

Accuracy of Physician Judgment for Diagnosis of Pneumonia in Transplant Patients with Fever in Emergency Settings

Acil Serviste Yüksek Ateşli Transplant Hastalarında Pnömoni Tanısının Koyulmasında Hekimin Klinik Kararının Değeri

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ABSTRACT Objective: The aim of the study is to determine the diagnostic accuracy of emergency physician judgment for diagnosis of pneumonia in transplant patients with fever in emergency settings. **Material and Methods:** This prospective, convenience sample study was performed in a tertiary care university emergency department. All solid organ transplant patients presenting to the emergency department with fever as a chief complaint, between 08:00 and 24:00 hours were enrolled into the study. Before performing chest X-ray, according to the clinical findings of pneumonia, emergency physician need to assign a pre-chest X-ray level of certainty for pneumonia using a visual analog scale from 0 mm to 100 mm, with 100 mm being the most certain. The chest X-ray reports were classified into three groups: Normal, pneumonia (having pulmonary infiltrates diagnostic and suggestive of pneumonia) and abnormal but not pneumonia. **Results:** Of the 77 study patients, 10 (13%) patients were diagnosed as pneumonia. Sensitivity, specificity and positive and negative likelihood ratio of the judgment of emergency physician in diagnosing pneumonia in our patients population were 70% [95% confidence interval (CI): 35-91], 94% (95% CI: 84-98), 11.7 (95% CI: 4.1-32.9) and 0.31 (95% CI: 0.12-0.82), respectively. **Conclusion:** In the presence of clinical signs of pneumonia, diagnostic accuracy of emergency physician judgment was high for diagnosis of pneumonia in transplant patients with fever in emergency settings.

Key Words: Transplantation; pneumonia; emergency medicine; decision making

ÖZET Amaç: Bu çalışmanın amacı, acil serviste, yüksek ateşli transplant hastalarında pnömoni tanısının konulmasında acil tıp uzman doktorunun klinik kararının doğruluğunu araştırmaktır. **Gereç ve Yöntemler:** Bu çalışma bir üniversite hastanesi acil servisinde ileriye dönük, uygun hastalar çalışmaya alınarak gerçekleştirilmiştir. Acil uzman doktorunun acil serviste çalıştığı 08:00-24:00 saatleri arasında, acil servise ana şikayet olarak ateş nedeniyle başvuran tüm solid organ transplantasyonu yapılmış hastalar çalışmaya alınmıştır. Acil Tıp Uzman Doktoru hastanın akciğer grafisi çekilmeden ve değerlendirmeden önce, hastanın pnömoniyeye ait klinik bulgularına göre, 0-100 mm'lik görsel analog skala kullanarak, 100 mm en kesin değer olacak şekilde, hastanın pnömoni olma olasılığını işaretledi. Çalışma sonucunda akciğer grafisi sonuçları üç grup altında sınıflandırılmıştır: Normal akciğer grafisi, pnömoni (pnömoniyeye destekleyecek tanınal pulmoner infiltrasyonlar), anormal fakat pulmoner enfeksiyon değil. **Bulgular:** Çalışmaya alınan 77 hastanın içinde 10 hastaya pnömoni tanısı konulmuştur. Çalışmaya alınan hasta popülasyonunda, pnömoni tanısının konulmasında acil uzman doktorunun klinik kararının duyarlılığı, seçiciliği, pozitif ve negatif olma olasılığı sırasıyla %70 [%95 güven aralığı (GA): %35-91], %94 (%95 GA %84-98), 11,7 (%95 GA: 4,1-32,9) ve 0,31 (%95 GA: 0,12-0,82). **Sonuç:** Acil serviste ateş yüksekliği olan transplant hastalarında pnömoni klinik bulgularının varlığında, acil tıp uzman doktorları yüksek klinik olasılıkla pnömoni tanısını koyabilmektedir.

