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The limited value of triage vital signs in predicting influenza infection in children aged 5 years and under in the emergency department

A single-center retrospective cross-sectional study

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Abstract

Diagnosing influenza in children aged 5 years and under can be challenging because of their difficulty in verbalizing symptoms. This study aimed to explore the value of the triage heart rate (HR), respiratory rate (RR), and temperature, either alone or when combined with individual symptoms and signs, in predicting influenza infection in this age group.

This was a retrospective study covering 4 influenza seasons from 2017 to 2019 in an emergency department (ED) in Hong Kong. We recruited patients ≤5 years of age who had an reverse transcription polymerase chain reaction influenza test within 48 hours of ED presentation. The diagnostic performance of the triage HR, RR, and temperature was evaluated as dichotomized or categorized values with diagnostic odds ratios (DORs) calculated based on different age-appropriate thresholds. Linear discriminant analysis was performed to assess the combined discriminatory effect of age, HR, RR, and temperature as continuous variables.

Of 322 patients (median age 26 months), 99 had influenza A and 13 had influenza B infection. For HR and RR dichotomized based on age-appropriate thresholds, the DORs ranged from 1.16 to 1.54 and 0.78 to 1.53, respectively. A triage temperature ≥39.0 °C had the highest DOR (3.32) among different degrees of elevation of temperature. The diagnostic criteria that were based on the presence of fever and cough and/or rhinitis symptoms had a higher DOR compared with the Centers for Disease Control and Prevention influenza-like illness criteria (4.42 vs 2.41). However, combining HR, RR, or temperature with such diagnostic criteria added very little to the diagnostic performance. The linear discriminant analysis model had a high specificity of 92.5%, but the sensitivity (18.3%) was too low for clinical use.

Triage HR, RR, and temperature had limited value in the diagnosis of influenza in children ≤5 years of age in the ED. Fever and cough and/or rhinitis symptoms had a better diagnostic performance than the Centers for Disease Control and Prevention influenza-like illness criteria in predicting influenza in this age group.

Abbreviations: APLS = advanced pediatric life support, CDC = Centers for Disease Control and Prevention, CI = confidence interval, DOR = diagnostic odds ratio, ED = emergency department, GHK = Gleneagles Hong Kong Hospital, HR = heart rate, ILI = influenza-like illness, LDA = linear discriminant analysis, NPV = negative predictive value, PPV = positive predictive value, RR = respiratory rate, RT-PCR = reverse transcription polymerase chain reaction, SD = standard deviation, SpO_2 = peripheral oxygen saturation.

Keywords: emergency department, influenza, predictive value of tests, preschool child, triage, vital signs

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1. Introduction

Influenza is a major cause of respiratory illness in preschool children and a substantial burden on health services worldwide.[1] In the United States, the estimated annual hospitalization rate is 0.9 per 1000 children, and the outpatient visit rate is 10 to 250 times higher.[2] Children 6 to ≤23 months of age have the greatest number of emergency department (ED) visits (18 visits per 1000 children).[3] Healthy infants and young children are at a higher risk of complications and hospitalization compared with older children because of a weaker immune system and a lack of previous exposure to influenza viruses.[4,5]

During the flu season, differentiation of influenza from other respiratory infections in preschool children who present to the ED with acute febrile illness or respiratory symptoms is important in guiding clinical management. Rapid and accurate diagnosis of influenza can lead to prompt initiation of antiviral therapy, fewer ancillary diagnostic tests, fewer hospitalizations, prompt initiation of hospital infection control measures, and less unnecessary antibiotic use.[6–11] However, clinical diagnosis is difficult and can be inaccurate.[12] Preschool children with seasonal influenza can present with a variety of non-specific symptoms and may not yet be able to verbalize symptoms such as headache and myalgia to their caregivers.[13] Detection of viral RNA by reverse transcriptase polymerase chain reaction (RT-PCR) is highly sensitive and specific for both influenza A and B infection, and it has replaced viral culture as the gold standard for diagnosis.[14] However, samples are usually sent to specialized laboratories with testing done in batch, resulting in a long turnaround time. Further, the extra cost of the test may not be affordable for parents who pay out of pocket.

The value of individual signs and symptoms in predicting influenza in preschool children has been evaluated in previous studies. While some symptoms, such as fever,[13,15,16] cough,[13,15,16] rhinorrhea,[15] headache,[17] absence of wheeze,[13] and pharyngitis[17] have been shown to be useful predictors, many other studies have shown contradictory results,[18–20] probably due to different study methods and populations. The adult-derived Centers for Disease Control and Prevention (CDC) definition of influenza-like illness (ILI), that is, presence of fever ≥37.8 °C and cough and/or sore throat is highly sensitive (92%) but not specific (10%) in this age group.[13] Empirical antiviral treatment based on such criteria without testing may result in overtreatment.

