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Original Contributions

FACTORS ASSOCIATED WITH INFLUENZA IN AN EMERGENCY DEPARTMENT SETTING

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☐ **Abstract—Background: Emergency departments (EDs) become more overcrowded during peak respiratory virus season. Distinguishing influenza from other viruses is crucial to implement social distancing practices, early treatment, and prompt disposition. Objectives: We sought to determine factors associated with influenza among a prospective cohort of consecutive ED patients with acute respiratory illness (ARI). Methods: Between December 2016 and March 2017, trained research assistants screened consecutive ED patients with ARI symptoms. ARI criteria included measured fever at home or in the ED >38°C and a cough, sore throat, or rhinorrhea with a duration of symptoms >12 hours and <1 week. After consent, research assistants collected demographics and clinical history using a standardized data form, and patients had a polymerase chain reaction–based assay that is nearly 100% sensitive for influenza. Univariate analysis was conducted on all predictor variables. Significant variables were entered into a multivariate logistic regression model to find factors that were independently associated with influenza. Results: One hundred nineteen patients consented to enrollment and 31% were found to be positive for influenza. Myalgia, the absence of gastrointestinal symptoms (no diarrhea or vomiting), sore throat, chills, headache, and oxygen saturation ≥97% were significant on univariate analysis and were entered into the multivariate model. Myalgia (adjusted odds ratio [AOR] 3.9), the absence of gastrointestinal symptoms (AOR 4.7), and oxygen saturation ≥97% (AOR 2.8) were significant independent factors of influenza. Conclusion: The presence of myalgia, the absence of gastrointestinal symptoms, and oxygen saturation ≥97% are factors that can help distinguish influenza from other acute respiratory illnesses in the ambulatory ED population.** © 2018 Elsevier Inc. All rights reserved.

☐ **Keywords—acute respiratory illness; influenza; nosocomial infections; predictors**

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INTRODUCTION

Influenza is estimated to cause 200,000 hospitalizations and 20,000 deaths in the United States annually (1). During peak respiratory virus season, emergency departments (EDs) and ambulatory care clinics experience increased resource demand associated with increased volume, limited isolation areas, and workflows that reduce efficiency (2). Rapid patient triage can improve patient care in myriad ways. Early treatment of influenza with oseltamivir is underused yet can reduce complications and symptom duration and it is recommended by the Centers for Disease Control and Prevention, the World Health Organization, and the Infectious Disease Society of America (3–6). Cohorting suspected cases of influenza can reduce nosocomial infections among the inherently vulnerable ED patient population and is recommended by the World Health Organization (7,8). Lastly, it can reduce the inappropriate prescription of antibiotics for viral illnesses—a crucial part of antibiotic stewardship.

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While research has put much effort into creating algorithms and clinical prediction tools to discriminate between patients with influenza and those with other respiratory illnesses, two meta-analyses have concluded that these models are not robust enough to guide clinical care (9,10). However, these studies have multiple limitations. The majority were conducted in outpatient settings—just three studies were conducted in the ED where we would expect the illness to be more severe (11–13).

Furthermore, most researchers collected data regarding symptoms via patient verbal report or retrospectively via chart review. As compared with a comprehensive, prospective, review of systems approach, these methods prohibit researchers from identifying and defining all important predictor variables before data collection. Such incomplete data has the potential to leave out important predictors, reducing the model's utility. In addition, they result in a heterogeneous collection of predictors across studies making the findings difficult to compare.

During our testing of a rapid device for influenza triage in the ED we a priori and prospectively sought to determine factors that are associated with and that may help discriminate influenza from other causes acute respiratory illness (ARI).

MATERIALS AND METHODS

We conducted a prospective observational cohort study of ambulatory patients presenting to the ED of a university-affiliated tertiary care hospital during peak flu season. The university's institutional review board approved the study. Every day during the 12-week period between December 2016 and March 2017 from 7 AM to 10 PM, trained ED research assistants screened all ED patients. Those eligible were then consented and enrolled. We defined eligible patients as those with ARI symptoms: measured fever at home or in the ED >38°C, and a cough, sore throat, or rhinorrhea with a duration of symptoms >12 hours and <1 week. Those transported to the ED by ambulance or who had already received oseltamivir for the presenting illness were excluded.

