



# Clinical manifestations and outcomes of respiratory syncytial virus infection in adult hospitalized patients

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## ABSTRACT

**Background:** Respiratory syncytial virus (RSV) is an important virus found in adult hospitalized patients.

**Objectives:** To study the clinical outcomes of hospitalized patients aged  $\geq 15$  years and diagnosed with RSV infection.

**Study design:** Both retrospective and prospective cohort studies were conducted at a university hospital between May 2014 and December 2015. Results: RSV was detected in 86 of 1562(5.5%) adult hospitalized patients suspected of respiratory viral infection. Sixty-nine patients were included in the study. RSV was detected by RT-PCR (82.6%), IFA (10.1%), and both RT-PCR and IFA (7.3%). Most patients (87.0%) were aged  $\geq 50$  years. Cardiovascular diseases, pulmonary diseases, immunocompromised hosts, and diabetes were the major comorbidities. The common manifestations were cough (92.8%), dyspnea (91.3%), sputum production (87.0%), tachypnea (75.4%), wheezing (73.9%), and fever (71.0%). Fifty-five patients (79.7%) were diagnosed with pneumonia. Hypoxemia ( $SpO_2 \leq 92\%$ ) was found in 53.6% patients. Twenty-five of 69(36.2%) patients developed respiratory failure and required ventilatory support. Cardiovascular complications were found in 24.6% of patients. Congestive heart failure, acute myocardial infarction (MI), new atrial fibrillation, and supraventricular tachycardia were found in 9(13.0%), 7(10.1%), 4(5.8%), and 3(4.3%) of 69 patients, respectively. Overall mortality was 15.9%. Pneumonia (81.8%) and acute MI (18.2%) were the major causes of death.

**Conclusions:** Most adult hospitalized patients with RSV infection were of advanced age and had comorbidities. Cardiopulmonary complications were the major causes of death. Management and prevention of RSV infection in these vulnerable groups are necessary.

## 1. Background

Respiratory syncytial virus (RSV) is an important cause of acute respiratory infection (ARI) in infants and young children [1–3]. Nevertheless, it has been recognized as a cause of adult ARI, especially in the elderly, those with comorbidities, and immunocompromised hosts, which leads to hospitalization and increases morbidity and mortality [1,4–8]. The prevalence of RSV infection in adults varies from 3% to 13% depending on age groups, underlying diseases, diagnostic techniques, study periods, and geographic regions. [3–5,7–9]. In addition, disease severity ranges from mild to severe acute respiratory illness [4]. A total of 4%–16% of adult patients with RSV infection

required hospitalization [3,4,10], with high complications including cardiopulmonary complications and mortality [4,5,8,11]. There were a few data of adult hospitalized patients with RSV infection, with high complications, in Thailand; [3,12,13] however, additional clinical data are required for planning patient management and also disease prevention in this region.

## 2. Objectives

The objective of the study was to determine the clinical manifestations and outcomes of RSV infection in adult hospitalized patients.

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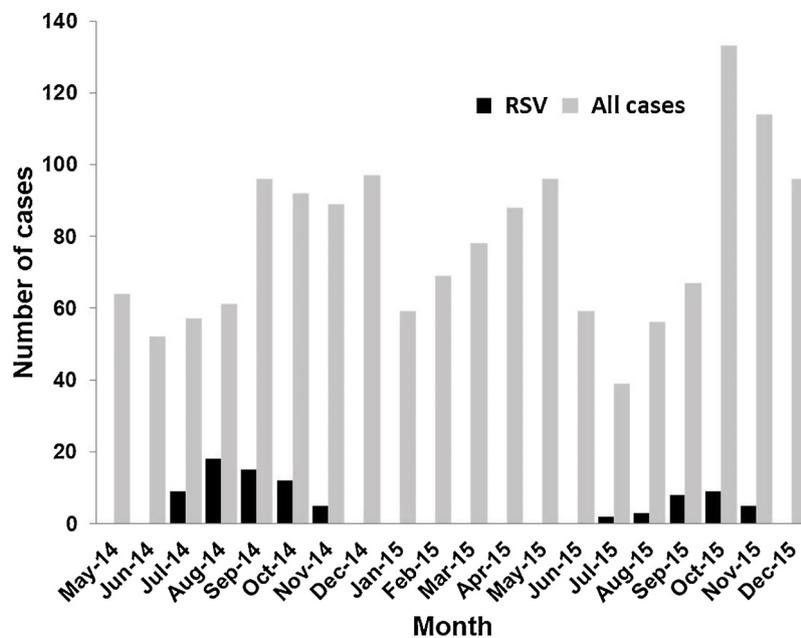


Fig. 1. All cases (n = 1562) of adult hospitalized patients who sent their respiratory specimens to detect respiratory syncytial virus (RSV). RSV was found in 86 patients (5.5%) over two consecutive rainy seasons.

