

RESEARCH

Open Access



Co-infections during SARS-CoV-2 infection in hematologic patients and cell therapy recipients in the omicron era: a Spanish hematopoietic stem cell transplantation and cell therapy group study

Pedro Chorão^{1,2*}, Alex Avendaño³, Inmaculada Heras⁴, Francesco Aiello⁵, Mireia Micó-Cerdá^{6,7}, Ana Arrufat Bel⁸, Valentín García-Gutierrez⁹, María T. Olave¹⁰, Marina Acera Gómez³, Ildefonso Espigado¹¹, María Ángeles Cuesta-Casas¹², Clara González-Santillana¹³, José Ángel Hernández-Rivas¹⁴, Alicia Roldán-Pérez^{15,16}, Jorge Labrador^{17,18}, Marta Villalba^{1,2}, Lourdes Vázquez³, Carolina Garcia Vidal⁵, Rodrigo Martino⁸, Javier López-Jiménez⁹, Ángel Cedillo¹⁹, Carlos Solano^{6,7,20}, Irene García-Cadenas⁸, José Luís Piñana^{6,7} and on behalf of the Infectious Complications Subcommittee of the Spanish Hematopoietic Stem Cell Transplantation Cell Therapy Group (GETH-TC)

Abstract

Background Although SARS-Cov-2 outcomes have improved in the Omicron era, the synergistic or additive effects between SARS-CoV-2 Omicron variants and other microbiological agents in adult hematologic patients have been little explored. We aimed to characterize co-infection types, identify risk factors for co-infection and determine co-infection-related mortality in hematologic patients and recipients of cellular therapy with a first episode of SARS-CoV-2 infection in the Omicron era.

Methods Retrospective national Spanish registry analysis of 692 consecutive patients with hematological disease including receptors of cellular therapy from December 2021 to May 2023.

Results The co-infection rate was 9% ($n = 64$), 30% of which were polymicrobial. Bacterial, viral, and fungal agents affected 64%, 30%, and 11% of patients, respectively. Among the microbiologically confirmed agents ($n = 82$), the most common sites of identification were lower respiratory tract (33%), urinary tract (27%) and bloodstream (17%). Multivariable analysis identified cardiopathy (hazard ratio [HR] 1.69), CAR-T therapy (HR 3.42) and pneumonia (HR 5.54) as conditions associated with co-infection. Considering all-cause mortality at day 180 after SARS-CoV-2 detection, co-infection was associated with lower survival (71% versus 92%). Risk factors at COVID-19 diagnosis for non-relapse

*Correspondence:

Pedro Chorão
pedro_chorao@iislafe.es

Full list of author information is available at the end of the article



© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

mortality (NRM) were co-infection (HR 4.28), age \geq 64 years old (HR 2.55), active hematological treatment (HR 2.13) and under corticosteroid treatment (HR 3.21). In co-infected patients, the only identified factor increasing NRM was corticosteroid use (HR 3.33) at the time of SARS-CoV-2 detection.

Conclusions SARS-CoV-2 co-infection are relatively frequent in hematologic patients and cellular therapy recipients in the Omicron era. Patients with ischemic cardiopathy, those presenting with pneumonia and recipients of CAR-T are at a higher risk of developing a co-infection, while co-infection, age \geq 64 years old, active hematological therapy and corticosteroid treatment showed higher NRM. Improvements in identifying and managing concurrent infections during SARS-CoV-2 are needed to further reduce morbimortality in hematologic patients.

Highlights

- Hematological patients with SARS-CoV-2 had a co-infection rate of 9% (30% with polymicrobial agents).
- Ischemic cardiopathy, CAR-T therapy and pneumonia increase the risk of co-infection.
- Co-infection significantly increases non-relapse mortality.

Keywords SARS-CoV-2, Omicron, Co-infections

Background

In the Omicron era of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), mass vaccination and available treatments have decreased the severity and mortality of coronavirus disease 2019 (COVID-19) in hematological patients [1]. Nonetheless, several factors are associated with severe disease course, such as older age, autologous hematopoietic stem cell transplantation (SCT) or chimeric antigen receptor T-cell (CAR-T) therapy, corticosteroids at the time of infection, incomplete vaccination, prior anti-CD20 monoclonal antibodies, and comorbidities like diabetes or cardiomyopathy [2]. As with community-acquired respiratory virus (CARV) infections in allogeneic SCT (allo-SCT), the virus itself, along with immunosuppression status, may predispose patients to an increased risk of co-infections, which can further worsen their prognosis [3].

As a new CARV, SARS-CoV-2 may also favor co-infection in this vulnerable population. Studies in adult solid cancer patients [4] and pediatric SCT recipients [5] reported a 17–27% co-infection incidence, with higher attributable morbidity and mortality, especially in the case of bacterial and fungal co-infection. These numbers are over double the rate reported in the general population [6]. Nonetheless, not all co-infections seem to have equal impact, and COVID-19 outcomes seem unaltered by viral co-infection in the general population [7]. In adult hematologic patients, however, the synergistic or additive effects between SARS-CoV-2 Omicron variants and other microbiological agents have been little explored.

The current study aims to characterize co-infection types, identify risk factors for co-infection and determine co-infection-related mortality in large cohort of immunosuppressed patients with hematologic disease receiving cellular therapy (including allo-SCT, autologous-SCT and CAR-T cell therapy) with a first detected SARS-CoV-2 infection in the Omicron era.

Methods

Study population and inclusion criteria

This retrospective multicentric analysis included all patients from the Infectious Complications Subcommittee (GRUCINI) of the Spanish Group on Hematopoietic Transplant and Cellular Therapy (GETH-TC) Omicron variant of concern (VOC) SARS-CoV-2 database. This database includes data from consecutive immunocompromised patients with hematological diseases (including cellular therapy) diagnosed with the first documented SARS-CoV-2 episode through molecular and/or antigen tests at 13 Spanish centers between December 27, 2021 and May 30, 2023, with last follow-up on July 10, 2023. Data retrospectively collected in this registry have been described elsewhere [2]. The local Research Ethics Committee of the Hospital Clínico Universitario de Valencia approved the study (reference code 35.21), which was carried out in accordance with the Declaration of Helsinki and its amendments, and applicable national regulatory requirements. The Research Ethics Committee approved the waiver of informed consent for study inclusion.

Definitions

SARS-CoV-2 strains were inferred from the epidemiological data available in Spain [8]. Co-infection was defined as the presence of a clinically significant microbiological agent identified in microbiology studies or clinical infection co-occurring at any point during COVID-19, and requiring additional specific antimicrobial therapy administered independently of COVID-19 management at the discretion of the attending physician. Respiratory viruses without antiviral options were also classed as co-infection. Additionally, infections documented before COVID-19 were considered co-infection if antimicrobial therapy was ongoing and the infection still active at the time of SARS-CoV-2 detection. Site-specific infection definitions were based on physician-reported clinical and microbiological findings, together with updated

definitions from Centers for Disease Control and Prevention [9–12]. Invasive fungal diseases were further classified according to international consensus guidelines [13].

