Clinical manifestations of influenza and performance of rapid influenza diagnostic test: A university hospital setting

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Abstract

Background: Rapid influenza diagnostic test (RIDT) is a diagnostic tool that detects the influenza virus nucleoprotein antigen. The RIDT is widely used in clinical practice because it is simple and cost-effective, and provides results within 10-15 minutes.

Objective: We aimed at evaluating the sensitivity and specificity of the Sofia® RIDT compared with the Luminex® multiplex polymerase chain reaction (PCR). The other goal was to determine the predicting factors for diagnosing influenza among individuals with influenza-like illness (ILI).

Method: Patients with ILI who had the results of both tests were retrospectively reviewed. We determined the performances of the RIDT.

Results: A total of 473 patients were included with a median age of 58 (interquartile range 41-74) years. Of these, 47.1% were male, and 16.2% were diagnosed with influenza by the RIDT or RT-PCR’s positive test. For influenza A, the RIDT showed a sensitivity of 76.3% (95% confidence interval [CI] 59.8-88.6) and a specificity of 97.9% (95% CI 96.1-99.0), whereas for influenza B, it showed a sensitivity of 47.1% (95% CI 23.0-72.2) and a specificity of 97.1% (95% CI 95.2-98.5). Patients with influenza were more likely to present with fever (81.8% vs 63.1%), cough (81.8% vs 66.1%), and rhinorrhea (41.6% vs 26.5%) compared to those without influenza (P < 0.05, all), and had a higher proportion of pneumonia (19.5% vs 10.6%, P = 0.029) and acute respiratory distress syndrome (5.2% vs 1.5%, P = 0.063). The predicting factors for influenza among patients presented with ILI were cough (odds ratio [OR] 2.77; 95% CI 0.21-0.81, P = 0.010), rhinorrhea (OR 1.87; 95% CI 1.03-3.36, P = 0.037), and higher body temperature (OR 1.64; 95% CI 1.23-2.19, P = 0.001).

Conclusions: The sensitivity of the RIDT for the diagnosis of influenza is fair in contrast to the specificity. Among patients with ILI, cough, rhinorrhea, and higher body temperature might be factors for predicting influenza.

Keywords
diagnosis, influenza, polymerase chain reaction, rapid test
1 | INTRODUCTION

Influenza is a respiratory virus that is highly contagious and easily spreads from person to person by droplet transmission.\(^1\)\(^-\)\(^3\) It can involve multiple organ systems such as respiratory tract, cardiovascular, and musculoskeletal, leading to morbidity and mortality.\(^1\)\(^-\)\(^3\) Accordingly, there is a high number of influenza cases in Thailand. The overall influenza cases during 2017-2019 are more than 150,000 cases per year, with an estimated annual incidence of more than 250 per 100,000 population.\(^4\) Also, influenza leads to a high economic burden in Thailand compared to other countries.\(^5\)

Several different approaches are currently available for the diagnosis of influenza viruses. Reverse transcription-polymerase chain reaction (RT-PCR) is the most traditional powerful approach for the identification of influenza viruses in most laboratories. It is a molecular assay that can identify influenza virus RNA or nucleic acids in respiratory specimens, and it has very high sensitivity and specificity.\(^6\),\(^7\) Previous studies have demonstrated that RT-PCR shows superior sensitivity compared to viral culture and is now accepted as the new gold standard test for diagnostic influenza.\(^8\)\(^-\)\(^10\)

Rapid influenza diagnostic test (RIDT) is another influenza diagnostic tool that detects the influenza virus nucleoprotein antigen.\(^7\) The RIDT is widely used in clinical practice to diagnose influenza because it is simple to use and provides the results within 10-15 minutes.\(^11\) In Thailand, the RIDT is commonly used in many rural hospitals because it is simple, convenient, and low cost. Prior studies demonstrated the sensitivity of RIDT varies, ranging between 40% and 95% compared to RT-PCR.\(^12\)\(^-\)\(^16\) Furthermore, the RIDT has a high false-negative rate of 30%.\(^9\) Multiplex RT-PCR extended the utility of nucleic acid amplification techniques that allows the timely simultaneous detection of multiple types of respiratory virus.\(^9\) The benefit of the use of multiplex RT-PCR is the detection of other respiratory virus infections. Multiplex RT-PCR also has high sensitivity (97%) and specificity (95%) in detecting influenza virus infection compared with conventional RT-PCR.\(^9\)\(^,\)\(^17\) Thus, the multiplex RT-PCR can be used as a gold standard of diagnosis influenza.\(^18\)

