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

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Characteristics and outcomes of intensive care unit patients with respiratory syncytial virus compared to those with influenza infection: a multicentre matched cohort study

Running title: RSV vs. influenza in ICU patients

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ABSTRACT

Background.

The characteristics and outcomes of adult patients with respiratory syncytial virus (RSV) infection who require intensive care unit (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 ICU patients with RSV infection, and how do they compare to those of ICU patients with influenza infection?

Study Design and Methods.

This retrospective, multicentre study in France and Belgium (17 sites) compared the characteristics and outcomes of adult ICU patients with RSV infection *versus* 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 multivariable 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 analysed. Patients with RSV infection were significantly more likely to have an underlying chronic respiratory condition (60.2% *versus* 40.1%, p<0.001) and to be immunocompromised (35% *versus* 26.2%, p=0.02) than patients with influenza infection. There were several differences in clinical signs and biological data at diagnosis between the groups. In-hospital mortality was not significantly different in the two groups (23.9% in the RSV group *versus* 25.6% in the influenza group, p=0.63), even after adjustment for prognostic factors in a multivariable model.

Interpretation.

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

Respiratory Syncytial Virus (RSV) is a RNA virus mainly known for causing potentially life-threatening acute bronchiolitis in young children. Adults are also commonly infected by RSV, but often present with limited (or even no) symptoms restricted to the upper respiratory tract, and are generally considered to have better outcomes than young children.[1-3] In particular, RSV has been found to explain 4–22% of influenza-like illnesses in adults.[4-8] Nevertheless, RSV infection can be life-threatening in some adults, in particular among immunocompromised hosts, such as haematopoietic cell transplant recipients.[7,9]

The recent development and implementation of rapid and sensitive diagnostic tools (e.g., targeted RSV polymerase chain reaction [PCR]-based assays, and multiplex panels) has greatly increased our ability to detect RSV infection. 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 3-11% of respiratory samples from patients admitted to the intensive care unit (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 ICU patients with respiratory symptoms because of its well known morbidity and mortality, but there are no data specifically comparing RSV and influenza infections in adult ICU patients.

We therefore conducted a retrospective multicentre study to compare the characteristics and outcomes of adult ICU patients with RSV infection with those of adult ICU patients with influenza infection.

METHODS

Study design and setting

This observational, retrospective, matched cohort study involved 15 ICUs in France and 2 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 01 November 2011 to 30 April 2018. This interval was chosen because patients hospitalised in participating ICUs during this period were routinely tested for RSV and influenza if they had suggestive signs and symptoms. The study was approved by ethics committees in France (SRLF

committee, ref: CESRLF18-28) and Belgium (ULB-Erasme committee, ref: P2018/562). The study objectives, eligibility criteria, data, and outcomes were pre-determined in our study protocol. The results are reported in accordance with the STROBE guidelines (see **Appendix p 7** for checklist).

Patients

All patients meeting the following criteria were included in the study: (1) detection of RSV in a respiratory tract specimen (i.e., nasopharyngeal swab, tracheal aspirate, or bronchoalveolar lavage specimen) between 01 November 2011 and 30 April 2018; (2) diagnosis of RSV infection made during the ICU stay, or within one week before ICU admission; (3) age ≥ 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 subjects who: (1) were from the same ICU; (2) had detection of influenza in a respiratory tract specimen in the same winter season between 01 November 2011 and 30 April 2018 as the patient with RSV infection; (3) matched as closely as possible to the index case with RSV infection, in terms of date of diagnosis; (4) were ≥ 18 years of age at time of diagnosis.

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

Study objectives and endpoints

Clinical characteristics and outcomes of ICU patients with RSV infection were compared with those of ICU patients 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 from any cause during the index hospital stay in acute care facilities. Deaths occurring after transfer to long-term care facilities (e.g., rehabilitation facilities) were not included. A secondary objective was to compare the clinical and biological characteristics of RSV and influenza infections in ICU patients. Other secondary objectives included comparisons of the following parameters in ICU patients with RSV infection and ICU patients with influenza infection: mortality during the index ICU stay, length of ICU and hospital stay, and modes (low flow oxygen, high flow oxygen, non invasive ventilation, invasive

