BMJ Open

Disease burden caused by RSV compared to influenza among adults.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-060805
Article Type:	Original research
Date Submitted by the Author:	05-Jan-2022
Complete List of Authors:	Hämäläinen, Aleksi; University of Eastern Finland Institute of Clinical Medicine; Kuopio University Hospital Savinainen, Ellamaria; University of Eastern Finland Institute of Clinical Medicine; Kuopio University Hospital Hämäläinen, Sari; Kuopio University Hospital Sivenius, Katariina; Kuopio University Hospital Kauppinen, Juha; ISLAB Koivula, Irma; Kuopio University Hospital Patovirta, Riitta-Liisa; Kuopio University Hospital
Keywords:	Respiratory infections < THORACIC MEDICINE, Epidemiology < INFECTIOUS DISEASES, Infection control < INFECTIOUS DISEASES

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: Disease burden caused by RSV compared to influenza among adults.

Authors: Aleksi Hämäläinen[1,2], Ellamaria Savinainen[1,2], Sari Hämäläinen[2], Katariina Sivenius[2], Juha Kauppinen[3], Irma Koivula[2], Riitta-Liisa Patovirta[2]

Affiliations

[1] University of Eastern Finland Institute of Clinical Medicine, Kuopio, Pohjois-Savo, FI

[2] Department of Medicine, Kuopio University Hospital, Kuopio, Pohjois-Savo, FI

[3] Eastern Finland Laboratory Centre Joint Authority Enterprise (ISLAB), Kuopio, Pohjois-Savo, FI

Corresponding author: Aleksi Hämäläinen

Department of Medicine, Kuopio University Hospital, Kuopio, Pohjois-Savo, FI

Yliopistonranta 1, 70210 Kuopio

E-mail: aleh@student.uef.fi

Phone number: +358405496077

Word count: 3074

Keywords: Respiratory infections; Epidemiology; Infection control

Abstract

Objectives: Respiratory syncytial virus (RSV) is one of the most important causes of lower respiratory tract illnesses. In this study, we examined the number and severity of RSV infections among adult patients. The underlying diseases and background information of patients with RSV were examined and compared to the patients with influenza.

Design: Retrospective cohort study.

Setting: Patients receiving tertiary care services in Kuopio University Hospital (KUH) district in Eastern Finland.

Participants: 725 patients (152 with RSV infection and 573 with influenza) treated in KUH between November 2017 and May 2018.

Primary and secondary outcome measures: Hospitalization and mortality.

Results: Compared to influenza, RSV caused a more serious disease in terms of hospitalization (84.2% vs. 66.0%, p<0.001), incidence of pneumonia (37.5% vs. 23.2%, p<0.001), need for antibiotics (67.1% vs. 47.3%, p<0.001) and supplementary oxygen (50.7% vs. 31.2%, p<0.001). The all-cause mortality during hospitalization and 30 days after discharge was higher among the RSV-infected patients (8.6% vs. 3.5%, p=0.010). Solid malignancies (23.1% vs. 5.0%, p=0.042), chronic kidney disease (30.8% vs. 5.8%, p=0.011) and higher number of underlying conditions (3.2 vs. 2.2, p=0.016) were more common among the RSV-

infected non-survivors compared to survivors. RSV was an independent risk factor for hospitalization (aOR 2.035; 95% CI 1.17 to 3.55) and mortality (aOR 2.288; 95% CI 1.09 to 4.81) compared to influenza.

Conclusions: Among all the screened patients, those with RSV infection were older and had more underlying conditions than patients with influenza. They had increased likelihood of hospitalization and mortality when compared to influenza. Solid malignancies and chronic kidney disease seemed to be independent risk factors for death among RSV-infected patients. During RSV and influenza epidemics, it is important to test patients with respiratory symptoms for RSV and influenza to prevent the spread of the infections among elderly and chronically ill patients.

Strengths and limitations of this study

- Respiratory syncytial virus (RSV) is one of the most important causes of lower respiratory tract illnesses.
- RSV has been discovered to cause mortality equal or close to the mortality related to influenza among elderly patients.
- This retrospective cohort study compares the effects of multiple background factors on clinical outcomes in RSV- and influenza-infected adult patients.
- The major limitation of the study was that there was no possibility to gather information about patient recovery from primary care facilities.
- During the study, there was a major RSV epidemic in Finland explaining the high number of RSV infections compared to influenza.

Introduction

Respiratory syncytial virus (RSV) is one of the most important causes of lower respiratory tract illnesses [1]. RSV bronchitis or pneumonia can lead to hospitalization and even death, especially in elderly people with underlying conditions [2]. A major RSV epidemic is observed in Finland every other winter, often starting in November-December. In addition, minor epidemics occur between the major ones [3,4].

In adults ≥50 years of age, RSV is responsible for 1-10% of acute respiratory tract infections [5]. RSV hospitalization rates in adults ≥65 years of age are estimated to be 1/1000 and 0.3/1000 person-years in industrialized and developing countries, respectively [6]. The mortality rate among the elderly patients treated in hospital due to RSV infection varies between 1.1-15.9% [7,8,9,10,11,12] and the 30-day all-cause mortality rate varies between 3.2-13.7% [9,10,12,13,14].

Among elderly patients living in long-term care facilities, RSV is estimated to cause 7.2-11.4% of the hospitalizations among patients with chronic pulmonary diseases [2]. The hospitalized patients with RSV infection and influenza-like symptoms have often immunosuppressive medication, hematological malignancy, or other malignancy [15,16]. In immunocompromised patients, RSV is reported to account for 2.8-10.3% of all acute respiratory tract infections, and 8.6-20.0% of all respiratory viral infections [5]. 30-70% of the patients admitted to hospital because of RSV have cardiovascular disease [7,9,14,15]. During hospitalization, 14-25% of the patients with RSV infection experience a cardiovascular complication such as worsening heart failure, myocardial infarction, or stroke [7,8,13]. Adults that are obese are more likely to be hospitalized from RSV infection and influenza than normal-weight adults [17]. Smoking is associated with higher risk of hospital admissions after influenza infection [18].

Among adult patients hospitalized because of RSV infection, hypoxemia is reported in 53-68% and pneumonia in 31-80% of the patients [7,8,11,13,14,15,16]. Empiric antibiotics are used on 76-95% of the patients [7,8,10], and blood cultures are positive in 4% of the patients [8]. 10-25% of the RSV-infected hospitalized adults require treatment in intensive care unit (ICU) [10,11,16] and mechanical ventilation is needed for 10-36% of the patients [7,8,10]. The average duration of hospitalization has been reported to range from 4 to 9 days [8,10,12,13,16].

When compared to the prevalence of influenza, the prevalence of RSV has been estimated to be up to twice as high among patients at risk and over 65 years [19]. In Finland, seasonal influenza has been estimated to cause 500-1000 excess deaths annually [20]. The patients hospitalized due to RSV are older, have more chronic diseases and are more likely living in long-term care compared to influenza [8,14,15,21]. Among elderly patients aged over 65 years, the in-hospital mortality related to RSV has been estimated to be equal or close to the mortality related to influenza [5,15]. However, the 30-day mortality rate has been estimated to be higher among RSV patients [14]. The patients with RSV infection have more often underlying lung diseases, need more often supplemental oxygen and ventilatory support, and develop more complications, such as pneumonia, than the patients with influenza [8,13,14,15].

Objectives

The aim of the study was to examine the number and severity of RSV infections among adults over the age of 18 in Eastern Finland during an RSV epidemic. The prevalence of several chronic conditions is higher in the study area than elsewhere in Finland [22]. Thus, we also aimed to examine the underlying diseases and background information of patients with RSV and to compare them to corresponding factors among patients with influenza.

Methods

Study subjects

This retrospective cohort study was carried out in Kuopio University Hospital (KUH). KUH is one of Finland's five university hospitals. The hospital is a 600-bed teaching hospital that provides tertiary care services to approximately 800,000 citizens in Central and Eastern Finland. Patients treated in KUH due to influenza and RSV were identified retrospectively from the information-management system of Eastern Finland Laboratory Centre (ISLAB) between November 2017 and May 2018. During the study time, there was a major RSV epidemic in Finland [3]. Patients under 18-years of age and patients with mixed infections (influenza and RSV) were excluded from the study. Also, patients from regional hospitals were excluded if there was a lack of availability of electronical medical records.

Data collection

We collected clinical data by using electronic medical records. For general characteristics and background information we observed age, body mass index (BMI, kg/m2), gender, smoking status, type of housing and underlying conditions. All underlying conditions were classified according to the 2021 ICD-10-CM codes: hypertension (ICD-10-CM I10-I15), ischemic heart disease (ICD-10-CM I20-I25), heart failure (ICD-10-CM I50), cerebrovascular disease (ICD-10-CM I60-70), COPD (ICD-10-CM J44), asthma (ICD-10-CM J45), solid malignancy (ICD-10-CM C00-C80), hematological malignancy (ICD-10-CM C81-C96), diabetes (ICD-10-CM E08-E13), chronic kidney disease (ICD-10-CM N18) and dementia (ICD-10-CM F00-F03). In addition, the patients with immunosuppressive medication due to other diseases were identified. Type of housing was

divided into living independently and living with daily support (nursing homes, home care). Smoking status was divided into smokers and non-smokers. The requirement and duration of hospitalization, requirement of supplemental oxygen and non-invasive ventilation support (bilevel positive airway pressure, continuous positive airway pressure or nasal high flow), requirement of treatment in ICU and duration of ICU care, requirement of invasive ventilation, blood culture sample results, use of antibiotics, prevalence of pneumonia, all-cause mortality during hospitalization and during the following 30 days after discharge were documented. The diagnosis of pneumonia was made by treating physicians based on clinical status, laboratory tests and X-rays.

Laboratory methods

The nasopharyngeal samples of influenza and RSV were taken from the patients during hospital visits. The samples were stored in Copan UTM-RT tubes for transport. The fresh samples were analyzed with Xpert Xpress FLU/RSV test (Cepheid) according to the manufacturer's instructions in the clinical microbiology laboratory of KUH (Eastern Finland Laboratory Centre Joint Authority Enterprise, ISLAB).