Our study aimed at evaluating the performance of the RIDT, Sofia\(^\text{®}\) influenza A+B fluorescent immunoassay (FIA), using the Luminex\(^\text{®}\) multiplex RT-PCR as the gold standard. The other objective was to determine the predicting factors that might guide the physicians to diagnose influenza among individuals who present with influenza-like illness (ILI) and have a positive result of either the RIDT or RT-PCR.

2 | MATERIALS AND METHODS

We retrospectively reviewed patients’ medical records who were concurrently performed nasopharyngeal swabs to test both Sofia\(^\text{®}\) influenza A+B FIA and Luminex\(^\text{®}\) multiplex RT-PCR test in Ramathibodi Hospital (a 1300-bed medical school hospital in Bangkok, Thailand). Patients with positive Sofia\(^\text{®}\) influenza A+B FIA or Luminex\(^\text{®}\) multiplex RT-PCR between January 2014 and December 2018 were identified from the Virological Department of Pathology database, Faculty of Medicine Ramathibodi Hospital.

Inclusion criteria were (a) age more than 15 years and (b) having ILI, which were fever, cough, rhinorrhea, sore throat, muscle aches, headache, and fatigue.\(^19\) Exclusion criteria were unavailable medical data records for the review. The sample size was calculated by the formula of Z\(^2\)\(\alpha\)\(p(1-p)/d^2\) with substituted specificity (p) with 0.9, Z\(\alpha\) with 1.96, and standard deviation (d) with 0.05. The calculated sample size plus 10% dropout was 153. The specificity that is used to calculate the sample size is from the study of the RIDT in Thailand.\(^20\)

Demographic data were retrieved and reviewed, including age, gender, and underlying disease (eg, diabetes, hypertension, airway disease, cardiovascular disease, malignancy, HIV infection, immunosuppressive therapy, transplantation status, and pregnancy). Information of signs and symptoms was obtained by reviewing the medical records. In addition, the results of laboratory investigations and chest radiography were also reviewed. Data regarding the length of stay, treatment, and clinical outcomes were obtained from the hospital database. A patient diagnosed with influenza infection was defined by positive results of the RIDT or multiplex RT-PCR analysis.

Rapid influenza diagnostic test\(^17\): The Sofia\(^\text{®}\) influenza A+B FIA (Quidel Corporation, CA, USA) is a fluorescent immunoassay that uses advanced immunofluorescence-based lateral-flow technology to detect influenza A and influenza B viral nucleoprotein antigens using the Sofia analyzer platform, which contains a microprocessor-controlled optics unit that scans the nitrocellulose test strip’s length; therefore, the strip is exposed to UV light from the emitting diode. A positive result is determined by detecting a fluorescent signal at levels above a signal threshold set on a negative-control line. This process is controlled by a specific algorithm embedded in the Sofia analyzer. The Sofia analyzer automatically scans the test strip, analyzes the fluorescence data, and calculates and reports the result. The Sofia\(^\text{®}\) influenza A+B FIA testing was performed, followed by the manufacturer’s recommendations. After the sample was prepared, it was incubated for 15 minutes before being analyzed.

