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ORIGINAL ARTICLE

Burden of primary influenza and respiratory syncytial virus pneumonia in hospitalised adults: insights from a 2-year multi-centre cohort study (2017–2018)

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influenza, respiratory syncytial virus, pneumonia, NIV failure, inhospital death.

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Abstract

Background: Viral community-acquired pneumonia (CAP) is a potentially serious illness, particularly in adult patients with underlying chronic conditions. In addition to the most recent SARS-CoV-2, influenza, and respiratory syncytial virus (RSV) are considered the most relevant causes of viral CAP.

Aims: To describe the clinical features of hospitalised adults admitted for influenza-A/B and RSV pneumonia and analyse, according to aetiology, factors associated with non-invasive ventilation (NIV) failure and in-hospital death (IHD).

Methods: This was a retrospective and multi-centre study of all adults who were admitted for laboratory-confirmed influenza-A/B or RSV pneumonia, during two consecutive winter seasons (October–April 2017–2018 and 2018–2019) in three tertiary hospitals in Portugal, Italy and Cyprus.

Results: A total of 356 adults were included in the study. Influenza-A, influenza-B and RSV were deemed to cause pneumonia in 197 (55.3%), 85 (23.9%) and 74 (20.8%) patients, respectively. Patients with both obstructive sleep apnoea or obesity hypoventilation syndrome and influenza-A virus pneumonia showed a higher risk for NIV failure (odds ratio (OR) 4.66; 95% confidence interval (CI) 1.42–15.30). Patients submitted to NIV showed a higher risk for IHD, regardless of comorbidities (influenza-A OR 3.00; 95% CI 1.35–6.65, influenza-B OR 4.52; 95% CI 1.13–18.01, RSV OR 5.61; 95% CI 1.26–24.93).

Conclusion: The increased knowledge of influenza-A/B and RSV pneumonia burden may contribute to a better management of patients with viral CAP.

Introduction

Viral community-acquired pneumonia (CAP) is a potentially serious illness accounting for relevant rates of admission, mortality and high hospital costs, particularly in adult patients with underlying chronic conditions. In addition to the most recent SARS-CoV-2, influenza and respiratory syncytial virus (RSV) are considered the most relevant causes of viral CAP.[1] Several scores for patients presenting with CAP, establishing site of care, predicting risk for shock, need for intensive care or mechanical ventilation and mortality have been described.[2–6] The choice of timing and type of ventilation in patients suffering from CAP with respiratory failure is also an open debate, as benefit from non-invasive ventilation (NIV) seems to be more evident in selected patients.[7,8] However, there is limited evidence of the uselfulness of both these

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predictive rules and NIV in patients suffering from viral CAP[9–11] and new data might aid clinicians to grasp priorities and timely manage care level. The aims of the present study were to describe the clinical features of hospitalised adults admitted for influenza A/B and RSV pneumonia and to analyse, according to aetiology, factors associated with NIV failure and inhospital death (IHD).

Methods

This work was a secondary analysis from a retrospective and multi-centre study of all patients (age ≥18 years) who were admitted for laboratory-confirmed influenza A/B or RSV infection during two consecutive winter seasons (October–April 2017–2018 and 2018–2019) in three tertiary hospitals in Portugal, Italy and Cyprus.[12] In this study, all patients admitted for laboratory-confirmed community-acquired influenza A/B or RSV pneumonia were included. The laboratory confirmation was based on a positive Xpert Flu/RSV PCR (Cepheid Diagnostics, Sunnyvale, CA, USA) on nasopharyngeal swabs obtained from patients with signs or symptoms of viral infection (abnormal body temperature, hypoxia, dyspnoea, cough, sputum, chest pain, anorexia, lethargy, headache, myalgia, diarrhoea) and presenting with a pulmonary infiltrate on chest X-ray performed on admission. The infection was characterised as community-acquired if symptoms pertaining to viral infection began up to 72 h from admission. Patients with viral co-infections (i.e. influenza A + influenza B viruses, influenza A or influenza B virus + RSV) were excluded. Variables assessed are listed in Table 1. Use of ventilation was defined as NIV and/or invasive mechanical ventilation (IMV) use. NIV failure was defined as the need to switch to endotracheal intubation and IMV. Patients who were submitted to NIV and died were not considered having NIV failure, as NIV was considered the ceiling of care for these patients.

This study was conducted in accordance with the Declaration of Helsinki. Formal ethical approval was obtained by the institutional review board of the coordinating centre (Central Lisbon Hospital Centre, no. 762_2019). Informed consent was not deemed required for the purposes of this study.

