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Demographics and clinical burden of disease among RSV-hospitalized older adults in Italy: A retrospective cohort study

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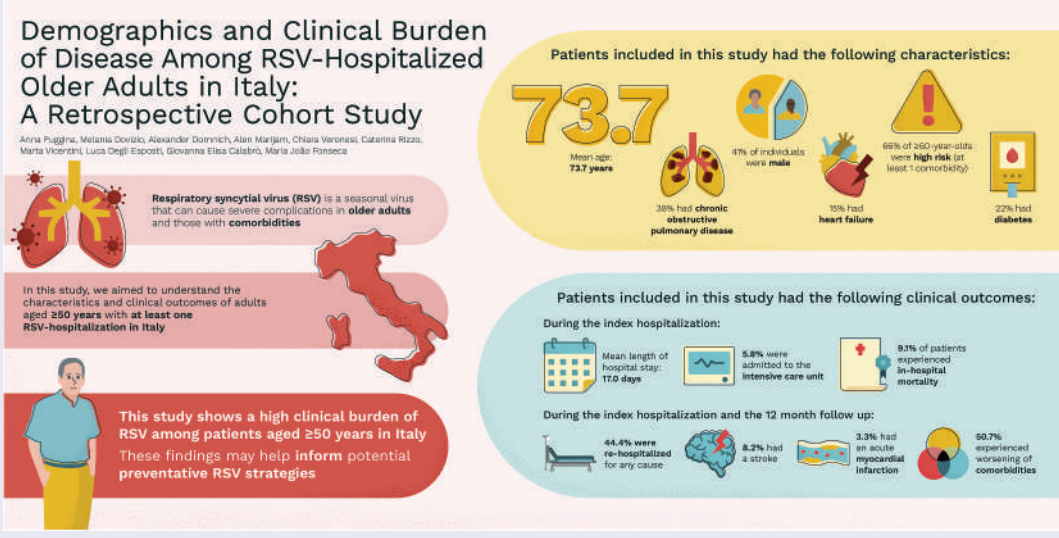
ABSTRACT

Respiratory syncytial virus (RSV) is a leading cause of acute respiratory infection and can lead to severe disease in older adults or those with comorbidities. This analysis aims to evaluate the demographic and clinical burden of RSV hospitalizations among older adults in Italy and inform potential preventative strategies. Adults aged ≥50 years with ≥1 hospitalization discharge diagnosis for RSV from 2010 to 2021 were included. Demographic characteristics before the first RSV hospitalization and clinical outcomes during this hospitalization and the 12 months following are described. Of the 243 patients, mean (SD) age was 73.7 (13.1) years, 40.7% were male, and the most common comorbidities were chronic obstructive pulmonary disease (37.9%), diabetes (21.8%), and heart failure (15.2%). Mean length of index hospitalization was 17.0 days, during which 9.1% of patients died. At index or during the 12-month follow-up, 5.8% had an intensive care unit admission, 61.3% were prescribed antibiotics, 8.2% had a stroke, and 3.3% had an acute myocardial infarction. During the 12-month follow-up, approximately, half of patients experienced worsening of preexisting comorbidities, with notable rates of re-hospitalization and mortality (44.4% and 29.6%). This study shows a high clinical burden of RSV among older adults in Italy, emphasizing a need for improved RSV surveillance, and may guide policymakers and healthcare providers in making informed recommendations for, and implementation of, RSV vaccination in Italy.



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Introduction

Respiratory syncytial virus (RSV) is a seasonal virus that causes acute respiratory infections (ARIs), including upper and lower respiratory tract diseases (URTD, LRTD).[1] These infections, which can progress to severe disease, may lead to complications, exacerbation of preexisting comorbidities, hospitalization, and death, especially in vulnerable populations.[1,2] RSV infections are common in adults and the risk of developing

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severe complications increases with age and presence of comorbidities, likely due to a more compromised immune system or changes in lung physiology.[3,4] Comorbidities associated with increased severity of RSV infection include lung disease, heart disease, and diabetes.[1]

There is a significant estimated global annual burden of RSV in older adults in high-income countries.[5] Using 2019 global population data to model estimates, Savic et al. suggested that there could be 5.2 million RSV-acute respiratory infections (ARI) cases, 470,000 hospitalizations, and 33,000 in-hospital deaths in adults aged ≥60 years in high-income countries.[5] Meanwhile, the RSV Consortium in Europe has estimated RSV-associated hospitalizations in adults in 28 European Union (EU) countries, reporting that RSV causes a high annual number of hospital admissions in adults across the EU (approximately 160,000 per year), with roughly 92% of cases occurring in adults aged ≥65 years.[6] However, these studies are limited by the uncertainty in testing, ascertainment, and coding of RSV.

There are a limited number of studies specifically reporting the clinical burden of RSV in Italy. Every year, there are an estimated 290,000 cases of RSV-ARI, 26,000 hospitalizations, and 1,800 in-hospital deaths in Italian adults aged ≥60 years.[5] Consistent with the rest of Europe, rates of RSV-hospitalization in Italy increase with age and presence of comorbidities, such as chronic obstructive pulmonary disease (COPD), asthma, and cardiovascular disease (CVD).[3] RSV is also associated with increased functional impairment in those aged ≥65 years and those with comorbidities.[7] In a recent systematic literature review investigating RSV disease burden in Italy, the prevalence of RSV was estimated at 4.4% in adults older than working age, with in-hospital mortality as high as 7.2%. However, the study also reported that some RSV clinical outcomes, such as complications and hospitalization rate, were unavailable.[8] In addition to age and comorbidities, factors such as socioeconomic disparities, geographic variability, and healthcare access may influence hospitalization rates in Italy. Prolonged hospitalizations and potential re-hospitalization following RSV infection have a societal and economic impact, highlighting the need for comprehensive public health strategies and targeted interventions to mitigate these burdens. Indeed, the economic impact of RSV hospitalizations among older adults in Italy is also high in those with comorbidities and immunocompromising conditions.[9] In addition, costs associated with RSV hospitalizations are significantly higher than costs associated with hospitalizations for any other cause.[9]

Despite the literature reporting a significant RSV burden in high-income countries, after adjusting for case under-ascertainment, it has been estimated that the true burden of RSV-associated hospitalization could be 2.2 times higher.[10] In Italy, accurate disease burden measurement requires a clear case definition,[11] yet RSV surveillance currently relies on influenza-like illness (ILI) and fever-based case definitions, which may lead to under-reporting and underestimation.[12,13] Many adults with mild-to-moderate RSV do not exhibit fever, resulting in missed cases since they present different symptoms than those typical to ILI.[12] In addition, the ILI case definition underestimates RSV-ARI cases by up to ninefold,[14] and diagnostic testing for RSV is not universally performed, with several available tests showing suboptimal sensitivity.[15,16] Additional challenges include under-reporting and misclassification of RSV in International Classification of Diseases (ICD) codes and under-ascertainment due to varied testing and sampling methodologies.[15–17] Addressing these issues with precise case definitions and enhanced diagnostic strategies is essential for an accurate understanding of RSV's epidemiological impact in Italy.

