

# Respiratory Viral Infections in Pragmatically Selected Adults in Intensive Care Units: A Prospective Cohort Study

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## Research Article

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# Abstract

## Background

Respiratory viruses can be detected in 18.3% to 48.9% of critically ill adults with severe respiratory tract infections (RTIs). The present study aims to assess the clinical significance of respiratory viruses in pragmatically selected adults in medical intensive care unit patients and to identify factors associated with viral respiratory viral tract infections (VRTIs).

## Methods

We conducted a prospective study on critically ill adults with suspected RTIs without recognized respiratory pathogens. Viral cultures with monoclonal antibody identification, in-house real-time polymerase chain reaction (PCR) for influenza virus, and FilmArray® respiratory panel were used to detect viral pathogens. Multivariable logistic regression was applied to identify factors associated with VRTIs.

## Results

Sixty-four (40.5%) of the included 158 critically ill adults had respiratory viruses detected in their respiratory specimens. The commonly detected viruses included influenza virus (20), followed by human rhinovirus/enterovirus (11), respiratory syncytial virus (9), human metapneumovirus (9), human parainfluenza viruses (8), human adenovirus (7), and human coronaviruses (2). The FilmArray® respiratory panel detected respiratory viruses in 54 (34.6%) patients, but showed negative results for seven of 13 patients with influenza A/H3 infection. In the multivariable logistic regression model, patient characters associated with VRTIs included those aged < 65 years, household contact with individuals with upper RTI, the presence of fever, cough with sputum production, and sore throat.

## Conclusions

Respiratory viruses were not uncommonly detected in the pragmatically selected adults with critical illness. Selective multiplex PCR testing for respiratory viruses is a practical strategy, and the detection rate could be further improved in selected patient population.

# Background

Respiratory viruses can cause upper and lower respiratory tract infections (RTIs) including seasonal colds, otitis media, bronchiolitis, pneumonia, and acute deterioration of chronic lung diseases, in patients with and without suppressed immunity<sup>1,2</sup>. Viral pathogens may cause 24.5% of cases of community-acquired pneumonia requiring hospitalization in adults, as modern multiplex molecular diagnostic assays

are applied<sup>3,4</sup>. Moreover, up to 10% of community-acquired pneumonia is concurrently caused by viral and bacterial pathogens<sup>3</sup>.

Respiratory viruses had been detected in respiratory specimens in 18.3% of critically ill adults requiring invasive mechanical ventilation<sup>5</sup>. The detection rates are higher, ranging from 20.5–49.0%, in patients with community or hospital-acquired lower respiratory tract infections admitted to intensive care units (ICUs)<sup>5–14</sup>. Human rhinovirus, influenza virus, and human parainfluenza viruses (HPIVs) are the most frequently detected viruses<sup>5–9</sup>. In terms of disease severities requiring timely actions, critically ill patients are considered appropriate candidates for respiratory viral panel testing<sup>15</sup>.

As the expense of the molecular tests remains high, universal testing for all patients with suspected RTIs may not be a cost-effective strategy, since more than half events are caused by bacteria or other non-infectious etiologies<sup>3</sup>. Proper selection for patients to test is required to maximize the clinical benefits in medical care, either by early initiation of antiviral agents, avoidance of unnecessary invasive studies, or shorter antibiotic exposure<sup>15</sup>. Patients with known bacterial pathogens may be less likely to benefit from testing for respiratory viruses, since discontinuation of antimicrobial therapy is not a reasonable option for them. The current study aims to assess the clinical significance of respiratory viruses in pragmatically selected adults in medical ICUs and to delineate clinical variables associated with viral RTIs (VRTIs).

## Methods

### Study design and population

We conducted a prospective study from May 2017 to December 2018 at a 42-bed medical ICU in a tertiary hospital with more than 1300 beds in southern Taiwan. The cases aged at least 20 years with suspected VRTIs were considered for inclusion. Similar to the real-world practice, those with positive results of microbiological tests indicative of specific causative pathogens, such as positive rapid antigen tests, blood cultures, or significant bacteria on Gram stain for endotracheal aspirates, were excluded. Written informed consents were obtained from the patients or surrogate decision-makers. The study was approved by the institutional review board of National Cheng Kung University Hospital (IRB No.: B-ER-105-350). All experiments were performed in accordance with relevant guidelines and regulations

