## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | The disease burden caused by respiratory syncytial virus compared to influenza among adults: a retrospective cohort study from Eastern Finland in 2017-2018. |
| **AUTHORS** | Hämäläinen, Aleksi; Savinainen, Ellamaria; Hämäläinen, Sari; Sivenius, Katariina; Kauppinen, Juha; Koivula, Irma; Patovirta, Riitta-Liisa |

## VERSION 1 – REVIEW

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| **REVIEWER** | Ison, Michael G.<br>Northwestern Univ, Infectious Diseases |
| **REVIEW RETURNED** | 04-Mar-2022 |

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| **GENERAL COMMENTS** | I have no substantive comments to strengthen the paper. |

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| **REVIEWER** | Wang, Jianwei<br>Peking Union Medical College |
| **REVIEW RETURNED** | 15-Apr-2022 |

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| **GENERAL COMMENTS** | In this study, the authors investigated the prevalence of respiratory syncytial virus (RSV) or Influenza virus (IFV) as well as parameters related to the risk of severe infections in adult patients suffered from respiratory tract infections. They found that RSV-infected patients were considered suffered higher rate of hospitalization, incidence of pneumonia, need for antibiotics and supplementary oxygen, mortality 30 days after discharge compared with IFV-infected patients. It is important to evaluate disease burden caused by important respiratory virus, especially RSV and IFV, the major causes of lower respiratory tract infections.<br>1. My main concern is the inclusion criteria and exclusion criteria. Do the authors include only patients in whom it was possible to obtain a respiratory sample? What were the clinical characteristics of the population studied (ie, comorbidities, therapy before admission, etc)?<br>Another question is about the control. As only patients positive for RSV or IFVs were involved, how to decide the risk factor without knowing the number of patients visit the hospital during the study period, especially patients suffered from underlying diseases.<br>2. The authors used molecular test for the presence of RSV and IFV. Whether other common respiratory pathogens were screened and how about the distribution?<br>3. The authors should describe other conventional microbiology tests in addition to culture for etiology as related results were indicated in the paper.<br>4. According to the literature, RSV infections would cause mainly mild symptoms in young adults and higher rate of symptomatic |

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| | infections in elderly, while IFVs normally caused symptomatic infections across different age groups. It is considerable that RSV-positive patients were older and had more underlying conditions as these factors would be risk factor for RSV-infections. The conclusion that RSV-positive patients were older with higher rate of underlying diseases than that of IFVs should consider the power of the demographic information?<br>5. In table 1, the age range, mean, median (IQR) should be provided. The corresponding number in line titled “number of underlying conditions, (n) mean (SD)” should be modified as no number related to “n”. |

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| **REVIEWER** | Yu, Caizheng<br>Huazhong University of Science and Technology |
| **REVIEW RETURNED** | 09-Oct-2022 |

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| **GENERAL COMMENTS** | 1、In Table 2, “13,4” might be a writing error (page 7, line 32)<br>2、”BMI was categorized to <20 and >30” (page 5, line 34), reference is the needed for grouping.<br>3、In Table3 ”Number of underlying conditions” could be shown as medians (IQR)<br>4、Whether this study has received ethical approval？(page 5, line 42) The subjects of the study are patients, and ethical approval is still required. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Dr. Michael G. Ison, Northwestern Univ
Comments to the Author:
I have no substantive comments to strengthen the paper.

Reviewer: 2
Dr. Jianwei Wang, Peking Union Medical College
Comments to the Author:
In this study, the authors investigated the prevalence of respiratory syncytial virus (RSV) or Influenza virus (IFV) as well as parameters related to the risk of severe infections in adult patients suffered from respiratory tract infections. They found that RSV-infected patients were considered suffered higher rate of hospitalization, incidence of pneumonia, need for antibiotics and supplementary oxygen, mortality 30 days after discharge compared with IFV-infected patients. It is important to evaluate disease burden caused by important respiratory virus, especially RSV and IFV, the major causes of lower respiratory tract infections. My main concern is the inclusion criteria and exclusion criteria. Do the authors include only patients in whom it was possible to obtain a respiratory sample? What were the clinical characteristics of the population studied (ie, comorbidities, therapy before admission, etc)? Another question is about the control. As only patients positive for RSV or IFVs were involved, how to decide the risk factor without knowing the number of patients visit the hospital during the study period, especially patients suffered from underlying diseases.

