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## **Non-influenza respiratory viruses in adult patients admitted with influenza-like illness a 3-year prospective multicenter study**

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### ► To cite this version:

François Benezit, Paul Loubet, Florence Galtier, Charlotte Pronier, Nezha Lenzi, et al.. Non-influenza respiratory viruses in adult patients admitted with influenza-like illness a 3-year prospective multicenter study. *Infection*, 2020, 48 (4), pp.489-495. 10.1007/s15010-019-01388-1 . hal-02498632

**HAL Id: hal-02498632**

**<https://univ-rennes.hal.science/hal-02498632>**

Submitted on 26 May 2020

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1 **Non-influenza respiratory viruses in adult patients admitted with influenza-**  
2 **like illness: A three-year prospective multicenter study**

3

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48

49 **ABSTRACT**

50 **Purpose** To describe the burden, and characteristics, of influenza-like illness (ILI) associated  
51 with non-influenza respiratory viruses (NIRV).

52 **Methods** We performed a prospective, multicenter, observational study of adults admitted  
53 with ILI during 3 influenza seasons (2012-2015). Patients were screened for picornavirus,  
54 respiratory syncytial virus (RSV), coronavirus, human metapneumovirus, adenovirus,  
55 bocavirus, parainfluenza virus, and influenza, by PCR on nasopharyngeal samples. We  
56 excluded patients coinfecting with NIRV and influenza.

57 **Results** Among 1421 patients enrolled, influenza virus was detected in 535 (38%), and NIRV  
58 in 215 (15%), mostly picornavirus (n=61), RSV (n=53), coronavirus 229E (n=48), and human  
59 metapneumovirus (n=40). In-hospital mortality was 5% (NIRV), 4% (influenza), and 5% (no  
60 respiratory virus). As compared to influenza, NIRV were associated with age (median, 73  
61 years vs. 68,  $P=0.026$ ), chronic respiratory diseases (53% vs. 45%,  $P=0.034$ ), cancer (14% vs.  
62 9%,  $P=0.029$ ), and immunosuppressive drugs (21% vs. 14%,  $P=0.028$ ), and inversely  
63 associated with diabetes (18% vs. 25%,  $P=0.038$ ). On multivariable analysis, only chronic  
64 respiratory diseases (OR 1.5 [1.1-2.0],  $P=0.008$ ), and diabetes (OR 0.5 [0.4-0.8],  $P=0.01$ )  
65 were associated with NIRV detection.

66 **Conclusions** NIRV are common in adults admitted with ILI during influenza seasons.  
67 Outcomes are similar in patients with NIRV, influenza, or no respiratory virus.

68

69 **Keywords** Influenza-like illness; Influenza; picornavirus; respiratory syncytial virus;  
70 coronavirus; human metapneumovirus

## 71 **Introduction**

72 Non-influenza respiratory viruses (NIRV) are responsible for a substantial proportion of  
73 influenza-like illness (ILI), and pneumonia [1,2], although epidemiological data on their  
74 burden are scarce. The pathogenicity of viruses recently discovered, such as human  
75 metapneumovirus in 2001, or bocavirus in 2005 [3,4], remains poorly characterized. Even  
76 NIRV discovered earlier (e.g. parainfluenza virus, respiratory syncytial virus (RSV), or  
77 adenovirus), have attracted limited clinical interest thus far, as a result of the absence of rapid  
78 tests routinely available, and the lack of vaccine or antiviral treatment with proven clinical  
79 efficacy [1,2,5,6]. The advent of highly sensitive and specific point-of-care tests for  
80 simultaneous detection of the main respiratory viruses is an opportunity to investigate the role  
81 of NIRV in common acute respiratory febrile illness, including the risk factors for, and the  
82 characteristics of, NIRV-associated ILI. These data may have important implications,  
83 including i) screening and early implementation of respiratory isolation for patients with  
84 NIRV to prevent nosocomial transmission; ii) identification of the major NIRV that should be  
85 targeted for development of antivirals or vaccines. We aimed to determine the characteristics  
86 of, and the risk factors for NIRV among adults admitted with ILI during influenza seasons in  
87 France.