A few studies have demonstrated the potential value of vital signs in diagnosis. Heinonen et al[20] found that fever as a physical sign outdid all other symptoms in children and an incremental elevation in temperature increased the likelihood of influenza. Nguyen et al[21] found that an outpatient automated screening system using a multivariable logistic regression model based on facial temperature, heart rate (HR), and respiratory rate (RR) had a high sensitivity (93%) and specificity (91%) in predicting influenza. However, their study did not recruit preschool children. Furthermore, the interpretation of HR and RR in young children is more complicated because the normal values vary with age. Several age-appropriate threshold values have been established to facilitate interpretation,[22–25] but these have not been considered in previous studies.

To our knowledge, no studies have investigated the value of the routinely collected triage vital signs, including HR, RR, and temperature, in predicting influenza in preschool children aged 5 years and under in the ED. Such information is important in risk stratification and selection of the right patients for RT-PCR testing. Therefore, we aimed to evaluate the diagnostic performance of the triage HR and RR, and their deviations from different age-appropriate thresholds, as well as triage temperature in predicting laboratory-confirmed influenza infection in preschool children in the ED, either alone or when combined with the clinical symptoms and signs.

2. Methods

This was a single-center retrospective cross-sectional study covering 4 influenza seasons, as announced by the Centre for Health Protection of the Department of Health in Hong Kong: February 19, 2017 to April 8, 2017 (predominantly influenza A H3); May 7, 2017 to August 26, 2017 (predominantly influenza A H3); December 31, 2017 to May 31, 2018 (predominantly influenza B); and December 23, 2018 to April 6, 2019 (predominantly influenza A H1). The Centre for Health Protection is the public health authority in Hong Kong, which runs a regular influenza surveillance program in different healthcare settings and provides a weekly update of influenza activity in the community to healthcare workers and the public. We followed the STROBE guidelines in reporting this study.

We conducted this study in the 24-hour Outpatient & Emergency Department of Gleneagles Hong Kong Hospital (GHK), which is a private tertiary ED affiliated with The University of Hong Kong Health System. It is staffed by emergency medicine specialists, resident doctors, and registered and enrolled ED nurses. It has around-the-clock access to laboratory services, including RT-PCR tests for respiratory pathogens, imaging studies, pediatric consultation services, and inpatient pediatric beds. In 2018/2019, the annual census was 24,000, of whom 14% were aged under 14 years. This study was approved by the Research Ethics Committee of GHK, with informed consent waived because of the retrospective nature of the study and anonymity of the data analysis.

We recruited patients who were aged ≤5 years with a clinical suspicion of influenza infection and from whom a nasopharyngeal swab for influenza RT-PCR testing was ordered by the attending physician within 48 hours of presentation during the study periods. Eligible patients were identified from the electronic medical record system of GHK using the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes related to influenza infection (Table S1, Supplemental Digital Content, http://links.lww.com/MD/G473). In GHK ED, diagnostic coding with International Statistical Classification of Diseases and Related Health Problems, 10th revision codes by the attending clinician is mandatory for every case before ED discharge or hospital admission. We excluded patients with an RT-PCR result known before ED presentation (e.g., prior testing in other health facilities), patients with both HR and RR missing at triage, and patients with a sample collected after 48 hours of admission because of the possibility of nosocomial infection, a cutoff commonly adopted by other studies on community-acquired infections.[26]

The following data were collected with a standardized electronic spreadsheet: age; sex; triage category; triage vital signs, including HR, RR, temperature, blood pressure (if available), and peripheral oxygen saturation (SpO_2); reported symptoms and signs, RT-PCR test results; and patient outcome. Triage vital signs were recorded by duty triage nurses before consultation and RT-PCR testing. HR and SpO_2 were measured

with a pulse oximeter (Nellcor Bedside SpO_2 Patient Monitoring System; Covidien, Mansfield, MA). RR was counted routinely by triage nurses. Tympanic temperature was measured using an infrared thermometer with an ear probe (Braun ThermoScan PRO6000; WelchAllyn, Marlborough, MA). Symptoms were extracted as documented in the triage and consultation notes. The CDC ILI criteria were determined based on the symptoms reported by the patient's parents in the clinical notes.

HR and RR were recorded as both continuous and dichotomized values (normal or abnormal) based on age-appropriate threshold values of the Advanced Pediatric Life Support (APLS) guidelines,[22] Pediatric Canadian Triage and Acuity Scale,[23] Fleming normal reference values,[24] and Chan normal reference values (derived from ethnically Chinese children in Hong Kong).[25] For the APLS guidelines, we used the threshold for upper and lower limits.[22] For the Pediatric Canadian Triage and Acuity Scale, we used both the ±standard deviation (SD) and ±2 standard deviations (SDs) from the normal range at different ages as thresholds.[23] For Fleming normal reference values, we used <1st or >99th centile and <10th or >90th centile as cutoff points.[24] For Chan normal reference values, we used <2.5th or >97.5th centile and <10th or >90th centile as cutoff points.[25] Triage temperature was categorized as ≥37.8 °C, ≥38.5 °C, ≥39.0 °C, ≥39.5 °C or ≥40 °C.

