Original Article

Survey of Respiratory Virus in Patients Hospitalised for Acute Exacerbations of Heart Failure – A Prospective Observational Study

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Abstract

Introduction: Respiratory virus (RV) infections have been implicated in acute exacerbation of cardiopulmonary conditions. This study aimed to determine the prevalence of RV infections in patients admitted to the cardiology unit with acute decompensated heart failure (ADHF) in a tertiary hospital in Singapore. Materials and Methods: This was a single-centre, prospective observational study. A total of 194 adults (aged >21) admitted to the Singapore General Hospital with ADHF were recruited. A nasopharyngeal swab was taken for multiplex polymerase chain reaction (PCR) detection of influenza virus, rhinovirus, parainfluenza virus (HPIV), human coronavirus (HcoV), adenovirus, human bocavirus (HboV), human metapneumovirus (hMPV), and respiratory syncytial virus (RSV). Results: Twenty-five (13%) had RVs detected by RV multiplex PCR. These comprised 9 rhinoviruses (36%), 4 influenza A viruses (16%), 3 HPIV (12%), 3 HCoV (12%), 2 adenoviruses (8%), 1 human HBoV (4%), 1 hMPV (4%), and 1 RSV (4%). Symptoms-wise, cough was significantly more common in the PCR-positive group (48% vs 24%, *P* = 0.02). There were no statistically significant differences in laboratory investigations (haemoglobin, leukocytes, platelets, creatine kinase, creatine kinase-muscle/brain, troponin T), and radiology findings between RV PCR-positive and -negative groups. The PCR-positive group did not have increased mortality or length of hospital stay. Conclusion: This study identified a considerable burden of RVs in our ADHF cohort, and highlights the need for prevention of RVs in this group of patients. We also recognised the difficulty with clinical diagnosis of RVs in ADHF patients.

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Key words: Cardiac failure, Heart disease, Influenza, Respiratory tract infections, Respiratory virus infections

Introduction

Congestive heart failure (CHF) is a growing global health problem, affecting 11.8% of people over the age of 60.[1] Acute decompensated heart failure (ADHF) is the leading reason for hospitalisation in CHF patients, and is associated with substantial rates of mortality and morbidity of 5% to 14%.[2,3] In Singapore, heart failure (HF) is also associated with considerable cardiac and non-cardiac mortality.[4] Respiratory virus (RV) infections have been implicated in acute exacerbation of cardiopulmonary conditions.[5] In particular, influenza and respiratory syncytial viruses (RSV) were diagnosed in 21% of elderly patients with underlying cardiac and/or pulmonary comorbidities hospitalised for acute cardiopulmonary exacerbations.[6] Likewise, another study also showed that influenza, RSV, rhinovirus, coronavirus, and human metapneumovirus (hMPV) were detectable in 17% of elderly patients admitted to critical care units with acute cardiorespiratory failures.[5] In addition, epidemiological studies and randomised controlled trials have demonstrated the benefit of influenza vaccination in reducing the risk of cardiovascular and cerebrovascular events.[7-18]

However, most of the patients in these studies had an underlying respiratory, rather than cardiac condition, precluding any proper characterisation of respiratory infections in a cohort of ADHF patients. In fact, the prevalence of viral respiratory pathogens in patients admitted with ADHF has not been reported to date. This study aimed to establish the prevalence of RV infections in adults with underlying cardiac disorders admitted with ADHF.

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Materials and Methods

Subjects

Subjects were recruited from the cardiology wards of the Singapore General Hospital. All adults (aged >21) admitted through the accident and emergency department with a diagnosis of New York State Heart Association (NYHA) Class III or IV acute heart failure were eligible. Patients diagnosed with ADHF were flagged for recruitment. Any patient with end stage renal failure (ESRF) (defined as chronic kidney disease [CKD] stage >4 with fluid overload) or exacerbation of chronic obstructive pulmonary disease (COPD) was excluded. All subjects gave informed consent. Our research was carried out in compliance with the Helsinki Declaration and approval was obtained from our hospital's Institutional Review Board (SingHealth Centralised Institutional Review Board, Reference No.: 2012/650/F).

