

Characteristics and Outcomes of Patients in the ICU With Respiratory Syncytial Virus Compared With Those With Influenza Infection

A Multicenter Matched Cohort Study

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BACKGROUND: The characteristics and outcomes of adult patients with respiratory syncytial virus (RSV) infection who require ICU admission are poorly defined. Although several studies in adults with RSV infection have been published in recent years, they did not focus specifically on critically ill patients.

RESEARCH QUESTION: What are the characteristics and outcomes of adult patients in the ICU with RSV infection and how do they compare with those of patients in the ICU with influenza infection?

STUDY DESIGN AND METHODS: This retrospective, multicenter study in France and Belgium (17 sites) compared the characteristics and outcomes of adult patients in the ICU with RSV infection vs those with influenza infection between November 2011 and April 2018. Each patient with RSV infection was matched by institution and date of diagnosis with a patient with influenza infection. In-hospital mortality was compared between the two groups, with adjustment for prognostic factors in a multivariate model (sex, age, main underlying conditions, and concurrent bloodstream infection).

RESULTS: Data from 618 patients (309 with RSV infection and 309 with influenza infection) were analyzed. Patients with RSV infection were significantly more likely to have an underlying chronic respiratory condition (60.2% vs 40.1%; $P < .001$) and to be immunocompromised (35% vs 26.2%; $P = .02$) than patients with influenza infection. Several differences in clinical signs and biological data at diagnosis were found between the groups. In-hospital mortality was not significantly different between the two groups (23.9% in the RSV group vs 25.6% in the influenza group; $P = .63$), even after adjustment for prognostic factors in a multivariate model.

INTERPRETATION: Adult patients in the ICU with RSV infection differ from adult patients in the ICU with influenza in terms of comorbidities and characteristics at diagnosis. RSV infection was associated with high in-hospital mortality, approaching 25%. In multivariate analysis, RSV infection was associated with a similar odds of in-hospital death compared with influenza infection.

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KEY WORDS: community-acquired respiratory virus; influenza; mechanical ventilation; mortality; RSV

ABBREVIATIONS: CPK = creatine phosphokinase; RSV = respiratory syncytial virus

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Take-home Points

Study Question: What are the characteristics and outcomes of adult patients in the ICU with respiratory syncytial virus (RSV) infection and how do they compare with those of adult patients in the ICU with influenza infection?

Results: In this retrospective, multicenter, matched-cohort study, adult patients in the ICU with RSV infection differed significantly from those with influenza in terms of comorbidities and clinical characteristics at diagnosis. RSV infection was associated with a high in-hospital mortality rate approaching 25%, which was comparable with that of influenza infection in multivariate analysis.

Interpretation: A need exists to identify interventions to prevent and treat effectively severe RSV infection in adults.

Respiratory syncytial virus (RSV) is an RNA virus mainly known for causing potentially life-threatening acute bronchiolitis in young children. Adults also are

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infected by RSV commonly, but often demonstrate limited (or even no) symptoms restricted to the upper respiratory tract and generally are considered to have better outcomes than young children.¹⁻³ In particular, RSV has been found to explain 4% to 22% of influenza-like illnesses in adults.⁴⁻⁸ Nevertheless, RSV infection can be life-threatening in some adults, in particular among immunocompromised people, such as hematopoietic cell transplant recipients.^{7,9}

The recent development and implementation of rapid and sensitive diagnostic tools (eg, targeted RSV polymerase chain reaction-based assays and multiplex panels) has increased our ability to detect RSV infection greatly. In our institutions, as well as in many others, testing for RSV infection has become routine practice for critically ill patients with signs and symptoms of respiratory tract infection, and it is relatively common to detect RSV infection in these patients. RSV has been identified in 3% to 11% of respiratory samples from patients admitted to the ICU for lower respiratory tract infection.¹⁰⁻¹³

The characteristics and outcomes of RSV infection in adult patients requiring ICU admission have not been well described. Although several studies in adults with RSV infection have been published in recent years,^{1,4-6,14-16} they did not specifically focus on critically ill patients. Influenza is another respiratory virus routinely tested for in patients in the ICU with respiratory symptoms because of its well-known morbidity and mortality, but no studies specifically have compared RSV and influenza infections in adult patients in the ICU. Therefore, we conducted a retrospective multicenter study to compare the characteristics and outcomes of adult patients in the ICU with RSV infection with those of adult patients in the ICU with influenza infection.