The gold standard was defined as the result of RT-PCR tests for the detection of influenza A or B or other respiratory viruses in the nasopharyngeal swab sample. Testing was based on the individual physician's clinical judgment rather than the ILI definition. All samples were collected in either the ED or the ward by a trained nurse within 48 hours of presentation. RT-PCR tests were performed by trained laboratory technicians using a commercial assay kit covering influenza A and B and respiratory syncytial virus (GeneXpert Flu assay; Cepheid, Sunnyvale, CA) or multi-panel kit (Biofire Filmarray multiplex PCR system; Biofire Diagnostics, LLC, Salt Lake City, UT). The laboratory technicians were blinded to the triage vital signs.

2.1. Sample size calculation

We based our sample size calculation on the estimated sensitivity of abnormal HR in predicting influenza infection. We did not choose RR because it is not measured in all pediatric patients at triage. The sample size required was based on the following equation:

$$n = \frac{Z^2 S_N(1-S_N)}{w^2 P}$$

where Z is the number of SDs in half the 2-tailed confidence interval, S_N is the anticipated sensitivity of the diagnostic test, w is the precision of the estimation, and P is the influenza prevalence.

For a 95% confidence interval (CI), $Z = 1.96$ SD. As for S_N, we could not estimate the sensitivity of abnormal HR in predicting influenza in children ≤5 years because of a lack of similar study. We assumed S_N to be 0.5 for a more conservative sample size requirement. We set the precision at $w = 0.1$, i.e., the true sensitivity value will fall within 0.1 of the observed value.[27,28] Given the prevalence of influenza during flu season of around 30%, the total sample size, including negative cases, was calculated as 321.

2.2. Statistical analysis

No imputation was performed for the missing values. Descriptive statistics were used to analyze the distribution of characteristics of the study population. Categorical variables were reported as proportions, and continuous variables as mean ± SD or median with interquartile range, as appropriate. The results of RT-PCR tests were dichotomized as positive (influenza A or B) and negative (other respiratory viruses, bacteria, or no pathogens detected). We then determined the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic odds ratios (DORs) and their respective CIs of abnormal HR and RR based on different age-appropriate threshold values, as well as different degrees of elevation of triage temperature, the presence of individual symptoms and signs, and abrupt onset of symptoms (defined as symptom onset ≤24 hours), in predicting laboratory-confirmed influenza.

The DOR is a single indicator of diagnostic performance, which ranges from 0 to infinity and does not depend on the disease prevalence. A value of 1 means that the test does not discriminate between patients with the disease and those without it.[29] For vital sign values with a DOR >1.5, we combined them with clinical symptoms and signs that had the highest DORs and evaluated their combined diagnostic performance. In addition, we repeated the analysis after excluding cases with coinfection, which might include mixed clinical presentations of influenza A or B with other infections. We also evaluated their diagnostic performance in predicting influenza A and B only.

The data were further analyzed using linear discriminant analysis (LDA) with age and triage HR, RR, and temperature entered as continuous variables. The sensitivity, specificity, PPV, NPV, and DOR of the discrimination score were calculated. We repeated the analysis after excluding cases with coinfection and when only influenza A and B were predicted separately.

The Statistical Package for the Social Sciences for Windows version 23.0 (IBM Corp., Armonk, NY) was used for data analysis. A P-value <.05 was considered statistically significant.

3. Results

During the study periods, 325 patients were identified. One patient was excluded because of prior testing with the result available before presenting to the ED. Two were excluded because of missing both HR and RR values. In total, 322 patients were analyzed, and their demographic and clinical characteristics are summarized in Table 1. Overall, the median age was 26 months (interquartile range 14.0–39.3) and the female to male ratio was 1:1.2. RT-PCR tests showed influenza A and influenza B in 99 (30.7%) and 13 (4.0%) patients, respectively. Among those with influenza A infection, 34 were subtyped H1 pdm2009, 12 were subtyped H3, and 55 were not subtyped. Coinfection with influenza and another organism was detected in 17 patients.

The diagnostic performance of abnormal HR and RR values, dichotomized based on various age-appropriate thresholds, is shown in Tables 2 and 3. In general, the sensitivity decreased and specificity increased as the HR or RR deviated more from the threshold values. Interestingly, the PPV and NPV of abnormal HR and RR were around 30% and 60%, respectively, regardless of the cutoff points used. For HR values, the DORs ranged from 1.16 to 1.54 based on different guidelines. An HR <10th or >90th centile of the Fleming normal reference values had the highest DOR (1.54, 95% CI 0.89–2.67). As for RR values, the

Table 1

Demographic and clinical characteristics of the study population.