Anahtar Kelimeler: Transplantasyon; pnömoni; acil tıp; karar verme

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The number of transplant patients evaluated in emergency departments (EDs) of tertiary care centers by the attending emergency physicians (AEP) is increasing. These patients come to the ED with a number of medical emergencies.¹ Infections are one them and most common causes of morbidity and mortality in transplant patients who are treated with immunosuppressive drugs.²

In a transplant patient, fever may be the first and only sign and symptom of the infection. Fever in a transplant patient should necessitate an aggressive workup, even for relatively subtle presentations.³ Initial evaluation of these patients usually includes a complete history, physical exam, ancillary tests such as complete blood count, serum creatinine, liver functions, urinalysis, bacterial and fungal cultures of blood and urine, cyclosporine or tacrolimus blood levels, renal ultrasonography and chest radiography.⁴

Therefore, all transplant patients with fever during ED admission receive an elaborate diagnostic evaluation. However, the diagnostic accuracy of emergency physician judgment for diagnosis of pneumonia in transplant patients with fever has not been evaluated.

The aim of the study is to determine the diagnostic accuracy of emergency physician judgment for diagnosis of pneumonia in transplant patients with fever in emergency settings.

MATERIAL AND METHODS

STUDY DESIGN AND SETTINGS

This prospective, cohort study was performed in an ED of a tertiary-care university hospital with attendances of approximately 80,000 adult visits per year. This study was reviewed and approved by Institutional Review Board.

SELECTION OF PARTICIPANTS

All transplanted patients presenting to the ED with fever as a chief complaint were enrolled into the study. Fever was defined as having a single oral temperature of $\geq 38^{\circ}\text{C}$. Patient with a previous enrollment, who were unable to give informed con-

sent, less than 18 years of age and those missed follow up data were excluded from the study.

STUDY PROTOCOL

Paramedics initially performed the selection of transplant patients with fever at the triage unit. Verbal informed consent was obtained from each patient before study enrollment. The informed consent included patient's name, aim and expected benefits of the study, and the rights of patients during the study.

All patients were initially evaluated by AEPs. Emergency residents did not take place in initial workups. All patients underwent a full medical history and physical exam. Routine laboratory tests, immunosuppressive drug levels and poster-anterior chest X-rays were obtained in all patients at presentation. Furthermore, bacterial and fungal blood and urine cultures were requested if needed, and posterior-anterior chest X-rays were obtained.

Before obtaining chest X-ray, AEP's assigned a pre-chest X-ray level of certainty for pneumonia using a visual analogue scale (VAS) from 0 mm to 100 mm, with 100 mm being the most certain. This tool has previously been validated certainty in the medical literature.^{5,6} The VAS values reflecting the certainty of the decisions of the AEPs were categorized as low (0-50 mm) and high (51-100 mm), respectively.

A standard study form was filled up by the AEP for every study patient. The study form included demographic features of the patients, transplanted organ, type of the donor, immunosuppressive drugs and their levels, full medical history, vital signs, examination findings, clinical decision-making of AEPs for the level of certainty of pneumonia and patient disposition.

Dyspnea, cough, sputum production, chest pain and wheezing were defined as suspicious clinical clues on patient's history suggesting pneumonia.

Tachypnea (respiratory rate above 20/min), localized rhonchi, rales or decreased respiratory sounds and hypoxia were defined as abnormal clinical signs on physical exam suggesting pneumonia.

All chest X-rays were evaluated by a professor of radiology (G.A.) twice to prevent inter-rater variability in reading. Chest X-ray reports were classified into three groups: Normal, pneumonia (having pulmonary infiltrates diagnostic and suggestive of pneumonia) and abnormal but not pneumonia.

Diagnosis of the pneumonia was made with both radiographic evidence including chest X-rays and thorax computerized tomography (CT), and clinical follow up data.

STUDY OUTCOMES

Primary outcome measure was to evaluate how many patients were correctly diagnosed as having pneumonia or not having pneumonia by AEPs before the X-ray and to see how many among false positive and false negative were correctly diagnosed by the X-ray; to report sensitivity, specificity and positive and negative likelihood ratios of final diagnosis compared with the judgment of AEP and/or with the single anamnesis and physical exam data.

Secondary outcome measures were describing the demographic features of the transplant patient, mortality and rejection within one year after ED presentation.

