

CORRESPONDENCE **OPEN ACCESS**

# 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

Jon Salmanton-García<sup>1,2,3,4</sup> | Francesco Marchesi<sup>5</sup> | Milan Navrátil<sup>6,7</sup> | Iker Falces-Romero<sup>8,9</sup> | Maria Ilaria Del Principe<sup>10</sup> | Jorge Labrador<sup>11,12</sup> | Klára Piukovics<sup>13</sup> | Verena Petzer<sup>14</sup> | Monika M. Biernat<sup>15,16</sup> | Michail Samarkos<sup>17</sup> | Dario Leotta<sup>18</sup> | Nicola Fracchiolla<sup>19</sup> | Anna Dąbrowska-Iwanicka<sup>20</sup> | Antonio Vena<sup>21</sup> | Benjamín Višek<sup>22</sup> | Yavuz M. Bilgin<sup>23</sup> | Jens Van Praet<sup>24</sup> | Mario Virgilio Papa<sup>25</sup> | Inmaculada Heras Fernando<sup>26</sup> | Francesca Farina<sup>27</sup> | Luboš Drgoňa<sup>28</sup> | Josip Batinić<sup>29,30,31</sup> | Barbora Weinbergerová<sup>32</sup> | Nurettin Erben<sup>33</sup> | Joanna Drozd-Sokołowska<sup>34</sup> | Patricia García-Ramírez<sup>35</sup> | Annarosa Cuccaro<sup>36</sup> | Martin Čerňan<sup>37</sup> | Nicola Sgherza<sup>38</sup> | Tobias Lahmer<sup>39</sup> | Donald C. Vinh<sup>40</sup> | Gaëtan Planteveve<sup>41</sup> | Alberto López-García<sup>42</sup> | Chiara Cattaneo<sup>43</sup> | Nikola Pantić<sup>44</sup> | Sofya Khostelidi<sup>45</sup> | Julio Dávila-Valls<sup>46</sup> | Andrés Soto-Silva<sup>47</sup> | László Imre Pinczés<sup>48</sup> | Ferenc Magyari<sup>48</sup> | Reham Abdelaziz Khedr<sup>48</sup> | Michelina Dargenio<sup>49</sup> | Martijn Bakker<sup>50</sup> | Igor Stoma<sup>51</sup> | Carolina Garcia-Vidal<sup>52</sup> | Ildefonso Espigado<sup>53</sup> | Claudio Cerchione<sup>54</sup> | Caterina Buquicchio<sup>55</sup> | Zlate Stojanoski<sup>56</sup> | Gabriele Magliano<sup>57</sup> | Stefanie K. Gräfe<sup>58</sup> | Avinash Aujayeb<sup>1,2,3,4,59</sup> | Lucia Prezioso<sup>60</sup> | Vladimir Otašević<sup>61</sup> | Maria Merelli<sup>44</sup> | Erica Mackenzie<sup>62</sup> | Andreas Glenthøj<sup>63</sup> | Eleni Gavriilaki<sup>64</sup> | Noha Eisa<sup>65,66</sup> | Mario Delia<sup>67,68</sup> | Alessandro Busca<sup>38</sup> | Ahlam Almasari<sup>69</sup> | Tatjana Adžić-Vukičević<sup>68</sup> | Ivana Urošević<sup>44</sup> | Uluhan Sili<sup>70</sup> | Carolina Miranda-Castillo<sup>71</sup> | Gustavo-Adolfo Méndez<sup>72</sup> | Stef Meers<sup>73</sup> | Monia Marchetti<sup>74</sup> | Nicola Coppola<sup>75</sup> | Gökçe Melis Çolak<sup>76</sup> | Darko Antić<sup>71</sup> | Ditte Stampe Hersby<sup>44,77</sup> | Pellegrino Musto<sup>64</sup> | Milče Cvetanoski<sup>38,78</sup> | Martin Schönlein<sup>57</sup> | Tommaso Francesco Aiello<sup>79</sup> | Elena Arellano<sup>80</sup> | Davide Nappi<sup>54</sup> | Sonia Martín-Pérez<sup>55</sup> | Mirjana Mitrović<sup>46</sup> | Raul Cordoba<sup>44,77</sup> | Romane Prin<sup>42</sup> | Marta Callejas-Charavia<sup>81</sup> | Gina Varricchio<sup>35</sup> | Martina Bavastro<sup>25</sup> | Alessandro Limongelli<sup>82</sup> | Amalia N. Anastasopoulou<sup>82</sup> | Alessandra Romano<sup>17</sup> | Dominik Wolf<sup>18</sup> | Kevin Nguyen<sup>14</sup> | Lukas Van Den Ven<sup>1,2,3,4</sup> | Alessia Di Pilla<sup>1,2,3,4</sup> | Antonio Giordano<sup>83,84</sup> | Oliver A. Cornely<sup>83,84</sup> | Livio Pagano<sup>2,3,4,83,84,85</sup>