### Clinical data collection

Electronic medical records of included patients were reviewed for demographic variables, clinical manifestations, contact history, chronic illness, laboratory results within 48 hours upon presentation, virological studies, causes of respiratory distress, mechanical ventilation, acute respiratory distress syndrome (ARDS), concurrent non-viral respiratory pathogens, severity scores grading by Acute Physiology and Chronic Health Evaluation II (APACHE II) on the first ICU day and Sequential Organ Failure Assessment (SOFA) score on the day of first respiratory specimen collection, length of ICU or hospital

stay, duration of mechanical ventilation, ICU and 28-day mortality. In addition, one of the authors (CT Cia or JC Lee) obtained symptom details from the patients or their relatives upon inclusion.

The number of critically ill adults with virologically confirmed influenza during the study period was retrieved from severe influenza notification records, to quantify the clinical burden of influenza, as some cases might be excluded from this study due to positive rapid tests for influenza.

## Definitions

ARDS and its severities were defined according to the Berlin definition<sup>16</sup>. Vasopressor use was defined as norepinephrine, vasopressin, epinephrine, dopamine, or phenylephrine administration for 120 minutes or longer. Septic shock was defined as vasopressor use and hyperlactatemia without hypovolemia, based on the Sepsis-3 consensus<sup>17</sup>.

## Virological studies

Nasopharyngeal swab (NPS), throat swab (TS), or bronchoalveolar lavage (BAL) from ICU patients were examined by viral cultures, real-time polymerase chain reaction (PCR) for influenza virus, and BioFire® FilmArray® respiratory panel (BioFire Diagnostics, Salt Lake City, Utah, USA). The swabs were placed into in-house or commercially available viral transport medium (Copan Diagnostics, Murrieta, California, USA). Flocked swabs, instead of conventional cotton swabs, were used for the collection of nasopharyngeal or throat samples since April 2018. The decision to perform a bronchoscopy was made by the treating physicians. Other microbiological studies were ordered according to clinical needs.

Respiratory specimens in transport medium were inoculated to cell lines, including human lung carcinoma (A549), human embryonic rhabdomyosarcoma (RD), and Madin-Darby canine kidney (MDCK) cells. Tubes with cytopathic effect were confirmed by D<sup>3</sup>® Ultra 8™ DFA (direct fluorescent antibody) Respiratory Virus Screening and ID Kit (Diagnostic Hybrids, Athens, Ohio, USA), which was able to detect influenza A and B viruses, respiratory syncytial virus (RSV), human adenovirus (HAdv), HPIV 1–3, and human metapneumovirus (HMPV). Those without cytopathic effects were blindly stained by the same kit after inoculation for 10 days.

Nucleic acid amplification of influenza viruses was performed on LightCycler® 480 real-time PCR machine (Roche Diagnostics, Rotkreuz, Switzerland) after RNA extraction with LabTurbo 48 Compact auto-extraction System (Taigen Bioscience Corp., Taipei, Taiwan). The sequences of influenza primers and probes were provided by the World Health Organization and the Taiwan Centers of Disease Control (Additional File 1, Table S1).

The FilmArray® respiratory panel tests were performed by mixing 300 µL of VTM with sample buffer, injection into a test pouch containing reagents for nucleic extraction, PCR amplification, and detection of pathogen targets, including HAdv, human coronavirus (HCoV)-229E, HCoV-HKU1, HCoV-OC43, HCoV-NL63, HMPV, human rhinovirus/enterovirus (RV/EV), influenza A (A, A/H1, A/H1-2009, A/H3), influenza B, HPIV 1–4, RSV, and three bacteria (*Bordetella pertussis*, *Chlamydia pneumoniae*, and *Mycoplasma*

*pneumoniae*). The pouches (version 1.7) were inserted into the FilmArray® instrument (version 2.0). An equivocal result was reported as negative. Since the panel was not a routine test during the study period, the treating physician might not be informed of the results timely.

## Statistical analysis

All statistical analyses were performed using R 4.0.2 (R Foundation for Statistical Computing, <http://www.R-project.org/>, Vienna, Austria). Continuous variables were presented as means  $\pm$  standard deviations or medians (1st – 3rd quartile). Student's t test or Wilcoxon rank-sum test was applied for the between-group comparisons for normally or non-normally distributed variables, respectively. Category variables were compared by Pearson's  $\chi^2$  test or Fisher's exact test when appropriate. The Wilson score was applied for confidence interval (CI) estimates of binomial proportions. A  $p$  value of less than 0.05 was considered to be statistically significant.