Statistical analysis

Descriptive data are shown as absolute (*n*) and relative (%) frequencies for categorical data and as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate, for continuous variables. Chi-squared or Fisher's exact test for categorical variables and analysis of variance (ANOVA) with Bonferroni correction or Kruskal-Wallis tests, as appropriate, for continuous variables were used to evaluate differences in baseline characteristics according to the aetiology of pneumonia. On univariate analysis, odds ratios (OR) and their 95% confidence intervals (CI) were calculated to identify factors associated with NIV failure and IHD according to aetiology of pneumonia and estimate the strength of those associations. Multivariable analysis models were

Table 1 Clinical features of patients admitted for influenza and RSV pneumonia

	All (356)	Influenza A, 55.3 (197)	Influenza B, 23.9 (85)	RSV, 20.8 (74)	*P*-value
Mean age ± SD (years)	69.1 ± 16.1	68.3 ± 15.9	68.9 ± 15.8	71.2 ± 16.9	0.411
Male	53.7 (191)	57.9 (114)	52.9 (45)	43.2 (32)	0.098
Smoker	18 (64)	20.3 (40)	18.8 (16)	10.8 (8)	0.188
Diabetes	25.6 (91)	23.9 (47)	29.4 (25)	25.7 (19)	0.618
COPD or asthma	30.1 (107)	27.9 (55)	28.2 (24)	37.8 (28)	0.260
OSA or OHS	6.5 (23)	7.6 (15)	3.5 (3)	6.8 (5)	0.438
CHF	25.3 (90)	23.9 (47)	27.1 (23)	27 (20)	0.789
CKD	16.6 (59)	15.7 (31)	10.6 (9)	25.7 (19)	**0.034**
SOT recipient	3.7 (13)	3.1 (6)	2.4 (2)	6.8 (5)	0.251
Haematological neoplasm	14.3 (51)	14.7 (29)	11.8 (10)	16.2 (12)	0.707
Solid neoplasm	5.6 (20)	4.1 (8)	4.7 (4)	10.8 (8)	0.109
Ventilation	32 (114)	35.5 (70)	25.9 (22)	29.7 (22)	0.251
Non-invasive ventilation	23.3 (83)	25.9 (51)	17.7 (15)	23 (17)	0.323
Invasive mechanical ventilation	18.8 (67)	23.4 (46)	15.3 (13)	10.8 (8)	**0.040**
Non-invasive ventilation failure	43.4 (36)	52.9 (27)	40 (6)	17.7 (3)	**0.037**
Median length of stay (IQR) (days)	10 (6.5–17.5)	11 (7–18)	8 (6–16)	11 (7–16)	0.170
Inhospital death	16 (57)	17.3 (34)	15.3 (13)	13.5 (10)	0.739

Note: Bold values denote statistical significance.

All data are shown as relative, % and absolute (*n*) frequencies unless otherwise stated. CHF, chronic heart failure (Class II New York Heart Association or worse); CKD, chronic kidney disease (Kidney Disease, Improving Global Outcomes 2012, stage 3A or worse); COPD, chronic obstructive pulmonary disease; IQR, interquartile range; OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnoea; RSV, respiratory syncytial virus; SD, standard deviation; SOT, solid organ transplant.

Table 2 Uni- and multivariable analyses for factors associated with NIV failure and inhospital death in patients admitted for influenza A, influenza B and RSV pneumonia

