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ORIGINAL RESEARCH

RSV Risk Profile in Hospitalized Adults and Comparison with Influenza and COVID-19 Controls in Valladolid, Spain, 2010–2022

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ABSTRACT

Introduction: We aimed to describe the risk profile of respiratory syncytial virus (RSV) infections among adults ≥ 60 years in Valladolid from January 2010 to August 2022, and to compare them with influenza and COVID-19 controls.

Methods: This was a retrospective cohort study of all laboratory-confirmed RSV infections identified in centralized microbiology database during a 12-year period. We analyzed risk factors for RSV hospitalization and severity (length of stay, intensive care unit admission, in-hospital death or readmission < 30 days) and compared severity between RSV patients vs. influenza and COVID-19 controls using multivariable logistic regression models.

Results: We included 706 RSV patients (635 inpatients and 71 outpatients), and 598 influenza and 60 COVID-19 hospitalized controls with comparable sociodemographic profile. Among RSV patients, 96 (15%) had a subtype identified: 56% A, 42% B, and 2% A + B. Eighty-one percent of RSV patients had cardiovascular conditions, 65% endocrine/metabolic, 46% chronic lung, and 43% immunocompromising conditions. Thirty-six percent were coinfected (vs. 21% influenza and 20% COVID-19; $p = < .0001$ and 0.01). Ninety-two percent had signs of lower respiratory infection (vs. 85% influenza and 72% COVID-19, $p = < .0001$) and 27% cardiovascular signs (vs. 20% influenza and 8% COVID-19, $p = 0.0031$ and 0.0009). Laboratory parameters of anemia, inflammation, and hypoxemia were highest in RSV. Among RSV, being a previous smoker (adjusted OR 2.81 [95% CI 1.01, 7.82]), coinfection (4.34 [2.02, 9.34]), and having cardiovascular (3.79 [2.17, 6.62]), neurologic (2.20 [1.09, 4.46]), or chronic lung (1.93 [1.11, 3.38]) diseases were risks for hospitalization. Being resident in care institutions (1.68 [1.09, 2.61])

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or having a coinfection (1.91[1.36, 2.69]) were risks for higher severity, while RSV subtype was not associated with severity. Whereas RSV and influenza patients did not show differences in severity, RSV patients had 68% (38–84%) lower odds of experiencing any severe outcome compared to COVID-19.

Conclusions: RSV especially affects those with comorbidities, coinfections, and living in care institutions. RSV vaccination could have an important public health impact in this population.

Keywords: Respiratory syncytial virus; Influenza; SARS-CoV-2; Hospitalization; Adult patients

Key Summary Points

Why carry out the study?
We described the risk profile of 706 respiratory syncytial virus (RSV) patients among adults aged ≥ 60 years and compared them with 635 influenza and 60 COVID-19 controls (from the early phase of the pandemic).
What was learned from the study?
More than 80% of RSV patients had cardiovascular conditions, 65% endocrine/metabolic, 46% chronic lung, and 43% immunocompromised conditions.
Among RSV patients, smoking, underlying coinfection or cardiovascular, neurologic, or chronic lung diseases were risks for hospitalization. Care institution residence and coinfection were risks for higher severity.
RSV patients presented with an advanced acute respiratory infection and had similar severity outcomes to influenza but less than early pandemic COVID-19 patients.
RSV vaccination could have an important public health impact among older adults.

INTRODUCTION

Respiratory syncytial virus (RSV) is increasingly recognized as an important cause of illness in adults [1]. Since 1970, the virus has been considered a serious pathogen, especially in the elderly and in those with underlying medical conditions [2–4]. RSV outbreaks are usually observed during the fall and winter in the northern hemisphere, but there is also inter-seasonal activity [5]. It has been described that RSV waves in adults follow the same bi-annual pattern of severe and less severe seasons as in children, with a timely association between those waves [6]. During the coronavirus disease 2019 (COVID-19) pandemic and respective mitigation strategies, there was a decrease of RSV circulation during the Autumn–Winter of 2020, followed by a reappearance of an unprecedented late epidemic wave in Spring–Summer 2021, while during the 2021–2022 and 2022–2023 seasons, a reestablishment of the pre-pandemic circulation pattern was seen [7–9].

In Spain, 2022–2023 RSV hospitalization rates were estimated at 69.6 and 273.6 per 100,000 in people aged 65–79 and ≥ 80 years, respectively [8]. However, although RSV infection is frequently diagnosed in infants, the disease burden in adults is largely under ascertained [10–15]. In that regard, a recent Spanish modeling study estimated that cardiorespiratory RSV-attributable hospitalization rates were up to 16 times higher than those based on reported RSV-specific codes, ranging from 438–476 per 100,000 (2016–2019) in adults aged ≥ 60 years [16].

The development of an RSV vaccine has been challenging [17]. In the last two decades, after the discovery of the F-protein prefusion configuration [18], several RSV vaccines targeting this antigen have been developed for infants and adults, including pregnant women [19–24]. Currently, two vaccines for older adults already received marketing approval by the European Medicines Agency and the Food and Drug Administration (FDA) [25, 26], and a third by the FDA [27]. These recent approvals have revolutionized the field and call for more studies

characterizing the disease, the risk factors, and its outcomes in the older adult population.

