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Clinical features of respiratory syncytial virus and influenza infections in hospitalized adults across three Italian regions

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Abstract

Acute respiratory infections (ARIs) are important causes of morbidity and mortality globally. Respiratory syncytial virus (RSV) is a highly transmissible viral pathogen that is associated with ARIs, with both RSV and influenza virus infections being leading causes of hospitalization in older (especially frail) individuals. However, prospectively collected data on the incidence of RSV infection are scarce. This prospective study sought to estimate the prevalence of and characterize RSV and influenza virus infection in hospitalized patients.

Adult patients (18 years of age) who were admitted to the respiratory ward of three major hospitals in northern Italy were included in the study and, therefore, had a nasal swab and underwent routine clinical, laboratory, and imaging testing. The primary objective was to estimate the prevalence of influenza virus and RSV infection in these patients.

A total of 246 patients were recruited, 36 of whom had a viral or bacterial respiratory infection. Of these, 9 (3.7% of the total included patients or 25.0% of those with any infection) tested positive for the influenza virus, 5 (55.6%) of whom developed acute respiratory failure, with one dying by 3 months post-discharge. A further 3 patients (1.2% of the total included patients or 8.3% of those with any infection) tested positive for RSV. The three patients with RSV had a greater level of dyspnea and greater severity than those with any infection, and all had pneumonia and developed acute respiratory failure, with one dying during hospitalization.

Influenza and RSV infections were identified in patients hospitalized in respiratory wards in Northern Italy. The severe nature of the disease in these patients, including a high rate of pneumonia, emphasizes the importance of preventative measures to protect this vulnerable population and, in particular, vaccination.

Key words: respiratory syncytial virus, influenza virus, respiratory tract infections, hospitalization, comorbidity.

Introduction

Acute respiratory infections (ARIs) are important causes of morbidity and mortality globally. For example, in 2021 ARIs were the fifth leading cause of death globally, and the second cause of death due to a communicable disease (behind coronavirus disease 2019 [COVID-19]) [1]. Respiratory syncytial virus (RSV) is a viral pathogen that is associated with ARIs, and that is highly transmissible, generating clusters of infections, especially over the winter and early spring months [2]. Clinically, older adults, especially those with chronic respiratory or cardiovascular diseases, are at higher risk of severe RSV infection [3,4], and although RSV typically infects the upper respiratory tract, if the lower airways are involved infection can be associated with pneumonia or exacerbations of asthma or chronic obstructive pulmonary disease (COPD) [5]. Importantly, both RSV and influenza virus infections are leading causes of hospitalisation in older (especially frail) individuals [4,6], emphasising the importance of RSV and influenza vaccination in this population [7-9].

Despite the availability of sensitive diagnostic techniques for the identification of RSV in biological samples it is often underdiagnosed, and as a consequence the impact of RSV infection on hospitalisation and mortality may be underestimated. In particular, limited data are available on RSV infection in patients in Italy, although it is known that a high proportion of patients discharged after hospitalisation with influenza die after discharge (5.5% in one study, 50% of whom died in the 30 days after discharge [10]). In addition, limited retrospective data have been published for patients hospitalised with RSV [11,12], and prospectively collected data are scarce, and thus the outcome, clinical presentation, risk factors and markers (including prognostic) of RSV infection are largely unknown. The study described in this manuscript sought to estimate the prevalence of, and to characterise, RSV and influenza virus infection in hospitalised patients by using prospective data.

Materials and Methods

This prospective, observational study was conducted in three major hospitals in Northern Italy – the University Hospital of Ferrara, the Carlo Poma Hospital in Mantova and the Hospital Ca' Foncello in Treviso. These are hospital hubs for their three respective regions, and it is therefore likely that all patients with severe ARIs in these regions would be treated there. Although it had been intended that the study would run between October 2023 and April 2024, delays in ethics committee approval and subsequent study set-up meant that the study initiated in November 2023 in Ferrara, February 2024 in Mantua, and April 2024 in Treviso.