Multiplex RT-PCR\(^27\): The Luminex\(^\text{®}\) NxTAG-respiratory virus panel (RVP) assay is a capillary electrophoresis-based multiplex RT-PCR assay that can detect nucleic acids from multiple respiratory viruses and bacteria extracted from respiratory specimens, including influenza A, influenza A H1, influenza A H3, influenza B, respiratory syncytial virus (RSV) A, RSV B, coronavirus (229E, OC43, NL63, and HKU1), metapneumovirus, rhinovirus, adenovirus, parainfluenza (PIV) type 1-4 virus 1, human bocavirus, Chlamydia pneumoniae, and Mycoplasma pneumoniae. The RVP is comprised of four separate multiplex reactions. The first multiplex RT-PCR included enterovirus, rhinovirus, influenza A virus, influenza B virus, and metapneumovirus. The second multiplex RT-PCR included RSV A/B, HKU1, OC43, and adenovirus. The third multiplex RT-PCR included PIV types 1-4. The fourth multiplex RT-PCR included 229E, NL63, metapneumovirus, human bocavirus, C pneumoniae, and M pneumoniae.

RT-PCR was initiated with a reverse transcriptase step at 50°C for 30 minutes and a 15-minute denaturation at 95°C, followed by 50 amplification cycles consisting of 30 seconds at 94°C, 45 seconds...
at 58°C (for multiplex RT-PCRs 1 and 2), or 51°C (for multiplex RT-PCRs 3 and 4), and 12 seconds at 72°C. After amplification, the fragment-size analysis was performed on the applied biosystems 3130xl genetic analyzer.

Median values (with interquartile range, IQR) were used to describe patients’ baseline characteristics, and laboratory investigations as continuous data and frequencies were used for categorical data. Chi-square or Fisher’s exact tests and the Wilcoxon rank-sum test were used to comparing categorical and continuous variables between the two groups, respectively. Univariate and multivariate logistic regression analyses were performed to determine the factors associated with the diagnosis of influenza. After assessing the multicollinearity of variance inflation factors, variables with P < 0.05 in the univariate analysis were considered in a multivariate logistic regression model. Variables were included in a multiple logistic regression model using forwarding stepwise selection, and those with a level of significance P < 0.05 were retained in the model. The odds ratio (OR) and 95% confidence interval (CI) were estimated. A P-value <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 16.0 (StataCorp LLC, College Station, TX, USA).

3 | RESULTS

A total of 959 patients performed nasopharyngeal swab and tested both Sofia® influenza A+B FIA and Luminex® multiplex RT-PCR were enrolled. A total of 488 patients were excluded from the analysis for the following reasons: age under 15 years old (n = 139), incomplete medical record (n = 240), and lacked presentation of ILI (n = 109). Finally, 473 patients were eligible for inclusion in the analysis. Of all, 77 (16.3%) patients were diagnosed with influenza with either a positive result of the RIDT or RT-PCR. The performance of the Sofia® influenza A+B FIA test is shown in Table 1. For influenza A, the RIDT showed a sensitivity of 76.3% (95% CI 59.8-88.6) and a specificity of 97.9% (95% CI 96.1-99.0). For influenza B, the RIDT showed a sensitivity of 47.1% (95% CI 23.0-72.2) and a specificity of 97.1% (95% CI 95.2-98.5). The RIDT had a positive predictive value (PPV) of 76.3% (95% CI 59.8-88.6) for influenza A and 38.1% (95% CI 18.1-61.6) for influenza B and a negative predictive value (NPV) of 97.9% (95% CI 96.1-99.0) for influenza A and 98.0% (95% CI 96.3-99.1) for influenza B. The RIDT had an accuracy of 96.2% for detect influenza A and 95.3% for detect influenza B.

Of 473 patients, the median (IQR) age was 58 (41-74) years, and 47.1% were male. The median (IQR) duration of illness was 2 (1-3) days, and 74.6% were hospitalized. Approximately 90% had at least any underlying disease. Common underlying diseases were hypertension (38.9%), chronic kidney disease (32.4%), and diabetes (24.6%). Patients with a diagnosis of influenza had a lower proportion of underlying disease (84.4% vs 91.4%, P = 0.058), including airway disease (3.9% vs 11.6%, P = 0.042) and cancer (18.1% vs 33.8%, P = 0.007). Patients diagnosed with influenza had a higher proportion of fever (81.8% vs 63.8%, P = 0.002), cough (81.8% vs 66.1%, P = 0.007), and rhinorrhea (41.6% vs 26.5%, P = 0.008) compared to those without a diagnosis of influenza. Patients with a diagnosis of influenza presented with higher median body temperature than those without a diagnosis of influenza (38.3°C vs 38.1°C, P = 0.003). Baseline characteristics, signs, and symptoms of 473 patients presented with ILI are shown in Table 2.