Enrolment and Study Period

Recruitment took place from 1 December 2012 to 31 May 2013, which contained the 2 flu seasons in the tropics following the Northern and Southern Hemisphere winters.[19] Demographic, medical and drug history, presenting clinical symptoms and physical findings were recorded. Chest radiographs and blood samples for full blood count, electrolytes, and cardiac enzymes (troponin T, creatinine kinase [CK], and creatinine kinase-muscle/brain [CK-MB]) were obtained on all patients. Patients were followed up for 28 days from recruitment.

Respiratory Virus Polymerase Chain Reaction (PCR)

Subjects underwent nasopharyngeal swabs using Dacron-tipped swabs within 48 hours of admission, which were analysed within 24 hours by RV multiplex PCR (Seegene Anyplex II 16 Detection Multiplex PCR kit, Seegene) according to the manufacturer's instructions using the Bio-Rad CFX96 Real-Time PCR Detection System (CA, USA). In brief, the swabs were added to 1.0 ml of 1x phosphate buffered saline and vortexed vigorously. The swab suspension (500 µL) was then added to the NucliSens easyMAG automated instrument (BioMerieux, France) for total nucleic acid extraction. The final volume of elution was 55 µL. Of this, 8 µL of nucleic acid extract was used for PCR performed using the Seegene Anyplex II RV16 Detection Multiplex PCR kit (Seegene, Korea). This assay simultaneously detected 16 types of human respiratory viral pathogens (influenza A and B, human parainfluenza virus (HPIV) 1/2/3/4, RSV subtypes A and B, hMPV, human coronavirus (HCoV) (229E/NL63/OC43), rhinovirus A/B/C, enterovirus, adenovirus and human bocavirus (HboV) 1/2/3/4. The PCR reaction was performed on the Applied Biosystems 9700 thermocycler and the results were read by capillary electrophoresis (QIAxcel, Qiagen, Germany).

Outcome Measurements

Primary outcome was detection of RV by PCR in a nasopharyngeal swab. Secondary outcomes (assessed in all patients) included clinical, laboratory, and radiological features, 28-day mortality, and length of hospital stay (LOS).

Statistics

Data was analysed using SPSS software (version 13 for Windows; SPSS Inc, US). Descriptive statistics of data were expressed as frequencies, percentages, mean ± standard deviation (SD). Differences in characteristics between participants were performed with the χ^2/Fisher's exact test; 95% confidence intervals were reported, and 2-sided *P* value of less than 0.05 was taken to be statistically significant.

Results

Subjects

Between 1 December 2012 and 31 May 2013, 508 patients admitted with the primary diagnosis of ADHF were screened for eligibility. A total of 267 patients were excluded, and of 241 eligible patients, 194 patients (males, 71%) gave informed consent. All patients completed 28 days' follow-up after recruitment (Fig. 1).

Baseline demographics were similar in patients with or without positive RV PCR and are summarised in Table 1. The mean age of the study population was 64.2 (standard