After obtaining consent, physicians tested patients for influenza A, influenza B, and respiratory syncytial virus using the Roche Cobas Liat Influenza A/B and respiratory syncytial virus test. In a multisite study including 1656 prospectively collected and retrospectively identified nasopharyngeal samples, this rapid polymerase chain reaction (PCR)–based assay was shown to be near 100% sensitive and >97% specific for influenza (14). During this study, our research team simultaneously conducted a study of this system's test characteristics as compared to the criterion standard of hospital laboratory PCR, and the results showed a sensitivity of 100% and specificity of 95.2% in this population (15).

At the time of enrollment, research assistants also collected predefined information using a standardized form, including demographics, clinical history of the current illness, relevant medical history, clinical findings, and symptoms elicited in a yes/no review of systems manner. We conducted a univariate analysis on all predictor variables and entered significant variables ($p < 0.05$) into a multivariate logistic regression model to find factors that were independently associated with influenza. We used a backward stepwise regression to calculate the final model. Multivariate sample size estimates allow for one variable to be included in the model for every eight to 10 positive flu results (16).

RESULTS

During the study period, 213 consecutive patients were eligible for enrollment. Of these patients, 119 consented to enrollment and a nasopharyngeal swab for point-of-care PCR testing; 31.0% were positive for influenza, 21.8% were positive for respiratory syncytial virus (RSV), and 47.1% were negative for either virus. Patient characteristics and p values from the univariate analysis with a positive influenza test as the dependent variable are described in Table 1.

Myalgia, the absence of gastrointestinal (GI) symptoms (no diarrhea or vomiting), sore throat, headache, chills, and oxygen saturation ≥97% were significant in the univariate analysis ($p < 0.05$) and were entered into the multivariate model.

Sore throat (adjusted odds ratio [AOR] 1.43 [95% confidence interval {CI} 0.50–4.09), headache (AOR 1.76 [95% CI 0.55–5.61]), and chills (AOR 2.31 [95% CI 0.76–7.01]) were removed from the final model using a backward stepwise regression approach. The final model (Table 2) revealed independent predictors of influenza in this ambulatory ED population and included myalgia (AOR 5.64), the absence of GI symptoms (AOR 5.26), and oxygen saturation ≥97% (AOR 3.03; all p values < 0.05). Presence of myalgia had low sensitivity (29.7% [95% CI 15.9–47.0%]) but good specificity (92.7% [95% CI 84.8–97.3%), while the absence of GI symptoms had good sensitivity (89.2% [95% CI 74.6–97.0%]) but low specificity (30.5% [95% CI 20.8–41.6%]). The sensitivity and specificity of oxygen saturation ≥97% were moderate and low, respectively.

DISCUSSION

In patients with defined ARI, the presence of myalgia, the absence of GI symptoms, and oxygen saturation ≥97% can help discriminate influenza from other respiratory viruses in an ED triage population. The presence of myalgia

Table 1. Characteristics of Patients With Acute Respiratory Illness and Influenza Test Results