Analyses

Data were collected from electronical medical records into an SPSS file and the data analysis was completed using SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). The general characteristics were summarized using descriptive statistics. The statistical analyses between categorical variables were done by using the chi-square ($\chi 2$) test. The Fisher's exact test was used instead of chi-square test when analyzing categorical variables, if any cells had low (<5) minimum expected count. The two-tailed t-test was used for the comparison between continuous variables, and descriptive statistics were used to summarize means (standard deviation, SD). Univariate and multivariable logistic regression analyses were used to calculate the crude odds ratios and adjusted odds ratios (aORs) of the factors associated with hospitalization and all-cause mortality during hospitalization and 30 days after discharge. BMI was categorized to <20 and >30 for the logistic regression analysis. In the multivariable model, only the variables with a p value <.100 at univariate analysis were included, and the final model was built using a stepwise forward procedure to calculate the adjusted odds ratios (aORs). The Hosmer-Lemeshow (HL) test was used for goodness of fit for logistic regression models. The results with a p-value lower than 0.05 were counted statistically significant.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Results

Study population

In total, 2484 patients with positive screening test results for influenza and RSV were identified at ISLAB between November 2017 and May 2018. Patients under 18-years of age, patients without electronical medical record available and patients with mixed infections (influenza and RSV, n= 6) were excluded from the study. After this, total of 725 patients (152 with RSV infection and 573 with influenza infection) were included in the study. BMI was available on 99 (65.1%) of the RSV-infected patients and on 396 (69.1%) of the influenza-infected patients. Smoking status was available on 115 (75.7%) of the RSV-infected patients and on 412 (71.9%) of the influenza-infected patients. Other characteristics and all hospital events were available on all patients in the electronical medical record.

Characteristics

The characteristics of the study population are presented in Table 1. The RSV-infected patients were significantly older than the influenza-infected patients (mean 73.3 vs. 68.1 years, SD 15.1 vs. 18.4, p<0.001). They were also more likely to have diagnoses of hypertension (60.5% vs. 45.5%, p=0.001) and heart failure (17.8% vs. 10.5%, p=0.014) than the patients with influenza infection. There were no significant differences in gender, smoking status, housing status or other underlying conditions between patients with influenza and RSV infections, but the patients with RSV infection had more underlying conditions (mean 2.32 vs. 1.93, SD 1.44 vs. 1.51, p=0.005) than those with influenza infection.

Table 1. Characteristics of the study population.

	RSV n=152 n (%)	Influenza n=573 n (%)	P-value
Male	75 (49.3)	262 (45.7)	0.427
Age (years), mean (SD)	73.3 (15.1)	68.1 (18.4)	<0.001
BMI (kg/m2), mean (SD)	27.0 (5.7)	27.3 (5.7)	0.560
Smoking status Smoking Non-smoker	 26 (17.1) 89 (58.6)	 89 (15.5) 323 (56.4)	0.454
Housing status Independent Supported	 102 (67.1) 50 (32.9)	 418 (72.9) 155 (27.1)	0.155
Number of underlying conditions, (n) mean (SD)	2.32 (1.44)	1.93 (1.51)	0.005
Hypertension	92 (60.5)	261 (45.5)	0.001
Ischemic heart disease	51 (33.6)	154 (26.9)	0.104
Heart failure	27 (17.8)	60 (10.5)	0.014
Cerebrovascular disease	28 (18.4)	77 (13.4)	0.121
COPD	20 (13.2)	57 (9.9)	0.253
Asthma	39 (25.7)	135 (23.6)	0.590
Solid malignancy	10 (6.6)	47 (8.2)	0.509
Hematological malignancy	7 (4.6)	16 (2.8)	0.257*
Diabetes	34 (22.4)	122 (21.3)	0.774
Chronic kidney disease	12 (7.9)	43 (7.5)	0.872
Dementia	22 (14.5)	71 (12.4)	0.495
Immunosuppressive medication	11 (7.2)	65 (11.3)	0.142

Continuous variables (age, BMI, number of underlying conditions) are presented as mean and standard deviation (SD), categorical variables are presented as number (n) and percent (%). P-values were calculated with two-tailed t-test for continuous variables and with chi-square ($\chi 2$) test and Fisher's exact test among categorical variables.

*RSV r*espiratory syncytial virus, *BMI b*ody mass index, *COP*D chronic obstructive pulmonary disease

* = calculated with Fischer's Exact Test.

Hospitalization

The hospital events of the study population are presented in Table 2. The patients with RSV infection were hospitalized more often than those with influenza (84.2% vs. 66.0%, p<0.001). During hospitalization, the RSV-infected patients needed supplementary oxygen (50.7% vs. 31.2%, p<0.001) and developed pneumonia (37.5% vs. 23.2%, p<0.001) more often than patients with influenza. Blood culture positivity was detected

more often (4.6% vs. 1.7%, p=0.045) and antibiotics were used more often (67.1% vs. 47.3%, p<0.001) among patients with RSV than those with influenza. The all-cause mortality during hospitalization and 30 days after discharge was higher among RSV-infected patients than among those infected by influenza (8.6% vs. 3.5%, p=0.010). There was no significant difference in the in-hospital all-cause mortality between the two groups.

Table 2. Outcomes and hospital events of the study population.

	RSV n=152 n (%)	Influenza n=573 n (%)	P-value
Hospitalized Discharged from ER	128 (84.2) 24 (15.8)	378 (66.0) 195 (34.0)	<0.001
Hospital treatment (days), mean (SD)	4.5 (4.5)	4.1 (5.7)	0.311
Need of supplementary oxygen	77 (50.7)	179 (31.2)	<0.001
Non-invasive ventilation	17 (11.2)	50 (8.7)	0.352
ICU admission	6 (3.9)	23 (4.0)	0.970
ICU treatment duration (days), mean (SD)	2.5 (0.8)	5.3 (4.3)	0.123
Invasive ventilation	2 (1.3)	4 (0.7)	0.383*
Pneumonia	57 (37.5)	133 (23.2)	<0.001
Positive blood cultures	7 (4.6)	10 (1.7)	0.045*
Antibiotic used	102 (67.1)	272 (47.3)	<0.001
Hospital all-cause mortality	5 (3.3)	15 (2.6)	0.413
All-cause mortality during hospitalization and 30 days after discharge	13 (8.6)	20 (3.5)	0.010
Time from hospitalization to death (days), mean (SD)	13,4 (15.3)	8.1 (12.4)	0.447

Continuous variables (hospital treatment duration, ICU treatment duration, time from hospitalization to death) are presented as mean and standard deviation (SD), categorical variables are presented as number (n) and percent (%). P-values were calculated with two-tailed t-test for continuous variables and with chi-square ($\chi 2$) test and Fisher's exact test for categorical variables.

RSV respiratory syncytial virus, *ER* emergency room, *ICU* intensive care unit

* = calculated with Fischer's Exact Test.

In blood cultures of RSV patients, *Streptococcus pneumoniae* was found among 2 patients. *Klebsiella pneumoniae*, *Prevotella oralis*, *Staphylococcus epidermidis*, *Escherichia coli* and *Streptococcus viridans* were found in the blood cultures of one patient each. In the blood cultures of influenza-infected patients, *Staphylococcus aureus* was found among 3 patients, and *Streptococcus pneumoniae* in 2 patients. Positive blood cultures for *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Streptococcus dysgalactiae subsp. equisimilis* and *Proteus mirabilis* were detected each in one patient. In one patient with influenza, blood cultures were positive, but the pathogen remained unknown.

Altogether, 27 different antibiotics and 591 courses of antibiotics were used during the hospitalizations. In the RSV and influenza infected patients, 47 (30.9%) vs. 154 (26.9%) received a single antibiotic, 44 (28.9%) vs. 87 (15.2%) received two different antibiotics, 8 (5.3%) vs. 24 (4.2%) received 3 different antibiotics and 2 (1.3%) vs. 6 (1.0%) patients received 4 different antibiotics. One (0.2%) patient with influenza infection received 5 different antibiotics during hospitalization.

Factors associated with hospitalization and mortality

Crosstabulation of the baseline characteristics affecting all-cause mortality during hospitalization and 30 days after discharge is presented in Table 3. Non-surviving RSV-infected patients had significantly more underlying conditions (3.2 vs. 2.2, p=0.016), solid malignancies (23.1% vs. 5.0%, p=0.042) and chronic kidney disease (30.8% vs. 5.8%, p=0.011) than the survivors. In patients with influenza, underlying heart failure was more common among the non-survivors than the survivors (30.0% vs. 9.8%, p=0.012). The non-survivors were also significantly older (83.6 vs. 67.5 years, p<0.001) and lived in supported housing more often than the survivors (55.0% vs. 26.0%, p=0.004).

Table 3. Comparison of the characteristics between RSV-infected non-survivors and survivors and influenza-infected non-survivors and survivors during hospitalization and 30 days after discharge.

	RSV non-survivors (n=13) n (%)	RSV survivors (n=139) n (%)	p-value	Influenza non-survivors (n=20) n (%)	Influenza survivors (n=553) n (%)	p-value
Male Female	5 (38.5) 8 (61.5)	70 (50.4) 69 (49.6)	0.412	9 (45.0) 11 (55.0)	253 (45.8) 300 (54.2)	0.947
Age (years), mean (SD)	77.5 (15.2)	73.0 (15.1)	0.304	83.6 (10.0)	67.5 (18.4)	<0.001
BMI >30 (kg/m2)	2 (15.4)	22 (15.8)	0.623*	2 (10.0)	109 (19.7)	0.435*
BMI <20 (kg/m2)	0 (0)	7 (100)	0.502*	1 (5.0)	26 (4.7)	0.511*
Smoking	2 (15.4)	24 (17.3)	0.598*	0 (0)	89 (16.1)	0.109*
Number of underlying conditions, (n) mean (SD)	3.2 (1.8)	2.2 (1.3)	0.016	2.2 (1.3)	1.9 (1.5)	0.426
Supported housing	6 (46.2)	44 (31.2)	0.222*	11 (55.0)	144 (26.0)	0.004
Hypertension	8 (61.5)	84 (60.4)	0.938	8 (40.0)	253 (45.8)	0.612
Ischemic heart disease	7 (53.8)	44 (31.7)	0.097*	6 (30.0)	148 (26.8)	0.460
Heart failure	4 (30.8)	23 (16.5)	0.179*	6 (30.0)	54 (9.8)	0.012*
Cerebrovascular disease	5 (38.5)	23 (16.5)	0.065*	4 (20.0)	73 (13.2)	0.276*
COPD	2 (15.4)	18 (12.9)	0.534*	1 (5.0)	56 (10.1)	0.390*
Asthma	1 (7.7)	38 (27.3)	0.106*	6 (30.0)	129 (23.3)	0.323*
Solid malignancy	3 (23.1)	7 (5.0)	0.042*	3 (15.0)	44 (8.0)	0.221*
Hematological malignancy	1 (7.7)	6 (4.3)	0.472*	1 (5.0)	15 (2.7)	0.438*
Diabetes	4 (30.8)	30 (21.6)	0.324*	3 (15.0)	119 (21.5)	0.353*
Chronic kidney disease	4 (30.8)	8 (5.8)	0.011*	1 (5.0)	42 (7.6)	0.548*
Dementia	1 (7.7)	21 (15.1)	0.409*	3 (15.0)	68 (12.3)	0.460*
Immunosuppressive medication	3 (23.1)	8 (5.8)	0.054*	2 (10.0)	63 (11.4)	0.599*