Even though there have been some Spanish single-center, single-season prospective studies comparing RSV to influenza, the number of patients has been low, and generalizability of results is challenging. One study found an 8% prevalence of RSV in patients hospitalized with influenza-like illness, suggesting that RSV is a major cause of moderate-to-severe respiratory infection, similar to influenza. When comparing 95 RSV and 114 influenza cases, RSV patients were older and their disease more frequently healthcare-related, leading to more antibiotic use and hospitalization, with higher mortality [28]. Another study including 54 RSV and 198 influenza cases found that clinical signs were similar and suggested that RSV patients were more likely to be prescribed antibiotics (without discontinuing them after viral diagnosis) and to be readmitted to the hospital [29], while another study including 63 RSV and 221 influenza cases reported that RSV patients presented a higher association with active neoplasia, dependency in basic activities of daily life, immunosuppression due to chronic glucocorticoid use, bacterial coinfection, and admission to an intensive care unit (ICU) [30].

In order to better understand this infection in the older adult population, and to contribute to its awareness when new preventive vaccines are available, we aimed to describe the demographic, clinical, and microbiological characteristics of all laboratory-confirmed RSV infections among adults aged ≥ 60 years in Valladolid during a 12-year period, and to compare them with influenza and COVID-19 controls.

METHODS

Study Design

This was a retrospective cohort study of all RSV-positive infections among adults aged ≥ 60 years in Valladolid between January 1, 2010 and August 31, 2022. We identified influenza and COVID-19 hospitalized controls in the same database. We first described the demographic, clinical, and microbiological characteristics of RSV, influenza, and COVID-19 patients, and then we performed several comparisons: (1) between hospitalized and non-hospitalized RSV patients, we identified risk factors for hospitalization; (2) among hospitalized RSV patients, we identified risks for higher severity; (3) between RSV and influenza patients, we compared severe clinical outcomes; and (4) between RSV and COVID-19 patients, we compared severe clinical outcomes.

Study Setting

The study was conducted at two tertiary-care hospitals which cover the entire Valladolid population of approximately 520,000 inhabitants, including 200,000 (38.5%) people aged ≥ 60 years.

Data Sources

All patients with polymerase chain reaction (PCR) viral diagnoses were identified from the *MICROB* database, which is the Valladolid centralized database for microbiology results for all in- and out-patient respiratory infections. The multiplex-type molecular methods used during study period were: Luminex NxTAG Respiratory Pathogens™ (Luminex, USA), Biomerieux FilmArray RP™ (Biomerieux, France), GenXpert Influenza, RSV rapid diagnostic™ (Cepheid, USA) and Seegene AllPlex Respiratory Panel™ (Seegene, South Korea). These panels identify the following respiratory pathogens: RSV A and B; influenza A, B, H1 and H3; human CoV-OC43, NL63, HKU1 and 229E; parainfluenza 1, 2, 3 and 4; human metapneumovirus; human bocavirus; adenovirus; rhinovirus/enterovirus; *Chlamydophila pneumoniae; Mycoplasma pneumonia; Legionella pneumophila, Bordetella pertussis*, and *Bordetella parapertussis*. Microbiological records were linked with individual primary care and/or hospital electronic medical records. Data were anonymized and then transferred into a standardized data collection instrument.

Study Population

The *MICROB* database was used to identify adults aged ≥ 60 years with a positive PCR result for RSV, influenza or SARS-COV-2 diagnosed as part of standard-of-care between January 1, 2010 and August 31, 2022.

After identifying RSV in- and out-patients, all influenza and COVID-19 hospitalized controls available in the dataset were included. If a patient had both infections in the same hospitalization episode (RSV and influenza or RSV and COVID-19), it was excluded from the respective comparative analysis. If an RSV patient was hospitalized more than once during the study period, only the first hospitalization was considered.

Data Collection

Laboratory and medical records were reviewed and manually abstracted by trained staff. Data were collected in terms of patient demographics (age, sex, resident in a care institution); vaccination history (influenza and COVID-19); risk factors/comorbidities (selected based on literature review [31–35]); presenting signs and symptoms; laboratory, images, and microbiology results (including anti-infective treatments); and outcomes including hospital length of stay, admission to ICU and length of stay, mechanical ventilation and length of use, in-hospital death and readmission to hospital. Variables are detailed in Tables 1 and 2.

For the comparative study, the independent variables collected were age, sex, resident in a care institution, influenza vaccination, COVID-19 vaccination, smoker status at admission (current, former, never), presence and type of immunocompromising condition, chronic lung disease, cardiovascular or cerebrovascular condition, kidney disease, liver disease, endocrine or metabolic disorder, neurologic condition, or coinfection. All comorbidities were categorized as yes if they were mentioned in the medical chart.

Outcomes were either hospitalization or a composite indicator of severity (based on literature review [33–37]), defined by the presence of any of these parameters: extended length of hospital stay (length ≥ mean plus 2 days [i.e., 11 days]), ICU admission, in-hospital death or readmission to hospital within 30 days.