88

## 89 **Methods**

### 90 **Study design and population**

91 We analyzed cases of laboratory-confirmed NIRV infection during three consecutive  
92 influenza seasons (2012/2013, 2013/2014, and 2014/2015), in a post-hoc analysis of patients  
93 hospitalized with community-acquired ILI, and enrolled in the FLUVAC study. FLUVAC is a  
94 prospective observational study of influenza vaccine efficacy conducted in six university

95 hospitals in France (Cochin Hospital, Paris; Bichat Hospital, Paris; Pontchaillou Hospital,  
96 Rennes; Dupuytren Hospital, Limoges; Montpellier University Hospital; Edouard Herriot  
97 Hospital, Lyon). Patients were invited to participate during periods of influenza circulation  
98 (from December to March). We collected data on non-institutionalized adults (>18 years),  
99 who were hospitalized for at least 24 h with ILI, with symptoms onset less than 7 days prior  
100 to sampling, through an active surveillance system staffed by trained healthcare professionals.  
101 ILI was defined as a combination of two criteria: (i) at least one of the following symptoms:  
102 fever ( $\geq 38^{\circ}\text{C}$ ), headache, myalgia or malaise, and (ii) at least one of the following respiratory  
103 symptoms: cough, sore throat, or shortness of breath (dyspnea) [7]. The characteristics and  
104 outcome of patients with influenza [8,9], and RSV [10] in this cohort have been previously  
105 reported.

#### 106 **Clinical data**

107 We collected data on demographic, chronic underlying diseases, hospital admission during  
108 the previous 12 months, smoking status, hospitalization ward, and main characteristics of  
109 current ILI, including date of onset, date of admission, length of hospital stay, and outcome  
110 (i.e. complications, and in-hospital mortality). Data were collected on a standardized  
111 questionnaire from medical records, and face-to-face interviews with patients.

#### 112 **Virology**

113 Tests for respiratory viruses were performed in nasopharyngeal swabs from all patients by  
114 means of multiplex reverse transcription-polymerase chain reaction (mRT-PCR).  
115 Bronchoalveolar lavage fluid samples and tracheal aspirates ordered by the physician in  
116 charge were also tested. Samples were initially tested in the virology laboratory of each  
117 participating hospital by means of real-time influenza A & B PCR. All samples were then sent  
118 to the French National Influenza Reference Center (CNR-Lyon) for confirmation. RNA and

119 DNA were extracted with the automated Easymag system from BioMérieux (Marcy l'Etoile,  
120 France), and influenza viruses were detected with an in-house real-time RT-PCR protocol  
121 [11]. Samples were also screened for a panel of NIRV: adenovirus (52 serotypes), human  
122 bocaviruses 1-4, human coronaviruses (229E, NL63, OC43, HKU1), human  
123 metapneumoviruses 1-4, parainfluenza viruses 1–4, picornavirus, and RSV, by real-time PCR,  
124 using the Respiratory Multiwell System (MWS) r-gene® on an ABI 7300 analyzer.

## 125 **Ethics**

126 The FLUVAC study (clinicaltrials.gov NCT02027233) respected Good Epidemiological and  
127 Clinical Practices in clinical research and the Declaration of Helsinki, and was approved by  
128 institutional review board. All study participants provided informed consent for respiratory  
129 viruses testing and data collection.

## 130 **Statistical analysis**

131 We first described the characteristics of all patients hospitalized with ILI who tested positive  
132 for at least one NIRV. Results were expressed as mean and standard deviation (SD), or  
133 median and interquartile range (IQR) for quantitative variables, and n (%) for qualitative  
134 variables. Missing data for each variable were excluded from the denominator. Factors  
135 associated with NIRV infection were analyzed by using two different comparison groups: i)  
136 patients with negative tests for both NIRV and influenza; ii) patients with documented  
137 influenza. The Wilcoxon rank sum test or Fisher's exact test was used, as appropriate, for  
138 univariable comparisons. For multivariable analysis, we used a backward stepwise logistic  
139 regression model, using NIRV test results (positive/negative) as the dependent variable.  
140 Covariables tested in the multivariable model were all variables with a *P*-value <0.2 in the  
141 univariable analysis. Results were expressed as odds ratios (OR) and adjusted OR (aOR) with  
142 95% confidence intervals (CI). A *P*-value of 0.05 or less was considered statistically

143 significant. All analyses were performed using R software (v3, R Foundation for Statistical  
144 Computing, Vienna, Austria) [12].