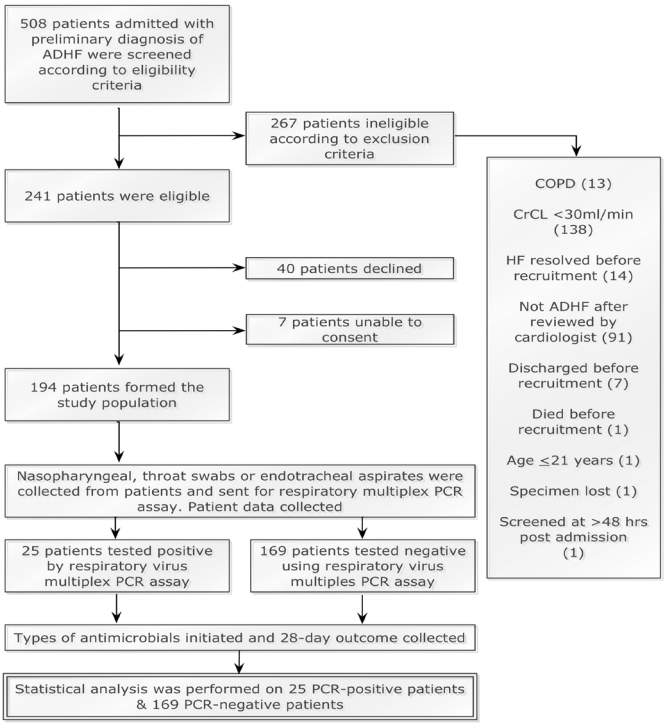

Fig. 1. Flow chart illustrating the recruitment of patients for the present study. ADHF: Acute decompensated heart failure; COPD: Chronic obstructive pulmonary disease; CrCl: Creatinine clearance; HF: Heart failure; PCR: Polymerase chain reaction.

Table 1. Demographic and Clinical Data of Studied Patients

Demographics	All (n = 194)	PCR+ (n = 25)	PCR- (n = 169)	*P* Value
Age, mean (SD)	64.2 (11.9)	62.0 (10.1)	64.5 (12.2)	0.28
Gender, male (%)	138 (71)	19 (76)	119 (70)	0.64
Race (%)				
Chinese	134 (69)	14 (56)	120 (71)	0.13
Malay	35 (18)	10 (40)	25 (15)	0.0022
Indian	24 (12)	1 (4)	23 (14)	0.17
Others	1 (1)	0 (0)	1 (1)	1.00
Active smoker (%)	28 (14)	2 (8)	26 (15)	0.59
Obesity (%)	18 (9)	3 (12)	15 (8.9)	0.71
Previous heart failure (%)	104 (54)	13 (52)	91 (55)	0.83
Hypertension (%)	139 (72)	18 (72)	121 (71)	1.00
Diabetes mellitus (%)	97 (50)	11 (44)	86 (51)	0.67
Hyperlipidaemia (%)	134 (69)	19 (76)	115 (68)	0.49
Ischaemic heart disease (%)	112 (58)	13 (52)	99 (59)	0.67
Cardiac arrhythmia (%)	46 (24)	6 (24)	40 (24)	1.00
Valvular heart disease (%)				
Valve stenosis	13 (7)	2 (8)	11 (7)	0.68
Regurgitation	34 (18)	3 (12)	31 (18)	0.58
Valve replacement surgery	10 (5)	1 (4)	9 (5)	1.00
Renal impairment (%)	26 (13)	3 (12)	23 (14)	1.00
Anaemia (%)	37 (19)	4 (16)	33 (20)	0.79
Rheumatic heart disease (%)	9 (5)	1 (4)	8 (5)	1.00
Mortality (%)	1 (1)	0 (0)	1 (1)	1.00
Length of stay, mean (SD)	6.80 (6.5)	6.92 (3.9)	6.80 (6.5)	0.90

PCR: Polymerase chain reaction; SD: Standard deviation

deviation [SD] 11.9) years, which is consistent with the demographics of HF patients in Singapore.[20] Our patients were predominately Chinese (69%), consistent with the demographics of the local population. The prevalence of pre-existing conditions in the study population included HF (54%), ischaemic heart disease (58%), hypertension (72%), diabetes mellitus (50%), hyperlipidaemia (69%) and cardiac arrhythmias (24%). Of note, there were more Malays in the RV PCR-positive group (40%) compared with the PCR-negative group (18%).