	Patients with laboratory-confirmed influenza infection (n = 112)	Patients with other infections (n = 210)
Age—median (IQR), month	28.0 (15.3–40.0)	26.0 (14.0–39.0)
Gender—no. (%)		
Female	53 (47.3)	94 (44.8)
Male	59 (52.7)	116 (55.2)
Comorbidities—no. (%)	6 (5.4)	10 (4.8)
Current flu vaccination—no. (%)	11 (9.8)	21 (10.0)
Triage HR—mean (SD), mm Hg	148.9 (22.2)	146.2 (22.7)
Triage RR—mean (SD), breath per minute	24.4 (5.5)	25.3 (4.4)
Triage temperature—mean (SD), °C	38.8 (1.0)	38.2 (1.0)
Pathogens identified—no. (%)		
Influenza A		
H1 pdm2009	34 (30.4)	0 (0)
H3	12 (10.7)	0 (0)
Not subtyped	55 (49.1)	0 (0)
Influenza B	13 (11.6)	0 (0)
Other viruses		
Adenovirus	0 (0)	14 (6.7)
Coronaviruses	3 (2.7)	8 (3.8)
Human metapneumovirus	3 (2.7)	13 (6.2)
Parainfluenza viruses	4 (3.6)	26 (12.4)
Respiratory syncytial virus	2 (1.8)	24 (11.4)
Rhinovirus or enterovirus	4 (3.6)	47 (22.4)
Bacteria		
Haemophilus influenzae	3 (2.7)	8 (3.8)
Staphylococcus aureus	0 (0)	3 (1.4)
Streptococcus	3 (2.7)	5 (2.4)
Mycoplasma	5 (4.5)	11 (5.2)
Coinfection—no. (%)	17 (15.2)	0 (0)
Hospital admission—no. (%)	54 (48.2)	115 (54.8)
ICU admission—no. (%)	0 (0)	0 (0)

HR = heart rate, ICU = intensive care unit, IQR = interquartile range, N/A = not applicable, RR = respiratory rate, SD = standard deviation.

DORs were between 0.78 and 1.53, based on different thresholds. A RR < or > the APLS normal range had the highest DOR (1.53, 95% CI 0.87–0.68). None of the DORs of abnormal HR and RR values had the lower bound of the 95% CI clearly above 1.

The diagnostic performance of different degrees of temperature elevation in predicting influenza is shown in Table 4. The DOR of a triage temperature ≥39.0 °C was the highest (DOR 3.32, 95% CI 2.04–5.40). However, both the sensitivity (50.9%, 95% CI 41.3–60.4%) and PPV (53.3%, 95% CI 43.4–62.9%) were too low for diagnosis of influenza if such a temperature threshold is used.

Table 5 shows the diagnostic performance of individual symptoms and signs in predicting influenza. The DORs of fever, cough, and malaise were 3.04 (95% CI 0.66–13.96), 2.25 (95% CI 1.18–4.27), and 1.78 (0.87–3.64), respectively. The DOR of rhinitis symptoms, including runny nose, sneezing, and/or stuffiness, was very close to 1.5 (DOR 1.46, 95% CI 0.88–2.41). The physical finding of a congested or inflamed throat had a DOR of 2.0 (95% CI 1.23–3.24). The DOR of onset of symptoms within 24 hours was only 1.31 (95% CI 0.82–2.09). When we combined these symptoms together, we found that the diagnostic criteria that were based on the presence of fever and

Table 2

Diagnostic performance in predicting influenza infection of abnormal heart rate values based on threshold values in current pediatric guidelines.

	Total number of patients with abnormal HR, n = 318 (%)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	DOR (95% CI)
APLS (< or > normal range)	165 (51.9)	56.0 (46.1–65.4)	50.2 (43.3–57.2)	37.0 (29.7–44.9)	68.6 (60.6–75.7)	1.28 (0.81–2.04)
PedCTAS (1 SD from normal range)	188 (59.1)	64.2 (54.4–73.0)	43.5 (36.8–50.6)	37.2 (30.4–44.6)	70.0 (61.2–77.6)	1.38 (0.86–2.23)
PedCTAS (2 SDs from normal range)	90 (28.3)	30.3 (22.0–39.9)	72.7 (66.1–78.5)	36.7 (26.9–47.5)	66.7 (60.1–72.7)	1.16 (0.70–1.93)
Fleming et al (<10th or >90th centile)	234 (73.6)	78.9 (69.8–85.9)	29.2 (23.2–35.9)	36.8 (30.6–43.3)	72.6 (61.6–81.5)	1.54 (0.89–2.67)
Fleming et al (<1st or >99th centile)	160 (50.3)	55.0 (45.2–64.5)	52.2 (45.2–59.1)	37.5 (30.1–45.5)	69.0 (61.1–76.0)	1.33 (0.84–2.12)
Chan et al (<10th or >90th centile)	240 (75.5)	78.0 (68.8–85.1)	25.8 (20.2–32.4)	35.4 (29.4–41.9)	69.2 (57.6–78.9)	1.23 (0.71–2.14)
Chan et al (<2.5th or >97.5th centile)	174 (54.7)	59.6 (49.8–68.8)	47.8 (40.9–54.8)	37.4 (30.2–45.0)	69.4 (61.1–76.7)	1.36 (0.85–2.17)

APLS = adult pediatric life support, CI = confidence interval, DOR = diagnostic odds ratio, HR = heart rate, NPV = negative predictive value, PedCTAS = Canadian Triage and Acuity Scale Pediatric Guidelines, PPV = positive predictive value, SD = standard deviation.

