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Influenza and respiratory syncytial virus infections in the oldest-old continent**This is the author's manuscript**

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- 1 Influenza and respiratory syncytial virus infections in the oldest-old continent
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27 **Summary**

28 **Introduction:** SARS-CoV-2 dramatically revealed the sudden impact of respiratory viruses in our
29 lives. Influenza and respiratory syncytial virus (RSV) infections are associated with high rates of
30 morbidity, mortality, and an important burden on healthcare systems worldwide, especially in elderly
31 patients. The aim of this study was to identify severity predictors in the oldest-old admitted with
32 Influenza and/or RSV infections.

33 **Methods:** This is a multicentre, retrospective study of all oldest old patients (≥ 85 years-old) admitted
34 for laboratory-confirmed Influenza and/or RSV infection in three tertiary hospitals in Portugal, Italy,
35 and Cyprus over two consecutive winter seasons. The outcomes included the following: pneumonia
36 on infection presentation, use of non-invasive ventilation (NIV), and in-hospital death (IHD). The
37 association with possible predictors, including clinical features and type of virus infection, was
38 assessed using uni- and multivariable analyses.

39 **Results:** 251 oldest old patients were included in the study. Pneumonia was evident in 32.3% (n=81).
40 NIV was implemented in 8.8% (n=22) and IHD occurred in 13.9% (n=35). Multivariable analyses
41 revealed that chronic obstructive pulmonary disease (COPD) or asthma was associated with
42 pneumonia (OR 1.86; 95% CI 1.02-3.43; p=0.045). COPD or asthma (OR 4.4; 95% CI 1.67-11.6;
43 p=0.003), RSV (OR 3.12; 95% CI 1.09-8.92; p=0.023) and Influenza-B infections (OR 3.77; 95% CI
44 1.06-13.5; p=0.041) were associated with NIV use, respectively, while chronic kidney disease was
45 associated with IHD (OR 2.50; 95% CI 1.14-5.51; p=0.023).

46 **Discussion:** Among the oldest-old, chronic organ failure such as COPD or asthma and CKD predicted
47 pneumonia and IHD, respectively, beyond the importance of viral virulence itself. These findings
48 could impact on public health policies such as fostering Influenza immunization campaigns, home-
49 based care programmes and end-of-life care. Filling knowledge gaps is crucial to set priorities and
50 advise on transition model of care that best fits the oldest-old.

51

52 **Keywords:** oldest-old; influenza; respiratory syncytial virus; geriatrics; pneumonia

53 **Introduction**

54 SARS-CoV-2 dramatically revealed the sudden impact and the utmost importance of respiratory
55 viruses in our lives. Influenza and respiratory syncytial virus (RSV) infections are associated with
56 high rate of morbidity, mortality, and an important burden on healthcare systems worldwide,
57 especially among elderly patients [1-6]. Oldest-old is a term meant to include people aged 85 years
58 and older that represent a growing population in the old European continent. Despite being a non-
59 homogeneous group, they are professionally retired individuals that usually experience
60 multimorbidity, disability and may face a limited life expectancy. Recent evidence suggests that there
61 is a high research interest towards addressing their needs and establishing the best standard of care
62 [7,8]. Especially in epidemiological research, oldest old patients are considered to be a part of the
63 wider age group of the elderly (≥ 65 years-old) and there is limited published evidence about
64 predictors of severity of illness and mortality in viral infections, such as caused by Influenza and RSV.
65 The aim of this study was to describe the clinical features of an oldest old population admitted with
66 Influenza and/or RSV infections in three southern European hospitals over two consecutive winter
67 seasons and identify predictors of pneumonia, non-invasive ventilation (NIV) and in-hospital death
68 (IHD). Such knowledge might provide insight to assist healthcare policymakers managing chronic
69 conditions, improving patient satisfaction and reduce hospital utilization.