**Correspondence:** Jon Salmanton-García ([jon.salmanton-garcia@uk-koeln.de](mailto:jon.salmanton-garcia@uk-koeln.de))

**Received:** 22 July 2025 | **Revised:** 30 October 2025 | **Accepted:** 10 November 2025

**Keywords:** hematological malignancy | neglected | opportunistic infection | real-world data | respiratory syncytial virus

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

Oliver A. Cornely and Livio Pagano shared senior authorship.

For affiliations refer to page 10.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2025 The Author(s). *American Journal of Hematology* published by Wiley Periodicals LLC.

(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 ( $\geq 18$  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 ( $\pm 10$  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  $\geq 2$  comorbidities, most often chronic cardiopathy ( $n = 93$ , 38.3%) and diabetes mellitus ( $n = 33$ , 13.6%). Neutrophils  $\geq 1000/\mu\text{L}$  and lymphocytes  $\geq 500/\mu\text{L}$  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			
	<i>n</i>	%	<i>p</i>	<i>n</i>	%	<i>p</i>	<i>n</i>	%	<i>p</i>	<i>n</i>	%	<i>p</i>	<i>n</i>	%	<i>p</i>	
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]			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			Influenza			RSV vs. influenza			RSV vs. SARS-CoV-2			p
	n	%		n	%		n	%		n	%		
Vaccination ≤ 365 days before infection													<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	138	68.0	144	70.9			0.590
2+	73	30.0	59	33.1	52	29.2	65	32.0	59	29.1			
<i>Chronic cardiopathy</i>	93	38.3	93	52.2	68	38.2	87	42.9	79	38.9			0.480
<i>Chronic pulmonary disease</i>	31	12.8	24	13.5	22	12.4	26	12.8	23	11.3			0.761
<i>Diabetes mellitus</i>	33	13.6	25	14.0	26	14.6	28	13.8	26	12.8			0.884
<i>Liver disease</i>	12	4.9	12	6.7	8	4.5	7	3.4	10	4.9			0.622
<i>Obesity</i>	15	6.2	12	6.7	11	6.2	10	4.9	13	6.4			0.669
<i>Renal impairment</i>	21	8.6	6	3.4	13	7.3	21	10.3	16	7.9			0.491
<i>Smoking history</i>	25	10.3	24	13.5	20	11.2	25	12.3	23	11.3			0.878
Neutrophils at infection onset													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			Influenza			RSV vs. influenza			RSV vs. SARS-CoV-2			RSV vs. SARS-CoV-2			
	n	%	p	n	%	p	n	%	p	n	%	p	n	%	p	
																n
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)

Pathogen	RSV			Influenza			RSV vs. influenza			RSV vs. SARS-CoV-2			RSV		
	<i>n</i>	%	<i>p</i>	<i>n</i>	%	<i>p</i>	<i>n</i>	%	<i>p</i>	<i>n</i>	%	<i>p</i>	<i>n</i>	%	<i>p</i>
Influenza	0	0.0		178	100.0		0	0.0		0	0.0		0	0.0	
RSV alone	216	88.9		0	0.0	100.0	178	100.0		0	0.0		203	100.0	
RSV in coinfection <sup>a</sup>	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															
<i>Cough</i>	182	75.2		126	70.8	0.338	135	75.8		84	41.4		152	74.9	<0.001
<i>Fever</i>	137	56.6		130	73.0	0.004	103	57.9		95	46.8		112	55.2	0.268
<i>Rhinorrea</i>	54	22.3		25	14.0	0.124	37	20.8		41	20.2		39	19.2	0.619
<i>Lung impairment</i>	46	19.0		27	15.2	0.240	33	18.5		16	7.9		36	17.7	0.007
<i>Respiratory distress</i>	49	20.2		34	19.1	0.894	36	20.2		19	9.4		42	20.7	0.003
Summarized															
<i>No symptoms</i>	16	6.6		5	2.8	0.333	9	5.1		37	18.2		15	7.4	<0.001
<i>Only non-pulmonary symptoms</i>	144	59.3		122	68.5		110	61.8		127	62.6		121	59.6	
<i>At least pulmonary symptoms</i>	83	34.2		51	28.7		59	33.1		39	19.2		67	33.0	
Infection severity															
Asymptomatic	1	0.4		2	1.1	0.268	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 vs. influenza						RSV vs. SARS-CoV-2								
	RSV			Influenza			RSV			SARS-CoV-2			RSV		
	n	%	p	n	%	p	n	%	p	n	%	p	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]		0.608	14 (6-26) [1-119]		0.608	19 (7-31) [1-126]		0.121	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]		0.473	13.5 (6-26) [1-119]		0.473	15.5 (7-30) [1-82]		0.403	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]		0.010	5 (3-24) [3-24]		0.010	12.5 (9-28) [5-56]		0.078	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		5	2.5		2	1.0	
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]		0.608	7 (5-13) [3-18]		0.608	10 (8-14) [3-32]		0.363	8 (5-14) [3-28]		0.363
Infection treatment															
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		30	14.8		39	19.2	
Fungal	14	5.8		5	2.8		11	6.2		7	3.4		12	5.9	