The multivariable logistic regression was performed to identify the factors associated with the detection of respiratory viruses. The parameters not readily available at the time of virological testing were not included into the regression models. The cases with missing data were excluded from the corresponding analyses. Of continuous variables such as age, C-reactive protein, and procalcitonin, we tried modeling with clinically relevant cut-off values to enhance their clinical applicability. Factors with a  $p$  value of less than 0.15 in simple regressions were included into the multivariable model. The effect sizes were presented by odds ratios (OR) with 95% CIs.

## Results

One hundred and fifty-eight critically ill adults with 167 respiratory specimens (NPS 154, TS 2, and BAL 11) were included during the study period. All patients were tested by the FilmArray® panel, while one and seven patients did not undergo nucleic acid amplification for influenza viruses and viral cell cultures, respectively. The first specimen collection was obtained at a median of one day (0–1 day) after ICU admission.

Respiratory viruses were detected in 64 (40.5%) patients, *i.e.*, 64 patients with VRTIs. The comparisons of clinical data between patients with or without detection of respiratory virus are demonstrated in Table 1. Patients with VRTIs were younger (median age: 62.5 vs. 69.0 years,  $p = 0.003$ ), but there were no differences in terms of chronic illness, disease severity, and clinical outcomes, including mortality rate and length of ICU or hospital stay between the two groups.

Table 1  
Clinical characteristics of patients with and without viral respiratory tract infections (VRTIs).

	All (n = 158)	With VRTIs (n = 64)	Without VRTIs (n = 94)	p value
Demographic				
Age	68 (56.25–77)	62.5 (49.25–75)	69 (60.25–79)	0.003
Male sex	87 (55%)	29 (45.3%)	58 (61.7%)	0.268
Hospital stay	16 (10–28)	16 (10–25.25)	16 (10–29.75)	0.980
Comorbidity				
Hypertension	72 (45.6%)	29 (45.3%)	43 (45.7%)	0.974
Diabetes mellitus	47 (29.7%)	19 (29.7%)	28 (29.8%)	0.992
Chronic kidney disease	45 (28.5%)	19 (29.7%)	24 (27.7%)	0.836
Heart failure	37 (23.4%)	16 (25.0%)	21 (22.3%)	0.761
Coronary artery disease	28 (17.7%)	14 (21.9%)	14 (14.9%)	0.348
COPD	25 (15.8%)	8 (12.5%)	17 (18.1%)	0.419
Malignancies	24 (15.2%)	8 (12.5%)	16 (17.0%)	0.503
Autoimmune diseases	11 (7.0%)	3 (4.5%)	8 (8.7%)	0.529
Bronchiectasis	8 (5.0%)	5 (7.8%)	3 (3.2%)	0.279
Asthma	4 (2.5%)	2 (3.1%)	2 (2.1%)	1.000
Hepatic cirrhosis	2 (1.3%)	0 (0%)	2 (2.1%)	0.517
Severity & outcomes				
Vasopressor use	64 (40.5%)	26 (40.6%)	38 (40.4%)	1.000
Septic shock	32 (20.3%)	15 (23.4%)	17 (18.1%)	0.638
Mechanical ventilation	128 (81.0%)	52 (81.3%)	76 (80.9%)	0.984
ARDS	60 (38.0%)	29 (45.3%)	31 (33.0%)	0.297

VRTI viral respiratory tract infection, COPD chronic obstructive pulmonary disease, ARDS acute respiratory disease syndrome, APACHE II Acute Physiologic Assessment and Chronic Health Evaluation II, SOFA Sequential Organ Failure Assessment, MV mechanical ventilation, ICU intensive care unit.

<sup>a</sup> on the ICU admission day.

<sup>b</sup> on the day obtaining the first respiratory specimen.