	Outcomes			
	Univariate analysis		Multivariable analysis	
Characteristics	NIV failure OR (95% CI)	Inhospital death OR (95% CI)	NIV failure OR (95% CI)	Inhospital death OR (95% CI)
Influenza A virus pneumonia				
Age	**0.95 (0.92–0.98)**	1.00 (0.98–1.03)	**0.96 (0.93–0.99)**	1.01 (0.98–1.04)
Male	1.54 (0.65–3.63)	1.41 (0.65–3.05)	1.41 (0.56–3.54)	1.49 (0.67–3.32)
Diabetes	1.73 (0.72–4.18)	1.99 (0.89–4.42)		
CHF	**0.22 (0.05–0.98)**	0.49 (0.18–1.37)	0.35 (0.07–1.73)	
CKD	0.63 (0.17–2.25)	1.50 (0.58–3.83)		
COPD or asthma	0.40 (0.13–1.23)	1.09 (0.48–2.46)		
OSA or OHS	**5.11 (1.65–15.80)**	1.84 (0.54–6.17)	**4.66 (1.42–15.30)**	
NIV	—	**2.78 (1.28–6.02)**		**3.00 (1.35–6.65)**
NAI treatment	1.66 (0.36–7.57)	0.39 (0.14–1.05)		
Influenza B virus pneumonia				
Age	1.00 (0.95–1.06)	1.01 (0.97–1.06)	1.00 (0.94–1.06)	1.02 (0.98–1.08)
Male	1.85 (0.32–10.70)	1.51 (0.45–5.07)	1.38 (0.22–8.63)	1.40 (0.39–4.97)
Diabetes	2.59 (0.48–13.82)	1.07 (0.29–3.89)		
CHF	1.38 (0.23–8.10)	2.77 (0.81–9.38)		
CKD	5.14 (0.79–33.24)	1.68 (0.30–9.21)		
COPD or asthma	**5.90 (1.00–34.69)**	1.74 (0.50–5.99)	5.55 (0.90–34.09)	
OSA or OHS	†	†		
NIV	—	**3.87 (1.05–14.24)**		**4.52 (1.13–18.01)**
NAI treatment		0.78 (0.14–4.13)		
Respiratory syncytial virus pneumonia				
Age	0.96 (0.90–1.03)	0.98 (0.94–1.02)		0.97 (0.93–1.02)
Male	0.64 (0.05–7.44)	2.19 (0.56–8.54)		2.88 (0.65–12.68)
Diabetes	1.47 (0.12–17.22)	0.28 (0.03–2.40)		
CHF	1.36 (0.11–15.97)	2.00 (0.50–8.00)		
CKD	1.47 (0.12–17.22)	0.69 (0.13–3.58)		
COPD or asthma	†	1.78 (0.46–6.81)		
OSA or OHS	†	1.66 (0.16–16.63)		
NIV	—	**4.33 (1.07–17.39)**		**5.61 (1.26–24.93)**

†Omitted for no cases.

Note: Bold values denote statistical significance.

CHF, chronic heart failure (Class II New York Heart Association or worse); CI, confidence interval; CKD, chronic kidney disease (kidney disease: improving global outcomes 2012 stage 3A or worse); COPD, chronic obstructive pulmonary disease; NAI, neuraminidase inhibitor; NIV, non-invasive ventilation; OHS, obesity hypoventilation syndrome; OR, odds ratio; OSA, obstructive sleep apnoea.

then fitted to investigate the independent effects of clinical variables that turned out to be significantly associated with the outcomes (NIV failure and IHD) at univariate analysis, adjusting for possible confounders like age and gender. For all tests, a P-value ≤ 0.05 was considered significant. All analyses were performed using Stata 16.

Results

A total of 356 adults were admitted for influenza A/B and RSV pneumonia during the study period in the three centres. Influenza A, influenza B and RSV were deemed to cause pneumonia in 197 (55.3%), 85 (23.9%) and 74 (20.8%) patients respectively.

Clinical features of patients included in the study are reported in Table 1. Overall, mean age was 69.1 ± 16.1 years, 53.7% were men and 18% were current active smokers. The main co-morbidities observed were chronic obstructive pulmonary disease (COPD) or asthma (30.1%), diabetes (25.6%) and congestive heart failure (25.3%). Ventilatory support was implemented in 32% of patients, with NIV used in 23.3%, and 43.4% of these having failed. Median length of stay was 10 days (IQR 6.5–17.5), whereas IHD was 16%. Antiviral therapy with neuraminidase inhibitor was given in 88.8%

($n = 175$) and 87.1% ($n = 74$) of patients with influenza A and influenza B pneumonia respectively (data not shown).

Comparing the three groups according to viral aetiology of pneumonia, patients with RSV pneumonia suffered more from chronic kidney disease (CKD; Kidney Disease: Improving Global Outcomes 2012, stage 3A or worse, $P = 0.034$), whereas patients with influenza A pneumonia suffered more frequently from NIV failure ($P = 0.037$) and were more frequently submitted to IMV ($P = 0.040$) than patients of the other two groups.

Results of univariate and multivariable analyses that evaluated the association of clinical variables with NIV failure and IHD according to aetiology of pneumonia are shown in Table 2.