70

71 **Methods**

72 This is a multicentre, retrospective study of all oldest old patients (≥ 85 years-old) who were either
73 admitted to the hospital for laboratory-confirmed Influenza and/or RSV infection or developed it
74 during the course of admission for other causes, from 1 October 2017 to 30 April 2018 and from 1
75 October 2018 to 30 April 2019 in three tertiary hospitals in Portugal, Italy and Cyprus. The laboratory
76 confirmation was based on a positive Xpert Flu/RSV PCR (Cepheid Diagnostics, Sunnyvale, CA,
77 USA) and/or Allplex Respiratory Panel (Allplex, Seegene, Republic of Korea) on naso/oropharyngeal
78 swabs obtained from patients with signs or symptoms of viral infection. For patients with more than

79 one positive PCR in a seasonal period, the first episode was considered for study purposes. The
80 infection was characterized as hospital-acquired if symptoms pertaining to viral infection began after
81 72 h from admission. Variables assessed included demographics, smoking status, co-morbidities,
82 virus type, nosocomial acquisition, pulmonary infiltrate on chest x-ray taken when symptoms were
83 observed, neuraminidase inhibitor use, length of stay (from admission to discharge), NIV, mechanical
84 ventilation and IHD.

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

88

89 *Statistical analysis*

90 Descriptive data are shown as absolute (n) and relative (%) frequencies for categorical data and as
91 mean \pm standard deviation (SD) and median and interquartile range (IQR), as appropriate, for
92 continuous variables. On univariate analysis, chi-square test for categorical variables, and t-Student
93 or Wilcoxon rank-sum test, as appropriate, for continuous variables were carried out to identify
94 factors associated with pneumonia, NIV and IHD. Odds ratios (OR) and their 95% confidence
95 intervals (95%CI) were also calculated to estimate the strength of those associations. Multivariable
96 analysis models were then fitted to investigate the independent effects of type of virus infection and
97 clinically variables that turned out to be significantly associated with the outcomes at univariate
98 analysis, adjusting for possible confounders like age and gender.

99 For all tests, a p-value ≤ 0.05 was considered significant.

100 All analyses were performed with Stata 14.

101

102 **Results**

103 A total of 1,151 patients ≥ 18 years-old were admitted for Influenza A/B and/or RSV infections during
104 the study period in the three centres. Oldest old patients were 251 (21.8%), of which 30 (12%) had
105 hospital-acquired Influenza A/B and/or RSV infections.

106 Clinical features of oldest old patients included in the study were reported in Table 1. Mean age was
107 89.4 ± 3.9 [range, 85 to 103] years, 79 (31.5%) were men and 3.6% was current active smoker. The
108 co-morbidities mainly observed were diabetes (22.7%), COPD or asthma (24.7%), CHF (47%) and
109 CKD (19.5%). The viral agents identified were Influenza-A (56.6%), Influenza-B (15.9%), RSV
110 (25.9%), Influenza-A+Influenza-B (1.2%) and Influenza-A+RSV (0.4%) co-infections. Among
111 Influenza-A infections, H3N2 was the most common (68.5%) followed by H1N1 (13%), 18.5% not
112 having been subtyped. Radiological signs of pneumonia were present on the chest x-ray exams of
113 32.3% (n=81) following laboratory diagnosis of viral infection; 8.8% (n=22) were submitted to NIV
114 and only one patient (0.4%) was invasively mechanically ventilated. Thirty-five patients (13.9%) did
115 not survive admission. Among patients submitted to NIV, 72.7% (n=16) survived admission.
116 Antiviral treatment with a neuraminidase inhibitor was started in 60.6% of patients. Mean length of
117 stay of patients with community- and hospital-acquired infections was 12 ± 11.1 (median 9, IQR 6-
118 14) and 27.8 ± 28.7 (median 20, IQR 8-30) days, respectively ($p < 0.01$). Overall IHD was 13.9%,
119 being 14% and 13.3% for community- and hospital-acquired infections, respectively, with no
120 significant difference.

121 Results of univariate and multivariable analyses were shown in Table 2.

122 Since at univariate analysis FLU-A infection turned out to be a significant protective factor for NIV
123 use ($p = 0.009$)...