Methods

Study Design and Setting

This observational, retrospective, matched cohort study involved 15 ICUs in France and two in Belgium. Adult patients with RSV and influenza infection were identified in each institution by systematic screening of local microbiological databases for the period from November 1, 2011, through April 30, 2018. This interval was chosen because patients hospitalized in participating ICUs during this period were tested routinely for RSV and influenza if they showed suggestive signs and symptoms. The study was approved by ethics committees in France (SRLF committee; Identifier: CESRLF18-28) and Belgium (ULB-Erasme committee; Identifier: P2018/562). The study objectives, eligibility criteria, data, and outcomes were

predetermined in our study protocol. The results are reported in accordance with the STROBE guidelines ([e-Appendix 1](#)).

Patients

All patients meeting the following criteria were included in the study: (1) detection of RSV in a respiratory tract specimen (ie, nasopharyngeal swab, tracheal aspirate, or BAL specimen) between November 1, 2011, and April 30, 2018; (2) diagnosis of RSV infection made during the ICU stay or within 1 week before ICU admission; and (3) age $\geq$ 18 years at time of diagnosis.

Each patient with RSV infection was matched with a patient with influenza infection (1:1 ratio). Matched patients were those who: (1) were from the same ICU; (2) had a respiratory tract specimen that showed detection of influenza in the same winter season between November 1, 2011, and April 30, 2018, as the patient with RSV infection; (3) matched as closely as possible to the index patient with RSV infection in terms of date of diagnosis; and (4) age $\geq$ 18 years at time of diagnosis.

Nucleic acid amplification tests generally were used to diagnose viral infection in the participating centers during the study period, but we also included patients who had a viral infection detected using other methods (ie, antigen detection tests or viral culture). For nucleic acid amplification tests, results typically were available within 48 h in the participating centers. We excluded patients who demonstrated RSV and influenza infection concomitantly; in case of sequential infections, only the first incident infection was included.

Study Objectives and End Points

Clinical characteristics and outcomes of patients in the ICU with RSV infection were compared with those of patients in the ICU with influenza infection. Our primary objective was to compare in-hospital mortality in these two groups of patients. In-hospital mortality was defined as death resulting from any cause during the index hospital stay in acute care facilities. Deaths occurring after transfer to long-term care facilities (eg, rehabilitation facilities) were not included. A secondary objective was to compare the clinical and biological characteristics of RSV and influenza infections in patients in the ICU. Other secondary objectives included comparisons of the following parameters in patients in the ICU with RSV infection and patients in the ICU with influenza infection: mortality during the index ICU stay, length of ICU and hospital stay, and methods (low-flow oxygen, high-flow oxygen, noninvasive ventilation, invasive ventilation, use of prone positioning, or need for extracorporeal membrane oxygenation) and duration of respiratory support.

Data Collected

Data were collected retrospectively by local investigators using a standardized case report form that included demographic and clinical data (date of hospital and ICU admission; reason for ICU admission; SAPS II score; comorbidities, including chronic respiratory diseases, immunodeficiency, and other comorbidities listed in [Table 1](#); smoking status; and pregnancy). We defined young and previously healthy patients as those who were between 18 and

59 years of age and had none of the following underlying conditions: immunodeficiency; chronic respiratory, cardiac, kidney, or hepatic disease; diabetes; or neurological disability. We collected the date of diagnosis of viral infection (defined as the day on which the respiratory tract specimen showing positive results was collected) and testing method used (nucleic acid amplification test, antigen detection test, or viral culture). We recorded clinical signs and symptoms and blood test results (WBC count, platelet count, creatinine concentration, creatine phosphokinase [CPK] concentration, liver tests, pH, PaCO_2 , and PaO_2 to FiO_2 ratio) at the time of diagnosis of viral infection. We noted if the patients had received a diagnosis of ARDS (defined using the Berlin definition¹⁷) and presence of clinical signs of airway obstruction (defined as the presence of wheezing, a prolonged expiratory phase, diminished breath sounds on lung auscultation, or a combination thereof). We also recorded the presence of additional respiratory events at the time of the viral infection (eg, pulmonary embolism, heart failure, or other event), as well as the presence of microbiologically documented bacterial coinfections (defined as bacterial infections proven by blood culture, cultures of respiratory tract specimens considered as clinically relevant by the treating physician, or both). Finally, we collected data related to any treatments, including respiratory support, vasopressor agents, antibiotics, antiviral therapy, and steroids.