145

## 146 **Results**

### 147 **Characteristics of patients with influenza-like illness, and virus distribution**

148 Overall, 1452 patients hospitalized with ILI were enrolled. Median age was 70 years [IQR,  
149 54-82], 780 patients were male (54%), 1155 (80%) had at least one chronic underlying  
150 disease (mostly respiratory or heart diseases), 661 (46%) had been hospitalized in the  
151 previous 12 months, and 644 (44%) had been vaccinated against influenza. Among the 1452  
152 patients tested, 781 (54%) were positive for at least one respiratory virus. We excluded the 31  
153 patients (2% of total), who had simultaneous detection of influenza virus, and NIRV. Among  
154 the 1421 remaining patients, influenza virus was detected in 535 (38%), and NIRV in 215  
155 patients (15%), including 7 with two NIRV. The NIRV detected were picornavirus, n=61  
156 (27%), RSV, n=53 (24%), coronavirus 229E, n=48 (22%), human metapneumovirus, n=40  
157 (18%), adenovirus, n=12 (5%), and bocavirus, n=8 (4%). No parainfluenza virus was  
158 detected. Flow chart is presented in Figure 1. The proportion of positive tests for influenza  
159 and for NIRV remained similar during the two first influenza seasons; a significant increase  
160 of influenza cases was noted in 2014-2015 winter (Table 1).

### 161 **Characteristics of patients with non-influenza respiratory viruses (Table 2)**

162 The 215 patients with at least one NIRV detected, had a median age of 73 years [60-83], 116  
163 (54%) were male, and 174 (81%) had at least one chronic underlying disease, mostly  
164 respiratory (n=114, 53%), or heart diseases (n=90, 42%). Fifty-two patients (24%) were  
165 current smokers, 44 (21%) were taking immunosuppressive drugs, and 4 were pregnant (27%

166 of women less than 50-year-old). Mean duration of ILI at the time of admission was 3.0 days  
167 [2-4]. Main symptoms were fever (78%), cough (78%), dyspnea (74%), weakness or malaise  
168 (26%), headache (22%), and myalgia (21%). Ninety-four patients developed at least one  
169 complication during hospital stay, including pneumonia, n=68 (32%), and respiratory failure,  
170 n=47 (22%). Median length of stay was 8 days [5-17]. ICU admission was required for 16  
171 patients (11%). Eleven patients died during hospitalization (5%).

172 **Comparison of patients who tested positive for non-influenza respiratory viruses, and i)**  
173 **patients with influenza; ii) patients with no respiratory virus detected (Table 2)**

174 Patients who tested positive for NIRV were older than patients with influenza (median, 73  
175 years versus 68,  $P=0.026$ ), more likely to have chronic respiratory diseases (53% versus 45%,  
176  $P=0.034$ ), solid cancer (14% versus 9%,  $P=0.029$ ), and to be on immunosuppressive drugs  
177 (21% versus 14%,  $P=0.028$ ), but less likely to have diabetes (18% versus 25%,  $P=0.038$ ).  
178 Fever was less common with NIRV than influenza (79% vs 90%,  $P<0.001$ ). Outcomes were  
179 similar, including complications, median length of stay, and in-hospital mortality. On  
180 multivariable analysis, only chronic respiratory disease (OR 1.5 [1.1-2.0],  $P=0.008$ ), and  
181 diabetes (OR 0.5 [0.4-0.8],  $P=0.01$ ), were significantly associated with NIRV.

182 When compared to patients with no detection of respiratory virus, patients who tested  
183 positive for NIRV were more likely to have chronic respiratory diseases (53% versus 44%,  
184  $P=0.024$ ), to be pregnant (27% versus 5%,  $P=0.021$ ), and on immunosuppressive drugs (21%  
185 versus 15%,  $P=0.041$ ), but less likely to have diabetes (18% versus 27%,  $P=0.011$ ). Weakness  
186 was less common in patients with NIRV than in patients who tested negative for all  
187 respiratory viruses (26% vs 33%,  $P=0.047$ ). Regarding outcome, pneumonia was more  
188 common in patients who tested positive for NIRV (32% vs 24%,  $P=0.019$ ).

## 190 **Discussion**

191 In this prospective multicenter study performed during three influenza seasons in France, at  
192 least one NIRV was found in 15% of patients admitted with ILI, the major players being  
193 picornavirus (27%), RSV (24%), coronavirus 229E (22%), and human metapneumovirus  
194 (18%). NIRV were more common in patients with chronic respiratory diseases, and less  
195 common in patients with diabetes, whatever the comparison group (patients with influenza, or  
196 patients with no respiratory virus), and these associations remained significant in  
197 multivariable analysis. Although patients with NIRV were more likely to develop pneumonia  
198 than patients with no respiratory virus, mortality was similar in patients with NIRV, in  
199 patients with influenza, and in patients with no respiratory virus, at 4-5%.