ventilation, use of prone positioning, or need for extracorporeal membrane oxygenation [ECMO]) 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; co-morbidities, including chronic respiratory diseases, immunodeficiency, and other co-morbidities listed in **Table 1**; smoking status; 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 positive respiratory tract specimen was collected), and testing method used (nucleic acid amplification test, antigen detection test, or viral culture). We recorded clinical signs/symptoms and blood test results (white blood cell count, platelet count, creatinine concentration, creatine phosphokinase [CPK] concentration, liver tests, pH, PaCO2, and PaO2/FiO2 ratio) at the time of diagnosis of viral infection. We noted if there was a diagnosis of acute respiratory distress syndrome (ARDS, defined using the Berlin definition [17]), and presence of clinical signs of airway obstruction (defined as the presence of wheezing, a prolonged expiratory phase, and/or diminished breath sounds on lung auscultation). We also recorded the presence of additional respiratory events at the time of the viral infection (e.g., pulmonary embolism, heart failure, or other event), as well as the presence of microbiologically-documented bacterial co-infections (defined as bacterial infections proven by blood culture, and/or cultures of respiratory tract specimens considered as clinically relevant by the treating physician). 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 means (± standard deviation) or medians (interquartile range [IQR]), 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 (i.e., RSV *versus* influenza)

with the primary endpoint of in-hospital mortality, conditional logistic regression modeling was used. For this multivariable 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 (i.e., with a p value < 0.20 in the univariate analysis). Given our research question, factors that were more likely to be consequences of the viral infection than confounders (e.g., severity scores and other markers of severity at the time of diagnosis of viral infection) were not included in our multivariable model; we also excluded factors that were present in < 5% of our study population. Kaplan-Meier survival curves were used to represent in-hospital mortality in both groups and compared using shared frailty survival models.[18] Patients who were discharged alive from hospital were considered as censored. A two-sided p value of < 0.05 was considered as statistically significant. Analyses were performed in Stata/SE 16.1 for Windows.

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 centres are given in **e-Table 1**). The median time period between hospital admission and ICU admission was similarly short in both groups (0 days, IQR: 0 to 1 days). The test that detected the viral infection was typically performed on the day of ICU admission (median time between ICU admission and viral testing: 0 days in both groups, interquartile range: 0 to 1 days) and was a nucleic acid amplification test in 92.7% of the patients (573/618). The majority of the positive tests (70.7%, 437/618) were performed on nasopharyngeal specimens, followed by bronchoalveolar 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 01 October and 30 April.

Past medical history

Compared to ICU patients with influenza infection, those with RSV infection were significantly more likely to have an underlying chronic respiratory condition (60.2% [186/309] *versus* 40.1% [124/309], p < 0.001) and to be immunocompromised (35% [108/309] *versus* 26.2% [81/309], p = 0.02). The frequencies of all comorbidities are shown in **Table 1**. Only 6.3% of the patients were considered as young and previously healthy (39/618, see

definition above); this proportion was significantly lower in the RSV group than in the influenza group (2.9% [9/309] *versus* 9.7% [30/309], p = 0.001).

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 have signs of airway obstruction than those with influenza infection (49.5% [149/301] *versus* 39.5% [118/299], p = 0.01) at the time of diagnosis. By contrast, patients with influenza infection more often had ARDS at the time of diagnosis (21.7% [67/309] *versus* 14.6% [45/309], p = 0.02). Patients with RSV infection also had a significantly lower body temperature than those with influenza infection (mean temperature: 38 ± 1.2 °C *versus* 38.5 ± 1.1 °C, p < 0.001) and were less likely to report myalgia (4.9% [15/309] *versus* 13.9% [43/309], p < 0.001).

Biological characteristics at diagnosis also varied between the groups, with thrombocytopenia, serum CPK concentration ≥ 1.000 UI/L, and serum ALAT concentration > 50 IU/L significantly less frequent in the RSV group than in the influenza group (**Table 1**).

Just over 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 *versus* 35.9% [111/309] in the influenza group, p = 0.86) and the mean PaO2/FiO2 ratios were similar in the two groups (additional details in **Table 1**). The proportion of patients requiring vasopressor support at the time of diagnosis was also similar in the RSV and influenza groups (27.6% [85/309] *versus* 32.1% [99/309], p = 0.18). The mean sequential organ failure assessment (SOFA) score was slightly but significantly lower in the patients with RSV infection than in those with influenza infection (5 ± 3 *versus* 6 ± 4, p = 0.02). Additional data on illness severity at the time of diagnosis of viral infection are provided in **Table 1.**

Co-infections and specific therapies

In the 24 hours 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 (see **Table 1**, and **e-Table 3** for additional details).