After obtaining informed consent, all adult patients who were admitted to the respiratory ward during the study period had a nasal swab, and underwent routine clinical, laboratory and imaging testing, including microbiological evaluation of relevant pathogens (bacteria, viruses and fungi) according to standard procedures at each ward. Molecular RSV and influenza tests were performed on the swabs (Treviso: Allplex™ Respiratory Panel Assays, Seegene Inc, Seoul, South Korea; Ferrara and Montova: Xpert® Xpress Flu/RSV, Cepheid, Sunnyvale, CA, USA). In addition, demographics, clinical presentation at the time of admission (including blood laboratory data, symptoms assessed using a visual analogue scale [VAS] and the modified Medical Research Council dyspnoea scale [mMRC], and health status using a VAS), and comorbidities (using the Charlson Comorbidity Index [13]) were recorded. Both of the VASs in the study used a 0–100 scale, with 0 indicating low patient-perception of symptoms or low health status burden. Severity at admission was assessed by the National Institute of Allergy and Infectious Disease Ordinal Scale (NIAID-OS), which ranges from 0 (not hospitalised and with no limitation of activities) to 8 (death).

For analysis purposes, patients were grouped according to the presence of ARI, and of bacterial or viral infections. The presence of ARI was defined as at least two respiratory symptoms or signs for at least 24 hours or at least one respiratory symptom or sign plus one systemic symptom or sign for at least 24 hours (*Supplementary Material - Methods* for the list of symptoms and signs). In addition, patients were grouped according to the presence of influenza virus or RSV. The non-infected population was defined as hospitalised patients with no microbiological isolation, regardless of whether they were symptomatic or not. The any-infection group included all laboratory-confirmed patients to any pathogen.

To ensure data were representative, the study included all patients 18 years of age admitted to the respiratory ward of the three hospitals, and who provided informed consent, with no other inclusion or exclusion criteria applied. The study was approved by the independent ethics committees at each institution, and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice.

Outcomes

The primary objective was to estimate the prevalence of infection with influenza virus and RSV among adults in a respiratory care unit. As secondary objectives, the baseline characteristics were compared between groups according to the presence of ARIs and of bacterial or viral infections, and the baseline characteristics were described in the two groups who tested positive for influenza virus and RSV.

Sample size and statistical methods

The study was not formally powered. Based on available literature, RSV prevalence among patients hospitalised with an ARI was estimated at 4.4%. It was anticipated that between 2200 and 2400 patients would be admitted in total to the three hospitals over the period October 2023 to April 2025, all of whom would agree to take part in the study, and that this would therefore be the total study population. Therefore, the expected number of patients testing positive for RSV would have been 96–106. However, due to delays in ethics committee approval, the study period was severely shortened, which reduced the sample size. For secondary comparisons between groups, continuous data were evaluated using t-test for normally distributed data and Wilcoxon test for non-normally distributed data, with categorical data evaluated using Chi-square test. Statistical tests were performed at a significance level of 0.05. All analyses were performed using STATANow/BE 18.5. All other data (including the primary objective) were analysed descriptively only.

Results

A total of 246 patients recruited, the baseline characteristics of whom, stratified by presence of ARI and infection are in Table 1. There were few statistically significant differences in baseline characteristics between these groups of patients. Those with ARI were on average younger than non-ARI individuals (p=0.003) and had a lower (i.e., less severe) Charlson Comorbidity Index score (p<0.001) and lower eosinophil (p=0.001) and lymphocyte (p=0.003) counts, but were more likely to have radiologically confirmed pneumonia (p=0.000) and had a higher (i.e., worse) NIAID-OS score (p=0.004; *Supplementary Table 1*). Similarly, compared with patients who did not test positive for any infection, those who tested positive had on average a lower Charlson Comorbidity Index score (p=0.046) and lower eosinophil (p<0.001) and lymphocyte (p<0.001) counts, but were more likely to have radiologically-confirmed pneumonia (p=0.000) and had a higher NIAID-OS score (p=0.010) . Although the numbers of patients who tested positive for bacterial infections or viral infections were small, therefore limiting the conclusions that can be drawn from these data, compared with patients who did not test positive for any infection, those in these two groups were significantly more likely to have pneumonia (p=0.000 and 0.003 for bacterial and viral infections, respectively) and a higher NIAID-OS score (p=0.009 and 0.023), with the presence of a viral infection associated with significantly lower eosinophil (p<0.001) and lymphocyte (p<0.001) counts. There were no differences between groups for any of the other baseline characteristics presented in Table 1. The mean duration of hospitalisation was 14.5 (SD 11.8) days in the overall population,