STATISTICAL ANALYSIS

The study data were analyzed using SPSS 16.0 (Statistical Package for Social Sciences) for Windows. The numeric data were presented as mean \pm standard deviation or median (interquartile ratio). The categorical variables were presented as rates. Comparison of two independent groups with numeric variables was performed by Student-t test as the groups distributed normally or Mann Whitney U test as the groups not normally distributed. The diagnostic utility of physician judgment was displayed by using sensitivity, specificity, positive likelihood ratio [LR(+)] and negative likelihood ratio [LR(-)], 95% confidence intervals. Comparisons of two groups with categorical variables were performed by Chi-square test or Fischer's exact test if one of the expected values was under five. Normality analyses were performed by Kolmogorov

Smirnov test. All the hypotheses were constructed as two tailed and the p value ≤ 0.05 was accepted as statistically significant.

RESULTS

A total of 103 transplanted patients were assessed for eligibility during the two years study period and 77 patients were included in the study. Twenty-six patients were excluded from the study because of the following reasons: Eight patients did not give consent, 12 patients had previous enrollment during the study period and there was no follow up data in six patients.

CHARACTERISTICS OF THE STUDY SUBJECTS

The mean age of the study participants was 35 ± 10 years and 54.5% (n=42) of the patients were males. Of the 77 study patients, 71 (92.2%) had renal and six patients had liver transplantation. The demographic and clinical features and outcomes of pa-

TABLE 1: The demographic and clinical features and outcomes of patients.

Age in years (mean \pm SD)	35 \pm 12
Transplanted organ (R/L)	71/6
Gender (Male/female)	42/35 (54.5/45.5)
Vital signs (mean \pm SD)	
SBP (mm-Hg)	133 \pm 25
DBP (mm-Hg)	80 \pm 17
Pulse Rate (/min)	114 \pm 21
Fever (0C)	38.7 \pm 0.78
RR (/min)	19 \pm 11
O ₂ saturation	97 \pm 2
Admission to the hospital (%)	56 (72.7)
Use of the immunosuppressive drugs (%)	77 (100)
Prednisolone	75 (97.4)
Mycophenolic acid	21 (27.3)
Mycophenolate mofetil	40 (51.9)
Sirolimus	6 (7.8)
Evorelimus	12 (15.6)
Tacrolimus	30 (39)
Cyclosporine	46 (59.7)
Mortality rate in one year (%)	1 (1.3)
Rejection rate in one year (%)	3 (3.9)
Normal Function (%)	73 (94.8)

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; RR: Respiratory rate.

TABLE 2: Initial emergency department presentation of the study patients

Initial presentation	n (%)
Fever	18 (23.4)
Cough	13 (16.9)
Dysuria	10 (13)
Diarrhea	6 (7.8)
Vomiting/Nausea	6 (7.8)
Sore Throat	5 (6.5)
Headache	5 (6.5)
Flu-like symptoms	5 (6.5)
Abdominal pain	4 (5.2)
Chest pain	2 (2.6)
Flank pain	1 (1.3)
Hip pain	1(1.3)
Foot pain	1(1.3)
TOTAL	77

tients were shown in Table 1. Abnormal history and clinical signs on physical exam suggesting pneumonia were cough/sputum in 45 (58.5%), dyspnea in 6 (7.8%), chest pain in 7 (9.1%), tachypnea in 9 (11.7%), localized rhonchi in 3 (3.9%), rales in 7 (9.1%), decreased respiratory sounds in 1 (1.3%) and hypoxia in 3 (3.9%) patients. Initial emergency department presentations of the study patients were shown in Table 2.

MAIN RESULTS

Of the 77 study patients, 10 (13%) patients were diagnosed as pneumonia. Furthermore 17 (22.1%) patient's chest X-ray was abnormal but they did not have pneumonia.

The VAS values reflecting the certainty of the decisions of the AEPs were categorized as low (0-50 mm) and high (51-100 mm), respectively. Sixty five patients (84.4%) were categorized as low and 12 patients (15.6%) were categorized as a high

probability. Using patients' chest X-rays, CT results and clinical follow up data as the gold standards, sensitivity, specificity and LR (+) and LR (-) of the judgment of AEP in diagnosing pneumonia in our patients population were 70% (95 CI: 35-91%), 94% (95% CI: 84-98), 11.7 (95% CI: 4.1-32.9) and 0.31 (95% CI: 0.12-0.82), respectively (Table 3).