Laboratory and radiographic findings of 473 patients present with ILI are shown in Table 3. There was no statistically significant difference in the laboratory and radiologic findings between patients with and without influenza (P > 0.05, all). However, patients with influenza were more likely to have a higher percentage of neutrophil count (76% vs 75%, P = 0.069) and hematocrit (35% vs 33%, P = 0.071).

Of all, 20.3% had at least one complication, 72.3% had clinical improvement, and overall mortality was 1.6%. Patients with influenza had a significant higher proportion of complications (28.6% vs 17.7%, P = 0.048), especially pneumonia (19.5% vs 10.6%, P = 0.029) and acute respiratory distress syndrome (5.2% vs 1.5%, P = 0.063). However, the mortality rate was not significantly different between patients with and without influenza (2.6% vs 1.5%, P = 0.682). Patients with influenza were more likely to receive an antiviral drug (90.9% vs 48.8%, P < 0.001) and less likely to receive antibiotics (49.3% vs 81.8%, P < 0.001) (Table 4).

By multivariate logistic regression analysis, the predicting factors for a diagnosis of influenza were cough (OR 2.77; 95% CI 0.21-0.81, P = 0.010), rhinorrhea (OR 1.87; 95% CI 1.03-3.36, P = 0.037), and body temperature (OR 1.64 per 1°C increased; 95% CI 1.23-2.19, P = 0.001). In contrast, longer duration of symptoms (OR 0.86 per 1 day increased; 95% CI 0.75-0.99, P = 0.037) and having cancer (OR 0.41; 95% CI 0.21-0.81, P = 0.037) were less likely associated with a diagnosis of influenza (Table 5).

4 | DISCUSSION

In our study, Sofia® influenza A+B FIA has high specificity for diagnosing both influenza A and B. However, Sofia® influenza
A+B FIA's sensitivity is fair for influenza A diagnosis and low for influenza B diagnosis. The difference in baseline characteristics, clinical presentations, laboratory findings, complications, and outcomes between patients with and without influenza is also determined. We also reported the predicting factors for a diagnosis of influenza among individuals presented with ILI: cough, rhinorrhea, and higher body temperature. In contrast, a longer duration of symptoms and having cancer as an underlying