In accordance with local clinical practice, hematologic patients with respiratory symptoms were routinely screened for SARS-CoV-2 via PCR, along with multiplex PCR for common seasonal respiratory viruses, using upper respiratory secretions and/or sputum. When radiological findings suggested an infection other than SARS-CoV-2, bronchoalveolar lavage (BAL) was performed whenever feasible. Blood and urine cultures were obtained in cases of fever, along with additional microbiological tests guided by clinical presentation. For patients at high risk of fungal infections, galactomannan and beta-glucan antigen monitoring in peripheral blood was conducted as per local center protocols. Respiratory infections with microbiologically documented agents in sputum were classified by the treating physician as upper or lower respiratory tract according to clinical symptoms and radiology signs. Sputum microbiological findings were classified as upper respiratory tract infection in the absence of either lower respiratory symptoms or radiology signs suggesting lower respiratory tract involvement, assessed by either chest X-ray or computed tomography scan. Lower respiratory tract was considered in cases of pulmonary involvement in radiology studies compatible with the identification of a well-known pulmonary pathogen in the sputum along with lower respiratory symptoms. However, pathogens such as *Staphylococcus spp* (except *Staphylococcus aureus*), *Streptococcus spp* (except *Streptococcus pneumoniae*) and *Enterococcus spp* (such as *Enterococcus faecalis* or *faecium*) were not considered causative pneumonia agents when isolated in sputum or BAL, even in the context of pulmonary involvement as per radiology studies. Likewise, *Candida spp* was not classed as a co-infective agent if isolated in sputum and/or BAL [14]. Consensus guidelines were also used to define cytomegalovirus [CMV] [15] and CARV [16] infections. Co-infection was not considered in cases of fever of unknown origin without another positive microbiologic sample besides SARS-CoV-2 or untreated microbiological colonization.

Regarding patient characteristics, comorbid cardiopathy was defined by ischemic heart disease, heart failure or clinically significant valvular heart disease, and pneumopathy by any diagnosed lung disease, either structural or functional, according to patient charts. Active treatment was any chemoimmunotherapy directed at treating or maintaining response to hematologic disease, or immunosuppressant use for prophylaxis or treatment in SCT cases. Corticosteroids therapy was defined by ≥ 15 mg per day of prednisone or equivalent doses of methylprednisolone, dexamethasone or hydrocortisone

at the time of SARS-CoV-2 detection, except when used as replacement therapy for adrenal insufficiency.

Endpoints and statistical analysis

The primary endpoints were to characterize co-infection types and their impact on non-relapse mortality (NRM) at 6 months after SARS-CoV-2 detection. Secondary endpoints included identifying conditions associated with higher incidence of co-infection and determining which conditions were linked to higher NRM in co-infected patients.

Categorical variables were presented as percentages and compared using Pearson chi-square test, while continuous variables were presented as median values with ranges and compared with Mann–Whitney U or Kruskal–Walis test as appropriate. Fine-Gray subdistribution hazard models were used to identify risk factors for co-infection at 60 days after COVID-19 diagnosis. For this analysis, death from any cause before co-infection occurred was considered as a competitive event. For 6-month NRM, death directly related to hematological disease was considered as a competitive event. For both analyses, supervised stepwise backward analysis based on the Akaike Information Criteria for goodness of fit was performed on variables with $p < 0.10$ in the univariable analysis in order to select the covariates to be included in the final multivariable model. Cumulative incidence curves were built to visually illustrate the effect of the identified conditions associated with NRM. Kaplan Meier curves were used to illustrate the effect of co-infection on survival. The level of significance was set at < 0.05 (2-sided) for all comparisons. Statistical analysis was conducted with R (The CRAN project), using the *cmprsk* (version 2.2–12) and *crrstep* (version 2024.1.1) packages.

Results

Patient, disease, and SARS-CoV-2 infection characteristics by co-infection status

The 692 patients enrolled had a median age of 64 years (range, 19–93) and 42% were female. The most common hematologic diseases were Hodgkin and non-Hodgkin lymphoproliferative disorders (47%), followed by multiple myeloma (20%) and acute leukemia (19%). The main patient characteristics by co-infection status are summarized in Table 1. Patients with co-infection showed higher rates of comorbid cardiopathy (specifically, ischemic heart disease), had received more prior lines of therapy for hematological disease, and were more likely to be recipients of CAR-T therapy and on corticosteroids at the time of SARS-CoV-2 detection. Additionally, co-infected patients showed higher rates of fever and pneumonia, required more oxygen support, were more likely to be receiving remdesivir therapy, and had higher hospitalization and intensive care unit (ICU) admission rates.

Table 1 Patient, disease, and SARS-CoV-2-related characteristics by co-infection diagnosis

Characteristics	No co-infection	Co-infection	p value
Number of patients, n (%)	628 (91)	64 (9)	
Age in years, median (range)	63 (19–93)	67 (30–92)	0.34
≥ 65 years, n (%)	292 (47)	35 (55)	0.26
Sex, female, n (%)	260 (42)	27 (42)	1.00
Active smoker, n (%)	49 (8)	6 (9)	0.84
Hypertension, n (%)			0.12
Yes	218 (35)	29 (45)	
Unknown	9 (1)	2 (3)	
Cardiopathy, n (%)			0.007
Ischemic heart disease	95 (15)	19 (30)	
Heart failure	13 (2)	0	
Pneumopathy, n (%)			0.13
Yes	52 (8)	10 (16)	
Unknown	17 (3)	1 (2)	
Hematological disease, n (%)			0.64
Acute myeloid leukemia	90 (14)	10 (16)	
Acute lymphoid leukemia	28 (4)	2 (3)	
Myelodysplastic neoplasms	48 (8)	3 (5)	
Chronic myeloproliferative neoplasm	27 (4)	2 (3)	
Chronic lymphoid leukemia	55 (9)	4 (6)	
Non-Hodgkin B-cell lymphoma	193 (31)	22 (34)	
Non-Hodgkin T-cell lymphoma	16 (3)	0	
Multiple myeloma	119 (19)	18 (28)	
Hodgkin Lymphoma	34 (5)	3 (5)	
Non-malignant diseases	18 (3)	0	
Lines of treatment, median (range)	1 (0–6)	1.5 (0–9)	<0.001
Anti-CD20 antibodies, n (%)	185 (30)	20 (31)	0.88
Stem cell transplant, n (%)			0.14
Autologous	111 (18)	17 (27)	
Allogeneic	134 (21)	9 (14)	
CAR-T, n (%)	26 (4)	10 (16)	<0.001
Active treatment, n (%)	163 (26)	14 (22)	0.57
Steroid therapy n (%)	73 (12)	29 (45)	<0.001
SARS-CoV-2 vaccine doses, median (range)	3 (0–7)	3 (0.6)	0.58
≥ 3 doses, n (%)	480 (76)	46 (72)	0.51
Clinical COVID-19 characteristics, n (%)			
Fever	190 (30)	41 (64)	<0.001
Pneumonia	87 (14)	39 (61)	<0.001
Oxygen therapy	54 (9)	30 (47)	<0.001
Hospital admission	132 (21)	27 (42)	<0.001
ICU admission	8 (1)	9 (14)	<0.001
SARS-CoV-2 treatment, n (%)	430 (69)	50 (78)	0.15
Nirmatrelvir/Ritonavir	220 (35)	9 (14)	0.001
Remdesivir	213 (34)	41 (64)	<0.001
All-cause mortality at 6 months*, n/evaluable patients (%)	44/377 (12)	18/49 (37)	<0.001

CAR-T chimeric antigen receptor T-cell, ICU intensive care unit

*Censoring alive patients with at least 6 months of follow-up after SARS-CoV-2 detection

Co-infection characteristics

The overall cumulative incidence of co-infection with SARS-CoV-2 in this cohort was 9% (95% confidence interval [95%CI] 7–11). The median time between co-infection occurrence and SARS-CoV-2 detection

was 1 day (interquartile range 0–13 days, range: –16–42 days). Five patients were diagnosed with a co-infection within 5 days before SARS-CoV-2, all with bacterial infections (one with concurrent viral and another fungal co-infection). Another three patients were still receiving

treatment for active/uncontrolled co-infection: one had a pulmonary fungal infection diagnosed 10 days before SARS-CoV-2 detection, another developed pneumonia by *P. aeruginosa* with bacteremia 12 days prior, and the third had ongoing *E. cloacae* cellulitis diagnosed 16 days previously. Finally, four patients with active COVID-19 had been diagnosed with a co-infection over one month.