Statistical Analysis

Patient clinical and biological data at the time of viral infection diagnosis are described. Categorical variables are presented as numbers and frequencies. Continuous variables are presented as mean $\pm$ SD or median (interquartile range), as appropriate. Matching was taken into account in the analysis; we compared the characteristics and outcomes of patients with RSV infection with those of patients with influenza infection using the Wilcoxon matched-pairs signed-rank test, Mann-Whitney *U* test, paired *t* test, McNemar test, or Stuart-Maxwell test, as appropriate. To study the association of the type of virus (ie, RSV vs influenza) with the primary end point of in-hospital mortality, conditional logistic regression modeling was used. For this multivariate analysis, we selected a priori covariates identified in the scientific literature as having a potential association with mortality. We also included variables associated with in-hospital mortality in our study cohort (ie, with a *P* value of $< .20$ in the univariate analysis). Given our research question, factors that were more likely to be consequences of the viral infection than confounders (eg, severity scores and other markers of severity at the time of diagnosis of viral infection) were not included in the multivariate model; we also excluded factors that were present in $< 5\%$ of the study population. Kaplan-Meier survival curves were used to represent in-hospital mortality in both groups and were compared using shared frailty survival models.¹⁸ Patients who were discharged alive from hospital were considered to be censored. A two-sided *P* value of $< .05$ was considered to be statistically significant. Analyses were performed in Stata/SE version 16.1 software for Windows (StataCorp).

Results

Included Patients

A total of 618 patients from 17 ICUs were included (309 patients with RSV infection and 309 matched patients with influenza infection; characteristics of the participating centers are shown in [e-Table 1](#)). The

median period between hospital admission and ICU admission was similarly short in both groups (0 days; interquartile range, 0-1 day). The test that detected the viral infection typically was performed on the day of ICU admission (median time between ICU admission and viral testing, 0 days in both groups; interquartile

range, 0-1 day) and was a nucleic acid amplification test in 92.7% of patients (573/618). Most of the positive test results (70.7% [437/618]) were from nasopharyngeal specimens, followed by BAL fluid (18.1% [112/618]) and tracheal aspirate specimens (10.7% [66/618]; no significant difference between study groups). The vast majority of the episodes of RSV infection (97.1% [300/309]) were detected between October 1 and April 30.

Past Medical History

Compared with patients in the ICU with influenza infection, those with RSV infection were significantly more likely to have an underlying chronic respiratory condition (60.2% [186/309] vs 40.1% [124/309]; $P < .001$) and to be immunocompromised (35% [108/309] vs 26.2% [81/309]; $P = .02$). The frequencies of all comorbidities are shown in Table 1. Only 6.3% of the patients were considered to be young and previously healthy (39/618; see definition provided previously herein); this proportion was significantly lower in the RSV group than in the influenza group (2.9% [9/309] vs 9.7% [30/309]; $P = .001$).

Characteristics and Severity at Time of Diagnosis of Viral Infection

Clinical presentation varied between the study groups (see Table 1 and e-Table 2 for additional details regarding patients with RSV infection). Patients with RSV infection were significantly more likely to show signs of airway obstruction than those with influenza infection (49.5% [149/301] vs 39.5% [118/299]; $P = .01$) at the time of diagnosis. By contrast, patients with influenza infection more often had a diagnosis of ARDS at the time of influenza diagnosis (21.7% [67/309] vs 14.6% [45/309]; $P = .02$). Patients with RSV infection also demonstrated a significantly lower body temperature than those with influenza infection (mean temperature, 38 ± 1.2 °C vs 38.5 ± 1.1 °C; $P < .001$) and were less likely to report myalgia (4.9% [15/309] vs 13.9% [43/309]; $P < .001$). Biological characteristics at diagnosis also varied between the groups, with thrombocytopenia, serum CPK concentration of $\geq 1,000$ UI/L, and serum ALAT concentration of > 50 IU/L significantly less frequent in the RSV group than in the influenza group (Table 1).

Just more than one-third of patients in both groups were receiving invasive mechanical ventilation at the time of diagnosis of the viral infection (36.6% [113/309] in the RSV group vs 35.9% [111/309] in the influenza group; $P = .86$) and the mean Pao₂ to FiO₂ ratios were similar in

the two groups (Table 1). The proportion of patients requiring vasopressor support at the time of diagnosis also was similar in the RSV and influenza groups (27.6% [85/309] vs 32.1% [99/309]; $P = .18$). The mean sequential organ failure assessment score was slightly but significantly lower in the patients with RSV infection than in those with influenza infection (5 ± 3 vs 6 ± 4 ; $P = .02$). Additional data on illness severity at the time of diagnosis of viral infection are provided in Table 1.