Statistical Methods

For the descriptive part of the study, demographics, clinical, and microbiological characteristics and outcomes were described by infecting virus (RSV, influenza, SARS-CoV-2). Significance was tested using two-sided chi-square or Fisher's exact tests (categorical variables) and Student *t* or Mann–Whitney *U* tests (continuous variables), p value < 0.05 was considered statistically significant.

For the comparative part of the study, a series of multivariable regression models were used to identify risk factors for hospitalization and for experiencing any severe outcome among RSV patients, and to compare severity between RSV vs. influenza and COVID-19 patients. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. A stepwise approach with both entry and exit level p values < 0.1 was used in multivariable logistic regression models to identify potential confounders and to determine risk factors associated with disease outcomes. After the statistically significant covariates were selected by the stepwise approach, they were combined with the clinically significant covariates (such as age) into the final analyses. Only patients with complete data for models were analyzed, missing data were not imputed. All data were processed and analyzed using SAS Studio, an online interface for SAS Version 9.04.01M7P08062020 (release date March 16, 2023).

Ethical Approval

This study was approved by the Ethics Committee of the Hospital Clinico Universitario de Valladolid under the code PI-22–2729.

Table 1 Comparison of demographic characteristics and risk factors of hospitalized respiratory syncytial virus (RSV), influenza, and COVID-19 cases in Valladolid, 2010–2022

	RSV (*N* = 635) *n* (%)	**Influenza (*N* = 598) *n* (%)**	**COVID-19 (*N* = 60) *n* (%)**	***p* value RSV vs. influenza**	***p* value RSV vs. COVID-19**
Age (years) mean (SD)	79.5 (9.4)	79.5 (9.4)	78.6 (10)	0.90	0.45
Age median (min, max)	81.0 (60, 102)	80.5 (60, 101)	78.0 (60, 98)		
Sex, female	343 (54.0)	320 (53.5)	31 (51.7)	0.86	0.79
Resident care institution	128 (20.2)	105 (17.6)	13 (21.7)	0.27	0.74
Influenza vaccinated	244 (38.4)	232 (38.8)	23 (38.3)	0.91	1.00
COVID-19 vaccinated	26 (4.1)	21 (3.5)	16 (26.7)	0.66	< 0.0001*
Smoker status				0.37	0.02*
Current	55 (8.7)	59 (9.9)	0 (0.0)		
Former	172 (27.1)	137 (22.9)	13 (21.7)		
Never	46 (7.2)	48 (8.0)	3 (5.0)		
At least 1 immunocompromising condition	272 (42.9)	222 (37.1)	19 (31.7)	0.04*	0.10
Malignant neoplasm (last 5 years)	99 (15.6)	82 (13.7)	8 (13.3)	0.38	0.85
Asplenia	4 (0.6)	1 (0.2)	0 (0.0)	0.38	1.00
Immunosuppressive drugs	199 (31.3)	145 (24.2)	13 (21.7)	0.01*	0.14
Immune system disorder	38 (6.0)	38 (6.3)	3 (5.0)	0.81	1.00
Under radiotherapy treatment	4 (0.6)	2 (0.3)	0 (0.0)	0.69	1.00
At least 1 chronic lung disease	293 (46.1)	245 (41.0)	17 (28.3)	0.07	0.01*
Bronchiectasis	25 (4.4)	25 (4.2)	2 (3.3)	0.89	1.00
Chronic obstructive pulmonary disease	149 (23.5)	121 (20.2)	10 (16.7)	0.19	0.26
Asthma	74 (11.6)	61 (10.2)	3 (5.0)	0.47	0.13
Apnea–hypopnea syndrome	50 (7.9)	53 (8.9)	2 (3.3)	0.54	0.30
Respiratory failure	35 (5.5)	32 (5.3)	1 (1.7)	1.00	0.35
Use of home oxygen	104 (16.4)	86 (14.4)	7 (11.7)	0.34	0.46
At least 1 cardiovascular or cerebrovascular condition	515 (81.1)	462 (77.3)	44 (73.3)	0.11	0.17
Congenital heart disease	5 (0.8)	2 (0.3)	0 (0.0)	0.45	1.00