As there is no RSV-specific treatment, severe RSV cases mainly receive supportive care, such as supplemental oxygen, intravenous fluids, intubation, and mechanical ventilation.[18] The European Medicines Agency has approved the use of three RSV vaccines for the prevention of RSV in adults aged ≥60 years.[19–21] The Vaccination Calendar for Life, an alliance of scientific and professional societies of public health physicians, pediatricians, and general practitioners in Italy, recommends RSV vaccination for those aged ≥75 years and those aged ≥60 years with comorbidities.

More data on the clinical burden of RSV in Italy would support policymakers and clinicians in making informed decisions about RSV vaccination recommendation and implementation strategies in Italy. This study aims to assess the demographic and clinical characteristics of older adults hospitalized for RSV in Italy and describe the short- and long-term outcomes associated with RSV hospitalizations in this population.

Patients and methods/materials and methods

Data source

An observational retrospective analysis was performed on secondary use data extracted from six administrative databases from a pool of Italian Local Health authorities (LHAs) geographically distributed across 11 out of 20 Italian regions, covering approximately 20% of the Italian population. For this analysis, LHA databases were selected by their geographical distribution (Northern/Central/Southern Italy), by data completeness, and by the high-quality linked datasets. These databases store all data concerning the healthcare resources reimbursed by the Italian National Health Service (NHS). Universal healthcare coverage in Italy allows completeness and comprehensiveness of the information contained in these databases, which have been used in previous epidemiological studies.[22] Patients included in these databases are representative, in terms of demographic variables (age and sex), of the overall Italian population.[23,24]

The six administrative databases were the following: a beneficiaries database, containing demographic information on all included patients; a pharmaceuticals database, containing prescription information on all included patients; a hospitalization database, containing hospitalization data for all included patients; a diagnostic test and specialist/outpatient visit database, containing information on tests and visits for all included patients; a patient waiver database, containing active payment waiver codes; and a laboratory test results database, containing laboratory results for a subsample of LHAs.

To guarantee patients' privacy and in full compliance with the European General Data Protection Regulation (GDPR) (2016/679), an anonymous univocal numeric code was assigned to each included participant. No identifiers related to patients were provided to the authors. Appropriate data anonymization procedures are implemented by the LHAs. Anonymous univocal numeric codes allowed electronic linking of patient records across six databases, integrating data to represent patients' entire clinical history. To ensure data reliability and consistency, quality control measures were carried out during the analysis process. These measures included (i) verifying the correct record linkage between the various databases to ensure that all relevant data for each patient were accurately integrated; (ii) ensuring the accurate and consistent anonymous identification of each patient; (iii) validating the correct and coherent identification of diseases among included subjects, based on their clinical characteristics, type of treatment, and follow-up events. These processes helped harmonize data across different sources and addressed potential discrepancies in patient identifiers or variables, thereby enhancing the reliability and replicability of the study. All results of the analyses were produced as aggregated summaries, preventing them from being directly or indirectly attributed to individual patients. Informed consent was not required (pronouncement of the Data Privacy Guarantor Authority, General Authorization for personal data treatment for scientific research purposes – number 9/2014), and approval was obtained from the ethics committees of the involved Local Health Units.

Study design and patient population

Patients within the Italian administrative databases aged ≥50 years (at the index date) who had at least one hospitalization with a primary or secondary discharge diagnosis of RSV (comprising hospitalization due to RSV [ICD-9-CM code 079.6], acute RSV bronchiolitis [ICD-9-CM code 466.11], or RSV pneumonia [ICD-9-CM code 480.1]) from January 1, 2010, to December 31, 2021, were included in this analysis. The index date was defined as the date of the first RSV hospitalization within the study period. Patients were included in the analysis once, based on the first RSV-hospitalization. Subsequent RSV-hospitalizations within 12 months of the first hospitalization were recorded as an outcome, and RSV-hospitalizations occurring after the 12-month follow-up period were not counted toward this analysis. In order to collect long-term (as well as short-term) outcomes, patients were followed up for a 12-month period after their index date (Supplementary Figure S1). To prevent missing data, patients who transferred to a different LHA during the study period were excluded from this analysis.

Data collection

Demographic characteristics at the index date (age, sex), clinical characteristics during the baseline period (Charlson comorbidity index [CCI] and presence of comorbidities), and clinical outcomes during the 12-month follow-up were extracted from six administrative databases. Outcomes for patients aged ≥50 years were stratified by age at index date (≥50 years, ≥60 years, ≥65 years, and ≥75 years). Patients aged ≥60 years were further stratified by whether they were high risk, by the presence of specific comorbidities (COPD, heart failure, diabetes), and by whether they were immunocompromised. Patients were defined as high risk by the presence of at least one of the following comorbidities: COPD, asthma, diabetes, heart failure, advanced liver disease, and renal disease. Immunocompromised patients were defined by the presence of at least one of the following criteria: hematopoietic stem cell transplant (HSCT), solid organ transplantation, chronic inflammatory diseases, human immunodeficiency virus (HIV), end-stage renal disease (ESRD), cancer, and immunosuppressive therapy. Full details as well as the codes and criteria for the identification of comorbidities and immunocompromised patients are shown in Supplementary Table S1.

Clinical outcomes during the first RSV hospitalization and 12-month follow-up included the number and percentage of patients who: had a post-index hospital readmission, underwent invasive hospital procedures (codes for invasive procedures are detailed in Supplementary Table S1), developed RSV or LRTD (an occurrence of RSV was defined as reinfection [i.e., following the initial RSV hospitalization] and occurrence of LRTD was defined as infection either during the index RSV-hospitalization or during the 12-month follow-up period), had an acute myocardial outcome, presented a worsening of preexisting conditions (codes and proxies in Supplementary Table S1), were prescribed with several classes of medications, or died due to any cause during the index hospitalization, within a month of the index hospitalization or during the 12-month follow-up period. Worsening of a preexisting comorbidity was defined as at least one hospitalization due to a specific comorbidity after the index date, among those who already had comorbidity before the index date. Hospitalizations for a specific comorbidity were identified using codes and proxies, which are detailed in Supplementary Table S1.