Most patients received ≥ 72 hours of therapeutic antibiotics during the studied episode of infection (65.1% in the RSV group [200/307] *versus* 60.5% in the influenza group [187/319], p = 0.20). 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 = 0.22). 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 *versus* 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] *versus* 20.4% in the influenza group [63/309], p = 0.75). In-hospital mortality was not significantly different in the two study groups (23.9% in the RSV group [74/309] *versus* 25.6% in the influenza group [79/309], crude odds ratio: 0.91, 95% confidence interval: 0.63 to 1.33, p = 0.63). Kaplan-Meier survival curves are shown in **Figure 1.** To investigate the association between the type of viral infection (i.e., RSV *versus* 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 multivariable analysis (**Table 3**), RSV infection was associated with a similar odds of in-hospital death compared to influenza infection in ICU patients (adjusted odds ratio: 0.80, 95% confidence interval: 0.49 to 1.30, p = 0.37).

Apart from mortality, almost half the patients from both groups required endotracheal intubation and invasive ventilation at some point during their ICU stay (49.2% of patients with RSV infection [152/309] *versus* 46.8% of patients with influenza infection [144/308], p = 0.49). The incidence of ARDS during the ICU stay was significantly higher in the influenza group than in the RSV group (28.5% [88/309] *versus* 20.4% [63/309], p = 0.01), and significantly more patients required prone positioning and/or ECMO at some point during their ICU stay in the influenza group than in the RSV group (11.3% [35/308] *versus* 4.2% [13/309], p < 0.001). Lengths of ICU and hospital stay and durations of mechanical ventilation also did not differ significantly between the RSV and influenza groups (**Table 2**).

DISCUSSION

In this large multicentre study, adult ICU patients with RSV infection differed from adult ICU patients 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 multivariable analysis, RSV infection was associated with a similar odds of in-hospital death compared to influenza infection.

To the best of our knowledge, our study is the largest to date in patients admitted to the ICU with RSV infection. Our results show that severe RSV infection mainly occurs in patients with comorbidities. Indeed, previously young (18 to < 60 years of age) and healthy subjects represented only around 3% of all cases of RSV infections in our ICU cohort. RSV infection was more frequently associated with the presence of an underlying chronic respiratory condition and/or immunodeficiency compared to influenza infection. These findings are similar to those from previous studies that looked at adults with RSV infection, but did not specifically focus on those requiring ICU admission.[7,14,15] The association between severe RSV infection and immunodeficiency has been previously studied in adult haematopoietic cell transplant recipients,[9] but our 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 was more often 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 epidemiological association between RSV infection and bronchiolitis in children, and with the fact that almost 50% of the patients in the RSV group in our cohort had COPD and/or asthma. By contrast, influenza infection was more often associated with ARDS, which is characterised 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 and/or lack of detailed information on characteristics present at diagnosis.[1,2,5,7,8,14,15,22] In our study, patients with influenza infection were significantly more likely to have 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 as there is some overlap 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 ICU patients with RSV infection died during the hospital stay, comparable to the mortality rate of patients with influenza infection, even after adjustment for comorbidities and other important prognostic factors in a multivariable 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 which was at least comparable to

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 RSV cases with local influenza cases. Also, our study was not industry-supported. However, our study also has several limitations, in addition to its retrospective design. Firstly, testing for respiratory viruses was typically performed in patients with signs and symptoms of respiratory tract infection, and not systematically in all ICU patients. We therefore probably missed some cases of viral infection, especially atypical ones. Secondly, 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 might be a coincidental finding unrelated to the patient's critically ill condition.[12,26] However, more than 95% of patients had respiratory symptoms and relatively few had another detected cause for their respiratory condition, supporting causality between the viral infections detected and the relatively poor outcomes. Thirdly, the management of patients was not homogeneous between the centres (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 (as RSV patients and their matched influenza controls were managed by the same ICU teams during the same period). Fourthly, because of the retrospective design, there was a significant amount of missing data for some biological parameters (e.g., CPK and ALAT values) and a probable underestimation of some clinical symptoms (e.g., myalgia and headache). There may also have been considerable variability in 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. Fifthly, we did not correct for multiple comparisons and the fragility index of some significant comparisons was low. Last, the observed differences between RSV and influenza infections may not be applicable to different settings, e.g., 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 suggests that RSV infection differs from influenza infection in adult ICU patients in terms of characteristics at diagnosis, but is associated with a similar in-hospital mortality rate of around 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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Authors' contributions.