200 Few studies have evaluated the epidemiology of NIRV in patients with symptoms  
201 suggestive of acute respiratory tract infection. Tanner *et al.* performed a prospective study  
202 during the 2009-2010 winter season in Central England, both in hospitals, and in general  
203 practitioner offices [13]. The two main NIRV were RSV (31%), and picornavirus (24%), as in  
204 our study, but the authors did not test for coronavirus, and bocavirus. Ambrosioni *et al.*  
205 conducted a two year-prospective study in one referral centre in Switzerland [14], and their  
206 findings were in line with ours, with two main differences: i) coronaviruses were more  
207 heterogeneous, and included 229E, NL63, OC43, and HKU1 strains; ii) human  
208 metapneumovirus was rare, at around 5%, with no significant difference between upper and  
209 lower respiratory tract samples, and between adults younger than 65 years, and elderly.

210 Previous studies have identified age >65 years as a risk factor for NIRV, as well as  
211 chronic respiratory diseases [1,6,14,15]. For the latter, experimental studies suggested that  
212 NIRV may trigger acute exacerbation of chronic obstructive pulmonary diseases (COPD)

213 [16–18]. Interestingly, chronic respiratory diseases remained associated with NIRV in our  
214 study, even when the comparison group was patients with influenza, and even in  
215 multivariable analysis. This suggests a specific pathogenicity of NIRV in this population, that  
216 may be more prone to decompensate during NIRV infection than during influenza. Treatment  
217 with immunosuppressive drugs was also associated with NIRV in our study, whatever the  
218 comparison group, but the association was no longer significant on multivariable analysis,  
219 which suggests that confounding factors are involved. The lower prevalence of diabetes  
220 mellitus in patients with NIRV, as compared to patients with influenza, and to patients with  
221 no respiratory virus, in our study, was not expected. Diabetes has been associated with a  
222 broad range of infectious diseases [19,20], including upper respiratory tract infection in some  
223 studies [19], but not all [21]. Although the lower prevalence of diabetes in patients with NIRV  
224 as compared to patients with influenza could be related to stronger association between  
225 diabetes, and influenza, than between diabetes, and NIRV, we have no explanation for the  
226 lower prevalence of diabetes in patients with NIRV as compared to patients with no  
227 respiratory virus.

228         Our study has limitations. Firstly, we have no data to support causality between the  
229 presence of NIRV in upper respiratory samples, and the ILI that required admission. Other  
230 pathogens may be involved (e.g. bacteria), and NIRV may merely be a bystander infectious  
231 agent with no role in the symptoms reported. The lack of a control population with no  
232 respiratory symptoms is another limitation that precludes any conclusion on the pathogenicity  
233 of NIRV. Secondly, we only performed systematic tests for influenza, and a selection of  
234 NIRVs, although other pathogens have been associated with acute respiratory infections [22].  
235 Thirdly, our study was limited to influenza seasons, in one country, and its findings may not  
236 apply to other settings. However, our study has strengths, including its prospective,  
237 multicentre design, and the standardization of viral tests for all adult patients admitted with

238 predefined ILI, during three consecutive influenza seasons. These strengths, and the limited  
239 number of missing data, reduce the risk of potential biases. Our study adds another brick in  
240 the wall by contributing to better characterization of the burden of NIRV in adult patients  
241 with suspicion of acute respiratory tract infections. The identification of transmissible, NIRV,  
242 in 15% of adult patients admitted with ILI would advocate for more systematic testing of  
243 these patients, especially those with chronic respiratory diseases. This would allow early  
244 respiratory isolation, as to prevent nosocomial transmission of NIRV, which may have severe  
245 consequences on patients with chronic respiratory diseases, and patients on  
246 immunosuppressive drugs.

247

248 **Acknowledgements** The current work received no funding. However, the study sites received  
249 funding from Sanofi Pasteur and Sanofi Pasteur MSD for the FLUVAC study. Vaccine  
250 producers had no role in the study design, data analysis, decision to publish or preparation of  
251 the manuscript

252

### 253 **Compliance with ethical standards**

254 **Conflict of interest** The authors declare no competing interest related to the study. O Launay  
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256 travel support to attend scientific meetings from pharmaceutical companies.

