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Beyond the Usual Suspects: RSV Infection in Patients With Hematological Malignancies Compared to Influenza and SARS-COV-2—A Report From the EPICOVIDEHA/EPIRESEHA Registry

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To the Editor,

Respiratory syncytial virus (RSV) is a major cause of acute respiratory infections and seasonal hospitalisations, particularly among immunocompromised adults [1]. In patients with hematological malignancies, RSV can cause severe complications, including pneumonia, respiratory failure, and death, especially in those with lymphopenia, recent HSCT, or comorbidities [2]. Although antivirals, monoclonal antibodies, and vaccines exist for other high-risk groups, their efficacy in this population remains uncertain [3]. Screening and diagnostic protocols are inconsistent, treatments are often empiric, and hematological patients are largely excluded from clinical trials. Moreover, comparative data versus influenza and SARS-CoV-2 are limited, impeding the development of targeted, evidence-based prevention and management strategies for this vulnerable group [4].

This study used the EPICOVIDEHA/EPIRESEHA registry [5] to describe RSV infection in adults with hematological malignancies

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(Jan 2023–Dec 2024), comparing it with influenza and SARS-CoV-2. Data were collected via the international registry (NCT04733729), with ethical approval from Fondazione Policlinico Gemelli (ID 3226); consent was waived due to anonymization.

Eligible participants were adults (≥18 years) with laboratory-confirmed RSV and active hematological malignancy treatment within the past 5 years. Exclusions were benign hematologic conditions, solid tumors, age <18, treatment-free >5 years, or RSV diagnosis based only on imaging (Figure S1). Collected data included demographics, malignancy type/status, recent therapy, RSV diagnostics, clinical presentation, infection severity, antivirals, hospitalization, prior-year RSV vaccination, and survival. Malignancy was classified as controlled (partial/complete remission) or active (stable, refractory, newly diagnosed). Infection severity was categorized as asymptomatic, mild, severe, or critical. Asymptomatic cases were defined as patients without symptoms at onset who remained at home. Mild cases included those presenting with extra-pulmonary symptoms managed at home, or patients who were asymptomatic at onset but required hospitalization. Severe disease was defined by the presence of pulmonary symptoms (such as cough, dyspnea, or sputum production) regardless of setting, or by hospitalization with any non-respiratory symptom. Critical disease encompassed all cases requiring ICU admission, irrespective of symptoms at onset. Data were reviewed by hematology and infectious disease specialists; incomplete or inconsistent records were excluded.

Two matching analyses were conducted—RSV versus influenza and RSV versus SARS-CoV-2—matching for age (±10 years), viral season, and malignancy type/status; sex was matched when feasible. Categorical variables are counts/percentages, continuous variables as medians with IQR and absolute ranges. Fisher's exact or chi-square tests compared categorical data; Mann–Whitney U tests for continuous variables. Survival was assessed via Kaplan–Meier estimates with log-rank tests. Univariable Cox regression identified mortality predictors, with variables $p \leq 0.1$ entered into multivariable Cox regression using backward elimination. Hazard ratios (HR) with 95% confidence intervals (CI) were reported. Predictors included demographics, malignancy subtype/status, comorbidities, recent therapies (chemotherapy, immunotherapy, targeted therapy, HSCT, CAR-T, or none), co-infections, symptom burden, infection severity, antiviral use, secondary infections, and care setting. Analyses were performed in SPSS v25.0; significance set at $p \leq 0.05$.

Between January 2023 and December 2024, 243 patients with confirmed RSV infection were evaluated. Male predominance was observed ($n = 140$, 57.6%), with median age 64 years (IQR 52–73; range 18–93) (Table 1). Geographical distribution is in Table S1.