In categorical variables, males were compared to females, patients with BMI >30 to patients with BMI ≤30, patients with BMI <20 to patients with BMI ≥20, smokers to non-smokers, patients living in supported housing to patients living independently. The patients with certain underlying condition were compared to those without the underlying condition in question. Continuous variables (age, number of underlying conditions) are presented as mean and standard deviation (SD), categorical variables are presented as number (n) and percent (%). P-values were calculated with two-tailed t-test for continuous variables and with chi-square ($\chi 2$) test and Fisher's exact test among categorical variables.

RSV respiratory syncytial virus, *BMI* Body mass index, *COP*D chronic obstructive pulmonary disease

* = calculated with Fischer's Exact Test.

In multivariable logistic regression analyses among all study patients, RSV infection (p=0.012), age (p=0.003), smoking (p=0.001) and number of underlying conditions (p<0.001) were positively associated

with the likelihood of hospitalization (Table 4). RSV infection (p=0.029), age (p<0.001) and solid malignancies (p=0.042) were positively associated with the all-cause mortality during hospitalization and 30 days after discharge (Table 5).

Table 4: Univariable and multivariable logistic regression analyses of factors associated with hospitalization among all study population (n=725).

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
RSV infection	2.751 (1.721-4.398)	<0.001	2.035 (1.167-3.546)	0.012
Male gender	0.929 (0.676-1.277)	0.650		
Age (years)	1.032 (1-023-1.042)	<0.001	1.021 (1.007-1.035)	0.003
BMI >30	1.290 (0.816-2.039)	0.276		
BMI <20	0.893 (0.415-1.920)	0.772		
Smoking	1.995 (1-189-3.346)	0.009	2.621 (1.502-4.573)	0.001
Number of underlying conditions	1.611 (1.418-1.830)	<0.001	1.433 (1.210-1.696)	<0.001
Supported housing	1.546 (1.069-2.238)	0.021		
Hypertension	2.864 (2.047-4.007)	<0.001		
Ischemic heart disease	2.445 (1.641-3.644)	<0.001		
Heart failure	3.342 (1.738-6.425)	<0.001		
Cerebrovascular disease	2.502 (1.449-4.317)	0.001		
COPD	3.190 (1.609-6.325)	0.001		
Asthma	1.323 (0.901-1.942)	0.153		
Solid malignancy	1.891 (0.960-3.725)	0.065		
Hematological malignancy	0.806 (0.337-1.929)	0.628		
Diabetes	2.310 (1.481-3.602)	<0.001		
Chronic kidney disease	1.434 (0.754-2.729)	0.272		
Dementia	1.205 (0.739-1.964)	0.455		
Immunosuppressive medication	0.814 (0.492-1.346)	0.422		

The HL confirmed the goodness of fit for the multivariable model (p=0.138). In categorical variables, males were compared to females, patients with BMI >30 to patients with BMI ≤30, patients with BMI <20 to patients with BMI ≥20, smokers to non-smokers, patients living in supported housing to patients living independently. The patients with certain underlying condition were compared to those without the underlying condition in question.

RSV respiratory syncytial virus, *BMI* Body mass index, *COP*D chronic obstructive pulmonary disease

Table 5: Univariable and multivariable logistic regression analyses of factors associated with all-cause mortality during hospitalization and 30 days after discharge among all study population (n=725).

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
RSV infection	2.586 (1.255-5.327)	0.010	2.288 (1.089-4.806)	0.029
Male gender	1.188 (0.586-2.407)	0.633		
Age (years)	1.065 (1.031-1.100)	<0.001	1.063 (1.029-1.099)	<0.001
BMI >30 (kg/m2)	0.702 (0.229-2.155)	0.537		
BMI <20 (kg/m2)	0.746 (0.097-5.761)	0.779		
Smoking	0.411 (0.094-1.807)	0.239		
Number of underlying conditions	1.290 (1.037-1.606)	0.022		
Supported housing	2.848 (1.410-5.753)	0.004		
Hypertension	0.991 (0.493-1.994)	0.981		
Ischemic heart disease	1.693 (0.826-3.470)	0.151		
Heart failure	3.473 (1.593-7.570)	0.002		
Cerebrovascular disease	2.328 (1.050-5.160)	0.037		
COPD	0.835 (0.249-2.804)	0.771		
Asthma	0.846 (0.361-1.985)	0.701		
Solid malignancy	2.793 (1.103-7.075)	0.030	2.703 (1.038-7.039)	0.042
Hematological malignancy	2.061 (0.463-9.187)	0.343		
Diabetes	0.981 (0.418-2.305)	0.965		
Chronic kidney disease	2.293 (0.848-6.196)	0.102		
Dementia	0.935 (0.321-2.721)	0.901		
Immunosuppressive medication	1.562 (0.585-4.173)	0.374		

The HL confirmed the goodness of fit for the multivariable model (p=0.607). In categorical variables, males were compared to females, patients with BMI >30 to patients with BMI ≤30, patients with BMI <20 to patients with BMI ≥20, smokers to non-smokers, patients living in supported housing to patients living independently. The patients with certain underlying condition were compared to those without the underlying condition in question.

*RSV r*espiratory syncytial virus, *BMI* Body mass index, *COP*D chronic obstructive pulmonary disease

Discussion

We examined the number and severity of RSV and influenza infections among adult patients in KUH district in Eastern Finland during the 2017-2018 RSV epidemic season. The majority of the patients in both groups were elderly and had several underlying conditions, but most of them were living independently. However, because of the high general morbidity in population of Eastern Finland, the impact of epidemic RSV and influenza is considerable [22].

Consistent with previous studies, the patients with RSV were older and had significantly more underlying conditions than those with influenza [8,14,15,21], especially high blood pressure and heart failure. Compared to influenza, RSV caused a more serious disease in terms of hospitalization, secondary pneumonia, blood culture positivity, need for antibiotics and supplementary oxygen. In addition, the all-cause mortality during hospitalization and 30 days after discharge was higher among the RSV-infected patients than those with influenza (8.6% vs 3.5%) as found in earlier studies [8,14,15,21]. In multivariate analyses, RSV remained as a significant independent risk factor to hospitalization (aOR 2.0, p=0.012) and mortality (aOR 2.3, p=0.029) compared to influenza. The majority of the deaths due to influenza infection occurred during hospitalization, whereas the majority of the deaths due to RSV infection occurred within 30 days after discharge. RSV-infected patients in our study were generally older and their burden of diseases was heavier compared to patients with influenza. This may reflect the limited ability of many elderly

patients to recover from serious illness and therefore explain the high mortality after discharge from hospital.

Regarding hospital events in RSV-infected patients, the time in hospital treatment (4.5 days vs 4-9 days), incidence of pneumonia (37,5% vs 31-80%) and positive results in blood cultures (4.6% vs 4%) were in accordance with other studies [7,8,11,12,13,14,15]. However, hypoxemia and the need of supplementary oxygen (50.7% vs 53-68%), ICU admission (3.9% vs 10-25%) and the use of invasive ventilation (1.3% vs 10-36%) were less common in our study [7,8,10,11,13]. Separate Step Down Units (SDUs) are in active use in our own hospital and this might be one explanation for the low ICU admissions. SDUs provide an intermediate level of care between ICU and the medical wards. One of these SDUs is located in our pulmonary unit, where intensive observation, treatment and oxygen support like high nasal flow oxygen therapy and non-invasive ventilation are available. Especially fragile patients and patients with treatment limitations e.g., withholding of life-sustaining treatment, are treated in SDUs instead of ICU. Interestingly, a decision not to initiate or escalate a life-sustaining treatment in terminal illness in accordance with expressed wishes of the patient or surrogate is a widespread practice in Finland. These decisions are more common in elderly patients, non-surgical patients and those, who have more comorbidities, malignancy and cardiovascular or respiratory insufficiency [23]. This description correlates quite nicely to hospitalized RSV-patients in this paper. The exact number of patients who denied intensive treatment in present study is not known but they also exist. Despite the differences in treatment compared to earlier studies, in-hospital mortality rate (3,3%) was generally low and in accordance with earlier studies (1.1%-15.9%) [7,8,10,11,12].

The use of antibiotics among both RSV-infected (67.1%) and influenza-infected (47.3%) patients was common in our study, but lower than reported earlier among RSV-infected patients (76-95%) [7,8,10]. Among patients with influenza, the proportion of patients treated with prophylactic antibiotics has been reported to be as high as 96.6% [24]. In our study, the proportion of patients with influenza treated with antibiotics was significantly lower. In both groups, the proportion of those who received antibiotics was higher than the amount of actual pneumonia diagnoses. In Finland, the antimicrobial resistance has remained low compared to other countries in European Union due to strict antimicrobial policy [25]. The lower usage of antibiotics in our study did not increase the mortality rate in RSV-infected patients compared to other studies where the use of antibiotics had been studied [7,8,10].

The number of deceased patients in our study was low, which is in line with previous studies conducted with RSV- and influenza-infected patients [7,8,9,10,11,12,13,14]. Solid malignancies and chronic kidney disease were more common among the RSV-infected non-survivors, who also had more underlying conditions than the survivors in general. Age and heart failure were more common among non-survivors than survivors in influenza-infected patients, but not in RSV-infected patients. In earlier studies, older age has been reported to be a significant factor predicting mortality in RSV-infected patients [8,9,12,13,14]. Age and previous hematological disease have been reported to be associated with an increased risk of death during the first 21 days of hospitalization among both RSV- and influenza-infected patients [12]. As far as we know, our finding that solid malignancies and chronic kidney disease are factors predicting mortality in RSV infections, has not been reported before.