Length of Hospital Stay and Mortality

The overall mean LOS was 6.80 days (SD 6.5) (Table 1). No significant difference in the LOS was found between PCR-negative and PCR-positive patients (mean 6.80 vs 6.92 days, respectively). No mortality was observed during 28-day follow-up in the PCR-positive group. One patient in the PCR-negative group died due to end-stage HF from underlying dilated cardiomyopathy; he underwent extracorporeal membrane oxygenation (ECMO) and ventricular assist device (VAD) placement but succumbed to complications related to bowel ischaemia.

PCR Findings and Clinical Characteristics

RV PCR results are summarised and shown in Figure 2 and Table 2. PCR was positive in 25 patients (13%), with the commonest viruses being rhinoviruses (36%), influenza A (16%), HPIV (12%) and HCoV (12%). One patient had 2

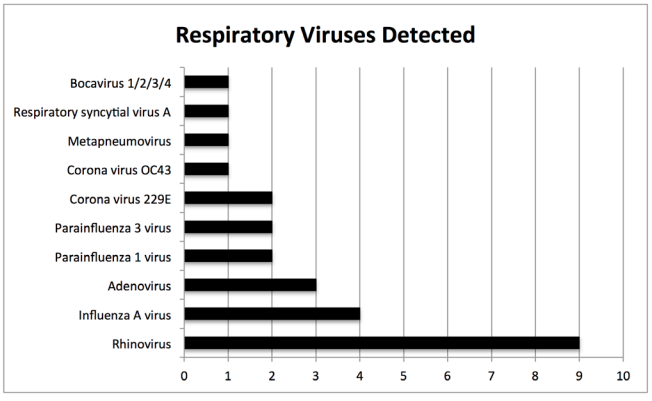

Fig. 2. Graph showing the frequency of respiratory viruses identified by PCR in hospitalised patients with ADHF. One patient tested positive for both adenovirus and parainfluenza 1 virus in single swab. ADHF: Acute decompensated heart failure; PCR: Polymerase chain reaction.

Table 2. ADHF Patients with Positive Respiratory Virus PCR

Number of Subjects with Positive PCR (n = 25)	No. of Isolates (%)
Rhinovirus*	9 (36)
Influenza A virus†	4 (16)
Adenovirus	2 (8)
Coronavirus 229E*	2 (8)
Coronavirus OC43	1 (4)
HPIV1	1 (4)
HPIV1 + adenovirus	1 (4)
HPIV3	2 (8)
hMPV	1 (4)
Bocavirus	1 (4)
RSV A	1 (4)

hMPV: Human metapneumovirus; HPIV: Human parainfluenza virus; PCR: Polymerase chain reaction; RSV: Respiratory syncytial virus
*One patient was recruited twice, and had 2 viruses: rhinovirus in the first admission and coronavirus 229E in the second admission 28 days later.
†Two patients received oseltamivir therapy against influenza A after testing positive by PCR.

Table 3. Clinical Symptoms and Signs of ADHF Patients

Symptoms	PCR+ (n = 25) (%)	PCR- (n = 169) (%)	*P* Value
Cough	12 (48)	40 (24)	0.02
Sputum	5 (20)	18 (11)	0.19
Fever or sweating	2 (8)	19 (11)	1.00
Chills	1 (4)	1 (1)	0.24
Chest pain or tightness	11 (44)	52 (31)	0.25
Runny nose	0 (0)	1 (1)	1.00
Headache	1 (4)	1 (1)	0.24
Fatigue	0 (0)	3 (2)	1.00
Dypsnoea	22 (88)	160 (95)	0.19
Palpitations	1 (4)	18 (11)	0.48
Loss of appetite	1 (4)	8 (5)	1.00
Limb swelling	11 (44)	90 (53)	0.40
Abdominal pain	1 (4)	2 (1)	0.34
Abdominal distension	2 (8)	19 (11)	1.00
Giddiness	2 (8)	5 (3)	0.22
Abnormal chest sounds	24 (96)	154 (91)	0.70
Cardiac arrhythmia	0 (0)	12 (7)	0.37
Elevated JVP	12 (48)	80 (47)	1.00

GCS: Glasgow Coma Scale; JVP: Jugular venous pressure; PCR: Polymerase chain reaction

viruses (adenovirus and HPIV1) on the same swab. Another patient was readmitted and enrolled a second time 28 days later, and tested positive for rhinovirus and HCoV 229E on the 2 different occasions. Most PCR-positive patients were not prescribed antivirals, except for 2 influenza A-positive patients who received oseltamivir within 24 hours of admission upon receipt of PCR results.

