Original Article

Clinical characteristics and outcomes of human rhinovirus positivity in hospitalized children

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Abstract:

BACKGROUND: The clinical relevance of positive human rhinovirus (HRV) in hospitalized patients is unclear. Our objective was to describe the clinical characteristics and outcomes of HRV positivity in a heterogeneous population of hospitalized children, compared to those positive for another respiratory virus and those where no respiratory virus was detected.

METHODS: A retrospective case–control study of children hospitalized between January 2014 to April 2015 who had a respiratory viral specimen collected. Clinical and laboratory data were collected, and baseline characteristics and clinical variables were compared.

RESULTS: During the study period, there were 671 specimens obtained from 577 patients that were processed for the respiratory viral polymerase chain reaction assay, of which 198 were positive for HRV, 167 positive for another respiratory virus, and 306 where no respiratory virus was detected. A history of asthma was significantly associated with HRV-positive patients (odds ratio [OR] 3.71; $P < 0.001$). On multivariate analysis, HRV-positive patients had a higher requirement for mechanical ventilation (OR 1.44), lower rates of readmission (OR 0.53), and lower mortality (OR 0.35) compared to patients with no respiratory virus isolated; however, none were statistically significant. HRV-positive patients did have a significantly shorter length of stay (LOS) compared with patients with no respiratory virus isolated (difference–0.35; $P = 0.001$). Similar outcomes were seen in patients positive for other respiratory viruses.

CONCLUSIONS: HRV-positive hospitalized pediatric patients with a heterogeneous set of clinical diagnoses had higher association with asthma compared to patients who had another, or no, respiratory virus isolated. HRV-positive patients had shorter LOS compared to patients who had no respiratory viruses isolated. These findings suggest that HRV positivity in hospitalized pediatric patients may not lead to adverse clinical outcomes, although asthma is a risk factor regardless of clinical comorbidities and diagnoses. Further research is warranted to understand the predisposition of asthma to HRV positivity.

Keywords:

Children, comorbidity, diagnostics, hospitalization, respiratory virus, severity

Human rhinovirus (HRV) is a cause of the common cold and has been implicated in acute lower respiratory tract infections[1-6] as well as asthma exacerbations.[7-11] Although HRV has been associated with acute life-threatening events in infants[12] and acute respiratory hospitalizations in children,[1-6,13] it has also been detected in up to 44% of asymptomatic cases,[14-18] making interpretation, and clinical relevance, of a positive HRV result in children unclear.

Few studies have looked at the relevance of HRV positivity on clinical outcomes in hospitalized children,[1] nor accounted for a broad spectrum of clinical comorbidities and diagnoses. The objective of our study was to examine HRV positivity in hospitalized children with heterogeneous

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clinical comorbidities and diagnoses, and to compare characteristics, clinical management and outcomes with other hospitalized children who received respiratory viral testing during the same period.

Methods

We conducted a retrospective case–control study from January 2014 to April 2015 of patients within the Fairview Health System network of Minnesota. This health system includes four community hospitals with a pediatric unit, and the University of Minnesota Masonic Children's Hospital, a 96-bed academic tertiary care children's hospital.

Our inclusion criteria consisted of children up to 18 years of age who had a respiratory viral polymerase chain reaction (PCR) specimen obtained during hospitalization. Patients who were discharged from the emergency department were excluded. If a patient had multiple positive respiratory viral specimens during a hospital encounter, only the first positive result was selected. Readmissions within a 2-month interval were excluded and readmissions ≥2 months intervals were treated as independent events.

Clinical diagnoses and comorbidities (asthma, cystic fibrosis, other pulmonary disorders, cardiac, renal, hematologic, neurologic, and metabolic disorder) were based on the International Classification of Diseases, Ninth Revision codes and laboratory results obtained closest to the time of the respiratory viral test, hospital length of stay (LOS), 14-day readmission, and mortality were extracted from the medical record. Criteria for hospitalization, respiratory viral testing, and discharge was based on clinical judgment of the physician and based on presenting symptoms and signs, underlying comorbidities, suspected or confirmed clinical diagnoses, and laboratory results. As respiratory viral testing was performed at the discretion of the provider and is not part of routine care, each patient had a clinical indication to warrant testing. This study was approved by the Institutional Review Board of the University of Minnesota.

