RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

DOI: 10.4274/atfm.galenos.2021.74755
Ankara Üniversitesi Tıp Fakültesi Mecmuası 2021;74(Suppl 1):89-96

MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Do the Rapid Influenza Diagnostic Tests Results Reflect the Truth?

İnfluenza Hızlı Tanı Testi Sonuçları Gerçeği Yansıtıyor mu?

Tuğba Yanık Yalçın[1], Çiğdem Erol[1], Saliha Aydın[2], Nuran Sarı[1], Özlem Kurt Azap[1], Hande Arslan[1]

[1]Başkent University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey
[2]Ankara University Faculty of Medicine, Department of Public Health, Ankara, Turkey

Abstract

Objectives: Influenza (flu) causes seasonal epidemics and has led to numerous pandemics worldwide. Its rapid diagnosis and treatment are critical. This study evaluated the correlation between rapid influenza diagnostic test (RIDT) results and clinical reflection.

Materials and Methods: A total of 795 patients who were performed the RIDT during the 2018-2019 influenza season were included. According to the test results, the patients were then divided into two groups. The Flu+ group was composed of patients with positive diagnostic test results, while the Flu- group was those with negative test results.

Results: The data of 795 patients with 248 positive RIDTs were compared with the data of 547 patients with negative test results. Fever was present in 199 (80.2%) patients in the Flu+ group and in 209 (38.2%) patients in the Flu- group (p<0.001). Cough was noted in 170 (68.5%) patients in the Flu+ group and in 251 (45.9%) patients in the Flu- group (p<0.001). There were 106 patients (42.7%) in Flu+ group and 44 (7.9%) in the Flu- group (p<0.001), who had myalgia. The presence of fever was 4.7-fold, myalgia was 4.5-fold, and cough was 2.4-fold, signifying the risk of being influenza-positive (74.9% sensitivity, 79.7% specificity).

Conclusion: The results of our study are compatible with the known influenza clinic. Myalgia is almost as common as fever in patients. While limited, RIDTs are useful to clinicians in the diagnosis of influenza infection. While rapid influenza diagnostic tests are preferred due to their ease of use and low cost, even if negative, the clinician's examination findings and clinical diagnosis are important, particularly in patients in the risk group.

Key Words: Rapid Diagnostic Test, Influenza, Antigen Test

Öz

Amaç: Grip, mevsimsel salgınlara ve dünya çapında çok sayıda pandemiye yol açar. Bu nedenle hızlı teşhis ve tedavisi önemlidir. Bu çalışmada influenza hızlı tanı testleri (RIDT) sonuçları ile klinik arasındaki korelasyon değerlendirildi.

Gereç ve Yöntem: 2018-2019 influenza sezonunda hastanemizde RIDT yapılan toplam 795 hasta çalışmaya dahil edildi. Test sonuçlarına göre hastalar iki gruba ayrıldı. Tanı testi sonucu pozitif olan hastalar influenza pozitif (Flu+) gruba, tanı testi sonucu negatif olan hastalar influenza negatif (Flu-) gruba dahil edildi.

Bulgular: RIDT'si pozitif olan 248 hastanın verileri, tanı testi sonucu negatif olan 547 hastanın verileri ile karşılaştırıldı. Ateş, Flu+ grupta 199 (%80,2), Flu- grupta 209 (%38,2) hastada mevcuttu (p<0,001). Flu+ grupta 170 (%68,5), Flu- grupta 251 (%45,9) hastada öksürük eşlik ediyordu (p<0,001). Miyalji, Flu+ grupta 106 (%42,7), Flu- grupta 44 (%7,9) hastada vardı (p<0,001). Çalışmamızın sonuçlarına göre ateş varlığı 4,7 kat, miyalji varlığı 4,5 kat ve öksürük varlığı 2,4 kat influenza pozitifliğini öngörmektedir (%74,9 duyarlılık, %79,7 özgüllük).

Sonuç: Çalışmamızın sonuçları bilinen influenza kliniği ile uyumludur. Hastalarda miyalji yakınması neredeyse ateş kadar sık görülmektedir. İnfluenza hızlı tanı testleri sınırlı duyarlılıkları ile birlikte influenza enfeksiyonunun teşhisinde klinisyenler için faydalıdır. RIDT'ler, kullanım kolaylığı ve düşük maliyeti nedeniyle tercih edilirken, negatif sonuca rağmen, özellikle risk grubundaki hastalarda klinisyenin muayene bulguları ve klinik tanısı önemlidir.