257

258

259 **Appendix**

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281 **Fig. 1** Flow chart of patients hospitalized with influenza-like illness, and viruses detected in  
282 respiratory sample

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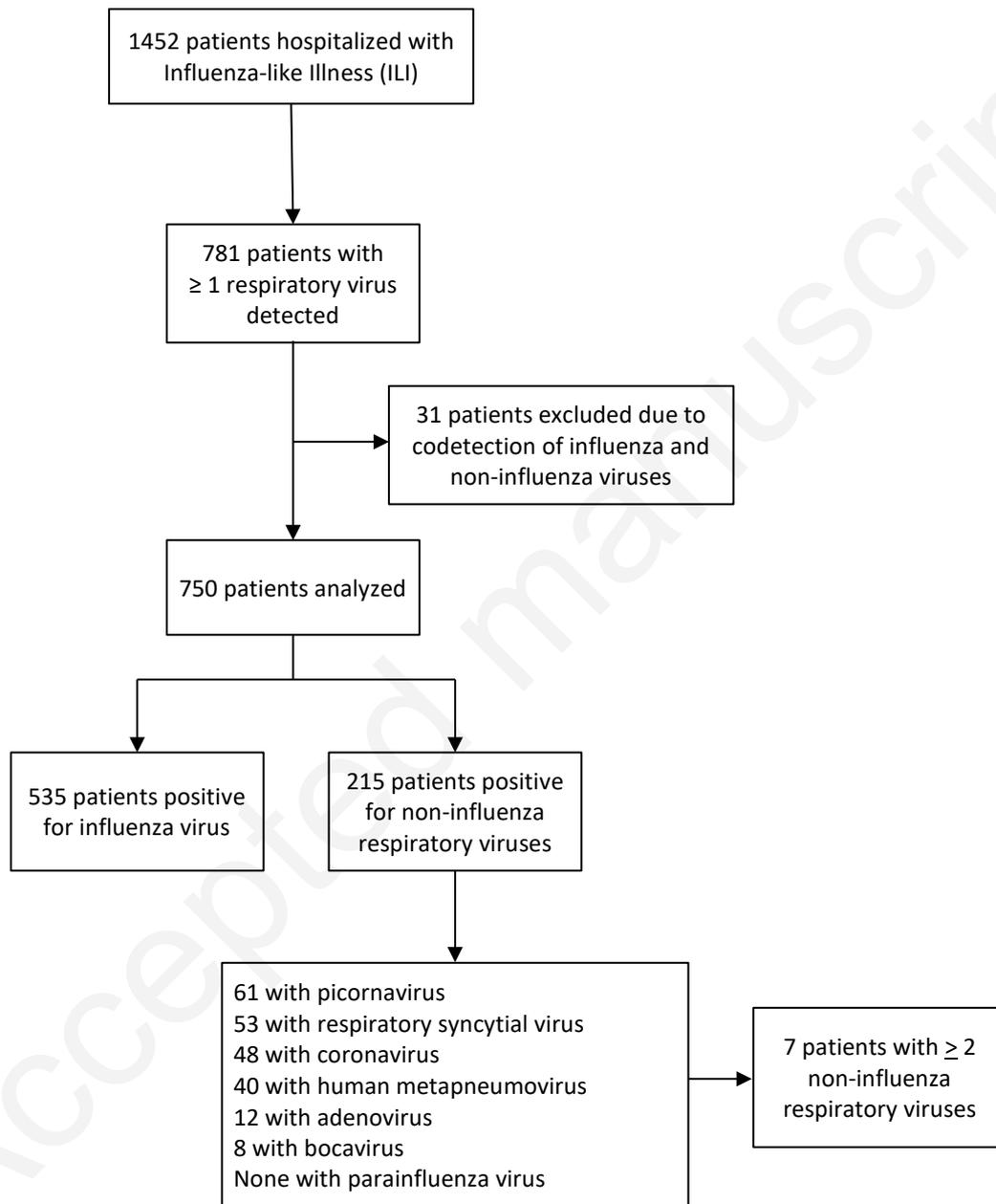
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293 **Table 1** Number and percentage of patients hospitalized with influenza-like illness who tested  
 294 positive for non-influenza respiratory viruses, and for influenza, by year.