Presence of a patient anamnesis suggesting pneumonia (cough, sputum, dyspnea, chest pain and wheezing) was significantly different between two groups; cough: 7 (70%) vs. 12 (17.9%), $p=(0.031)$; sputum 5 (50%) vs. 2 (3%), $p=(0.037)$; dyspnea 4 (40%) vs. 3 (4%) $p=(0.002)$; chest pain: 4 (40%) vs. 5 (7.5%) $p=(0.004)$; wheezing: 4 (40%) 15 (22.4%) $p=(0.014)$, respectively.

Patient's physical exam suggesting pneumonia was statistically different between two groups; Tachypnea: 4 (40%) vs. 5 (7.5%) $p=0.014$; hypoxia: 2 (20%) vs. 1 (1.5%) $p=0.043$; rales: 6 (60%) vs. 1 (1.5%) $p<0.001$; localized rhonchi: 3 (30%) vs. 0 (0%) $p=0.002$. respectively. Characteristics of patients' history and physical examination findings and demographic and clinical features on admission according to the presence or the absence of pulmonary infection were shown in Table 4.

Seven (22.6%) were diagnosed with pulmonary infection in patients with a possible history of pneumonia ($n=31$) and three (6.5%) patients were diagnosed with pulmonary infection in patients with a negative history of pneumonia ($n=46$), ($p=0.08$). Seven (53.8%) patients with at least one of the signs of pneumonia ($n=13$) and three (4.7%) patients without any of the signs of pneumonia had been diagnosed as pneumonia ultimately ($p<0.001$). When the patients were categorized as having any of the symptoms or signs of pneumonia ($n=34$) or not ($n=43$), seven (20.6%) patients in the first group and three (7%) patients in the second groups were di-

TABLE 3: The diagnostic accuracy of the judgment of AEP in diagnosing pneumonia.

	Sensitivity (95% CI)	Specificity (95% CI)	LR(+) (95% CI)	LR(-) 95% CI:
Clinical Judgment of Physician	70% (35-91%)	94% (84-98%)	11.7 (4.1-32.9)	0.31 (0.12-0.82)

CI: confidence interval; LR: likelihood ratio; AEP: Attending emergency physicians..

TABLE 4: Characteristics of patients history and physical examination findings and demographic and clinical features on admission according to the presence or the absence of pulmonary infection.

n (%)	Patients with Pulmonary Infection (10)	Patients without Pulmonary Infection (67)	p
Gender (Male/female)	7/3 (70/30)	35/32 (52.2/47.8)	0.293
Transplanted organ (R/L)	10/0 (100/0)	61/6 (91/9)	1.000
Donor (Live/cadaver)	9/1 (90/10)	52/15 (77.6/22.4)	0.678
Usage of immunosuppressive drugs			
Prednisolone (use/not use)	10/0 (100/0)	65/2 (97/3)	1.000
Mycophenolic acid	1/9 (10/90)	20/47 (29.9/70.1)	0.270
Mycophenolate mofetil	5/5 (50/50)	35/32 (52.2/47.8)	1.000
Sirolimus	2/8 (20/80)	4/63 (6/94)	0.172
Evorelimus	1/9 (10/90)	11/56 (16.4)	1.000
Tacrolimus	3/7 (30/70)	27/40 (40.3/59.7)	0.732
Cyclosporine	7/3 (70/30)	39/28 (58.2/41.8)	0.731
Cough (present/not present)	7/3 (70/30)	12/55 (17.9/82.1)	0.031
Sputum	5/5 (50/50)	2/65 (3/97)	0.037
Dyspnea	4/6 (40/60)	3/64 (4.5/95.5)	0.002
Chest pain	4/6 (40/60)	5/62 (7.5/92.5)	0.004
Wheezing	4/6 (40/60)	15/52 (22.4/77.6)	0.014
Sore throat	2/8 (20/80)	14/53 (20.9/79.1)	1.000
Rinorrhea	1/9 (10/90)	26/41 (38.8/61.2)	0.676
Headache	1/9 (10/90)	26/41 (38.8/61.2)	0.090
Tachypnea (present/not present)	4/6 (40/60)	5/62 (7.5/92.5)	0.014
Hypoxia	2/8 (20/80)	1/66 (1.5/98.5)	0.043
Rales	6/4 (60/40)	1/66 (1.5/98.5)	0.000
Localized Rhonchi	3/7 (30/70)	0/67 (0/100)	0.002
Asymmetric Breath Sounds	0/10 (0/100)	1/66 (1.5/98.5)	1.000
Hyperemic Pharynx	4/6 (40/60)	22/45 (32.8/67.2)	1.000