Among patients with influenza A virus pneumonia, older patients (OR 0.96; 95% CI 0.93–0.99) showed a lower risk and those with obstructive sleep apnoea or obesity hypoventilation syndrome (OSA or OHS, OR 4.66; 95% CI 1.42–15.30) showed a higher risk for NIV failure, whereas no factors were identified in both those with influenza B virus and RSV pneumonia after adjusting for possible confounders. Patients submitted to NIV showed a higher risk for IHD, regardless of comorbidities (influenza A: OR 3.00, 95% CI 1.35–6.65; influenza B: OR 4.52, 95% CI 1.13–18.01: RSV: OR 5.61, 95% CI 1.26–24.93).

Discussion

The present study provided a comprehensive analysis of influenza A/B and RSV pneumonia burden in a large cohort of southern European hospitalised adults. While patients with RSV pneumonia were found to suffer from CKD more than those with influenza pneumonia, all the other comorbidities were largely similar. We also documented that patients who suffered from influenza A pneumonia tended to have higher rates of both NIV failure and IMV. Among these, patients with OSA or OHS showed a higher risk for NIV failure but comparable risk of IHD. Patients submitted to NIV showed a higher likelihood of IHD regardless of both viral aetiology and comorbidities.

Viral CAP is a relevant cause of hospitalisation, being present in more than 30% of patients admitted for influenza and RSV infections.[1,13–16] The burden of disease severity for both the infections are similar, especially in older adults.[13,16] Advanced age, immunodepression and cardiopulmonary disease were reported to be the main predictors of pneumonia.[1] Our findings also highlighted that patients hospitalised for RSV pneumonia had a higher rate of CKD corroborating evidence of higher incidence of comorbidities in patients infected with RSV.[13,15]

The widespread NIV use over the decades did not permit full clarification of its generalizability in patients with viral pneumonia in terms of reduction of IMV rate, hospital stay, mortality, and increased mortality following NIV failure.[16–19] In addition, evidence available so far mainly regarding NIV management of patients with influenza A (H1N1) pneumonia, and a little data supports NIV use in patients with influenza B or RSV pneumonia.

Overall, the NIV implementetion rate in our cohort (23.3%) was comparable in the three patients groups, quite lower than recent reports mostly performed in intensive care unit (ICU) settings[17–19] and more similar to a large cohort of patients admitted for influenza or RSV infections.[16] Nevertheless, our data on NIV failure (43.4%) are similar to those reported in ICU patients,[17–19] highlighting in this context both the relevant weight in terms of both severity of influenza A pneumonia and NIV use as a first and immediate attempt of support. Factors associated with NIV failure, mainly reported in ICU patients with influenza A (H1N1) pneumonia, are related with the presence of two or more lung quadrant opacities, other-than-respiratory organ disfunction and the use of corticosteroids.[17–19] Our study analysed the relevance of comorbidities and identified patients with OSA or OHS and influenza A pneumonia to be at higher risk for NIV failure. The fact that some of these patients were already on chronic ambulatory bi-level positive airway pressure ventilation therapy probably highlighted the reduced non-invasive therapeutic field in presence of these comorbidities. Older patients were found to have a lower risk of NIV failure but it was probably due to accepting NIV as a ceiling for therapeutic effort in these patients.

Conversely, the present study was underpowered for identifying factors associated with the outcomes for both influenza B and RSV pneumonia patients due to the reduced samples size, stressing the need for further studies to fill this gap of knowledge.

Our data on overall IHD (16%) were consistent with evidence ranging from 5.6% to 44.4% according to disease severity and care level,[1,10,13–20] and identified patients submitted to NIV at higher risk for a fatal outcome. This finding is probably partial because our study did not assess severity of organ dysfunction on pneumonia presentation but seemed to be more relevant than both viral aetiology and comorbidities. Therefore, it should encourage clinicians to implement a more defined predictive tool for choosing who and how to ventilate.[10,17–20]

The present study had limitations. Since respiratory viruses can be present in the upper airways without causing illness, our study using PCR with nasopharyngeal swabs may have overestimated the frequency of

influenza and RSV as a cause of CAP. In addition, the limited number of patients with influenza B and RSV pneumonia hindered the identification of risk factors for the considered outcomes. Several factors contributing to pneumonia severity and mortality including frailty scores, viral subtype, presence of mixed viral and bacterial pneumonia, respiratory failure, and occurrence of systemic complications were not assessed. In addition, post-discharge assessments were also not conducted.

Conclusion

Adults hospitalised for influenza and RSV pneumonia have a high need of care and risk of mortality. The choice of NIV as first respiratory support seems to weigh more than underlying chronic conditions in terms of IHD and should be cautioned and based more on accurate and reliable prediction tools. The increased knowledge of influenza A/B and RSV pneumonia burden may contribute to a better management of patients with viral CAP.

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