Of the 64 patients with reported co-infection, six (9%) were clinically diagnosed (four with lobar pneumonia, one with septic arthritis, and one with a urinary tract infection; Table 2). Of the 58 remaining patients, 41 (70%) had one documented microbiological agent, 11 (19%) had two, five (9%) had three and one (2%) had four. At least one bacterial co-infection was detected in 64% ($n=41$), viral in 30% ($n=19$), and fungal in 13% ($n=8$). Among the 82 microbiological isolates, the most common sites of identification were the lower respiratory tract (27 agents, 33%), urinary tract (22 agents, 27%), and bloodstream (14 agents, 17%).

Of the 25 possible/confirmed LRTI cases, 24% ($n=6$) had bronchoalveolar lavage (BAL)-confirmed

co-infection, while others were diagnosed based on clinical and imaging findings and pathogen identification by sputum induction or upper respiratory tract swab. The most common agents were gram-negative bacteria ($n=11$, 41%), followed by CARV and molds ($n=7$, 22% each). Upper respiratory infections ($n=9$, 10%) were mostly viral, with one bacterial case. UTIs were predominantly caused by gram-negative (68%), led by *Escherichia coli* ($n=9$, 41%). Gram-positive bacteria, particularly coagulase-negative *Staphylococcus spp* ($n=6$, 43%), predominated in BSI.

Risk factors for co-infections

Variables identified in univariable analysis as significantly increasing the risk of co-infection were hypertension, cardiopathy, pneumopathy, malignant hematological diseases, number of treatment lines for hematological disease, CAR-T therapy, steroid treatment, fever and pneumonia at COVID-19 diagnosis, and need for oxygen therapy and hospital admission. In multivariable analysis, cardiopathy, CAR-T therapy, and

Table 2 Clinical and microbiological classification of co-infection during SARS-CoV-2 infection

Blood stream infection (BSI), CVC-related BSI [†] or viral infection	N= 14	Upper respiratory (swab, sputum)	N=9	Lower respiratory (sputum, BAL)	N= 17	Lower respiratory (sputum, BAL)	N= 14
Gram negative		Gram negative		Gram negative		Viruses	
<i>Campylobacter jejuni</i>	1	<i>Haemophilus influenzae</i>	1	<i>Escherichia coli</i>	1	Enterovirus	1
<i>Pseudomonas aeruginosa</i>	2	Viruses		<i>Haemophilus influenzae</i>	2	Influenza A	2
<i>Escherichia coli</i>	1	Rhinovirus/Enterovirus	3	<i>Moraxella catarrhalis</i>	1	Cytomegalovirus	1
<i>Salmonella enterica</i>	1	Influenza A	3	<i>Pseudomonas aeruginosa</i>	4	Syncytial Respiratory Virus	2
Gram positive		Syncytial Respiratory Virus	1	<i>Klebsiella oxytoca</i>	1	Rhinovirus	1
<i>Staphylococcus coagulase negative</i>	2	Parainfluenza	1	<i>Streptococcus pneumoniae</i>	1	Molds	
<i>Staphylococcus epidermidis</i>	3			<i>Enterobacter cloacae</i>	1	<i>Scedosporium apiospermum</i>	1
<i>Staphylococcus hominis</i>	1			Gram positive		<i>Aspergillus fumigatus</i>	2
Virus				<i>Rothia mucilaginosa</i>	1	Probable IFI	3
Cytomegalovirus	2			<i>Staphylococcus aureus</i>	1	Yeast	
Yeast				Clinically defined		<i>Pneumocystis jirovecii</i>	1
<i>Candida parapsilosis</i>	1			Pneumonia with consolidation	4		
Urinary tract	N= 23	Soft tissue and mucosa	N= 5	Feces/intestine	N= 5	Other sites	N= 1
Gram negative		Gram positive		Gram negative		Clinically defined	
<i>Aeromonas caviae</i>	1	<i>Streptococcus pyogenes</i>	1	<i>Clostridioides difficile</i>	2	Septic arthritis	1
<i>Enterobacter cloacae</i>	1	<i>Enterococcus faecalis</i>	1	<i>Campylobacter jejuni</i>	2		
<i>Escherichia coli</i>	9	Gram negative		Viruses			
<i>Proteus mirabilis</i>	2	<i>Enterobacter cloacae</i>	1	Enterovirus	1		
<i>Pseudomonas aeruginosa</i>	2	Viruses					
Gram positive		<i>Herpes simplex virus</i>	2				
<i>Enterococcus faecalis</i>	5						
<i>Enterococcus faecium</i>	1						
<i>Streptococcus anginosus</i>	1						
Clinically defined							
Urinary tract infection	1						

CAR-T chimeric antigen receptor T-cell, CI confidence interval, OR odds ratio, IFI invasive fungal infection

pneumonia development were independently associated with co-infection (Table 3).

Causes of death and impact of co-infection on non-relapse mortality

At a median follow-up of 223 days, 82 patients (12%) died at a median of 59 days (range, 4–412 days) after SARS-CoV-2 detection. In 35 patients (42%), progression/relapse of hematologic disease was the primary cause of death, while 26 (32%) died from COVID-19-related

complications, nine (11%) from cellular-therapy related complications and the remaining 12 cases (15%) from other causes (seven from comorbid diseases, two from secondary malignancies, and three from unknown/unreported causes). The overall COVID-related mortality rate was therefore 3.7% (26/692) in the current series.

Of the 64 co-infected patients, 24 patients died. In 11 patients (17%) this was primarily due to co-infection: seven succumbed to active pulmonary infections (three fungal, two fungal with bacterial co-infections, one

Table 3 Factors for increased risk of co-infection during SARS-CoV-2 infection at 60 days after SARS-CoV-2 diagnosis

Variables	Groups	Co-infection (Fine and Gray analysis)			
		Univariate		Multivariate	
		HR (CI 95%)	p	HR (CI 95%)	p
Age	< 64 years	Reference			
	≥ 64 years	1.27 (0.77–2.10)	0.34	-	-
Sex	Male	Reference			
	Female	1.11 (0.68–1.84)	0.67	-	-
Smoker	No	Reference			
	Yes	1.28 (0.56–2.94)	0.56	-	-
Hypertension	No/Unknown	Reference			
	Yes	1.65 (1.00–2.71)	0.048	Not significant*	-
Cardiopathy	No	Reference			
	Yes	1.94 (1.13–3.34)	0.017	1.69 (1.01–2.83)	0.048
Pneumopathy	No/Unknown	Reference			
	Yes	2.03 (1.05–3.96)	0.037	Not significant*	-
Disease	Benign	Reference			
	Acute leukemia	22.1 (10.5–46.7)	< 0.001	Not significant*	-
	MDS/MPN	9.75 (2.88–33.0)	< 0.001		-
	Lymph	26.4 (15.3–45.4)	< 0.001		-
Lines of treatment	(continuous)	1.26 (1.10–1.44)	0.001	Not included	-
	< 3	Reference			
Anti-CD20 antibodies	≥ 3	2.20 (1.28–3.78)	0.004	Not significant*	-
	No	Reference			
Transplant	Yes	1.13 (0.67–1.91)	0.65	-	-
	No	Reference			
CAR-T	Autologous	1.58 (0.89–2.79)	0.12	-	-
	Allogeneic	0.65 (0.30–1.39)	0.27	-	-
	No	Reference			
Active treatment	Yes	3.77 (1.98–7.18)	< 0.001	3.42 (1.91–6.14)	< 0.001
	No	Reference			
Steroid treatment	Yes	0.63 (0.33–1.21)	0.17	-	-
	No	Reference			
Fever	Yes	5.06 (3.08–8.32)	< 0.001	1.61 (0.87–3.01)	0.13
	No	Reference			
Pneumonia	Yes	3.73 (2.22–6.26)	< 0.001	Not significant*	-
	No	Reference			
Oxygen	Yes	7.83 (4.70–13.0)	< 0.001	5.54 (2.86–10.7)	< 0.001
	No	Reference			
Hospital admission	Yes	7.46 (4.56–12.2)	< 0.001	Not significant*	-
	No	Reference			
	Yes	2.56 (1.55–4.22)	< 0.001	Not significant*	-
	No	Reference			