Anahtar Kelimeler: Hızlı Tanı Testleri, Grip, Antijen Testi

Address for Correspondence/Yazışma Adresi: Tuğba Yanık Yalçın
Başkent University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey
Phone: +90 312 203 68 68 E-mail: drtugbayalcin@gmail.com **ORCID ID:** orcid.org/0000-0001-5996-8639
Received/Geliş Tarihi: 18.06.2021 **Accepted/Kabul Tarihi:** 03.08.2021

Introduction

Influenza (flu) is an acute upper respiratory disease that is caused by influenza viruses. Flu causes seasonal epidemics and has caused many pandemics worldwide. Although it is generally a self-limiting disease, it ranges from mild to severe and can result in children being unable to attend school, a reduced workforce, and economic difficulties. Therefore, countries closely follow influenza-like illnesses (ILI) and influenza species, and the World Health Organization publishes the data globally on the FluNet website. Influenza surveillance aims to determine the activity of the disease and the circulating virus strains and detect the presence of a new strain early. Additionally, it aims to determine the risk groups and the vaccine content for the next season. Within the scope of influenza surveillance, sentinel surveillance has been carried out since 2005 in the form of "ILI Surveillance" in both our country and globally. In our country, influenza surveillance is reported weekly on influenza.gov.tr, and seasonal influenza activity is observed between October and March. According to the National Influenza Surveillance's report, 86.4% of the circulating viruses were reported as influenza A and 13.5% as influenza B during the 2018-2019 seasonal flu season (1).

By using available diagnostic methods and appropriately interpreting the results, patients who apply can be diagnosed correctly. A timely diagnosis reduces unnecessary laboratory tests and the inappropriate use of antibiotics while increasing the effectiveness of infection prevention and control measures and the appropriate use of antiviral drugs (2). Rapid influenza diagnostic tests (RIDTs) are widely used due to financial issues in countries with limited resources, and due to their rapid results and ease of use in many other regions, molecular systems are developing rapidly. RIDTs are immunological tests that can identify the presence of influenza A and B viral nucleoprotein antigens in respiratory samples and display the results qualitatively (positive and negative). RIDTs have a low or medium sensitivity (10%-70%) and a high specificity (90%-99%). In the high influenza activation period, a positive result is definitively positive, whereas a negative result may be a false negative. Factors, such as having symptoms compatible with influenza, the time from symptom onset to sampling, and influenza activity in the population, are important in interpreting the results. Antigen tests are not sufficient for the diagnosis of influenza (3). A polymerase chain reaction (PCR) or viral culture test is recommended. However, these tests are expensive, and even if the results are negative, the clinician's evaluation is important.

In this study, we aimed to investigate the correlation between RIDTs results and patients clinical status, laboratory values and accordance of literature.

Materials and Methods

Patients

In this analytical study, patients over the age of 18 performed an Influenza rapid antigen test (SofiaTM) in the microbiology laboratory of Başkent University Hospital from October 1, 2018 to March 1, 2019 (seasonal influenza). The patients were subsequently divided into two groups based on their test results. Patients with positive diagnostic test results comprised the Flu+ group, and those with negative test results formed the Flu- group.

Data Collection

The patients' demographic and laboratory data were obtained by review of medical records: patient demographics (gender, age, comorbidity), initial symptoms (fever, cough, sore throat, myalgia, dyspnea, confusion), and laboratory data [white blood cell, neutrophil, lymphocyte, neutrophil/lymphocyte ratio (NLR), platelet, C-reactive protein (CRP), procalcitonin]. By evaluating initial symptoms, laboratory data, hospitalization and intensive care unit (ICU) admission the compliance of the RIDT results with the clinical situation was examined. An infectious diseases specialist and an infectious diseases technician retrospectively recorded from our hospital's data system the numerical and categorical variables of a total of 795 patients. In this study, the guidelines on strengthening the reporting of observational studies in epidemiology (STROBE) were followed. This research was approved by Başkent University Institutional Review Board (project no: KA20/408) and supported by Başkent University Research Fund.

Statistical Analysis

The compatibility of numerical data to normal distribution was tested in the assessment. Data with parametric characteristics were expressed as arithmetic mean ± standard deviation, and two independent groups were compared using the Student's t-test. The Mann-Whitney U test was employed to contrast two independent groups by showing those without parametric features as the median and interquartile range of distribution (Q1-Q3). Nominal data were expressed as number (n) and percentage (%), and the chi-square test was utilized to allow group comparisons. With the possible factors determined in multivariate analysis, the Backward logistic regression (LR) method of LR analysis was used to assess independent predictors in predicting the diagnosis of influenza. Those with $p<0.20$ in the univariate analysis were included in the multivariate analysis. The odds ratio in logistic regression analysis was calculated within the 95% confidence interval (CI). The Hosmer Lemeshow test evaluated the fit of the model, while the receiver operating characteristic (ROC) curve estimation assessed the model's adequacy. Statistical analyses were conducted using the

IBM® SPSS© 25 software with Medcalc version 14.8.1 package program. The conditions below 5% of the type 1 inaccuracy level were interpreted as statistically significant.