Table 1 continued

	RSV (*N* = 635) *n* (%)	Influenza (*N* = 598) *n* (%)	COVID-19 (*N* = 60) *n* (%)	*p* value RSV vs. influenza	*p* value RSV vs. COVID-19
High blood pressure	431 (67.9)	393 (65.72)	39 (65.0)	0.43	0.66
Hypertensive heart disease	40 (6.3)	31 (5.2)	6 (10.0)	0.46	0.27
Coronary artery disease	117 (18.4)	86 (14.4)	4 (6.7)	0.06	0.02*
Congestive heart failure	137 (21.6)	84 (14.0)	6 (10.0)	0.0006*	0.04*
Heart transplant	0 (0.0)	1 (0.2)	0 (0.0)	0.48	N/A
Arrythmia	203 (32.0)	145 (24.2)	12 (20.0)	0.0029*	0.06
Cardiac valve disorders	85 (13.4)	65 (10.9)	6 (10.0)	0.19	0.55
Cerebrovascular disease	67 (10.5)	58 (9.7)	7 (11.7)	0.64	0.83
Pulmonary hypertension	22 (3.5)	23 (3.8)	0 (0.0)	0.76	0.25
Pulmonary embolism	1 (0.2)	2 (0.3)	0 (0.0)	0.61	1.00
Peripheral vascular disorder	21 (3.3)	12 (2.0)	0 (0.0)	0.22	0.24
Deep venous thrombosis	6 (0.9)	9 (1.5)	0 (0.0)	0.44	1.00
Other cardiovascular or cerebrovascular condition	7 (1.1)	10 (1.7)	0 (0.0)	0.47	1.00
At least 1 kidney disease	116 (18.3)	90 (15.0)	12 (20.0)	0.15	0.73
At least 1 liver disease	59 (9.3)	43 (7.2)	4 (6.7)	0.21	0.64
At least 1 endocrine or metabolic disorder	410 (64.6)	358 (59.9)	38 (63.3)	0.10	0.89
Obesity	100 (15.7)	81 (13.5)	7 (11.7)	0.27	0.40
Diabetes	172 (27.1)	168 (28.1)	16 (26.7)	0.69	0.94
At least 1 neurologic condition	191 (30.1)	182 (30.4)	16 (26.7)	0.90	0.66
At least 1 coinfection	230 (36.2)	124 (20.7)	12 (20.0)	< .0001*	0.01*
Bacterial	72 (11.3)	82 (13.7)	4 (6.7)		
Viral	88 (13.9)	12 (2.01)	1 (1.7)		
Fungal	14 (2.2)	10 (1.7)	0 (0.0)		
Bacterial + viral	31 (4.9)	6 (1.0)	3 (5.0)		
Bacterial + fungal	14 (2.2)	13 (2.2)	4 (6.7)		
Viral + fungal	4 (0.6)	0 (0.0)	0 (0.0)		
Bacterial + viral + fungal	7 (1.1)	1 (0.2)	0 (0.0)		

*Statistically significant

Table 2 Comparison of clinical characteristics of hospitalized respiratory syncytial virus (RSV), influenza, and COVID-19 cases in Valladolid, 2010–2022

	RSV ($N=635$) *n* (%)	Influenza ($N=598$) *n* (%)	COVID-19 ($N=60$) *n* (%)	*p* value RSV vs. influenza	*p* value RSV vs. COVID-19
Signs and symptoms at admission					
General symptoms (at least 1)	417 (65.7)	454 (75.9)	46 (76.7)	< .0001*	0.09
Fever	219 (34.5)	276 (46.1)	29 (48.3)	< .0001*	0.04*
Malaise	63 (9.9)	84 (14.0)	12 (20.0)	0.03*	0.03*
Fatigue	65 (10.2)	79 (13.2)	6 (10.0)	0.11	1.00
Headache	16 (2.5)	22 (3.7)	3 (5.0)	0.25	0.22
Myalgia	36 (5.7)	42 (7.0)	5 (8.3)	0.35	0.39
Edema	135 (21.3)	104 (17.4)	5 (8.3)	0.10	0.02*
Cognitive impairment	111 (17.5)	113 (18.9)	19 (31.7)	0.55	0.01*
Exanthema	1 (0.2)	0 (0.0)	0 (0.0)	1.00	1.0
Other general	24 (3.8)	42 (7.0)	0 (0.0)	0.02*	0.25
Gastrointestinal symptoms (at least 1)	57 (9.0)	59 (9.9)	11 (18.3)	0.63	0.04*
Loss of appetite	12 (1.9)	15 (2.5)	5 (8.3)	0.56	0.01*
Vomits	27 (4.2)	30 (5.0)	2 (3.3)	0.59	1.00
Abdominal pain	10 (1.6)	4 (0.7)	3 (5.0)	0.18	0.09
Diarrhea	10 (1.6)	16 (2.7)	3 (5.0)	0.23	0.09
Other gastrointestinal	8 (1.3)	4 (0.7)	0 (0.0)	0.39	1.00
Acute upper respiratory tract infection (at least 1)	482 (75.9)	422 (70.6)	38 (63.3)	0.04*	0.04*
Cough	469 (73.9)	411 (68.7)	33 (55.0)	0.05	0.0037*
Odynophagia	15 (2.4)	24 (4.0)	5 (8.3)	0.11	0.02*
Rhinorrhea/nasal congestion	89 (14.0)	55 (9.2)	1 (1.7)	0.01*	0.0039*
Sneezing	30 (4.7)	13 (0.2)	0 (0.0)	0.02*	0.10
Anosmia	1 (0.2)	0 (0.0)	3 (5.0)	1.00	0.0023*
Ageusia	1 (0.2)	0 (0.0)	2 (3.3)	1.00	0.02*
Other upper respiratory	7 (1.1)	10 (1.7)	1 (1.7)	0.47	0.52
Acute lower respiratory tract infection (at least 1)	588 (92.6)	508 (84.9)	43 (71.7)	< .0001*	< .0001*