Lymphoma ($n = 63$, 25.9%) and plasma cell disorders ($n = 60$, 24.7%) were most prevalent. Hematological malignancy was controlled in 48.1% ($n = 117$). Up to 30.0% ($n = 73$) had ≥2 comorbidities, most often chronic cardiopathy ($n = 93$, 38.3%) and diabetes mellitus ($n = 33$, 13.6%). Neutrophils ≥1000/μL and lymphocytes ≥500/μL were seen in 65.8% ($n = 160$) and 56.0% ($n = 136$) of patients. Immunochemotherapy ($n = 74$, 30.5%) and conventional chemotherapy ($n = 45$, 18.5%) were common recent treatments (Table 1).

RSV was the sole pathogen in 88.5% ($n = 215$), with coinfections reported mainly with SARS-CoV-2 ($n = 14$, 5.9%). At RSV infection onset, 59.3% ($n = 114$) of patients had extra-pulmonary symptoms, 34.2% ($n = 83$) had pulmonary involvement, and 6.6% ($n = 16$) were asymptomatic. The most frequently reported symptoms were cough ($n = 182$; 75.2%) and fever ($n = 137$; 56.6%), followed by rhinorrhea ($n = 54$; 22.3%), respiratory distress ($n = 49$; 20.2%), and radiographic lung impairment ($n = 46$; 19.0%). Severe disease occurred in 63.8% ($n = 155$), and 27.2% ($n = 66$) were classified as mild. Hospital admission was required in 182 patients (74.9%), with a median stay of 14 days (IQR 7–26; range 1–119). ICU admission was necessary for 21 (8.6%), with a median ICU stay of 8 days (IQR 5–13; range 2–28). Specific antiviral therapy was administered in 17.7% ($n = 43$); most ($n = 154$, 63.4%) received supportive care. Secondary infections were mainly bacterial ($n = 44$, 18.1%) (Table 1).

The 30-day mortality rate was 6.2% ($n = 15$), with causes including hematological malignancy alone ($n = 4$, 1.6%), combined with RSV ($n = 6$, 2.5%), or RSV alone ($n = 3$, 1.2%). Mortality was significantly associated with fungal infections (aHR 5.059; 95% CI: 1.583–16.166; $p = 0.006$) and bacterial infections (aHR 3.264; 95% CI: 1.089–9.784; $p = 0.035$) (Tables 1 and S2).

RSV vs. influenza comparison ($n = 178$ each) showed key differences: influenza patients were more often vaccinated (11.2% vs. 0.6%; $p < 0.001$), had more chronic cardiopathy (52.2% vs. 38.2%; $p = 0.010$), and fever (57.9% vs. 73.0%; $p = 0.004$) and received more antivirals (82.0% vs. 15.2%; $p < 0.001$). RSV patients more frequently received immunoglobulins/corticosteroids (16.9%) and had more bacterial (21.3% vs. 12.4%; $p = 0.033$) and viral (5.6% vs. 1.1%; $p = 0.035$) secondary infections. RSV cases spent fewer days in intermediate care (median 5 vs. 12; $p = 0.010$) (Table 1).

RSV vs. SARS-CoV-2 comparison ($n = 203$ each): SARS-CoV-2 patients were more often vaccinated (9.4% vs. 0.5%; $p < 0.001$). RSV patients had fewer asymptomatic infections (7.4% vs. 18.2%) but presented more often with pulmonary involvement (33.0% vs. 19.2%; $p < 0.001$). Compared with SARS-CoV-2, RSV cases demonstrated significantly higher frequencies of cough (74.9% vs. 41.4%; $p < 0.001$), lung impairment (17.7% vs. 7.9%; $p = 0.007$), and respiratory distress (20.7% vs. 9.4%; $p = 0.003$), as well as higher rates of severe disease (62.1% vs. 40.4%; $p < 0.001$) and hospitalization (74.4% vs. 54.2%; $p < 0.001$). Treatment differed: SARS-CoV-2 patients received more antivirals/corticosteroids (68.5% vs. 14.3%), while most RSV patients received none (69.0% vs. 27.1%; $p < 0.001$) (Table 1).

No significant differences in 30-day survival were observed among RSV, influenza, and SARS-CoV-2 patients (Figure 1).

