Received: 28 August 2020 | Revised: 10 January 2021 | Accepted: 8 March 2021

DOI: 10.1002/jmv.26938

SHORT COMMUNICATION

JOURNAL OF MEDICAL VIROLOGY WILEY

Severity of RSV infection in Southern European elderly patients during two consecutive winter seasons (2017–2018)

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Abstract

In Europe, the respiratory syncytial virus (RSV) surveillance system is very heterogeneous and there is growing evidence of the importance of RSV infections resulting in hospitalization of elderly patients. The aim of this study was to assess the severity of RSV infection in the elderly living in the aged Southern European countries. We conducted a retrospective study of elderly patients (≥65-year old) admitted for laboratory-confirmed RSV infection in three tertiary hospitals in Portugal, Italy, and Cyprus over two consecutive winter seasons (2017–2018). Uni-multivariable analyses were carried out to evaluate the effect of clinical variables on radiologically confirmed pneumonia, use of noninvasive ventilation (NIV), and in-hospital death (IHD). A total of 166 elderly patients were included. Pneumonia was evident in 29.5%. NIV was implemented in 16.3%, length of stay was 11.8 ± 12.2 days, and IHD occurred in 12.1%. Multivariable analyses revealed that the risk of pneumonia was higher in patients with chronic kidney disease (CKD) (odds ratio [OR]: 2.57; 95% confidence interval [CI]: 1.12–5.91); the use of NIV was higher in patients with obstructive sleep apnea or obesity hypoventilation syndrome (OSA or OHS) (OR: 5.38; 95% CI: 1.67–17.35) and CKD (OR: 2.52; 95% CI: 1.01–6.23); the risk of IHD was higher in males (OR: 3.30; 95% CI: 1.07–10.10) and in patients with solid neoplasm (OR: 9.06; 95% CI: 2.44–33.54) and OSA or OHS (OR: 8.39; 95% CI: 2.14–32.89). Knowledge of factors associated with RSV infection severity may aid clinicians to set priorities and reduce disease burden. Development of effective antiviral treatment and vaccine against RSV is highly desirable.

KEYWORDS

elderly, geriatrics, obstructive sleep apnea, obesity hypoventilation syndrome, pneumonia, respiratory syncytial virus

1 | INTRODUCTION

Viral respiratory tract infections are a major public health concern, as highlighted by severe acute respiratory syndrome coronavirus 2 pandemic recently, especially when these affect patients with age-related chronic diseases.[1] Influenza and respiratory syncytial virus (RSV) are major viral pathogens causing acute respiratory tract infections associated with relevant rates of admission, mortality, and high hospital costs, especially among older adults.[2–11] In Europe, the RSV surveillance system is very heterogeneous due to the lack of uniform case definition and it often detects RSV infections within the existing surveillance system for influenza.[12–14] There is growing evidence of the importance of RSV infections resulting in hospitalization of elderly patients and for which no vaccines and targeted therapeutic options are available. There is also limited published evidence on factors associated with disease severity that may aid in setting priorities for elderly patients hospitalized due to RSV infection in the aged Southern European countries. The aims of this study were to describe the clinical features of elderly patients admitted for RSV infection and to identify factors associated with pneumonia, use of noninvasive ventilation (NIV), and in-hospital death (IHD).

2 | METHODS

This was a secondary analysis of data collected in a retrospective cohort study that assessed virulence of seasonal viruses responsible for lower respiratory tract infections in hospitalized adults from October 1, 2017 to April 30, 2018 and from October 1, 2018 to April 30, 2019 in three tertiary hospitals with a total capacity of 4500 beds in Portugal, Italy, and Cyprus.[15]

In this study, we included all elderly patients (≥65-year old) who were admitted to the hospital for laboratory-confirmed community-acquired RSV infection. The laboratory confirmation was based on a positive Xpert Flu/RSV PCR (Cepheid Diagnostics) on nasopharyngeal swabs obtained from patients with signs or symptoms of viral infection. The infection was characterized as community-acquired if symptoms pertaining to viral infection began up to 72 h from admission. Pneumonia was defined as an acute lower respiratory tract infection associated with new radiographic shadowing for which there is no other explanation. Variables assessed are listed in Table 1.