(Continues)

TABLE 1 | (Continued)

	RSV			Influenza			RSV			RSV vs. influenza			RSV vs. SARS-CoV-2		
	n	%	p	n	%	p	n	%	p	n	%	p	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
<i>Hematological malignancy</i>	4	1.6		2	1.1		4	2.2		3	1.5		4	2.0	
<i>Hematological malignancy, Virus</i>	6	2.5		6	3.4		3	1.7		2	1.0		4	2.0	
<i>Virus</i>	3	1.2		6	3.4		1	0.6		2	1.0		2	1.0	
<i>Other reasons</i>	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.

<sup>a</sup>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.

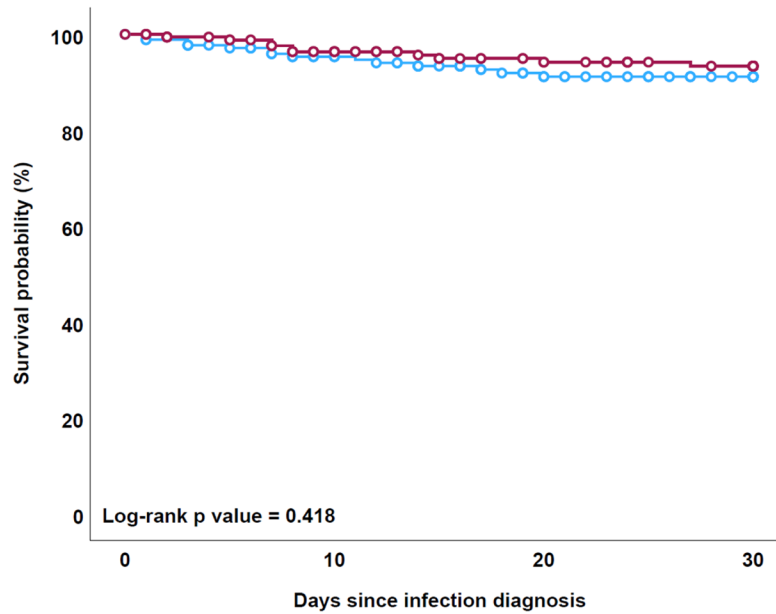
Coinfections were rare, with SARS-CoV-2 most common, reflecting their co-circulation in hematological patients [2]. Asymptomatic RSV was uncommon; most initially had extrapulmonary symptoms, progressing to pulmonary involvement in approximately two-thirds, underscoring the need for close monitoring. 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