Our multicenter observational study of 243 patients with hematological malignancies and RSV infection offers new insights into the clinical presentation and therapeutic challenges of RSV in this population. By comparing RSV with influenza and SARS-CoV-2, we identified distinct clinical patterns and highlighted several unmet needs that are critical for improving care.

Lymphoid neoplasms—especially lymphoma and plasma cell disorders—were most common, reflecting known susceptibility

TABLE 1 | Clinical description of RSV cases and subsequent comparison with influenza and SARS-CoV-2 patients.

			RSV vs. influenza					RSV vs. SARS-CoV-2				
	RSV		Influenza		RSV			SARS-CoV-2		RSV		
	n	%	*n*	%	*n*	%	*p*	*n*	%	*n*	%	*p*
Sex							0.275					
Female	103	42.4	62	34.8	73	41.0		79	38.9	83	40.9	0.761
Male	140	57.6	116	65.2	105	59.0		124	61.1	120	59.1	
Age, *median (IQR) [range]*	64 (52–73) [18–93]		63 (54–72) [19–86]		63 (54–71) [18–87]		0.820	63 (53–71) [18–91]		63 (53–71) [18–93]		0.971
Underlying malignancy							—					—
Lymphoma	63	25.9	51	28.7	51	28.7		55	27.1	55	27.1	
Plasma cell disorders	60	24.7	46	25.8	46	25.8		51	25.1	51	25.1	
Acute myeloid leukemia	48	19.8	43	24.2	43	24.2		45	22.2	45	22.2	
Chronic lymphocytic leukemia	20	8.2	11	6.2	11	6.2		13	6.4	13	6.4	
Acute lymphoblastic leukemia	24	9.9	16	9.0	16	9.0		21	10.3	21	10.3	
Myelodysplastic syndrome	12	4.9	6	3.4	6	3.4		9	4.4	9	4.4	
Chronic myeloid malignancies	11	4.5	4	2.2	4	2.2		8	3.9	8	3.9	
Aplastic anemia	5	2.1	1	0.6	1	0.6		1	0.5	1	0.5	
Status underlying malignancy at infection onset							—					—
Controlled malignancy	117	48.1	85	47.8	85	47.8		96	47.3	96	47.3	
Active malignancy	126	51.9	93	52.2	93	52.2		107	52.7	107	52.7	

(Continues)

TABLE 1 | (Continued)

	RSV		RSV vs. influenza					RSV vs. SARS-CoV-2				
	RSV		Influenza		RSV			SARS-CoV-2		RSV		
	n	%	*n*	%	*n*	%	*p*	*n*	%	*n*	%	*p*
Vaccination ≤ 365 days before infection							< 0.001					< 0.001
Not vaccinated	239	98.4	158	88.8	177	99.4		184	90.6	202	99.5	
Influenza	0	0.0	20	11.2	0	0.0		0	0.0	0	0.0	
RSV	4	1.6	0	0.0	1	0.6		0	0.0	1	0.5	
SARS-CoV-2	0	0.0	0	0.0	0	0.0		19	9.4	0	0.0	
Comorbidities at infection onset												
0–1	170	70.0	119	66.9	126	70.8	0.492	138	68.0	144	70.9	0.590
2+	73	30.0	59	33.1	52	29.2		65	32.0	59	29.1	
Chronic cardiopathy	93	38.3	93	52.2	68	38.2	0.010	87	42.9	79	38.9	0.480
Chronic pulmonary disease	31	12.8	24	13.5	22	12.4	0.875	26	12.8	23	11.3	0.761
Diabetes mellitus	33	13.6	25	14.0	26	14.6	1.000	28	13.8	26	12.8	0.884
Liver disease	12	4.9	12	6.7	8	4.5	0.491	7	3.4	10	4.9	0.622
Obesity	15	6.2	12	6.7	11	6.2	1.000	10	4.9	13	6.4	0.669
Renal impairment	21	8.6	6	3.4	13	7.3	0.156	21	10.3	16	7.9	0.491
Smoking history	25	10.3	24	13.5	20	11.2	0.629	25	12.3	23	11.3	0.878
Neutrophils at infection onset							0.667					0.065
< 500	31	12.8	21	11.8	26	14.6		16	7.9	26	12.8	
500–999	22	9.1	20	11.2	17	9.6		10	4.9	20	9.9	
≥ 1000	160	65.8	118	66.3	113	63.5		137	67.5	130	64.0	