	N = 119		
Patient Characteristics	Negative, n = 82 (%)	Positive, n = 37 (%)	*p* Value
Age (years), median (range)	3.6 (0–91)	15.4 (0–79)	0.191
0–<12 months	15 (18.3)	2 (5.4)	
12 months–<6 years	32 (39.0)	3 (8.1)	
6–<18 years	8 (9.8)	16 (43.2)	
18–<65 years	22 (26.8)	13 (35.1)	
≥65 years	5 (6.1)	3 (8.1)	
Sex			0.843
Male	41 (50.6)	18 (48.7)	
Female	40 (49.4)	19 (51.4)	
Race			0.799
White, non-Hispanic	15 (18.3)	7 (18.9)	
Hispanic	47 (57.3)	19 (51.4)	
Nonwhite/non-Hispanic	20 (24.4)	11 (29.7)	
History of smoking	9 (11.0)	4 (11.1)	1.000
Unvaccinated	31 (38.3)	18 (51.4)	0.188
History of cancer	7 (8.5)	1 (2.7)	0.432
History of pulmonary disease	12 (14.6)	8 (21.6)	0.345
History of cardiovascular disease	6 (7.3)	0 (0.0)	0.175
Associated symptoms			
Myalgia	6 (7.3)	11 (29.7)	0.001
Anorexia	26 (31.7)	12 (32.4)	0.937
Fatigue	7 (8.5)	5 (13.5)	0.512
Headache	10 (12.2)	12 (32.4)	0.009
Chest pain	4 (4.9)	5 (13.5)	0.134
Absence of gastrointestinal symptoms	57 (69.5)	33 (89.2)	0.021
Sore throat	22 (26.8)	19 (51.4)	0.009
Cough	76 (92.7)	33 (89.2)	0.499
Congestion	38 (46.3)	15 (40.5)	0.556
Chills	10 (12.2)	12 (32.4)	0.011
Clinical findings			
Tachycardia*	46 (56.1)	18 (48.7)	0.451
Tachypnea*	11 (13.4)	2 (5.4)	0.340
Hypertension*	32 (39.0)	11 (29.7)	0.329
Oxygen saturation ≥97%	40 (51.3)	27 (75.0)	0.017
Wheezing	12 (14.6)	6 (16.2)	0.824

* Defined by age-related cut points.

could help rule in and the presence of GI symptoms could help rule out influenza infection; however, no single predictor presented here is able to definitively discriminate an influenza infection from another ARI, and the study was not powered such that a composite of variables could be tested to create a clinical prediction tool. Research has been mostly limited to the outpatient clinic setting, and this is the first study performed prospectively in an acute ED setting. Previous studies suggested that fever plus cough, sore throat, or headache are predictive of the flu; however, only two of these studies systematically asked patients about GI symptoms—one of the which similarly found a lack of GI symptoms to be a significant predictor (11,13,17–22). Indeed, we found sore throat and headache to be significant in our univariate analysis, but when combined with oxygen saturation and GI symptom data, they were no longer significant. In addition, concluding that cough and fever ≥38°C were predictors of flu could be problematic given that these are criteria for any ARI and are required to gain entry into many of the studies (9).

Furthermore, this investigation highlights some of the limitations of large secondary analysis studies where important variables are often not available or were not carefully ascertained within the datasets (23,24). The presence of myalgia, an independent predictor in our study, was inconsistently found to be a predictor in similar studies. This was likely dependent on if, or how, the presence of myalgia was ascertained. A systematic review weighting large database studies found myalgia to not be significant (10). As such, we have shown the importance of accurately collecting data and including important variables in such studies, such as the presence of myalgia or GI symptoms. In future studies, we hope that these variables will be included and specifically asked to the patient.

Limitations

Our study's main limitation was its low sample size. The study was conducted during peak ED hours, 7 days a week, and consecutive patients were screened for eligibility as defined by the Centers for Disease Control and Prevention's ARI criteria. At the time of the study, the point-of-care PCR test, while cleared by the U.S. Food and Drug Administration, was not yet approved by the hospital for use in medical decision-making. Therefore, many patients refused the nasopharyngeal swab because the results could not be used to guide care. While this could have introduced bias into our study, we found no demographic differences among participants and nonparticipants.

Table 2. Multivariate Analysis of Factors Associated With a Positive Influenza Test

Variable	AOR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Myalgia	5.64 (1.72–18.5)	29.7 (15.9–47.0)	92.7 (84.8–97.3)	64.7 (38.3–85.8)	74.5 (64.9–82.6)
Absence of gastrointestinal symptoms	5.26 (1.35–20.4)	89.2 (74.6–97.0)	30.5 (20.8–41.6)	36.7 (26.8–47.5)	86.2 (68.3–96.1)
Oxygen saturation ≥97%	3.03 (1.17–7.81)	75.0 (57.8–87.9)	48.7 (37.2–60.3)	40.3 (28.5–53.0)	80.9 (66.7–90.9)

AOR = adjusted odds ratio; CI = confidence interval; NPV = negative predictive value; PPV = positive predictive value.
Hosmer–Lemeshow goodness of fit test (chi-squared = 0.988, $p = 0.912$).