Results

Patient Characteristics

Başkent University Hospital serves as a 350-bed tertiary healthcare institution. In our hospital microbiology laboratory, 3,471 influenza rapid antigen tests were performed on 3,165 patients during the 2018-2019 influenza season. A total of 2,352 tests belonged to patients under 18 years of age, and 324 patient data could not be accessed. Data from 795 patients including those with 248 RIDT positive results were compared with data from 547 patients with negative influenza diagnostic tests. In the Flu+ group, 193 (77.8%) of patients applied to the hospital from the outpatient clinics and 41 (16.5%) from the emergency department. In the Flu- group, 347 (63.4%) patients applied from the outpatient clinics, and 61 (11.2%) patients were from the emergency department. In certain patients, influenza-like symptoms were observed while hospitalized and screened for influenza diagnosis. In this group, 14 (5.6%) patients who tested positive were included in the Flu+ group, while 139 (25.4%) patients became part of the Flu- group following a negative test (Figure 1).

In the Flu+ group, 216 patients were influenza A positive, 24 were influenza B positive, and 7 were influenza A and B positive. The median age was 50 in the Flu+ group (minimum: 18, maximum: 98), while the median age in the Flu- group was 59 (minimum: 19, maximum: 100). The gender distribution was similar between the two groups, with a predominance of females: 154 cases (62.1%) in Flu+ and 318 cases (58.1%) in Flu- groups (p=0.292). The comorbidities of patients in both groups (hypertension, diabetes mellitus, coronary artery disease, chronic renal failure, chronic pulmonary disease, solid-organ transplantation, hematological malignancy, solid-organ malignancy, chronic rheumatic diseases, chronic neurological disorders, thyroid disorders) were evaluated. The comorbidity rate (69.1%; p<0.001) and the rate of patients with chronic pulmonary disease (13.7%; p=0.001) were higher in the Flu- group. Thirty-nine patients in the Flu+ group (15.7%) and 57 in the Flu- group (10.4%) were undergoing immunosuppressive therapy due to malignancy, organ transplants, or rheumatic diseases (p=0.03). At presentation, 64 (24.8%) patients in Flu+ group and 163 (29.8%) patients in the Flu- group had abnormal lung examinations (p=0.082).

When the presenting symptoms of the patients were evaluated, fever was noted in 199 (80.2%) patients in the Flu+ group and in 209 (38.2%) patients in the Flu- group (p <0.001). Moreover, 170 (68.5%) patients in the Flu+ group and 251 (45.9%) patients in the Flu- group (p<0.001) had cough. In both groups, myalgia was present: 106 (42.7%) in the Flu+ group and 44 (7.9%) in the Flu- group (p<0.001). Ninety-six (37.2%) patients in the Flu+ group and 100 (18.1%) patients in the Flu- group (p<0.001) had sore throats. While the number of patients with dyspnea at presentation was 31 (12.5%) in the Flu+ group, it was higher in the Flu- group with 140 (25.6%) patients (p<0.001). The number of patients presenting with impaired consciousness was 11 (4.4%) in the Flu+ group and 36 (6.7%) in the Flu- group. The distribution of symptoms in both groups is given in Figure 2.

In the treatment, oseltamivir was used in 238 (96%) patients in the Flu+ group and in 256 (46.8%) patients in the Flu- group (p<0.001). The number of patients who died during the 30-day follow-up was 9 (3.6%) in the Flu+ group (Table 1).

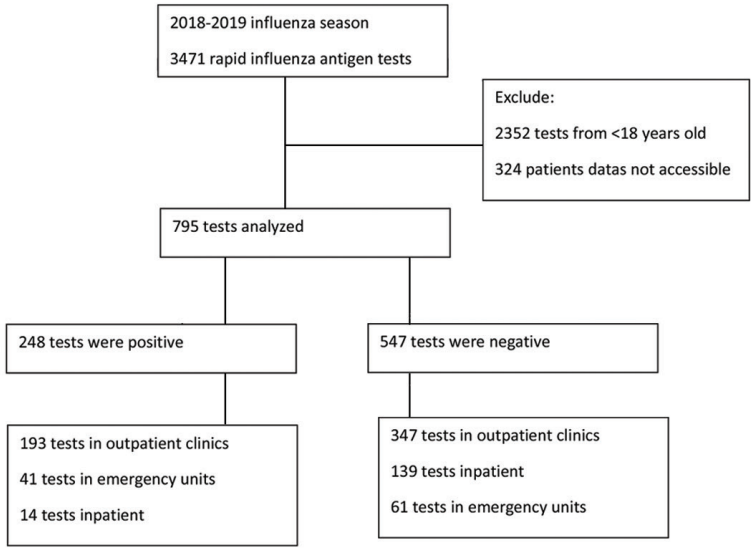

Figure 1: Study flow diagram

Laboratory Values Analysis

In the analysis of laboratory values of white blood cell, neutrophil, lymphocyte, and platelet were significantly low in Flu+ group (p<0.001, p<0.001, p=0.002, p<0.001 respectively), however NLR, CRP and procalcitonin values were not significantly difference between Flu+ and Flu- groups (p=0.397, p=0.374, p=0.476 respectively) (Table 2).

