV detection was 7% in the whole cohort and 16% in those with LRTD. We identified 3 conditions associated with higher mortality in recipients with LRTD: absolute lymphocyte count $<0.1 \times 10^9$/mL, corticosteroid use, and ICU admission (hazard ratios: 10.8, 4.68, and 8.22, respectively; $P < .01$).

Conclusions. Seasonal HCoV after allo-HSCT may involve LRTD in many instances, leading to a significant morbidity.

Keywords. seasonal human coronavirus; HCoV-NL63; HCoV-229E; HCoV-OC43; HCoV-HKU1; community-acquired respiratory virus; allogeneic hematopoietic stem cell transplantation; immunocompromised; upper and lower respiratory tract disease; immunodeficiency score index; multiplex PCR assay.

The development of molecular technologies and the widespread use of multiplex polymerase chain reaction (PCR) assays for community-acquired respiratory virus (CARV) screening allows epidemiologic and clinical characterization of seasonal human coronavirus (HCoV) infections in immunocompromised patients [1–3]. Coronaviruses are a group of enveloped viruses with nonsegmented, single-stranded, and positive-sense RNA genomes. Of the 4 genera of coronaviruses, *Gammacoronavirus* and *Deltacoronavirus* exclusively infect animals, whereas most of the *Alphacoronavirus* and some of the *Betacoronavirus* genera are well recognized to infect humans [4]. Among the 7 known HCoV subtypes that affect humans, 229E and NL63 belong to *Alphacoronavirus*, whereas *Betacoronavirus* includes OC43 and HKU1 belonging to lineage

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A, severe acute respiratory syndrome coronavirus (SARS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to lineage B, and Middle East respiratory syndrome coronavirus (MERS-CoV) to lineage C [5]. Prior and recent outbreaks of zoonotic HCoV infections such as SARS-CoV [6–8], MERS-CoV [9], and recently SARS-CoV-2 [10, 11], support the idea that coronavirus could be one of the most rapidly evolving viruses owing to its high genomic nucleotide substitution rates and recombination [12]. However, seasonal HCoVs (NL63, 229E, OC43, and HKU1) have circulated globally in the human population for decades and although they contribute to approximately one-third of common colds in humans, their severity seems to be not as devastating as the zoonotic coronavirus outbreaks, with no fatalities in pediatric patients [13] and relatively low mortality rate (4%) in elderly patients with chronic obstructive pulmonary disease [14]. Nevertheless, knowledge of the consequence of seasonal HCoV respiratory infection in highly immunocompromised patients, such as recipients of allogeneic stem cell transplantation (allo-HSCT), remains poorly characterized to date.

CARV epidemiology in allo-HSCT recipients parallels the epidemiology in the general population [15], although these respiratory infections are particularly threatening after allo-HSCT [16–18]. Early studies showed that HCoVs were detected in lung tissues in transplant recipients developing severe pneumonia [19–22]. Compared to other CARVs, prior reports with a small number of cases suggest that HCoV upper respiratory tract disease (URTD) and/or lower respiratory tract disease (LRTD) were quite frequent after allo-HSCT, representing 11%–14% of all CARVs [1–3]. In contrast to previous observations, recent smaller studies have shown that HCoVs could involve the lower respiratory tract in many instances in allo-HSCT recipients (14%–33%) [1, 3]. Overall mortality of such cases ranged from 11% to 54% at 3 months after HCoV, detection that was similar to that seen in respiratory syncytial virus, influenza virus, and parainfluenza virus LRTD in allo-HSCT recipients [1, 3, 23].

In this large, retrospective, international multicenter cohort, we aimed to characterize epidemiological and clinical features, risk factors, and outcome of seasonal HCoV infections in a severe immunocompromised population: allo-HSCT recipients.

PATIENTS AND METHODS

Study Population

This is a retrospective collaborative multicenter cohort study between the Infectious Diseases Working Party of the European Society for Blood and Marrow Transplantation (EBMT) and the Infectious Complications Subcommittee of the Spanish Hematopoietic Stem Cell Transplantation and Cell Therapy Group, focused on allo-HSCT recipients with URTD/LRTD symptoms caused by seasonal HCoV types (NL63, 229E, OC43, or HKU1), which were detected by multiplex PCR panels. The EBMT is a scientific organization that collects data from associated centers that perform HSCT through a web-based registry called ProMISe in accordance with standards at every center for patient confidentiality and good clinical practice.

Inclusion Criteria and Data Preparation

The EBMT participating centers were requested to include all consecutive allo-HSCT recipients (children and adults) with laboratory-documented seasonal HCoV respiratory infection during the period 1 January 2012 to 30 January 2019. All consecutive HCoV respiratory infection episodes per recipient that occurred from the day of conditioning regimen to the last follow-up during the aforementioned period were included. The inclusion of HCoV cases that were detected during conditioning but before stem cell infusion is justified by the potential negative impact of pretransplant CARV detection [24]. The exclusion criterion was baseline disease relapse or progression before HCoV detection.

During the study period, all allo-HSCT procedures were registered in ProMISe by completing the essential medical data form. This form is mandatory for all centers belonging to the EBMT network. Data that are more detailed were collected using a second transplant form that contained specific information regarding a description of respiratory symptoms, HCoV-related hospital admission, oxygen requirement, and intensive care unit (ICU) admission. Variables such as immunosuppressant drugs, corticosteroids, the presence of signs or symptoms of acute or chronic graft-vs-host disease (GVHD), prior development of bronchiolitis obliterans syndrome, and variables for immunodeficiency scoring index (ISI) computation [25] (ie, lymphocyte count, neutrophil count, myeloablative conditioning regimen, age, corticosteroid therapy, and GVHD) were requested at the time of CARV PCR screening.