The Xpert Flu/RSV PCR is an automated, random-access, multiplex real-time, reverse transcription polymerase chain reaction assay for the detection of influenza A, influenza B, and RSV, which is unable to discriminate among influenza A subtypes. All samples

TABLE 1 Comparison of clinical features of elderly patients admitted for respiratory syncytial virus infection according to the age group

	65–74 years, *n* = 41 (%)	75–84 years, *n* = 62 (%)	85 years and older, *n* = 63 (%)	All, *n* = 166 (%)
Mean age ± *SD* (years)	69.1 ± 2.9	79.6 ± 2.9	89.8 ± 3.9	80.9 ± 8.7
Male	24 (58.5)	25 (40.3)	14 (22.2)[a]	63 (38)
Smoker	6 (14.6)	8 (12.9)	2 (3.2)	16 (9.6)
Diabetes	14 (34.2)	27 (43.6)	14 (22.2)[a]	55 (33.1)
COPD or asthma	21 (51.2)	24 (38.7)	19 (30.2)	64 (38.6)
OSA or OHS	7 (17.1)	5 (8.1)	4 (6.4)	16 (9.6)
CHF	15 (36.6)	29 (46.8)	31 (49.2)	75 (45.2)
CKD	6 (14.6)	20 (32.3)	13 (20.6)	39 (23.5)
Solid neoplasm	6 (14.6)	7 (11.3)	3 (4.8)	16 (9.6)
Influenza A or B virus coinfection	5 (12.2)	5 (8.1)	1 (1.6)	11 (6.6)
Pneumonia on presentation	7 (17.1)	20 (32.3)	22 (34.9)	49 (29.5)
Noninvasively ventilated	6 (14.6)	11 (17.7)	10 (15.9)	27 (16.3)
Mean length of stay ± *SD* (days)	10.9 ± 9.8	13.9 ± 16.5	10.4 ± 7.4	11.8 ± 12.2
In-hospital death	6 (14.6)	5 (8.1)	9 (14.3)	20 (12.1)

Abbreviations: COPD, chronic obstructive pulmonary disease; 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); OSA or OHS, obstructive sleep apnea or obesity hypoventilation syndrome.

[a]Statistically significant lower frequency.

collected during routine labs working hours were run on the same day, whereas samples collected at other times were tested the next day.

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

2.1 | Statistical analysis

Descriptive data are shown as absolute (*n*) and relative (%) frequencies for categorical data and as mean ± *SD* for continuous variables. χ^2 and Kruskal–Wallis tests, as appropriate, were used to evaluate differences in baseline characteristics according to the age group. Logistic regression analysis was performed to identify factors associated with pneumonia, NIV use, and IHD, using a two-step model. First, a univariate analysis including age, gender, current active smoker, diabetes, chronic obstructive pulmonary disease (COPD) or asthma, obstructive sleep apnea or obesity hypoventilation syndrome (OSA or OHS), chronic heart failure (CHF) (Class II New York Heart Association or worse), chronic kidney disease (CKD) (KDIGO 2012, Stage 3A or worse), solid neoplasm, influenza A or B coinfection, and radiological signs of pneumonia was run to evaluate independent factors associated with the outcomes. Second, all the significant or clinically relevant factors were included in a multivariable analysis, adjusting for age and gender.

For all tests, a $p \leq .05$ was considered significant.

All analyses were performed with SPSS v. 25.0 (IBM Corp.).

3 | RESULTS

The number of elderly patients included in the study was 166, of which 41 (24.7%), 62 (37.3%), and 63 (38%) were 65–74, 75–84, and 85-year old and above, respectively.

Clinical features and comparison according to age group of patients included in the study are reported in Table 1.

The mean age was 80.9 ± 8.7 (range, 65–102] years, 63 (38%) were men, and 9.6% were current active smokers. The main comorbidities observed were diabetes in (33.1%), COPD or asthma (38.6%), CHF (45.2%), CKD (23.5%), OSA or OHS (9.6%), and solid neoplasm (9.6%). Influenza A and B virus coinfection was detected in six and five patients, respectively, with an overall rate of 6.6%. Radiological signs of pneumonia were present on the chest X-ray exams of 29.5% (*n* = 49); 16.3% (*n* = 27) were submitted to NIV, and seven patients (4.2%) were invasively mechanically ventilated. Among patients submitted to NIV or invasive mechanical ventilation, 74.1% (*n* = 20) and 57.1% (*n* = 4) survived admission, respectively. The mean length of stay was 11.8 ± 12.2 days and IHD was 12.1% (*n* = 20), with 14.6%, 8.1%, and 14.3% for the youngest-, middle-, and oldest old, respectively.