Table 2 continued

	RSV (*N* = 635) *n* (%)	Influenza (*N* = 598) *n* (%)	COVID-19 (*N* = 60) *n* (%)	*p* value RSV vs. influenza	*p* value RSV vs. COVID-19
Dyspnea	435 (68.5)	346 (57.9)	27 (45.0)	0.0001*	0.0005*
Tachypnea	108 (17.0)	92 (15.4)	7 (11.7)	0.49	0.36
Polypnea	1 (0.2)	0 (0.0)	0 (0.0)	1.00	1.00
Apnea	1 (0.2)	0 (0.0)	0 (0.0)	1.00	1.00
Pleuritic chest pain	52 (8.2)	38 (6.3)	3 (5.0)	0.23	0.61
Sputum production	305 (48.0)	247 (41.3)	9 (15.0)	0.02*	< .0001*
Wheezing	473 (74.5)	374 (62.5)	28 (46.7)	< .0001*	< .0001*
Croup/laryngotracheobronchitis	1 (0.2)	0 (0.0)	0 (0.0)	1.00	1.00
Bronchiolitis	4 (0.6)	1 (0.2)	0 (0.0)	0.38	1.00
Bronchitis	17 (2.7)	11 (1.9)	0 (0.0)	0.35	0.39
Chronic obstructive pulmonary disease exacerbation	8 (1.3)	1 0.2)	0 (0.0)	0.04*	1.00
Bronchiectasis exacerbation	3 (0.5)	0 (0.0)	0 (0.0)	0.25	1.00
Pneumonia	11 (1.7)	4 (0.7)	1 (1.7)	0.12	1.00
Atelectasis	21 (3.3)	15 (2.5)	0 (0.0)	0.50	0.24
Cyanosis	6 (0.9)	10 (1.7)	0 (0.0)	0.32	1.00
Acute respiratory distress syndrome	1 (0.16)	0 (0.0)	0 (0.0)	1.00	1.00
Other lower respiratory	1 (0.16)	0 (0.0)	1 (1.7)	1.00	0.17
Cardiovascular symptom (at least 1)	171 (26.9)	118 (19.7)	5 (8.3)	0.0031*	0.0009*
Congestive heart failure	14 (2.2)	1 (0.2)	0 (0.0)	0.0010*	0.62
Arrythmia	100 (15.7)	68 (11.37)	2 (3.3)	0.03*	0.01*
Other cardiovascular	80 (12.6)	60 (10.0)	3 (5.0)	0.18	0.10
Hemorrhagic manifestations	5 (0.8)	6 (1.0)	1 (1.7)	0.77	0.42
Neurologic symptoms	1 (0.2)	7 (1.2)	1 (1.7)	0.03*	0.17
Other symptoms	50 (7.9)	82 (13.7)	8 (13.3)	0.0012*	0.14
Laboratory data at admission					
Anemia	205 (32.3)	146 (24.4)	10 (16.7)	0.0024*	0.01*
Leukopenia	30 (4.7)	36 (6.0)	3 (5.0)	0.38	0.76

Table 2 continued

	RSV (*N* = 635) *n* (%)	Influenza (*N* = 598) *n* (%)	COVID-19 (*N* = 60) *n* (%)	*p* value RSV vs. influenza	*p* value RSV vs. COVID-19
Leukocytosis	217 (34.2)	157 (26.2)	10 (16.7)	0.0029*	0.01*
Neutropenia	20 (3.1)	9 (1.5)	1 (1.7)	0.06	1.00
Neutrophilia	227 (35.7)	163 (27.3)	8 (13.3)	0.0014*	0.0003*
Thrombocytopenia	115 (18.1)	118 (19.7)	11 (18.3)	0.47	1.00
Thrombocytosis	28 (4.4)	19 (3.2)	2 (3.3)	0.30	1.00
Protein-C-reactive elevated	445 (70.0)	381 (63.7)	28 (46.7)	0.02*	0.0004*
Atrial natriuretic peptide	112 (17.6)	100 (16.7)	5 (8.3)	0.71	0.07
Hypoxemia	295 (46.5)	257 (43.0)	10 (16.7)	0.23	< 0.0001*
Images (X-ray or CT scan) at admission					
Pulmonary infiltrates	129 (20.3)	104 (17.4)	23 (38.3)	0.19	0.0028*
Cardiac enlargement	127 (20.0)	72 (12.0)	3 (5.0)	0.0001*	0.0028*
Severity parameters					
Admission to intensive care unit (ICU)	41 (6.5)	41 (6.9)	16 (26.7)	0.82	< .0001*
ICU length of stay				0.84	0.03*
Mean (SD)	14.2 (12.5)	13.4 (15.9)	27.7 (23.7)		
Median (min, max)	9.0 (2.0, 50.0)	7.50 (1.0, 58.0)	2.5 (2.0, 68.0)		
Readmission to ICU	1 (0.16)	5 (0.84)	0 (0.00)	0.12	1.00
Mechanical ventilation	26 (4.09)	27 (4.52)	6 (10.00)	0.78	0.04*
Mechanical ventilation length of use				0.99	0.07
Mean (SD)	10.9 (9.70)	10.8 (11.9)	22.8 (19.3)		
Median (min, max)	7.00 (2.0, 39.0)	6.50 (1.0, 42.0)	17.0 (7.0, 55.0)		
In-hospital death	73 (11.5)	64 (10.7)	13 (21.7)	0.72	0.03*
Hospital length of stay				0.57	< .0001*
Mean (SD)	12.2 (12.3)	11.8 (11.2)	23.7 (23.9)		
Median (min, max)	9.0 (1.0, 161)	8.0 (1.0, 92.0)	18.0 (3.0, 131)		
Hospital readmission < 30 days	91 (14.3)	56 (9.4)	6 (10.0)	0.06	1.00

*Statistically significant

RESULTS

We analyzed 706 RSV patients, including 635 hospitalized and 71 outpatients. For the hospitalized patients, we identified 598 influenza and 60 COVID-19 controls. Among RSV infections, 96 (15.1%) had a subtype identified: 56.3% A, 41.7% B, and 2.1% A+B. While during 2016–2018 subtype testing was anecdotical, subtype A was more frequent in 2019 (51.9%) and 2020 (75.0%), while subtype B prevailed in 2021 (78.6%) and 2022 (63.2%) (Supplementary Table 1).