Definitions

Upper respiratory tract disease was defined as the combination of upper respiratory symptoms (rhinorrhea, sinusitis, otitis, or pharyngitis), identification of seasonal HCoVs by PCR assay, and the absence of LRTD symptoms and/or any pulmonary infiltrates on chest radiograph or computed tomographic scan of the lung. We classified LRTD as possible, probable, or confirmed, as previously described [26]. There were no probable episodes because bronchoscopies were not performed in patients without radiological proof of pulmonary involvement. We defined episodes as URTD or LRTD according to ECIL-4 recommendations [27]. An infectious disease episode was considered to be resolved when complete remission of respiratory symptoms was observed. A further episode of a respiratory tract infectious disease required the presence of a symptom-free period of at least 2 consecutive weeks from the resolution of the previous episode and/or the isolation of a different subtype of HCoV in conjunction with the onset of new respiratory

Table 1. Multiplex Polymerase Chain Reaction Platforms According to Type Performance of Community-Acquired Respiratory Viruses

PCR Platform[a]	Transplant Centers/Episodes, No. (%)[b]	HCoVs					Influenza A/B	HMPV	HPIV 1–4	RSV A/B	EvRh	HBoV	ADV
		Non-subtypable	NL63	OC43	HKU1	229E							
Allplex Respiratory Panel 1-2-3/Anyplex RV16	4 (11.4)/52 (11.4)	…	D	D	N	D	D	D	D	D	D	D	D
Argene Respiratory	6 (17.1)/52 (11.4)	D	I	I	I	I	D	D	D	D	D	D	D
BioFire FilmArray Respiratory	3 (8.6)/42 (9.2)	…	D	D	D	D	D	D	D	D	D	N	D
FTD respiratory pathogens 33	1 (2.9)/7 (1.5)	…	D	D	D	D	D	D	D	D	D	D	D
Multiplex RT-nested PCR assay[c]	1 (2.9)/12 (2.6)	…	N	D	N	D	N	N	D	N	D	N	N
NxTAG Respiratory Pathogen Panel	3 (8.6)/15 (3.3)	…	D	D	D	D	D	D	D	D	D	D	D
CLART R PNEUMOVIR 1	1 (2.9)/1 (0.2)	…	N	N	N	D	D	D	D	D	D	D	D
RespiFinder	7 (20.0)/156 (34.3)	…	D	D	D	D	D	D	D	D	D	D	D
xTAG Respiratory Viral Panel	1 (2.9)/30 (6.6)	…	D	D	D	D	D	D	D	D	D	D	D
Unknown with subtype identification[d]	11 (31.4)/58 (12.7)	…	D	D	D	D	D	D	D	D	D	D/N	D
Unknown without subtype identification[b]	5 (14.3)/24 (5.3)	D	U	U	U	U	D	D	D	D	D	D/N	D

Abbreviations: ADV, adenovirus; D, detectable by the polymerase chain reaction platform; EvRh, enterovirus/rhinovirus; HBoV, human bocavirus; HCoV, human coronavirus; HMPV, human metapneumovirus; HPIV, human parainfluenza virus; I, detectable but indistinguishable from other human coronavirus subtypes by the polymerase chain reaction platform; N, not detectable by the polymerase chain reaction platform; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; U, unknown whether polymerase chain reaction platform is able to distinguish between HCoV subtypes.

[a]None of the multiplex PCR platforms was able to detect Middle East respiratory syndrome coronavirus (MERS-CoV) and/or severe acute respiratory syndrome coronavirus (SARS-CoV).

[b]Total of 31 participating transplant centers; some transplant centers reported use of different PCR panels over the course of the study.

[c]In-house platform: Coiras MT, Aguilar JC, Garcia ML, et al. Simultaneous detection of 14 respiratory viruses in clinical specimens by 2 multiplex reverse-transcription nested PCR assays. J Med Virol 2004; 72:484–95.

[d]Unknown PCR platforms: Outsourcing diagnostic services to independent institutes rendered the PCR platform used to detect HCoV unidentifiable. Depending on the degree of detail from the virology reports, unknown PCR platforms were distinguished according to HCoV subtype identification. Unknown PCR platforms were confirmed to detect the 4 conventional HCoV subtypes (NL63, OC43, HKU1, 229E) but not MERS-CoV or SARS-CoV.

symptoms. Acute and chronic GVHD, including bronchiolitis obliterans syndrome, was diagnosed according to standard criteria [28].

A coinfection was defined as a significant co-pathogen detected in a concurrent nasopharyngeal, bronchoalveolar lavage, or blood sample obtained during the course of HCoV infection.

Technical and Diagnostic Considerations

CARV testing in respiratory samples was performed with different multiplex PCR platforms. Details regarding the CARV type's performance for each PCR test are provided in Table 1. In brief, 5 of 9 commercial multiplex PCR assays and other unspecified PCR platforms were able to detect and discriminate all 4 common HCoV subtypes, whereas 1 commercial PCR assay only detected 3 of 4 HCoVs (NL63, 229E, and OC43), 1 in-house PCR assay only detected 2 HCoVs (229E and OC43), and 1 commercial PCR assay only detected the 229E subtype. A commercial multiplex PCR assay detected the 4 strains of HCoV but was not able to discriminate among them. Finally, an unknown PCR platform was able to detect all 4 HCoVs without information on HCoV subtype, and HCoVs in these cases were classified as nonsubtypable.

Endpoints and Statistical Analysis

The primary objective of the study was to describe epidemiological and clinical characteristics of URTD and LRTD in allo-HSCT recipients with seasonal HCoV infection. We also analyzed differences in clinical manifestations among HCoV subtypes as well as risk factors for HCoV-related hospital admission, oxygen requirement, LRTD involvement, and all-cause mortality by day 90 after HCoV detection, the latter in recipients with LRTD. We selected day 90 as a cutoff for mortality analysis to capture HCoV-related late events since CARV shedding could be >12 weeks in allo-HSCT recipients [17].