Julien COUSSEMENT, Benjamin ZUBER, Charlotte VANDUEREN and David GRIMALDI contributed to the study conception and design. All authors participated to local data collection, except the study statistician (Hassane NJIMI). Julien COUSSEMENT, Hassane NJIMI and David GRIMALDI did the data analysis. The first draft of the manuscript was written by Julien COUSSEMENT and David GRIMALDI and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. Julien COUSSEMENT and David GRIMALDI are the guarantors, taking responsibility for the integrity of the work.

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Other contributions.

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Availability of data and material.

Data collected for the study, including de-identified individual participant data and a data dictionary defining each field in the set, will be made available to researchers who provide a methodologically sound proposal to the corresponding author with a signed data access agreement, at any point.

Members of the study group

Individual collaborators that participated actively in this study and are members of the study group are listed below:

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TAKE-HOME POINTS

Study question.

What are the characteristics and outcomes of adult ICU patients with RSV infection, and how do they compare to those of adult ICU patients with influenza infection?

Results.

In this retrospective multicentre matched cohort study, adult ICU patients 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 to that of influenza infection in multivariable analysis.

Interpretation.

There is a need to identify interventions to effectively prevent and treat severe RSV infection in adult patients.

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TABLES AND FIGURES

Table 1. Characteristics of patients with RSV infection compared to patients with influenza infection

	RSV (n = 309)	Influenza (n = 309)	p-value
Male	169 (54.7)	177 (57.3)	0.52
Age at diagnosis, year, mean ± SD	67.2 ± 15.0	65.3 ± 15.6	0.13
Comorbidities			
Underlying chronic respiratory condition	186 (60.2)	124 (40.1)	**< 0.001**
Chronic obstructive pulmonary disease	120 (38.8)	76 (24.6)	**< 0.001**
Asthma	39 (12.6)	27 (8.7)	0.12
Other chronic respiratory condition(s) *	55 (17.8)	35 (11.3)	**0.02**
Long-term oxygen therapy	36 (11.7)	11 (3.6)	**< 0.001**
Immunodeficiency	108 (35.0)	81 (26.2)	**0.02**
Solid organ transplantation	12 (3.9)	10 (3.2)	0.62
Allogeneic HCT	6 (1.9)	4 (1.3)	0.53
Cancer / haematologic malignancy (without allogeneic HCT)	61 (19.7)	57 (18.4)	0.68
Chemotherapy in last month	29 (9.4)	16 (5.2)	**0.04**
Current use of immunosuppressive medication **	56 (18.1)	35 (11.3)	**0.02**
Chronic heart failure	53 (17.2)	47 (15.2)	0.51
Cirrhosis	9 (2.9)	10 (3.2)	0.81
Chronic kidney disease * **	40 (12.9)	35 (11.3)	0.53
Diabetes	69 (22.3)	79 (25.6)	0.33
Obesity (body mass index > 30 kg/m²)	51 (16.6)	45 (14.6)	0.49
Ongoing pregnancy	0 (0)	2 (0.6)	0.16
Current or former smoker, n = 552	174 (64.7)	172 (61)	0.44
Time between onset of symptoms and ICU admission, d, median (IQR), n = 591	3 (1-5)	3 (2-5)	0.71
Time between hospitalisation and ICU admission, d, median (IQR)	0 (0-1)	0 (0-1)	0.24
Reason for ICU admission			**< 0.001**
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, mean ± SD, n = 603	38 ± 1.2	38.5 ± 1.1	**< 0.001**
Respiratory	297 (96.7)	293 (95.1)	0.41
Cough, n = 615	156 (50.8)	173 (56.2)	0.17
Sputum, n = 614	110 (35.8)	77 (25.1)	**0.006**
Shortness of breath, n = 615	258 (84)	243 (78.9)	0.10
Signs of airway obstruction,‡ n = 600	149 (49.5)	118 (39.5)	**0.01**
ARDS	45 (14.6)	67 (21.7)	**0.02**
Extra-respiratory symptoms			
Myalgia	15 (4.9)	43 (13.9)	**< 0.001**