Comparison of Clinical Profile Between RSV and Influenza and COVID-19

RSV, influenza, and COVID-19 patients showed a comparable sociodemographic profile in terms of age and sex distribution, and in proportion of residents in a care institution. RSV patients were more frequently current smokers (8.6 vs. 0.0%, $p=0.0172$) and less vaccinated against SARS-CoV-2 than COVID-19 patients (4.1 vs. 26.7%, $p=<0.0001$). The most frequent comorbidities among RSV patients were cardiovascular (81.1%) – of which arrythmia, congestive heart failure, and coronary artery disease were significantly more frequent than in influenza and COVID-19 patients – followed by endocrine/metabolic (64.6%), chronic lung (46.1%), and immunocompromising (42.9%) conditions. Chronic lung and immunocompromising conditions (especially chronic use of immunosuppressive drugs) among RSV were more frequent than in COVID-19 and influenza patients, respectively. A coinfection was present in 36.2% of RSV patients, a proportion that was significantly higher than in influenza (20.7%, $p=<0.0001$) and COVID-19 (20.0%, $p=0.01$). Coinfection of RSV was more frequent with another virus (13.9%), bacteria (11.3%) and bacteria+virus (4.9%) (Table 1). The most frequent viruses were rhinovirus/enterovirus, coronavirus, and adenovirus, while the most frequent bacteria were *Staphylococcus aureus, Escherichia coli*, and *Streptococcus pneumoniae* (data not shown).

Regarding the clinical characteristics at hospital admission, RSV patients were those who significantly showed most signs of acute lower respiratory tract infection (92.6 vs. 84.9% influenza and 71.7% COVID-19, $p=<0.0001$) – marked by wheezing, dyspnea, and sputum production – and upper respiratory tract infection (75.9 vs. 70.6% and 63.3%, $p=0.04$, respectively) – predominantly cough and rhinorrhea. They also had the most cardiovascular signs (26.9% RSV vs. 19.7% and 8.3%, $p=0.0031$ and 0.0009, respectively) – remarkably arrhythmia and congestive heart failure – and cardiac enlargement in images (20.0 vs. 12.0% and 5.0%, $p=0.0001$ and 0.0028, respectively). Conversely, general symptoms like fever were significantly higher in COVID-19 and influenza patients, compared to RSV (48.3 and 46.1% vs. 34.5%, $p=0.0352$ and <0.0001, respectively). COVID-19 patients also had cognitive impairment (31.7 vs. 17.5%, $p=0.01$) and gastrointestinal symptoms twice as often (18.3 vs. 9.0%, $p=0.0365$) (Table 2).

CT scan or X-ray imaging showed a significantly higher proportion of pulmonary infiltrates in COVID-19 than in RSV patients (38.3 vs. 20.3%, $p=0.0028$) (Table 2). Among RSV patients, 51.7% were unilateral, 71.7% had an alveolar (vs. interstitial), and 55.8% a focal (vs. diffuse) pattern (Supplementary Table 2).

Laboratory parameters of anemia (32.3, 24.4, and 16.7%, $p=0.0024$ and 0.01) and inflammation were highest in RSV compared to influenza and COVID-19 patients, i.e., elevated protein-C-reactive (70.0, 63.7, and 46.7%, $p=0.0182$ and 0.0004, respectively), neutrophilia (35.7, 27.3, and 13.3%, $p=0.0014$ and 0.0003) and leukocytosis (34.2, 26.2, and 16.7%, $p=0.0029$ and 0.0058). Hypoxemia was present in almost half of RSV but significantly less in COVID-19 patients (46.5 vs. 16.7%, $p=<0.0001$) (Table 2). Sixty-five percent of RSV patients ($n=412$) received antibiotic treatment, although 73.7% ($n=304$) of them did not have a bacterial coinfection (Supplementary Table 3).