CAR-T chimeric antigen receptor T-cell, CI confidence interval, HR hazard ratio

*Excluded during the stepwise analysis from the final multivariate model

CARV and one CMV pneumonitis), three to bacterial UTIs, and one to disseminated herpes simplex infection. Of the remaining 13 patients, five (8%) died due to COVID-19 without active co-infection, four (6%) from disease relapse, and four (6%) from other complications.

Non-relapse mortality and risk factors

The cumulative incidence of NRM at day 90 and day 180 after SARS-CoV-2 detection was 4.3% (95%CI 2.7–5.8) and 6.2% (95%CI 4.2–8.2), respectively. Table 4 shows univariable and multivariable Fine-Gray analysis of NRM. We observed that co-infection, age ≥ 64 years old, active treatment for hematological disease, and corticosteroid use were independently associated with increased NRM. Overall survival at day 180 after SARS-CoV-2 detection was significantly lower in patients with co-infection

(Fig. 1). The cumulative incidence of NRM according to co-infection, age, active treatment and active corticosteroids is represented in Fig. 2a-d.

Univariable and multivariable analysis of the conditions associated with increased NRM in patients with co-infection showed that corticosteroid use significantly increased NRM (Table 5). Figure 3a represents NRM according to corticosteroid use at COVID-19 diagnosis. Regarding infectious agents, neither bacterial ($p=0.96$), fungal ($p=0.08$) nor viral ($p=0.46$) co-infection significantly increased NRM (Fig. 3b), although higher mortality was observed in patients with fungal co-infection. No significant differences in NRM were found between patients with gram-positive ($p=0.71$), gram-negative ($p=0.78$) or both types ($p=0.16$) of bacterial infection.

Table 4 Factors for increased risk of non-relapse mortality during SARS-CoV-2 infection at 180 days

Variables	Groups	Non-relapse mortality (Fine and Gray analysis)			
		Univariate		Multivariate	
		HR (CI 95%)	p	HR (CI 95%)	p
Co-infection	No	Reference			
	Yes	6.37 (3.26–12.4)	< 0.001	4.28 (2.06–8.90)	< 0.001
Age	< 64 years	Reference			
	≥ 64 years	3.20 (1.52–6.76)	0.002	2.55 (1.17–5.56)	0.018
Sex	Male	Reference			
	Female	1.12 (0.58–2.16)	0.74	-	-
Smoker	No	Reference			
	Yes	1.77 (0.72–4.36)	0.22	-	-
Hypertension	No/Unknown	Reference			
	Yes	2.50 (1.31–4.77)	0.006	Not significant*	-
Cardiopathy	No	Reference			
	Yes	2.59 (1.32–5.08)	0.006	Not significant*	-
Pneumopathy	No/Unknown	Reference			
	Yes	2.04 (0.85–4.89)	0.11	-	-
Disease	Benign	Reference			
	Acute leukemia	28.6 (12.7–64.6)	< 0.001	Not significant*	-
	MDS/MPN	19.9 (6.82–58.0)	< 0.001		-
	Lymph	22.1 (11.7–41.5)	< 0.001		-
Lines of treatment	(continuous)	1.09 (0.93–1.28)	0.28	-	-
	< 3	Reference			
	≥ 3	0.74 (0.29–1.90)	0.54	-	-
Anti-CD20 antibodies	No	Reference			
	Yes	1.47 (0.76–2.84)	0.26	-	-
Transplant	No	Reference			
	Autologous	0.47 (0.17–1.35)	0.16	-	-
	Allogeneic	0.58 (0.25–1.38)	0.22		
CAR-T	No	Reference			
	Yes	1.08 (0.26–4.47)	0.92	-	-
Active treatment	No	Reference			
	Yes	2.11 (1.11–4.04)	0.023	2.13 (1.06–4.27)	0.034
Steroid treatment	No	Reference			
	Yes	5.88 (3.09–11.2)	< 0.001	3.21 (1.54–6.69)	0.002

CAR-T chimeric antigen receptor T-cell, CI confidence interval, HR hazard ratio

*Excluded during the stepwise analysis from the final multivariate model

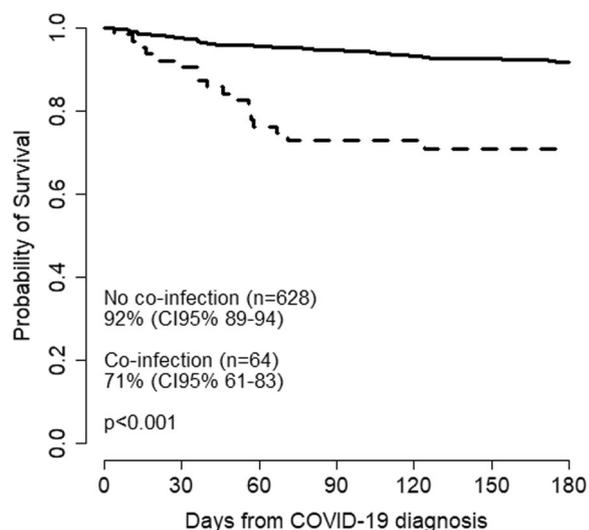


Fig. 1 Representation of overall survival of SARS-CoV-2 infected patients according to the presence or absence of co-infection

Discussion

This study reports a co-infection incidence of 9% (30% with polymicrobial infections) in a large cohort of hematologic patients with SARS-CoV-2 infection. The most common co-infection sites were the lower respiratory tract, urinary tract and bloodstream, and the most common pathogens corresponded to bacterial infection. Multivariable analysis identified ischemic cardiopathy, CAR-T therapy and pneumonia as conditions related to co-infection during SARS-CoV-2 infection. Co-infection was associated with higher NRM. Other conditions correlated with higher NRM were age ≥ 64 years old, active onco-hematological therapy and corticosteroid use. Interestingly, the use of corticosteroids was the only condition associated with higher NRM among co-infected cases. This study can deepen understanding of the characteristics, clinical behavior and conditions impacting survival in SARS-CoV-2 Co-infection in severely immunocompromised patients in the current Omicron era.

There are some limitations to our analysis that warrant consideration. The retrospective nature of the data collection may have introduced reporting and/or uncontrolled bias, and since antibody screening before enrollment was not performed, previous SARS-CoV-2 infections may not have been documented. Additionally, co-infection could have been underreported and/or underdiagnosed since only 24% of patients received BAL and most cases were managed in outpatient settings. Co-infection diagnosis and management were subject to physician and center discretion, which may have introduced some variability and potentially alter the generalizability of our results. Furthermore, by using the positive PCR result as the date of SARS-CoV-2 infection onset, the time between COVID-19 and co-infection was likely underestimated.