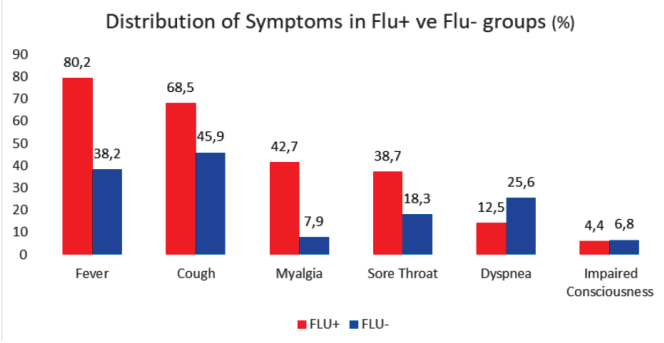

Figure 2: The distribution of initial symptoms

Table 1: Demographic characteristics of Flu+ and Flu- groups

	Flu (+)	Flu (-)	p-value
Age Mean ± SD	52±19.59	56.63±19.55	0.002
Gender Female n (%)	159 (61.6)	318 (58.1)	0.194
Hospital admission Yes n (%)	70 (27.1)	223 (40.8)	<0.001
Comorbidity Yes n (%)	169 (55)	378 (69.1)	<0.001
Hypertension n (%)	66 (25.6)	192 (35.2)	0.007
Diabetes mellitus	37 (14.3)	113 (20.7)	0.032
Coronary artery disease	35 (13.6)	88 (16.1)	0.353
Chronic pulmonary disease	21 (8.2)	75 (13.7)	0.001
Chronic renal failure	15 (5.8)	48 (8.8)	0.144
Solid-organ transplantation	20 (7.8)	43 (7.9)	0.957
Solid-organ malignancy	19 (7.4)	9 (1.6)	<0.001
Hematological malignancy	7 (2.7)	14 (2.6)	0.898
Chronic rheumatic diseases	13 (5)	17 (3.1)	0.177
Thyroid disorders	16 (6.2)	0	
Chronic neurological disorders	13 (5.1)	21 (3.8)	0.423
Immunosuppression Yes n (%)	39 (15.7)	57 (10.4)	0.03
Intensive care unit admission Yes n (%)	21 (8.5)	91 (16.6)	0.002
Mechanical ventilation Yes n (%)	10 (47.6)	53 (58.2)	0.37
Oseltamivir	238 (96)	256 (46.8)	<0.001
Exitus Yes n (%)	9 (3.6)	39 (7.1)	0.054

SD: Standard deviation

Comparison of Flu+ Group ICU and Non-ICU Patients

Twenty-one of the patients in the Flu+ group (8.4%; n=21/248) had been admitted to the ICU. When we compared the age, symptoms, and laboratory values of the patients in this group according to their ICU admission, the median age of the patients admitted to the ICU was 70, which was significantly higher than those without ICU admission (48) (p<0.001). Fever (42.9%) was low in patients with ICU admission, while dyspnea was significantly higher with 76.2% (p<0.001). Neutrophil, NLR, and CRP values were high in patients admitted to ICU (p=0.002, p<0.001, p<0.001, respectively). The median lymphocyte value was significantly lower at 630/µL (p<0.001). Mortality was higher in patients with ICU admission 42% (n=11) (Table 3). Laboratory values of Flu+ patients according to ICU admission showed with box-line graphs at Figure 3.

Univariate and Multivariate Analysis Results

In the univariate analysis, those with p<0.20 were used for multivariate analysis. The resulting model is given in Table 4 and 5. The fit of the model was evaluated by the Hosmer Lemeshow test (p=0.251). ROC analysis evaluated the adequacy of the model and found the area under the curve was 0.826 (95% CI: 0.794-0.855), its sensitivity was 74.9%, and the specificity was 79.7% (Figure 4).

According to these results, the presence of fever was 4.7-fold, myalgia was 4.5-fold, cough was 2.4-fold, and sore throat was 2.3-fold, indicating a higher risk of being influenza positive. Influenza positivity is 7% lower for every 10,000 units of increase in the white blood cell level and 25% lower for every 1,000 units of increase in the lymphocyte level.