Clinical findings of all patients upon admission are summarised in Table 3. Cough was more common among PCR-positive patients (48% vs 24%, $P = 0.02$). Other symptoms including sputum, dyspnoea and limb swelling were similar between PCR-positive and PCR-negative groups. Subjective symptoms of fever or sweating were reported in 19 patients with negative PCR, versus 2 patients with positive PCR ($P = 1.00$), but only 1 had documented fever (38.5°C). This patient was diagnosed with bacterial community-acquired pneumonia in addition to ADHF and tested negative for RVs.

Laboratory and Radiological Investigations

Laboratory results are summarised in Table 4. In summary, there were no statistically significant differences in laboratory findings between PCR-positive and -negative patients. Chest radiology findings also showed no significant differences between both groups (Table 5).

Discussion

Historically, multiple epidemiological studies have observed an increase in hospitalisation and mortality due to cardiopulmonary diseases during the winter seasons when RVs are circulating.[21] However, most of these studies recruited patients with both chronic pulmonary and cardiac conditions.[5,6,21,22] Although health policymakers are aware that influenza may cause serious illness in patients with COPD or ischaemic heart disease,[6,23] the impact of RVs in ADHF patients is yet to be defined. Therefore, we surveyed the prevalence of RVs in patients hospitalised for ADHF, as a first step in identifying a possible link between RV and HF. Our study shows that RVs are present in 13% of patients admitted with primary diagnosis of ADHF during the flu seasons. Our results thus highlight a considerable burden of RVs in ADHF patients.

In our study, rhinovirus was the most common pathogen detected. Rhinovirus has been implicated in exacerbations of chronic cardiopulmonary diseases in the elderly,[22] and even positively associated with pneumonia, exacerbations of COPD and CHF in older adults.[24] Since human rhinovirus is the most frequent cause of acute respiratory tract illnesses worldwide, its role as a precipitant of cardiac decompensation warrants further study.[25] Other less common viruses identified in this study were adenovirus (8%), hMPV (4%), HBoV (4%), RSV (4%), HPIV (12%), and coronavirus (12%). Adenovirus is a cardiotropic virus that has been implicated in myocarditis;[26] hMPV infection has

Table 4. Initial Laboratory Findings of Patients Admitted with Acute Decompensated Heart Failure

Laboratory Findings Mean (SD)	PCR+ (n = 25)	PCR- (n = 169)	*P* Value	95% Confidence Interval	
				Lower	Upper
WBC (x10^9/L)	9.14 (2.62)	8.32 (3.22)	0.12	-1.88	0.24
ALC (x10^9/L)	1.90 (0.80)	1.81 (0.90)	0.62	-0.44	0.27
ANC (x10^9/L)	6.22 (2.03)	5.63 (2.73)	0.21	-1.51	0.34
CRP (mg/L)	23.44 (45.93)	36.74 (59.33)	0.43	-21.46	48.07
Procalcitonin (ug/L)	6.79 (17.32)	0.45 (0.84)	0.31	-19.66	6.98
Haemoglobin (d/dL)	12.94 (2.627)	12.82 (3.10)	0.85	-1.28	1.06
Platelet (x10^9/L)	251.72 (61.48)	226.74 (76.77)	0.08	-563.64	2.68
ALP (u/L)	85.48 (47.82)	90.21 (47.18)	0.68	-18.19	27.66
ALT (u/L)	38.00 (42.13)	36.17 (34.20)	0.85	-21.68	18.03
AST (u/L)	52.45 (41.37)	47.81 (62.04)	0.67	-26.27	16.98
Bilirubin (umol/L)	19.90 (9.96)	25.15 (20.51)	0.06	-0.33	10.81
NTProBNP (pg/mL)	7465.16 (6141.13)	5672.97 (6942.68)	0.25	-4945.77	1361.39
Creatinine (umol/L)	109.70 (44.94)	106.42 (36.18)	0.74	-23.39	16.83
CCT (umol/L)	77.24 (41.32)	62.58 (26.28)	0.10	-32.12	2.79
Creatine kinase (u/L)	386.43 (760.93)	162.43 (143.13)	0.17	-553.70	-105.69
CK-MB (ug/L)	8.75 (18.78)	4.31 (4.95)	0.27	-2.59	3.71
Troponin T (ug/L)	0.37 (0.90)	0.11 (0.35)	0.18	-0.65	0.13