124 At univariate analysis, COPD or asthma were significantly associated with pneumonia (OR 1.93; 95%
125 CI 1.06-3.49) and use of NIV (OR 3.49; 95% CI 1.43-8.51); RSV infection turned out to be another
126 significant factor associated with NIV use (OR 3.51; 95% CI 1.27-9.68), while CKD was the only
127 clinical feature significantly associated with IHD (OR 2.52; 95% CI 1.15-5.52). Finally, we
128 considered three logistic regression models, where, for each outcome, age, gender, COPD or asthma

129 (for pneumonia and use of NIV models), CKD (for IHD model) and type of virus infection were the
130 independent variables.

131 Among all patients, multivariable analyses revealed that COPD or asthma were significantly
132 associated with radiologically confirmed pneumonia (OR 1.86; 95% CI 1.02-3.43; p=0.045); COPD
133 or asthma (OR 4.4; 95% CI 1.67-11.6; p=0.003), Influenza-B (OR 3.77; 95% CI 1.06-13.5; p=0.041)
134 and RSV infections (OR 3.12; 95% CI 1.09-8.92; p=0.023) were associated with NIV use; CKD
135 turned out to be the only predictor significantly associated with IHD (OR 2.50; 95% CI 1.14-5.51;
136 p=0.023).

137

138 **Discussion**

139 SARS-CoV-2 pandemic and its unsustainable burden supplanted every hierarchy of interest in
140 medical research but highlighted how viral infections knowledge is crucial in clinical practice.
141 Among the aged population, Influenza and RSV infections are important causes of hospital admission
142 during autumn and winter months.

143 The highlights of this study are the following findings: (1) the proportion of oldest old patients among
144 total hospitalizations was remarkable; (2) radiological pneumonia, use of NIV and IHD were
145 considerable; (3) Influenza-A H3N2 infection was the most prevalent; Influenza-B and RSV infection
146 were significantly associated with NIV use; (4) COPD or asthma was associated with both pneumonia
147 and NIV use; (5) CKD was a predictor of IHD.

148 To best of our knowledge, our line of research is quite novel and barely comparable to previous reports
149 given the higher mean age of patients involved.

150 Overall, the number of hospitalizations over the study period was remarkable comparing to recent
151 reports [9], showing that over two years one out of five admissions with Influenza and/or RSV
152 infections involved oldest-old. Moreover, in our study, hospital-acquired Influenza and/or RSV
153 infections were not identified as predictors of pneumonia, use of NIV and IHD for patients aged 65
154 years and older, moving away from evidence available so far [9,10].

155 Pneumonia on infection presentation was very frequent, in line with more recent reports [9-17],
156 revealing how an important proportion of patients showed a direct viral injury in lung parenchyma
157 and/or bacterial co-infection. However, despite being a life-threatening condition it was neither
158 predictive of NIV use nor of IHD.

159 The use of NIV was considerable when comparing with available evidence in a cohort of younger
160 patients [9]. This finding might be related to both the type of respiratory failure on infection
161 presentation and a remarkable rate of diagnosed or likely under-diagnosed chronic obstructive lung
162 disease [18]. Similarly, in our population NIV seemed to be effective since data about its use in
163 respiratory viral infections are limited and uncertain, especially in presence of pneumonia, hypoxicemic
164 respiratory failure, and SOFA \geq 5 and no COPD and/or cardiogenic pulmonary edema [19].

165 On the other hand, invasive mechanical ventilation rate was performed only once, probably according
166 to ethical and prognostic considerations such as coexistence of frailty and patient end-of-life
167 preferences. The discrepancy between the use of these two modalities of ventilation could be
168 presumably due to accept NIV as a ceiling of therapeutic effort.

169 IHD was also remarkable. Studies suggest mortality rate ranging from 4.1% to 9.8% [9-13,15-17,20]
170 and up to 24% in ICU patients [14]. Nevertheless, these studies were performed on elderly people
171 with lower median age while our data should be comprehensible for an oldest old cohort of patients.