	All (n = 158)	With VRTIs (n = 64)	Without VRTIs (n = 94)	p value
Moderate-to-severe	46 (29.1%)	21 (32.8%)	25 (26.6%)	0.533
APACHE II <sup>a</sup>	21.23 ± 7.66	19.98 ± 6.98	22.09 ± 8.10	0.083
SOFA score <sup>b</sup>	7.25 ± 3.71	7.44 ± 3.56	7.12 ± 3.81	0.590
MV days	4 (2–10)	4.5 (2–9.25)	4 (2–12)	0.892
ICU stay	8 (5–14)	8 (5–13)	8 (5–14)	0.691
Hospital stay	16 (10–28)	16 (10–25.25)	16 (10–29.75)	0.980
ICU mortality	24 (15.2%)	7 (10.9%)	17 (18.1%)	0.289
28-day mortality	23/152 (15.1%)	8/62 (12.9%)	15/90 (16.7%)	0.584
<i>VRTI</i> viral respiratory tract infection, <i>COPD</i> chronic obstructive pulmonary disease, <i>ARDS</i> acute respiratory disease syndrome, <i>APACHE II</i> Acute Physiologic Assessment and Chronic Health Evaluation II, <i>SOFA</i> Sequential Organ Failure Assessment, <i>MV</i> mechanical ventilation, <i>ICU</i> intensive care unit.				
<sup>a</sup> on the ICU admission day.				
<sup>b</sup> on the day obtaining the first respiratory specimen.				

The most commonly detected virus was influenza virus (20 patients: A/H1 6, A/H3 13, B 1), followed by RV/EV (11), RSV (9), HMPV (9), HPIVs (8), HAdV (7), and HCoV (2) (Fig. 1). To be noted, 57 adults admitted to medical ICUs with confirmed influenza were not included in the study, usually due to positive results in rapid antigen tests. The FilmArray® respiratory panel detected respiratory viruses in 54 patients and *M. pneumoniae* in one patient. Nine patients with negative results of the FilmArray® respiratory panel, but had VRTIs due to respiratory viruses detected by other tests, including influenza A/H3 (7), influenza A/H1 (1) and HAdV (1). Among eight patients with both NPS and BAL tested by the panel, two had discordant results: one HCoV-NL63 only in NPS and the other HAdV only in BAL. The remaining six patients had concordant NPS and BAL results, including one with influenza A/H3, one with hMPV, and four without viral pathogen. Viral cell cultures revealed respiratory viruses in 12 patients (influenza A: 3, HAdV: 3, RSV: 3, HPIV-3: 2, RV/EV: 1), accounting for 20.3% of 59 patients with VRTIs having viral cultures.

Twelve (18.8%) of 64 patients with and 25 (26.6%) of 94 patients without VRTIs had RTIs due to other pathogens. Of 12 patients with VRTIs, coexisting pneumonia caused by bacteria was present in nine patients, including two with *Klebsiella pneumoniae* and two with *Staphylococcus aureus* infections, while three patients had concurrent pulmonary aspergillosis. Of the latter, one had concurrent fusariosis and pneumocystis, and another biopsy-proven *Candida tropicalis* tracheobronchitis. Of co-infections due to non-respiratory viruses, one had cytomegalovirus pneumonitis and the other human simplex virus-1

tracheobronchitis. Among seven fatal patients with VRTIs (HAdV: 2, RSV: 2, RV/EV: 2, influenza A/H3: 1), two were complicated with concurrent bacterial pneumonia.

Among all 158 patients with respiratory distress, 22 (46.8%) of 47 patients with acute decompensated heart failure had VRTIs, while the proportions of VRTIs in patients with pneumonia, tracheobronchitis, acute exacerbation of chronic obstructive pulmonary disease, and asthma were 45.8% (38/83), 36.4% (4/11), 29.2% (4/24), and 50% (2/4), respectively. None of nine patients related to metabolic acidosis (5 patients), sepsis of unknown source (3), or *K. pneumoniae* bacteremia complicated by liver abscess (1) had VRTI.

The multivariable logistic regression analyses revealed the risk factors associated with VRTIs in Table 2. The variables significantly associated with VRTIs in the simple regression analysis but not in the multivariable model included myalgia, rhinorrhea, neutrophil-to-lymphocyte ratio > 12.5, and specimen collected by a flock swab. None of the blood biomarkers, such as white blood cell count, serum levels of C-reactive protein or procalcitonin, were predictive of the existence of VRTIs. Age less than 65 years old (OR, 4.61; 95% CI, 1.99–11.40), household contact with someone having upper RTI (OR, 4.28; 95% CI 1.82–10.82), the presence of fever (OR, 3.16; 95% CI 1.23–8.81), productive cough (OR, 3.42; 95% CI, 1.45–8.63), or sore throat (OR, 3.82; 95% CI 1.27–12.59), were significantly associated with VRTIs. The association of the number of the above variables with probability of VRTI was shown in Fig. 2 and Additional File 1, Table S2.