(Continues)

TABLE 1 | (Continued)

	RSV		RSV vs. influenza					RSV vs. SARS-CoV-2				
	RSV		Influenza		RSV			SARS-CoV-2		RSV		
	n	%	*n*	%	*n*	%	*p*	*n*	%	*n*	%	*p*
Lymphocytes at infection onset							0.914					0.155
≤ 200	37	15.2	28	15.7	29	16.3		20	9.9	30	14.8	
201–499	42	17.3	37	20.8	33	18.5		26	12.8	37	18.2	
≥ 500	136	56.0	96	53.9	95	53.4		119	58.6	111	54.7	
Last chemotherapy before infection							—					—
Conventional chemotherapy	45	18.5	40	22.5	33	18.5		39	19.2	40	19.7	
Demethylating agents	9	3.7	20	11.2	9	5.1		6	3.0	9	4.4	
Immuno-chemotherapy	74	30.5	69	38.8	57	32.0		72	35.5	64	31.5	
Targeted therapy	34	14.0	19	10.7	25	14.0		31	15.3	30	14.8	
alloHSCT	41	16.9	11	6.2	28	15.7		19	9.4	32	15.8	
autoHSCT	11	4.5	5	2.8	9	5.1		10	4.9	9	4.4	
CAR-T	3	1.2	2	1.1	3	1.7		3	1.5	3	1.5	
No treatment	22	9.1	9	5.1	10	5.6		20	9.9	12	5.9	
Supportive measures	4	1.6	3	1.7	4	2.2		3	1.5	4	2.0	
Infection diagnosis season							—					—
Winter 2023	50	20.6	24	13.5	24	13.5		38	18.7	38	18.7	
Interseason 2023	2	0.8	1	0.6	1	0.6		2	1.0	2	1.0	
Autumn 2023 to Winter 2024	175	72.0	148	83.1	148	83.1		153	75.4	153	75.4	
Interseason 2024	3	1.2	0	0.0	0	0.0		2	1.0	2	1.0	
Autumn 2024	9	3.7	5	2.8	5	2.8		6	3.0	6	3.0	

(Continues)

TABLE 1 | (Continued)

	RSV vs. influenza							RSV vs. SARS-CoV-2				
	RSV		Influenza		RSV			SARS-CoV-2		RSV		
	n	%	*n*	%	*n*	%	*p*	*n*	%	*n*	%	*p*
Pathogen							—					—
Influenza	0	0.0	178	100.0	0	0.0		0	0.0	0	0.0	
RSV alone	216	88.9	0	0.0	178	100.0		0	0.0	203	100.0	
RSV in coinfection[a]	22	11.1	0	0.0	0	0.0		0	0.0	0	0.0	
SARS-CoV-2	0	0.0	0	0.0	0	0.0		203	100.0	0	0.0	
Symptoms at infection onset												
Main symptoms												
Cough	182	75.2	126	70.8	135	75.8	0.338	84	41.4	152	74.9	< 0.001
Fever	137	56.6	130	73.0	103	57.9	0.004	95	46.8	112	55.2	0.268
Rhinorrea	54	22.3	25	14.0	37	20.8	0.124	41	20.2	39	19.2	0.619
Lung impairment	46	19.0	27	15.2	33	18.5	0.240	16	7.9	36	17.7	0.007
Respiratory distress	49	20.2	34	19.1	36	20.2	0.894	19	9.4	42	20.7	0.003
Summarized												
No symptoms	16	6.6	5	2.8	9	5.1	0.333	37	18.2	15	7.4	< 0.001
Only non-pulmonary symptoms	144	59.3	122	68.5	110	61.8		127	62.6	121	59.6	
At least pulmonary symptoms	83	34.2	51	28.7	59	33.1		39	19.2	67	33.0	
Infection severity							0.268					< 0.001
Asymptomatic	1	0.4	2	1.1	0	0.0		18	8.9	1	0.5	
Mild	66	27.2	42	23.6	47	26.4		89	43.8	59	29.1	
Severe	155	63.8	111	62.4	116	65.2		82	40.4	126	62.1	
Critical	21	8.6	23	12.9	15	8.4		14	6.9	17	8.4	
Stay during infection							0.376					< 0.001