The study we conducted was a retrospective cohort study. In the guidelines of the study hospital, all patients with flu-like symptoms are tested using nasopharyngeal samples for influenza and RSV during the epidemic season between November and May. However, the decision on whether to take

the test from an individual patient was made by the attending physician, and our study did not influence on attending physicians decision whether to take the sample from individual patients. We included all patients with positive test results to our retrospective study. Only patients under 18 years of age, patients with mixed influenza- and RSV-infections and patients with lack of availability of electronical medical records were excluded.

About the control, our study focuses on RSV, and since RSV and influenza were widely screened among patients with flu-like symptoms in the study hospital, we chose to compare RSV to influenza. During the design of the study, we considered a control group of patients with influenza-like illness and negative test result from RSV and influenza. However, the negative control group would have been very heterogenous, and therefore we decided to compare patients with RSV only to patients with influenza to gain reliable and comparable data. Due the retrospective and descriptive nature of our study, we did not calculate risk factors for specific outcomes before collecting the data.

The clinical characteristics of the population studied are cited in the first chapter of Discussion and more specific in the reference 22. The cited THL's morbidity index, which takes into account seven different disease groups and four different weight aspects. The disease groups included in the index are cancers, coronary artery disease (CAD), cerebrovascular diseases (CVD), musculoskeletal diseases (MSD), mental disorders, accidents and dementia Eastern Finland having a greater prevalence of diseases compared to other regions in Finland. In our study area in Central and Eastern Finland, the number of comorbidities in general population is high. Only patients with electronical medical record available were involved in the study, and therefore e.g., patients treated in regional hospitals before transmission to study hospital were not involved in the study due the missing electronical records.

The Objectives section was refined to clarify the comparison between patients with RSV and influenza. Also, the significance of morbidity in the study population for our study was highlighted.

2. The authors used molecular test for the presence of RSV and IFV. Whether other common respiratory pathogens were screened and how about the distribution?

In the study hospital, all patients with respiratory symptoms are routinely tested for influenza and RSV during the flu season. The routine test in question does not screen other respiratory pathogens than influenza or RSV. Screening for other respiratory pathogens is possible, but only individual patients with severe symptoms of unknown cause are screened for other pathogens. Therefore, data from other respiratory pathogens is available for some of the patients treated in the study hospital, but not in significant amounts. Therefore, we did not include data from other respiratory pathogens to our study.

3. The authors should describe other conventional microbiology tests in addition to culture for etiology as related results were indicated in the paper.

In the detection of influenza and RSV, polymerase chain reaction (PCR) -tests were used, not cultures. Laboratory methods section in Methods was corrected to specify the test in use. The other microbiology tests available during the study were nasopharyngeal test for other respiratory viruses (adenovirus, enterovirus, parainfluenza, metapneumovirus, bocavirus, rhinovirus, coronaviruses NL63, 229E, OC43), nasopharyngeal test for respiratory bacteria (Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumophila, Bordatella pertussis, Bordatella parapertussis) and specific nucleic acid tests, for example for Pneumocystis jirovecii. As described before in comment 2, there was no significant amount of data from other microbiology tests since only influenza and RSV

were routinely tested from patients with respiratory symptoms, and therefore we did not include results from other microbiology test in this study. Although COVID-19 was briefly discussed in the Discussion regarding the significance of obesity to hospitalization, our study was conducted before the COVID-19 pandemic.