The main characteristics of patients were reported by descriptive statistics on the total of the available information; median and range were used for continuous variables, and absolute and percentage frequency were used for categorical variables. Differences between groups were tested using linear or logistic regression models, using the generalized estimating equation method to take into account the dependence of observations, nested by patient. Variables with a P value < .1 in the univariate model were included in the multivariate analysis. In recipients with LRTD, the survival analysis was performed by using the Cox regression model. A P value < .05 was considered statistically significant. All P values were 2-sided. All the analyses were performed using the statistical software SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Patient Characteristics

Overall, we included 402 pediatric and adult allo-HSCT recipients with a median age of 46 years (range, 0.3–73.8 years) who developed 449 URTD/LRTD episodes of HCoV between January 2012 and January 2019 reported from 31 EBMT transplant centers in 13 countries around the world (including Europe, Asia, Australia, and South America). Clinical and transplant characteristics of the series are detailed in Table 2. The study population comprised a high-risk cohort, since 57% of the recipients were allografted from alternative donors (unrelated adult donor, cord blood units, or haploidentical family donors). There were 364 allo-HSCT recipients with 1 HCoV episode and 38 (9.5%) recipients with 2 or more HCoV episodes.

Epidemiological and Clinical Characteristics According to HCoV Subtype

Median time from allo-HSCT to first HCoV episode was 222 days (range, –12 days before stem cell infusion to 20 years after transplant). Seven cases (1.5%) were diagnosed before stem cell infusion, whereas most cases occurred within the first year of stem cell infusion (n = 262 [58%]). There were 434 episodes with only 1 HCoV subtype, whereas in 15 episodes (3%) we observed 2 or more HCoV subtypes in the same respiratory sample. In this series the most common HCoV was OC43 (n = 170 [38%]) followed by 229E (n = 97 [22%]), NL63 (n = 64 [14%]), and KHU1 (n = 54 [12%]). This order was maintained when we analyzed the HCoV subtypes diagnosed through multiplex PCR assays capable of detecting and differentiating all 4 HCoV strains (n = 306 [68%]): OC43 (n = 134 [43.5%]) followed by 229E (n = 64 [20.8%]) and by NL63 (n = 54 [17.5%]) and HKU1 (n = 54 [17.5%]). Seventy-nine episodes (17.5%) had nonsubtypable HCoVs.

Although HCoV circulated all year long, most of the episodes (n = 375 [83%]) were diagnosed during cold months (Figure 1A). We did not observe significant differences in HCoV subtype distribution between countries and continents. However, according to the year of HCoV detection, we observed a gradual increase of reported HCoV episodes over the years (from 28 HCoV episodes reported in 2012 to 97 in 2018). The *Alphacoronavirus* genus (subtypes 229E and NL63) predominated in 2012 and 2013, whereas *Betacoronavirus* (subtypes OC43 and HKU1) predominated from 2014 to 2018. Genera behaviors mainly correlate with OC43 and 229E prevalence each year (Figure 1B). Clinical characteristics according to HCoV subtype are summarized in Table 3.

Clinical and Laboratory Characteristics According to URTD/LRTD Involvement

Clinical and laboratory differences according to URTD or LRTD involvement are summarized in Table 4. Overall, 446 of 449 HCoV episodes (99%) involved the URTD (328 of them [73%] limited to URTD), whereas 121 (27%) had LRTD involvement (106 possible and 15 proven). A third of episodes (n = 153 [35%]) had fever at the time of HCoV detection, leading to hospital admission in 80 cases (18%), oxygen requirement in 56 cases (13%), and ICU admission in 13 cases (3%). As expected, the group developing HCoV LRTD had significantly higher rates of severe immunosuppression-related factors. Immunodeficiency scoring index variables (lymphopenia, active GVHD, corticosteroid therapy) as well as bacterial, fungal, and other CARV coinfections were significantly overrepresented in the HCoV LRTD group ($P \leq .05$ for all comparisons). Characteristics of significant co-pathogens including CARV, bacterial, and fungal agents are detailed in Table 5. As expected, HCoV LRTD showed higher rates of fever, hospital admission, oxygen requirement, and ICU admission ($P < .001$ for all comparisons).

Risk Factors for Hospital Admission, Oxygen Requirements, Lower Respiratory Tract Involvement, and Mortality

Logistic regression and Cox regression multivariate analyses of conditions associated with hospital admission, oxygen requirements, HCoV LRTD, and all-cause day 90 mortality in those with LRTD involvement are shown in Table 6.

We identified 5 conditions associated with hospital admission: HCoV LRTD (odds ratio [OR], 5.46), corticosteroid use (OR, 2.98), fever (OR, 2.3), myeloablative conditioning regimen (OR, 0.46), and HCoV infection occurring after the first year of transplant (OR, 2.15).

For oxygen requirement, we identified 4 independent risk factors: HCoV LRTD (OR, 11.86), corticosteroid therapy (OR, 6.46), fever (OR, 3.31), and immunoglobulin replacement within 2 months before HCoV detection (OR, 3.47).

Regarding the risk of LRTD, we identified 4 conditions associated with this event: absolute lymphocyte count (ALC) $<0.5 \times 10^9$/L (OR, 2.4), active GVHD (OR, 1.79), HCoV infection occurring after the first year of transplant (OR, 2.1), and fever (OR, 3.56).

Finally, the conditions associated with increased mortality in recipients developing HCoV LRTD were ALC $<0.1 \times 10^9$/L (hazard ratio [HR], 10.82), corticosteroid therapy (HR, 4.68), and ICU admission (HR, 8.22). Mortality of patients with LRTD increased according to the presence of these risk factors. Those with no risk factor or 1 risk factor had a mortality rate of 11% compared to those with 2–3 risk factors (57%) ($P < .0001$).