Table 3

Diagnostic performance in predicting influenza infection of abnormal respiratory rate values based on threshold values in current pediatric guidelines.

	Total number of patients with abnormal RR, n = 247 (%)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	DOR (95% CI)
APLS (< or > normal range)	159 (64.4)	70.6 (59.6–79.7)	38.9 (31.4–46.9)	37.7 (30.3–45.8)	71.6 (60.8–80.4)	1.53 (0.87–2.68)
PedCTAS (1 SD from normal range)	17 (6.9)	5.9 (2.2–13.8)	92.6 (87.1–95.9)	29.4 (11.4–56.0)	65.2 (58.6–71.3)	0.78 (0.27–2.30)
PedCTAS (2 SDs from normal range)	3 (1.2)	1.2 (0.1–7.3)	98.8 (95.1–99.8)	33.3 (1.8–87.5)	65.6 (59.2–71.4)	0.95 (0.09–10.66)
Fleming et al (<10th or >90th centile)	128 (51.8)	52.9 (41.9–63.7)	48.8 (40.9–56.7)	35.2 (27.1–44.1)	66.4 (57.1–74.6)	1.07 (0.63–1.81)
Fleming et al (<1st or >99th centile)	18 (7.3)	8.2 (3.7–16.8)	93.2 (87.9–96.4)	38.9 (18.3–63.9)	65.9 (59.4–72.0)	1.23 (0.46–3.30)
Chan et al (<10th or >90th centile)	84 (34.0)	36.5 (26.5–47.7)	67.3 (59.4–74.3)	36.9 (26.8–48.2)	66.9 (59.0–73.9)	1.18 (0.68–2.05)
Chan et al (<2.5th or >97.5th centile)	32 (13.0)	15.3 (8.7–25.1)	88.3 (82.1–92.6)	40.6 (24.2–59.2)	66.5 (59.7–72.7)	1.36 (0.64–2.91)

APLS = adult pediatric life support, CI = confidence interval, DOR = diagnostic odds ratios, NPV = negative predictive value, PedCTAS = Canadian Triage and Acuity Scale Pediatric Guidelines, PPV = positive predictive value, RR = respiratory rate, SD = standard deviation.

Table 4

Diagnostic performance in predicting influenza infection of different degrees of triage temperature elevation.

	Total number of patients satisfied criteria, n = 322 (%)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	DOR (95% CI)
Temperature ≥37.8 °C	232 (72.0)	81.3 (72.5–87.8)	32.9 (26.6–39.7)	39.2 (33.0–45.9)	76.7 (66.3–84.7)	2.12 (1.22–3.69)
Temperature ≥38.5 °C	153 (47.5)	63.4 (53.7–72.1)	61.0 (54.0–67.5)	46.4 (38.4–54.6)	75.7 (68.4–81.8)	2.70 (1.68–4.34)
Temperature ≥39.0 °C	107 (33.2)	50.9 (41.3–60.4)	76.2 (69.7–81.7)	53.3 (43.4–62.9)	74.4 (67.9–80.0)	3.32 (2.04–5.40)
Temperature ≥39.5 °C	66 (20.5)	30.4 (22.2–39.9)	84.8 (79.0–89.2)	51.5 (39.0–63.9)	69.5 (63.4–75.0)	2.42 (1.40–4.21)
Temperature ≥40.0 °C	14 (4.3)	4.5 (1.7–10.6)	95.7 (91.8–97.9)	35.7 (14.0–64.4)	65.3 (59.6–70.5)	1.04 (0.34–3.19)

CI = confidence interval, DOR = diagnostic odds ratios, NPV = negative predictive value, PPV = positive predictive value.

cough and/or rhinitis symptoms had a higher DOR compared with the CDC ILI criteria (4.42 vs 2.41) and other diagnostic criteria that were based on different combinations of symptoms and signs (Table 6).

The sensitivity, specificity, and DOR of the CDC ILI criteria were 86.6%, 27.1%, and 2.41, respectively. Both the HR <10th or >90th centile of the Fleming normal reference values and RR < or > the APLS normal range had a slightly higher specificity but lower sensitivity and DOR compared with the CDC ILI criteria. A triage temperature ≥37.8 °C had a comparable sensitivity, specificity, PPV, NPV, and DOR to the CDC ILI criteria.

Combining abnormal HR and RR values and temperature values with a DOR >1.5 with the diagnostic criteria that were based on fever and cough and/or rhinitis symptoms resulted in a

Table 5

Diagnostic performance of different symptoms and signs in predicting influenza infection.