4. According to the literature, RSV infections would cause mainly mild symptoms in young adults and higher rate of symptomatic infections in elderly, while IFVs normally caused symptomatic infections across different age groups. It is considerable that RSV-positive patients were older and had more underlying conditions as these factors would be risk factor for RSV-infections. The conclusion that RSV-positive patients were older with higher rate of underlying diseases than that of IFVs should consider the power of the demographic information?

In the conclusion above demographic information is essential, but although the high general morbidity in the population studied, patients with RSV in our study did not have an exceptionally high rate of comorbidities compared to previous similar studies [7,9,14,15]. This information was added into the first chapter of Discussion. Although not novel, this finding strengthens earlier findings [8,14,15,21], and our study adds new information for solid malignancies and chronic kidney disease, which were shown to be independent risk factors for death among RSV-infected patients.

5. In table 1, the age range, mean, median (IQR) should be provided. The corresponding number in line titled “number of underlying conditions, (n) mean (SD)” should be modified as no number related to “n”.

We calculated and added range and median (IQR) to all continuous variables in Tables 1, 2 and 3. Since previously only mean (SD) was used, and therefore we chose two-tailed t-test for continuous variables in the statistical analyses, after consulting statistician we decided to run new statistical analyses with Mann-Whitney U test among all continuous variables. The Analyses section in Methods, Results (Characteristics chapter 1, Hospitalization chapter 1, Factors associated with hospitalization and mortality chapter 1) and Tables 1, 2 and 3 were corrected according to the new statistical methods used.

After new analyses, the duration of treatment in the ICU was found to be longer in influenza-infected patients than those with RSV. This interesting finding was added to Results (Hospitalization, chapter 1) and Discussion (chapter 2). Also, our previous finding stating that non-surviving RSV-infected patients had significantly more underlying conditions in general than survivors was no longer statistically significant. The statement was therefore removed from Abstract (Results), Results (Factors associated with hospitalization and mortality, chapter 1) and Discussion (chapter 5). With all other continuous variables, the results remained unchanged. “N” was removed from all tables from the number of underlying conditions.

Reviewer: 3
Dr. Caizheng Yu, Huazhong University of Science and Technology
Comments to the Author:
1. In Table 2, “13,4” might be a writing error (page 7, line 32).

Typing error corrected from 13,4 to 13.4.

2. BMI was categorized to <20 and >30” (page 5, line 34), reference is the needed for grouping.

We changed the categorization from <20 kg/m^2 and >30 kg/m^2 to commonly used definitions of underweight (BMI < 18.5 kg/m^2) and obesity (BMI ≥ 30 kg/m^2). These classifications for BMI are in use by the NIH and the World Health Organization (WHO) for White, Hispanic, and Black individuals (Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1-253). The previous article cited was also added to References [23]. Instead of previously comparing patients with certain BMI to all other patients, we decided to compare underweight and obese patients to patients with BMI between underweight and obesity (BMI greater than or equal to 18.5 to 29.9 kg/m^2). New statistical analyses were run with the new limits, but no significant changes were found. Methods (Data Collection, Analysis), Tables 3, 4, 5 and Discussion (chapter 6) were corrected to reflect the changes made.

3. In Table3 ”Number of underlying conditions” could be shown as medians (IQR).

We calculated and added range and median (IQR) to all continuous variables in Tables 1, 2 and 3. Please see Reviewer 2 comment 5 for details.

4. Whether this study has received ethical approval? (page 5, line 42) The subjects of the study are patients, and ethical approval is still required.

This registry study has received ethical approval from the local ethics committee (the Research Ethics Committee of the Northern Savo Hospital District; 1107/13.02.00/2018). In the article, the ethical approval statement is located between Discussion and References according to the submission guidelines. In the Ethics approval, the ethical approval was moved before the statement the study was conducted according to the principles expressed in the Declaration of Helsinki to highlight the ethical approval.