Comparing clinical features of the three groups, patients 85 years and older showed a statistically significant lower frequency of male gender ($p < .01$) and diabetes ($p = .04$).

Results of univariable and multivariable analyses that evaluated the association of clinical variables with pneumonia, NIV use, and IHD are shown in Table 2. In univariate analysis, no statistically significant association between age and outcomes was found. Multivariable analyses revealed that the risk of pneumonia was higher in patients with CKD (odds ratio [OR]: 2.57; 95% confdience interval [CI]: 1.12–5.91); the use of NIV was higher in patients with OSA or OHS (OR: 5.38; 95% CI: 1.67–17.35) and CKD (OR: 2.52; 95% CI: 1.01–6.23); the risk of IHD was higher in males (OR: 3.30; 95% CI: 1.07–10.10) and in patients with solid neoplasm (OR: 9.06; 95% CI: 2.44–33.54) and OSA or OHS (OR: 8.39; 95% CI: 2.14–32.89).

4 | DISCUSSION

This study provided one of the largest assessments available so far of clinical features and factors contributing to RSV infection severity in Southern European elderly patients.

It showed how RSV infection can result in a remarkable proportion of elderly patients presenting with pneumonia, NIV use, and IHD. No association between age and outcomes was found. The risk of pneumonia and NIV use were higher in patients suffering from chronic conditions, such as CKD, whereas NIV use and the risk of IHD were both higher in patients with OSA or OHS. The risk of IHD was also higher in males and patients with solid neoplasm.

Overall, the number of hospitalized patients over the study period were in line with recent evidence, showing a higher prevalence of RSV infection in the elderly.[8,16] Radiological evidence of pneumonia as patchy sub-segmental alveolar infiltrates or lobar consolidation was frequent, in line with recent reports revealing that it is noted in 30%–50% of cases.[3] The poor outcomes were also documented and consistent with evidence avalable so far[5,7,17]: more than 15% of cases necessitated noninvasive ventilatory support and the overall IHD rate exceeded 10%. No association between age and outcomes was found. This finding, in discordance with a previous report,[5] could highlight that the elderly are a nonhomogeneous, wide age group that usually faces different levels of morbidity, disability, and geriatric conditions that may be overlooked in the traditional disease model.[18]

In addition, as clinical features were not so different among the three age groups studied, risk factors of RSV infection severity were examined overall, and some novelties were provided. The risk of pneumonia on infection manifestation was higher in patients with CKD, differing from evidence available so far, highlighting a double risk of a serious outcome including pneumonia for patients with COPD, CHF, hematopoietic stem cell transplantation, and lung transplant recipients.[2,19] The NIV use was higher in patients with CKD and OSA or OHS, revealing that, in this kind of patients, RSV probably caused infections with a respiratory failure that benefited from application of NIV. Finally, the risk of IHD was higher in males

TABLE 2 Univariable and multivariable analyses for factors associated with pneumonia, noninvasive ventilation, and in-hospital death in elderly patients admitted for RSV infection