Data analysis

Data were analyzed using STATA SE version 17.0 (StataCorp LLC, College Station, TX, USA). Continuous data were summarized in terms of the number of observations, mean, standard deviation (SD), median, lower and upper quartiles, and interquartile range (IQR) to provide a comprehensive description of the data and ensure that the descriptive statistics accurately reflected the characteristics of the dataset. While skewness was not explicitly calculated, the inclusion of both parametric and non-parametric measures helps mitigate the impact of non-normal distributions, offering a more complete understanding of the data. Categorical data were summarized in terms of the number and proportion of patients providing data, and no formal statistical comparisons were performed.

Results

Demographics and clinical characteristics

A total of 243 patients aged ≥50 years with at least one hospitalization with a diagnosis discharge code for RSV between

January 1, 2010, and December 31, 2021, were included in this analysis. The mean age of patients at the index date was 73.7 years and 40.7% were male. A high and very high CCI score was observed in 20.6% and 6.6% of patients, respectively, and the most common preexisting comorbidities were COPD (37.9%), diabetes (21.8%), and heart failure (15.2%). Among patients aged ≥50 years, 44.4% were immunocompromised.

Of the patients aged ≥60 years ($n = 201$), 65.7% were classified as high risk, meaning that the majority of those included in this analysis had at least one comorbidity. The most common preexisting comorbidities in patients aged ≥60 years were similar to those aged ≥50 years: COPD (40.3%), diabetes (23.9%), and heart failure (17.4%). Furthermore, 42.3% of patients aged ≥60 years were immunocompromised.

Demographic and clinical characteristics stratified by age and whether patients were high risk or had preexisting comorbidities are presented in Tables 1 and 2, respectively.

Clinical outcomes

The clinical outcomes recorded during index hospitalization and the 12-month follow-up period were stratified by age (Table 3) and for those aged ≥60 years, by risk status, presence of comorbidities, and immunocompromised status (Table 4).

Index hospitalization

The mean (SD) length of index hospitalization among those aged ≥50 years was 17.0 (20.8) days. A similar length of index hospitalization was observed for individuals aged ≥60 years, ≥65 years, and ≥75 years (Table 3). Among those aged ≥60 years with specific comorbidities, the longest index hospital stay was reported in those with heart failure (mean [SD] of 20.0 [20.0] days; Table 4).

Index and post-index hospitalization

During index hospitalization and 12 months following, 5.8% of patients aged ≥50 years were admitted to the intensive care unit (ICU; Table 3), 2.5% required intubation, 3.3% required high-flow oxygen therapy, and 7.0% required mechanical ventilation. Following the index hospitalization, 44.4% of individuals were re-hospitalized for any cause (Table 3 ; Figure 1). The 10 most common causes of re-hospitalization during the 12-month follow-up period are reported in Table 5; the most frequent principal diagnoses for re-hospitalization were related to the respiratory system (66.3%), circulatory system

Table 1. Baseline demographics for RSV-hospitalized patients in Italy between 2010 and 2021, stratified by age.

	≥50 years ($n = 243$)	≥60 years ($n = 201$)	≥65 years ($n = 176$)	≥75 years ($n = 120$)
Age, mean (SD)	73.7 (13.1)	77.8 (10.4)	80.1 (9.1)	85.0 (6.3)
Male, n (%)	99 (40.7)	78 (38.8)	61 (34.7)	38 (31.7)
CCI, mean (SD)	1.9 (1.5)	1.9 (1.5)	1.9 (1.4)	1.8 (1.4)
Low CCI = 0, n (%)	39 (16.0)	30 (14.9)	24 (13.6)	18 (15.0)
Medium CCI = 1 or 2, n (%)	138 (56.8)	117 (58.2)	106 (60.2)	70 (58.3)
High CCI = 3 or 4, n (%)	50 (20.6)	41 (20.4)	35 (19.9)	26 (21.7)
Very High CCI ≥ 5, n (%)	16 (6.6)	13 (6.5)	11 (6.3)	6 (5.0)
Preexisting conditions, n (%)				
COPD	92 (37.9)	81 (40.3)	71 (40.3)	45 (37.5)
Asthma	8 (3.3)	8 (4.0)	8 (4.5)	5 (4.2)
Diabetes	53 (21.8)	48 (23.9)	43 (24.4)	28 (23.3)
Heart failure	37 (15.2)	35 (17.4)	32 (18.2)	25 (20.8)
Advanced liver disease	4 (1.6)	4 (2.0)	4 (2.3)	4 (3.3)
Renal disease	31 (12.8)	30 (14.9)	26 (14.8)	19 (15.8)

Conditions were defined as preexisting if they were present before the index date. Abbreviations: CCI, Charlson Comorbidity Index; COPD, chronic pulmonary obstructive disorder; SD, standard deviation.

Table 2. Baseline demographics for RSV-hospitalized patients aged ≥60 years in Italy between 2010 and 2021, stratified by comorbidity and immunocompromised status.

	COPD ($n = 81$)	Heart failure ($n = 35$)	Diabetes ($n = 48$)	Immunocompromised ($n = 85$)
Age, mean (SD)	76.6 (9.9)	80.2 (10.6)	77.1 (10.3)	77.4 (10.0)
Male, n (%)	30 (37.0)	13 (37.1)	20 (41.7)	22 (25.9)
CCI, mean (SD)	2.1 (1.5)	2.7 (1.6)	2.8 (1.6)	2.4 (1.7)
Low CCI = 0, n (%)	5 (6.2)	<4	<4	8 (9.4)
Medium CCI = 1 or 2, n (%)	50 (61.7)	15 (42.9)	22 (45.8)	46 (54.1)
High CCI = 3 or 4, n (%)	19 (23.5)	13 (37.1)	18 (37.5)	22 (25.9)
Very High CCI ≥ 5, n (%)	7 (8.6)	6 (17.1)	7 (14.6)	9 (10.6)
Preexisting conditions, n (%)				
COPD	81 (100.0)	20 (57.1)	21 (43.8)	39 (45.9)
Asthma	7 (8.6)	<4	<4	5 (5.9)
Diabetes	21 (25.9)	15 (42.9)	48 (100.0)	14 (16.5)
Heart failure	20 (24.7)	35 (100.0)	15 (31.3)	16 (18.8)
Advanced liver disease	<4	<4	<4	3 (3.5)
Renal disease	17 (21.0)	12 (34.3)	10 (20.8)	18 (21.2)

Conditions were defined as preexisting if they were present before the index date. Abbreviations: CCI, Charlson Comorbidity Index; COPD, chronic pulmonary obstructive disorder; SD, standard deviation.

Table 3. Clinical outcomes, at the index hospitalization and during the 12-month follow-up, for RSV-hospitalized patients in Italy between 2010 and 2021, stratified by age.