Among all study patients, smoking (aOR 2.621, p=0.001) was positively associated with the increased risk of hospitalization, but not with mortality. The result is in line with previous studies, where the positive association with likelihood of hospitalization has been observed, but effect on mortality has been less conclusive [18]. Unlike reported previously [17], obesity was not associated with the increased risk of hospitalization among influenza-infected and RSV-infected patients in our study. In current study, 15.8% of the patients with RSV and 19.8% with influenza were obese (BMI over 30kg/m2), while on average in Finland 26.1% of men and 27.5% of women over 30-years or age are obese [26]. Still, only 12.1% of the

deceased patients in our study with influenza or RSV were obese. When compared to COVID-19, the difference is remarkable, since 28.9% of the deceased patients aged 20 years and older with COVID-19 have been reported to be obese [27].

The study was carried out in a tertiary care hospital, and there was no possibility to gather information about patient recovery from primary care facilities, which is a limitation. During the study period, there was a major RSV epidemic in Finland, which explains the high number of RSV infections compared to influenza infections. During this time, influenza B was more common than influenza A in Finland and total number of influenza infections was higher than in previous years explained by the high prevalence of influenza B [20]. However, there was no significant difference in excess mortality compared to previous influenza seasons during the study time [20].

In our study RSV infection was associated with increased likelihood of hospitalization and mortality compared to influenza. The patients with RSV infection were older and had more underlying conditions than the patients with influenza. No difference in BMI or smoking status was found, but solid malignancies and chronic kidney disease were shown to be independent risk factors for death among RSV-infected patients. During RSV and influenza epidemics, it is important to test all hospitalized patients with respiratory symptoms to prevent the spread of infection by using contact and respiratory precautions as well as isolation and cohorting of infected patients. The same practices are important in managing COVID-19 infected patients.

Patient consent for publication: Not applicable.

Ethics approval: This study was conducted according to the principles expressed in the Declaration of Helsinki [28], and it was approved by a local ethics committee (the Research Ethics Committee of the Northern Savo Hospital District; 1107/13.02.00/2018).

Data availability statement

Due to legal and ethical restrictions, no additional data is available.

Contributors: **Aleksi Hämäläinen**: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft and Reviewing & Editing, Visualization; **Ellamaria Savinainen**: Conceptualization, Validation, Resources, Investigation, Data Curation, Writing - Original Draft and Reviewing & Editing, Visualization; **Sari Hämäläinen**: Conceptualization, Methodology, Validation, Formal analysis, Writing - Review & Editing, Visualization; **Katariina Sivenius**: Conceptualization, Methodology, Validation, Formal analysis, Writing - Review & Editing, Visualization; **Juha Kauppinen**: Conceptualization, Methodology, Data Curation, Writing - Review & Editing; **Irma Koivula**: Conceptualization, Methodology, Validation, Writing - Reviewing & Editing, Visualization; **Riitta-Liisa Patovirta**: Conceptualization, Methodology, Writing - Review & Editing, Supervision, Project administration. All authors approved the final version of the manuscript.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Competing interests: None declared.

References

1. Simoes EA. Respiratory syncytial virus infection. Lancet 1999;**354**(9181):847-52.

2. Falsey A, Hennessey P, Formica M, *et al*. Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults. N Engl J Med 2005;**352**(1), 1749–1759.

3. Tartuntataudit Suomessa 2020, Finnish Institute for Health and Welfare.

4. Li Y, Reeves RM, Wang X, *et al*. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. Lancet Glob Health. 2019;**7**(8):e1031-e1045.

5. Tin Tin Htar M, Yerramalla MS, Moisi JC, *et al*. The burden of respiratory syncytial virus in adults: a systematic review and meta-analysis. Epidemiology and Infection 2020;**148**, E48.

6. Shi T, Denouel A, Tietjen AK, *et al.* Global Disease Burden Estimates of Respiratory Syncytial Virus-Associated Acute Respiratory Infection in Older Adults in 2015: A Systematic Review and Meta-Analysis. J Infect Dis. 2020;**222**(Supplement_7):S577-S583.

7. Chuaychoo B, Ngamwongwan S, Kaewnaphan B., *et al*. Clinical manifestations and outcomes of respiratory syncytial virus infection in adult hospitalized patients. Journal of Clinical Virology 2019;**117**: 103–108.

8. Cohen R, Babushkin F, Geller K, *et al*. Characteristics of hospitalized adult patients with laboratory documented Influenza A, B and Respiratory Syncytial Virus – A single center retrospective observational study. PLoS One 2019;**14**(3): e0214517.

9. Wyffels V, Kariburyo F, Gavart S, *et al*. A Real-World Analysis of Patient Characteristics and Predictors of Hospitalization Among US Medicare Beneficiaries with Respiratory Syncytial Virus Infection. Advanced Therapeutics 2020;**37**(3):1203–1217.

10. Vos LM, Oosterheert JJ, Hoepelman AIM, *et al*. External validation and update of a prognostic model to predict mortality in hospitalized adults with RSV: A retrospective Dutch cohort study. Journal of Medical Virology 2019;**91**(12):2117–2124.

11. Yoon JG, Noh JY, Choi WS, *et al.* Clinical characteristics and disease burden of respiratory syncytial virus infection among hospitalized adults. Scientific Reports 2020;**10**(1):12106.

12. Prasad N, Newbern EC, Trenholme AA, *et al*. The health and economic burden of respiratory syncytial virus associated hospitalizations in adults. PLoS ONE 2020;**15**(6): e0234235.

13. Lee N, Lui GCY, Wong KT, *et al*. High Morbidity and Mortality in Adults Hospitalized for Respiratory Syncytial Virus Infections. Clinical Infectious Diseases 2013;**57**(8), 1069–1077.

14. Zhang Y, Wang Y, Zhao J, *et al*. Severity and mortality of respiratory syncytial virus vs influenza A infection in hospitalized adults in China. Influenza and Other Respiratory Viruses 2020;**14**(5):483–490.

15. Ackerson B, Tseng HF, Sy LS, *et al*. Severe Morbidity and Mortality Associated With Respiratory Syncytial Virus Versus Influenza Infection in Hospitalized Older Adults. Clinical Infectious Diseases 2019;**69**(2):197–203.

16. Loubet P, Lenzi N, Valette M, *et al*. Clinical characteristics and outcome of respiratory syncytial virus infection among adults hospitalized with influenza-like illness in France. Clinical Microbiology and Infection 2017;**23**(4), 253–259.

17. Moser JS, Galindo-Fraga A, Ortiz-Hernández AA, *et al*. Underweight, overweight, and obesity as independent risk factors for hospitalization in adults and children from influenza and other respiratory viruses. Influenza Other Respir Viruses 2019;**13**(1):3-9.

18. Han L, Ran J, Mak YW, *et al*. Smoking and Influenza-associated Morbidity and Mortality: A Systematic Review and Meta-analysis. Epidemiology 2019;**30**(3):405-417.

19. Falsey A, Hennessey Patricia A, Formica M, *et al*. Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults. N Engl J Med 2005;**352**(1), 1749–1759.

20. Ikonen N, Murtopuro S, Haveri A, *et al*. Influenssakausi Suomessa, viikot 40/2017-20/2018: Seurantaraportti. Finland: National Institute for Health and Welfare; 2018.

21. Kwon Y, Park S, Kim M., *et al*. Risk of mortality associated with respiratory syncytial virus and influenza infection in adults. BMC Infectious Diseases 2017;**17**(1), 785.

22. THL's Morbidity Index: https://thl.fi/en/web/thlfi-en/statistics-and-data/statistics-by-topic/morbidity/thl-s-morbidity-index. Accessed 4.1.2022.

23. Adamski J, Weigl W, Lahtinen P, *et al*. Intensive care patient survival after limiting life-sustaining treatment-The FINNEOL* national cohort study. Acta Anaesthesiol Scand. 2020;**64**(8):1144-1153.

24. Manohar P, Loh B, Nachimuthu R, *et al*. Secondary Bacterial Infections in Patients With Viral Pneumonia. Front Med (Lausanne) 2020;**7**:420.

25. European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net) - Annual Epidemiological Report 2019. Stockholm: ECDC; 2020

26. Koponen P, Borodulin K, Lundqvist A, et al. Terveys, toimintakyky ja hyvinvointi Suomessa - FinTerveys2017-tutkimus. Raportti 4/2018. Terveyden ja hyvinvoinnin laitos, Helsinki.

27. Gao M, Piernas C, Astbury NM, *et al*. Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based, cohort study. Lancet Diabetes Endocrinol. 2021;**9**(6):350-359.

28. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2000;**284**(23):3043-3045.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3
Bias	9	Describe any efforts to address potential sources of bias	3
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	3
		(*b*) Describe any methods used to examine subgroups and interactions	3
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	3
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	4
Outcome data	15*	Report numbers of outcome events or summary measures over time	4-7

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8 4-8 -
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

The disease burden caused by respiratory syncytial virus compared to influenza among adults: a retrospective cohort study from Eastern Finland in 2017-2018.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-060805.R1
Article Type:	Original research
Date Submitted by the Author:	28-Nov-2022
Complete List of Authors:	Hämäläinen, Aleksi; University of Eastern Finland Institute of Clinical Medicine; Kuopio University Hospital Savinainen, Ellamaria; University of Eastern Finland Institute of Clinical Medicine; Kuopio University Hospital Hämäläinen, Sari; Kuopio University Hospital Sivenius, Katariina; Kuopio University Hospital Kauppinen, Juha; ISLAB Koivula, Irma; Kuopio University Hospital Patovirta, Riitta-Liisa; Kuopio University Hospital
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Respiratory medicine, Epidemiology
Keywords:	Respiratory infections < THORACIC MEDICINE, Epidemiology < INFECTIOUS DISEASES, Infection control < INFECTIOUS DISEASES

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title: The disease burden caused by respiratory syncytial virus compared to influenza among adults: a retrospective cohort study from Eastern Finland in 2017-2018.