	Outcome								
	Univariate analysis						Multivariable analysis[a]		
	Pneumonia		NIV		In-hospital death		Pneumonia	NIV	In-hospital death
Characteristics		*p* Value		*p* Value		*p* Value	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age, mean ± SD (years)	82.1 ± 8.4	.22	81.4 ± 9.6	.75	80.6 ± 9.6	.88	1.04 (0.99–1.09)	1.02 (0.97–1.08)	1.05 (0.98–1.12)
Male, *n* = 63 (%)	22 (34.9)	.15	10 (15.9)	.55	12 (19.1)	**.03**	1.81 (0.84–3.90)	1.04 (0.40–2.71)	**3.30 (1.07–10.10)**
Smoker, *n* = 16 (%)	3 (18.8)	.25	1 (6.3)	.23	1 (6.3)	.40	-	-	-
Diabetes, *n* = 55 (%)	18 (32.7)	.32	12 (21.8)	.13	8 (14.6)	.32	-	-	-
COPD or asthma, n = 64 (%)	19 (29.7)	.55	13 (20.3)	.18	7 (10.9)	.47	1.05 (0.51–2.17)	-	-
OSA or OHS, *n* = 16 (%)	4 (25)	.46	7 (43.8)	**<.01**	5 (31.3)	**.03**	-	**5.38 (1.67–17.35)**	**8.39 (2.14–32.89)**
CHF, *n* = 75 (%)	19 (25.3)	.18	15 (20)	.17	9 (12)	.59	0.52 (0.24–1.12)	-	-
CKD, *n* = 39 (%)	16 (41)	.06	11 (28.2)	**.02**	5 (12.8)	.53	**2.57 (1.12–5.91)**	**2.52 (1.01–6.23)**	-
Solid neoplasm, *n* = 16 (%)	7 (43.8)	.15	4 (25)	.25	6 (37.5)	**<.01**	-	-	**9.06 (2.44–33.54)**
Influenza A or B coinfection, *n* = 11 (%)	3 (27.3)	.58	1 (9.1)	.44	3 (27.3)	.13	-	-	-

Note: Bold values denote statistically significant.

Abbreviations: 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; LOS, length of stay; NIV, noninvasive ventilation; OR, odds ratio; OSA or OHS, obstructive sleep apnea or obesity hypoventilation syndrome; RSV, respiratory syncytial virus.

[a]Adjusted for age and gender.

and in patients with solid neoplasm and OSA or OHS. The association between cancer and RSV infection is well documented[20] and viral infections must be kept in mind as differential diagnosis of fever in patients with cancer or on immunosuppressive treatment. The prognostic value of OSA or OHS for IHD is something new that deserves further research to investigate the immune response to RSV in the aging lung of patients bearing these comorbidities.

Our study had some limitations. Several factors contributing to infection severity and mortality including frailty scores, presence of bacterial coinfection, presence of viral coinfection other than influenza, respiratory failure, and occurrence of systemic complications were not assessed. The body mass index was not evaluated, and the prognostic value of obesity was not assessed. Moreover, our study lacks an assessment of post-discharge disability and follow-up.

In conclusion, elderly patients hospitalized for RSV infection bear high morbidity and mortality. Knowledge of factors associated with infection severity may aid clinicians to set priorities and reduce disease burden.

Development of effective antiviral treatment and vaccine against RSV is highly desirable.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Matteo Boattini, André Almeida, Eirini Christaki, Rossana Cavallo, and Cristina Costa designed the study. Matteo Boattini, André Almeida, Eirini Christaki, Torcato Moreira Marques, Valentina Tosatto, Gabriele Bianco, Marco Iannaccone, Georgios Tsiolakkis, Christos Karagiannis, Panagiota Maikanti, Lourenço Cruz, Diogo Antão, and Maria Inês Moreira acquired data. Matteo Boattini, André Almeida, and Eirini Christaki analyzed and interpreted data. Matteo Boattini wrote the paper. All authors revised the article critically and approved the final version.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was conducted in accordance with the Declaration of Helsinki. Formal ethical approval was obtained by the institutional review board of the coordinating center (Central Lisbon Hospital Center, no. 762_2019).