We did not find differences in outcomes among pediatric (<18 years of age) and adult (≥18 years of age) patients. The rate of LRTD, hospital admission, oxygen support, and overall mortality of pediatric recipients compared to adults were 31% vs 26% ($P = .6$), 7% vs 18% ($P = .15$), 18% vs 12% ($P = .3$), and 2% vs 7% ($P = .3$), respectively.

Mortality and Cause of Death

The all-cause mortality rate at 3 months after HCoV detection was 7% (n = 31) for the entire group. Mortality of

Table 2. Patient and Transplant Characteristics (n = 402)

Characteristic	No. (%)
Age at allo-HSCT, y, median (range)	46.6 (0.3–73.8)
<18	40 (10)
≥18	362 (90)
Male sex	245 (60.9)
Baseline disease	
AL/MDS/MPD	241 (60)
Chronic leukemia	32 (8)
Lymphoid disorders	86 (21.4)
Other	39 (9.7)
Missing data	4 (1)
Disease status at transplant	
Complete remission	219 (54.5)
Partial remission	43 (10.7)
Active disease at transplant	64 (15.9)
Other	76 (18.9)
Prior autologous HSCT	21 (5.2)
Period of transplant	
2017–2018	105 (26.1)
2015–2016	122 (30.3)
2013–2014	88 (21.9)
Before 2013	87 (21.6)
Conditioning regimen	
No conditioning	3 (0.7)
RIC	198 (49.3)
MAC	192 (47.8)
Missing data	9 (2.2)
Type of donor	
HLA-identical sibling donor	157 (39.1)
Unrelated donor	169 (42)
Unrelated umbilical cord blood	17 (4.2)
Haploidentical family donor	45 (11.2)
Other	11 (2.7)
Missing	3 (0.7)
Peripheral blood stem cell source	332 (82.6)
HLA fully matched	242/307 (78.8)
ATG as a part of conditioning regimen	147/398 (36.9)
GVHD prophylaxis	
Sirolimus-tacrolimus	20 (5)
Tacrolimus or CsA + MTX	204 (50.7)
Posttransplant cyclophosphamide	51 (12.7)
CsA + PDN and others	116 (28.9)
No prophylaxis regimen	4 (1.0)
Missing data	7 (1.7)
No. of HCoV episodes	
1	364 (90.5)
≥2	38 (9.5)
Time from allo-HSCT to first episode of HCoV, median (range)	222 (–12 d to 20.7 y)
Time from allo-HSCT to first episode of HCoV (category)	
Until day 180	173 (43)
Day 181–1 y	89 (22.1)
1–2 y	76 (18.9)
>2 y	64 (15.9)
Follow-up after last episode of HCoV, y, median (95% CI)	2.32 (2.09–2.52)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations. AL, acute leukemia; allo-HSCT, allogeneic hematopoietic stem cell transplantation; ATG, antithymocyte globulin; CI, confidence interval; CsA, cyclosporine A; GVHD, graft-vs-host disease; HCoV human coronavirus; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MPD, myeloproliferative disease; MTX, methotrexate; PDN, prednisone; RIC, reduced-intensity conditioning .

recipients with HCoV limited to URTD was 3.5% (n = 11) whereas it was 16% (n = 20) ($P < .0001$) in those with LRTD. According to coronavirus genera, 3-month overall mortality was 3% in the *Alphacoronavirus* group vs 7% in the *Betacoronavirus* group ($P = .28$) in both URTD/LRTD, whereas it was 3% vs 10% for those with LRTD, respectively ($P = .25$).

Fifteen recipients died by day 30 after HCoV diagnosis. Ten additional recipients died at day 60 and 6 more recipients died by day 90 after HCoV diagnosis. In total, 11 and 20 recipients with URTD or LRTD died, respectively. The respective numbers of death by day 30, day 60, and day 90 were 6, 3, and 1 for URTD and 9, 6 and 5 for LRTD.

Cause of death in recipients who died by day 30 after HCoV detection were relapse (n = 5), GVHD (n = 4), infectious respiratory failure (n = 3), and other complications (n = 3: VOD, systemic infection and unknown cause). The additional 10 deaths occurring by day 60 were due to disease relapse (n = 5), infectious respiratory failure (n = 2), and other causes (n = 3; graft failure, bleeding disorder, and unknown cause). For the remaining 6 patients who died by day 90 after HCoV detection, the causes of death were disease relapse (n = 2), GVHD (n = 1), infectious respiratory failure (n = 2), and other causes (n = 1; GVHD and bleeding disorder). Overall, 10 patients (3%) died from infectious respiratory failure.

DISCUSSION

This study shows that HCoV episodes in the setting of allo-HSCT predominate during cold months, with OC43 (38%) being the most common HCoV subtype. The detection of seasonal HCoV was associated with considerable morbidity after allo-HSCT and was frequently accompanied by co-pathogens in the lower respiratory tract leading to hospitalization, oxygen requirement, and ICU admission in a not irrelevant proportion of cases. Three-month overall mortality after HCoV detection was 7% in the whole cohort and 16% in those with LRTD. We identified several risk factors for different outcomes that could be of value for close clinical monitoring and/or risk stratification for future clinical trials.