<b>Influenza season</b>	<b>Non-influenza respiratory virus (NIRV), n (%)</b>	<b>Influenza, n (%)</b>	<b>Co-infection influenza + NIRV, n (%)</b>	<b>No respiratory virus, n (%)</b>	<b>Total</b>
<b>2012/2013</b>	64 (14%) <sup>ref</sup>	149 (33%) <sup>ref</sup>	13 (3%) <sup>ref</sup>	222 (50%) <sup>ref</sup>	448
<b>2013/2014</b>	76 (19%) <sup>NS</sup>	101 (25%) <sup>NS</sup>	11 (3%) <sup>NS</sup>	219 (54%) <sup>NS</sup>	407
<b>2014/2015</b>	75 (13%) <sup>NS</sup>	285 (48%) <sup>**</sup>	7 (1%)*	230 (38%) <sup>**</sup>	597
<b>Total</b>	215 (15%)	535 (37%)	31 (2%)	671 (46%)	1452

295  
 296 Chi square test was done to compare the evolution, with 2012/2013 as the reference season.  
 297 <sup>Ref</sup>, reference; <sup>NS</sup>, non significant; \*,  $P < 0.05$ ; \*\*,  $P < 0.001$ ;  
 298 NIRV, non-influenza respiratory virus

299  
 300

301 **Table 2** Comparison between patients who tested positive for non-influenza respiratory virus  
 302 (NIRV), patients with influenza, and patients with no respiratory virus

	<b>NIRV</b> n=215 (15%)	<b>Influenza</b> n=535 (38%)	<b>P-value for comparison between NIRV and influenza</b>	<b>No respiratory virus</b> n=671 (47%)	<b>P-value for comparison between NIRV and no virus</b>
<b>Men</b>	116 (54%)	269 (50%)	0.36	380 (57%)	0.47
<b>Median age, years (IQR)</b>	73 (60-83)	68 (53-81)	<b>0.026</b>	70 (54-83)	0.11
<b>Age &gt;= 65 years</b>	141 (66%)	310 (58%)	0.053	398 (59%)	0.10
<b>Median BMI, kg/m2 (IQR)</b>	24.5 (21-28)	24.9 (22-28)	0.25	24,8 (21-29)	0.32
<b>Chronic diseases</b>	174 (81%)	423 (79%)	0.56	537 (80%)	0.77
Chronic respiratory disease	114 (53%)	237 (45%)	<b>0.034</b>	296 (44%)	<b>0.024</b>
Chronic heart disease	90 (42%)	222 (42%)	0.93	287 (43%)	0.81
Cancer	31 (14%)	48 (9%)	<b>0.029</b>	84 (13%)	0.48
Diabetes	39 (18%)	135 (25%)	<b>0.038</b>	179 (27%)	<b>0.011</b>
<b>Immunosuppressive drugs</b>	44 (21%)	75 (14%)	<b>0.028</b>	98 (15%)	<b>0.041</b>
<b>Pregnancy</b>	4 (27%)	8 (16%)	0.45	3 (5%)	<b>0.021</b>
<b>Current smokers</b>	52 (24%)	121 (23%)	0.38	138 (21%)	0.16
<b>Median time from symptoms onset to admission, days (IQR)</b>	3.0 (2-4)	3.5 (2-4)	0.46	3.0 (2-5)	0.27
<b>Symptoms</b>					
Fever ( $\geq 38^{\circ}\text{C}$ )	169 (79%)	480 (90%)	<b>&lt;0.001</b>	520 (78%)	0.78
Weakness/Malaise	55 (26%)	165 (31%)	0.14	219 (33%)	<b>0.047</b>
Headache	47 (22%)	134 (25%)	0.33	167 (25%)	0.32
Myalgia	44 (21%)	116 (22%)	0.66	153 (23%)	0.44
Cough	167 (78%)	434 (81%)	0.28	506 (76%)	0.54
Dyspnea	160 (74%)	393 (73%)	0.78	517 (77%)	0.36
<b>Complications</b>	94 (44%)	248 (47%)	0.50	266 (40%)	0.28
Pneumonia	68 (32%)	152 (29%)	0.96	160 (24%)	<b>0.019</b>
Respiratory failure	47 (22%)	125 (23%)	0.69	135 (20%)	0.54
ARDS	20 (9%)	55 (10%)	0.78	50 (7%)	0.38
Heart failure	30 (14%)	78 (15%)	0.85	80 (12%)	0.41
ICU admission	16 (11%)	26 (10%)	1.0	39 (9%)	0.50
<b>Median length of stay, days (IQR)</b>	8 (5-17)	10 (4-23)	0.15	8 (3-16)	0.47
<b>Mortality</b>	11 (5%)	23 (4%)	0.69	32 (5%)	0.85

303 NIRV, non-influenza respiratory virus; BMI, Body mass index; IQR, Interquartile range; SD,  
 304 Standard deviation, ARDS; Acute respiratory distress syndrome; ICU, intensive care unit

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Accepted manuscript