### 3. Study design

#### 3.1. Subjects

Both retrospective and prospective cohort studies were conducted at the Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. Hospitalized patients aged  $\geq 15$  years and diagnosed with respiratory syncytial virus (RSV) infection by real-time reverse transcriptase polymerase chain reaction (RT-PCR) and/or indirect immunofluorescence assay (IFA) were included in the study. A written informed consent was obtained before the enrollment. The Siriraj Institutional Review Board reviewed and approved the study protocol (COA no.336/2015). All recruited patients were treated according to the standard of care of the hospital. Clinical manifestations, comorbidities, laboratory data, treatment, and outcomes were recorded until discharge or death for analysis.

#### 3.2. Virologic methods

Specimens from nasopharyngeal wash, throat swab, sputum, tracheal suction, or bronchoalveolar lavage of the hospitalized patients suspected of respiratory viral infection were sent to the virology laboratory, Department of Microbiology, Faculty of Medicine, Siriraj Hospital to detect RSV. Real time RT-PCR and IFA techniques were performed following the standard protocols. The real time RT-PCR was performed by using the NucliSens nucleic acid extraction kit (Biomerieux, Marcy l'Etoile, France), a Proflu<sup>+</sup> assay (Genprobe Bedford, MA, USA), and CFX96 (Bio-rad, USA) real-time thermocycler. The IFAs were performed using a monoclonal antibody specific to RSV (cat.# 5006, Millipore, USA) and antimouse immunoglobulin labeled with FITC (cat.# 5008, Millipore).

#### 3.3. Definition

Immunocompromised patients were defined as patients who received chemotherapy, corticosteroids  $> 20$  mg/day prednisolone equivalent, hematologic malignancy, or HIV infection. Pneumonia was diagnosed if patients had fever, cough, and dyspnea with new pulmonary infiltrates on chest radiography. Acute bronchitis was defined

as an acute respiratory infection manifested predominantly by cough without pneumonia, common cold, or exacerbation of asthma or COPD [14]. Chest radiography was independently interpreted by two chest radiologists who did not know the clinical course of patients. If the results were discordant, the consensus was made after the discussion. Hospital-acquired pneumonia (HAP) was defined as pneumonia that developed 48 h or more after admission without endotracheal intubation. Ventilator-acquired pneumonia (VAP) was defined as pneumonia that developed more than 48 h after endotracheal intubation [15,16]. COPD exacerbation was defined as a sustained worsening of the COPD patients' condition beyond normal day-to-day variations, acute onset and necessitates a change in regular medication [17]. Asthma exacerbation was defined by changes in symptoms and rescue use, which were outside the patients' usual range of day-to-day variation [18]. Worsening or new congestive heart failure were diagnosed by cardiologists based on clinical signs, laboratory investigation such as chest radiography and echocardiography.

