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# Mortality and morbidity of Human Metapneumovirus infection in the pre COVID19 Era, the value of of Charlson Comorbidity Index on outcome predictions

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## Abstract

**Abstract Introduction:** Human metapneumovirus (HMPV) was recently recognized as an important cause of seasonal respiratory tract infections mainly in children and immunocompromised adults. The use of Charlson Comorbity index (CCI) to predict outcome in hospitalized patients has been validated in several settings. **Objective**: Describe the clinical characteristics of adult patients with HMPV infection, evaluate the value to the CCI in predicting outcome. **Methods**: Single center retrospective chart review study of hospitalized patients with HMPV infection in 2017. **Results**: 22 adult patients with a mean age of 65 years were reviewed. The mean CCI was 4.6±2.6. The overall mortality was 22%. Abnormal chest radiograph (CXR) was reported in 15 patients. CCI was not different between survivors and non survivors. Non survivors were more likely to have abnormal CXR and higher fever at the time of diagnosis, required mechanical ventilation or were treated for other concomitant infections. **Conclusion:** The average of CCI was 4.5 which was not significantly different between survivors and non survivors. Mortality rate was elevated at 22% and is likely associated with admission to the ICU and presence of another concomitant infection.

## Introduction

Human metapneumovirus (HMPV) is a paramyxovirus that causes respiratory tract infections in humans. It was discovered in 2001 in the Netherlands. Infection is most common in winter and spring in temperate climates. This pathogen commonly affects children however adults are affected as well. HMPV is like Respiratory Syncytial Virus (RSV) and has been frequently compared to it. Transmission from person to person is thought to be through nasopharyngeal secretions (1). Incubation period is thought to be five to six days in most cases. Clinical manifestations vary in severity; in the adult population they commonly include cough, nasal congestion, rhinorrhea, dyspnea, hoarseness, wheezing, and fever to a lesser extent. Laboratory studies are generally nonspecific but may include leukocytosis, rise in transaminases or worsening kidney function. Chest radiograph most often is normal (2). The clinical course of HMPV infection is generally mild and may be asymptomatic. Young children and geriatric patients generally are thought to have the most severe clinical manifestations (3). Children have traditionally been studied more extensively since the disease is more common in this population. The increased number and severity of underlying comorbidities may predispose to a worse outcome. HPMV was reported to have a higher prevalence among Human Immunodeficiency Virus infected individuals (4) and leads to devastating illness in patients with hematologic malignancies (5).

HMPV has been demonstrated to affect type 2 alveolar epithelial cells and bronchial cells in Macaques. It has been shown to cause alveolar and interstitial inflammation (6).

Because HMPV tends to occur in the winter and early spring, it may frequently be associated with a coinfection with another virus or bacteria. Dual infections can occur up to 22% (7) and may lead to a more severe disease outcome as well. Up until recently it was difficult to estimate

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the prevalence of this infection however with the increasing popularity of multiplex respiratory viral PCR, HMPV is detected much more efficiently.

In this manuscript we will discuss the results of our retrospective study of all adult patients diagnosed with HPMV admitted to our hospital during the year 2017. We will describe the spectrum of clinical manifestations and try to determine the usefulness of the Charlson Comorbidity Index (tool used since 1987 to predict the mortality associated with certain underlying chronic diseases) to predict worse outcome. We hypothesized that similarly to COVID19, infection due to HMPV may be associated with greater morbidity and mortality especially in patients who have a high Charlson Comorbidity Index. Our hospital serves the lower Hudson Valley of New York State.

**Methods**

a- Data collection

This is a retrospective cohort study; we conducted a chart review of all adults (18 years or more) patients diagnosed with HPMV admitted to our hospital in 2017.

Demographics, clinical, laboratory, radiographic, treatments and outcome data were collected at the time of admission or the time when the multiplex PCR was taken for patients who developed the infection during hospitalization. The Charlson Comorbidity Index scores were calculated for every patient.

b- Statistical analysis

Collected data are summarized using descriptive statistics, mean median and standard deviation for continuous variables, and numbers and percentages for categorical variables. To assess if there is significant relationship between two categorical variables among survivors and non survivors, we used X2 and Fisher exact test analysis while for continuous variables we used the Student T test analysis. A p- value less than 0.05 was considered significant.

**Results**

In this retrospective study we found 22 hospitalized adult patients that were diagnosed with human metapneumovirus infections, 20 of them community acquired and 2 nosocomial. The clinical characteristics of those patients can be reviewed in detail in table1. In summary the mean age was 65 and 50 % were female. The mean duration of illness prior to diagnosis was 4.5 days. Most patients complained of cough and dyspnea, 85.7% and 71% respectively. Fever and rhinorrhea were reported only in 36.3% and 38%.