	≥50 years (*n* = 243)	≥60 years (*n* = 201)	≥65 years (*n* = 176)	≥75 years (*n* = 120)
Index hospitalization				
Length of index hospital stay (days), mean (SD)	17.0 (20.8)	16.4 (16.0)	16.2 (14.3)	17.1 (15.3)
Length of index hospital stay (days), median (IQR)	12 (7–20)	12 (7–20)	13 (7–20)	13 (7–21)
Index and post-index hospitalization, n (%)				
ICU admission (index included)	14 (5.8)	11 (5.5)	9 (5.1)	6 (5.0)
Hospitalization reporting intubation procedure (index included)	6 (2.5)	5 (2.5)	4 (2.3)	<4
Hospitalization reporting high-flow oxygen therapy (index included)	8 (3.3)	6 (3.0)	6 (3.4)	4 (3.3)
Hospitalization reporting other continuous mechanical ventilation (index included)	17 (7.0)	13 (6.5)	11 (6.3)	6 (5.0)
All-cause post-index hospitalization	108 (44.4)	88 (43.8)	77 (43.8)	52 (43.3)
Diagnosis (index and post-index), n (%)				
RSV/LRTD*	62 (25.5)	48 (23.9)	43 (24.4)	30 (25.0)
AMI, n (%)	8 (3.3)	7 (3.5)	7 (4.0)	6 (5.0)
Stroke, n (%)	20 (8.2)	20 (10.0)	17 (9.7)	14 (11.7)
Deaths (index and post-index), n (%)				
Deaths during index hospitalization (in-hospital mortality)	22 (9.1)	20 (10.0)	19 (10.8)	16 (13.3)
Deaths within 1-month post-index hospitalization	36 (14.8)	34 (16.9)	33 (18.8)	26 (21.7)
All-cause deaths within 12 months post-index hospitalization	72 (29.6)	68 (33.8)	64 (36.4)	50 (41.7)

*Patients with at least one record of RSV during the follow-up (not including the index hospitalization) or LRTD during the index hospitalization or follow-up. Abbreviations: AMI, acute myocardial infarction; ICU, intensive care unit; IQR, interquartile range; LRTD, lower respiratory tract disease; RSV, respiratory syncytial virus; SD, standard deviation.

Table 4. Clinical outcomes, at the index hospitalization and during the 12-month follow-up, for RSV-hospitalized patients aged ≥60 years in Italy between 2010 and 2021, stratified by whether they were high risk, had specific comorbidities or were immunocompromised.

	High risk (*n* = 132)	COPD (*n* = 81)	Heart failure (*n* = 35)	Diabetes (*n* = 48)	Immuno-compromised (*n* = 85)
Index hospitalization					
Length of index hospital stay (days), mean (SD)	16.2 (15.3)	17.1 (16.6)	20.0 (20.0)	18.5 (17.8)	16.4 (14.0)
Length of index hospital stay (days), median (IQR)	12 (7–21)	12 (8–21)	14 (9–23)	12 (7–23)	13 (8–20)
Index and post-index hospitalization, n (%)					
ICU admission (index included)	8 (6.1)	7 (8.6)	<4	<4	5 (5.9)
Hospitalization reporting intubation procedure (index included)	<4	<4	<4	<4	<4
Hospitalization reporting high-flow oxygen therapy (index included)	5 (3.8)	5 (6.2)	<4	0 (0.0)	4 (4.7)
Hospitalization reporting other continuous mechanical ventilation (index included)	10 (7.6)	8 (9.9)	<4	4 (8.3)	6 (7.1)
All-cause post-index hospitalization	61 (46.2)	35 (43.2)	18 (51.4)	25 (52.1)	45 (52.9)
Diagnosis (index and post-index), n (%)					
RSV/LRTD*	30 (22.7)	20 (24.7)	6 (17.1)	10 (20.8)	26 (30.6)
AMI, n (%)	4 (3.0)	<4	0 (0.0)	<4	<4
Stroke, n (%)	14 (10.6)	7 (8.6)	<4	6 (12.5)	8 (9.4)
Deaths (index and post-index), n (%)					
Deaths during index hospitalization (in-hospital mortality)	13 (9.8)	10 (12.3)	<4	6 (12.5)	6 (7.1)
Deaths within 1-month post-index hospitalization	24 (18.2)	15 (18.5)	6 (17.1)	11 (22.9)	12 (14.1)
All-cause deaths within 12 months post-index hospitalization	49 (37.1)	28 (34.6)	14 (40.0)	20 (41.7)	31 (36.5)

*Patients with at least one record of RSV during the follow-up (not including the index hospitalization) or LRTD during the index hospitalization or follow-up. Abbreviations: AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disorder; ICU, intensive care unit; IQR, interquartile range; LRTD, lower respiratory tract disease; RSV, respiratory syncytial virus; SD, standard deviation.

(20.6%), and infectious/parasitic diseases (9.5%). Among high-risk individuals aged ≥60 years, 46.2% were re-hospitalized in the 12 months after the initial RSV hospitalization. Furthermore, among individuals aged ≥60 years with specific comorbidities, 43.2% with COPD, 51.4% with heart disease, and 52.1% with diabetes were hospitalized for any cause. Of patients who were immunocompromised, 52.9% were hospitalized for any cause during the 12-month follow-up (Table 4).

Reinfection with RSV (i.e., not including the RSV occurrence that led to the index hospitalization) or LRTD during the index hospitalization and the 12-month follow-up period occurred in 25.5% of patients aged ≥50 years. Similar values were reported for the other age groups (Table 3). The proportion of patients reinfected with RSV or experiencing LRTD was highest among the immunocompromised population (30.6%; Table 4). Among those aged ≥50 years, 3.3% experienced acute myocardial infarction (AMI), and 8.2% experienced a stroke during the 12-month follow-up period (index hospitalization included). These values were 5.0% and 11.7%, respectively, among those aged ≥75 years (Table 3).

The worsening of preexisting comorbidities, namely COPD, diabetes, heart failure, and renal disease, during the 12-month follow-up period occurred in approximately 50% of patients (Table 6, Figure 2).

The 10 most frequently prescribed medications at index hospitalization and during the 12-month follow-up period are reported in Table 7. The most frequently prescribed medications were for acid-related disorders (66.3%), antibiotics for systemic use (61.3%), anti-thrombotic agents (51%), and drugs for obstructive airway diseases (44.9%).