TABLE 5: Initial history, physical examination, chest x-ray results and additional diagnostic imaging to verify pulmonary infection of the patients with pulmonary infection.

	History of suggesting pulmonary infection	Signs of suggesting pulmonary infection	Initial chest X-ray result	Additional diagnostic imaging
Patient I	Yes	Yes	Infiltration	None
Patient II	Yes	Yes	None	Chest X-ray
Patient III	Yes	Yes	Infiltration	None
Patient IV	No	No	Infiltration	None
Patient V	No	No	Infiltration	None
Patient VI	Yes	Yes	Infiltration	None
Patient VII	Yes	Yes	None	Chest X-ray
Patient VIII	No	Yes	Infiltration	None
Patient IX	No	Yes	Infiltration	None
Patient X	Yes	Yes	None	Thorax CT

agnosed with pneumonia eventually ($p=0.097$). Initial history, physical examination, chest X-ray results and additional diagnostic imaging to verify

pulmonary infection of the patients with pulmonary infection were shown in Table 5. Final diagnosis of the study patients was shown in Table 6.

TABLE 6: Final diagnosis of the study patients.

Final diagnosis	n (%)
Urinary tract infection	27 (35.1)
Upper respiratory tract infection	13 (16.9)
Fever of unknown origin	11 (14.3)
Pneumonia	10 (13)
Acute gastroenteritis	6 (7.8)
Lower respiratory tract infection	4 (5.2)
Toxic liver disease	2 (2.6)
Diverticulitis	1 (1.3)
Anal abscess	1 (1.3)
Osteomyelitis	1 (1.3)
Hyponatremia	1 (1.3)

DISCUSSION

We evaluated the diagnostic accuracy of physician judgment to diagnose pneumonia in febrile transplant patients in emergency settings with this clinical cohort study. We found that diagnostic accuracy of emergency physician judgment had moderate sensitivity and high specificity for diagnosis of pneumonia in transplant patients with fever. Chest X-ray is consistent with the several studies in normal population. In one of these studies, Okimoto et al. investigated the clinical predictors for detection of pneumonia as a guide to suggest further X-ray.⁷ They concluded that using of chest X-ray to confirm a diagnosis of pneumonia in adults recommended if the patients had fever, cough, sputum and coarse crackles.⁷ Another study by Aagaard et al. examined which clinical factors contribute to the clinician suspicion of pneumonia and ordering the chest X-ray.⁸ They concluded that clinicians appear to incorporate much of current evidence-based recommendations into their clinical suspicion of pneumonia and decision to order a chest X-ray in the evaluation of pneumonia. Furthermore, advanced patient age (>75) and physical findings on chest examination influence clinician practice in obtaining a chest X-ray.⁸

Pneumonia in transplant patients is definitely dangerous and associated with significant mortality and morbidity. In our study, the over-

all incidence of pneumonia and mortality rate among transplant patients were 13 % and 1.3% respectively, and these results were not similar to that reported in previous studies, which were 8-16% and 12.5 %, respectively.⁹⁻¹³ Mortality rate might be low in this study because of the small sample size. Symptoms and physical exam findings on presentation may not be typical in transplant patients.