### TABLE 2 Baseline characteristics, signs, and symptoms of 473 patients present with influenza-like illness

| Characteristics                          | Overall (n = 473) | Influenza test positive (n = 77) | Influenza test negative (n = 396) | P-value |
|------------------------------------------|------------------|----------------------------------|----------------------------------|---------|
| Median (IQR) age, years                  | 58 (41-74)       | 54 (36-71)                       | 58 (42-74)                       | 0.114   |
| Male gender, n (%)                       | 223 (47.1)       | 32 (41.6)                        | 191 (48.2)                       | 0.283   |
| Underlying diseases, n (%)               | 427 (90.2)       | 65 (84.4)                        | 362 (91.4)                       | 0.058   |
| Diabetes                                 | 104 (21.9)       | 19 (24.6)                        | 85 (21.4)                        | 0.534   |
| Hypertension                             | 191 (40.3)       | 30 (38.9)                        | 161 (40.6)                       | 0.781   |
| Airway disease                           | 49 (10.3)        | 3 (3.9)                          | 46 (11.6)                        | 0.042   |
| Cardiovascular disease                   | 94 (19.8)        | 13 (16.8)                        | 81 (20.4)                        | 0.472   |
| Cirrhosis                                | 9 (1.9)          | 3 (1.5)                          | 6 (1.5)                          | 0.168   |
| Chronic kidney disease                   | 133 (28.1)       | 25 (32.4)                        | 108 (27.2)                       | 0.354   |
| Cancer                                   | 148 (31.9)       | 14 (18.1)                        | 134 (33.8)                       | 0.007   |
| HIV infection                            | 8 (1.6)          | 2 (2.6)                          | 6 (1.5)                          | 0.622   |
| Pregnancy                                | 2 (0.4)          | 1 (1.3)                          | 1 (0.2)                          | 0.299   |
| Obesity                                  | 3 (0.6)          | 1 (1.3)                          | 2 (0.5)                          | 0.414   |
| Transplant status                        | 69 (14.5)        | 15 (19.4)                        | 54 (13.6)                        | 0.184   |
| Chemotherapy                             | 126 (26.6)       | 14 (18.1)                        | 112 (28.2)                       | 0.067   |
| Corticosteroid therapy                   | 50 (10.5)        | 10 (13)                          | 40 (10.1)                        | 0.451   |
| Immunosuppressive therapy                | 80 (16.9)        | 20 (25.9)                        | 60 (15.1)                        | 0.020   |
| Median (IQR) duration of illness, days   | 2 (1-3)          | 2 (1-3)                          | 2 (1-3)                          | 0.123   |
| Symptom, n (%)                           |                  |                                  |                                  |         |
| Fever                                    | 314 (66.3)       | 63 (81.8)                        | 251 (63.8)                       | 0.002   |
| Cough                                    | 325 (68.1)       | 63 (81.8)                        | 262 (66.1)                       | 0.007   |
| Sore throat                              | 53 (11.2)        | 11 (14.2)                        | 42 (10.6)                        | 0.349   |
| Dyspnea                                  | 137 (28.9)       | 23 (29.8)                        | 114 (28.7)                       | 0.848   |
| Headache                                 | 22 (4.6)         | 4 (5.1)                          | 18 (4.5)                         | 0.769   |
| Myalgia                                  | 51 (10.7)        | 12 (15.6)                        | 39 (9.8)                         | 0.138   |
| Rhinorrhea                               | 137 (28.9)       | 32 (41.6)                        | 105 (26.5)                       | 0.008   |
| Vomit                                    | 12 (2.5)         | 1 (1.3)                          | 11 (10)                          | 0.700   |
| Diarrhea                                 | 16 (3.3)         | 1 (1.3)                          | 15 (3.8)                         | 0.489   |
| Fatigue                                  | 16 (3.3)         | 3 (3.9)                          | 13 (3.3)                         | 0.733   |
| Alteration of consciousness              | 31 (6.5)         | 7 (9.1)                          | 24 (6.1)                         | 0.326   |
| Vital signs                              |                  |                                  |                                  |         |
| Median (IQR) body temperature, °C        | 38.2 (37.4-38.7) | 38.3 (38-39)                     | 38.1 (37.3-38.7)                 | 0.003   |
| Median (IQR) systolic blood pressure, mm Hg | 128 (113-141)   | 132 (118-145)                    | 127 (113-140)                    | 0.162   |
| Median (IQR) diastolic blood pressure, mm Hg | 73 (63-80)    | 64 (75-82)                       | 73 (63-80)                       | 0.270   |
| Median (IQR) heart rate, beats/min       | 97 (83-111)      | 100 (82-117)                     | 97 (83-110)                      | 0.398   |
| Median (IQR) respiratory rate, breaths/min | 20 (20-24)    | 20 (20-24)                       | 20 (20-24)                       | 0.424   |
| Median (IQR) oxygen saturation, %        | 98 (96-100)      | 98 (95-99)                       | 98 (96-100)                      | 0.150   |
| Hospitalization, n (%)                   | 353 (74.6)       | 50 (64.9)                        | 303 (76.5)                       | 0.033   |