Our study confirms that seasonal HCoVs predominate during cold months [29] also in allo-HSCT recipients. In line with several reports in the general population [29–31], the most common seasonal HCoV in our series was OC43, belonging to the *Betacoronavirus* genus. Although we observed subtle differences over the years in HCoV subtypes' prevalence, it is noteworthy to mention that the *Betacoronavirus* genus (subtypes OC43 and HKU1) predominated from 2014 onward. This fact, along with the recent pandemic caused by SARS-CoV-2, another *Betacoronavirus*, suggests that differential characteristics of the *Betacoronavirus* genus may provide a biological advantage to survive and spread among humans as compared to the *Alphacoronavirus* genus. From

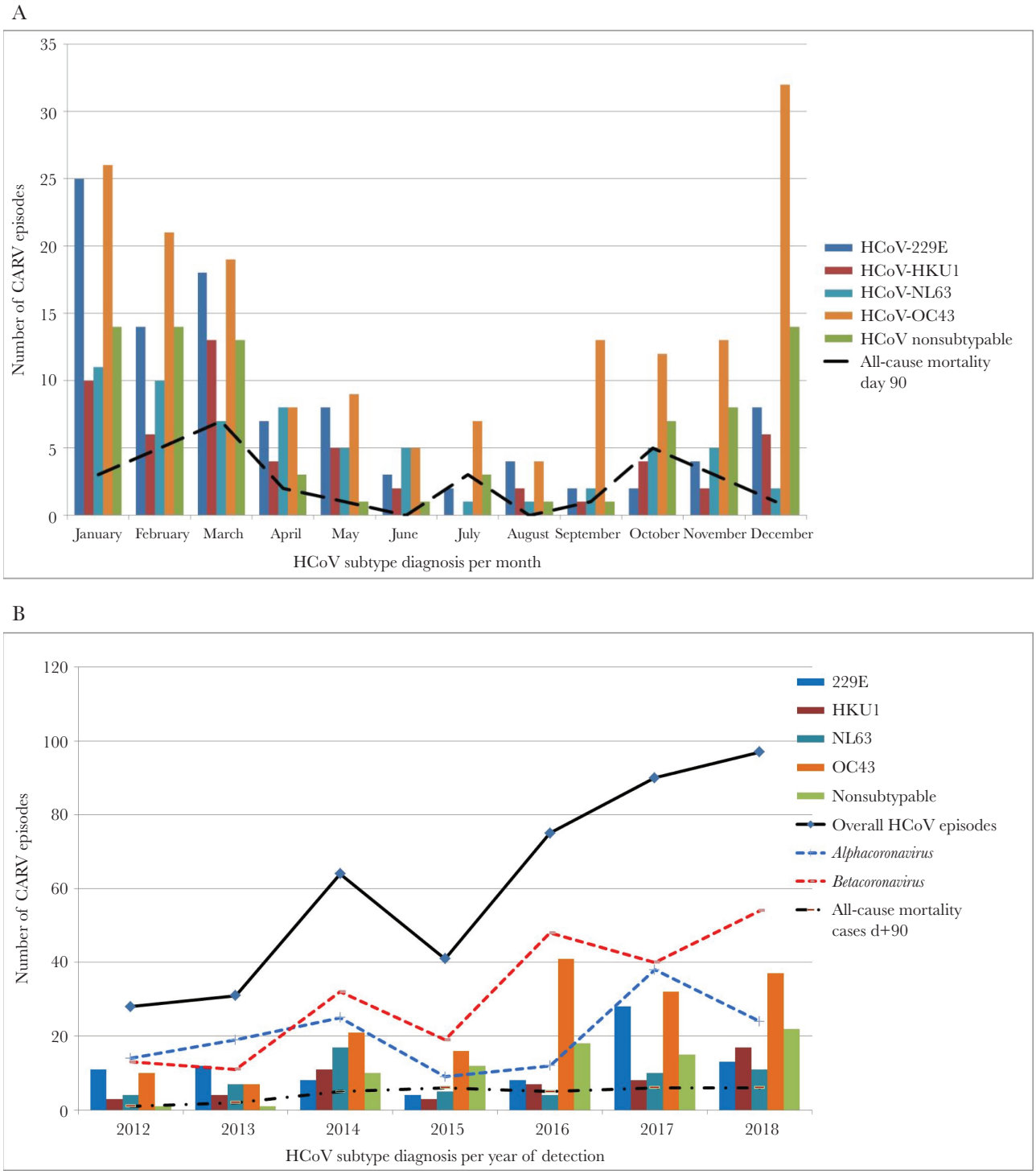

Figure 1. Seasonality of human coronavirus (HCoV) infections in recipients of allogeneic hematopoietic stem cell transplant. *A*, HCoV serotype according to month of detection. *B*, HCoV serotype according to season. Abbreviations: CARV, community-acquired respiratory virus; HCoV, human coronavirus.

2012 we observed a continuous increase in the number of reported seasonal HCoV episodes, which is in line with a prior report [1]. This observation is likely related to an increase of awareness in the importance of monitoring viral infections in allo-HSCT recipients and to an increased widespread use of multiplex PCR assay as a first-line test, progressively incorporating the 4 HCoV subtypes, for CARV screening in clinical practice over years [32].

Seasonal HCoV usually causes mild respiratory illnesses in the general population. Although prior studies and reviews suggested that seasonal HCoVs may occasionally cause LRTDs after

Table 3. Type of Human Coronavirus (HCoV) and Mortality According to HCoV Type, Timing of Infection, and Upper or Lower Respiratory Tract Disease