Another limitation of our study is the young age of our population. At our institution, the ED population is approximately 30% pediatric for all cases. However, 63.9% of this study population was <18 years of age, which is much younger than that of comparable studies. This is likely secondary to the high burden of RSV experienced during flu season by young children. As a result, we had a high rate of RSV positivity among the influenza-negative patients, which could have precipitated high oxygen saturation as a predictor of influenza infection that had not been previously appreciated. While influenza can cause pneumonia, it rarely presents with lung disease in the ambulatory setting compared with RSV and bacterial pneumonia. Given lack of ample comparison data, it is unclear if our finding is related to the younger age of our patients and their acuity or because we recorded oxygen saturation, which is not a routine measurement in ambulatory settings where most other studies of this nature have been conducted.

In addition, our study was conducted over the course of a single flu season. It is reasonable to suspect that as influenza strains vary year to year, so could the clinical presentation. Lastly, our study included patients from a single academic center. While the incidence and severity of the flu can vary among geographic regions, its presentation and criterion standard diagnosis using PCR technology does not. Therefore, it is realistic to expect that the significant results from this prospective study on consecutive patients would be generalizable to similar ED populations.

CONCLUSION

The clinical predictors we found are simple to ascertain and could be easily used at triage to improve patient care in ambulatory care settings during influenza season (25). Despite our small sample size, our study is methodologically rigorous in the way in which we systematically collected symptomatic and clinical data from patients and revealed potential variables to consider in future studies. While our study was not powered to have the ability to create an algorithm or regression tree ready for clinical validation, we hope our effort here will serve as the methodological backbone of future large, multicenter studies that aim to create a reliable clinical prediction tool for influenza. The availability of such a tool can guide triage and have multiple potential benefits to both patients and health care systems: reducing nosocomial infections by incorporating it into social distancing measures, reducing costs and length of stay for patients, increasing appropriate use of antiviral medication, and reducing the inappropriate use of antibiotics.

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ARTICLE SUMMARY

1. Why is this topic important?

Influenza season wreaks havoc on our health care system annually by overburdening our already stressed emergency departments (EDs) and hospitals. In the absence of a reliable, affordable, and rapid point-of-care test for influenza, a clinical diagnosis of influenza would allow us to provide therapy faster, reduce length of stay, and possibly reduce nosocomial infections.

2. What does this study attempt to show?

We attempt to show that a syndromic formula for influenza could be created if stronger methodologic approaches to collecting the data are implemented. In contrast to other studies that have asked the same question and obtained heterogeneous results, we took a prospective approach to thoroughly and systematically define and obtain factors that distinguish influenza from other acute respiratory illnesses. The method of ascertaining data as presented here is critical if we aim to create such a clinical prediction tool.

3. What are the key findings?

In patients with defined acute respiratory illness, the presence of myalgia, the absence of gastrointestinal symptoms, and oxygen saturation $\geq$97% on room air could potentially help discriminate influenza from other respiratory viruses in an ED triage population.

4. How is patient care impacted?

In the ED, distinguishing influenza from other respiratory illnesses could improve patient care in a myriad ways. Research shows that antibiotics and antivirals are not optimally prescribed for acute respiratory illnesses in the acute setting given the lack of rapid, reliable tests. Differentiating between bacterial and viral etiologies in the ED would allow providers to prescribe oseltamivir as recommended by the Centers for Disease Control and Prevention, Infectious Diseases Society of America, and the World Health Organization for the treatment of influenza. In addition, length of stay in the ED could be shortened and fewer tests could be ordered—both actions save costs and reduce ED overcrowding. Lastly, it could help reduce nosocomial infections, as patients suspected to have influenza could be cohorted into one shared room while receiving treatment.