The respiratory viral PCR test has been previously described.[19] The assay (GenMark's eSensor Respiratory Viral Panel, GenMarkDx, Carlsbad, CA) incorporates a multiplex reverse transcription-PCR amplification followed by suspension array detection. The respiratory viruses tested include adenovirus Groups B, C, and E; influenza A virus (including subtype determination); influenza B virus; human metapneumovirus; parainfluenza virus types 1, 2, and 3; respiratory syncytial virus types A and B; and HRV.[19] The test was carried out at the Infectious Diseases Diagnostic Laboratory for the entire Fairview Health System, commencing on January 8, 2014. It was performed daily, Monday to Friday, with results typically available in 24 h.

Statistical analysis

Patients were sorted into three groups based on whether their respiratory viral PCR detected HRV with or without another respiratory virus, some other respiratory virus, or no respiratory virus. Primary outcome measures were requirement for mechanical ventilation, LOS, 14-day readmission, and mortality. Descriptive statistics were shown as frequencies and percentages, or as a mean/median (range), as appropriate. Natural log transformation was applied for data with skewed distribution. P value is calculated from two-sample t-test or Wilcoxon signed-rank test for continuous variables and Chi-square test for categorical variables. On univariate analysis after applying Bonferroni's adjustment for multiple comparisons, $P \leq 0.05/3 = \leq 0.016$ was considered statistically significant. Multivariate analysis using ANOVA was performed controlling for age at admission, sex, race, medical unit, and number of comorbidities. P value was adjusted for multiple comparisons by Tukey's method and $P \leq 0.05$ was considered statistically significant. During summer-fall of 2014, there was an epidemic of *Enterovirus* D68 which cross-reacted with HRV on the respiratory viral PCR assay.[20] To account for this potential confounder, we performed a separate analysis excluding all data during this period (August 2014–January 2015). All data management was performed using Microsoft Excel 2011 v. 14.5.6 and statistical analyses were performed using SAS v. 9.3 (SAS Institute, Cary, NC). Graphs were plotted in R (http://www.r-project.org).

Results

Over the 16-month period, there were a total of 671 respiratory viral PCR specimens obtained from separate hospital encounters of 577 patients. Of these, 198 specimens were positive for HRV only, 167 were positive for another respiratory virus with or without HRV, and 307 had no respiratory virus detected [Table 1]. Respiratory viruses detected included HRV (55.7%), respiratory syncytial virus (21.8%), *Human metapneumovirus* (11.3%), adenovirus (9.0%), parainfluenza type 3 (6.5%), influenza A (4.0%), influenza B (2.8%), parainfluenza type 2 (1.7%), and parainfluenza type 1 (0.9%).

The mean age for patients who tested positive for HRV was 3.23 years, compared to 3.06 for patients positive for other respiratory viruses. Patients where no respiratory virus was detected were significantly older at 6.09 years ($P < 0.001$). In addition, patients with no respiratory virus detected had more comorbid