Characteristic	All HCoV Cases	Nonsubtypable	OC43	NL63	HKU1	229E	*P* Value
No. of episodes[a]	449	79	170	64	54	97	
URTD	446/449 (99.3)	77 (97.5)	170 (100)	63 (98.4)	54 (100)	97 (100)	.2
LRTD	121 (26.9)	29 (36.7)	41 (24.1)	19 (29.7)	16 (29.6)	20 (20.6)	.1
Possible	106 (23.6)	23 (29.1)	39 (22.9)	16 (25)	14 (25.9)	18 (18.6)	.5
Proven	15 (3.3)	6 (7.6)	2 (1.2)	3 (4.7)	2 (3.7)	2 (2.1)	
Fever	153/442 (34.6)	31/79 (39.2)	58/168 (34.5)	24/62 (38.7)	19/52 (36.5)	25/95 (26.3)	.1
CRP, mg/dL, median (range)	12 (0–560)	13.7 (0.1–560)	12.0 (0–346.6)	17.5 (0–296)	13.9 (0–347)	8 (0–358)	.4
ISI							.6
Low	152 (37.1)	26 (35.1)	65 (42.8)	17 (30.4)	19 (35.8)	30 (33.7)	
Moderate	221 (53.9)	40 (54.1)	75 (49.3)	34 (60.7)	27 (50.9)	53 (59.6)	
High	37 (9)	8 (10.8)	12 (7.9)	5 (8.9)	7 (13.2)	6 (6.7)	
Empirical antibiotic	276/443 (62.3)	48/79 (60.8)	106/167 (63.5)	40/63 (63.5)	28/53 (52.8)	60/95 (63.2)	.9
Immunoglobulin support	92/435 (21.1)	16/73 (21.9)	29/169 (17.2)	18/63 (28.6)	16/54 (29.6)	22/91 (24.2)	.2
Hospitalization	80/442 (18.1)	17/79 (21.5)	26/167 (15.6)	13/64 (20.3)	9/53 (17.0)	18/94 (19.1)	1
Oxygen support	56/441 (12.7)	18/79 (22.8)	19/168 (11.3)	5/59 (8.5)	9/54 (16.7)	9/96 (9.4)	.06
ICU	13/448 (2.9)	6/79 (7.6)	3/170 (1.8)	1/64 (1.6)	1/54 (1.9)	2/96 (2.1)	.1
URTD/LRTD 30-day OM	15/449 (3.3)	6/79 (7.6)	3/170 (1.8)	2/64 (3.1)	2/54 (3.7)	2/97 (2.1)	.4
LRTD 30-day OM	9/121 (7.4)	6/29 (20.7)	2/41 (4.9)	0/19 (0.0)	0/16 (0.0)	1/20 (5)	.06
URTD/LRTD 90-day OM	31/449 (6.9)	13/79 (16.5)	10/170 (5.9)	3/64 (4.7)	4/54 (7.4)	2/97 (2.1)	.02
LRTD 90-day OM	20/121 (16.5)	13/29 (44.8)	4/41 (9.8)	1/19 (5.3)	1/16 (6.3)	1/20 (5)	.015

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CRP, C-reactive protein; HCoV, human coronavirus; ICU, intensive care unit; ISI, immunodeficiency score index; LRTD, lower respiratory tract disease; OM, overall mortality; URTD, upper respiratory tract disease.

[a]The sum of the episodes does not match the overall number of episodes (n = 449) since multiple community-acquired respiratory viruses (CARVs) were detected in the same respiratory sample in 15 (3%) CARV episodes. The 90-day all-cause mortality after CARV co-viral infection was 10% (17 of 165). Sixty-one co-virus infectious episodes occurred within the first 6 months after stem cell infusion and mortality was 15% (9 of 61). Sixteen of 164 (10%) and 14 of 59 (24%) patients with URTD and LRTD CARV co-viral infection died, respectively. Finally, 7 of 19 (37%) patients with LRTD CARV co-viral infection died within the first 6 months after stem cell infusion.

allo-HSCT [2, 33], our study showed that 27% of allo-HSCT recipients with HCoV may develop LRTD. This is in line with prior reports where LRTD occurred in 14%–33% of cases [1, 3]. Although we report a relevant rate of HCoV LRTD, attributing LRTD to HCoV is challenging due to the frequent presence of co-pathogens. In addition, it should be noted that the only way to establish the true effect of HCoV in the lungs is through the demonstration of HCoV antigens and/or RNA in lung tissues. The observation that 18% of HCoV cases required hospital admission, 13% oxygen support, and 3% ICU admission indicates that seasonal HCoV could be related with a severe course in these highly immunosuppressed patients. Although recipients with isolated URTD had a relatively low overall mortality rate at 3 months after HCoV detection (3.5%), those who developed pulmonary complications showed a significant higher mortality rate (16%). This observation was also true when we looked at day 30 mortality, which could be a more accurate time point to evaluate direct effects of HCoV (1.8% vs 7.4%, respectively, $P = .01$). These facts support recent findings from a retrospective study where the detection of HCoV in the LRT was significantly related with higher rates of respiratory support and mortality in immunocompromised hosts, similar to that of established respiratory pathogens including respiratory syncytial virus, influenza virus, and human parainfluenza virus [23]. Importantly, we did not observe significant differences in terms of severity and mortality among HCoV subtypes.

The large number of cases included herein allowed us to identify several risk factors that influenced outcomes. We differentiated 2 types of risk factors: first, variables considered as surrogate markers of a profound immunosuppression status (corticosteroids, ALC <0.5 or <0.1 × 10^9/mL, conditioning regimen intensity, immunoglobulin replacement, and the presence of active GVHD): second, those related to the HCoV clinical behavior (LRTD, fever, HCoV after the first year of allo-HSCT, and ICU admission). Of note, we did not find any differences among children and adult allo-HSCT. Most of the risk factors we identified have been previously recognized as risk factors of poor outcome in other CARV studies in the allo-HSCT setting, such as corticosteroid use, GVHD, ALC, LRTD, ICU admission, and conditioning regimen intensity [34]. However, for the first time we identified immunoglobulin replacement and HCoV infection beyond the first year of allo-HSCT as risk factors for severity. Immunoglobulin replacement may discriminate patients with severe posttransplant immunoparesis and may thereby identify an increased risk of severe infections. In addition, immunoglobulin G levels have previously been recognized as a risk factor of poor outcome in other CARVs in allo-HSCT recipients [35, 36]. In contrast, the development of HCoV infection beyond 1 year after transplant is a somewhat unexpected finding since prior studies indicated that early CARV infections had a worse outcome

Table 4. Clinical and Biological Characteristics of Human Coronavirus Infection Episodes in Allogeneic Hematopoietic Stem Cell Transplant Recipients According to Upper or Lower Respiratory Tract Involvement