Table 2

Simple and multivariable regressions for factors associated with viral respiratory tract infections.

Variables	Odds ratio (95% CI)	<i>p</i> value	Odds ratio (95% CI)	<i>p</i> value
Age < 65 years	3.23 (1.67–6.34)	< 0.001	4.61 (1.99–11.40)	< 0.001
Household contact with a person having upper RTI	2.76 (1.42–5.45)	0.003	4.28 (1.82–10.82)	0.001
Clinical symptoms				
Rhinorrhea	3.70 (1.87–7.47)	< 0.001	2.15 (0.86–5.53)	0.103
Sore throat	3.68 (1.65–8.60)	0.002	3.82 (1.27–12.59)	0.021
Myalgia	2.95 (1.30–6.97)	0.011	2.16 (0.78–6.16)	0.139
Productive cough	2.87 (1.18–7.56) <sup>a</sup>	0.024	3.42 (1.45–8.63) <sup>b</sup>	0.007
Fever	2.29 (1.05–5.34)	0.044	3.16 (1.23–8.81)	0.020
Dyspnea	2.11 (0.47–14.75)	0.369		
Dry cough	1.48 (0.55–4.21) <sup>a</sup>	0.442		
Headache	1.35 (0.48–3.73)	0.561		
Malaise	1.14 (0.60–2.18)	0.678		
Altered mental status	0.64 (0.24–1.56)	0.347		
Laboratory tests				
White blood cell count	1.00 (1.00–1.00)	0.513		
Leukocytosis <sup>c</sup>	0.75 (0.40–1.43)	0.389		
Leukopenia <sup>d</sup>	1.10 (0.21–5.19)	0.897		
NLR	1.01 (0.99–1.04)	0.231		

Variables	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
NLR > 12.5	1.79 (0.90–3.55)	0.094	2.43 (1.00–6.16)	0.053
C-reactive protein (CRP) <sup>e</sup>	1.00 (0.99–1.01)	0.849		
CRP ≥ 89 mg/L	2.14 (0.44–11.31)	0.348		
Procalcitonin (PCT) <sup>f</sup>	1.01 (0.97–1.06)	0.601		
PCT > 0.35 ng/mL	1.63 (0.58–4.62)	0.355		
Flocked swab use	1.99 (1.04–3.84)	0.038	2.10 (0.94–4.83)	0.073
<i>CI</i> /confidence interval, <i>RTI</i> /respiratory infection, <i>NLR</i> neutrophil-to-lymphocyte ratio.				
<sup>a</sup> Compared to no cough.				
<sup>b</sup> Compared to no or dry cough.				
<sup>c</sup> White blood cell count > 11,000 /μL				
<sup>d</sup> White blood cell count < 4,000 /μL				
<sup>e</sup> Available in 27 patients				
<sup>f</sup> Available in 62 patients				

## Discussion

The current study assessed the prevalence of VRTIs in pragmatically selected adults with critical illness, when other causes were unable to fully explain the patients' respiratory distress and clinical presentation. A positivity rate of 40.5% in the present study is higher than that of non-selected patients receiving mechanical ventilation in ICUs<sup>5</sup>. The median time from ICU admission to specimen collection for multiplex test is one day, indicating that the tests were ordered according to clinical information obtained right after ICU admission, rather than reserving the tests for patients with negative results of bacterial cultures.

To our knowledge, the host variables predictive of VRTIs among critically ill patients had not been adequately investigated before, as previous studies included mainly demographic information, comorbidities, or laboratory results<sup>7–9</sup>. Age < 65 years old, household contact with an individual having upper RTI and the presence of fever, productive cough, or sore throat were linked to VRTIs. In the patients

presenting three of the above five characters, the probability of VRTIs is 60%. Considering the limited accuracy of clinical information from severely ill patients on respiratory support and their families, these associations of clinical symptoms and VRTIs may be more significant than that in the present study, which suggests the indispensability of thorough history taking even in critical care settings. The age factor could be attributed to a higher rate of non-infectious causes of respiratory distress in the elderly<sup>18,19</sup>. It is not surprising that traditional laboratory tests failed to detect respiratory viruses in clinical samples, since bacterial etiological pathogens could be noted in only 13.2% of the included patients.