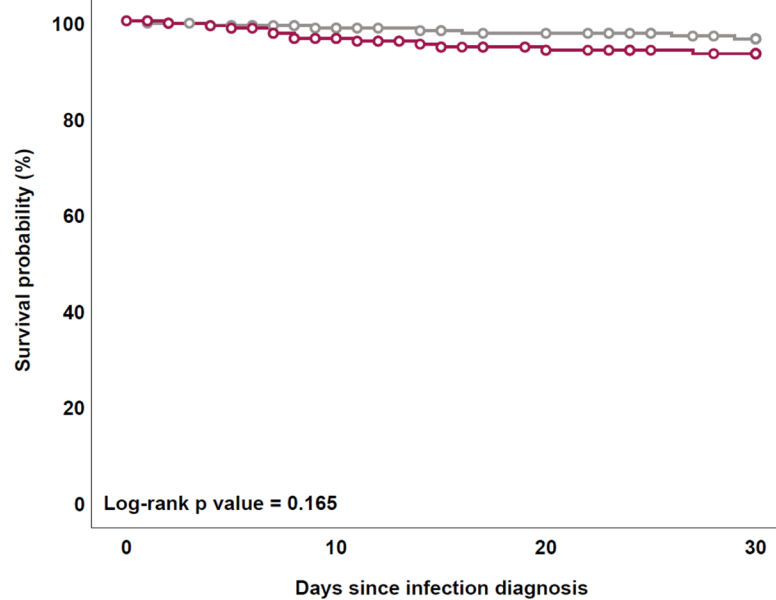
### A) RSV vs influenza



Number of patients at risk

<b>RSV</b>	178	149	124	110
<b>Influenza</b>	178	150	121	103

### B) RSV vs SARS-CoV-2



Number of patients at risk

<b>RSV</b>	203	172	144	129
<b>SARS-CoV-2</b>	203	187	177	166

**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.

#### Funding

This study was funded by AstraZeneca GmbH (AstraZeneca Germany), which had no role in the design, data collection, analysis, interpretation, or writing of the manuscript.

#### Affiliations

<sup>1</sup>Institute of Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany | <sup>2</sup>Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf (CIO ABCD), University of Cologne, Cologne, Germany | <sup>3</sup>Department I of Internal Medicine, European Confederation for Medical Mycology (ECMM) Excellence Center, University of Cologne, Cologne, Germany | <sup>4</sup>German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany | <sup>5</sup>Hematology and Stem Cell Transplant Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy | <sup>6</sup>Department of Haematology, University Hospital Ostrava, Ostrava, Czech Republic | <sup>7</sup>Department of Haematology, Faculty of Medicine, University of Ostrava, Ostrava, Czech Republic | <sup>8</sup>Clinical Microbiology and Parasitology Department, Hospital Universitario La Paz, IdiPaz, Madrid, Spain | <sup>9</sup>CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain | <sup>10</sup>Hematology, Department of Biomedicine and