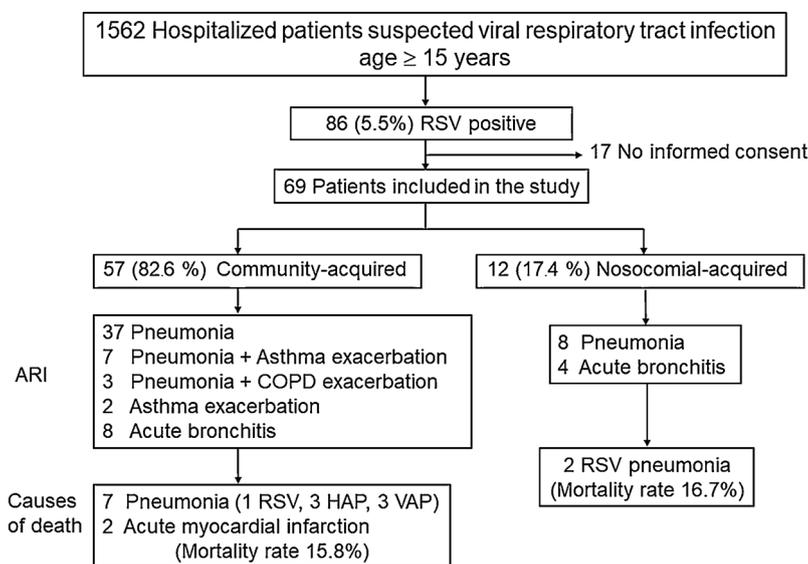
#### 3.4. Statistical analysis

The PASW statistics 18.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis. Categorical data were described as percentages. Normally distributed continuous data were presented as mean and standard deviation (SD), whereas non-normally distributed data were presented as median and interquartile range (IQR). Categorical and continuous variables were compared between groups using Chi-square test or Fisher's Exact test and unpaired *t*-test or Mann-Whitney test as appropriate. Multiple logistic regression analysis was performed to identify the risk factors of complications and were presented as odds ratio and 95% confidence interval. A *p*-value of  $< 0.05$  was considered a statistically significant difference.

## 4. Results

#### 4.1. Clinical manifestations

Respiratory specimen of 1562 adult hospitalized patients suspected of respiratory viral infection were sent to detect RSV during May 2014 and December 2015. RSV was detected in 86 (5.5%) of patients in 5



**Fig. 2.** Summary of clinical outcomes in terms of ARI and mortality of community-acquired and nosocomial-acquired RSV infections in adult hospitalized patients.

RSV, respiratory syncytial virus; ARI, acute respiratory illness; COPD, chronic obstructive pulmonary disease; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.

months a year between July and November during two consecutive rainy seasons (Fig. 1). Sixty-nine RSV positive patients provided written informed consent and were included in the study. RSV was detected by RT-PCR (82.6%), IFA (10.1%) and both RT-PCR and IFA (7.3%). Clinical outcomes in terms of acute respiratory illnesses (ARI) and mortality are demonstrated in Fig. 2. Community-acquired and nosocomial-acquired RSV infections were found in 57 (82.6%) and 12 (17.4%) patients, respectively. Twenty-one of 57 (36.8%) community-acquired RSV infected patients had a history of contact with persons having acute respiratory tract infection in their families. The nosocomial-acquired infections were detected during outbreak, 5 patients at hematologic ward, and 7 patients at general medical ward. Pneumonia was the most common ARI in both groups. Mortality rates of the community-acquired and nosocomial-acquired RSV infections were 15.8% (9 of 57) and 16.7% (2 of 12), respectively. The clinical manifestations of community-acquired and nosocomial-acquired RSV infections were similar, and the data were combined for analysis.

The median age of patients was 72 years (IQR 58–81 years) (Table 1). Sixty of 69 (87.0%) patients aged ≥ 50 years with the highest prevalence (36.2%) of age 65–79 years. Among patients aged < 50 years, 7 of 9 (77.8%) were immunocompromised hosts (3 hematologic malignancy, 2 hematopoietic stem cell transplant recipients, and 2 connective tissue diseases on immunosuppressive drugs). Females were the predominant. All patients had at least one comorbidity. The most common comorbidities were pre-existing cardiovascular diseases (33.3%), pulmonary diseases (29.0%), immunocompromised hosts (29.0%), diabetes (29.0%), and chronic kidney diseases (26.1%).

The median duration of symptoms at presentation was 3 days (IQR 2–3.5 days). The common presenting symptoms (Table 2) were cough (92.8%), dyspnea (91.3%), sputum production (87.0%), and history of fever (81.2%). Rhinorrhea was present in 46.4% of patients. The common initial physical findings were tachypnea (75.4%), wheezing (73.9%), and fever (43.5%). Wheezing was found in 69.6% (39 of 56) of patients after excluding asthma or COPD. Fever (BT ≥ 37.8 °C) was found in approximately 71.0% patients in the first 2 days of admission with mean temperature 38.7 ± 0.6 °C. After excluding hematologic malignancy and bacterial co-infection, the median white blood counts were 7995 cells/mm<sup>3</sup> (IQR 5,632–10,842 cells/mm<sup>3</sup>). Median neutrophil and lymphocyte counts were 72.6% (IQR 60.0–84.2 %) and 16.6% (IQR 9.0–24.5%), respectively.