compared with 15.4 (13.9), 12.9 (7.7), 13.8 (5.8) and 15.0 (8.8) days in the ARI, any infection, and viral and bacterial infection groups, respectively, with no statistically significant differences between groups.

The presence of ARI signs and symptoms were also compared between the groups. As would be expected, the prevalence was significantly higher in the ARI group than the non-ARI group ($p<0.05$; *Supplementary Table 2*). In addition, compared with patients who did not have a detectable infection, systemic signs or symptoms were more common in patients with any infection ($p=0.021$), and in those with a viral ($p=0.010$) or bacterial ($p=0.023$) infection, with the presence of a viral infection also associated with a greater likelihood of upper respiratory symptoms ($p=0.002$).

Nine of the 246 patients (3.7%) tested positive for influenza virus (equivalent to 25.0% of the 36 patients with any infection; Table 2). Given these small numbers, the baseline characteristics of these patients were not formally compared between groups. However, patients with influenza appeared to be younger, were more likely to be female and current smokers, and had a numerically lower Charlson Comorbidity Index than the rest of the group with an infection. These patients also had lower eosinophil and lymphocyte counts, with elevated markers of systemic inflammation (i.e., C-reactive protein [C-RP] and procalcitonin). Five of the patients in this group (55.6%) developed acute respiratory failure, and one had died by 3 months post-discharge. Their mean duration of hospitalisation was 14.0 (6.3) days.

A further three patients (1.2% of the overall 246 analysed, or 8.3% of the 36 with any infection) tested positive for RSV. Most of the characteristics of this group were consistent with the rest of the group with an infection – but they had a greater level of dyspnoea (both when assessed using the VAS and the mMRC) and a higher (i.e., worse) NIAID-OS score. In addition, these patients had a higher neutrophil count, and lower eosinophil and lymphocyte counts, with lower levels of markers of systemic inflammation than the rest of the group with an infection – although the mean values of these systemic markers were still elevated compared with normal values. Of note, all three patients had pneumonia and developed acute respiratory failure, and one died during hospitalisation. Their mean duration of hospitalisation was 13.0 (5.2) days.

Discussion

The primary objective of this study was to estimate the prevalence of influenza virus and RSV infection among hospitalised adults. Of the 246 patients included in the analyses, 3.7% and 1.2% tested positive for influenza and RSV, respectively – or 25.0% and 8.3%, respectively, of those with any infection. The baseline characteristics of these two groups of patients suggest

they are especially complex cases – particularly those who were RSV positive. Both groups of patients had markedly lower eosinophil and lymphocyte counts than the rest of the patients with an infection. Given viral respiratory infections are typically associated with increased sputum eosinophil levels [14,15], the low eosinophil counts in this study are unexpected (indeed seven of the 12 patients with a viral infection had an eosinophil count of 0 cells/μL), but could be due recruitment of eosinophils into the respiratory system, or may suggest that these patients received oral corticosteroids either prior to or in the emergency room. In addition, acute respiratory failure was common in these patients – with all of those who were RSV positive having both acute respiratory failure and pneumonia. Furthermore, patients who tested positive for RSV had both increased dyspnoea and a high NIAID-OS score, again emphasising the high disease severity in this group of patients. This high disease burden is consistent with an analysis of hospitalised adults aged 60 years, in which RSV infection was associated with greater odds of pneumonia, intensive care unit admission, COPD exacerbations, and mortality within 1 year post-admission [12].