172 Infection due to Influenza-A H3N2 was the most prevalent, RSV infection was also very frequent,
173 confirming that epidemic viral subtypes and their affinity for the lower respiratory tract differ
174 according to the study period [21]. Severity of illness and IHD due to RSV infection were similar as
175 compared to Influenza viruses but according to literature, these can vary from season to season [9,22].

176 Therefore, the role of virus type in morbidity and mortality remains controversial. Our study set forth
177 only a virus-type association with NIV use. Our findings might suggest that RSV and Influenza-B
178 probably caused infections with a clinical scenario that benefited from application of NIV [23] more
179 than Influenza-A.

180 COPD or asthma was independently associated with pneumonia on infection presentation and NIV
181 use, suggesting the importance of the aged lung [18] and the attempt to overcome respiratory failure
182 through this widespread and generally well-tolerated ventilation technique.

183 CKD was the only significant predictor IHD and it could represent an interesting clinical tool. Indeed,
184 previous studies included acute kidney injury and renal disease as predictors of mortality and disease
185 severity, respectively [9,12] but no prognostic factors have been identified for oldest-old.

186 Our study had limitations. A 72-h period might have led to misclassify the community- vs. hospital-
187 acquisition of the viral infection since evidence suggests longer incubation periods [24]. Several
188 factors contributing to disease severity and mortality including nursing home residency, frailty scores,
189 bedridden status, immunization status, malnutrition, sarcopenia, presence of mixed viral and bacterial
190 pneumonia, respiratory failure, occurrence of systemic complications and physicians' attitude
191 towards more intensive care were not assessed. Moreover, our study lacks an assessment of post-
192 discharge disability and follow-up.

193 In conclusion, this study provided one of the largest assessments available so far of clinical features
194 and factors contributing to severity of illness in the oldest-old admitted with Influenza and/or RSV
195 infections in Southern Europe. Chronic organ failure such as COPD or asthma and CKD predicted
196 pneumonia and IHD, respectively, surpassing the importance of viral virulence. These findings could
197 impact on public health policies such as fostering Influenza immunization campaigns, home-based
198 care programmes [25] and end-of-life care. Filling knowledge gaps is crucial to set priorities and
199 advise on transition model of care that best fits the oldest-old.

200

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203 expertise.

204 **Compliance with Ethical Standards**

205 **Funding:** no funding was received for this study.

206 **Conflict of Interest:** the authors declare that they have no conflict of interest.

207 **Ethical approval:** This study was conducted in accordance with the Declaration of Helsinki. Formal
208 ethical approval was obtained by the institutional review board of the coordinating centre (Central
209 Lisbon Hospital Centre, no. 762_2019).

210 **Informed consent:** Informed consent was not deemed required for the purposes of this study.

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302 Table 1. Clinical features of oldest old population included in the study.

303

Oldest old patients (n)	251
Mean age ± SD (years)	89.4 ± 3.9
Male	31.5 (79)
Smoker	3.6 (9)
Diabetes	22.7 (57)
COPD or asthma	24.7 (62)
Obstructive Sleep Apnea or <i>Obesity hypoventilation syndrome</i>	4 (10)
CHF (class II NYHA or worse)	47 (118)
CKD (KDIGO 2012 stage 3A or worse)	19.5 (49)
Haematological neoplasm	3.2 (8)
Solid neoplasm	5.6 (14)
Type of virus infection	
Influenza-A	56.6 (142)
H1N1	12.7 (18)
H3N2	69 (98)
Unsubtyped	18.3 (26)
Influenza-B	15.9 (40)
RSV	25.9 (65)
Co-infection (Influenza-A+ Influenza-B)	1.2 (3)
Co-infection (Influenza-A+ RSV)	0.4 (1)
Pneumonia on presentation	32.3 (81)
Antiviral therapy with neuraminidase inhibitor	60.6 (152)
Non-invasively ventilated	8.8 (22)
Invasively mechanically ventilated	0.4 (1)
Hospital-acquired Influenza-A/B and/or RSV infection	12 (30)
Mean length of stay ± SD (days) of patients with community-acquired Influenza-A/B and/or RSV infection Median (IQR)	12 ± 11.1 9 (6-14)
Mean length of stay ± SD (days) of patients with hospital-acquired Influenza-A/B and/or RSV infection Median (IQR)	27.8 ± 28.7 20 (8-30)
In-hospital death	13.9 (35)
Patients with community-acquired Influenza-A/B and/or RSV infection	14 (31)
Patients with hospital-acquired Influenza-A/B and/or RSV infection	13.3 (4)