Characteristic	HCoV URTD (n = 328)	HCoV LRTD (n = 121)	*P* Value
Transplant characteristics			
Age, y			
<18	29 (8.8)	13 (10.7)	.6
≥18	299 (91.2)	108 (89.3)	
ATG as part of conditioning	123/326 (37.7)	46/119 (38.7)	.8
GVHD prophylaxis			
No prophylaxis regimen	2 (0.6)	2 (1.7)	
Sirolimus-tacrolimus	16 (4.9)	5 (4.1)	
Tacrolimus or CsA + MTX	169 (51.5)	59 (48.8)	
Posttransplant cyclophosphamide	45 (13.7)	9 (7.4)	
CsA + PDN and others	92 (28.0)	43 (35.5)	
Missing	4 (1.2)	3 (2.5)	
HLA mismatch	53/255 (20.8)	24/93 (25.8)	.4
Type of donor			
HLA-identical sibling donor	127 (38.7)	45 (37.2)	
Unrelated donor	136 (41.5)	57 (47.1)	
Unrelated umbilical cord blood	15 (4.6)	3 (2.5)	
Haploidentical family donor	39 (11.9)	11 (9.1)	
Other	9 (2.7)	4 (3.3)	
Missing	2 (0.6)	1 (0.8)	
ISI[a]			
ANC $<0.5 \times 10^9$/L	26/298 (8.7)	12/116 (10.3)	.4
Missing data	30	5	
ALC $<0.2 \times 10^9$/L	28 (9.6)	21 (18.1)	.01
Missing data	35	5	
Age at HCoV, y, median (range)	48.8 (0.5–74.3)	51.4 (0.4–72.8)	.9
Age ≥40 y	210 (64.0)	81 (66.9)	.7
Myeloablative conditioning regimen	152/320 (47.5)	55/117 (47.0)	1
Missing data	7	2	
No conditioning	1	2	
GVHD (acute or chronic)	113/328 (34.5)	59/120 (49.2)	.01
Missing data	0	1	
Corticosteroids	124/328 (37.8)	68/119 (57.1)	.001
Missing data	0	2	
Recent or preengraftment allo-HSCT	14/328 (4.3)	8/121 (6.6)	.3
ISI			
Low risk (0–2)	123 (37.5)	29 (24.0)	.003
Moderate risk (3–6)	150 (45.7)	71 (58.7)	
High risk (7–12)	21 (6.4)	16 (13.2)	
Missing data	34 (10.4)	5 (4.1)	
Other characteristics[a]			
On immunosuppressants	222/328 (67.7)	80/120 (66.7)	1
ALC $<0.1 \times 10^9$/L	20/293 (6.8)	17/116 (14.7)	.01
ALC $<0.5 \times 10^9$/L	72/293 (24.6)	46/116 (39.7)	.002
RVI characteristics and clinical consequences			
CARV LRTD			
Possible	…	106/121 (87.6)	
Proven	…	15/121 (12.4)	
HCoV subtype			
OC43	129/266 (48.5)	41/93 (44.1)	
NL63	45/265 (17.0)	19/93 (20.4)	
KHU1	38/211 (18.0)	16/85 (18.8)	
229E	77/279 (27.6)	20/95 (21.1)	
Nonsubtypable	50/328 (15.2)	29/121 (24.0)	
Hospital admission	28/325 (8.6)	52/117 (44.4)	<.0001
ICU admission	1/328 (0.3)	12/120 (10.0)	.001

Table 4. Continued

Characteristic	HCoV URTD (n = 328)	HCoV LRTD (n = 121)	*P* Value
Fever during CARV	86/323 (26.6)	67/119 (56.3)	<.0001
Prior BOS	26/327 (8.0)	13/120 (10.8)	.3
IgG level, mg/dL, median (range)	669 (3.4–16 300)	540 (4.5–5470)	.2
Antibiotic use	172/325 (52.9)	104/118 (88.1)	<.0001
Immunoglobulin support	57/320 (17.8)	35/115 (30.4)	.01
Median time of diagnosis after SC infusion (range)	243.5 (–12 d to 20.7 y)	291.0 (–12 d to 17.3 y)	.9
Day 30 overall mortality rate	6/328 (1.8)	9/121 (7.4)	.01
Day 90 overall mortality rate	11/328 (3.4)	20/121 (16.5)	<.0001
Median time to death, y (95% CI)	2.38 (2.14–2.66)	2.85 (2.11–3.20)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ALC, absolute lymphocyte count; allo-HSCT, allogeneic hematopoietic stem cell transplantation; ANC, absolute neutrophil count; ATG, antithymocyte globulin; BOS, bronchiolitis obliterans syndrome; CARV, community-acquired respiratory virus; CI, confidence interval; CsA, cyclosporine A; GVHD, graft-vs-host disease; HCoV, human coronavirus; HLA, human leukocyte antigen; ICU, intensive care unit; IgG, immunoglobulin G; ISI, immunodeficiency score index; LRTD, lower respiratory tract disease; MTX, methotrexate; PDN, prednisone; RVI, respiratory virus infection; SC, stem cells; URTD, upper respiratory tract disease.

[a]All variables were captured at the time of CARV diagnosis.

[37]. However, transplant physicians tend to lengthen clinical follow-up in allo-HSCT recipients beyond the first year after transplantation. Therefore, there might be a selection bias in that only long-term survivors with severe HCoV infection have looked for medical attention or testing.