In the formal comparisons of the baseline characteristics, although there were few statistically significant differences, patients with ARI symptoms or with a confirmed viral or bacterial infection were at increased risk of radiologically-confirmed pneumonia than those with no ARI symptoms or those with no confirmed infection, suggesting that most patients had been correctly categorised based on clinical examination – although a quarter of the patients who were considered 'non-infected' had radiologically-confirmed pneumonia. Of note, the four groups of patients with ARI or a confirmed infection had lower mean eosinophil and lymphocyte counts than the comparator groups (non-ARI and non-infected), and there were no statistically significant differences between groups in either C-RP or procalcitonin concentrations, despite a suggestion from a previous study that raised C-RP levels are indicative of bacterial infection and could be used to guide antibiotic prescribing [16] – although a secondary or concomitant bacterial infection prompted by a primary respiratory virus infection cannot be excluded [14,17]. Taken together, these could suggest that by the time these patients were hospitalised they had started to recover from the initial infection. This is consistent with the finding that the most common ARI involvement was lower respiratory signs or symptoms (in 92.0% of the ARI group and 91.7–100% of patients with an infection), followed by systemic signs or symptoms (68.1% and 61.1–76.9%, respectively), and with few patients having upper respiratory symptoms (8.8% and 0–23.1%, respectively). However, 83.3% of patients in the 'non-infected' group had lower respiratory signs or symptoms (as did 78.2% in the non-ARI group).

The detection of viral and bacterial infections in this study was based on nasal swab results – the current 'gold standard'. A total of 113 patients met the fairly strict criteria for ARI signs and symptoms, but only 36 tested positive for any infection. This suggests that nasal swabs may not be the best way of excluding the presence of these infections. One option is that patients may have upper respiratory tract infections in the early phase, with that infection then migrating – and most patients are hospitalised only a week or so after the onset of symptoms (by which point it might be too late to identify virus presence in the upper airways). Alternatively, the currently available molecular tests may not be sufficiently sensitive (in a pooled analysis, rapid antigen tests were only 64% sensitive for the detection of RSV [18]). Of course, this also has an impact on the accuracy of the influenza and RSV prevalence data – patients who were influenza or RSV negative according to the nasal swab data may have actually had influenza or RSV infections. Indeed, in an analysis of data from outpatient clinics, of 27 RSV-related exacerbations, seven were detected only by nasal swab, 16 only by serology, and four by both methods [19].

A strength of the study is the 'real-life' nature, both of the data collected, and the patients and physicians involved. The results therefore reflect patients who are actually admitted to a typical specialist respiratory ward in Italy. This also makes the results more difficult to interpret, since rather than recruiting a highly selected population as is typical of a controlled clinical trial, the population is 'all comers', since patients without infections are also admitted to these wards (from lung cancer to exacerbations of lung fibrosis or respiratory failure) – and even those patients who do have an infection may also have substantial other underlying diseases (as indicated by the Charlson Comorbidity Index scores). This means that, for example, the dyspnoea and health status values reported do not only reflect worsening due to an onset of an infection, but are influenced by any underlying disease. Furthermore, the 'non-infected' comparator group is, by definition, a group of individuals who have been hospitalised as a consequence of some worsening of a respiratory disease, and are therefore not a typical 'healthy' control group. This conclusion is supported by the finding that patients with ARI signs or symptoms had a significantly lower Charlson Comorbidity Index score than the non-ARI group.