Prevention, University of Rome Tor Vergata, Rome, Italy | <sup>11</sup>Department of Hematology, Research Unit, Hospital Universitario de Burgos, Burgos, Spain | <sup>12</sup>Facultad de Ciencias de la Salud, Universidad Isabel I, Burgos, Spain | <sup>13</sup>Department of Internal Medicine, South Division Faculty of Medicine University of Szeged, Szeged, Hungary | <sup>14</sup>Department of Hematology and Oncology, Comprehensive Cancer Center Innsbruck (CCCI), Medical University of Innsbruck (MUI), Austrian Comprehensive Cancer Network (ACCN), Innsbruck, Austria | <sup>15</sup>Department of Haematology, Blood Neoplasms, and Bone Marrow Transplantation, Wroclaw, Poland | <sup>16</sup>Medical University, Wroclaw, Poland | <sup>17</sup>Laikon Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece | <sup>18</sup>AOU Policlinico Rodolico San Marco, Catania, Italy | <sup>19</sup>Hematology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy | <sup>20</sup>Department of Lymphoid Malignancies, Maria Sklodowska-Curie National Research Institute of Oncology, Warszawa, Poland | <sup>21</sup>IRCCS AOU San Martino (IRCCS Ospedale Policlinico San Martino), Genova, Italy | <sup>22</sup>University Hospital Hradec Králové, Hradec Králové, Czech Republic | <sup>23</sup>Department of Internal Medicine, ADRZ, Goes, the Netherlands | <sup>24</sup>Department of Nephrology and Infectious Diseases, AZ Sint-Jan Brugge AV, Brugge, Belgium | <sup>25</sup>Azienda Ospedaliera Sant'Anna e San Sebastiano, Caserta, Italy | <sup>26</sup>Hospital Morales Meseguer, Murcia, Spain | <sup>27</sup>Hematology and Bone Marrow Transplantation, IRCCS San Raffaele Scientific Institute, Milan, Italy | <sup>28</sup>Department of Oncohematology, Comenius University and National Cancer Institute, Bratislava, Slovakia | <sup>29</sup>Division of Hematology, Department of Internal Medicine, University Hospital Centre Zagreb, Zagreb, Croatia | <sup>30</sup>School of Medicine, University of Zagreb, Zagreb, Croatia | <sup>31</sup>Croatian Cooperative Group for Hematological Diseases (KROHEM), Zagreb, Croatia | <sup>32</sup>Department of Internal Medicine – Hematology and Oncology, Masaryk University Hospital Brno, Brno, Czech Republic | <sup>33</sup>Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine Eskisehir Osmangazi University, Eskisehir, Turkey | <sup>34</sup>Department of Hematology, Transplantation and Internal Medicine, Medical University of Warsaw, Warsaw, Poland | <sup>35</sup>Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Spain | <sup>36</sup>Hematology Unit, Center for Translational Medicine, Azienda USL Toscana NordOvest, Livorno, Italy | <sup>37</sup>Department of Hemato-Oncology, Faculty of Medicine and Dentistry, Palacky University and University Hospital Olomouc, Olomouc, Czech Republic | <sup>38</sup>Hematology and Stem Cell Transplantation Unit, AOUC Policlinico, Bari, Italy | <sup>39</sup>Medizinische Klinik II, Klinikum rechts der Isar, TU München, Munich, Germany | <sup>40</sup>McGill University Health Centre, Montreal, Canada | <sup>41</sup>Head ICU and CRC, Centre Hospitalier Victor DUPOUY, Argenteuil, France | <sup>42</sup>Fundacion Jimenez Diaz University Hospital, Health Research Institute IIS-FJD, Madrid, Spain | <sup>43</sup>Hematology Unit, ASST-Spedali Civili, Brescia, Italy | <sup>44</sup>Clinic of Hematology, University Clinical Center of Serbia, Belgrade, Serbia | <sup>45</sup>North-Western State Medical University Named After Iliá Ilich Méchnikov, Saint-Petersburg, Russia | <sup>46</sup>Hospital Nuestra Señora de Sonsoles, Ávila, Spain | <sup>47</sup>Faculty of Medicine, University of Chile, Infectious Diseases Unity, Salvador Hospital of Santiago, Santiago de Chile, Chile | <sup>48</sup>Division of Hematology, Department of Internal Medicine, University of Debrecen, Debrecen, Hungary | <sup>49</sup>Department of Pediatric Hematology/Oncology, National Cancer Institute-Cairo University, Children's Cancer Hospital, Cairo, Egypt | <sup>50</sup>Hematology and Stem Cell Transplant Unit, Lecce, Italy | <sup>51</sup>University Medical Center Groningen, Groningen, the Netherlands | <sup>52</sup>Gomel State Medical University, Gomel, Belarus | <sup>53</sup>Hospital Clinic, Barcelona, Spain | <sup>54</sup>Department of Hematology, University Hospital Virgen Macarena – University Hospital Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS/CSIC), Universidad de Sevilla (Departamento de Medicina), Sevilla, Spain | <sup>55</sup>Istituto Romagnolo per lo Studio dei Tumori 'Dino Amadori' – IRST, Meldola, Italy | <sup>56</sup>Ematologia con Trapianto, Ospedale Dimeicoli Barletta, Barletta, Italy | <sup>57</sup>University Clinic of Hematology, Skopje, Republic of North Macedonia | <sup>58</sup>ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy | <sup>59</sup>Universitätsklinikum Hamburg Eppendorf, Hamburg,

Germany | <sup>60</sup>Northumbria Healthcare, Newcastle, UK | <sup>61</sup>Hospital University of Parma – Hematology and Bone Marrow Unit, Parma, Italy | <sup>62</sup>Azienda Sanitaria Universitaria del Friuli Centrale, Udine, Italy | <sup>63</sup>University of Kansas Medical Center, Kansas City, USA | <sup>64</sup>Department of Hematology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark | <sup>65</sup>Hematology Department-BMT Unit, General Hospital of Thessaloniki ‘George Papanikolaou’, Thessaloniki, Greece | <sup>66</sup>2nd Propedeutic Department of Internal Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece | <sup>67</sup>Faculty of Medicine, Mansoura University, Mansoura, Egypt | <sup>68</sup>King Faisal Specialist Hospital, Jeddah, Saudi Arabia | <sup>69</sup>Stem Cell Transplant Center, AOU Citta’ della Salute e della Scienza, Turin, Italy | <sup>70</sup>Head of Clinic of Hematology, Clinical Center of Novi Sad, Novi Sad, Serbia | <sup>71</sup>Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Marmara University, Istanbul, Turkey | <sup>72</sup>Hospital Rey Juan Carlos, Móstoles, Spain | <sup>73</sup>Servicio de Infectología y Control de Infecciones, Hospital Escuela de Agudos Dr. Ramón Madariaga, Posadas, Misiones, Argentina | <sup>74</sup>AZ KLINA, Brasschaat, Belgium | <sup>75</sup>Hematology and Transplant Unit, Azienda Ospedaliera SS Antonio e Biagio e Cesare Arrigo, Alessandria, Italy | <sup>76</sup>Department of Mental Health and Public Medicine, University of Campania, Naples, Italy | <sup>77</sup>Faculty of Medicine, University of Belgrade, Belgrade, Serbia | <sup>78</sup>Department of Precision and Regenerative Medicine and Ionian Area, ‘Aldo Moro’ University School of Medicine, Bari, Italy | <sup>79</sup>Department of Oncology, Hematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany | <sup>80</sup>Department of Infectious Diseases, Hospital Clinic de Barcelona, University of Barcelona, IDIBAPS, Barcelona, Spain | <sup>81</sup>CRA from CRC Centre Hospitalier Victor DUPOUY, Argenteuil, France | <sup>82</sup>Ospedale Policlinico San Martino, Genoa, Italy | <sup>83</sup>Hematology, Fondazione Policlinico Universitario Agostino Gemelli – IRCCS, Rome, Italy | <sup>84</sup>Hematology, Università Cattolica del Sacro Cuore, Rome, Italy | <sup>85</sup>Clinical Trials Centre Cologne (ZKS Köln), Faculty of Medicine, University Hospital Cologne, University of Cologne, Cologne, Germany