Coinfections and Specific Therapies

In the 24 h before and after the viral infection diagnosis, a bloodstream infection was detected in 7.4% of the patients (46/618) and a bacterial pathogen was detected in a respiratory specimen in 26.1% of the patients (161/617). These two rates did not differ significantly between the influenza and RSV groups (Table 1, e-Table 3).

Most patients received ≥ 72 h of therapeutic antibiotics during the studied episode of infection (65.1% in the RSV group [200/307] vs 60.5% in the influenza group [187/319]; $P = .20$). Steroids were administered to 11% of the patients with RSV infection (34/309) and 8.1% of the patients with influenza infection (25/309; $P = .22$). In terms of antiviral therapy, 68.9% of the patients with influenza infection received oseltamivir (213/309). In the RSV group, one patient received ribavirin (0.3%) and four others were included in a clinical trial comparing presatovir vs placebo (1.3%).

Patient Outcomes

About 20% of patients died during the index ICU stay in both groups (19.4% in the RSV group [60/309] vs 20.4% in the influenza group [63/309]; $P = .75$). In-hospital mortality was not significantly different in the two study groups (23.9% in the RSV group [74/309] vs 25.6% in the influenza group [79/309]; crude OR, 0.91; 95% CI, 0.63-1.33; $P = .63$). Kaplan-Meier survival curves are shown in Figure 1. To investigate the association between the type of viral infection (ie, RSV vs influenza) and in-hospital mortality, conditional logistic regression modeling was used to adjust for nine covariables: sex, age, underlying conditions (chronic respiratory condition, immunodeficiency, chronic kidney disease, chronic heart failure, diabetes, obesity), and concurrent bloodstream infection. In this multivariate analysis (Table 3), RSV infection was associated with a similar odds of in-hospital death compared with influenza infection in patients in the ICU (adjusted OR, 0.80; 95% CI, 0.49-1.30; $P = .37$).

Apart from mortality, almost half the patients from both groups required endotracheal intubation and invasive

TABLE 1] Characteristics of Patients With RSV Infection Compared With Patients With Influenza Infection

Characteristic	RSV Infection (n = 309)	Influenza Infection (n = 309)	P Value
Male sex	169 (54.7)	177 (57.3)	.52
Age at diagnosis, y	67.2 ± 15.0	65.3 ± 15.6	.13
Comorbidities			
Underlying chronic respiratory condition	186 (60.2)	124 (40.1)	< .001
COPD	120 (38.8)	76 (24.6)	< .001
Asthma	39 (12.6)	27 (8.7)	.12
Other chronic respiratory condition(s) ^a	55 (17.8)	35 (11.3)	.02
Long-term oxygen therapy	36 (11.7)	11 (3.6)	< .001
Immunodeficiency	108 (35.0)	81 (26.2)	.02
Solid organ transplantation	12 (3.9)	10 (3.2)	.62
Allogeneic HCT	6 (1.9)	4 (1.3)	.53
Cancer or hematologic malignancy (without allogeneic HCT)	61 (19.7)	57 (18.4)	.68
Chemotherapy in last month	29 (9.4)	16 (5.2)	.04
Current use of immunosuppressive medication ^b	56 (18.1)	35 (11.3)	.02
Chronic heart failure	53 (17.2)	47 (15.2)	.51
Cirrhosis	9 (2.9)	10 (3.2)	.81
Chronic kidney disease ^c	40 (12.9)	35 (11.3)	.53
Diabetes	69 (22.3)	79 (25.6)	.33
Obesity (BMI > 30 kg/m ²)	51 (16.6)	45 (14.6)	.49
Ongoing pregnancy	0 (0)	2 (0.6)	.16
Current or former smoker, n = 552	174 (64.7)	172 (61)	.44
Time between onset of symptoms and ICU admission, d, n = 591	3 (1-5)	3 (2-5)	.71
Time between hospitalization and ICU admission, d	0 (0-1)	0 (0-1)	.24
Reason for ICU admission			< .001
De novo respiratory failure	125 (40.5)	163 (52.8)	
Acute on chronic respiratory failure	131 (42.4)	81 (26.2)	
Other	53 (17.1)	65 (21)	
Signs and symptoms at time of diagnosis of viral infection			
Temperature, °C, n = 603	38 ± 1.2	38.5 ± 1.1	< .001
Respiratory	297 (96.7)	293 (95.1)	.41
Cough, n = 615	156 (50.8)	173 (56.2)	.17
Sputum, n = 614	110 (35.8)	77 (25.1)	.006
Shortness of breath, n = 615	258 (84)	243 (78.9)	.10
Signs of airway obstruction, ^d n = 600	149 (49.5)	118 (39.5)	.01
ARDS	45 (14.6)	67 (21.7)	.02
Extracranial symptoms			
Myalgia	15 (4.9)	43 (13.9)	< .001
Headache	11 (3.6)	23 (7.4)	.03
Laboratory results at time of diagnosis			
WBC count 4-12,000/mm ³ , n = 596	144 (48.2)	173 (58.2)	.22
Thrombocytopenia (< 150,000/mm ³), n = 587	81 (27.8)	113 (38.2)	.001
Creatinine, mg/dL, n = 602	1.37 ± 1.32	1.49 ± 1.35	.17
CPK ≥ 1,000 IU/L, n = 281	8 (6.3)	26 (16.9)	.01