Discussion

The present study is based on rapid influenza antigen tests, and the results are consistent with the symptom distribution of influenza patients in the literature (4,5). Our research found that fever, cough, myalgia, and sore throat were high in the influenza-positive patient group.

Logistic regression analysis (74.9% sensitivity, 79.7% specificity) revealed the presence of fever to be 4.7-fold and myalgia to be 4.5-fold, predictive for influenza diagnosis; cough or sore throat was found to be a 2-fold increased risk. Similarly, it has been shown in the literature that myalgia, cough, and sore throat are clinical predictors in the presence of influenza (6-8). However, only fever and cough are included in the diagnosis of ILI, while myalgia is a common symptom in influenza patients.

Dyspnea was high in the influenza-negative group, but the number of patients with chronic pulmonary disease in this

Table 2: Analysis of laboratory values

Laboratory value	Flu+	Flu-	p-value
White blood cells (/µl) Median (Q1-Q3)	6,880 (4,780-8,730)	8,320 (6,355-11,067)	<0.001
Neutrophil (/µl) Median (Q1-Q3)	4,530 (3,000-6,390)	5,615 (3,787-8,277)	<0.001
Lymphocyte (/µl) Median (Q1-Q3)	1150 (780-1,640)	1,380 (895-1,965)	0.002
Neutrophil/lymphocyte ratio Median (Q1-Q3)	3.98 (2.2-6.5)	3.98 (2.2-7.6)	0.397
Platelet (/µl) Mean ± SD	201,292±67,858	226,063±85,434	<0.001
CRP (mg/L) Median (Q1-Q3)	23.4 (10.8-61)	23 (6-82.5)	0.374
Procalcitonin (µg/L) Median (Q1-Q3)	0.86 (0.46-3.2)	0.72 (0.2-3.7)	0.467