Table 3 Risk factors associated with respiratory syncytial virus (RSV)-related hospitalization in Valladolid, 2010–2022

Variable	Adjusted OR	(95% CI)
Sex, male vs. female	1.42	(0.83, 2.45)
Resident in care institutions	1.61	(0.61, 4.21)
Smoker (current)	3.48	(0.95,12.8)
Smoker (previous)	2.81	(1.01, 7.82)*
Chronic lung disease	1.93	(1.11, 3.38)*
Cardiovascular or cerebrovascular disease	3.79	(2.17, 6.62)*
Immunocompromising condition	0.86	(0.45, 1.48)
Liver disease	5.05	(0.83, 30.6)
Kidney disease	1.09	(0.45, 2.63)
Endocrine or metabolic disorder	1.09	(0.62, 1.89)
Neurologic condition	2.20	(1.09, 4.46)*
Coinfection	4.34	(2.02,9.34)*

*Statistically significant

OR odds ratio, *95% CI* 95% confidence interval

Table 4 Risk factors associated with respiratory syncytial virus (RSV) severity (length of hospital stay ≥ 11 days, intensive care unit admission, in-hospital death, or readmission to hospital within 30 days) in Valladolid, 2010–2022

Variable	Adjusted OR	(95% CI)
Sex, male vs. female	0.94	(0.67, 1.31)
Resident in care institutions	1.68	(1.09, 2.61)*
Smoker (current)	0.84	(0.36, 1.95)
Smoker (previous)	0.77	(0.39, 1.55)
Immunocompromising condition	1.01	(0.72, 1.41)
Chronic lung disease	1.00	(0.78, 1.46)
Cardiovascular or cerebrovascular disease	1.18	(0.76, 1.84)
Kidney disease	1.16	(0.75, 1.77)
Liver disease	1.27	(0.70, 2.28)
Endocrine or metabolic disorder	1.08	(0.73, 1.52)
Neurologic condition	1.23	(0.85, 1.76)
Coinfection	1.91	(1.36,2.69)*

OR odds ratio, *95% CI* 95% confidence interval

*Statistically significant

RSV Risk Factors for Hospitalization

Among RSV patients, significant risk factors for hospitalization in the multivariable analysis were previous smoker (adjusted OR 2.81 [95% CI 1.01, 7.82]), while current smoker was borderline significant (3.48 [0.95, 12.8]), to have at least one coinfection (4.34 [2.02, 9.34]), at least one cardiovascular disease (3.79 [2.17, 6.62]), at least one neurologic condition (2.20 [1.09, 4.46]) or at least one chronic lung disease (1.93 [1.11, 3.38]) (Table 3).

RSV Risk Factors for Severity

For hospitalized RSV patients, significant risk factors associated with severity in the multivariable analysis were to be resident in a care institution (adjusted OR 1.68 [95% CI 1.09, 2.61]) and to have a coinfection (1.91 [1.36, 2.69]) (Table 4). RSV subtype was not associated with higher severity (A vs. B, adjusted OR 1.33 [95% CI 0.50, 3.54]) (Supplementary Table 4).

Table 5 Comparison of severity among hospitalized respiratory syncytial virus (RSV), influenza, and COVID-19 cases in Valladolid, 2010–2022

Severity indicator	RSV vs. influenza		RSV vs. COVID-19	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Length of hospital stay ≥ 11 days	1.20 (0.95, 1.52)	1.09 (0.85, 1.41)	0.28 (0.15, 0.49)*	0.24 (0.13, 0.46)*
Admission to intensive care unit	0.94 (0.60, 1.46)	0.89 (0.57, 1.40)	0.19 (0.10, 0.36)*	0.18 (0.09, 0.35)*
In-hospital death	1.08 (0.76, 1.54)	1.09 (0.74, 1.59)	0.46 (0.24, 0.89)*	0.54 (0.26, 1.15)
Readmission to hospital	1.52 (0.98, 2.35)	1.52 (0.98, 2.36)	0.91 (0.28, 2.93)	0.91 (0.28, 2.92)
Any severe outcome	1.32 (1.05, 1.65)*	1.27 (0.98, 1.63)	0.30 (0.16, 0.57)*	0.32 (0.16, 0.62)*

*Statistically significant

OR odds ratio, *95% CI* 95% confidence interval

Comparison of Severity Between RSV and Influenza and COVID-19

Whereas RSV and influenza patients did not show differences in any severity parameters, RSV patients were 76% (54–87%) less likely to experience a hospital stay longer than 11 days, 82% (65–91%) less likely to be admitted to the ICU, and had 68% (38–84%) lower odds of having any severe outcome compared to early pandemic COVID-19 cases (Table 5).

DISCUSSION

To our knowledge, this is the first study that assesses individual medical health records in a large sample of hospitalized RSV-confirmed older adults in Spain. In this study, we have achieved a more granular understanding of the clinical syndrome that RSV causes in this population and of the risk factors associated with hospitalization and other severe outcomes. Additionally, we have contrasted these features with two other frequent and potentially serious viral infections, influenza and COVID-19, for which there are established preventive vaccination programs [38].

As expected [28–30, 33, 36], our elderly RSV population had a considerable burden of comorbidities: predominantly cardiovascular, endocrine/metabolic, and chronic lung and immunocompromising conditions. Many of them, along with smoking or neurologic conditions, were proven to be risk factors for hospitalization and hence should be specifically considered when selecting high-risk groups for vaccination programs. Remarkably, cardiovascular diseases such as arrythmias and congestive heart failure exacerbations were previously analyzed as RSV main drivers for hospitalization in Spanish [16] and other populations [33, 37, 39–41].

In line with previous findings [30, 33, 42–44], residents in a care institution were at higher risk for hospitalization. It would seem reasonable to assume that targeted vaccination programs for these groups would also yield a high impact and cost-benefit profile [45]. This is particularly true when considering long-term sequalae of RSV infection [46] such as myalgic encephalopathy or recurrent seizures [47], and prolonged functional decline [48].