Table 1: Characteristics of the three respiratory virus test study populations

Characteristic	HRV-positive (*n*=198)	ORV-positive (*n*=167)	RV-negative (*n*=307)	*P*
Age (years), mean (range)	3.23 (0.01-18)	3.06 (0.03-18)	6.07 (0-18)	<0.001
Male sex (%)	104 (52.5)	89 (53.3)	161 (52.6)	0.99
Race/ethnicity (%)				
Caucasian	119 (61.7)	99 (62.3)	186 (65.7)	0.72
African-American	34 (17.6)	34 (21.4)	41 (14.5)	
Hispanic	12 (6.2)	13 (8.2)	20 (7.1)	
Other[a]	28 (14.5)	13 (8.2)	36 (12.7)	
Location where viral test was ordered (%)				
Inpatient	172 (86.9)	153 (91.6)	239 (78.1)	<0.001
PICU	26 (13.1)	14 (8.4)	67 (21.9)	
Comorbidity (%)				
Total number, mean (range)	2.5 (0-8)	2.3 (0-8)	3.1 (0-8)	<0.001
Any comorbidity	176 (88.9)	148 (88.6)	276 (90.2)	0.91
Asthma	77 (38.9)	38 (22.8)	60 (19.6)	<0.001
Cystic fibrosis	15 (7.6)	23 (13.8)	57 (18.6)	0.008
Other pulmonary	15 (7.6)	8 (4.8)	26 (8.5)	0.34
Cardiac	60 (30.3)	41 (24.6)	125 (40.9)	0.005
Hepatic	15 (7.6)	7 (4.2)	33 (10.8)	0.03
Renal	11 (5.6)	18 (10.8)	48 (15.7)	0.002
Hematologic	84 (42.4)	63 (37.7)	175 (57.2)	<0.001
Metabolic, including diabetes	137 (69.2)	131 (78.4)	248 (81.1)	0.01
Neurologic	26 (13.1)	18 (10.8)	67 (21.9)	0.005
Immunosuppression	58 (29.3)	37 (22.2)	107 (35.0)	0.09
Pregnancy	0	0	0	N/A
Morbid obesity	1 (0.5)	0	3 (1.0)	0.41
Long-term (current) use of aspirin	0	0	0	N/A
Other clinical diagnoses (%)				
Viral pneumonia	19 (9.6)	24 (14.4)	4 (1.3)	<0.001
Bacterial pneumonia	45 (22.7)	59 (35.3)	71 (23.2)	0.01
Bacteremia	9 (4.6)	2 (1.2)	29 (9.5)	<0.001
Bacterial meningitis	0	0	2 (0.7)	0.30
Urinary tract infection	11 (5.6)	8 (4.8)	26 (8.5)	0.21
RV isolation (%)				
>1 RV isolated	32 (16.2)	17 (10.2)	N/A	0.10
Laboratory results (%)				
White blood count, 109/L				0.001
Leukocytosis ≥15 (%)	29 (21.1)	20 (17.0)	52 (20.3)	
Leukopenia ≤1.5 (%)	6 (4.4)	3 (2.5)	14 (5.5)	
Mean (range)	11.1 (0.0-29.9)	10.1 (0.2-26.8)	10.4 (0.1-47.2)	0.36
Platelet count, 109/L				
Thrombocytosis ≥500 (%)	10 (7.1)	6 (5.0)	13 (5.0)	<0.001
Thrombocytopenia ≤150 (%)	28 (19.9)	18 (15.0)	66 (25.5)	
Mean (range)	285.5 (6.0-696.0)	262.5 (10.0-687.0)	252.1 (4.0-824.0)	0.62
Log CRP, mean (range)	2.96 (1.06-5.40)	3.28 (1.06-6.00)	3.20 (1.06-6.15)	0.23
Procalcitonin, mean, ng/mL (range)	1.4 (0.06-4.8)	5.7 (0.06-55.5)	2.6 (0.08-34.25)	0.83
Medications (%)				
Received antivirals				
Oseltamivir	5 (2.5)	22 (13.2)	7 (2.3)	0.001
Ribavirin	0	1 (0.6)	1 (0.3)	0.57
Received antibacterials				
Vancomycin	46 (23.2)	33 (19.8)	120 (39.2)	<0.001
Ceftriaxone/cefotaxime	27 (13.6)	25 (15.0)	54 (17.7)	0.42
Penicillin/ampicillin	3 (1.5)	2 (1.2)	4 (1.3)	0.76
Clinical course and management (%)				
Required mechanical ventilation	89 (45.0)	72 (43.1)	101 (33.0)	0.05

Contd...

Table 1: Contd...