Headache	11 (3.6)	23 (7.4)	**0.03**
Laboratory results at time of diagnosis			
White blood cell count 4 - 12.000/mm^3, n = 596	144 (48.2)	173 (58.2)	0.22
Thrombocytopaenia (< 150.000/mm^3), n = 587	81 (27.8)	113 (38.2)	**0.001**
Creatinine, mg/dL, mean ± SD, n = 602	1.37 ± 1.32	1.49 ± 1.35	0.17
CPK ≥ 1.000 IU/L, n = 281	8 (6.3)	26 (16.9)	**0.01**
ALAT > 50 IU/L, n = 525	56 (21.5)	75 (28.3)	**0.04**
pH, mean ± SD, n = 582	7.32 ± 0.14	7.34 ± 0.12	0.10
PaCO2, mmHg, mean ± SD, n = 582	54 ± 23	46 ± 18	**< 0.001**
PaO2/FiO2 ratio, mean ± SD, n = 573	217 ± 122	204 ± 110	0.18
Illness severity at time of diagnosis of viral infection			
SOFA score, mean ± SD, n = 609	5 ± 3	6 ± 4	**0.02**
SAPS-II score, mean ± SD, n = 613	42 ± 16	40 ± 18	0.12
Use of vasopressors	85 (27.6)	99 (32.1)	0.18
Respiratory support			**0.048**
Low flow oxygen therapy	90 (29.1)	102 (33)	
High flow nasal cannula	25 (8.1)	38 (12.3)	
Non-invasive 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)			0.27
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)	
Co-infections †			
Bloodstream infection	21 (6.8)	25 (8.1)	0.56
Bacterial pathogen detected in respiratory specimen, n = 617	84 (27.2)	77 (24.9)	0.52
Antiviral therapy			
Oseltamivir	N/A	213 (68.9)	
Ribavirin	1 (0.9)	N/A	

Matching was taken into account in the analysis (see Methods section). Data are n (%) unless otherwise indicated. d: days. n: number of data analysed (when < 618). ARDS: acute respiratory distress syndrome. CPK: creatine phosphokinase. HCT: haematopoietic cell transplantation. ICU: intensive care unit. N/A: not available. RSV: respiratory syncitial virus. * other chronic respiratory conditions were obstructive sleep apnoea (n = 48), interstitial lung disease (n = 23), obesity hypoventilation syndrome (n = 20), and bronchiectasis (n = 17). ** defined as use of systemic corticosteroids (i.e., any dose if > 1 month, or ≥ 1 mg/kg/day prednisolone equivalent if ≤ 1 month) and/or use of any other immunosuppressive medication. *** chronic kidney disease was defined as estimated glomerular filtration rate < 60 ml/min per 1.73 m^2. ‡

defined as the presence of sibilant wheezing, prolonged expiratory phase, and/or diminished breath sounds on lung auscultation. † within 24 hours before or after a diagnosis of viral infection (see additional details in **e-Table 3**).

Table 2. Patient outcomes according to type of viral infection (RSV *versus* influenza)

	RSV (n = 309)	Influenza (n = 309)	p-value
In-hospital mortality	74 (23.9)	79 (25.6)	0.63
Hospital length of stay (for overall cohort), d, median (IQR)	16 (10-28)	15 (8-28)	0.35
Hospital length of stay (for survivors), d, median (IQR), n = 465	17 (10-29)	16 (9-29)	0.87
In-ICU mortality	60 (19.4)	63 (20.4)	0.75
ICU length of stay (for survivors), d, median (IQR), n = 495	6 (3-11)	6 (3-11)	0.99
Length of mechanical ventilation (for survivors), d, median (IQR), n = 296	5 (2-11)	5 (3-12)	0.59
ARDS during ICU stay	63 (20.4)	88 (28.5)	**0.01**
Maximal form of respiratory support during ICU stay			**0.001**
Low flow oxygen therapy	66 (21.4)	82 (26.6)	
High flow nasal cannula	20 (6.5)	30 (9.7)	
Non-invasive 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)	