(Continues)

TABLE 1 | (Continued)

	RSV		RSV vs. influenza					RSV vs. SARS-CoV-2				
	RSV		Influenza		RSV			SARS-CoV-2		RSV		
	n	%	*n*	%	*n*	%	*p*	*n*	%	*n*	%	*p*
Home	61	25.1	42	23.6	42	23.6		93	45.8	52	25.6	
Hospital	161	66.3	113	63.5	121	68.0		96	47.3	134	66.0	
Overall days in hospital, median (IQR) [range]	14 (7–26) [1–119]		13 (5–23) [1–128]		14 (6–26) [1–119]		0.608	19 (7–31) [1–126]		14 (6–26) [1–119]		0.121
Overall days in normal ward, median (IQR) [range]	14 (7–26) [1–119]		10 (5–21) [1–128]		13.5 (6–26) [1–119]		0.473	15.5 (7–30) [1–82]		14 (6–26) [1–119]		0.403
Overall days in intermediate care, median (IQR) [range]	7 (4–24) [3–38]		12 (3–19) [1–37]		5 (3–24) [3–24]		0.010	12.5 (9–28) [5–56]		6.5 (4–16) [3–24]		0.078
Hospital, ICU	21	8.6	23	12.9	15	8.4		14	6.9	17	8.4	
No mechanical ventilation	3	1.2	4	2.2	2	1.1	0.673	5	2.5	2	1.0	0.242
Non-invasive	6	2.5	10	5.6	5	2.8		4	2.0	5	2.5	
Invasive	12	4.9	9	5.1	8	4.5		5	2.5	10	4.9	
Overall days in ICU, median (IQR) [range]	8 (5–13) [2–28]		9 (5–12) [1–30]		7 (5–13) [3–18]		0.608	10 (8–14) [3–32]		8 (5–14) [3–28]		0.363
Infection treatment							< 0.001					< 0.001
No treatment	154	63.4	28	15.7	121	68.0		55	27.1	140	69.0	
Antivirals ± corticosteroids	43	17.7	146	82.0	27	15.2		139	68.5	29	14.3	
Immunoglobulins	16	6.6	0	0.0	12	6.7		0	0.0	12	5.9	
Corticosteroids	30	12.3	4	2.2	18	10.1		9	4.4	22	10.8	
Secondary infections												
Bacterial	44	18.1	22	12.4	38	21.3	0.033	30	14.8	39	19.2	0.290
Fungal	14	5.8	5	2.8	11	6.2	0.200	7	3.4	12	5.9	0.348

(Continues)

TABLE 1 | (Continued)

	RSV		RSV vs. influenza					RSV vs. SARS-CoV-2				
			Influenza		RSV			SARS-CoV-2		RSV		
	n	%	*n*	%	*n*	%	*p*	*n*	%	*n*	%	*p*
Other viral	16	6.6	2	1.1	10	5.6	0.035	9	4.4	12	5.9	0.655
Mortality, d30	15	6.2	14	7.9	10	5.6	0.527	7	3.4	12	5.9	0.348
Reason for mortality							0.084					0.775
Hematological malignancy	4	1.6	2	1.1	4	2.2		3	1.5	4	2.0	
Hematological malignancy, Virus	6	2.5	6	3.4	3	1.7		2	1.0	4	2.0	
Virus	3	1.2	6	3.4	1	0.6		2	1.0	2	1.0	
Other reasons	2	0.8	0	0.0	2	1.1		0	0.0	2	1.0	