#### 4.2. Respiratory complications

Chest X-rays were performed for all patients. Pneumonia and acute

**Table 1**  
Baseline characteristics of RSV infection in adult hospitalized patients (n = 69).

Characteristic	Number (%)
Age, years, median (IQR)	72 (58–81)
15 - 34	5 (7.3)
35 - 49	4 (5.8)
50 - 64	16 (23.2)
65 - 79	25 (36.2)
≥ 80	19 (27.5)
Sex: Female	52 (75.4)
Hypertension	46 (66.7)
Dyslipidemia	30 (43.5)
Cardiovascular diseases <sup>a</sup>	23 (33.3)
Pulmonary diseases <sup>b</sup>	20 (29.0)
Immunocompromised patients <sup>c</sup>	20 (29.0)
Diabetes mellitus	20 (29.0)
Chronic kidney disease	18 (26.1)
Old stroke	12 (17.4)
Bedridden	8 (11.6)
Solid malignancy	5 (7.3)

IQR, interquartile range.

<sup>a</sup> Cardiovascular diseases: coronary artery disease, congestive heart failure, atrial fibrillation.

<sup>b</sup> Pulmonary diseases: asthma, chronic obstructive pulmonary disease, bronchiectasis, previously treated tuberculosis.

<sup>c</sup> Immunocompromised patients: hematologic malignancy, hematopoietic stem cell transplantation, on immunosuppressive drugs, on corticosteroid treatment > 20 mg/day prednisolone equivalent or human immunodeficiency virus (HIV) infection.

bronchitis were diagnosed in 79.7% (55/69) and 17.4% (12/69) patients, respectively (Fig. 2). Chest radiography findings of pneumonia were diffuse interstitial infiltrations alone 60.0% (33/55), mixed diffuse interstitial and alveolar infiltrations 30.9% (17/55), and alveolar infiltrations alone 9.1% (5/55). Exacerbations were occurred in 9 of 10 asthma and all 3 COPD patients. Hypoxemia (peripheral oxygen saturation (SpO<sub>2</sub>) ≤ 92%) was found in 26 patients (37.7%) at the initial presentation and increased to 37 patients (53.6%) during the hospitalization. Twenty-five of 69 (36.2%) patients developed acute respiratory failure and required ventilatory support (22 patients needed invasive mechanical ventilation and 3 patients required non-invasive ventilation).

**Table 2**  
Presenting symptoms and initial physical findings of adult hospitalized patients with RSV infection ( $n = 69$ ).

Presenting symptoms	$n$ (%)	Initial physical findings	$n$ (%)
Cough	64(92.8)	Wheezing/rhonchi	58(84.0)
Dyspnea	63(91.3)	Wheezing alone	51(73.9)
Sputum production	60(87.0)	Tachypnea	52(75.4)
History of fever	56(81.2)	Fever <sup>a</sup>	30 (43.5)
Rhinorrhoea	32 (46.4)	Tachycardia	39 (56.5)
Audible wheezing	16 (23.2)	Crepitation	40 (58.0)
Sore throat	12 (17.4)	Use of accessory respiratory muscles	35 (50.7)
Nasal congestion	11 (15.9)	Hypoxemia <sup>b</sup>	26 (37.7)
Sneezing	10 (14.5)	Alteration of consciousness	17 (24.6)
Nausea/vomiting	10 (14.5)		
Myalgia	9 (13.0)		
Diarrhea	7 (10.1)		
Chest pain	3 (4.3)		

<sup>a</sup> BT  $\geq 37.8$  °C; Fever within 2 days of admission was increased to 49(71.0%).

<sup>b</sup> Peripheral oxygen saturation (SpO<sub>2</sub>)  $\leq 92\%$  and needed oxygen supplement.

#### 4.3. Cardiovascular complications

Seventeen of 69 patients (24.6%) developed cardiovascular complications and 9 of 17 (52.9%) patients had pre-existing cardiovascular diseases (CVD). Congestive heart failure (CHF), acute myocardial infarction (MI), new atrial fibrillation (AF), and supraventricular tachycardia (SVT, heart rate 130, 160 and 220 beats/min) were found in 9 (13.0%), 7 (10.1%), 4 (5.8%), and 3 (4.3%) of 69 patients, respectively. Four of 9 CHF patients had worsening CHF. Among 5 new onset CHF patients, 4 patients had pre-existing coronary artery disease and valvular heart disease, and the other one had no previous diagnosis of CVD but had left ventricular ejection fraction (LVEF) 33.5% during RSV infection. All acute MI were diagnosed as non-ST-elevation MI (NSTEMI). Five of 7 (71.4%) acute MI had concomitant CHF. Three of 7 (42.8%) acute MI patients were first diagnosed, and all had the risk factors of coronary artery disease (DM, hypertension and dyslipidemia). The pre-existing coronary arterial disease (CAD) was the risk factor of overall cardiovascular complications in hospitalized adult patients with RSV infection with odds ratio 6.18, (95% CI 1.18–32.5),  $p = 0.03$ , adjusted for age, sex, HT, DLP, DM, pre-existing CHF, arrhythmia, and VHD.