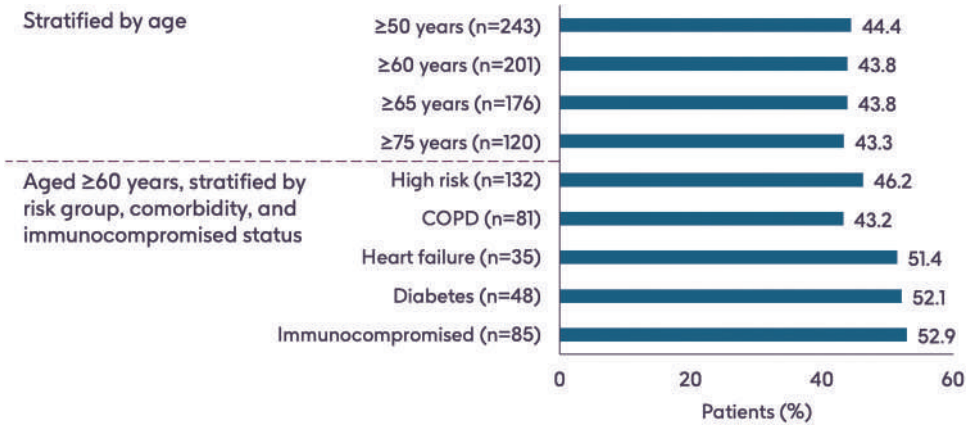

Figure 1. All-cause post-index hospitalization during the 12-month follow up. Abbreviations: COPD, chronic obstructive pulmonary disease; RSV, respiratory syncytial virus

Table 5. Most common causes of re-hospitalization during the 12-month follow-up in RSV-hospitalized patients aged ≥50 years and ≥60 years in Italy between 2010 and 2021.

	≥50 years ($n = 243$)		≥60 years ($n = 201$)	
Cause of hospitalization	n	%	n	%
Respiratory system	161	66.3	133	66.2
Circulatory system	50	20.6	44	21.9
Infectious and parasitic diseases and disorders	23	9.5	21	10.4
Myeloproliferative diseases and disorders (poorly differentiated neoplasms)	19	7.8	13	6.5
Blood and blood-forming organs and immunological disorders	15	6.2	8	4.0
Digestive system	12	4.9	11	5.5
Musculoskeletal system and connective tissue	11	4.5	8	4.0
Nervous system	11	4.5	11	5.5
Kidney and urinary tract	10	4.1	8	4.0
Factors influencing health status*	6	2.5	4	2.0

*Factors influencing health status included: persons encountering health services for examinations, genetic carrier and genetic susceptibility to disease, resistance to antimicrobial drugs, estrogen receptor status, retained foreign body fragments, hormone sensitivity malignancy status, persons with potential health hazards related to communicable diseases, persons encountering health services in circumstances related to reproduction, encounters for other specific healthcare, persons with potential health hazards related to socioeconomic and psychosocial circumstances, do not resuscitate status, blood type, body mass index, persons encountering health services in other circumstances, persons with potential health hazards related to family and personal history and certain conditions influencing health status.[25]

Table 6. Worsening of preexisting comorbidities for RSV-hospitalized patients aged ≥50 years, ≥60 years and ≥65 years in Italy between 2010 and 2021.

	≥50 years ($n = 243$)		≥60 years ($n = 201$)		≥65 years ($n = 176$)	
	At baseline, n	Worsening comorbidity, n (%)	At baseline, n	Worsening comorbidity, n (%)	At baseline, n	Worsening comorbidity, n (%)
COPD	92	47 (51.1)	81	42 (51.9)	71	39 (54.9)
Diabetes	53	26 (49.1)	48	24 (50.0)	43	23 (53.5)
Heart failure	37	20 (54.1)	35	18 (51.4)	32	18 (56.3)
Renal disease	31	15 (48.4)	30	15 (50.0)	26	11 (42.3)

Abbreviations: COPD, chronic obstructive pulmonary disease.

Mortality

During the index hospitalization, in-hospital mortality occurred in 9.1% of patients aged ≥50 years. In the month following index hospitalization, 14.8% of patients died. In-hospital deaths and deaths within the month of index hospitalization increased with age, reaching 13.3% and 21.7%, respectively, in those aged ≥75 years (Table 3, Figure 3). In-hospital mortality for patients considered high risk was 9.8%, while 18.2% died within a month of index hospitalization (Table 4, Figure 4). During the 12-month follow-up period, 29.6% of patients aged ≥50 years died due to any cause (Table 3) and all-cause mortality was 37.1% in high-risk patients.

Discussion

It is widely noted that the incidence of RSV infection is high in older adults and those with comorbidities,[3] with RSV infections in these individuals often leading to severe complications.[4] Understanding the clinical burden of RSV is central to decision-making and patient management, to facilitate effective disease prevention and treatment. This retrospective cohort study investigated the demographic characteristics and clinical outcomes among older adults in the 12 months following RSV hospitalization in Italy.

The demographic characteristics of patients included in this study corroborate the notion that RSV incidence is higher in older individuals and those with comorbidities; the mean age

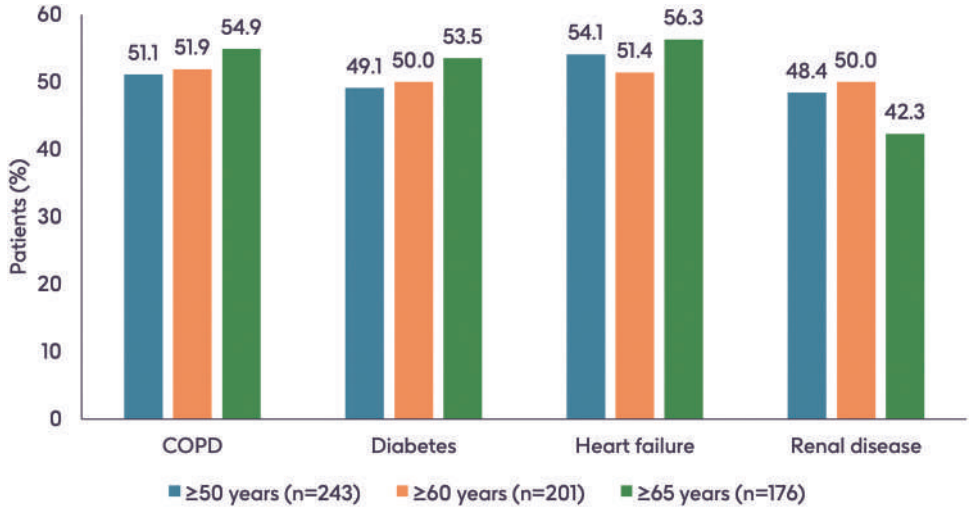

Figure 2. Worsening of pre-existing comorbidities for RSV-hospitalized patients aged ≥50 years in Italy between 2010 and 2021, stratified by age. Abbreviations: COPD, chronic obstructive pulmonary disease; RSV, respiratory syncytial virus.