Sore throat and myalgia were even less frequently reported in 14.2% and 23.8% respectively.

The mean temperature at the time of diagnosis was 98±1.5. 68% had an abnormal chest x-ray. Leucocyte count was usually normal with a mean of 8.4±4.1. The mean CCI was 4.6±2.6 (1-11). The overall length of hospital stay ranged from 2 to 28 days with an average of 10 days (excluding the 2 nosocomial cases). About 36.3 % (8/22) of patients required care in the intensive care unit (ICU) for an average length of stay of 3±5.8 days (excluding one nosocomial case diagnosed in the ICU). 22% (5/22) of patients died (Table 1). Among the 15/22 patients who had abnormal chest radiograph (CXR) most 13/15 had bilateral infiltrates (5 were alveolar versus 6 interstitial and 2 mixed). All patients who died had an abnormal CXR with a trend to statistical significances. Compared to the group of patients who survived the group of patients who died did not have a significant statistical difference in terms of CCI, age, gender and ethnicity, smoking or alcohol use. Patient who died were more likely to have higher fever at the time of diagnosis but other vital signs such as heart rate, blood pressure, oxygenations, respiratory rate were not significantly different among the two groups.

Patients who were admitted to the ICU either required mechanical ventilation or were treated for other concomitant infections. They were more likely to die and had longer ICU stay compared to those who survived (Table 2).

**Discussion**

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Our Study is the first to evaluate the Charlson Comorbidity Index in adult patients hospitalized with acute respiratory infection secondary to HMPV and look at its predictive value on mortality in this patient population. CCI was initially proposed in 1987 and was tested for its ability to predict risk of death from comorbid disease in a 10-year follow-up Cohort (9). It has been validated in patients with renal cell carcinoma (10) post radical cystectomy (11) and internal medicine related complications post hip arthroplasty (12). It proved to be good at prediction of long-term functional outcome for the stroke population (13). It is also proved to independently predicts short- and long-term mortality in acutely ill hospitalized elderly adults (14).

While the CCI was not found to be associated with an increased risk of mortality in our cohort of HMPV infection, an elevated CCI was shown recently to predict poor prognosis in hospitalized patient with coronavirus disease (COVID19) and end stage renal disease on hemodialysis (15) and in general in patients with COVID 19 in a recent meta-analysis (16). In another study by Setter et al, although the Charlson Comorbidity Index Score was different between survivors and non survivors in patients with severe acute respiratory infections, its performance was not optimal (17). In that study most patients studied had influenza pneumonia and few had HPMV. The low number of patients in our study precludes us to make strong conclusions regarding the value of CCI, however it was noted that most patients had a high CCI with a mean of 4.6 which explains the high mortality rate of 22% which is not unusual and was even reported to be 50% in an outbreak among elderly patients in a long-term care facility (LTCF) (18).

This mortality rate even exceeds that related to COVID19 in LTCF which was reported recently to be 14% (153751/1090729) (19). It is worth noting that unlike COVID19, HMPV causes severe disease in young children ranging from croup like, asthma exacerbations, bronchiolitis and pneumonia with a peak age of ranging from 5 to 22 months old which is older than those with RSV (20). Unlike infections due to SARS-Cov2, HMPV infections are seasonal with winter epidemics occurring from December to April in the northern hemisphere at the same time or just after RSV epidemics. This is likely due to the lower transmissibility of HMPV which is usually transmitted by contact with contaminated surfaces as opposed to SARS-Cov2 which is more transmissible, mainly via respiratory droplets and contact (21) and possibly airborne (22). In Our Study we noted that patients requiring ICU care and mechanical ventilation and those with bacterial or fungal superinfection had worse outcome and were more likely to die which is not unusual and seen in patients with influenza and COVID19 as well (23). In addition, having higher fever and abnormal CXR may indicate a worse outcome. The CXR findings were similar to what is seen with influenza or RSV lower respiratory tract infections which is different than radiographic findings described with COVID19 which are easily recognized due to its characteristic peripheral distribution (24). Other features that distinguish HMPV infection from the COVID19 due to the Omicron variants specifically is that most patients complained of cough and dyspnea, 85.7% and 71% respectively while rhinorrhea with nasal congestion, sore throat and myalgia were even less frequently reported in 38%, 14.2% and 23.8% respectively which is usually more prominent with the Omicron variants of SARS-Cov2 related infections with 70% of patients presenting with sore throat (25).