Authors: Aleksi Hämäläinen[1,2], Ellamaria Savinainen[1,2], Sari Hämäläinen[2], Katariina Sivenius[2], Juha Kauppinen[3], Irma Koivula[2], Riitta-Liisa Patovirta[2]

Affiliations

[1] University of Eastern Finland Institute of Clinical Medicine, Kuopio, Pohjois-Savo, FI

[2] Department of Medicine, Kuopio University Hospital, Kuopio, Pohjois-Savo, FI

[3] Eastern Finland Laboratory Centre Joint Authority Enterprise (ISLAB), Kuopio, Pohjois-Savo, FI

Corresponding author: Aleksi Hämäläinen

Department of Medicine, Kuopio University Hospital, Kuopio, Pohjois-Savo, FI

Yliopistonranta 1, 70210 Kuopio

E-mail: aleh@student.uef.fi

Phone number: +358405496077

Word count: 3157

Keywords: Respiratory infections; Epidemiology; Infection control

Abstract

Objectives: Respiratory syncytial virus (RSV) is one of the most important causes of lower respiratory tract illnesses. In this study, we examined the number and severity of RSV infections among adult patients. The underlying diseases and background information of patients with RSV were examined and compared to the patients with influenza.

Design: Retrospective cohort study.

Setting: Patients receiving tertiary care services in Kuopio University Hospital (KUH) district in Eastern Finland.

Participants: 725 patients (152 with RSV infection and 573 with influenza) treated in KUH between November 2017 and May 2018.

Primary and secondary outcome measures: Hospitalization and mortality.

Results: Compared to influenza, RSV caused a more serious disease in terms of hospitalization (84.2% vs. 66.0%, p<0.001), incidence of pneumonia (37.5% vs. 23.2%, p<0.001), need for antibiotics (67.1% vs. 47.3%, p<0.001) and supplementary oxygen (50.7% vs. 31.2%, p<0.001). The all-cause mortality during hospitalization and 30 days after discharge was higher among the RSV-infected patients (8.6% vs. 3.5%, p=0.010). Solid malignancies (23.1% vs. 5.0%, p=0.042) and chronic kidney disease (30.8% vs. 5.8%, p=0.011) were more common among the RSV-infected non-survivors compared to survivors. RSV was an

independent risk factor for hospitalization (aOR 2.035; 95% CI 1.17 to 3.55) and mortality (aOR 2.288; 95% CI 1.09 to 4.81) compared to influenza.

Conclusions: Among all the screened patients, those with RSV infection were older and had more underlying conditions than patients with influenza. They had increased likelihood of hospitalization and mortality when compared to influenza. Solid malignancies and chronic kidney disease seemed to be independent risk factors for death among RSV-infected patients. During RSV and influenza epidemics, it is important to test patients with respiratory symptoms for RSV and influenza to prevent the spread of the infections among elderly and chronically ill patients.

Strengths and limitations of this study

- Respiratory syncytial virus (RSV) is one of the most important causes of lower respiratory tract illnesses.
- RSV has been discovered to cause mortality equal or close to the mortality related to influenza among elderly patients.
- This retrospective cohort study compares the effects of multiple background factors on clinical outcomes in RSV- and influenza-infected adult patients.
- The major limitation of the study was that there was no possibility to gather information about patient recovery from primary care facilities.
- During the study, there was a major RSV epidemic in Finland explaining the high number of RSV infections compared to influenza.

Introduction

Respiratory syncytial virus (RSV) is one of the most important causes of lower respiratory tract illnesses [1]. RSV bronchitis or pneumonia can lead to hospitalization and even death, especially in elderly people with underlying conditions [2]. A major RSV epidemic is observed in Finland every other winter, often starting in November-December. In addition, minor epidemics occur between the major ones [3,4].

In adults ≥ 50 years of age, RSV is responsible for 1-10% of acute respiratory tract infections [5]. RSV hospitalization rates in adults ≥65 years of age are estimated to be 1/1000 and 0.3/1000 person-years in industrialized and developing countries, respectively [6]. The mortality rate among the elderly patients treated in hospital due to RSV infection varies between 1.1-15.9% [7,8,9,10,11,12] and the 30-day all-cause mortality rate varies between 3.2-13.7% [9,10,12,13,14].

Among elderly patients living in long-term care facilities, RSV is estimated to cause 7.2-11.4% of the hospitalizations among patients with chronic pulmonary diseases [2]. The hospitalized patients with RSV infection and influenza-like symptoms have often immunosuppressive medication, hematological malignancy, or other malignancy [15,16]. In immunocompromised patients, RSV is reported to account for 2.8-10.3% of all acute respiratory tract infections, and 8.6-20.0% of all respiratory viral infections [5]. 30-70% of the patients admitted to hospital because of RSV have cardiovascular disease [7,9,14,15]. During hospitalization, 14-25% of the patients with RSV infection experience a cardiovascular complication such as worsening heart failure, myocardial infarction, or stroke [7,8,13]. Adults that are obese are more likely to be hospitalized from RSV infection and influenza than normal-weight adults [17]. Smoking is associated with higher risk of hospital admissions after influenza infection [18].

Among adult patients hospitalized because of RSV infection, hypoxemia is reported in 53-68% and pneumonia in 31-80% of the patients [7,8,11,13,14,15,16]. Empiric antibiotics are used on 76-95% of the patients [7,8,10], and blood cultures are positive in 4% of the patients [8]. 10-25% of the RSV-infected hospitalized adults require treatment in intensive care unit (ICU) [10,11,16] and mechanical ventilation is needed for 10-36% of the patients [7,8,10]. The average duration of hospitalization has been reported to range from 4 to 9 days [8,10,12,13,16].

When compared to the prevalence of influenza, the prevalence of RSV has been estimated to be up to twice as high among patients at risk and over 65 years [19]. In Finland, seasonal influenza has been estimated to cause 500-1000 excess deaths annually [20]. The patients hospitalized due to RSV are older, have more chronic diseases and are more likely living in long-term care compared to influenza [8,14,15,21]. Among elderly patients aged over 65 years, the in-hospital mortality related to RSV has been estimated to be equal or close to the mortality related to influenza [5,15]. However, the 30-day mortality rate has been estimated to be higher among RSV-infected patients [14]. The patients with RSV infection have more often underlying lung diseases, need more often supplemental oxygen and ventilatory support, and develop more complications, such as pneumonia, than the patients with influenza [8,13,14,15].

Objectives

The aim of the study was to examine the number and severity of RSV infections among adult patients in Kuopio University Hospital district in Eastern Finland during the RSV epidemic. We also examined the underlying diseases and background information of patients with RSV. The results were compared to patients with influenza. The population in the study area has more underlying diseases than the average Finnish population, and therefore we focused on the disease burden in the outcomes of patients with RSV [22].

Methods

Study subjects

This retrospective cohort study was carried out in Kuopio University Hospital (KUH). KUH is one of Finland's five university hospitals. The hospital is a 600-bed teaching hospital that provides tertiary care services to approximately 800,000 citizens in Central and Eastern Finland. Patients treated in KUH due to influenza and RSV were identified retrospectively from the information-management system of Eastern Finland Laboratory Centre (ISLAB) between November 2017 and May 2018. During the study time, there was a major RSV epidemic in Finland [3]. Patients under 18-years of age and patients with mixed infections (influenza and RSV) were excluded from the study. Also, patients from regional hospitals were excluded if there was a lack of availability of electronical medical records.

Data collection

We collected clinical data by using electronic medical records. For general characteristics and background information we observed age, body mass index (BMI, kg/m^2), gender, smoking status, type of housing and underlying conditions. All underlying conditions were classified according to the 2021 ICD-10-CM codes: hypertension (ICD-10-CM I10-I15), ischemic heart disease (ICD-10-CM I20-I25), heart failure (ICD-10-CM I50), cerebrovascular disease (ICD-10-CM I60-70), COPD (ICD-10-CM J44), asthma (ICD-10-CM J45), solid malignancy (ICD-10-CM C00-C80), hematological malignancy (ICD-10-CM C81-C96), diabetes (ICD-10-CM E08-E13), chronic kidney disease (ICD-10-CM N18) and dementia (ICD-10-CM F00-F03). In addition, the

patients with immunosuppressive medication due to other diseases were identified. Type of housing was divided into living independently and living with daily support (nursing homes, home care). Patients with BMI greater than or equal to 30 kg/m^2 were defined as obese and patients with BMI under 18.5 kg/m^2 were defined as underweight [23]. Smoking status was divided into smokers and non-smokers. The requirement and duration of hospitalization, requirement of supplemental oxygen and non-invasive ventilation support (bilevel positive airway pressure, continuous positive airway pressure or nasal high flow), requirement of treatment in ICU and duration of ICU care, requirement of invasive ventilation, blood culture sample results, use of antibiotics, prevalence of pneumonia, all-cause mortality during hospitalization and during the following 30 days after discharge were documented. The diagnosis of pneumonia was made by treating physicians based on clinical status, laboratory tests and X-rays.

Laboratory methods

The nasopharyngeal samples of influenza and RSV were taken from the patients during hospital visits. The samples were stored in Copan UTM-RT tubes for transport. The fresh samples were analyzed with multiplex polymerase chain reaction assay for detecting influenza A and B virus and respiratory syncytial virus nucleic acids in respiratory tract specimens (Xpert Xpress FLU/RSV test, Cepheid) according to the manufacturer's instructions in the clinical microbiology laboratory of KUH (Eastern Finland Laboratory Centre Joint Authority Enterprise, ISLAB).