	Total number of patients with symptom or sign, n (%)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	DOR (95% CI)
Fever	309 (96.0)	98.2 (93.1–99.7)	5.2 (2.8–9.4)	35.6 (30.3–41.2)	84.6 (53.7–97.3)	3.04 (0.66–13.96)
Cough	257 (79.8)	87.5 (79.6–92.7)	24.3 (18.8–30.8)	38.1 (32.2–44.4)	78.5 (66.2–87.3)	2.25 (1.18–4.27)
Sore throat	35 (10.9)	8.9 (4.6–16.2)	88.1 (82.7–92.0)	28.6 (15.2–46.5)	64.5 (58.6–69.9)	0.73 (0.34–1.57)
Rhinitis symptoms	219 (68.0)	73.2 (63.9–80.9)	34.8 (28.4–41.7)	37.4 (31.1–44.2)	70.9 (61.0–79.2)	1.46 (0.88–2.41)
Shortness of breath	29 (9.0)	5.4 (2.2–11.8)	89.0 (83.8–92.8)	20.7 (8.7–40.3)	63.8 (58.0–69.3)	0.46 (0.18–1.17)
Malaise	34 (10.6)	14.3 (8.6–22.5)	91.4 (86.6–94.7)	47.1 (30.2–64.6)	66.7 (60.9–72.0)	1.78 (0.87–3.64)
Headache	11 (3.4)	1.8 (0.3–6.9)	95.7 (91.7–97.9)	18.2 (3.2–52.2)	64.5 (58.9–69.8)	0.40 (0.09–1.90)
Vomiting	76 (23.6)	21.4 (14.5–30.4)	75.2 (68.7–80.8)	31.6 (21.7–43.4)	64.2 (57.9–70.1)	0.83 (0.48–1.44)
Abdominal pain	22 (6.8)	8.0 (4.0–15.1)	93.8 (89.4–96.5)	40.9 (21.5–63.3)	65.7 (60.0–71.0)	1.32 (0.55–3.20)
Diarrhea	37 (11.5)	6.3 (2.8–12.9)	85.7 (80.1–90.0)	18.9 (8.6–35.7)	63.2 (57.2–68.7)	0.4 (0.17–0.94)
Reduced oral intake	161 (50.0)	48.2 (38.7–57.8)	49.0 (42.1–56.0)	33.5 (26.4–41.5)	64.0 (56.0–71.3)	0.90 (0.57–1.42)
Decrease in playfulness	34 (10.6)	11.6 (6.6–19.4)	90.0 (84.9–93.6)	38.2 (22.7–56.4)	65.6 (59.8–71.0)	1.18 (0.57–2.46)
Irritability	34 (10.6)	11.6 (6.6–19.4)	90.0 (84.9–93.6)	38.2 (22.7–56.4)	65.6 (59.8–71.0)	1.18 (0.57–2.46)
Congested or inflamed throat	187 (58.1)	68.8 (59.2–77.0)	47.6 (40.7–54.6)	41.2 (34.1–48.6)	74.1 (65.7–81.1)	2.0 (1.23–3.24)
Sputum sound on chest auscultation	27 (8.4)	9.8 (5.2–17.3)	92.4 (87.7–95.4)	40.7 (23.0–61.0)	65.8 (60.0–71.1)	1.32 (0.59–2.95)
Crepitation on chest auscultation	16 (5.0)	1.8 (0.3–6.9)	93.3 (88.8–96.2)	12.5 (2.2–39.6)	64.1 (58.4–69.4)	0.25 (0.06–1.14)
Wheezing	21 (6.5)	3.6 (1.2–9.4)	91.9 (87.1–95.1)	19.0 (6.3–42.6)	64.1 (58.4–69.5)	0.42 (0.14–1.28)
Skin rash	22 (6.8)	5.4 (2.2–11.8)	92.4 (87.7–95.4)	27.3 (11.6–50.4)	64.7 (58.9–70.0)	0.69 (0.26–1.81)
Onset of symptoms within 1 day	134 (42.0)	46.4 (36.9–56.1)	60.3 (53.3–66.9)	38.1 (29.9–46.9)	68.1 (60.8–74.6)	1.31 (0.82–2.09)

CI = confidence interval, DOR = diagnostic odds ratios, NPV = negative predictive value, PPV = positive predictive value.

Table 6

Impact on predicting influenza infection of combining abnormal vital signs with different combinations of symptoms and signs.