Table 7. Most commonly prescribed therapies at the index hospitalization and during the 12-month follow-up in RSV-hospitalized patients aged ≥50 years and ≥60 years in Italy between 2010 and 2021.

		≥50 years ($n = 243$)		≥60 years ($n = 201$)	
ATC CODE	Prescription drugs	n	%	n	%
A02	Drugs for acid-related disorders	161	66.3	133	66.2
J01	Antibacterials for systemic use	149	61.3	123	61.2
B01	Anti-thrombotic agents	124	51	111	55.2
R03	Drugs for obstructive airway diseases	109	44.9	88	43.8
H02	Corticosteroids for systemic use	109	44.9	88	43.8
C07	Beta blocking agents	97	39.9	80	39.8
C03	Diuretics	96	39.5	83	41.3
C09	Agents acting on the renin-angiotensin system	94	38.7	81	40.3
A11	Vitamins	64	26.3	55	27.4
C10	Lipid modifying agents	63	25.9	57	28.4

Abbreviations: ATC, Anatomical Therapeutic Chemical.

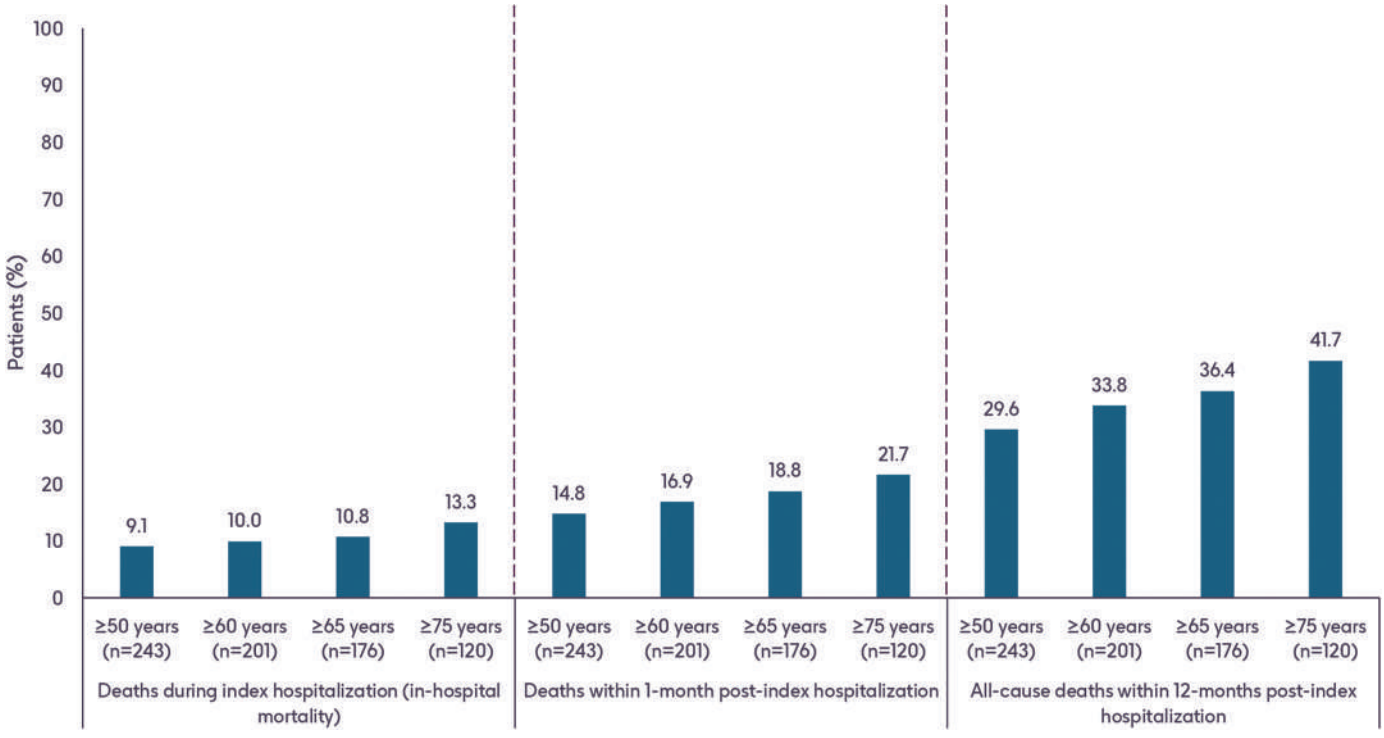

Figure 3. Mortality among RSV-hospitalized patients aged ≥50 years in Italy between 2010 and 2021, stratified by age. Abbreviations: RSV, respiratory syncytial virus.