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REFERENCES

1. Nanda A, NVRK Vura, Gravenstein S. COVID-19 in older adults. *Aging Clin Exp Res*. 2020;32:1199-1202. https://doi.org/10.1007/s40520-020-01581-5
2. Nam HH, Ison MG. Respiratory syncytial virus infection in adults. *BMJ*. 2019;366:l5021. https://doi.org/10.1136/bmj.l5021
3. Branche AR, Falsey AR. Respiratory syncytial virus infection in older adults: an under-recognized problem. *Drugs Aging*. 2015;32:261-269. https://doi.org/10.1007/s40266-015-0258-9
4. Haber N. Respiratory syncytial virus infection in elderly adults. *Med Mal Infect*. 2018;48:377-382. https://doi.org/10.1016/j.medmal.2018.01.008
5. Lee N, Lui GCY, Wong KT, et al. High morbidity and mortality in adults hospitalized for respiratory syncytial virus infections. *Clin Infect Dis*. 2013;57:1069-1077. https://doi.org/10.1093/cid/cit471
6. 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;206:56-62. https://doi.org/10.1093/infdis/jis309
7. Kwon YS, Park SH, Kim MA, et al. Risk of mortality associated with respiratory syncytial virus and influenza infection in adults. *BMC Infect Dis*. 2017;17:785. https://doi.org/10.1186/s12879-017-2897-4
8. Bruyndonckx R, Coenen S, Butler C, et al. Respiratory syncytial virus and influenza virus infection in adult primary care patients: association of age with prevalence, diagnostic features, and illness course. *Int J Infect Dis*. 2020;95:384-390. https://doi.org/10.1016/j.ijid.2020.04.020
9. Ackerson B, An J, Sy LS, Solano Z, Slezak J, Tseng HF. Cost of hospitalization associated with respiratory syncytial virus infection versus influenza infection in hospitalized older adults. *J Infect Dis*. 2020:jiaa183. https://doi.org/10.1093/infdis/jiaa183
10. 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;352:1749-1759. https://doi.org/10.1056/NEJMoa043951
11. Zwaans WA, Mallia P, van Winden ME, Rohde GG. The relevance of respiratory viral infections in the exacerbations of chronic obstructive pulmonary disease—a systematic review. *J Clin Virol*. 2014;61:181-188. https://doi.org/10.1016/j.jcv.2014.06.025
12. Broberg EK, Waris M, Johansen K, Snacken R, Penttinen P, European Influenza Surveillance Network. Seasonality and geographical spread of respiratory syncytial virus epidemics in 15 European countries, 2010 to 2016. *Euro Surveill*. 2018;23:17-00284. https://doi.org/10.2807/1560-7917.ES.2018.23.5.17-00284
13. Sáez-López E, Pechirra P, Costa I, et al. Performance of surveillance case definitions for respiratory syncytial virus infections through the sentinel influenza surveillance system, Portugal, 2010 to 2018. *Euro Surveill*. 2019;24:1900140. https://doi.org/10.2807/1560-7917.ES.2019.24.45.1900140
14. Pellegrinelli L, Galli C, Bubba L, et al. Respiratory syncytial virus in influenza-like illness cases: epidemiology and molecular analyses of four consecutive winter seasons (2014-2015/2017-2018) in Lombardy (Northern Italy). *J Med Virol*. 2020. https://doi.org/10.1002/jmv.25917
15. Almeida A, Boattini M, Christaki E, et al. Comparative virulence of seasonal viruses responsible for lower respiratory tract infections: a southern European multi-centre cohort study of hospital admissions. *Infection*. 2021. https://doi.org/10.1007/s15010-020-01569-3
16. Sundaram ME, Meece JK, Sifakis F, Gasser RA, Jr, Belongia EA. Medically attended respiratory syncytial virus infections in adults aged ≥ 50 years: clinical characteristics and outcomes. *Clin Infect Dis*. 2014;58:342-349. https://doi.org/10.1093/cid/cit767
17. Chuaychoo B, Ngamwongwan S, Kaewnaphan B, et al. Clinical manifestations and outcomes of respiratory syncytial virus infection in adult hospitalized patients. *J Clin Virol*. 2019;117:103-108. https://doi.org/10.1016/j.jcv.2019.07.001

18. Cigolle CT, Langa KM, Kabeto MU, Tian Z, Blaum CS. Geriatric conditions and disability: the health and retirement study. *Ann Intern Med*. 2007;147:156-164. https://doi.org/10.7326/0003-4819-147-3-200708070-00004
19. 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:ofy316. https://doi.org/10.1093/ofid/ofy316
20. 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;23:253-259. https://doi.org/10.1016/j.cmi.2016.11.014

How to cite this article: Boattini M, Almeida A, Christaki E, et al. Severity of RSV infection in Southern European elderly patients during two consecutive winter seasons (2017–2018). *J Med Virol*. 2021;93:5152-5157. https://doi.org/10.1002/jmv.26938