#### 4.4. Antimicrobial treatment

Sixty-five (94.2%) and 51 (73.9%) patients received initial empirical antibiotics and antiviral drugs (oseltamivir), respectively. After confirmed RSV infection, 32 (46.4%) patients received oral ribavirin in cases of respiratory failure that needed mechanical ventilator, hematologic malignancy, immunosuppressive therapy, or HIV infection. Mortality rates in patients treated with oral ribavirin compared to those without oral ribavirin were 18.8% (6/32) vs 13.5% (5/37),  $p$ -value 0.553. Sputum specimens were collected in 54 (78.3%) patients, but only 18 of 54 (33.3%) specimens were acceptable for bacterial culture. Bacterial co-infection with RSV identified by sputum culture were found in 6(8.7%) patients, *Haemophilus influenzae* (1), *Klebsiella pneumoniae* (1), *Pseudomonas aeruginosa* (2), *Acinetobacter baumannii* (1), and *Pasteurella multocida* (1). Hemoculture for bacteria was performed on 65 patients (94.2%). Three patients had concomitant bacteremia, *Escherichia coli* (2), and *Aeromonas hydrophila* (1). One patient with *E. coli* bacteremia had urinary tract infection, whereas the source of infection including sputum culture was not identified in other two patients.

**Table 3**  
Mortality in RSV-infected patients.

Type	Age	Causes of death	Comorbidities
Nosocomial-acquired	32	RSV pneumonia	AML with agranulocytosis
	38	RSV pneumonia	MM with agranulocytosis
Community-acquired	95	RSV pneumonia	Dementia, Asthma
	74	HAP ( <i>S.maltophilia</i> )	HT, DLP, DM, AF, Asthma
	90	HAP ( <i>K.pneumoniae</i> )	Bed ridden, Parkinsonism
	90	HAP ( <i>A. baumannii</i> )	HT, DLP, CKD, Old CVA
	64	VAP ( <i>A. baumannii</i> )	Bed ridden, Dementia, HT, DLP, CKD, Anemia, CHF
	67	VAP ( <i>A. baumannii</i> )	HT, old CVA, severe COPD
	93	VAP ( <i>A. baumannii</i> )	Anemia
76	Acute MI with CHF	HT, CAD, CHF, Asthma	
78	Acute MI	HT, DLP, CKD	

RSV, respiratory syncytial virus; AML, acute myeloid leukemia; MM, multiple myeloma.

HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia; MI, myocardial infarction.

CHF, congestive heart failure; HT, hypertension; DLP, dyslipidemia; DM, diabetes mellitus.

AF, atrial fibrillation; CKD, chronic kidney disease; CVA, cerebrovascular accident.

COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease.

#### 4.5. Mortality (Table 3)

The overall mortality rate was 15.9% (11 of 69 patients). Two patients of nosocomial RSV infection had hematologic malignancy with agranulocytosis. They received oral ribavirin, empirical antibiotics, and antifungal drugs; however, RSV persisted and had no evidence of other organisms (bacteria or fungus). Nine patients of community-acquired RSV infection were of advanced age (64–95 years) and had comorbidities. Pneumonia (9 of 11, 81.8%) and acute MI (2 of 11, 18.2%) were the most and the second common causes of death.

### 5. Discussion

Most (87.0%) adult hospitalized patients with RSV infection of age  $\geq 50$  years had comorbidities. RSV is an important pathogen not only in patients of age  $\geq 65$  years but also in the age range 50–64 years, which was similar to previous studies [9,19,20]. Nevertheless, we found the highest prevalence in age range 65–79 years (36.2%). The major comorbidities were pre-existing cardiopulmonary diseases, hematologic malignancy, immunocompromised hosts and DM. These findings were similar to the results of previous studies [4,6,11,19,21]. RSV infection is a seasonal disease [3,22,23]. We found RSV infection in the hospitalized patients during rainy seasons, which was similar to the results of a previous study in another region of Thailand [3]. The common manifestations were cough, dyspnea, sputum production, fever, wheezing, and tachypnea, similar to the previous studies. [6,9,11,21,24] Nevertheless, nasal congestion and rhinorrhoea were not the predominant symptoms in our study. These findings suggested predominant involvement of lower respiratory tract, which might be associated with disease severity.