Abbreviations: alloHSCT, allogeneic hematopoietic stem cell transplantation; autoHSCT, autologous hematopoietic stem cell transplantation; CAR-T, chimeric antigen receptor T-cell therapy; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; *n*, number (sample size); RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a]Observed RSV co-infections included: SARS-CoV-2 ($n = 13$ cases), influenza ($n = 5$), metapneumovirus and rhinovirus ($n = 3$, each), parainfluenza ($n = 2$), and rhinovirus and SARS-CoV-2 ($n = 1$).

of lymphoproliferative disorders to respiratory viruses due to impaired immunity and frequent use of B-cell–depleting therapies like rituximab and daratumumab [6], which hinder humoral responses and prolong infection vulnerability.

Over half of patients had active hematological malignancies at RSV diagnosis, likely contributing to the observed severity and high hospitalization rate. Active disease increases inflammatory burden, cumulative immunosuppression, and reduces functional status [7]. In line with existing literature [8], cardiovascular disease and diabetes—common comorbidities in this cohort—are independently linked to worse outcomes in respiratory viral infections, further amplifying RSV severity.

Neutropenia or lymphopenia at diagnosis occurred in only ~10% of patients, lower than in high-risk populations like acute leukemia or HSCT recipients [2]. This likely reflects the predominance of indolent lymphoid malignancies, where immune impairment is driven more by treatment and chronic immunosuppression than cytopenias. About half of the cohort had recent chemotherapy or immunochemotherapy, supporting the link between recent therapy and RSV severity, consistent with prior reports [2, 3].

RSV vaccination coverage was minimal, much lower than influenza and SARS-CoV-2, likely due to the recent availability of RSV vaccines and their exclusion from national or disease-specific guidelines. By contrast, established recommendations and routine use of influenza and SARS-CoV-2 vaccines likely explain their higher uptake.

Coinfections were rare, with SARS-CoV-2 most common, reflecting their co-circulation in hematological patients [2]. Asymptomatic RSV was uncommon; most initially had extrapulmonary symptoms, progressing to pulmonary involvement in approximately two-thirds, underscoring the need for close monitoring. In contrast, SARS-CoV-2 was often asymptomatic, likely due to broader testing, whereas RSV diagnosis remains largely symptom-driven and hospital-based, potentially delaying care.

Hospitalization occurred in 75% of cases, though ICU admission was rare, indicating that RSV often requires inpatient care but less frequently leads to critical illness. Despite generally milder symptoms than influenza, RSV caused more secondary infections—mainly bacterial—affecting ~20% of patients and significantly contributing to mortality, likely due to RSV-induced epithelial injury.

Antiviral treatment, primarily ribavirin, was administered in fewer than 20% of cases. This limited use reflects the lack of randomized trial data supporting its efficacy and the absence of treatment guidelines for non-transplant patients with hematological malignancies. In contrast, influenza was more frequently treated with oseltamivir, which has a stronger evidence base. While COVID-19 benefits from multiple validated antiviral options, treatment of RSV remains empirical and inconsistently applied.

All-cause mortality was ~6%, with RSV as a primary or contributing factor in most deaths. Fatal cases were largely linked to secondary infections, supporting the role of RSV-induced epithelial damage in facilitating bacterial and fungal superinfections [9]. The higher rate of bacterial co-infection observed in RSV