(Continued)

TABLE 1] (Continued)

Characteristic	RSV Infection (n = 309)	Influenza Infection (n = 309)	P Value
ALAT > 50 IU/L, n = 525	56 (21.5)	75 (28.3)	.04
pH, n = 582	7.32 ± 0.14	7.34 ± 0.12	.10
Paco ₂ , mm Hg, n = 582	54 ± 23	46 ± 18	< .001
Pao ₂ to Fio ₂ ratio, n = 573	217 ± 122	204 ± 110	.18
Illness severity at time of diagnosis of viral infection			
SOFA score, n = 609	5 ± 3	6 ± 4	.02
SAPS II score, n = 613	42 ± 16	40 ± 18	.12
Use of vasopressors	85 (27.6)	99 (32.1)	.18
Respiratory support			.048
Low-flow oxygen therapy	90 (29.1)	102 (33)	
High-flow nasal cannula	25 (8.1)	38 (12.3)	
Noninvasive ventilation	81 (26.2)	58 (18.8)	
Invasive ventilation	113 (36.6)	111 (35.9)	
Including prone position	2 (0.6)	5 (1.6)	
Including ECMO	2 (0.6)	7 (2.3)	
Additional identified cause for respiratory failure (not infectious)			.27
No other cause identified	224 (72.5)	236 (76.4)	
Pulmonary embolism	6 (1.9)	2 (0.6)	
Heart failure	50 (16.2)	50 (16.2)	
Other cause	29 (9.4)	21 (6.8)	
Coinfections ^e			
Bloodstream infection	21 (6.8)	25 (8.1)	.56
Bacterial pathogen detected in respiratory specimen, n = 617	84 (27.2)	77 (24.9)	.52
Antiviral therapy			
Oseltamivir	N/A	213 (68.9)	
Ribavirin	1 (0.9)	N/A	

Data are presented as No. (%), mean ± SD, or median (interquartile range), unless otherwise indicated. Matching was taken into account in the analysis (see Methods section). CPK = creatine phosphokinase; ECMO = extracorporeal membrane oxygenation; HCT = hematopoietic cell transplantation; n = no. of data analyzed (when < 618); N/A = not available; RSV = respiratory syncytial virus; SOFA = sequential organ failure assessment.

^aIncludes OSA (n = 48), interstitial lung disease (n = 23), obesity hypoventilation syndrome (n = 20), and bronchiectasis (n = 17).

^bDefined as use of systemic corticosteroids (ie, any dose if > 1 mo or ≥ 1 mg/kg/d prednisolone equivalent if ≤ 1 mo), use of any other immunosuppressive medication, or both.

^cDefined as estimated glomerular filtration rate of < 60 mL/min/1.73 m².

^dDefined as the presence of sibilant wheezing, prolonged expiratory phase, diminished breath sounds on lung auscultation, or a combination thereof.

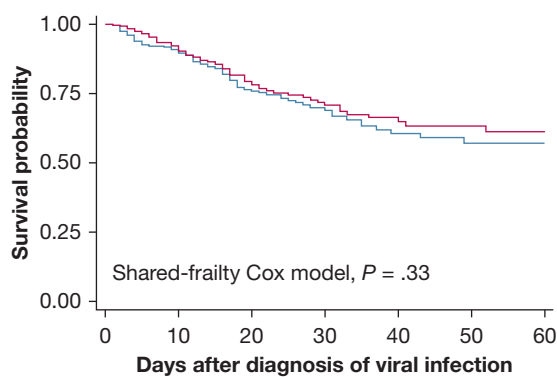
^eWithin 24 h before or after a diagnosis of viral infection (e-Table 3).

ventilation at some point during the ICU stay (49.2% of patients with RSV infection [152/309] vs 46.8% of patients with influenza infection [144/308]; $P = .49$). The incidence of ARDS during the ICU stay was significantly higher in the influenza group than in the RSV group (28.5% [88/309] vs 20.4% [63/309]; $P = .01$), and significantly more patients required prone positioning, extracorporeal membrane oxygenation, or both at some point during the ICU stay in the influenza group than in the RSV group (11.3% [35/308] vs 4.2% [13/309]; $P < .001$). Lengths of ICU and hospital stays and durations of

mechanical ventilation also did not differ significantly between the RSV and influenza groups (Table 2).