Analyses

Data was collected from electronical medical records into an SPSS file and the data analysis was completed using SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Mean, median and interquartile range (IQR: 25th - 75th percentile) were summarized using descriptive statistics. The statistical analyses between categorical variables were done by using the chi-square ($\chi 2$) test. The Fisher's exact test was used instead of chi-square test when analyzing categorical variables, if any cells had low (<5) minimum expected count. Mann-Whitney U test was used for the comparison between continuous variables. Univariate and multivariable logistic regression analyses were used to calculate the crude odds ratios and adjusted odds ratios (aORs) of the factors associated with hospitalization and all-cause mortality during hospitalization and 30 days after discharge. In the multivariable model, only the variables with a p value <.100 at univariate analysis were included, and the final model was built using a stepwise forward procedure to calculate the adjusted odds ratios (aORs). The Hosmer-Lemeshow (HL) test was used for goodness of fit for logistic regression models. The results with a p-value lower than 0.05 were counted statistically significant.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Results

Study population

In total, 2484 patients with positive screening test results for influenza and RSV were identified at ISLAB between November 2017 and May 2018. Patients under 18-years of age, patients without electronical medical record available and patients with mixed infections (influenza and RSV, n=6) were excluded from the study. After this, total of 725 patients (152 with RSV infection and 573 with influenza infection) were included in the study. BMI was available on 99 (65.1%) of the RSV-infected patients and on 396 (69.1%) of

the influenza-infected patients. Smoking status was available on 115 (75.7%) of the RSV-infected patients and on 412 (71.9%) of the influenza-infected patients. Other characteristics and all hospital events were available on all patients in the electronical medical record.

Characteristics

The characteristics of the study population are presented in Table 1. The RSV-infected patients were significantly older than the influenza-infected patients (mean 73.3 vs. 68.1, median 73 vs. 71 years, p=0.002). They were also more likely to have diagnoses of hypertension (60.5% vs. 45.5%, p=0.001) and heart failure (17.8% vs. 10.5%, p=0.014) than the patients with influenza infection. There were no significant differences in gender, smoking status, housing status or other underlying conditions between patients with influenza and RSV infections, but the patients with RSV infection had more underlying conditions (mean 2.32 vs. 1.93, median 2 vs. 2 underlying conditions, p=0.003) than those with influenza infection.

Table 1. Characteristics of the study population.

	RSV n=152 n (%)	Influenza n=573 n (%)	P-value
Male	75 (49.3)	262 (45.7)	0.427
Age (years) Range Mean (SD) Median (IQR)	 23-96 73.3 (15.1) 73 (65-86)	 18-100 68.1 (18.4) 71 (59-82)	 0.002
BMI (kg/m^2) Range Mean (SD) Median (IQR)	 15.4-43.2 27.0 (5.7) 25.6 (22.9-29.2)	 14.9-51.2 27.3 (5.7) 27.0 (23.4-30.8)	 0.297
Smoking status Smoking Non-smoker	 26 (17.1) 89 (58.6)	 89 (15.5) 323 (56.4)	 0.454
Housing status Independent Supported	 102 (67.1) 50 (32.9)	 418 (72.9) 155 (27.1)	 0.155
Number of underlying conditions Range Mean (SD) Median (IQR)	 0-6 2.32 (1.4) 2 (1-3)	 0-7 1.93 (1.5) 2 (1-3)	 0.003
Hypertension	92 (60.5)	261 (45.5)	0.001
Ischemic heart disease	51 (33.6)	154 (26.9)	0.104
Heart failure	27 (17.8)	60 (10.5)	0.014
Cerebrovascular disease	28 (18.4)	77 (13.4)	0.121
COPD	20 (13.2)	57 (9.9)	0.253
Asthma	39 (25.7)	135 (23.6)	0.590
Solid malignancy	10 (6.6)	47 (8.2)	0.509
Hematological malignancy	7 (4.6)	16 (2.8)	0.257*
Diabetes	34 (22.4)	122 (21.3)	0.774
Chronic kidney disease	12 (7.9)	43 (7.5)	0.872
Dementia	22 (14.5)	71 (12.4)	0.495
Immunosuppressive medication	11 (7.2)	65 (11.3)	0.142

Continuous variables (age, BMI, number of underlying conditions) are presented as mean and standard deviation (SD) and median and interquartile range (IQR: 25th - 75th percentile), categorical variables are presented as number (n) and percent (%). P-values were calculated with Mann-Whitney U test for continuous variables and with chi-square ($\chi 2$) test and Fisher's exact test for categorical variables.

*RSV r*espiratory syncytial virus, *BMI b*ody mass index, *COP*D chronic obstructive pulmonary disease

* = calculated with Fischer's Exact Test.

Hospitalization

The hospital events of the study population are presented in Table 2. The patients with RSV infection were hospitalized more often than those with influenza (84.2% vs. 66.0%, p<0.001). During hospitalization, the RSV-infected patients needed supplementary oxygen (50.7% vs. 31.2%, p<0.001) and developed pneumonia (37.5% vs. 23.2%, p<0.001) more often than patients with influenza. There was no difference in ICU admission between the groups, but the duration of the treatment in the ICU was longer in influenza-infected patients than those with RSV (mean 5.3 vs. 2.5, median 4 vs. 3 days, p=0.016). Blood culture positivity was detected more often (4.6% vs. 1.7%, p=0.045) and antibiotics were used more often (67.1% vs. 47.3%, p<0.001) among patients with RSV than those with influenza. The all-cause mortality during hospitalization and 30 days after discharge was higher among RSV-infected patients than among those infected by influenza (8.6% vs. 3.5%, p=0.010). There was no significant difference in the in-hospital all-cause mortality between the two groups.

Table 2. Outcomes and hospital events of the study population.

	RSV n=152 n (%)	Influenza n=573 n (%)	P-value
Hospitalized	128 (84.2)	378 (66.0)	<0.001
Discharged from ER	24 (15.8)	195 (34.0)	
Hospital treatment (days)			
Range	1-40	1-66	
Mean (SD)	4.5 (4.5)	4.1 (5.7)	0.425
Median (IQR)	5 (3-6)	5 (3-7)	
Need of supplementary oxygen	77 (50.7)	179 (31.2)	<0.001
Non-invasive ventilation	17 (11.2)	50 (8.7)	0.352
ICU admission	6 (3.9)	23 (4.0)	0.970
ICU treatment duration (days)			
Range	1-3	1-21	
Mean (SD)	2.5 (0.8)	5.3 (4.3)	0.016
Median (IQR)	3 (2-3)	4 (3-6)	
Invasive ventilation	2 (1.3)	4 (0.7)	0.383*
Pneumonia	57 (37.5)	133 (23.2)	<0.001
Positive blood cultures	7 (4.6)	10 (1.7)	0.045*
Antibiotic used	102 (67.1)	272 (47.3)	<0.001
Hospital all-cause mortality	5 (3.3)	15 (2.6)	0.413
All-cause mortality during hospitalization and 30 days after discharge	13 (8.6)	20 (3.5)	0.010
Time from hospitalization to death (days)			
Range	3-40	1-51	
Mean (SD)	13.4 (15.3)	8.1 (12.4)	0.266
Median (IQR)	6 (4-27)	4 (2-9)	

Continuous variables (hospital treatment duration, ICU treatment duration, time from hospitalization to death) are presented as mean and standard deviation (SD) and median and interquartile range (IQR: 25th - 75th percentile), categorical variables are presented as number (n) and percent (%). P-values were calculated with Mann-Whitney U test for continuous variables and with chi-square ($\chi 2$) test and Fisher's exact test for categorical variables.

RSV respiratory syncytial virus, *ER* emergency room, *ICU* intensive care unit

* = calculated with Fischer's Exact Test.

In blood cultures of RSV patients, *Streptococcus pneumoniae* was found among 2 patients. *Klebsiella pneumoniae*, *Prevotella oralis*, *Staphylococcus epidermidis*, *Escherichia coli* and *Streptococcus viridans* were found in the blood cultures of one patient each. In the blood cultures of influenza-infected patients, *Staphylococcus aureus* was found among 3 patients, and *Streptococcus pneumoniae* in 2 patients. Positive blood cultures for *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, *Streptococcus dysgalactiae subsp. equisimilis* and *Proteus mirabilis* were detected each in one patient. In one patient with influenza, blood cultures were positive, but the pathogen remained unknown.

Altogether, 27 different antibiotics and 591 courses of antibiotics were used during the hospitalizations. In the RSV and influenza infected patients, 47 (30.9%) vs. 154 (26.9%) received a single antibiotic, 44 (28.9%) vs. 87 (15.2%) received two different antibiotics, 8 (5.3%) vs. 24 (4.2%) received 3 different antibiotics and 2 (1.3%) vs. 6 (1.0%) patients received 4 different antibiotics. One (0.2%) patient with influenza infection received 5 different antibiotics during hospitalization.

Factors associated with hospitalization and mortality

Cross-tabulation of the baseline characteristics affecting all-cause mortality during hospitalization and 30 days after discharge is presented in Table 3. Non-surviving RSV-infected patients had significantly more often solid malignancies (23.1% vs. 5.0%, p=0.042) and chronic kidney disease (30.8% vs. 5.8%, p=0.011) than the survivors. In patients with influenza, underlying heart failure was more common among the non-survivors than the survivors (30.0% vs. 9.8%, p=0.012). The non-survivors were also significantly older (mean 83.6 vs. 67.5, median 83 vs. 70 years, p<0.001) and lived in supported housing more often than the survivors (55.0% vs. 26.0%, p=0.004).

Table 3. Comparison of the characteristics between RSV-infected non-survivors and survivors and influenza-infected non-survivors and survivors during hospitalization and 30 days after discharge.