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	DOR (95% CI)
CDC ILI criteria	86.6 (78.6–92.1)	27.1 (21.4–33.8)	38.8 (32.8–45.2)	79.2 (67.7–87.5)	2.41 (1.29–4.49)
Fever and cough and/or rhinitis	94.6 (88.2–97.8)	20.0 (14.926.2)	38.7 (32.9–44.8)	87.5 (74.1–94.8)	4.42 (1.82–10.75)
Fever and cough and/or malaise	86.6 (78.6–92.1)	28.6 (22.7–35.3)	39.3 (33.2–45.7)	80.0 (68.9–88.0)	2.59 (1.9–4.81)
Fever and cough and/or congested throat	95.5 (89.4–98.3)	15.2 (10.8–21.0)	37.5 (32.0–43.5)	86.5 (70.4–94.9)	3.85 (1.45–10.17)
Fever and cough and/or rhinitis + HR <10th or > 90th centile of Fleming reference values	76.1 (66.9–83.6)	41.6 (34.9–48.6)	40.5 (33.8–47.6)	77.0 (67.9–84.2)	2.28 (1.35–3.83)
Fever and cough and/or rhinitis + RR < or > APLS normal range	67.1 (55.9–76.6)	50.0 (42.1–57.9)	41.3 (33.1–50.0)	74.3 (64.9–82.0)	2.04 (1.18–3.52)
Fever and cough and/or rhinitis + triage temperature ≥37.8°C	78.6 (69.6–85.5)	46.2 (39.3–53.2)	43.8 (36.9–50.9)	80.2 (71.7–86.6)	3.15 (1.86–5.33)
Fever and cough and/or rhinitis + triage temperature ≥38.5°C	61.6 (51.9–70.5)	69.0 (62.3–75.1)	51.5 (42.7–60.2)	77.1 (70.3–82.8)	3.58 (2.21–5.79)
Fever and cough and/or rhinitis + triage temperature ≥39.0°C	49.1 (39.6–58.7)	80.5 (74.3–85.5)	57.3 (46.8–67.2)	74.8 (68.5–80.2)	3.98 (2.40–6.58)
Fever and cough and/or rhinitis + triage temperature ≥39.5°C	28.6 (20.6–38.0)	88.1 (82.7–92.0)	56.1 (42.4–69.0)	69.8 (63.8–75.2)	2.96 (1.65–5.31)

CDC = Centers for Disease Control and Prevention, CI = confidence interval, DOR = diagnostic odds ratio, HR = heart rate, ILI = influenza-like illness, NPV = negative predictive value, PPV = positive predictive value, RR = respiratory rate, SD = standard deviation.

modest improvement in specificity at the expense of sensitivity and DOR (Table 6). Combining a triage temperature ≥39.0°C with the diagnostic criteria that were based on fever and cough and/or rhinitis symptoms resulted in the highest DOR (3.98, 95% CI 2.40–6.58). The best balance between sensitivity and specificity was achieved by combining the diagnostic criteria that were based on fever and cough and/or rhinitis symptoms and a triage temperature ≥38.5°C. However, neither the sensitivity (61.6%, 95% CI 51.9–70.5%) nor specificity (69.0%, 95% CI 62.3–75.1%) were high enough to discriminate influenza from other infections.

Similar findings were observed when cases with coinfection were excluded (Tables S2–S6, Supplemental Digital Content, http://links.lww.com/MD/G473) and when we looked at the diagnostic performance of such values in predicting influenza A infection only (Tables S7–S11, Supplemental Digital Content, http://links.lww.com/MD/G473), although the DORs were generally higher. The number of influenza B infections was too small for analysis because the CIs were too wide to allow a meaningful conclusion (data not shown).

In total, 243 subjects had complete data for LDA with age, HR, RR, and temperature entered as continuous variables. A statistically significant model ($P < .004$) was generated as follows:

$$Y\ (X_1,\ X_2,\ X_3,\ X_4) = -34.6 + (0.003)X_1 + (-0.003)X_2 + (-0.08)X_3 + (0.96)X_4$$

where X_1 is the age in months, X_2 is HR, X_3 is RR, and X_4 is temperature. The model classifies a patient as infected with influenza when the Y value is positive and not infected when the Y value is negative. The diagnostic performance of the discrimination score in predicting influenza was sensitivity 18.3% (95% CI 10.9–28.7%), specificity 92.5% (95% CI 87.0–95.9%), PPV 55.6% (95% CI 35.6–74.0%), NPV 70.0% (95% CI 62.3–75.0%), and DOR 2.8 (95% CI 1.2–6.3). The model correctly classified 67.5% of cases. Similar findings were observed when the LDA was repeated after exclusion of cases with infection and when only influenza A infection was predicted (data not shown).

4. Discussion

In this study, we evaluated the diagnostic performance of the triage HR and RR, both as dichotomized values based on different age-appropriate thresholds and continuous variables, as well as temperature, in predicting influenza infection in preschool children aged 5 years and under in the ED. A similar approach has been used to predict serious infections in febrile children,[30,31] but such studies are lacking on influenza in young children. The prevalence of influenza infection in our cohort was 34.7%, which is comparable to other cohorts in previous diagnostic studies for seasonal influenza.[17,32] The low vaccination rate for seasonal influenza in our study is also consistent with the reported population rate among young children in Hong Kong.[33] The calculation of DORs with the paired sensitivity and specificity allowed us to compare our findings with the summary estimates for other clinical parameters reported in previous studies.[15,34]

Our findings show that HR and RR values dichotomized based on current pediatric guidelines have limited value in predicting influenza infection in young children. In general, abnormal HR and RR based on different age-appropriate thresholds had a lower sensitivity and DOR than the CDC ILI criteria in diagnosing influenza, despite a slightly higher specificity. The addition of HR and RR to the diagnostic criteria that were based on fever and cough and/or rhinitis did not improve the diagnostic performance. Although both the sensitivity and specificity improved after excluding coinfection and focusing on influenza A infection only, the diagnostic value of abnormal HR and RR values dichotomized based on age-appropriate thresholds was still limited.