Although the severity of COVID-19 is expected to influence the risk of co-infection, assessing this relationship is challenging due to the bidirectional and deeply intertwined nature of these factors, and was beyond the scope of this research. Nevertheless, our study has notable strengths. The large sample size allowed for adequate comparison of relevant clinical variables associated with co-infection development and enabled us to pinpoint subgroups with worse outcomes. Furthermore, by collecting data specific to co-infection, we were able to characterize the location and type of agents involved, which could prove useful to physicians in routine clinical practice.

The incidence of co-infection is seldom reported in hematological patients, even in a recent large Omicron VOC cohort [17]. A study of hospitalized patients across the general population reported a 7% rate of microbiologically confirmed co-infection [18], while another in hospitalized patients with respiratory co-infection found a 16% co-infection rate, of which just 2% of cases exhibited more than one pathogen [7]. These data support the immunocompromised state of our patients, considering that although 77% of our cohort remained ambulatory, we still observed a 9% co-infection incidence and 30% multiagent rate. Unfortunately, comparisons between the general population and hematological patients are hindered by the heterogeneity of studies, especially regarding agents studied, VOC eras and available SARS-CoV-2 treatments, resulting in a wide range of review-reported co-infection rates spanning from $< 1\%$ to almost half of patients [19–21]. Nonetheless, a study focused on cancer patients (including hematological malignancies) with 51% of patients hospitalized at COVID-19 diagnosis found a co-infection rate of 17%, and the authors reported a higher risk for co-infection in hematological patients than in solid tumor patients [4].

In addition to the higher incidence of co-infection in hematologic patients and cellular therapy recipients, the type of agent involved also merits attention. Bacterial infections clearly predominate in general population studies. Rates of fungal co-infection vary, with 8% reported as fungal in one study [18] and $< 0.1\%$ in another [6], contrasting with the 13% found herein. A study of viral co-infection in the general population reported a 20% rate [22], which is closer to the 30% we report. In patients requiring ICU admission, however, viral co-infection may be even higher [23]. In cancer patients, hematological malignancies seem to increase the risk of bacterial and viral co-infection, while the risk of fungal co-infection is statistically similar to that of patients with solid tumors [4]. Finally, one study found that co-infection in hospitalized general population patients increased mortality only if hospital-acquired [18], while another found no statistically significant increase in mortality [7].

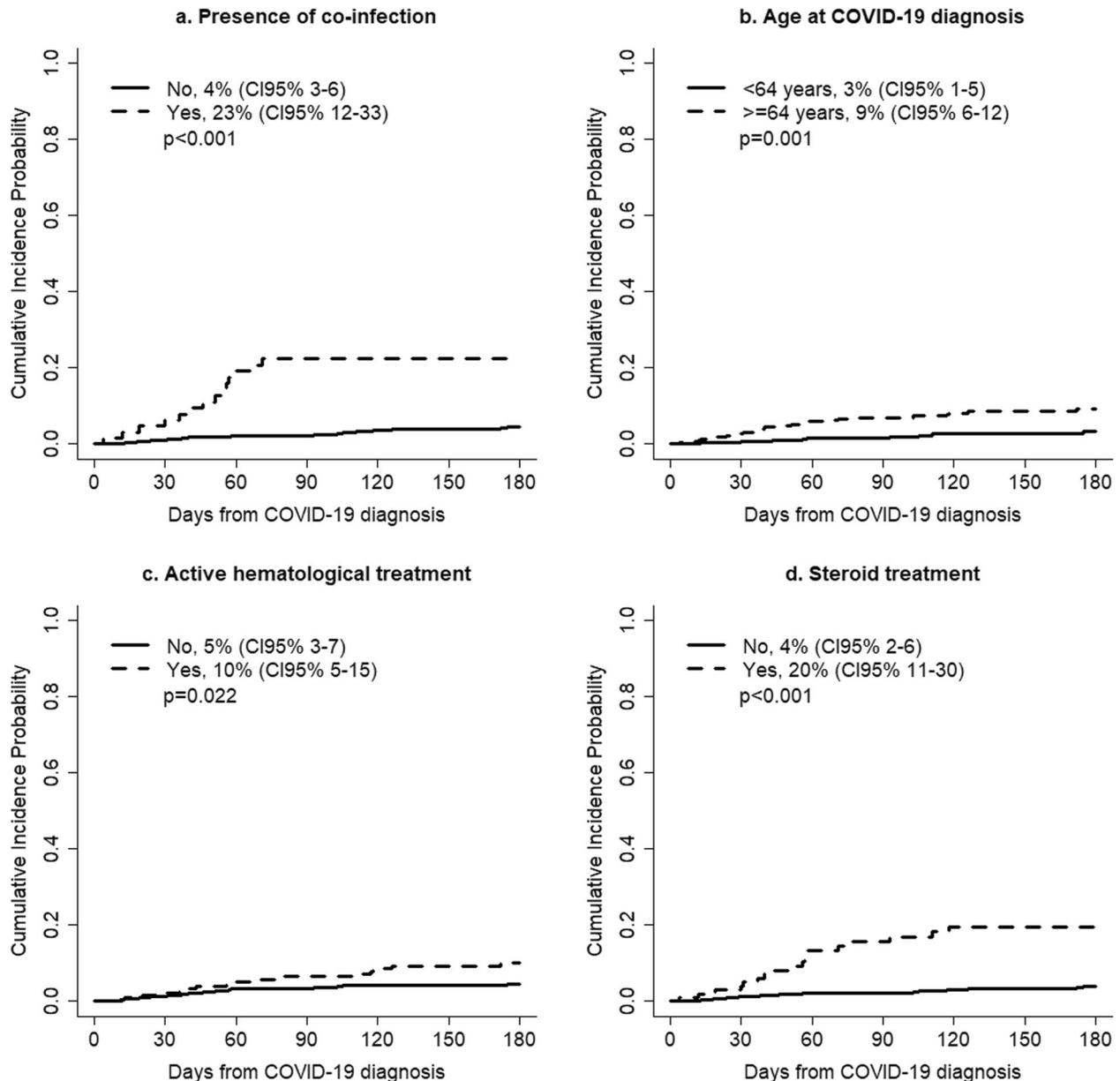


Fig. 2 Non-relapse mortality of SARS-CoV-2 patients according to (a) presence of co-infection, (b) age, (c) active hematological treatment, and (d) steroid treatment

Nevertheless, co-infection increased all-cause mortality in a study with cancer patients [4], which is echoed in our findings of increased NRM. Taking into account study heterogeneity, the overall evidence suggests that co-infection diagnoses during COVID-19 are more frequent in hematologic patients and can worsen clinical outcomes. Therefore, co-infection should be carefully ruled out in this vulnerable population.