In contrast to studies reporting higher severity of RSV subtype A [49–51], RSV subtype was not associated with severity in our analysis, although results must be taken with caution since only 15% of patients had a subtype identified. Both subtypes A and B were co-circulating in analyzed years, showing a biennial predominance pattern in this Spanish region (higher A in 2019–2020 vs. B in 2021–2022). Serotype and genotype

analyses must be included in any RSV national surveillance system, as these results may have important implications for understanding vaccines and antivirals effectiveness [49, 52, 53].

Although the clinical distinction between infections has been described as challenging [19], RSV predominantly showed signs and symptoms of upper and lower respiratory tract infection (including signs of respiratory distress such as wheezing, dyspnea, and hypoxia) compared to influenza and COVID-19 patients. As seen previously, RSV patients also had significantly higher levels of acute inflammation in their laboratory results [28–30] and a higher rate of coinfections [28, 30, 54]. Conversely, the clinical syndrome of influenza and COVID-19 was more general, marked by fever and malaise [28, 30], and in the case of COVID-19 more easily detectable in images. These results indicate that RSV patients were hospitalized with an advanced disease; whether this is the result of an actual more severe disease presentation – as reported in several studies – [28, 30, 34, 36, 55–58] or a delayed diagnosis due to lack of timely testing and disease severity awareness remains unclear.

Our study confirms that RSV outcomes were comparable to those of influenza. However, while readmission rates to hospital and in-hospital death were similar, COVID-19 patients had longer hospital stays and higher ICU admission rates. Since COVID-19 controls came from the early phases of the pandemic (March 2020–August 2022), when more virulent variants were circulating and vaccines and effective treatments were unavailable [59], the comparative results may not be currently reproducible. Replicating such a study at present would likely show lower COVID-19 morbidity and mortality than in our dataset since both decreased significantly as the pandemic progressed [60]. These findings are consistent with the ones from a similar study conducted in Germany [36], although in the German study RSV outcomes were more severe than influenza.

There were several limitations to our study. Firstly, those inherent to the retrospective use of medical health records, implying potential missing data since they were not collected primarily for the purpose of this study. Secondly, additional socioeconomic or environmental confounders were not included for the same data source limitation: these unmeasured confounders could potentially influence the study outcomes and should be considered when interpreting the results. Lastly, there is a potential selection bias favoring inclusion of severe RSV cases since we only included laboratory-confirmed RSV, and severe cases are likely more frequently tested than mild-to-moderate cases. These cases might be underrepresented, which could skew the severity comparisons between RSV, influenza, and COVID-19. In contrast, the main strength of our study is the large number of RSV cases and long study period (11 seasons), besides the granularity of the clinical and microbiological data analyzed, making it the most comprehensive series of RSV infection in Spanish older adults reported to date.

CONCLUSIONS

In conclusion, RSV can cause severe respiratory tract infections among adults aged 60 years and above, similar to that of influenza but less than early pandemic COVID-19 controls. However, a more contemporary comparison would likely reduce these differences. RSV especially affects patients with chronic underlying diseases, coinfections, and those living in chronic care institutions. Specific detection, prevention, and treatment of RSV is crucial to reduce its detrimental impact. It is therefore essential to confirm the viral diagnosis in acute respiratory infection cases, allowing for correct treatment and isolation measures. In addition, RSV vaccines should be part of the adult immunization program: experts from Spain recommend to prefer an age-based strategy over targeting high-risk groups [19], while a combined strategy of targeting ≥ 60 years age group and high-risk groups of < 60 years has been recommended in Germany [61]. The public-health impact of influenza and COVID-19 vaccination is encouraging and leads to suspect that RSV vaccination could potentially have comparable impact according to a recent retrospective, population-based cohort study from Spain [62].

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Author contribution. All authors attest they meet the International Committee of Medical Journal Editors criteria for authorship. Mariana Haeberer: conceptualization, methodology, data analysis, data review, writing of manuscript and handling of all revisions. Ivan Sanz-Muñoz: conceptualization and review. Marina Toquero Asensio and Alejandro Martín Toribio: data abstraction. Rong Fan, Yongzheng He, and Qing Liu: data analysis. Caihua Liang, Elizabeth Begier, Sonal Uppal, José M. Eiros, and Javier Castrodeza Sanz: manuscript review. Silvia Rojo-Rello, Marta Domínguez-Gil, Cristina Hernán-García, and Virginia Fernández-Espinilla: provided study data.

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Data availability. The datasets analyzed during the current study are not publicly available.

Declarations

Conflict of interest. Mariana Haeberer, Rong Fan, Qing Liu, Sonal Uppal, Caihua Liang, and Elizabeth Begier are employees of Pfizer and may own Pfizer stock. Yongzheng He has been hired by Pfizer to provide support for statistical analysis. Marina Toquero Asensio, Alejandro Martín Toribio, Silvia Rojo-Rello, Marta Domínguez-Gil, Cristina Hernán-García, Virginia Fernández-Espinilla, José M. Eiros, Javier Castrodeza Sanz, and Ivan Sanz-Muñoz received funding from Pfizer for data abstraction and manuscript review.

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