Discussion

In this large multicenter study, adult patients in the ICU with RSV infection differed from adult patients in the ICU with influenza in terms of comorbidities and clinical and biological characteristics at diagnosis. RSV infection was associated with an in-hospital mortality rate approaching 25%. In multivariate analysis, RSV



No. at risk							
RSV	309	233	128	70	47	32	23
Influenza	309	215	125	73	42	32	20

— RSV — Influenza

Figure 1 – Kaplan-Meier survival curves for patients with RSV infection and patients with influenza infection (in-hospital mortality). RSV = respiratory syncytial virus.

infection was associated with a similar odds of in-hospital death compared with influenza infection.

To the best of our knowledge, this study is the largest to date of patients admitted to the ICU with RSV infection. Our results show that severe RSV infection occurs mainly in patients with comorbidities. Indeed, previously young (18- < 60 years of age) and healthy people represented only approximately 3% of all patients with RSV infections in the ICU cohort. RSV infection was associated more frequently with the presence of an

underlying chronic respiratory condition, immunodeficiency, or both compared with influenza infection. These findings are similar to those from previous studies that looked at adults with RSV infection, but did not focus specifically on those requiring ICU admission.^{7,14,15} The association between severe RSV infection and immunodeficiency has been studied previously in adult hematopoietic cell transplant recipients,⁹ but this study confirms the increased susceptibility of other immunocompromised hosts to severe RSV infection.¹⁹

The characteristics of RSV infection at diagnosis differ from those of influenza infection in critically ill patients. In particular, RSV infection more often was associated with clinical signs of airway obstruction. This finding correlates with the known propensity of RSV for causing obstruction of distal airways,^{20,21} with the epidemiologic association between RSV infection and bronchiolitis in children, and with the fact that almost 50% of the patients in the RSV group in this cohort had a diagnosis of COPD, asthma, or both. By contrast, influenza infection more often was associated with ARDS, which is characterized by alveolar damage. Nevertheless, ARDS still occurred in 20% of the patients with RSV infection, highlighting the potential severity of this viral infection. Our study identified additional differences between RSV and influenza infections, which previous studies may not have detected because of smaller numbers of patients with RSV infection, lack of detailed information on characteristics present at diagnosis, or both.^{1,2,5,7,8,14,15,22}

TABLE 2] Patient Outcomes According to Type of Viral Infection (RSV vs Influenza)

Variable	RSV Infection (n = 309)	Influenza Infection (n = 309)	P Value
In-hospital mortality	74 (23.9)	79 (25.6)	.63
Hospital length of stay (for overall cohort), d	16 (10-28)	15 (8-28)	.35
Hospital length of stay (for survivors), d, n = 465	17 (10-29)	16 (9-29)	.87
In-ICU mortality	60 (19.4)	63 (20.4)	.75
ICU length of stay (for survivors), d, n = 495	6 (3-11)	6 (3-11)	.99
Length of mechanical ventilation (for survivors), d, n = 296	5 (2-11)	5 (3-12)	.59
ARDS during ICU stay	63 (20.4)	88 (28.5)	.01
Maximum form of respiratory support during ICU stay			.001
Low-flow oxygen therapy	66 (21.4)	82 (26.6)	
High-flow nasal cannula	20 (6.5)	30 (9.7)	
Noninvasive ventilation	71 (23)	52 (16.9)	
Invasive ventilation	152 (49.2)	144 (46.8)	
Including prone position	5 (1.6)	12 (3.9)	
Including ECMO	8 (2.6)	23 (7.5)	

Data are presented as No. (%) or median (interquartile range), unless otherwise indicated. Matching was taken into account in the analysis (see Methods section). ECMO = extracorporeal membrane oxygenation; RSV = respiratory syncytial virus.