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range.
We reported that Sofia® influenza A+B FIA’s specificity is high in diagnosing influenza A and B. Still, the sensitivity is fair in the diagnosis of influenza A and lowers in influenza B. The meta-analysis study

disease are less likely to be diagnosed with influenza. Cancer patients might have less contact with others and have better compliance for disease prevention.
of 26 commercial RIDT in Canada (including Binax tests, BinaxNow influenza test, QuickVue tests, and Quidel test) demonstrated that RIDT had a specificity of 98.2% and sensitivity of 62.3% for diagnosis both influenza A and influenza B.22 The studies in Australia and the United States reported the sensitivity and specificity of Sofia® influenza A+B FIA to detected influenza A were 41.5%-72.4% and 98.3%-99.2%, respectively, whereas sensitivity and specificity to detected influenza B was 33.3%-53.0% and 95%-99.5%, respectively.15,18,23 According to the previous studies, Sofia® influenza A+B FIA’s performance was similar to other commercial RIDT, which had high specificity.

In contrast, low sensitivity in the diagnosis of influenza A and B was reported.15,18,23 The performance of the RIDT in our study was similar to those of other studies. Sofia® influenza A+B FIA had a high specificity for the diagnosis of influenza A and B.15,18,23 The sensitivity of Sofia® influenza A+B FIA was high for the diagnosis of influenza A. Still, the sensitivity was low for this diagnosis of influenza B in our study. This might be explained by many factors such as duration of onset, improper specimen collection, and storage procedure before testing.12,24 Sensitivity of Sofia® influenza A+B FIA rapidly decreased by 40% after 5 days of symptom onset because viral shedding was decreased to an undetectable level.12 In addition, the sensitivities of RIDT were increased with the use of flocked swab or collected combined specimens (eg, pooled nasal and throat swab specimens).24

The most common clinical manifestations in our patients diagnosed with influenza were fever, cough, and rhinorrhea, comparable to those reported in Singapore and Japan studies.25,26 Thus, patients with these symptoms should be considered a diagnosis of influenza, especially during seasonal influenza and in the setting of resource constraints for the laboratory diagnosis. In our study, patients with influenza had a higher proportion of complications than those without influenza, whereas the study in Singapore reported a higher complication in a non-diagnosis of the influenza group (eg, bacterial infection).26 The most common complications in our patients were pneumonia and acute respiratory distress syndrome (ARDS). The common complication in patients with influenza reported by the studies in Japan, China, and the United States was pneumonia.7,25,27 In contrast, Singapore’s research said the most common complication was neurological complications such as seizures because most study populations were children.26 Most of our patients with influenza had improved in the outcomes, and a few cases died. The mortality rate in our study is similar to that reported from the others, 0.4%-6.7%.1,24-28 Most of the severe cases were elderly aged and had comorbidities.27,28

There are some limitations of this study. First, unavailable medical records and missing data such as a history of receiving influenza vaccine are common due to the retrospective study’s nature. Second, this study was conducted in a single center that might not be generalized to other populations or other settings. The low prevalence of influenza B in our study might have affected the performance of RIDT. However, our study’s benefit is evaluating the parameter associated with a diagnosis of influenza. This might help a physician decide on the diagnosis and treatment of influenza in a situation where any confirmation test could not be performed.

In conclusion, the Sofia® influenza A+B FIA can be one of the helpful diagnostic tools in diagnosing influenza. According to high specificity in Sofia® influenza A+B FIA, positive results in ILI patients are more likely to be true-positive results. On the other hand, we cannot exclude influenza because of Sofia® influenza A+B FIA’s negative result among patients with ILI. Thus, the RT-PCR should be used to confirm the influenza diagnosis among patients presented with ILI using the proposed clinical predicting factors where infrastructure is constrained.

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CONFLICT OF INTEREST
The authors declare that they have no competing interests.

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All authors had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT
All the authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported, and no important aspects of the study have been omitted.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
Ethical approval for this study was obtained from the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University (Approval Number: ID 472), and this study was performed under the Helsinki research ethics statement. This is a retrospective study; informed consent is not applied.
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