CRP: C-reactive protein, SD: Standard deviation

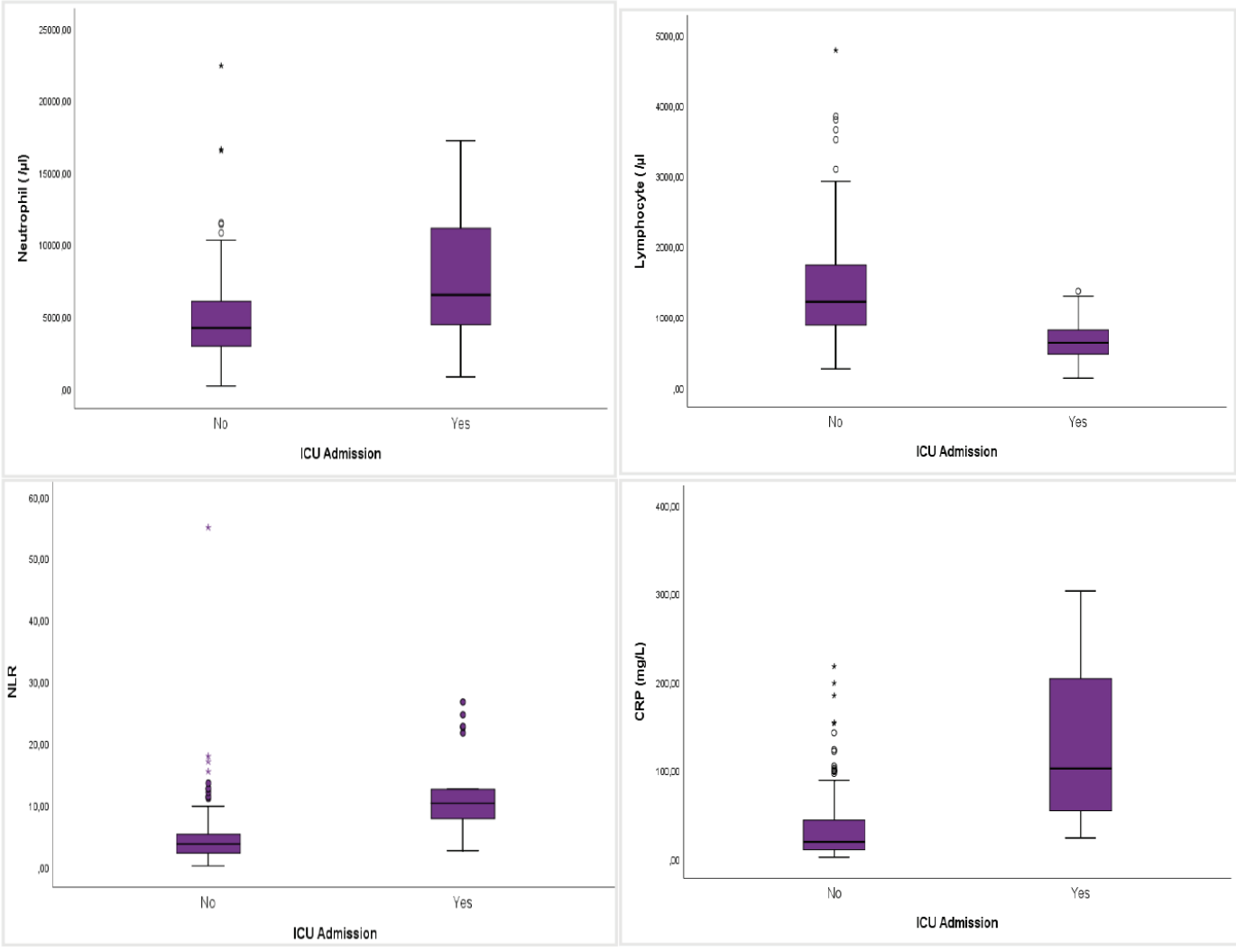

Figure 3: Laboratory values of Flu+ patients according to ICU admission with box-line graphs. ICU admitted patients' neutrophil, CRP and NLR were higher than non-ICU admitted patients; their lymphocyte levels are also lower.

Flu+: Patients with rapid influenza diagnostic test result positive, ICU: Intensive care unit, CRP: C-reactive protein, NLR: neutrophil/lymphocyte ratio

group was higher. Anderson et al. (7) have found that dyspnea and lung findings in physical examination were lower in influenza-negative individuals compared to influenza-positive individuals (7). Influenza viruses are one of the atypical pneumonia agents; clinical findings and radiology are generally inconsistent, reminding us that the examination findings are subtle in the diagnosis of viral pneumonia.

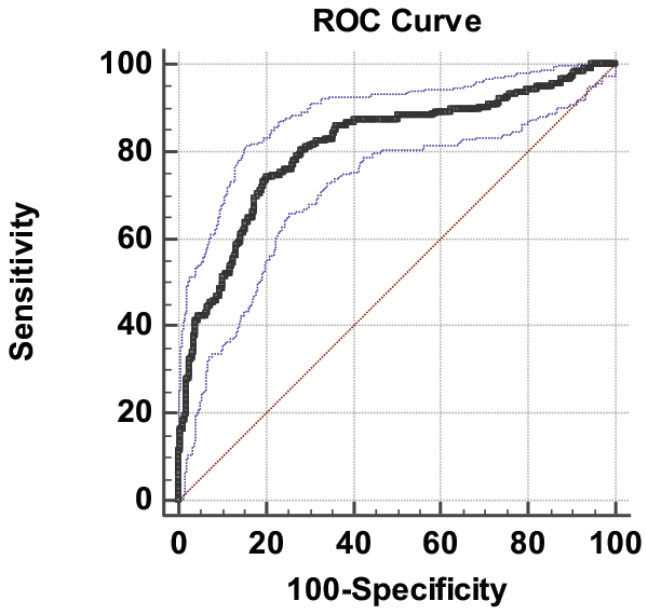

Figure 4: ROC curve. The ROC curve for the prediction of flu diagnosis based on the logistic regression model

N=612, R^2=0.268 (Cox-Snell), R^2=0.378 (Nagelkerke)

Model: $X^2(7)$=190,595 (p<0.001) Hosmer Lemeshow test: p=0.251

ROC: Receiver operating characteristic

The median age of the patients admitted to the ICU in the influenza-positive group was 70 and the fever symptom was low. Matsuno et al. (9) observed lower body temperatures in the elderly compared to young people. In another study, fever, cough, and acute onset disease were found to be 30% positive predictive value (PPV) for elderly patients, while it was found to be 70% PPV in young people (10). It should be kept in mind that fever will not be seen in the elderly due to immunosense. In our research, the mortality rate in patients admitted to the ICU was 40%. In the study of Wong et al. (4), hospitalization and mortality due to influenza were found to be significantly higher in individuals over 65 years of age. In the 2019-2020 influenza report of the Centers for Disease Control (CDC), 43% of influenza-associated hospitalizations were in individuals >65 years old, with 62% of deaths in this group (11). These results indicate that influenza is more life-threatening in the elderly and reinforces the importance of vaccination.