In the present study, radiologically confirmed pneumonia was present in 10 (13%) cases, two of whom had pneumonia in the absence of any symptoms or signs in patients' history and physical exam. The first patient was a 52-year-old woman who presented to ED with nausea, vomiting and fever. She had received renal transplantation from her sister 14 years ago. She was immunosuppressed with prednisolone, mycophenolate mofetil and cyclosporine (120 ng/ml). Her laboratory exam was normal except high C-reactive protein (CRP) (25.64 mg/dl) and leukocyte count (16.3×10^4). The second patient was a 52-year-old man who presented to ED with nausea and fever. He had the kidney transplantation from his wife 4 years ago. He had taken prednisolone and tacrolimus (11.93 ng/ml) for three years. His laboratory exam was normal except high CRP (12.67 mg/dl) level and leukocyte count (11.3×10^4). Since, there was not any other suspected focus of infections on the physical exam and acute phase reactants such as CRP level and leukocyte count (these tests were not specific to pneumonia) were increased in laboratory tests, chest X-rays were performed for detecting subtle pneumonia in both patients.

Of those 10 radiographically confirmed (13%) pneumonia patients, three patients had pneumonia in the absence of any radiologic findings on the patient's initial chest X-ray. However, there were signs and symptoms suggestive of pneumonia in three patients' history and physical examinations. In patients who are poorly hydrated, infiltrate may not be seen in the early stages of pneumonia.¹⁴ Furthermore, neutropenia patients may not able to mount the inflammatory response needed to develop an infiltrate visible on chest X-ray. The low inflammatory response due to the use of immuno-

suppressing drugs and poor hydration status in transplanted patients may explain the negative X-ray results. Moreover, initial chest radiography is not totally sensitive, and there can be significant inter-observer variability in the reading and interpretation of the radiograph.¹⁵ In transplant patients, a careful history and meticulous physical examination remain very imperative. However it should be noted that diagnostic utility of the physical examination is limited. Sileri et al. reported that the full triad (history, physical examination and radiography) was present in less than 50% of cases and chest pain was the only presentation on admission in two patients.⁹ Wipf et al. searched the utility of physical chest findings and inter-rater reliability in patients suspected of having pneumonia, the sensitivity of physical examination to diagnose pneumonia was 47% to 69%, with a specificity of 58% to 75%.¹⁶ They concluded that the most valuable signs in detecting pneumonia were unilateral rales and the traditional chest physical examination is not sufficiently accurate on its own to confirm or exclude the diagnosis of pneumonia.¹⁶ A febrile transplant patient with signs and symptoms of pneumonia but a negative chest radiograph or a patient with a radiograph suggestive of a new mass lesion, CT scan of the thorax may be indicated in the ED. In our study, patient X was a 35-year-old woman who presented to the ED with chest pain, cough and sputum. She had received renal transplantation from her mother two years ago. She was immunosuppressed with prednisolone, mycophenolic acid and cyclosporine (191 ng/ml). Her physical examination was normal except pulmonary rales in the right upper lobe. Her laboratory examination and initial chest X-ray were normal. She was admitted to the hospital. Despite antibiotics, the patient's condition was not improved. Repeated

chest X-ray showed bilaterally blunted costophrenic angles and increased air-bronchograms. After that, it was decided to take a high-resolution computed tomography (HRCT) and there was an aspergilloma in the right upper lobe of lung. Heussel et al. concluded that 60% of neutropenic bone marrow or stem cell recipients with persistent fever despite antibiotic treatment showed consolidation suggesting pneumonia on HRCT although the chest X-rays were still normal.¹⁷

LIMITATIONS

This study has several limitations. In retrospect, we should have planned to take all febrile transplant patients who presented to ED; however, the number of patients excluded from analysis was relatively small. Second limitation of the study was small sample size of this investigation, which may limit the ability to provide these conclusions. However, to the best of our knowledge, this study may be the first clinical trial to assess of diagnostic accuracy of emergency physician judgment for diagnosis of pneumonia in transplant patients with fever.

CONCLUSION

In the presence of clinical signs of pneumonia, diagnostic accuracy of emergency physician judgment was high for diagnosis of pneumonia in transplant patients with fever in emergency settings. Furthermore, in initial diagnostic evaluation of the ambulatory solid organ transplants patients with fever, ordering a chest X-ray may be limited to patients with symptoms and signs suggesting pneumonia in their history and physical examination.

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