## Conclusion

We described the clinical characteristics and outcomes of HMPV infection in 22 adult patients in an inpatient setting and how it differs from COVID19. Many patients had comorbid conditions with an average CCI of 4.5 which was not significantly different between survivors and non survivors. The mortality rate was elevated at 22% and associated with admission to intensive care unit as well as having another concomitant infection. Larger studies in adults are warranted to better understand which factors are more likely to increase morbidity and mortality in this patient population.

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Table 1. Clinical characteristics of study patients

| | Mean ±SD (range) or n/N(%) |
|---|---|
| Age, years | 65±17(33-95) |
| Sex(n), males | 11/22(50%) |

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| | Mean ±SD (range) or n/N(%) |
|---|---|
| Duration of illness prior to diagnosis, days | 4.5±3.5 (1-4) |
| Reported fever | 8/22 (36.3) |
| Rhinorrhea | 8/21 (38%) |
| Cough | 18/21 (85.7%) |
| Dyspnea | 15/21 (71.4%) |
| Sore throat | 3/21 (14.2%) |
| Myalgias | 5/21 (23.8%) |
| CCI | 4.6±2.6 (1-11) |
| Abnormal chest Xray | 15/22 (68.2%) |
| Temperature, F | 98±1.5 (96.9-101.8) |
| O2 Saturation, % | 95±2 (90-99) |
| Leukocytes x$10^3$/μL | 8.4±4.1 (2.6-17) |
| Duration of Steroids, days | 7±7.7 (0-24) |
| Requiring ICU care | 8/22 (36.3) |
| Hospital days | 10±8.7 (2-28)* |
| ICU days | 3±5.8 (0-23)** |
| Died | 5/22 (22%) |

SD: Standard Deviation, n: number of patients, N: total number of patients.

CCI: Charlson comorbidity index, ICU: Intensive care unit, * excluding 2 nosocomial cases, **excluding one case diagnosed in ICU.

Table2. Clinical, laboratory and radiographic characteristics of patients with Human Metapneumovirus at presentation, stratified by outcome.

| | Alive N=17 Mean ±SD or n(%) | Died N=5 Mean ±SD or n(%) | Student T test p value | Pearson Chi-Square p value/ Fisher's exact test p value |
|---|---|---|---|---|
| Age, years | 65± 18 | 65±15 | NS | |
| Sex, male | 10 (58%) | 1 (20%) | | NS |
| Race, Non White | 5 (29%) | 1 (20%) | | NS |
| Smoking | 3 (17.5%) | 3(60%) | | NS |
| ETOH use | 4 (23.5%) | 1(20%) | | NS |
| CCI | 4.5±3 | 5±3 | NS | |
| CCI>4 | 6 (35%) | 2 (40%) | | NS |
| SBP, mmHg | 121±19 | 120±24 | NS | |
| HR,beats/min | 89±17 | 98±19 | NS | |
| RR breath/min | 21±3 | 23±7 | NS | |
| Temperature, F | 98±1.2 | 99.7±1.9 | 0.025 | |
| O2 saturation% | 96±2 | 96±3 | NS | |
| Hospital stay,days* | 8.3±7.5 | 16.5±10.7 | NS | |
| Requiring ICU care | 4 (23.5%) | 4 (80%) | | 0.021/0.039 |
| ICU stay, days** | 1.6±3.2 | 9.5±10 | 0.011 | |
| Duration of illness prior to diagnosis, days | 4±3 | 6±4 | NS | |
| pO2, mmHg | 67±15 | 60±15 | NS | |

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| | Alive N=17 Mean ±SD or n(%) | Died N=5 Mean ±SD or n(%) | Student T test p value | Pearson Chi-Square p value/ Fisher's exact test p value |
|---|---|---|---|---|
| Leukocytes $x10^3/\mu L$ | 8.2±3.8 | 9.1±5.7 | NS | |
| Mechanical ventilation | 4 (23.5%) | 4 (80%) | | 0.021/0.039 |
| Acute kidney Injury | 3 (17.5%) | 1 (20%) | | NS |
| Dyspnea on presentation | 11(64.7%) | 4 (80%) | | NS |
| Presence of infiltrates on chest radiography | 10 (58%) | 5 (100%) | | 0.082/0.135 |
| Corticosteroid use | 5 (29%) | 3 (60%) | | NS |
| Concurrent Infections | 2 (11.7%) | 3 (60%) | | 0.024/0.055 |

SD: Standard Deviation; N: total number of patients in a category; n:number of patients; %:percentage; CCI: Charlson com