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Title: Prevalence and clinical significance of multiple simultaneous respiratory viral infection in adults
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Introduction:

In the past decade, respiratory multiplex polymerase chain reaction (RM-PCR) has been used increasingly for the detection of multiple respiratory viruses in each respiratory specimen. The amplification of multiple viral DNA sequences at once gives us an accurate estimation of viral load, which can be quantitatively interpreted by the cycle threshold (Ct) value. RM-PCR tests have higher sensitivity and efficiency compared to existing detection tests such as serological tests or culture.

Multiple respiratory viral infection (MRVI) diagnosed by RM-PCR is well known in the paediatric literature, however, less in adult research.

Aims:

- To find the prevalence of MRVI diagnosed in adults tested with RM-PCR during winter (May-October) in 2016 and 2017.
- To assess the background co-morbidity of adult patients with MRVI and compare (via Ct values) the severity of respiratory disease between this group and patients with single infections.
- To undertake a preliminary investigation on the possible clinical significance of MRVI in adults.

Impact: This project may help improve our understanding on the clinical significance of MRVI in adults.

Method:

Patients aged 20 years and above who had at least one positive viral isolate in the RM-PCR test done in the Canterbury region between May and October 2016 and 2017 were identified from Canterbury Health Laboratories Delphic Information System (CHL DIS). A retrospective observational study was carried out with these patients. Ct values from RM-PCR tests were recorded from CHL DIS. Patients' clinical information regarding age, sex, hospitalization and history of chronic respiratory disease (CRD) were accessed through Health Connect South. To have a control group to compare with, we matched each MRVI patient with at least 5 patients who were within 10 years age range and had single infections of the same viruses within 30 days. When evaluating the possible clinical significance of MRVI, length of hospitalization was used as a broad marker of disease morbidity. Nosocomial infections were noted. As age was a potential confounder, analyses were adjusted for age based on 4 age groups: 20-39, 40-59, 60-79, ≥ 80 years. Data was analysed with descriptive statistics and two-tailed t-tests were performed to find the p-values. A p-value < 0.05 was considered statistically significant.

Results:

For the time period considered, 3032 patients were identified, 188 (6.2%) of which had MRVI. Of the 188 co-infected patients, 6 had triple infections and 1 had a quadruple infection. MRVI was most common in the 60-79 age group (30%) and was least common in the ≥ 80 age group (20%). The most common co-pathogen was Influenza-A (n=99), followed by Rhinovirus (RV)

(n=71) and Coronavirus OC43 (n=37). Age-controlled matched patients with single infection comprised 51% (1552) of all patients.

The greatest background co-morbidity for the MRVI group was CRD. However, as this part of the research was not designed as a case-control study, a comparison was not available at this stage. There was no significant difference in the mean Ct values between the MRVI group and the control group for most viruses.

Regarding hospital admission, 72% of patients in MRVI group and 71% in control group were hospitalized. The length of hospitalization for the MRVI group and control group were a mean of 8 and 5 days respectively. The mean difference was statistically significant ($p=0.0021$), suggesting that MRVI was associated with longer hospitalization. When we stratified by age, this association still held across all age groups except for the 20-39 age group, but it was not statistically significant. Only the 2 most common combination of MRVI (Influenza viruses (Flu) + Coronaviruses (CoV) (20%), Flu+RV (15%)) were analysed in more detail as they had greater statistical power compared to the other combinations. Patients with Flu+RV co-infections on average had statistically significantly longer hospitalization than either virus alone. When we stratified by age, this effect still held across all age groups. Patients with Flu+CoV co-infections on average had statistically significantly longer hospitalization than CoV alone. When we stratified by age, this effect still held across all age groups except for the 20-39 age group. However, for both co-infections, the sample size of each age group was too small to prove statistical significance. For both co-infections 34% of all hospitalized patients had nosocomial infections, whereas for each virus alone, it was less than 7%. Thus, hospital-acquired secondary respiratory infection could be a reason for prolonged hospitalization in MRVI patients.

Conclusion:

MRVI was detected in 6.2% of patients who had at least one positive viral isolate in the RM-PCR test done between May and October 2016 and 2017. There was no significant difference in the mean Ct value of the viruses between the MRVI group and control group. Although there was no significant difference in the rate of hospitalization between MRVI group and control group, MRVI was associated with longer hospitalization in adults. We found this association after stratifying by age, indicating that age wasn't a confounder. This suggested that MRVI has some prognostic significance. We also found evidence of nosocomial infection, especially in the MRVI group. Further work is needed to tease out any further confounders associated with longer hospitalization in adult patients with MRVI.