Characteristic	HRV-positive (*n*=198)	ORV-positive (*n*=167)	RV-negative (*n*=307)	*P*
Length of hospital stay, mean, days (range)	11.5 (0.61-253.2)	8.0 (0.14-133)	18.2 (0.07-630.2)	0.002
Log length of hospital stay, mean (range)	1.5 (−0.49-5.53)	1.47 (−1.96-4.89)	1.93 (−0.38-6.45)	<0.001
Readmission within 14 days	18 (9.1)	8 (4.8)	47 (15.4)	0.12
Mortality	4 (2.0)	2 (1.2)	24 (7.8)	<0.001

[a]Does not include missing or unknown data. HRV=Human rhinovirus, N/A=Not applicable, ORV=Other RV, PICU=Pediatric Intensive Care Unit, RV=Respiratory virus, CRP=C-reactive protein

conditions (mean 3.1) compared to those who were positive for HRV (mean 2.5) or another respiratory virus (mean 2.3; *P* < 0.001). The only comorbidity that was significantly associated with HRV was a history of asthma (38.9% compared to 22.8% positive for another respiratory virus and 19.6% with no virus; *P* < 0.001).

Respiratory viral coinfection was noted in 32 specimens. Patients with HRV coinfection were noted more frequently compared to patients coinfected with other respiratory viruses (16.2% compared to 10.2%), but this was not a statistically significant difference (*P* = 0.10). The most common coinfecting respiratory viruses were respiratory syncytial virus (38%) followed by adenovirus (31%), parainfluenza type 3 (22%), and *Human metapneumovirus* (13%). Detection of HRV was noted most commonly among young children under 2 years of age and was generally more prominent in the summer-fall months [Figure 1], although our study period coincided with the epidemic of *Enterovirus* D68 during this season which had high cross-reactivity with HRV in the respiratory viral PCR assay.

On univariate analysis, HRV-positive patients were more likely to have a history of asthma compared with patients with no respiratory virus isolated (odds ratio [OR] 3.71, *P* < 0.001) [Figure 2] and remained significant even when compared to patients positive with another respiratory virus (OR 2.62; *P* < 0.001). Leukocytosis and thrombocytosis were most common in HRV-positive patients (21.1% and 7.1%, respectively), whereas leukopenia and thrombocytopenia were most common in patients with no virus detected (5.5% and 25.5%, respectively), and these differences were statistically significant (*P* = 0.001 and *P* < 0.001, respectively). For clinical outcomes, patients who had no respiratory virus detected had a longer mean hospital log LOS at 1.93 compared to 1.50 for HRV patients and 1.47 for those with other respiratory viruses (*P* < 0.001). Mortality was also highest in patients who had no respiratory virus detected (7.8%) compared to HRV patients (2.0%) and patients with other respiratory viruses (1.2%; *P* < 0.001). Oseltamivir use was, not surprisingly, highest in patients who had other respiratory viruses detected (13.2%) compared to HRV patients (2.5%) and patients with no respiratory virus detected (2.3%; *P* = 0.001). Vancomycin use was highest in patients with no respiratory
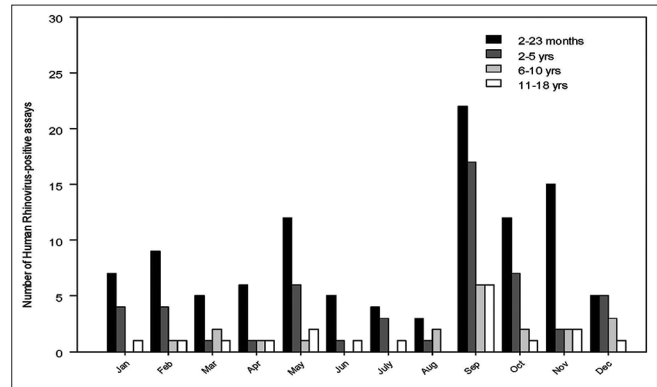

Figure 1: Monthly distribution of human rhinovirus positivity in hospitalized patients, by age group

virus detected (39.2%) compared to HRV-positive patients (23.2%) and patients positive for another respiratory virus (19.8%; *P* < 0.001).