### Acknowledgments

We would like to express our deepest gratitude to everyone who contributed to the development of this manuscript. In particular, we wish to pay special tribute to Dr. Alberto López-García. His dedication, knowledge, and unwavering support have been instrumental in advancing the EPICOVIDEHA/EPIRESEHA research since its inception. His legacy will endure through this work, and he will always be remembered with great appreciation and respect.

### 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.

### References

1. T. Shi, D. A. McAllister, K. L. O’Brien, et al., “Global, Regional, and National Disease Burden Estimates of Acute Lower Respiratory Infections due to Respiratory Syncytial Virus in Young Children in 2015: A Systematic Review and Modelling Study,” *Lancet* 390, no. 10098 (2017): 946–958.
2. S. Herrmann, S. Graefe, M. Christopheit, et al., “Respiratory Syncytial Virus Infection in Patients With Haematological Diseases: A Retrospective Multicentre Study,” *Infection* 53 (2025): 1341–1350.
3. F. Khawaja and R. F. Chemaly, “Respiratory Syncytial Virus in Hematopoietic Cell Transplant Recipients and Patients With Hematologic Malignancies,” *Haematologica* 104, no. 7 (2019): 1322–1331.
4. J. Salmanton-Garcia, F. Marchesi, M. Navratil, et al., “Respiratory Viruses in Patients With Hematological Malignancy in Boreal Autumn/Winter 2023–2024: EPICOVIDEHA-EPIFLUEHA Report,” *American Journal of Hematology* 100, no. 3 (2025): 358–374.
5. J. Salmanton-Garcia, F. Marchesi, F. Itri, et al., “Unveiling the Hidden Burden: From EPICOVIDEHA to EPIFLUEHA, Exploring the Epidemiology of Respiratory Viral Infections in Hematological Patients,” *Hema* 7, no. 11 (2023): e970.
6. M. S. Infante, J. Salmanton-Garcia, A. Fernandez-Cruz, et al., “B-Cell Malignancies Treated With Targeted Drugs and SARS-CoV-2 Infection: A European Hematology Association Survey (EPICOVIDEHA),” *Frontiers in Oncology* 12 (2022): 992137.
7. I. Ruiz-Camps and J. Aguilar-Company, “Risk of Infection Associated With Targeted Therapies for Solid Organ and Hematological Malignancies,” *Therapeutic Advances in Infectious Disease* 8 (2021).
8. N. Prasad, T. A. Walker, B. Waite, et al., “Respiratory Syncytial Virus-Associated Hospitalizations Among Adults With Chronic Medical Conditions,” *Clinical Infectious Diseases* 73, no. 1 (2021): e158–e163.
9. S. Manna, P. Baidara, and S. M. Mandal, “Molecular Pathogenesis of Secondary Bacterial Infection Associated to Viral Infections Including SARS-CoV-2,” *Journal of Infection and Public Health* 13, no. 10 (2020): 1397–1404.
10. M. Addo, O. Cornely, M. Denking, et al., “RSV Vaccination Strategies for High-Risk Patients 2023: A Collaborative Position Paper by Leading German Medical Societies and Organizations,” *Infection* 52, no. 1 (2024): 285–288.

### Supporting Information

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