### 6. Respiratory complications

The prevalence of pneumonia and acute respiratory failure, which required ventilatory support, was higher than those in previous studies, 79.7% vs 29%–67.5% and 36.2% vs 3.4%–17.0%, respectively [6,7,11,25–27]. Chest radiologic findings of RSV pneumonia in our study included predominant interstitial infiltrations (60.0% diffuse interstitial infiltrations alone and 30.9% mixed diffused interstitial and alveolar infiltrations). In contrast, those of most previous studies were consolidation or ground-glass opacity in unilateral and basilar in location [6,11,24,28]. However, our radiologic findings were similar to

those of a previous study conducted in rural Thailand by another research group [12].

## 7. Cardiovascular complications

Cardiovascular complications were found in 24.6% of patients including both worsening and new onset CHF, acute MI, new AF and SVT, and 52.9% of them had pre-existing cardiovascular diseases. The prevalence of cardiovascular complications in adult RSV infection had been reported in 14.3%–22.0% of patients [6,11]. A risk of overall cardiovascular complications in our study was pre-existing coronary arterial disease (CAD) with adjusted odds ratio 6.18, (95% CI 1.18–32.5),  $p = 0.03$ . In addition, we found that acute MI was the second cause of death. These supported the importance of cardiovascular complications in adult hospitalized patients with RSV infection. Patients with cardiovascular disease have higher rates of health care utilization for RSV-related illness and worse outcomes [29].

## 8. Antimicrobial treatment

Most patients received initial empirical antibiotics (94.2%) and oseltamivir (73.9%), which had no effect on RSV. We might reduce the unnecessary uses of antibiotics and anti-influenza drugs, if we knew pathogen earlier. Oral ribavirin was used in patients with severe respiratory failure who needed mechanical ventilator and immunocompromised hosts in our observational study; however, the benefit of treatment is not clear.

## 9. Mortality rate

The mortality rate was high (15.9%) compared to other studies (5.8%–11.9%) [4,6,21]. This might be because of severe RSV infection, where pneumonia was found in 79.7% of patients. In the adult hospitalized patients with RSV infection, mortality was higher in the elderly with comorbidities and young patients with hematologic malignancy. Cardiopulmonary complications such as pneumonia and acute MI were the most and the second causes of death, respectively.

High complications and mortality of RSV infection in our study supported the importance of RSV infection in adult hospitalized patients. RSV causing severe complications and high mortality in the elderly similar to or higher than influenza had been reported [7,11,30]. Adult severe pneumonia can occur in other viruses including human metapneumovirus (HMPV), human rhinovirus, parainfluenza virus, adenovirus, and coronavirus [5,10,31]. More studies of respiratory viral infections in adult patients are needed to identify the incidence and the impact of these viruses in Thailand. The mechanisms of these severe diseases in the elderly are not clear. However, the experimental studies in aged mice infected with RSV and/or HMPV demonstrated that CD4 + T lymphocytes, the cytokine response, or a defect in humoral response may be associated with the severity in this population [32,33].

## 10. The limitation of the study

The first limitation of the study is the combination of retrospective and prospective studies, even though most of the patient data were recorded by pulmonologists on duty. The retrospective study might affect the presenting symptoms of patients; however, it should not affect the clinical outcomes including cardiopulmonary complications and mortality. The second limitation is that only the respiratory specimens of patients suspected of respiratory viral infection were sent for the detection of RSV. It may lead to bias in the prevalence and clinical presentations. The prospective study of all adult hospitalized patients with acute respiratory illness should be conducted to determine the prevalence, clinical manifestations, and outcomes of the virus.

## 11. Conclusions

Most of the adult hospitalized patients with RSV infections aged  $\geq 50$  years old and had pre-existing cardiopulmonary diseases, hematologic malignancy, immunocompromised hosts, and DM. Pneumonia and acute MI were the major causes of death. Management and preventive strategies of RSV infection in these vulnerable groups in both community-acquired and hospital-acquired infections are necessary.

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## CRedit authorship contribution statement

**Benjamas Chuaychoo:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Sopita Ngamwongwan:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Bualan Kaewnaphan:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Niracha Athipanyasilp:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Navin Horthongkham:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Wannee Kantakamalakul:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Nisa Muangman:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing - original draft, Writing - review & editing.

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