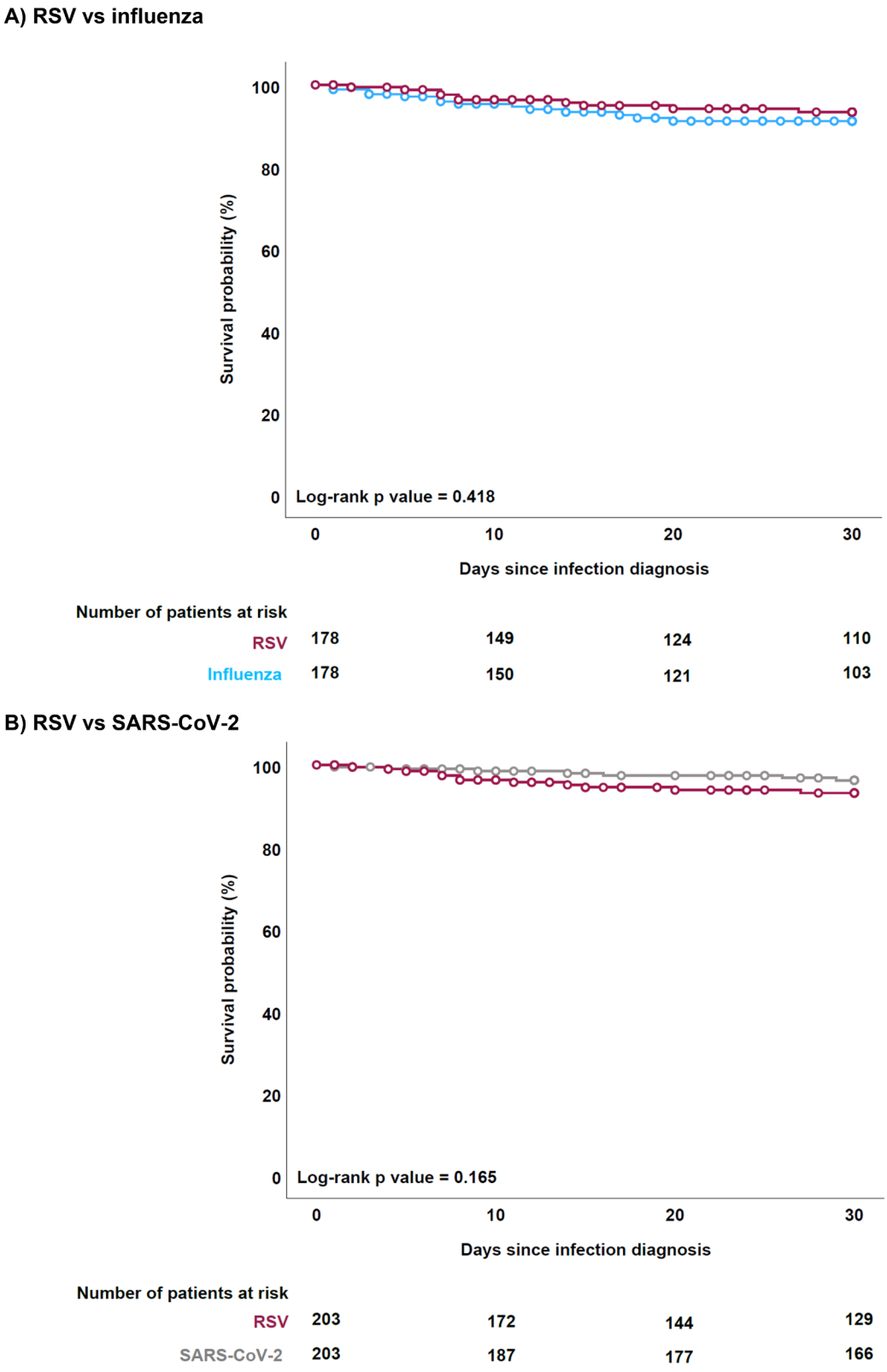

FIGURE 1 | Day 30 survival after infection diagnosis per pathogen.

compared with influenza may reflect several interrelated mechanisms. RSV is known to cause pronounced epithelial damage and impair mucociliary clearance, facilitating bacterial adherence and colonization of the lower respiratory tract. In addition, delayed diagnosis and the limited availability of specific antiviral or immunomodulatory therapies for RSV likely contribute to prolonged viral replication and immune dysregulation, further predisposing patients to secondary bacterial infection. In contrast, influenza is more routinely diagnosed and promptly treated with established antivirals, which may mitigate the risk of bacterial superinfection. This finding underscores the importance of improving timely RSV diagnostics, expanding vaccine

coverage, and developing effective antivirals to prevent secondary infections and improve outcomes in this high-risk population. Although invasive fungal disease occurred in only 5%–6% of cases, it carried very high mortality, underscoring the need to consider and manage superinfections in RSV-infected patients with hematological malignancies.