In our study, it was found that the CRP level correlated with ICU admission. In the Matsuno et al. (9) study, the CRP value, which is one of the acute inflammatory response parameters, was significantly higher in elderly patients diagnosed with influenza. This was associated with the low fever response in the elderly and thus with the delay in diagnosis. However, our

Table 3: Comparison of Flu+ group symptoms and laboratory values according to their intensive care unit admission

	Flu+ group		
	ICU admission n=21	Not ICU admission n=227	p-value
Age median (Q1-Q3)	70 (60-85)	48 (33-65)	<0.001
Fever n (%)	9 (42.9)	190 (83.7)	<0.001
Dyspnea n (%)	16 (76.2)	15 (6.6)	<0.001
White blood cell median (Q1-Q3)	7,920 (5,215-13,820)	6,765 (4,772-8,415)	0.11
Neutrophil median (Q1-Q3)	6,490 (4,175-11,835)	4,200 (2,932-6,060)	0.002
Lymphocyte median (Q1-Q3)	630 (425-850)	1,220 (860-1,680)	<0.001
NLR median (Q1-Q3)	10.2 (7.1-17)	3.65 (2.1-5.2)	<0.001
Platelet median (Q1-Q3)	$173x10^3$ ($134x10^3$-$220x10^3$)	$203x10^3$ ($161x10^3$-$242x10^3$)	0.063
CRP median (Q1-Q3)	101 (50-213)	18.9 (10-43)	<0.001
Procalcitonin median (Q1-Q3)	1.05 (0.49-4.02)	0.66 (0.1-0.32)	0.13
Exitus n (%)	8 (38.1)	1 (0.4)	<0.001

ICU: Intensive care unit, NLR: Neutrophil/lymphocyte ratio, CRP: C-reactive protein

interpretation is that we do not know of concomitant bacterial infections in these patients, but there was no significant difference in procalcitonin values between the groups with and without ICU admission. In several studies, evaluation with procalcitonin was found to be more appropriate than CRP in differentiating bacterial and viral infections (12-15). While Rodríguez et al. (16) stated that procalcitonin was significantly higher in influenza patients with community-acquired pneumonia coinfection, they did not find a significant increase in CRP.

A relatively decreased lymphocyte count is observed in influenza virus infections, as in many viral infections. Recent studies have investigated the relationship between neutrophil-lymphocyte ratio and various clinical conditions. In the Han et al. (17) study, NLR was found to be more sensitive in influenza infections compared to other hematological parameters (17). In our research, there was no difference between the NLR influenza-positive and negative groups, but the influenza-positive group was significantly higher in those with ICU admission. Significant lymphopenia was also present in those who were admitted to the ICU.

Antiviral treatment use was high in the influenza-positive group, but 48% of antiviral use was also available in the influenza-negative group. About half of these patients were over 65 years old. Influenza antigen tests have low to medium sensitivity, and the test result is affected by factors such as proper intake method and schedule, and correct storage. False-negative effects are also seen during the influenza season. If clinically indicated in the guidelines, it is recommended to initiate antiviral therapy (2,3).

Table 4: Univariate analysis

	OR (95% CI)	p-value
Age	0.98 (0.97-0.99)	<0.001
Fever	6.5 (4.5-9.3)	<0.001
Cough	2.5 (1.8-3.5)	<0.001
Sore throat	2.8 (2-3.9)	<0.001
Myalgia	8.7 (5.8-13)	<0.001
Dyspnea	0.4 (0.2-0.6)	<0.001
Chronic pulmonary disease	0.5 (0.33-0.94)	0.028
White blood cell (/10^3)	0.89 (0.84-0.93)	<0.001
Lymphocyte (/10^3)	0.72 (0.58-0.90)	0.005
NLR	0.96 (0.94-0.99)	0.023
Platelet (/10^4)	0.96 (0.93-0.99)	<0.001
CRP	0.99 (0.98-1.001)	0.156

OR: Odds ratio, CI: Confidence interval, CRP: C-reactive protein

Study Limitations

The limitation of the present study is the low level of evidence due to its retrospective design. Based on the test results, we divided the patients into groups such as Flu+ and Flu-. However, it was not enough to have a negative diagnosis of influenza. Confirmation by PCR or viral culture is recommended, especially for inpatients. We were aware that influenza patients are in the negative group.

Conclusion

In the diagnosis of influenza infections, RIDTs are useful, albeit limited, to clinicians. Although PCR tests are the gold standard in diagnosis, these tests can produce false-negative results due to factors such as transport, storage conditions, and preparation. Influenza diagnosis should be kept in mind, particularly during the influenza season, due to lack of fever in elderly patients, possibility of different symptoms, and increased mortality in delayed diagnosis. RIDTs are preferred for their ease of use and low cost; however, even if negative, examination findings and clinical diagnosis of clinicians are important, especially for patients in the risk group.