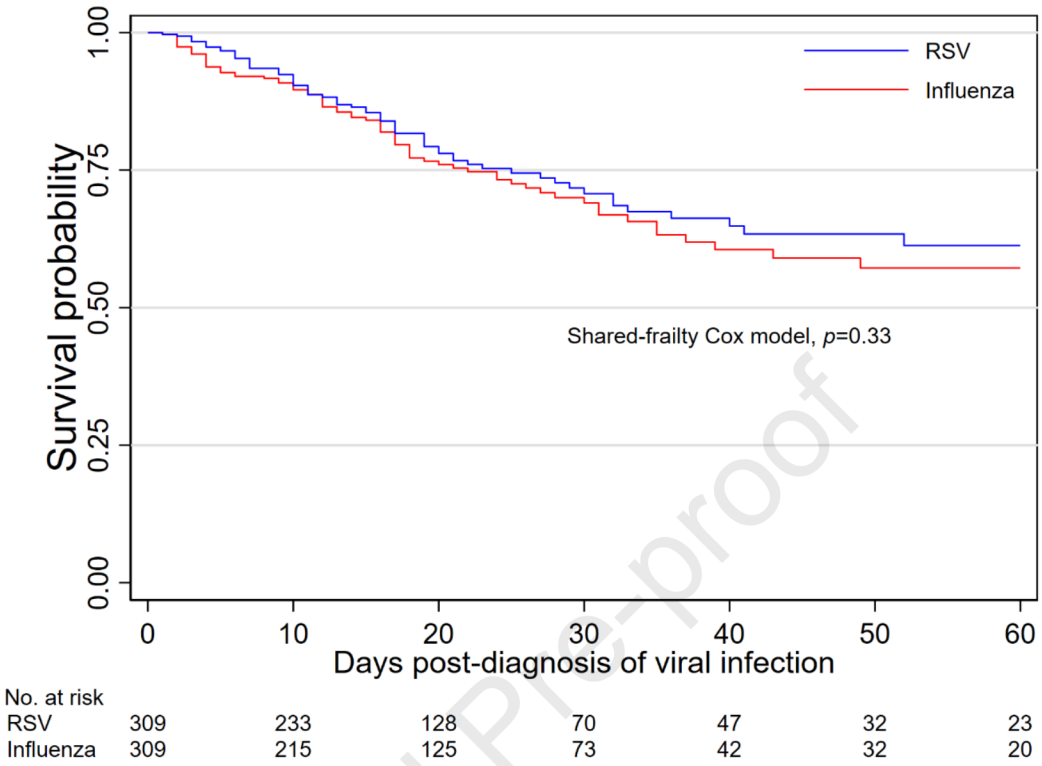
Matching was taken into account in the analysis (see Methods section). Data are n (%) unless otherwise indicated. ARDS: acute respiratory distress syndrome. d: days. ECMO: extracorporeal membrane oxygenation. ICU: intensive care unit. RSV: respiratory syncytial virus.

Table 3. Risk factors for in-hospital mortality after multivariable analysis by conditional logistic regression

Characteristic	adjusted OR [95% CI]	p-value
RSV infection (*versus* influenza infection)	0.80 [0.49 - 1.30]	0.37
Male	0.49 [0.23 - 1.04]	0.06
Age (years)	**1.05 [1.02 - 1.07]**	**< 0.001**
Underlying chronic respiratory condition	0.78 [0.39 - 1.58]	0.49
Underlying immunodeficiency	2.10 [0.99 - 4.44]	0.06
Underlying chronic kidney disease *	0.72 [0.26 - 2.01]	0.53
Underlying chronic heart failure	1.49 [0.57 - 3.90]	0.41
Diabetes	0.53 [0.20 - 1.38]	0.19
Obesity (body mass index > 30 kg/m^2)	1.26 [0.46 - 3.43]	0.65
Concurrent bloodstream infection	1.86 [0.65 - 5.37]	0.25

CI: confidence interval. OR: odds ratio. * chronic kidney disease was defined as estimated glomerular filtration rate < 60 ml/min per 1.73 m^2. All 618 patients (309 pairs) were included in this multivariable analysis (no missing data).

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



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