TABLE 3] Risk Factors for In-Hospital Mortality After Multivariate Analysis by Conditional Logistic Regression

Characteristic	Adjusted OR (95% CI)	P Value
RSV infection (vs influenza infection)	0.80 (0.49-1.30)	.37
Male sex	0.49 (0.23-1.04)	.06
Age, y	1.05 (1.02-1.07)	< .001
Underlying chronic respiratory condition	0.78 (0.39-1.58)	.49
Underlying immunodeficiency	2.10 (0.99-4.44)	.06
Underlying chronic kidney disease ^a	0.72 (0.26-2.01)	.53
Underlying chronic heart failure	1.49 (0.57-3.90)	.41
Diabetes	0.53 (0.20-1.38)	.19
Obesity (BMI > 30 kg/m ²)	1.26 (0.46-3.43)	.65
Concurrent bloodstream infection	1.86 (0.65-5.37)	.25

RSV = respiratory syncytial virus.

^aDefined as estimated glomerular filtration rate of < 60 mL/min/1.73 m². All 618 patients (309 pairs) were included in this multivariate analysis (no missing data).

In our study, patients with influenza infection were significantly more likely to show fever, myalgia, increased CPK level, thrombocytopenia, and transaminitis at diagnosis than were those with RSV infection. Whether these differences may be used to guide patient management remains to be determined, especially because some overlap exists between these two viral infections in terms of presentation.^{23,24} Related to this point, previous studies have shown that use of oseltamivir is relatively common early in the course of RSV infection.¹⁴

Almost one-quarter of the patients in the ICU with RSV infection died during the hospital stay, comparable with the mortality rate of patients with influenza infection, even after adjustment for comorbidities and other important prognostic factors in a multivariate model. Previous studies that looked at adults with RSV infection, but did not specifically focus on those requiring ICU admission, also found a mortality rate that was at least comparable with that of adult patients with influenza infection.^{1,14} In our study, ICU and hospital lengths of stay and durations of mechanical ventilation were comparable in patients with RSV infection and those with influenza infection. These findings, highlighting the potential burden of RSV infection in adults in the ICU, support the need to identify effective prophylactic and therapeutic interventions.²⁵

Interpretation

The strengths of our study include its large sample size and large number of recorded variables, as well as the comparison of patients with RSV with local

patients with influenza. Also, our study was not industry supported. However, our study also has several limitations, in addition to its retrospective design. First, testing for respiratory viruses typically was performed in patients with signs and symptoms of respiratory tract infection, and not systematically in all patients in the ICU. Therefore, we probably missed some cases of viral infection, especially atypical ones. Second, we are unable to demonstrate a causal relationship between the viral infections and patient outcomes. Because RSV and influenza infections can be asymptomatic, detection of these viruses may be a coincidental finding unrelated to the patient's critically ill condition.^{12,26} However, more than 95% of patients demonstrated respiratory symptoms and relatively few showed another detected cause for the respiratory condition, supporting causality between the viral infections detected and the relatively poor outcomes. Third, the management of patients was not homogeneous among the centers (but depended on local protocols), and this may have impacted patient outcomes. However, patients were matched by date and hospital, which should have reduced the risk of bias for the between-group comparisons (because patients with RSV infection and the matched control participants with influenza were managed by the same ICU teams during the same period). Fourth, because of the retrospective design, a significant amount of data were missing for some biological parameters (eg, CPK and ALAT values) and some clinical symptoms (eg, myalgia and headache) were

probably underestimated. Also, considerable variability may have characterized the appreciation of clinical signs of airway obstruction. Again, the fact that patients were matched by date and hospital probably limited the risk of bias for between-group comparisons. Fifth, we did not correct for multiple comparisons and the fragility index of some significant comparisons was low. Finally, the observed differences between RSV and influenza infections may not be applicable to different settings, for example, to adult patients not admitted to ICU, to areas with a different influenza vaccination coverage,

to areas where antiviral therapy is used differently, or to pandemic influenza.

In conclusion, our study suggested that RSV infection differs from influenza infection in adult patients in the ICU in terms of characteristics at diagnosis, but is associated with a similar in-hospital mortality rate of approximately 25%, comparable ICU and hospital lengths of stay, and similar rates and durations of mechanical ventilation. These findings highlight the need to identify interventions to prevent and treat severe RSV infection.

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Additional information: The e-Appendix and e-Tables can be found in the

Supplemental Materials section of the online article.