In spite of the exclusion of 57 cases of severe influenza, influenza virus remained to be the most commonly viral pathogen. The weighting of influenza virus is obviously underestimated in the viral etiologies of RTIs. Thus, our prevalence data supports empiric administration of anti-influenza agents to selected critically ill patients with suspected VRTIs. However, the FilmArray® respiratory panel failed to detect influenza A/H3 in 8 (61.5%) out of the 13 patients diagnosed by the in-house PCR using updated primers. As influenza viruses evolve rapidly, physicians should be cautious that commercially available molecular assays may provide unreliable results, if not updated frequently<sup>20</sup>.

As influenza virus, other respiratory viruses can cause significant morbidity and mortality in critically ill patients<sup>21,22</sup>, and in this study these viruses accounted for 68.8% of all VRTIs. Six of seven patients died in the ICUs were infected by non-influenza viruses. However, our case number is insufficient to compare clinical characteristics among different respiratory viruses and further studies are warranted.

Previous studies showed that clinical specimens from upper and lower respiratory tract specimens may yield discordant testing results, as noted in 2 (25%) of our 8 patients with both NPS and BAL samples tested for respiratory viral pathogens, in 11–36% of critically ill or immunosuppressed hosts<sup>5,6,23,24</sup>. Accordingly, etiological surveys using both upper and lower respiratory tract specimens ought to be considered in patients with highly suspected VRTIs.

Clinical application of multiplex respiratory viral assays had been expected to facilitate discontinuation or de-escalation of antibiotics<sup>25</sup>. Interestingly, several studies with the detection rates of < 25% for respiratory viruses invariably show no significant decline in antibiotic use [21–23]. When the prevalence of VRTIs exceeded 25%, the utilization of these assays was associated with favorable results on antimicrobial stewardship program (Additional File 1, Table S3)<sup>26–33</sup>. As none of these studies focus on ICU patients, our detection rate of 40.5% for viral pathogens in the selected patients suggested the need of further investigations into the impact of multiplex viral testing on reduction of unnecessary antibiotic use in selected critically ill patients.

Our study inherited several limitations. First, this is a single-center observation study and the study result cannot be generally applied to other clinical settings or healthcare facilities, since the distribution of respiratory viruses varies seasonally and geographically. Second, only 7% of our included patients had lower respiratory tract specimen tested, and thus the rate of VRTIs are likely to be underestimated<sup>5,6</sup>.

Third, the case of concurrent viral and non-viral RTIs were largely excluded since according to the study protocol, the initial clinical presentation would preclude respiratory virus tests.

## Conclusions

VRTIs were not uncommon in pragmatically selected adults with critical illness. Age < 65 years old, household contact with a person having upper RTI, and the presence of clinical symptoms of fever, productive cough, or sore throat, were associated VRTIs. To maximize clinical benefit, intensivists can consider selective application of multiplex molecular assays for respiratory viral pathogens, based on the above predictive variables. The sensitivity and specificity of the predicative model and clinical impact of VRTIs need to be further studied on larger prospective cohorts.

## Abbreviations

RTI

respiratory tract infection; ICU:intensive care unit; HCoV:human coronavirus; VRTI:viral respiratory tract infection; ARDS:acute respiratory distress syndrome; APACHE II:Acute Physiology and Chronic Health Evaluation II; SOFA:Sequential Organ Failure Assessment; NPS:nasopharyngeal swab; TS:throat swab; BAL:bronchoalveolar lavage; PCR:polymerase chain reaction; VTM:viral transport medium; RD:rhabdomyosarcoma; MDCK:Madin-Darby canine kidney; RSV:respiratory syncytial virus; HAdv:human adenovirus; HPIV:human parainfluenza virus; HMPV:human metapneumovirus; RV/EV:human rhinovirus/enterovirus; OR:odds ratio

## Declarations

## Authors' contributions

CTC, HPT, and WCK designed the study. CTC and JCL obtained the respiratory specimens and collected the clinical data. ITL, HPT, and JRW performed the virological studies and analyzed the results. CTC analyzed the data and drafted the manuscript. JCL, HPT and JRW revised the manuscript. WCK finalized the manuscript. All authors reviewed and approved the final manuscript.