Triage temperature appeared to have a better diagnostic value than HR and RR. A temperature ≥37.8°C alone had a comparable sensitivity, specificity, PPV, NPV, and DOR to the CDC ILI criteria in predicting influenza in young children. The specificity increased with a higher triage temperature, which is consistent with the findings reported by Heinonen et al.[20] However, the DOR peaked at 39°C, and a further increase in triage temperature did not result in a higher DOR. Combining the diagnostic criteria that were based on fever and cough and/or rhinitis symptoms with the presence of a triage temperature ≥38.5°C resulted in the best balance between sensitivity and specificity. However, both the sensitivity and specificity were still suboptimal in discriminating influenza from other infections in preschool children.

To put our findings on diagnostic performance into perspective, it is useful to compare them with the estimates for similar and other clinical parameters reported in the literature. For children of 0 to 4 years of age, Shah et al[15] reported the sensitivity, specificity, and DOR of the CDC ILI criteria as 87%, 31%, and 3.06, respectively—close to our estimates. Among various combination of symptoms, they found that a combina-

tion of fever, cough, and rhinorrhea achieved the best balance in diagnostic performance (sensitivity 85%, specificity 47%, and DOR 4.78), which is further supported by the findings of this study (sensitivity 94.6%, specificity 20.0%, and DOR 4.42).

Notably, the diagnostic performance of HR, RR, and temperature slightly improved after excluding cases with coinfection and when they were used to predict influenza A infection only. However, in clinical practice, teasing out coinfection before laboratory testing is difficult. Influenza A and B do not differ significantly in young children,[13,17] and differentiating them is less important when deciding antiviral treatment.

Some may argue that dichotomization of HR and RR values might result in information loss, leading to less discriminative models and reduction in statistical power.[35] Spruijt et al[30] demonstrated that prediction models that maintained HR and RR as continuous variables outperformed models using dichotomized values in predicting serious bacterial infections. Further, the commonly used age-appropriate threshold values were derived from healthy children[24,25] and were not intended for discriminating influenza from other infections. To address this argument, we ran LDA with HR, RR, and temperature entered as continuous variables. The effect of age on HR and RR was also factored in the model by entering age in months as a variable. We found that despite a high specificity (92.5%) and a higher DOR (2.8) of the resultant model, the sensitivity (18.3%) was too low to be useful for clinical use.

4.1. Limitations

This study has several limitations. First and foremost was its retrospective design and the inherent information bias. Data quality was affected by clinical documentation. Since both triage vital signs and laboratory results were data not influenced by subjective interpretation during data collection, we believe the risk of information bias was low. However, we were less confident with the parent-reported history of vaccination and documentation of individual symptoms. Second, triage vital sign assessment was limited to a single point in time. Measurements were subject to within-patient variability and interobserver bias, whose impact on the analysis is not known. Third, selection bias is possible. Selected patients were those with an RT-PCR test performed, who might be sicker than those without testing. Given the comparable influenza prevalence and vaccination rate with the population, we believe our sample is still representative of local preschool patients in the ED. However, the findings may not be generalizable to other settings with a different prevalence of influenza, vaccination rate, and case mix. Furthermore, these findings were generated during flu seasons. They are not applicable to patients outside the epidemic periods.

Despite these limitations, our study provides useful data in evaluating the diagnostic performance of triage HR, RR, and temperature in predicting influenza in preschool children aged $\leq$5 years in the ED. Based on our observation and analysis, we found that using the triage HR, RR, and temperature, either in the form of dichotomized or categorized values or continuous variables, had limited value in diagnosis. Combining these values with clinical symptoms and signs did not result in significantly better discrimination. Fever and cough and/or rhinitis and a triage temperature $\geq$38.5 °C achieved the best balance between sensitivity and specificity. However, neither the sensitivity and specificity were high enough in discriminating influenza from other infections. Fever and cough and/or rhinitis symptoms had a better diagnostic performance than the CDC ILI criteria in predicting influenza in this age group.

Author contributions

Rex Pui Kin Lam conceived and designed the study and developed the method. Rex Pui Kin Lam, Kin Ling Chan, Arthur Chi Kin Cheung, Kin Wa Wong, Lujie Chen, Vi Ka Chaang retrieved medical records, performed chart review, collected, and cross-checked data. Rex Pui Kin Lam and Eric Ho Yin Lau analyzed and interpreted the data. Patrick Chiu Yat Woo provided supervision. Rex Pui Kin Lam drafted the article. All authors contributed substantially to its revision and provided final approval. Rex Pui Kin Lam takes the responsibility for the paper as a whole.

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