On multivariate analysis [Table 2], after controlling for age, sex, race, medical unit, and number of comorbidities, HRV-positive patients had a higher requirement for mechanical ventilation (OR 1.44), lower rates of readmission (OR 0.53), and lower mortality (OR 0.35) compared to patients with no respiratory virus isolated [Table 2]; however, none of these results were statistically significant. HRV-positive patients did have a significantly shorter LOS compared with patients with no respiratory virus isolated (difference − 0.35; *P* = 0.001). By comparison, patients with another respiratory virus isolated also had a significantly shorter LOS (difference − 0.28; *P* = 0.008) compared to patients with no respiratory virus isolated. This cohort, similar to HRV-positive patients, had a higher requirement for mechanical ventilation (OR 1.54), lower rates of readmission (OR 0.33), and lower mortality (OR 0.43) compared to patients with no respiratory virus isolated, although these differences again were not statistically significant.

Discussion

This study evaluated almost 200 hospital encounters of pediatric patients who were HRV-positive and demonstrated that this population, compared to hospitalized patients who had another, or no, respiratory viruses detected, was significantly more likely to

Table 2: Multivariate analysis evaluating clinical characteristics, management and outcomes of human rhinovirus-positive patients compared to those positive and negative for other respiratory viruses

Outcome	OR (95% CI)					
	HRV versus no virus	P	Other virus versus no virus	P	HRV versus other virus	P
Required mechanical ventilation	1.44 (0.94-2.20)	0.10	1.54 (0.98-2.42)	0.06	0.93 (0.59-1.48)	0.77
Log length of stay*	−0.35 (−0.56--0.13)	0.001	−0.28 (−0.50--0.07)	0.008	−0.06 (−0.26-0.14)	0.56
Readmission within 14 days	0.53 (0.27-1.05)	0.07	0.33 (0.15-0.73)	0.006	1.62 (0.66-3.95)	0.29
Mortality	0.35 (0.11-1.09)	0.07	0.43 (0.10-1.91)	0.27	0.80 (0.14-4.71)	0.81
Antiviral usage	1.42 (0.44-4.54)	0.55	9.86 (3.72-26.10)	<0.001	0.14 (0.05-0.43)	<0.001
Antibacterial usage	0.57 (0.37-0.88)	0.01	0.59 (0.38-0.93)	0.02	0.97 (0.60-1.56)	0.89

*Statistical output is difference (not OR). OR=Odds ratio, HRV=Human rhinovirus, CI=Confidence interval
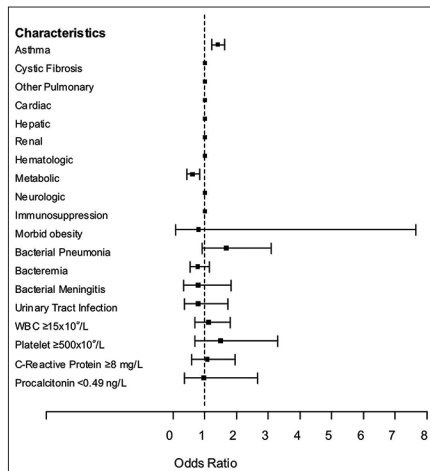

Figure 2: Odds ratio of characteristics in human rhinovirus-positive versus human rhinovirus-negative patients

have a history of asthma. Compared to patients with no respiratory virus detected, HRV-positivity was significantly associated with shorter LOS. Patients' positive for other respiratory viruses had similar outcomes to HRV-positive hospitalized patients.