The recent approval of RSV vaccines for older and immunocompromised adults is a major advance. Future studies should evaluate vaccine immunogenicity, safety, and effectiveness in patients with hematological malignancies, especially those on B-cell–depleting therapy [10]. Greater access to rapid and multiplex diagnostics could enable earlier detection, while clinical trials of new antivirals or combination therapies, as well as studies on prophylactic or pre-emptive strategies, are needed to guide future practice.

This study has several limitations, including its retrospective design, potential selection and reporting biases, incomplete or inconsistent RSV testing, lack of data on viral load, genotyping, and subtype, partial treatment information, and absence of immunological parameters, limiting assessment of host vulnerability.

RSV is a clinically significant respiratory infection in patients with hematological malignancies—especially those with active lymphoid neoplasms, recent chemotherapy, or coinfections—causing high hospitalization, secondary infection, and mortality rates. Compared with influenza and SARS-CoV-2, RSV remains underdiagnosed, undertreated, and under-vaccinated, highlighting the urgent need to improve vaccines, diagnostics, and therapies.

Author Contributions

J.S.-G., F.M., O.A.C., and L.P. contributed to study design and study supervision. J.S.-G. did the statistical plan and analysis. J.S.-G., F.M., O.A.C., and L.P. interpreted the data and wrote the paper. All the authors recruited and documented participants, critically read, reviewed, and agreed to publish the manuscript.

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Ethics Statement

Ethical approval was granted by the institutional review board of Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome (Study ID 3226), as well as by local ethics committees where applicable. Given the complete anonymization of patient data, the need for informed consent was waived in accordance with the specific requirements of participating institutions.

Conflicts of Interest

J.S.-G. has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Gilead, Menarini, and Pfizer; and has participated on a Data Safety Monitoring Board or Advisory Board for Pfizer, outside of the submitted work. O.A.C. has received grants or contracts from BMBF, Cidara, EU-DG RTD (101037867), F2G, Gilead, MedPace, MSD, Mundipharma, Octapharma, Pfizer, Scynexis; consulting fees from Abbvie, AiCuris, Biocon, Cidara, Gilead, IQVIA, Janssen, Matinas, MedPace, Menarini, Moderna, Molecular Partners, MSG-ERC, Noxxon, Octapharm, Pfizer, PSI, Scynexis, Seres; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Abbott, Abbvie, Al-Jazeera Pharmaceuticals/Hikma, Gilead, Grupo Biotoscana/United Medical/Knight, MedScape, MedUpdate, Merck/MSD, Noscendo, Pfizer, Shionogi, streamedup!; payment for expert testimony from Cidara; a German patent ("Geschlossene Inkubationssysteme mit verbessertem Atemwegszugang für Untersuchungsvorrichtungen," DE 10 2021 113 007.7), filed by the University of Cologne and listing Oliver A. Cornely as one of three inventors; participation on a Data Safety Monitoring Board or Advisory Board from Boston Strategic Partners, Cidara, IQVIA, Janssen, MedPace, PSI, Pulmocide, Shionogi, The Prime Meridian Group; stock or stock options from CoRe Consulting, EasyRadiology; and other financial or non-financial interests from Wiley, outside of the submitted work. Other authors declare no competing interests related to the submitted work. All authors had full access to the data and had final responsibility for the decision to submit for publication.

Data Availability Statement

The corresponding author can provide the data supporting the findings of this study upon a reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Supporting Information.