The main limitation of the study is associated with the delays in initiation – especially at two of the sites, with an associated substantial reduction in the number of patients actually recruited compared with the planned recruitment. This, in turn, led to a lower number of patients included in the study than originally expected, which reflects the challenges encountered during recruitment. Furthermore, COVID-19 had a significant impact on the incidence of a

range of seasonal respiratory virus infections, with a dramatically lower incidence of influenza and RSV during 2020–21 compared to pre-pandemic seasons [20], and although this study was conducted in the winter of 2023–24, it is unclear whether the results therefore reflect the 'real' epidemiology of these viruses. Ideally the study should be replicated in subsequent winter seasons, with the presence of RSV identified using both nasal swabs and serology, ideally as early as possible in the course of the infection (rather than on hospitalisation).

Conclusions

Influenza and RSV infections were identified in patients hospitalised in respiratory wards in Northern Italy. The complex and severe nature of the disease in these patients, including a high rate of pneumonia, emphasises the importance of preventative measures to protect this vulnerable population – and in particular vaccination against viral agents. This study thus provides additional support to the recommendations of international and local guidelines [21-23].

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Online supplementary material:
Methods. Definition of acute respiratory infection.
Supplementary Table 1. Statistical comparisons of baseline characteristics.
Supplementary Table 2. Statistical comparisons of acute respiratory infection symptoms.

Table 1. Baseline characteristics of the recruited patients grouped according to the presence of acute respiratory infection signs or symptoms, and infection.

	No ARI signs or symptoms (n=133)	ARI signs or symptoms (n=113)	Non-infected (n=210)	Patients with an infection		
				Any infection (n=36)	Viral infection (n=12)	Bacterial infection (n=14)
Age, years	69.1 (13.6) (n=132)	64.2 (13.9)	67.3 (13.7)	64.1 (14.9)	58.5 (14.8)	59.8 (16.9)
Sex, male	93 (69.9%)	70 (62.0%)	140 (66.6%)	23 (63.9%)	7 (58.3%)	12 (85.7%)
Smoking history						
Non-smokers	49 (36.8%)	50 (44.3%)	77 (36.8%)	22 (61.1%)	5 (41.7%)	9 (64.3%)
Ex-smokers	53 (39.8%)	35 (31.0%)	84 (40.1%)	9 (25.0%)	2 (16.7%)	2 (14.3%)
Current smokers	31 (23.3%)	26 (23.0%)	48 (22.9%)	4 (11.1%)	4 (33.3%)	3 (21.4%)
Missing	0	2 (1.8%)	0	1 (2.8%)	1 (8.3%)	0
Radiologically confirmed pneumonia	7 (5.3%)	74 (65.5%)	54 (26.2%)	27 (75.0%)	8 (66.7%)	11 (78.6%)
Charlson Comorbidity Index	5.0 (3.1) (n=130)	3.5 (2.4) (n=108)	4.4 (3.0) (n=206)	3.3 (2.4) (n=32)	2.6 (2.0) (n=11)	3.1 (2.8) (n=13)
VAS health status	59.0 (20.9) (n=120)	57.9 (21.1) (n=107)	59.4 (20.4) (n=192)	53.1 (23.2) (n=35)	45.8 (25.4)	58.6 (22.7)
VAS dyspnoea	24.7 (31.2) (n=128)	27.7 (31.9) (n=112)	26.6 (31.7) (n=204)	22.7 (30.1)	23.1 (28.3)	34.3 (35.6)
mMRC dyspnoea scale	2.1 (1.5) (n=131)	2.3 (1.4) (n=112)	2.2 (1.4) (n=207)	2.2 (1.5)	2.6 (1.2)	2.3 (1.5)
NIAID-OS	4.3 (1.1) (n=129)	4.6 (1.0) (n=112)	4.4 (1.0) (n=205)	4.9 (1.3)	4.9 (1.4)	5.2 (1.2)
Total white blood cell count, cells/μL	11,689.7 (24,235.2) (n=129)	10,702.2 (11,635.1)	11465.6 (20,862.5)	9871.9 (5600.0)	10,060.0 (4011.5)	9936.4 (3296.9)
Neutrophil count, cells/μL	7730.9 (8794.1) (n=128)	8287.6 (8181.1) (n=110)	7998.1 (8978.2) (n=202)	7932.5 (5163.1)	8575.0 (3828.2)	7793.6 (3144.5)
Eosinophil count, cells/μL	161.6 (217.5) (n=128)	109.6 (197.2) (n=110)	152.7 (219.6) (n=202)	52.5 (107.6)	7.5 (12.2)	60.7 (81.1)
Lymphocyte count, cells/μL	3543.3 (20,448.2) (n=128)	1569.8 (2673.4) (n=110)	2904.8 (16,391.0) (n=202)	1095.8 (537.0)	790.8 (433.4)	1234.3 (593.1)
C-reactive protein, mg/L	18.7 (164.3) (n=113)	69.5 (596.2) (n=102)	5.5 (8.2) (n=184)	14.1 (16.6) (n=31)	17.9 (16.8) (n=11)	17.6 (18.7) (Nn=12)
Procalcitonin, ng/mL	0.7 (2.9) (n=85)	3.2 (13.2) (n=78)	0.8 (3.3) (n=139)	7.6 (22.8) (n=24)	15.4 (34.2) (n=10)	4.0 (7.0) (n=8)