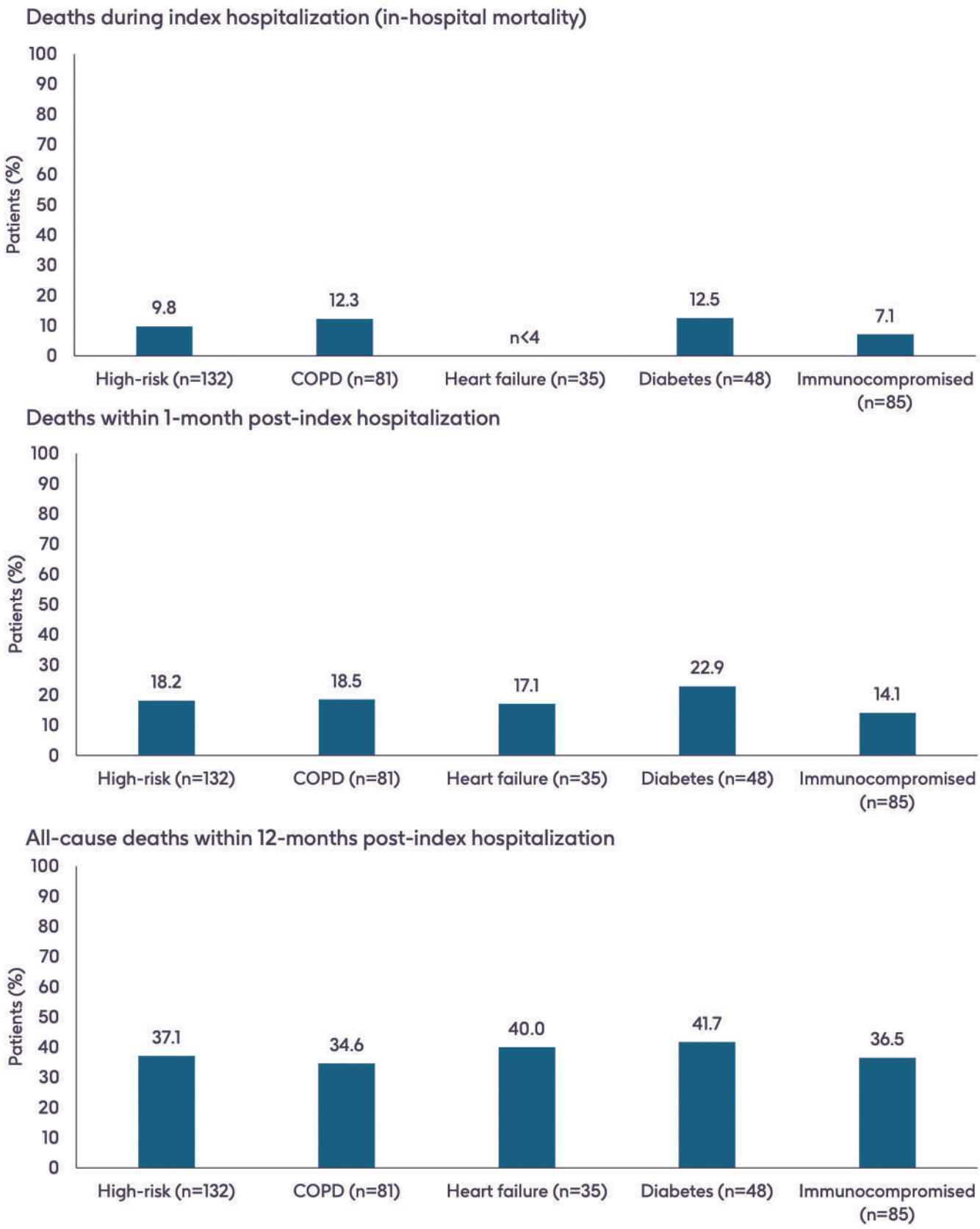

Figure 4. Mortality among RSV-hospitalized patients aged ≥60 years in Italy between 2010 and 2021, stratified by risk group, comorbidity, and immunocompromised status. To ensure patient anonymization, values are presented as n <4 for outcomes that were reported in fewer than four patients. Abbreviations: COPD, chronic obstructive pulmonary disease; RSV, respiratory syncytial virus.

was 73.7 years and 65.7% of patients had at least one comorbidity. When assessing the duration of index hospitalization in the cohort, mean (SD) length of index hospitalization was 17.0 (20.8) days, and the median (IQR) length of stay was 12 (7–20) days. While the data indicated high variance around the mean and a negative skew, results were consistent with those published elsewhere, where median (IQR) length of stay during a 2-year cohort study was 11 (7–16) for RSV hospitalized patients.[26] Additionally, in published literature, mortality among RSV-hospitalized individuals is reported to increase with age.[27,28] The present analysis further supports this notion, as nearly 10% of patients died during index hospitalization, and mortality in the month and year following index hospitalization was higher in those aged ≥75 years compared to those aged ≥50 years.

In general, reinfection with RSV is considered to have mild consequences.[7] However, the risk of more severe complications is higher in older adults and those with immunocompromising conditions, likely due to changes in lung physiology and weaker immune systems which decrease an individual's infection-fighting capacity.[4,7] In this study, a quarter of patients experienced RSV reinfection (not including the index hospitalization) or LRTD during the index hospitalization and 12-month follow-up period, with a higher rate of reinfection or LRTD in patients who were immunocompromised. These reinfection rates indicate a need for better RSV management strategies for high-risk populations, including increased vaccinations.

Older adults comprise a high proportion of RSV-associated hospitalizations. In a study investigating countries within the EU, 92% of adult RSV hospitalizations occurred in those aged ≥65 years.[6] Nearly half of patients included in this analysis were re-hospitalized for any cause during the 12-month follow-up period, with respiratory system-related causes forming the most common principal diagnosis. Furthermore, RSV is also associated with high levels of hospitalization among patients with comorbidities.[3,7] Here, re-hospitalization during the follow-up period occurred in 52.9% of patients who were immunocompromised. Together, these high re-hospitalizations levels indicate that older adults and high-risk patients often experience general health complications following RSV infection. Indeed, RSV has previously been shown to worsen health conditions; a study conducted in the UK and the Netherlands over three consecutive RSV seasons reported that 8.7% of outpatient-managed COPD exacerbations were due to RSV.[29] In the present analysis, during the 12 months following RSV hospitalization, approximately half of patients experienced worsening of preexisting comorbidities. The worsening of preexisting conditions due to RSV may contribute to higher morbidity and mortality, highlighting the importance of integrating RSV management into broader chronic disease care strategies.

It is important to note that during the 12-month follow-up period (index included), antibacterials for systemic use were the second most prescribed medication, with prescriptions recorded for over 60% of RSV-hospitalized individuals. High levels of antibiotic use among patients with RSV have been reported in Italy.[13,30] This finding should not be overlooked; overuse and misuse of antibiotics contribute to the increasingly pressing global threat of antimicrobial resistance, estimated to cause up to 10 million deaths per year by 2050.[31] Achieving a high rate of RSV vaccination coverage could reduce the number of clinical cases that often lead to antibiotic prescriptions and may complement national efforts to reduce antibiotic usage.[32]

Overall, this study highlights the clinical burden of RSV on older adults, which increases strain on healthcare systems by raising demand for hospital resources, thereby adding to the economic burden of disease. There is a clear need for enhanced long-term care solutions for older patients with RSV. One such option is to leverage preventative measures against initial RSV infection, such as vaccination, particularly among older adults, high-risk individuals, and those who are immunocompromised, to reduce the risk of more serious complications. Additionally, long-term clinical outcomes among adults with RSV are not commonly reported in the literature; this study adds to this limited body of evidence, reporting 12-month clinical outcomes in older adults hospitalized with RSV in Italy.

This study is characterized by some limitations. First, data were not originally collected for research purposes, but for the purpose of reimbursement. As much of this analysis, such as the diagnosis of RSV, comorbidities, and some clinical outcomes, relies on codes and proxies, coding input errors or even incomplete capture of certain variables may have occurred and impacted the analysis. Although administrative databases are primarily intended for administrative management, their use for healthcare research purposes is increasing, as they represent readily available sources of real-world healthcare data on a large population of unselected patients.[33]

Similar to previously conducted studies, this analysis is potentially limited by the underdiagnosis of RSV, due to current clinical practice, and research issues, such as the lack of a unified RSV definition for case research.[10,15] As a result, the number of RSV-associated hospitalizations in the adult and older adult population in industrialized countries is likely greater than is currently reported. Indeed, it is estimated that the incidence of RSV hospitalizations could be up to 2.2 times higher than that suggested in the literature,[10] with one study conducted across 937 hospitals in the United States finding that only 4.3% of patients hospitalized with lower respiratory tract infections were tested for RSV.[34] Until there is wider and more consistent testing of respiratory diseases, the true overall clinical burden of RSV will remain unknown. This underreporting may have led to the few RSV cases found, with only 243 patients aged ≥50 years with ≥1 hospitalization due to RSV captured by the database, leading to a small sample size in some subgroups.