Although LRT was the most reported site of possible/confirmed co-infection, only 24% of patients underwent BAL to confirm microbiological diagnosis. In a study with a large proportion of hematologic patients with SARS-CoV-2 infection, BAL was useful in diagnosing not only

co-infection, but also non-infectious causes [24], which may help in tailoring SARS-CoV-2 management. Taking into account the high yield of BAL in critical and non-critical COVID-19 patients [25], and that this procedure led to changes in clinical management in up to 52% of immunocompromised hosts with a LRTI [26], we found a lower percentage of microbiological identifications than might be expected. This can be partly explained by the preventive transmission measures adopted to minimize viral transmission to healthcare providers during the pandemic period, which precluded performing BAL in this setting. Nevertheless, given that pneumonia was identified as a risk factor for co-infection in our cohort,

Table 5 Univariable and multivariable analyses of conditions associated with increased 180-day co-infection non-relapse mortality in patients with co-infections during SARS-CoV-2 infection

Variables	Groups	Non-relapse mortality (Fine and Gray analysis)			
		Univariate		Multivariate	
		HR (CI 95%)	p	HR (CI 95%)	p
Age	< 64 years	Reference			
	≥ 64 years	4.96 (1.12–22.0)	0.035	3.23 (0.92–11.3)	0.067
Sex	Male	Reference			
	Female	1.37 (0.49–3.86)	0.55	-	-
Smoker	No	Reference			
	Yes	0.63 (0.10–4.03)	0.63	-	-
Hypertension	No/Unknown	Reference			
	Yes	2.72 (0.95–7.80)	0.063	Not significant*	-
Cardiopathy	No	Reference			
	Yes	2.75 (0.99–7.65)	0.053	Not significant*	-
Pneumopathy	No/Unknown	Reference			
	Yes	1.68 (0.49–5.80)	0.41	-	-
Disease	Acute leukemia	Reference			
	MDS/MPN	2.31 (0.37–14.4)	0.37	-	-
	Lymph	1.31 (0.28–6.06)	0.73	-	-
Lines of treatment	(continuous)	0.82 (0.59–1.14)	0.24	-	-
	< 3	Reference			
Anti-CD20 antibodies	≥ 3	0.34 (0.08–1.50)	0.15	-	-
	No	Reference			
Transplant	Yes	1.68 (0.59–4.73)	0.33	-	-
	No	Reference			
CAR-T	Autologous	0.34 (0.08–1.50)	0.15	-	-
	Allogeneic	0.33 (0.04–2.39)	0.27	-	-
Active treatment	No	Reference			
	Yes	0.83 (0.20–3.53)	0.80	-	-
Steroid treatment	No	Reference			
	Yes	1.45 (0.47–4.50)	0.52	-	-
Bacterial co-infection	No	Reference			
	Yes	3.51 (1.13–10.9)	0.030	3.33 (1.11–9.99)	0.032
Fungal co-infection	No	Reference			
	Yes	1.02 (0.35–3.02)	0.97	-	-
Viral co-infection	No	Reference			
	Yes	2.65 (0.98–7.19)	0.055	2.35 (0.93–5.91)	0.070
Co-infection agents	No	Reference			
	Yes	0.62 (0.17–2.26)	0.47	-	-
Co-infection agents	1	Reference			
	≥ 2	2.18 (0.79–6.03)	0.13	-	-

CAR-T chimeric antigen receptor T-cell, CI confidence interval, HR hazard ratio

*Excluded during the stepwise analysis from the final multivariate model

and considering the available evidence, we recommend that BAL be performed as part of the diagnostic algorithm in hematological patients and cellular-therapy recipients with SARS-CoV-2 and suspected pneumonia.

Among risk factors for co-infection, CAR-T therapy was associated with higher risk, which is likely related to the profound immunosuppressed status of these patients [27], especially due to prolonged B-cell aplasia and hypogammaglobulinemia. Additionally, it is well documented that CAR-T recipients have lower humoral immune responses

and faster antibody waning after complete SARS-CoV-2 vaccination [28]. These data could bring insight into the development of severe COVID-19 and prolonged SARS-CoV-2 shedding found in CAR-T cells [29], which may favor bacterial and fungal overgrowth, as well as concurrent viral reactivation and/or infection. Possible/confirmed LRTI was also associated with an increased risk of co-infection, which suggests that SARS-CoV-2 may directly alter the bronchial mucosa or pulmonary defensive mechanisms, as has been described in other CARVs [30, 31].

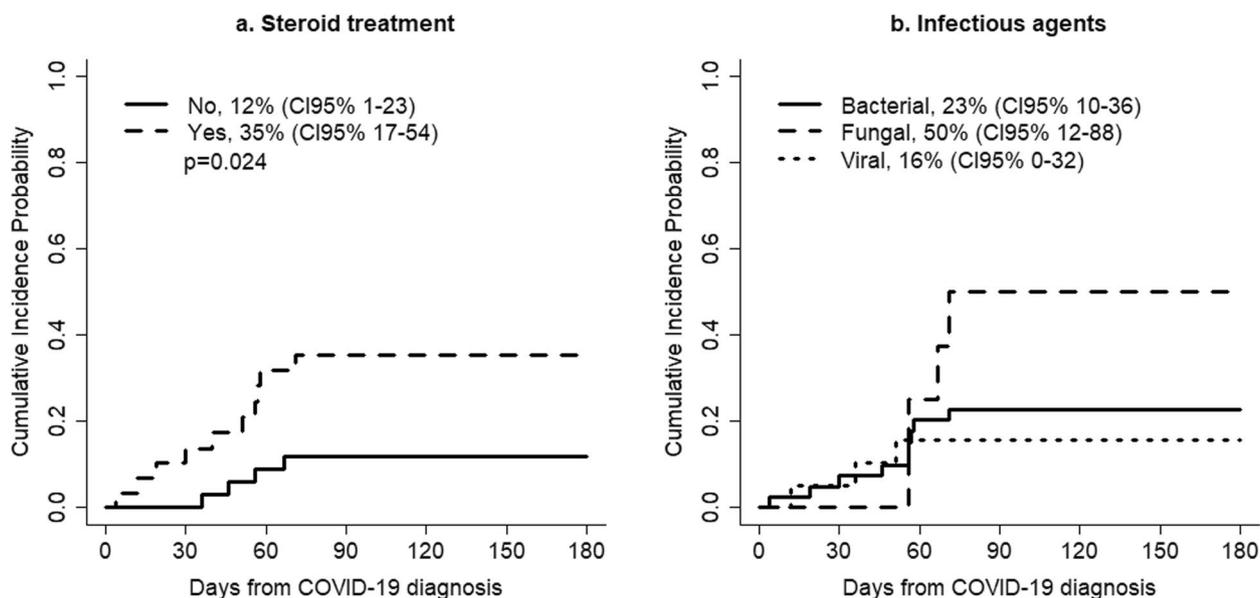


Fig. 3 Non-relapse mortality of SARS-CoV-2 co-infected patients according to (a) steroid treatment and (b) co-infective agent

Invasive fungal infection (IFI) co-infections are frequently reported in the context of other CARVs in the allo-SCT setting [32, 33], particularly in cases of CARV progression to LRTI [34]. The low number of IFI co-infections ($n=6$) in the current cohort impacted on our ability to find statistical significance in NRM; nonetheless, other studies have reported increased mortality in cancer patients [4]. Therefore, we recommend special caution and close monitoring of fungal co-infections during active SARS-CoV-2 infection. Another noteworthy condition associated with higher risk of co-infection was the presence of prior cardiopathy. SARS-CoV-2 itself can induce myocardial injury, arrhythmias and acute coronary syndrome [35]. Given that cardiopathy is linked to immune dysregulation [36] and an increased rate of respiratory and other types of infections [37], this association in hematological patients warrants further research.

We also identified age ≥ 64 years old and active treatment for hematological disease as risk factors for NRM, aligning with previous findings where these conditions have been commonly reported as predictors of adverse outcomes in hematology patients with COVID-19 [38]. A key finding of this study was corticosteroid use at SARS-CoV-2 detection as a covariate for NRM in both the whole cohort and in co-infected patients. While the RECOVERY trial demonstrated a significant but modest survival benefit for corticosteroids in the general population with COVID-19 [39], immunosuppressed patients were systematically excluded. Several studies in onco-hematological patients, including ours [2], have suggested a negative effect of corticosteroids not only in SARS-CoV-2 [40] but also in other CARVs [41].