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# Additional Information

## Competing interests

Funding: The study was funded by National Cheng Kung University Hospital (NCKUH-10608008). The BioFire® Filmarray® respiratory panel test kits were sponsored by Wei Mao Co., Ltd. (Taiwan).

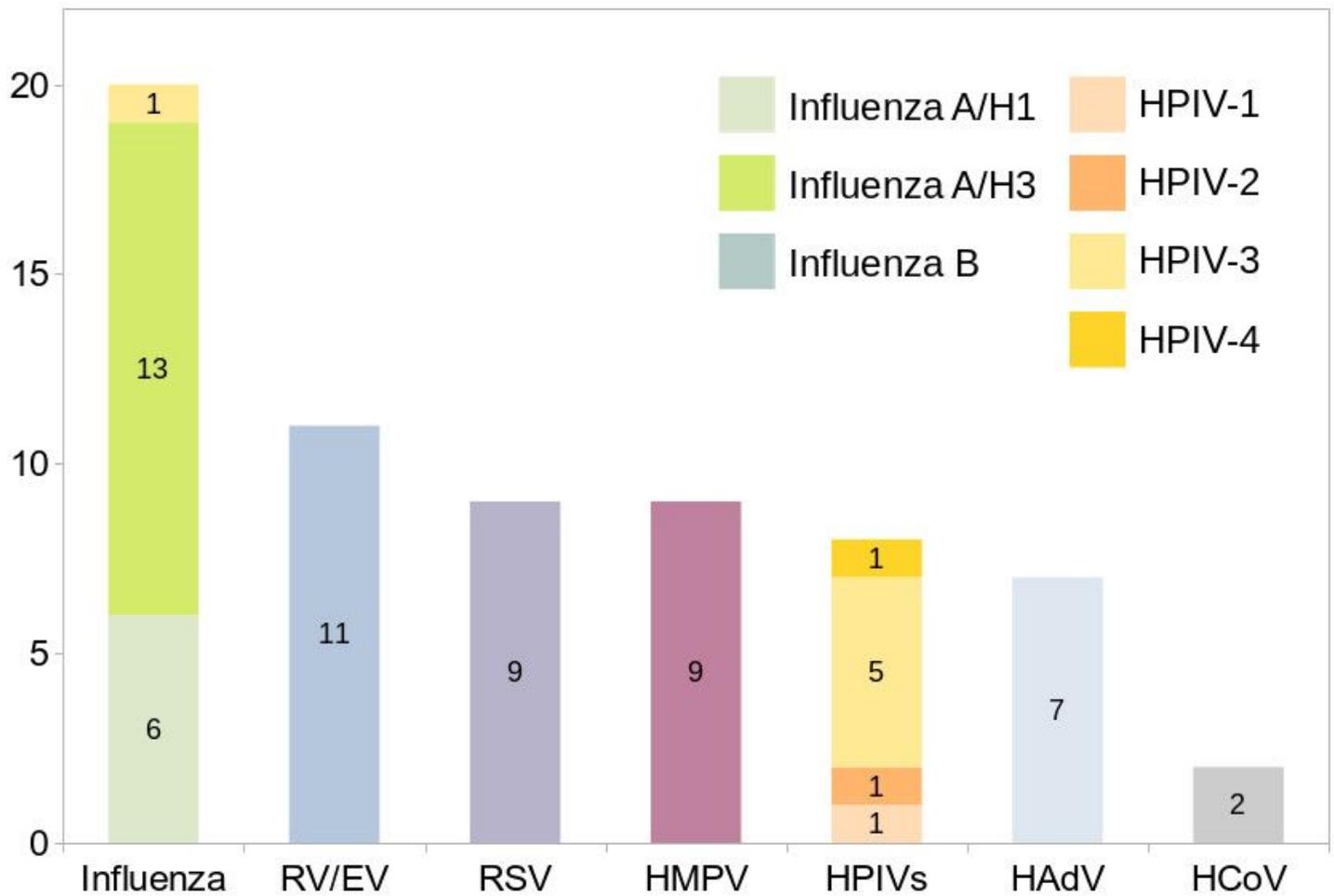
## Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

## References

The list of references is not available with this version. A reference list for a previous version of this manuscript is available in the supplemental file section.