Categorical variables are presented as number (percent), and continuous variables as mean (standard deviation); N values in brackets are the number of patients analysed when data for a variable are not available for the full population. ARI, acute respiratory infection (see supplement for definition); VAS, visual analogue scale; mMRC, modified Medical Research Council; NIAID-OS, National Institute of Allergy and Infectious Disease Ordinal Scale (ranging from 0 [not hospitalised and with no limitation of activities] to 8 [death]).

Table 2. Baseline characteristics of the recruited patients according to the presence of influenza and respiratory syncytial virus infection.

	Positive for influenza virus (n=9)	Positive for RSV (n=3)
Age, years	56.2 (11.7)	65.3 (23.9)
Sex, male	4 (44.4%)	3 (100%)
Smoking history		
Non-smokers	3 (33.3%)	2 (66.7%)
Ex-smokers	2 (22.2%)	0
Current smokers	4 (44.4%)	0
Missing	0	1 (33.3%)
Radiologically confirmed pneumonia	5 (55.6%)	3 (100%)
Acute respiratory failure	5 (55.6%)	3 (100%)
Died by 3 months post-discharge	1 (11.1%)	1 (33.3%)
Duration of hospitalisation (days)	14.0 (6.3)	13.0 (5.2)
Charlson Comorbidity Index	2.3 (1.8) (n=8)	3.7 (2.3)
VAS health status	48.9 (28.0)	36.7 (15.3)
VAS dyspnoea	15.6 (22.6)	45.7 (36.7)
mMRC dyspnoea scale	2.3 (1.3)	3.3 (0.6)
NIAID-OS	4.7 (1.5)	5.7 (0.6)
Total white blood cell count, cells/μL	9546.7 (4214.0)	11,600.0 (3568.2)
Neutrophil count, cells/μL	8013.3 (4024.0)	10,260.0 (3186.3)
Eosinophil count, cells/μL	8.9 (13.6)	3.3 (5.8)
Lymphocyte count, cells/μL	808.9 (388.6)	736.7 (650.4)
C-reactive protein, mg/L	19.8 (19.6) (n=8)	12.9 (2.6)
Procalcitonin, ng/mL	18.6 (38.0) (n=8)	2.7 (3.6) (n=2)

Categorical variables are presented as number (percent), and continuous variables as mean (standard deviation); N values in brackets are the number of patients analysed when data for a variable are not available for the full population. RSV, respiratory syncytial virus; VAS, visual analogue scale; mMRC, modified Medical Research Council; NIAID-OS, National Institute of Allergy and Infectious Disease Ordinal Scale (ranging from 0 [not hospitalised and with no limitation of activities] to 8 [death]).