Table 5: Multivariate analysis

Variable		B	SE	OR (%95 CI)	p
Constant		-1.799	0.351	0.165	<0.001
White blood cell (/10^3)		-0.074	0.03	0.929 (0.876-0.984)	0.013
Lymphocyte (/10^3)		-0.294	0.141	0.745 (0.565-0.983)	0.037
Fever	No	Reference			
	Yes	1.562	0.231	4,769 (3,032-7.5)	<0.001
Cough	No	Reference			
	Yes	0.892	0.217	2.44 (1,594-3,735)	<0.001
Myalgia	No	Reference			
	Yes	1.519	0.256	4,568 (2,765-7,549)	<0.001
Sore throat	No	Reference			
	Yes	0.841	0.256	2,319 (1,404-3,828)	0.001

SE: Standard error, OR: Odds ratio, CI: Confidence interval

Ethics

Ethics Committee Approval: This research was approved by Başkent University Institutional Review Board (project no: KA20/408) and supported by Başkent University Research Fund.

Informed Consent: Retrospective study.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: T.Y.Y., Ç.E., N.S., Ö.K.A., Design: T.Y.Y., Ç.E., S.A., Data Collection or Processing: T.Y.Y., Analysis or Interpretation: S.A., Literature Search: T.Y.Y., N.S., Writing: T.Y.Y., Ö.K.A., H.A.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: The authors received no financial support for the research and/or authorship of this article.

References

1. Weekly Influenza (Flu) Surveillance Report..Accessed November 28, 2020. https://grip.gov.tr/depo/influenza-raporu/2018/InfluenzaGrip_Surveyans_Raporu_2019_21-39._hafta.pdf.
2. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. Clin Infect Dis. 2019;68:e1-e47.
3. Guidance for Clinicians on the Use of Rapid Influenza Diagnostic Tests. Accessed November 28, 2020. https://www.cdc.gov/flu/pdf/professionals/diagnosis/clinician_guidance_ridt.pdf.
4. Wong PL, Sii HL, P'ng CK, et al. The effects of age on clinical characteristics, hospitalization and mortality of patients with influenza-related illness at a tertiary care centre in Malaysia. Influenza Other Respir Viruses. 2020;14:286-293.
5. Casalegno JS, Eibach D, Valette M, et al. Performance of influenza case definitions for influenza community surveillance: based on the French influenza surveillance network GROG, 2009-2014. Euro Surveill. 2017;22:30504.
6. Shah SC, Rumoro DP, Hallock MM, et al. Clinical predictors for laboratory-confirmed influenza infections: exploring case definitions for influenza-like illness. Infect Control Hosp Epidemiol. 2015;36:241-248.
7. Anderson KB, Simasathien S, Watanaveeradej V, et al. Clinical and laboratory predictors of influenza infection among individuals with influenza-like illness presenting to an urban Thai hospital over a five-year period. PLoS One. 2018;13:e0193050.
8. Monamele CG, Kengne-Nde C, Munshili Njifon HL, et al. Clinical signs predictive of influenza virus infection in Cameroon. PLoS One. 2020;15:e0236267.
9. Matsuno O, Kataoka H, Takenaka R, et al. Influence of age on symptoms and laboratory findings at presentation in patients with influenza-associated pneumonia. Arch Gerontol Geriatr. 2009;49:322-325.
10. Metlay JP, Schulz R, Li YH, et al. Influence of age on symptoms at presentation in patients with community-acquired pneumonia. Arch Intern Med. 1997;157:1453-1459.
11. Estimated Influenza Illnesses, Medical visits, Hospitalizations, and Deaths in the United States - 2019-2020 Influenza Season. Accessed November 26, 2020. https://www.cdc.gov/flu/about/burden/2019-2020.html.
12. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. Lancet. 2010;375:463-474.
13. Ingram PR, Inglis T, Moxon D, et al. Procalcitonin and C-reactive protein in severe 2009 H1N1 influenza infection. Intensive Care Med. 2010;36:528-532.
14. Cuquemelle E, Soulis F, Villers D, et al. Can procalcitonin help identify associated bacterial infection in patients with severe influenza pneumonia? A multicentre study. Intensive Care Med. 2011;37:796-800.
15. Pfister R, Kochanek M, Leygeber T, et al. Procalcitonin for diagnosis of bacterial pneumonia in critically ill patients during 2009 H1N1 influenza pandemic: a prospective cohort study, systematic review and individual patient data meta-analysis. Crit Care. 2014;18:R44.
16. Rodríguez AH, Avilés-Jurado FX, Díaz E, et al. Procalcitonin (PCT) levels for ruling-out bacterial coinfection in ICU patients with influenza: A CHAID decision-tree analysis. J Infect. 2016;72:143-151.
17. Han Q, Wen X, Wang L, et al. Role of hematological parameters in the diagnosis of influenza virus infection in patients with respiratory tract infection symptoms. J Clin Lab Anal. 2020;34:e23191.