References

- Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *N Engl J Med*. 2005;352(17):1749-1759.
- Hall CB, Long CE, Schnabel KC. Respiratory syncytial virus infections in previously healthy working adults. *Clin Infect Dis*. 2001;33(6):792-796.
- Munywoki PK, Koech DC, Agoti CN, et al. Influence of age, severity of infection, and co-infection on the duration of respiratory syncytial virus (RSV) shedding. *Epidemiol Infect*. 2015;143(4):804-812.
- Belongia EA, King JP, Kieke BA, et al. Clinical features, severity, and incidence of RSV illness during 12 consecutive seasons in a community cohort of adults ≥ 60 years old. *Open Forum Infect Dis*. 2018;5(12):ofy316.
- Falsey AR, McElhaney JE, Beran J, et al. Respiratory syncytial virus and other respiratory viral infections in older adults with moderate to severe influenza-like illness. *J Infect Dis*. 2014;209(12):1873-1881.
- Kestler M, Munoz P, Mateos M, Adrados D, Bouza E. Respiratory syncytial virus burden among adults during flu season: an underestimated pathology. *J Hosp Infect*. 2018;100(4):463-468.
- 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. *Clin Microbiol Infect*. 2017;23(4):253-259.
- Zambon MC, Stockton JD, Clewley JP, Fleming DM. Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. *Lancet*. 2001;358(9291):1410-1416.
- Chemaly RF, Shah DP, Boeckh MJ. Management of respiratory viral infections in hematopoietic cell transplant recipients and patients with hematologic malignancies. *Clin Infect Dis*. 2014;59(suppl 5):S344-S351.
- Choi SH, Hong SB, Ko GB, et al. Viral infection in patients with severe pneumonia requiring intensive care unit admission. *Am J Respir Crit Care Med*. 2012;186(4):325-332.
- Ong DS, Faber TE, Klein Klouwenberg PM, et al. Respiratory syncytial virus in critically ill adult patients with community-acquired respiratory failure: a prospective observational study. *Clin Microbiol Infect*. 2014;20(8):505-507.
- van Someren Greve F, Juffermans NP, Bos LDJ, et al. Respiratory viruses in invasively ventilated critically ill patients—a prospective multicenter observational study. *Crit Care Med*. 2018;46(1):29-36.
- Arabi YM, Fowler R, Hayden FG. Critical care management of adults with community-acquired severe respiratory viral infection. *Intensive Care Med*. 2020;46(2):315-328.
- Ackerson B, Tseng HF, Sy LS, et al. Severe morbidity and mortality associated with respiratory syncytial virus versus influenza infection in hospitalized older adults. *Clin Infect Dis*. 2019;69(2):197-203.
- Chen L, Han X, Li Y, Zhang C, Xing X. Comparison of clinical characteristics and outcomes between respiratory syncytial virus and influenza-related pneumonia in China from 2013 to 2019. *Eur J Clin Microbiol Infect Dis*. 2021.
- Lee N, Smith S, Zelyas N, et al. Burden of noninfluenza respiratory viral infections in adults admitted to hospital: analysis of a multiyear Canadian surveillance cohort from 2 centres. *CMAJ*. 2021;193(13):E439-E446.
- Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307(23):2526-2533.
- Gutierrez RG. Parametric frailty and shared frailty survival models. *Stata J*. 2002;2:22-44.
- Chatzis O, Darbre S, Pasquier J, et al. Burden of severe RSV disease among

- immunocompromised children and adults: a 10 year retrospective study. *BMC Infect Dis.* 2018;18(1):111.
20. Pickles RJ, DeVincenzo JP. Respiratory syncytial virus (RSV) and its propensity for causing bronchiolitis. *J Pathol.* 2015;235(2):266-276.
21. Carvajal JJ, Avellaneda AM, Salazar-Ardiles C, Maya JE, Kalergis AM, Lay MK. Host components contributing to respiratory syncytial virus pathogenesis. *Front Immunol.* 2019;10:2152.
22. To KKW, Chan KH, Ho J, et al. Respiratory virus infection among hospitalized adult patients with or without clinically apparent respiratory infection: a prospective cohort study. *Clin Microbiol Infect.* 2019;25(12):1539-1545.
23. Walsh EE, Peterson DR, Falsey AR. Is clinical recognition of respiratory syncytial virus infection in hospitalized elderly and high-risk adults possible? *J Infect Dis.* 2007;195(7):1046-1051.
24. Widmer K, Zhu Y, Williams JV, Griffin MR, Edwards KM, Talbot HK. Rates of hospitalizations for respiratory syncytial virus, human metapneumovirus, and influenza virus in older adults. *J Infect Dis.* 2012;206(1):56-62.
25. Simoes EA, DeVincenzo JP, Boeckh M, et al. Challenges and opportunities in developing respiratory syncytial virus therapeutics. *J Infect Dis.* 2015;211(suppl 1):S1-S20.
26. 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(suppl 7):S577-S583.