These findings further emphasize the need for judicious use of corticosteroids during COVID-19 infection in the absence of prospective randomized controlled trials in this vulnerable population.

Conclusions

SARS-CoV-2 co-infections are relatively frequent in hematologic patients and cellular therapy recipients in the Omicron era and significantly increase NRM. Patients with ischemic cardiopathy, those presenting with possible/confirmed LRTI, and recipients of CAR-T are at higher risk of developing co-infection, whereas older age (≥ 64 years old) and active hematological therapy showed higher NRM. Finally, corticosteroid use was associated with higher NRM across the whole cohort and in those with co-infection. Improvements in the identification and management of concurrent infections during SARS-CoV-2 are needed to further decrease morbimortality in hematologic patients.

Abbreviations

95%CI	95% Confidence interval
allo-SCT	Allogeneic stem cell transplant
BAL	Bronchoalveolar lavage
BSI	Bloodstream infection
CARV	Community-acquired respiratory virus
CAR-T	Chimeric antigen receptor T-cell
CMV	Cytomegalovirus
COVID-19	Coronavirus disease 2019
GETH-TC	Spanish Group on Hematopoietic Transplant and Cellular Therapy
GRUCINI	Infectious Complications Subcommittee
ICU	Intensive care unit
LRTU	Lower respiratory tract infection
OR	Odds ratio
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCT	Stem cell transplantation
UTI	Urinary tract infection
VOC	Variant of concern

Acknowledgements

REDCap is developed and supported by the Vanderbilt Institute for Clinical and Translational Research. We sincerely thank the Spanish Society of Hematology (SEHH) for their support in study diffusion and all hematology units from participating centers for their commitment. Finally, we also want to thank patients, nurses, and study coordinators for their contributions. Infectious Complications Subcommittee of the Spanish Hematopoietic Stem Cell Transplantation Cell Therapy Group (GETH-TC) Pedro Chorão^{1,2,*}, Alex Avendaño³, Inmaculada Heras⁴, Francesco Aiello⁵, Mireia Micó-Cerdá^{6,7}, Anna Arrufat Bel⁸, Valentín García-Gutierrez⁹, María T. Olave¹⁰, Marina Acera Gómez³, Ildefonso Espigado¹¹, Marian Cuesta-Casas¹², Clara González-Santillana¹³, José Ángel Hernández-Rivas¹⁴, Alicia Roldán-Pérez^{15,16}, Jorge Labrador^{17,18}, Marta Villalba^{1,2}, Lourdes Vázquez³, Carolina García Vidal⁵, Rodrigo Martino⁸, Javier López-Jiménez⁹, Ángel Cedillo¹⁹, Carlos Solano^{6,7,20}, Irene García-Cadenas⁸, and José Luis Piñana^{6,7}

Authors' contributions

All authors contributed to data retrieval. P.C. and J.L.P. performed the statistical analysis. P.C. and J.L.P. drafted the manuscript and integrated changes and suggestions made by A.V., I.H., F.A., M.M.C., A.A.B., V.G.G., M.T. O., M.A.G., I.E., M.C.C., C.G.S., J.A.H.R., A.R.P., J.L., M.V., L.V., C.G.V., R.M., J.L.J., A.C., C.S., I.G.C., all of whom also reviewed the manuscript and contributed to the final version.

Funding

No funding was received.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the GETH-TC secretariate upon reasonable request (<https://www.geth.es/contacto>).

Declarations

Ethics approval and consent to participate

The local Research Ethics Committee of the Hospital Clínico Universitario de Valencia approved the study (reference code 35.21), which was carried out in accordance with the Declaration of Helsinki and its amendments, and applicable national regulatory requirements. The Research Ethics Committee of the Hospital Clínico Universitario de Valencia approved the waiver of informed consent for study inclusion.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹Hematology Department, Hospital Universitari I Politècnic La Fe, Av. Fernando Abril Martorell, 106, 46026 València, Spain

²Hematology Research Group, Institut d'Investigació Sanitària La Fe, València, Spain

³Hematology Department, University Hospital of Salamanca (HUS/IBSAL), CIBERONC and Cancer Research Institute of Salamanca-IBMCC (USAL-CSIC), Salamanca, Spain

⁴Hematology Division, Hospital Morales Meseguer, Murcia, Spain

⁵Infectious Disease Division, Hospital Clinic, Barcelona, Spain

⁶Hematology Department, Hospital Clínico Universitario de Valencia, Valencia, Spain

⁷INCLIVA Biomedical Research Institute, Valencia, Spain

⁸Hematology Division, Hospital de La Santa Creu I Sant Pau, Barcelona, Spain

⁹Hematology Division, Hospital Ramon y Cajal, Madrid, Spain

¹⁰Hematology Division, Hospital Clínico Universitario Lozano Blesa, IIS Aragón, Saragossa, Spain

¹¹Hematology Division, Hospital Universitario Virgen Macarena– Hospital Universitario Virgen del Rocío, IBI-S-CSC, Universidad de Sevilla, Seville, Spain

¹²Hematology Division, Hospital Regional Universitario Carlos Haya, Málaga, Spain

¹³Hematology Division, Hospital de Fuenlabrada, Madrid, Spain

¹⁴Hematology Division, Hospital Universitario Infanta Leonor, Madrid, Spain

¹⁵Hematology Division, Hospital Universitario Infanta Sofía, Madrid, Spain

¹⁶Department of Medicine, Universidad Europea de Madrid, Madrid, Spain

¹⁷Research Unit, Hospital Universitario de Burgos, Burgos, Spain

¹⁸Hematology Department, Hospital Universitario de Burgos, Burgos, Spain

¹⁹Hematopoietic Stem Cell Transplantation and Cell Therapy Group (GETH-TC) Office, Madrid, Spain

²⁰Department of Medicine, School of Medicine, University of Valencia, Valencia, Spain