304 All data are shown as relative, %, and absolute (n) frequencies if not otherwise stated.

305 Abbreviations

306 COPD: chronic obstructive pulmonary disease; CHF: chronic heart failure; NYHA: New York Heart Association; CKD:
307 chronic kidney disease; KDIGO: Kidney Disease: Improving Global Outcomes (2012); RSV: respiratory syncytial
308 virus.

309 Table 2. Uni- and multivariable analyses for factors associated with pneumonia, non-invasive ventilation (NIV) and intra-hospital death in oldest old adults admitted with Influenza-
 310 A/B and/or RSV infection.
 311

Characteristics	Outcome											
	Univariate analysis						Multivariable analysis					
	Pneumonia		NIV		Death		Pneumonia		NIV		Death	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.95 (0.88-1.02)	0.151	1.04 (0.93-1.15)	0.485	1.04 (0.96-1.14)	0.341	0.96 (0.89-1.03)	0.246	1.05 (0.93-1.18)	0.436	1.05 (0.95-1.15)	0.334
Male	1.45 (0.83-2.54)	0.191	0.62 (0.22-1.73)	0.359	1.00 (0.46-2.15)	0.995	1.27 (0.71-2.30)	0.423	0.52 (0.16-1.68)	0.277	1.06 (0.47-2.40)	0.886
Diabetes	1.44 (0.78-2.66)	0.247	1.31 (0.49-3.52)	0.594	1.44 (0.64-3.20)	0.374	-	-	-	-	-	-
CHF (class II NYHA or worse)	0.74 (0.43-1.26)	0.270	2.10 (0.85-5.21)	0.108	2.10 (0.85-5.21)	0.108	-	-	-	-	-	-
CKD (KDIGO 2012 stage 3A or worse)	0.91 (0.46-1.78)	0.782	1.23 (0.43-3.53)	0.692	2.52 (1.15-5.52)	0.020	-	-	-	-	2.50 (1.14-5.51)	0.023
COPD or asthma	1.93 (1.06-3.49)	0.030	3.49 (1.43-8.51)	0.006	0.89 (0.38-2.07)	0.785	1.86 (1.02-3.43)	0.045	4.40 (1.67-11.6)	0.003	-	-
Type of virus infection												
Influenza-A	1	-	1	-	1	-	1	-	1	-	1	-
Influenza-B	0.89 (0.42-1.92)	0.774	2.76 (0.82-9.21)	0.100	1.72 (0.69-4.32)	0.246	0.90 (0.41-1.95)	0.782	3.77 (1.06-13.5)	0.041	1.77 (0.70-4.52)	0.231
RSV	1.14 (0.62-2.12)	0.672	3.51 (1.27-9.68)	0.015	1.11 (0.47-2.62)	0.817	1.16 (0.61-2.18)	0.654	3.12 (1.09-8.92)	0.023	1.11 (0.46-2.66)	0.813
Pneumonia on presentation	-	-	1.51 (0.62-3.69)	0.367	0.82 (0.37-1.79)	0.614	-	-	-	-	-	-
Hospital-acquired Influenza-A/B and/or RSV infection	0.60 (0.25-1.47)	0.264	0.33 (0.04-2.53)	0.286	0.94 (0.31-2.89)	0.918	-	-	-	-	-	-

312 Abbreviations
 313 NIV: non-invasive ventilation; CHF: chronic heart failure; NYHA: New York Heart Association; CKD: chronic kidney disease; KDIGO: Kidney Disease: Improving Global
 314 Outcomes (2012); COPD: chronic obstructive pulmonary disease; RSV: respiratory syncytial virus.

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