	RSV non-survivors (n=13) n (%)	RSV survivors (n=139) n (%)	p-value	Influenza non-survivors (n=20) n (%)	Influenza survivors (n=553) n (%)	p-value
Male Female	5 (38.5) 8 (61.5)	70 (50.4) 69 (49.6)	0.412	9 (45.0) 11 (55.0)	253 (45.8) 300 (54.2)	0.947
Age (years) Range Mean (SD) Median (IQR)	 39-94 77.5 (15.2) 81 (70-90)	 23-96 73.0 (15.1) 73 (64-86)	 0.195	 68-100 83.6 (10.0) 83 (77-93)	 18-98 67.5 (18.4) 70 (59-82)	 <0.001
Obesity	2 (15.4)	23 (16.5)	0.648*	2 (10.0)	111 (20.1)	0.308*
Underweight	0 (0)	4 (2.9)	0.708*	0 (0)	20 (3.6)	0.512*
Smoking	2 (15.4)	24 (17.3)	0.598*	0 (0)	89 (16.1)	0.109*
Number of underlying conditions Range Mean (SD) Median (IQR)	 1-6 3.2 (1.8) 3 (2-5)	 0-6 2.2 (1.3) 2 (1-3)	 0.059	 0-5 2.2 (1.3) 2 (1-3)	 0-7 1.9 (1.5) 2 (1-3)	 0.291
Supported housing	6 (46.2)	44 (31.2)	0.222*	11 (55.0)	144 (26.0)	0.004
Hypertension	8 (61.5)	84 (60.4)	0.938	8 (40.0)	253 (45.8)	0.612
Ischemic heart disease	7 (53.8)	44 (31.7)	0.097*	6 (30.0)	148 (26.8)	0.460
Heart failure	4 (30.8)	23 (16.5)	0.179*	6 (30.0)	54 (9.8)	0.012*
Cerebrovascular disease	5 (38.5)	23 (16.5)	0.065*	4 (20.0)	73 (13.2)	0.276*
COPD	2 (15.4)	18 (12.9)	0.534*	1 (5.0)	56 (10.1)	0.390*
Asthma	1 (7.7)	38 (27.3)	0.106*	6 (30.0)	129 (23.3)	0.323*
Solid malignancy	3 (23.1)	7 (5.0)	0.042*	3 (15.0)	44 (8.0)	0.221*
Hematological malignancy	1 (7.7)	6 (4.3)	0.472*	1 (5.0)	15 (2.7)	0.438*
Diabetes	4 (30.8)	30 (21.6)	0.324*	3 (15.0)	119 (21.5)	0.353*
Chronic kidney disease	4 (30.8)	8 (5.8)	0.011*	1 (5.0)	42 (7.6)	0.548*
Dementia	1 (7.7)	21 (15.1)	0.409*	3 (15.0)	68 (12.3)	0.460*
Immunosuppressive medication	3 (23.1)	8 (5.8)	0.054*	2 (10.0)	63 (11.4)	0.599*

In categorical variables, males were compared to females, obese (BMI ≥ 30 kg/m^2) and underweight (BMI < 18.5 kg/m^2) patients to patients with BMI greater than or equal to 18.5 to 29.9 kg/m^2, smokers to non-smokers and patients living in supported housing to patients living independently. The patients with certain underlying condition were compared to those without the underlying condition in question. Continuous variables (age, number of underlying conditions) are presented as mean and standard deviation (SD) and median and interquartile range (IQR: 25th - 75th percentile), categorical variables are presented as number (n) and percent (%). P-values were calculated with Mann-Whitney U test for continuous variables and with chi-square ($\chi 2$) test and Fisher's exact test for categorical variables.

*RSV r*espiratory syncytial virus, *BMI* Body mass index, *COP*D chronic obstructive pulmonary disease

* = calculated with Fischer's Exact Test.

In multivariable logistic regression analyses among all study patients, RSV infection (p=0.012), age (p=0.003), smoking (p=0.001) and number of underlying conditions (p<0.001) were positively associated with the likelihood of hospitalization (Table 4). RSV infection (p=0.029), age (p<0.001) and solid malignancies (p=0.042) were positively associated with the all-cause mortality during hospitalization and 30 days after discharge (Table 5).

Table 4: Univariable and multivariable logistic regression analyses of factors associated with hospitalization among all study population (n=725).

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
RSV infection	2.751 (1.721-4.398)	<0.001	2.035 (1.167-3.546)	0.012
Male gender	0.929 (0.676-1.277)	0.650		
Age (years)	1.032 (1-023-1.042)	<0.001	1.021 (1.007-1.035)	0.003
Obesity	1.419 (0.892-2.257)	0.140		
Underweight	1.233 (0.475-3.200)	0.667		
Smoking	1.995 (1-189-3.346)	0.009	2.621 (1.502-4.573)	0.001
Number of underlying conditions	1.611 (1.418-1.830)	<0.001	1.433 (1.210-1.696)	<0.001
Supported housing	1.546 (1.069-2.238)	0.021		
Hypertension	2.864 (2.047-4.007)	<0.001		
Ischemic heart disease	2.445 (1.641-3.644)	<0.001		
Heart failure	3.342 (1.738-6.425)	<0.001		
Cerebrovascular disease	2.502 (1.449-4.317)	0.001		
COPD	3.190 (1.609-6.325)	0.001		
Asthma	1.323 (0.901-1.942)	0.153		
Solid malignancy	1.891 (0.960-3.725)	0.065		
Hematological malignancy	0.806 (0.337-1.929)	0.628		
Diabetes	2.310 (1.481-3.602)	<0.001		
Chronic kidney disease	1.434 (0.754-2.729)	0.272		
Dementia	1.205 (0.739-1.964)	0.455		
Immunosuppressive medication	0.814 (0.492-1.346)	0.422		

The HL confirmed the goodness of fit for the multivariable model (p=0.138). In categorical variables, males were compared to females, obese (BMI ≥ 30 kg/m^2) and underweight (BMI < 18.5 kg/m^2) patients to patients with BMI greater than or equal to 18.5 to 29.9 kg/m^2, smokers to non-smokers, patients living in supported housing to patients living independently. The patients with certain underlying condition were compared to those without the underlying condition in question.

*RSV r*espiratory syncytial virus, *BMI* Body mass index, *COP*D chronic obstructive pulmonary disease

Table 5: Univariable and multivariable logistic regression analyses of factors associated with all-cause mortality during hospitalization and 30 days after discharge among all study population (n=725).

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
RSV infection	2.586 (1.255-5.327)	0.010	2.288 (1.089-4.806)	0.029
Male gender	1.188 (0.586-2.407)	0.633		
Age (years)	1.065 (1.031-1.100)	<0.001	1.063 (1.029-1.099)	<0.001
Obesity	0.633 (0.206-1.942)	0.424		
Underweight	-	-		
Smoking	0.411 (0.094-1.807)	0.239		
Number of underlying conditions	1.290 (1.037-1.606)	0.022		
Supported housing	2.848 (1.410-5.753)	0.004		
Hypertension	0.991 (0.493-1.994)	0.981		
Ischemic heart disease	1.693 (0.826-3.470)	0.151		
Heart failure	3.473 (1.593-7.570)	0.002		
Cerebrovascular disease	2.328 (1.050-5.160)	0.037		
COPD	0.835 (0.249-2.804)	0.771		
Asthma	0.846 (0.361-1.985)	0.701		
Solid malignancy	2.793 (1.103-7.075)	0.030	2.703 (1.038-7.039)	0.042
Hematological malignancy	2.061 (0.463-9.187)	0.343		
Diabetes	0.981 (0.418-2.305)	0.965		
Chronic kidney disease	2.293 (0.848-6.196)	0.102		
Dementia	0.935 (0.321-2.721)	0.901		
Immunosuppressive medication	1.562 (0.585-4.173)	0.374		

The HL confirmed the goodness of fit for the multivariable model (p=0.607). In categorical variables, males were compared to females, obese (BMI ≥ 30 kg/m^2) and underweight (BMI < 18.5 kg/m^2) patients to patients with BMI greater than or equal to 18.5 to 29.9 kg/m^2, smokers to non-smokers, patients living in supported housing to patients living independently. The patients with certain underlying condition were compared to those without the underlying condition in question.

*RSV r*espiratory syncytial virus, *BMI* Body mass index, *COP*D chronic obstructive pulmonary disease

Discussion

We examined the number and severity of RSV and influenza infections among adult patients in KUH district in Eastern Finland during the 2017-2018 RSV epidemic season. The majority of the patients in both groups were elderly and had several underlying conditions, but most of them were living independently. However, because of the high general morbidity in population of Eastern Finland, the impact of epidemic RSV and influenza is considerable [22]. Although the high general morbidity in the population studied, patients with RSV in our study did not have an exceptionally high rate of comorbidities compared to previous similar studies [7,9,14,15].

Consistent with previous studies, the patients with RSV were older and had significantly more underlying conditions than those with influenza [8,14,15,21], especially high blood pressure and heart failure. Compared to influenza, RSV caused a more serious disease in terms of hospitalization, secondary pneumonia, blood culture positivity, need for antibiotics and supplementary oxygen. In addition, the all-cause mortality during hospitalization and 30 days after discharge was higher among the RSV-infected patients than those with influenza (8.6% vs. 3.5%) as found in earlier studies [8,14,15,21]. In multivariate analyses, RSV remained as a significant independent risk factor to hospitalization (aOR 2.0, p=0.012) and mortality (aOR 2.3, p=0.029) compared to influenza. However, though patients with RSV had more serious

disease compared to influenza in many terms, the duration of the treatment in the ICU was longer in influenza-infected patients than those with RSV. The majority of the deaths due to influenza infection occurred during hospitalization, whereas the majority of the deaths due to RSV infection occurred within 30 days after discharge. RSV-infected patients in our study were generally older and their burden of diseases was heavier compared to patients with influenza. This may reflect the limited ability of many elderly patients to recover from serious illness and therefore explain the high mortality after discharge from hospital.

Regarding hospital events in RSV-infected patients, the time in hospital treatment (mean 4.5 vs. 4-9 days), incidence of pneumonia (37.5% vs. 31-80%) and positive results in blood cultures (4.6% vs. 4%) were in accordance with other studies [7,8,11,12,13,14,15]. However, hypoxemia and the need of supplementary oxygen (50.7% vs. 53-68%), ICU admission (3.9% vs. 10-25%) and the use of invasive ventilation (1.3% vs. 10-36%) were less common in our study [7,8,10,11,13]. Separate Step Down Units (SDUs) are in active use in our own hospital and this might be one explanation for the low ICU admissions. SDUs provide an intermediate level of care between ICU and the medical wards. One of these SDUs is located in our pulmonary unit, where intensive observation, treatment and oxygen support like high nasal flow oxygen therapy and non-invasive ventilation are available. Especially fragile patients and patients with treatment limitations e.g., withholding of life-sustaining treatment, are treated in SDUs instead of ICU. Interestingly, a decision not to initiate or escalate a life-sustaining treatment in terminal illness in accordance with expressed wishes of the patient or surrogate is a widespread practice in Finland. These decisions are more common in elderly patients, non-surgical patients and those, who have more comorbidities, malignancy and cardiovascular or respiratory insufficiency [24]. This description correlates quite nicely to hospitalized RSV-patients in this paper. The exact number of patients who denied intensive treatment in present study is not known but they also exist. Despite the differences in treatment compared to earlier studies, in-hospital mortality rate (3,3%) was generally low and in accordance with earlier studies (1.1%-15.9%) [7,8,10,11,12].