The strong correlation between HRV positivity and asthma has been well described.[4,5,7,21,22] However, previous studies have not evaluated HRV positivity among hospitalized patients with a broad spectrum of clinical comorbidities and diagnoses. Our study results are notable in that asthma appears to be a risk factor for HRV positivity regardless of the clinical diagnosis. Research on this topic indicates that airway epithelial cells, which are the primary site of infection and replication of HRV, play a key role in this process,[23] that HRV provokes symptoms through virus-specific cytopathic effects, rather than through direct cytotoxic effects,[24] and that interleukin-8, a chemoattractant and activator of neutrophils, is a major determinant of clinical outcomes of HRV infection.[25] However, the fundamental mechanism that underlies these associations is still largely unknown.

These findings support other studies that showed no significant difference between HRV and other respiratory viruses and severity of disease.[1] A prospective study of HRV in hospitalized children, which also enrolled asymptomatic controls, detected HRV in 15% of patients with respiratory illness but also in 13% of asymptomatic controls.[1] Clinical presentations and outcomes were similar among HRV species, and this study also noted that patients were less likely to have a LOS longer than 3 days compared to those with other viruses, although the median duration of stay was not different.[1] In adults, a prospective study demonstrated that while HRV was associated with a substantial number of emergency department visits and hospitalizations for acute respiratory illness, they were less likely to be hospitalized than to be seen in the outpatient setting.[26]

The lack of adverse outcomes among HRV-positive patients in our study may have been due to the prolonged positivity of HRV in nasal secretions, which has been documented to last up to 7 weeks[14,16] as well as the high rates of asymptomatic carriage.[6,14-18] A community surveillance study of respiratory viruses found that HRV was associated with symptoms in only 56% of episodes where it was detected and 93% of participants had HRV detected in at least one weekly sample within the study period.[14] Hence, our study population may have consisted of a large proportion of HRV-positive patients with asymptomatic carriage and those who had recovered from a respiratory illness, even though we excluded patients readmitted within a 2 months interval.

The epidemic of *Enterovirus* D68 during summer-fall of 2014 could be a potential confounder, as this virus cross-reacts with HRV on the respiratory viral PCR assay.[20] One would expect worse clinical outcomes in HRV-positive patients, although *Enterovirus* D68 has similar characteristics to HRV infections,[27,28] it is also associated with more severe disease.[29] However, this was not supported by our statistical analysis. When we performed a separate analysis excluding all data during this period (August 2014–January 2015), we did not find substantially difference results: both HRV-positive patients and patients positive for another respiratory virus still had a significantly shorter LOS compared to

patients with no respiratory virus detected (1.42 and 1.37, respectively, compared to 1.67 in log scale).

Our study has several limitations. This was a multicenter study which included one tertiary children's hospital and several community hospitals. Hence, while we consider this a strength, the findings may not be generalizable to other settings. Our study is limited in that molecular detection of nasopharyngeal samples does not precisely correlate with lower respiratory tract involvement, and PCR results may not reflect a causative pathogen directly attributable to the patient's hospitalization. Our laboratory PCR did not differentiate between HRV species and hence it is unknown whether HRV A and B were predominantly represented in our patient population, nor whether HRV C was more common in patients who had more severe disease, as has been previously reported.[12,21,30-32] Another limitation is that since HRV is frequently a part of coinfection, it is therefore difficult to definitively attribute findings to HRV or the other coinfecting respiratory virus. Furthermore, as the multiplex PCR panel detects a finite number of respiratory viruses, we may have missed other clinically relevant viruses including human bocavirus and *coronavirus*. While we adjusted for age in our multivariate analysis, we did not stratify our analysis by age group. Hence, we may have missed age-related associations.

Conclusions

This study provides data that hospitalized pediatric patients with a heterogeneous set of clinical comorbidities and diagnoses and who are HRV positive did not have adverse clinical outcomes compared to patients who had no respiratory viruses isolated. These patients had similar clinical outcomes to patients who had another respiratory virus isolated. This study also supports earlier evidence that HRV positivity is strongly associated with asthma and asthma appears to be a risk factor regardless of the clinical diagnosis. Further research is warranted to understand the predisposition of asthma to HRV positivity, to guide clinician interpretation of a positive test in a hospitalized patient.

Conflicts of interest
There are no conflicts of interest.

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