Received: 11 August 2024 / Accepted: 26 June 2025

Published online: 25 July 2025

References

- Piñana JL, Heras I, Aiello TF, García-Cadenas I, Vazquez L, Lopez-Jimenez J, et al. Remdesivir or nirmatrelvir/ritonavir therapy for omicron SARS-CoV-2 infection in hematological patients and cell therapy recipients. *Viruses*. 2023;15(10):2066.
- Piñana JL, Vazquez L, Heras I, Aiello TF, López-Corral L, Arroyo I, et al. Omicron SARS-CoV-2 infection management and outcomes in patients with hematologic disease and recipients of cell therapy. *Front Oncol*. 2024;19(14):1389345.
- Piñana JL, Pérez A, Chorão P, Guerreiro M, García-Cadenas I, Solano C, et al. Respiratory virus infections after allogeneic stem cell transplantation: Current understanding, knowledge gaps, and recent advances. *Transpl Infect Dis*. 2023;25(5):e14117.
- Satyanarayana G, Enriquez KT, Sun T, Klein EJ, Abidi M, Advani SM, et al. Coinfections in patients with cancer and COVID-19: a COVID-19 and Cancer Consortium (CCC19) study. *Open Forum Infect Dis*. 2022;9(3):ofac037.
- Averbuch D, De La Camara R, Tridello G, Knelange NS, Bykova TA, Iversen M, et al. Risk factors for a severe disease course in children with SARS-COV-2 infection following hematopoietic cell transplantation in the pre-Omicron period: a prospective multinational Infectious Disease Working Party from the European Society for Blood and Marrow Transplantation group (EBMT) and the Spanish Group of Hematopoietic Stem Cell Transplantation (GETH) study. *Bone Marrow Transplant*. 2023;58(5):558–66.
- Hughes S, Troise O, Donaldson H, Mughal N, Moore LSP. Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting. *Clin Microbiol Infect*. 2020;26(10):1395–9.
- Ma L, Wang W, Le Grange JM, Wang X, Du S, Li C, et al. Coinfection of SARS-CoV-2 and Other Respiratory Pathogens. *Infect Drug Resist*. 2020;13:3045–53.
- Ministerio de Sanidad, Centro de Coordinación de Alertas y Emergencias Sanitarias. Actualización de la situación epidemiológica de las variantes de SARS-CoV-2 en España. 2022. Available from: https://www.sanidad.gob.es/pr ofesionales/saludPublica/ccayes/alertasActual/nCov/documentos/COVID19_Actualizacion_variantes_20220523.pdf.
- Centres for Diseases Control and Prevention. CDC/NHSN surveillance definitions for specific types of infections. 2024. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf.
- Centres for Diseases Control and Prevention. Bloodstream Infection Event (Central Line-Associated Bloodstream Infection and Non-central Line Associated Bloodstream Infection). 2024. Available from: https://www.cdc.gov/nhsn/pdfs/pscmanual/4psc_clabscurrent.pdf.
- Centres for Diseases Control and Prevention. Urinary Tract Infection (Catheter-Associated Urinary Tract Infection [CAUTI] and Non-Catheter-Associated Urinary Tract Infection [UTI]) Events. 2024. Available from: <https://www.cdc.gov/nhsn/pdfs/pscmanual/7pscscauticurrent.pdf>.
- Centres for Diseases Control and Prevention. Pneumonia (Ventilator-associated [VAP] and non-ventilator-associated Pneumonia [PNEU]) Event. 2024. Available from: <https://www.cdc.gov/nhsn/pdfs/pscmanual/6pscvapcurrent.pdf>.
- Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the European organization for research and treatment of cancer and the mycoses study group education and research consortium. *Clin Infect Dis*. 2020;71(6):1367–76.

14. Meersseman W, Lagrou K, Spriet I, Maertens J, Verbeken E, Peetermans WE, et al. Significance of the isolation of *Candida* species from airway samples in critically ill patients: a prospective, autopsy study. *Intensive Care Med.* 2009;35(9):1526–31.
15. Ljungman P, Boeckh M, Hirsch HH, Josephson F, Lundgren J, Nichols G, et al. Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials: Table 1. Snyderman DR, editor. *Clin Infect Dis.* 2017;64(1):87–91.
16. Hirsch HH, Martino R, Ward KN, Boeckh M, Einsele H, Ljungman P. Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis and treatment of human respiratory syncytial virus, parainfluenza virus, metapneumovirus, rhinovirus, and coronavirus. *Clin Infect Dis.* 2013;56(2):258–66.
17. Blennow O, Salmanton-García J, Nowak P, Itri F, Van Doesum J, López-García A, et al. Outcome of infection with omicron SARS-CoV-2 variant in patients with hematological malignancies: an EPICOVIDEHA survey report. *Am J Hematol.* 2022;97(8):E312–7.
18. García-Vidal C, Sanjuan G, Moreno-García E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. *Clin Microbiol Infect.* 2021;27(1):83–8.
19. Musuza JS, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: a systematic review and meta-analysis. Huber VC, editor. *PLoS One.* 2021;16(5):e0251170.
20. Lai CC, Wang CY, Hsueh PR. Co-infections among patients with COVID-19: the need for combination therapy with non-anti-SARS-CoV-2 agents? *J Microbiol Immunol Infect.* 2020;53(4):505–12.
21. Feldman C, Anderson R. The role of co-infections and secondary infections in patients with COVID-19. *Pneumonia.* 2021;13(1):5.
22. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of Co-infection between SARS-CoV-2 and other respiratory pathogens. *JAMA.* 2020;323(20):2085.
23. Saade A, Moratelli G, Azoulay E, Darmon M. Herpesvirus reactivation during severe COVID-19 and high rate of immune defect. *Infect Dis Now.* 2021;51(8):676–9.
24. Franklin A, John TM, Khawaja F, Jiang Y, Yezpez E, Ahuja J, et al. Utility of bronchoalveolar lavage for the diagnosis and management of COVID-19 in patients with cancer. *J Infect Dis.* 2023;228(11):1549–58.
25. Tomassetti S, Ciani L, Luzzi V, Gori L, Trigiani M, Giuntoli L, et al. Utility of bronchoalveolar lavage for COVID-19: a perspective from the Dragon consortium. *Front Med.* 2024;2(11):1259570.
26. Jahn K, Karakioulaki M, Schumann DM, Hirsch HH, Leuzinger K, Grize L, et al. Impact of bronchoalveolar lavage on the management of immunocompromised hosts. *Eur J Intern Med.* 2024;120:52–61.
27. Stewart AG, Henden AS. Infectious complications of CART-cell therapy: a clinical update. *Ther Adv Infect Dis.* 2021;8:204993612110367.
28. Piñana JL, Martino R, Vazquez L, López-Corral L, Pérez A, Chorão P, et al. SARS-CoV-2-reactive antibody waning, booster effect and breakthrough SARS-CoV-2 infection in hematopoietic stem cell transplant and cell therapy recipients at one year after vaccination. *Bone Marrow Transplant.* 2023;58(5):567–80.
29. Dioverti V, Salto-Alejandre S, Haidar G. Immunocompromised patients with protracted COVID-19: a review of “Long Persisters.” *Curr Transplant Rep.* 2022;9(4):209–18.
30. Boeckh M. The challenge of respiratory virus infections in hematopoietic cell transplant recipients. *Br J Haematol.* 2008;143(4):455–67.
31. Alonso JM. Immunité et physiopathologie des infections de l'arbre respiratoire. *Médecine Mal Infect.* 2008;38(8):433–7.
32. Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. *Blood.* 2002;100(13):4358–66.
33. Garcia-Vidal C, Upton A, Kirby KA, Marr KA. Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation. *Clin Infect Dis.* 2008;47(8):1041–50.
34. Martino R, Piñana JL, Parody R, Valcarcel D, Sureda A, Brunet S, et al. Lower respiratory tract respiratory virus infections increase the risk of invasive aspergillosis after a reduced-intensity allogeneic hematopoietic SCT. *Bone Marrow Transplant.* 2009;44(11):749–56.
35. Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol.* 2020;17(9):543–58.
36. He B, Quan LP, Cai CY, Yu DY, Yan W, Wei QJ, et al. Dysregulation and imbalance of innate and adaptive immunity are involved in the cardiomyopathy progression. *Front Cardiovasc Med.* 2022;6(9):973279.
37. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-Nepriylsin Inhibition versus Enalapril in Heart Failure. *N Engl J Med.* 2014;371(11):993–1004.
38. Langerbeins P, Hallek M. COVID-19 in patients with hematologic malignancy. *Blood.* 2022;140(3):236–52.
39. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med.* 2021;384(8):693–704.
40. Garcia-Vidal C, Puerta-Alcalde P, Mateu A, Cuesta-Chasco G, Meira F, Lopera C, et al. Prolonged viral replication in patients with hematologic malignancies hospitalized with COVID-19. *Haematologica.* 2022;107(7):1731–5.
41. Damlaj M, Bartoo G, Cartin-Ceba R, Gijima D, Alkhateeb HB, Merten J, et al. Corticosteroid use as adjunct therapy for respiratory syncytial virus infection in adult allogeneic stem cell transplant recipients. *Transpl Infect Dis.* 2016;18(2):216–26.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.