## Figures



**Figure 1**

Respiratory viruses detected in 64 critically ill adults. RV/EV rhinovirus/enterovirus, RSV respiratory syncytial virus, HMPV human metapneumovirus, HPIV human parainfluenza virus, HAdV human adenovirus, HCoV human coronavirus.

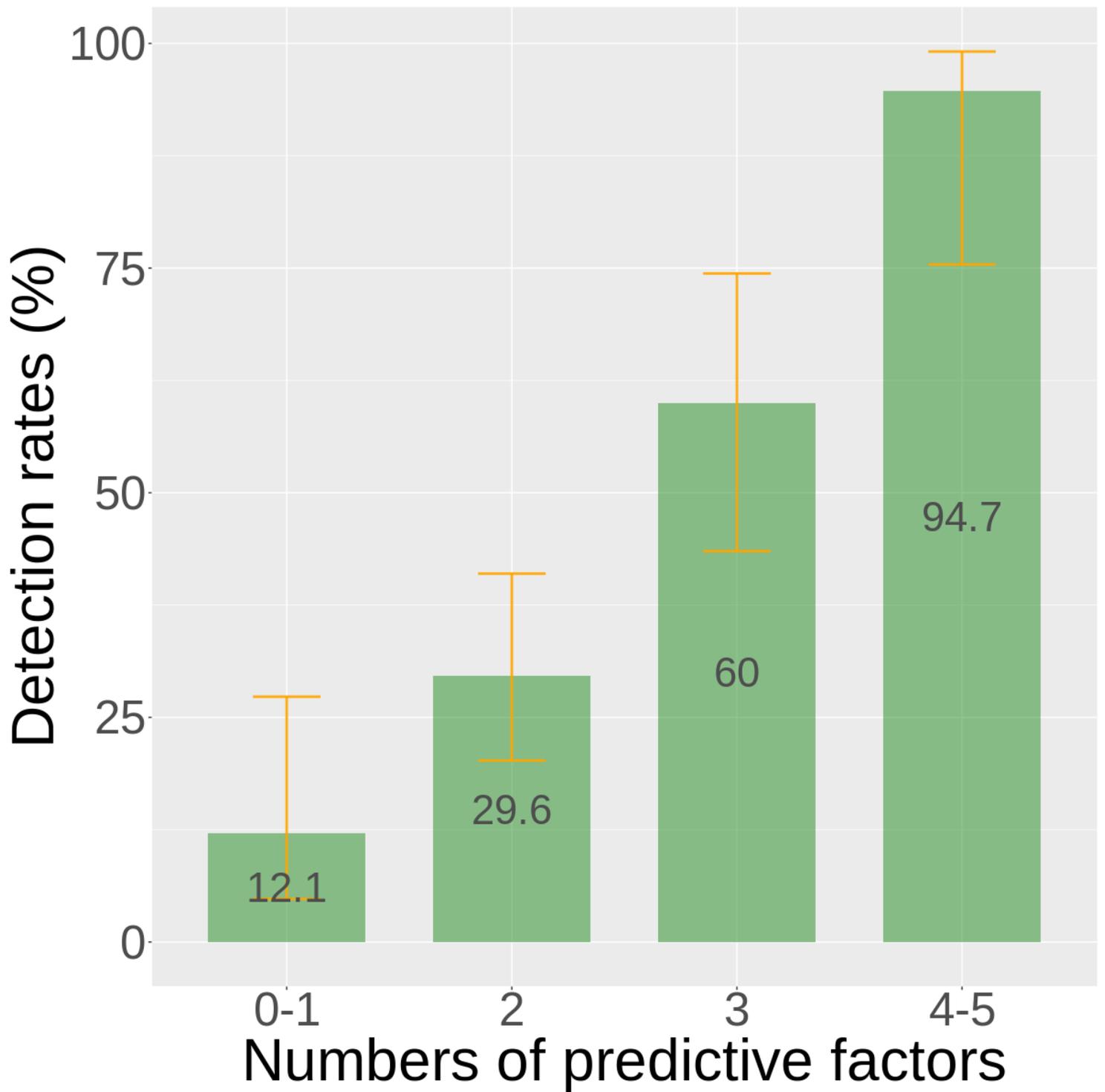


Figure 2

Numbers of predictive factors and detection rates of respiratory viruses. Error bars represent the 95% Wilson score confidence intervals of the point estimates.

## Supplementary Files

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