The limited RSV surveillance system and irrelevance of testing for RSV in the past due to a lack of specific treatments or vaccines means it is likely that no specific RSV ICD codes were given. As described above, the under-ascertainment of RSV is well established and so it is possible that cases of RSV, and therefore clinical outcomes associated with RSV, were not fully captured in this analysis.[17] Misclassification of RSV-coded hospitalizations has been reported in Denmark, and it is possible this also occurs in Italy, leading to potential

inaccuracies in conclusions and highlighting a limitation to using coding-based case identification.[17]

Although this analysis was conducted using a 20% sample of the Italian population, the sample used was deemed representative (in terms of age and sex) of the entire Italian population and, therefore, the clinical characteristics reported here are likely also representative.[23,24] However, it is important to acknowledge that the sample might not fully capture regional variations in healthcare access or RSV diagnosis rates. Any such variation may stem from differences in regional healthcare policies, diagnostic practices, and resource availability. Despite these potential limitations, the inclusion of data from LHAs across 11 regions provides a broad geographic distribution, which enhances the generalizability of the findings to a significant proportion of the Italian population.

Lastly, the 12-month follow-up data in this analysis were not compared to a non-RSV control population, and therefore, these outcomes may not be RSV-related. An in-depth analysis comparing post-index RSV clinical outcomes with a control-matched cohort is required to further understand the burden of disease associated with RSV. Regarding the overall study period, the present analysis spans 11 years and does not account for the potential impact of advances in RSV diagnosis and management during this timeframe. A temporal stratification of results could have provided insights into these advancements.

To plan and implement effective future preventive strategies in Italy, several barriers must be addressed. Awareness of RSV is low among older adults aged ≥50 years, with 60% unaware of the virus.[35] Currently, Italy's RSV surveillance system relies on an ILI case definition rather than ARI, which underestimates the incidence of RSV.[14] Accurate reporting of RSV cases and complications is essential, and shifting the surveillance system to ARI could be a critical first step. Enhanced testing and improved surveillance, along with increased vaccine availability, can help prevent cases and complications, benefiting fragile populations.[12]

Improving access to the RSV vaccine, such as through co-administration with the seasonal flu vaccine, could boost uptake and lower immunization barriers, leading to better public health outcomes. In Italy, health promotion and preventative strategies account for only 5% of the National Health Fund.[36] While the availability of new vaccines represents an opportunity to improve individual and collective protection, they can also create problems, such as the financial commitment that must be sustained for additional expenses, including costs for new vaccines and training. These aspects, combined with the limited availability of healthcare resources, may represent an obstacle to the inclusion of new RSV vaccinations in the Italian National Immunization Program, despite approval and recommendations of RSV vaccination by several other countries' health authorities and scientific societies.[37–40]

Regional differences in vaccination management and suboptimal collaboration among healthcare specialists can hinder program effectiveness. The integrated life course approach to vaccination, part of the European Immunization Agenda 2030, aims to ensure that everyone benefits from recommended immunizations throughout their life, using lessons from the COVID-19 pandemic to establish or reinforce immunization of older adults and those with comorbidities.[41] For the life course approach to vaccination to succeed, it is important that vaccination of fragile populations is organized in collaboration with different healthcare professionals. A collaborative approach is in line with that of value-based healthcare and considers the wider impact of vaccinations, including their personal, allocative, technical, and societal value.[42]

Future studies should focus on assessing the economic burden of RSV and how this impacts the NHS. Additionally, evaluating the cost-effectiveness of various RSV vaccination strategies within the Italian healthcare system context could provide valuable insights for optimizing resource allocation and improving patient outcomes. In addition, future studies should focus on inferential analysis to assess potential differences in demographics, clinical characteristics, and outcomes associated with RSV hospitalization between important patient subgroups.

Conclusions

Despite possible underestimation of RSV, this analysis reports demographic and clinical outcomes in older adults hospitalized for RSV in Italy. The 12-month clinical outcomes reported in this analysis highlight the importance of vaccination for individual protection, collective protection, and healthcare system sustainability. Italian RSV vaccination recommendations and inclusion of a diverse array of healthcare professionals to promote vaccine uptake among high-risk populations need to be established. Co-administration of the RSV vaccine with the seasonal influenza vaccine could further improve vaccination rates by offering increased accessibility. In conclusion, this analysis highlights an unmet need for preventative RSV strategies among older adults and those with comorbidities. Future prospective studies in both the inpatient and outpatient setting may help to describe long-term patient outcomes, natural history, and epidemiology of RSV in older adults. This analysis could be used to inform cost-effectiveness analyses in the Italian context that may assist policymakers and healthcare professionals in making informed decisions about recommendations for, and implementation of, RSV vaccination in Italy.

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Disclosure statement

AP, AM and MV: employees of and hold financial equities in GSK; MD and CV: employees of CliCon S.r.l; LDE: no conflicts of interest to declare; AD: received consulting fees from CSL Seqirus and VIHTALI, and payment or honoraria from SD Biosensor and CSL Seqirus; CR: received payment or honoraria from AstraZeneca, GSK, MSD, CSL Seqirus, and Sanofi; GEC: received grants or contracts, consulting fees, and payment or honoraria from GSK; participated on a Data Safety Monitoring Board or Advisory Board for GSK; Director of VIHTALI, a spin-off of Università Cattolica del Sacro Cuore, Rome, Italy; MJF: employee of, holds financial equities in GSK and has received support for attending meetings and/or travel from GSK as an employee.

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Authors' contributions

Substantial contributions to study conception and design: AP, MD, AM, MV, MJF; substantial contributions to analysis and interpretation of the data: AP, MD, AD, AM, CV, CR, MV, LDE, GEC, MJF; drafting the article or revising it critically for important intellectual content: AP, MD, AD, AM, CV, CR, MV, LDE, GEC, MJF; final approval of the version of the article to be published: AP, MD, AD, AM, CV, CR, MV, LDE, GEC, MJF.

Data availability statement

Data used for this publication was generated by CliCon S.r.l. For access to anonymized subject-level data, please contact CliCon S.r.l.

Ethical approval statement

This study complies with all applicable laws regarding participant privacy. No direct subject contact or primary collection of individual human subject data occurred. Results of this analysis were presented in tabular form and aggregate analyses omitted subject identification, meaning informed consent was not required.

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