ALC: Absolute lymphocyte count; ALP: Alkaline phosphatase; ALT: Alanine transaminase; ANC: Absolute neutrophil count; AST: Aspartate transaminase; CCT: Creatinine clearance test; CK-MB: Creatine kinase-muscle/brain; CRP: C-reactive protein; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PCR: Polymerase chain reaction; WBC: White blood cell count

Table 5. Chest X-Ray Findings of Patients on Admission with Acute Decompensated Heart Failure

X-Ray Findings	PCR+ (n = 25)	PCR- (n = 169)	*P* Value
Pulmonary oedema (%)	3 (12)	16 (10)	0.72
Cardiomegaly (%)	20 (80)	127 (75)	0.80
Bilateral pleural effusions (%)	9 (36)	57 (34)	0.83
Consolidation (%)	2 (8)	18 (11)	1.00

PCR: Polymerase chain reaction

also been associated with acute exacerbations in patients with underlying cardiopulmonary disease.[27]

In this study, more Malays were PCR-positive compared with other local races (Table 1). Similarly, a previous study by Pang et al also noted Malay ethnicity to be positively associated with influenza-A (H1N1) and coxsackie/echovirus mono-infections.[28] It was hypothesised that genetic differences may result in weaker immune responses against specific RVs in Malays compared to other local ethnicities; more studies are needed to understand this relationship.

In our study, only cough was significantly more common in PCR-positive ADHF patients ($P = 0.02$). Given the many overlapping clinical features (including cough, sputum and dyspnoea) between RV and ADHF, the diagnosis of concurrent RV infections in ADHF patients could be challenging and often overlooked. This can be especially true in the elderly, in whom classical RV symptoms such as fever, sore throat or myalgia are often absent.[29] Furthermore, laboratory parameters such as leukocyte counts and C-reactive protein (CRP) lack sensitivity and specificity for the diagnosis of RV infections,[30] and indeed were not different in this cohort, whether PCR-positive or negative (Table 4). Hence neither symptomatology nor blood tests can reliably indicate which ADHF patient might be concomitantly having, or might have had a recent RV infection. Findings from our study do not support routine screening of all ADHF patients for RV, as there were no differences in the overall management, mortality or LOS in patients with or without RV positivity.

To date, the causal relationship between RV infection and cardiac disease are mostly supported indirectly by influenza vaccine studies, which showed that vaccinations reduced the risk of acute coronary syndromes and strokes in high-risk patients.[7,9-18] Further studies to identify the mechanistic link between RV infections and acute cardiac events could lead to the development of novel preventative and therapeutic interventions.

Conclusion

Our study identified a considerable burden of RVs in ADHF. However, there is a general lack of awareness of comorbid RVs, given the difficulty with clinical diagnosis. Given the high morbidity and mortality of HF during acute exacerbations, prevention of precipitants is an important

component of care. Looking forward, future studies should further explore the role of preventive measures such as vaccinations in ADHF.

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