The use of antibiotics among both RSV-infected (67.1%) and influenza-infected (47.3%) patients was common in our study, but lower than reported earlier among RSV-infected patients (76-95%) [7,8,10]. Among patients with influenza, the proportion of patients treated with prophylactic antibiotics has been reported to be as high as 96.6% [25]. In our study, the proportion of patients with influenza treated with antibiotics was significantly lower. In both groups, the proportion of those who received antibiotics was higher than the amount of actual pneumonia diagnoses. In Finland, the antimicrobial resistance has remained low compared to other countries in European Union due to strict antimicrobial policy [26]. The lower usage of antibiotics in our study did not increase the mortality rate in RSV-infected patients compared to other studies where the use of antibiotics had been studied [7,8,10].

The number of deceased patients in our study was low, which is in line with previous studies conducted with RSV- and influenza-infected patients [7,8,9,10,11,12,13,14]. Solid malignancies and chronic kidney disease were more common among the RSV-infected non-survivors than survivors. Older age and heart failure were more common among non-survivors than survivors in influenza-infected patients, but not in RSV-infected patients. In earlier studies, older age has been reported to be a significant factor predicting mortality in RSV-infected patients [8,9,12,13,14]. Age and previous hematological disease have been reported to be associated with an increased risk of death during the first 21 days of hospitalization among both RSV- and influenza-infected patients [12]. As far as we know, our finding that solid malignancies and chronic kidney disease are factors predicting mortality in RSV infections, has not been reported before.

Among all study patients, smoking (aOR 2.621, p=0.001) was positively associated with the increased risk of hospitalization, but not with mortality. The result is in line with previous studies, where the positive association with likelihood of hospitalization has been observed, but effect on mortality has been less

conclusive [18]. Unlike reported previously [17], obesity was not associated with the increased risk of hospitalization among influenza-infected and RSV-infected patients in our study. In current study, 15.8% of the patients with RSV and 19.8% with influenza were obese (BMI greater than or equal to 30 kg/m^2), while on average in Finland 26.1% of men and 27.5% of women over 30-years of age are obese [27]. Still, only 15.4% of the deceased patients with RSV and 10.0% with influenza in our study were obese. When compared to COVID-19, the difference is remarkable, since 28.9% of the deceased patients aged 20 years and older with COVID-19 have been reported to be obese [28].

The study was carried out in a tertiary care hospital, and there was no possibility to gather information about patient recovery from primary care facilities, which is a limitation. During the study period, there was a major RSV epidemic in Finland, which explains the high number of RSV infections compared to influenza infections. During this time, influenza B was more common than influenza A in Finland and total number of influenza infections was higher than in previous years explained by the high prevalence of influenza B [20]. However, there was no significant difference in excess mortality compared to previous influenza seasons during the study time [20].

In our study RSV infection was associated with increased likelihood of hospitalization and mortality compared to influenza. The patients with RSV infection were older and had more underlying conditions than the patients with influenza. No difference in BMI or smoking status was found, but solid malignancies and chronic kidney disease were shown to be independent risk factors for death among RSV-infected patients. During RSV and influenza epidemics, it is important to test all hospitalized patients with respiratory symptoms to prevent the spread of infection by using contact and respiratory precautions as well as isolation and cohorting of infected patients. The same practices are important in managing COVID-19 infected patients.

Patient consent for publication: Not applicable.

Ethics approval: This registry study was approved by a local ethics committee (the Research Ethics Committee of the Northern Savo Hospital District; 1107/13.02.00/2018). This study was conducted according to the principles expressed in the Declaration of Helsinki.

Data availability statement

Due to legal and ethical restrictions, no additional data is available.

Contributors: **Aleksi Hämäläinen**: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft and Reviewing & Editing, Visualization; **Ellamaria Savinainen**: Conceptualization, Validation, Resources, Investigation, Data Curation, Writing - Original Draft and Reviewing & Editing, Visualization; **Sari Hämäläinen**: Conceptualization, Methodology, Validation, Formal analysis, Writing - Review & Editing, Visualization; **Katariina Sivenius**: Conceptualization, Methodology, Validation, Formal analysis, Writing - Review & Editing, Visualization; **Juha Kauppinen**: Conceptualization, Methodology, Data Curation, Writing - Review & Editing; **Irma Koivula**: Conceptualization, Methodology, Validation, Writing - Reviewing & Editing, Visualization; **Riitta-Liisa Patovirta**: Conceptualization, Methodology, Writing - Review & Editing, Supervision, Project administration. All authors approved the final version of the manuscript.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Competing interests: None declared.

References

1. Simoes EA. Respiratory syncytial virus infection. Lancet 1999;**354**(9181):847-52.

2. Falsey A, Hennessey P, Formica M, *et al*. Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults. N Engl J Med 2005;**352**(1), 1749–1759.

3. Tartuntataudit Suomessa 2020, Finnish Institute for Health and Welfare.

4. Li Y, Reeves RM, Wang X, *et al*. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. Lancet Glob Health. 2019;**7**(8):e1031-e1045.

5. Tin Tin Htar M, Yerramalla MS, Moisi JC, *et al*. The burden of respiratory syncytial virus in adults: a systematic review and meta-analysis. Epidemiology and Infection 2020;**148**, E48.

6. Shi T, Denouel A, Tietjen AK, *et al.* Global Disease Burden Estimates of Respiratory Syncytial Virus-Associated Acute Respiratory Infection in Older Adults in 2015: A Systematic Review and Meta-Analysis. J Infect Dis. 2020;**222**(Supplement_7):S577-S583.

7. Chuaychoo B, Ngamwongwan S, Kaewnaphan B., *et al*. Clinical manifestations and outcomes of respiratory syncytial virus infection in adult hospitalized patients. Journal of Clinical Virology 2019;**117**: 103–108.

8. Cohen R, Babushkin F, Geller K, *et al*. Characteristics of hospitalized adult patients with laboratory documented Influenza A, B and Respiratory Syncytial Virus – A single center retrospective observational study. PLoS One 2019;**14**(3): e0214517.

9. Wyffels V, Kariburyo F, Gavart S, *et al*. A Real-World Analysis of Patient Characteristics and Predictors of Hospitalization Among US Medicare Beneficiaries with Respiratory Syncytial Virus Infection. Advanced Therapeutics 2020;**37**(3):1203–1217.

10. Vos LM, Oosterheert JJ, Hoepelman AIM, *et al*. External validation and update of a prognostic model to predict mortality in hospitalized adults with RSV: A retrospective Dutch cohort study. Journal of Medical Virology 2019;**91**(12):2117–2124.

11. Yoon JG, Noh JY, Choi WS, *et al.* Clinical characteristics and disease burden of respiratory syncytial virus infection among hospitalized adults. Scientific Reports 2020;**10**(1):12106.

12. Prasad N, Newbern EC, Trenholme AA, *et al*. The health and economic burden of respiratory syncytial virus associated hospitalizations in adults. PLoS ONE 2020;**15**(6): e0234235.

13. Lee N, Lui GCY, Wong KT, *et al*. High Morbidity and Mortality in Adults Hospitalized for Respiratory Syncytial Virus Infections. Clinical Infectious Diseases 2013;**57**(8), 1069–1077.

14. Zhang Y, Wang Y, Zhao J, *et al*. Severity and mortality of respiratory syncytial virus vs influenza A infection in hospitalized adults in China. Influenza and Other Respiratory Viruses 2020;**14**(5):483–490.

15. Ackerson B, Tseng HF, Sy LS, *et al*. Severe Morbidity and Mortality Associated With Respiratory Syncytial Virus Versus Influenza Infection in Hospitalized Older Adults. Clinical Infectious Diseases 2019;**69**(2):197–203.

16. Loubet P, Lenzi N, Valette M, *et al*. Clinical characteristics and outcome of respiratory syncytial virus infection among adults hospitalized with influenza-like illness in France. Clinical Microbiology and Infection 2017;**23**(4), 253–259.

17. Moser JS, Galindo-Fraga A, Ortiz-Hernández AA, *et al*. Underweight, overweight, and obesity as independent risk factors for hospitalization in adults and children from influenza and other respiratory viruses. Influenza Other Respir Viruses 2019;**13**(1):3-9.

18. Han L, Ran J, Mak YW, *et al*. Smoking and Influenza-associated Morbidity and Mortality: A Systematic Review and Meta-analysis. Epidemiology 2019;**30**(3):405-417.

19. Falsey A, Hennessey Patricia A, Formica M, *et al*. Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults. N Engl J Med 2005;**352**(1), 1749–1759.

20. Ikonen N, Murtopuro S, Haveri A, *et al*. Influenssakausi Suomessa, viikot 40/2017-20/2018: Seurantaraportti. Finland: National Institute for Health and Welfare; 2018.

21. Kwon Y, Park S, Kim M., *et al*. Risk of mortality associated with respiratory syncytial virus and influenza infection in adults. BMC Infectious Diseases 2017;**17**(1), 785.

22. THL's Morbidity Index: https://thl.fi/en/web/thlfi-en/statistics-and-data/statistics-by-topic/morbidity/thl-s-morbidity-index. Accessed 4.1.2022.

23. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;**894**:i-xii, 1-253.

24. Adamski J, Weigl W, Lahtinen P, *et al*. Intensive care patient survival after limiting life-sustaining treatment-The FINNEOL* national cohort study. Acta Anaesthesiol Scand. 2020;**64**(8):1144-1153.

25. Manohar P, Loh B, Nachimuthu R, *et al*. Secondary Bacterial Infections in Patients With Viral Pneumonia. Front Med (Lausanne) 2020;**7**:420.

26. European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net) - Annual Epidemiological Report 2019. Stockholm: ECDC; 2020

27. Koponen P, Borodulin K, Lundqvist A, et al. Terveys, toimintakyky ja hyvinvointi Suomessa - FinTerveys2017-tutkimus. Raportti 4/2018. Terveyden ja hyvinvoinnin laitos, Helsinki.

28. Gao M, Piernas C, Astbury NM, *et al*. Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based, cohort study. Lancet Diabetes Endocrinol. 2021;**9**(6):350-359.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3
Bias	9	Describe any efforts to address potential sources of bias	3
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	3
		(*b*) Describe any methods used to examine subgroups and interactions	3
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	3
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	4
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	4
Outcome data	15*	Report numbers of outcome events or summary measures over time	4-8

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-9 4-8 -
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	10-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.