Our multivariate analyses have depicted the relevance of each type of risk factors according to the severity of the outcome analyzed. In this sense, hospital admission was mainly triggered by clinical factors (LRTD, fever, and allo-HSCT >12 months), whereas the need for oxygen support and pulmonary

Table 5. Coinfection Characteristics According to Upper or Lower Respiratory Tract Involvement

Coinfection	HCoV URTD (n = 328)	HCoV LRTD (n = 121)	*P* Value
CARV coinfections	102 (34)	50 (41)	.04
Human coronavirus	11 (3)	4 (3)	.9
Enterovirus/rhinovirus	14 (4)	8 (7)	.3
Respiratory syncytial virus	36 (11)	13 (11)	.9
Human metapneumovirus	6 (2)	5 (4)	.17
Human parainfluenza virus	13 (4)	10 (8)	.09
Adenovirus	4 (1)	4 (3)	.3
Human influenza virus	26 (8)	7 (6)	.5
Human bocavirus	7 (2)	1 (1)	.7
Bacterial coinfection	18 (5)	29 (24)	<.0001
Pseudomonas spp	4 (1)	5 (4)	.2
Streptococcus pneumoniae	1 (0.3)	2 (1.5)	.3
Moraxella catarrhalis	4 (1)	0	.2
Haemophilus influenzae	2 (0.5)	3 (2)	.3
Escherichia coli	1 (0.3)	3 (2)	.2
Klebsiella pneumoniae	2 (0.5)	2 (1.5)	.3
Mycobacterium tuberculosis	0	2 (1.5)	.2
Stenotrophomonas maltophilia	1 (0.3)	1 (1)	.5
Mycoplasma pneumoniae	1 (0.3)	1 (1)	.5
Legionella pneumophila	0	2 (1.5)	.15
Staphylococcus aureus	1 (0.3)	2 (1.5)	.5
Enterococcus spp	0	3 (2)	.2
Others	1 (0.3)	3 (2)	.2
Fungal coinfection	0	18 (15)	<.0001
Probable invasive pulmonary aspergillosis	…	11 (9)	
Pneumocystis jiroveci	…	6 (5)	
Mucormycosis	…	1 (1)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CARV, community-acquired respiratory virus; HCoV, human coronavirus; LRTD, lower respiratory tract disease; URTD, upper respiratory tract disease.

Table 6. Multivariate Analyses for Different Outcomes

Outcome and Variables	OR (95% CI)	*P* Value
Hospital admission (n = 442)[a]	Logistic regression	
HCoV LRTD	5.46 (2.85–10.49)	<.0001
Corticosteroids	2.98 (1.59–5.59)	.001
Fever at the time of HCoV	2.30 (1.20–4.39)	.01
Myeloablative[a]	0.46 (.24–.88)	.02
Allo-HSCT ≥12 mo	2.15 (1.15–4.01)	.02
Oxygen support (n = 441)[a]	Logistic regression	
HCoV LRTD	11.86 (5.73–24.52)	<.0001
Corticosteroids	6.46 (3.22–12.98)	<.0001
Fever at the time of HCoV	3.31 (1.57–6.98)	.002
Immunoglobulin replacement	3.47 (2.06–5.84)	<.0001
LRTD (n = 449)[a]	Logistic regression	
ALC <0.5 × 10^9/L, No. (%)	2.40 (1.32–4.35)	.004
Active GVHD at the time of RVI[a]	1.79 (1.05–3.06)	.03
Allo-HCT ≥12 mo	2.13 (1.20–3.79)	.01
Fever at the time of HCoV	3.56 (2.07–6.12)	<.0001
LRTD overall mortality (n = 121)[a]	Cox regression[b]	
ALC <0.1 × 10^9/L, No. (%)	10.82 (3.78–31.01)	<.0001
Corticosteroids	4.68 (1.62–13.54)	.0045
ICU admission	8.22 (2.55–26.50)	.0004

Abbreviations: ALC, absolute lymphocyte count; allo-HSCT; allogeneic stem cell transplantation; CI, confidence interval; GVHD, graft-vs-host disease; HCoV, human coronavirus; HR, hazard ratio; ICU, intensive care unit; LRTD, lower respiratory tract disease; OR, odds ratio; RVI, respiratory virus infection.

[a]Variables included in univariate analyses: type of donor, recipient age, donor/receptor human leukocyte antigen mismatch, conditioning regimen–based antithymocyte globulin, GVHD prophylaxis, absolute neutrophil count <0.5 × 10^9/L, ALC <0.2 × 10^9/L, ALC <0.1 × 10^9/L, immunossupressant drugs at the time of HCoV detection, periengraftment period, allo-HSCT <100 days, allo-HSCT <180 days, allo-HSCT <2 years, HCoV subtype (OC43, 229E, NL63, HKU1, and nonsubtypable), corticosteroid therapy >30 mg/day at the time of HCoV detection, oxygen support, mono- vs coinfections (respiratory viral, bacterial, and fungal), seasons (spring, summer, autumn, winter), prior bronchiolitis obliterans syndrome, immunoglobulin G level <400 mg/dL, and immunodeficiency score index.

[b]Values are presented as hazard ratio (95% CI).

involvement were both influenced by clinical and immunosuppression conditions (fever, LRTD, HCoV after the first year of allo-HSCT and corticosteroids, immunoglobulin replacement, ALC <0.5 × 10^9/L, and the presence of active GVHD, respectively). Last, mortality in recipients with LRTD was mainly influenced by immunosuppression factors (ALC <0.1 × 10^9/mL and corticosteroids). These observations emphasize the significant role of the immune system (humoral and cellular) in minimizing the severity of HCoV infections in this scenario.

We acknowledge that this study has some limitations, such as the retrospective nature of the analyses, the low proportion of bronchoalveolar lavage performed, the absence of lung tissue analyses to establish the real role of HCoV, and the use of several different PCR methods differing in their analytical performance for detection and identification of HCoV subtypes. In spite of this, our study has strengths that merit consideration. We included a large multicenter cohort of HCoV cases with detailed clinical and laboratory data in the molecular testing era.

In conclusion, we provide insights of seasonal HCoV infections after allo-HSCT in terms of epidemiology and clinical outcome. Our study supports that these infections can have moderate to severe direct and indirect consequences in a significant proportion of cases and that testing for seasonal HCoVs should be included in the CARV screening test in the allo-HSCT setting.

Notes

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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