Clinical prediction rule for pulmonary infiltrates

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ABSTRACT

Objectives: This study was designed to develop a clinical prediction rule that identifies adult patients with acute respiratory illness who would demonstrate a pneumonic infiltrate on a chest roentgenogram.

Materials and methods: The demographic, clinical, and chest radiologic data of 557 adult patients (derivation set) with acute respiratory illness were used to construct and to cross-validate a model using stepwise logistic regression procedure. A prospective sample of 100 patients (validation set) was used to validate the model. Results: The prevalence of pulmonary infiltrates among the derivation and the validation sets was 17% and 18%, respectively. The stepwise model identified documented fever (≥38°C), rales, colored sputum, dullness to percussion, absence of asthma, and bronchial breathing as significant factors that independently predict pneumonic infiltrates. The area under the receiver operating characteristics was 0.81 (95% CI, 0.77 to 0.85%). Thus, the probability that the logistic rule would correctly identify a patient with pneumonic infiltrates was 81% and the overall sensitivity and specificity of the rule were 78% and 94%, respectively with a total error rate of 8.4%. Both cross-validation and the prospective validation reaffirmed the robustness of the clinical prediction rule.

Conclusion: We concluded that the clinical prediction rule proved useful in identifying adult patients who are having pulmonary infiltrates. The model would be beneficial to assist physicians in deciding whether to order a chest roentgenogram.

Keywords: Pneumonia, Pulmonary Infiltrates, chest roentgenogram, prediction rule.

Saudi Medical Journal 1998; Vol. 19 (3):306-312

With the growing increase in the number and costs of laboratory and radiologic tests as well as the increasing reliance on them in clinical practice, there has been an expanding interest to assess the diagnostic yield and the impact of these tools on clinical decision. Of these tests, chest roentgenogram was subjected to a rigorous evaluation as long ago as the year 1947.[1] At our hospital, the role of chest roentgenography for patients who are routinely admitted and for those febrile, neutropenic cancer patients has been previously evaluated.[2,3] Chest roentgenography is carried out on patients with acute respiratory complaints principally to establish or rule out the diagnosis of pneumonia.[4] However, the prevalence of pneumonia among adults with respiratory infection is usually low (3%).[5] Even among patients presenting to an emergency department with acute respiratory illness, pneumonia was present in only 16% to 28% of them.[6,7] Therefore, patients with respiratory infection, but without pneumonia, often have unnecessary radiation exposure that also involves additional burden on

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Received December 1996. Accepted for publication in final form August 1997.

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health care resources. The necessity for chest x-ray for such patients can be determined more precisely if the probability of pneumonia can be predicted.

Several investigators have developed clinical prediction rules that can distinguish with varying degrees of precision the presence or absence of pneumonia among adults with respiratory illness.[6-9] In only a few studies were these rules either prospectively validated in patients other than those from which they were derived,[9] or were they assessed for reproducibility.[10] In this paper, we retrospectively studied adult patients with acute respiratory illness to derive a clinical prediction rule for pneumonic infiltrates. Furthermore, the derived model was cross-validated on the derivation sample and was also validated prospectively on a validation cohort set.

Materials and methods. This study was conducted at King Fahd Hospital of the University (KFHU), which is the main teaching facility in the Eastern Province of Saudi Arabia. Although the hospital primarily provides a tertiary health care, any patient is accepted at the emergency room without any restrictions.

Adult patients (16 years of age or older) attending the emergency room department of KFHU between January 1993 and December 1993 with acute respiratory illness and who had received a chest roentgenogram, were the subjects of the study. The study was approved by the Research and Ethical Committee, and no consent form was required.

A patient was considered to have an acute respiratory illness if presented with acute respiratory complaints such as cough, expectoration, pleuritic chest pain, dyspnea, or wheezing, with or without constitutional symptoms such as fever or chills. Their demographic information and data on symptoms, signs, comorbidity, and chest radiographic findings were abstracted retrospectively from the medical records. Data abstraction was performed by AAA and FMN who are senior internal medicine residents. According to the KFHU's regulations, all clinical information is required to be recorded on a standardized structured data form that are periodically monitored by the Quality Assurance and Audit Committee. The structured data forms were handwritten by the emergency room physicians or by the internal medicine residents. Symptoms, signs, or other data that were either not recorded on the data form or were recorded as unknown were considered to be absent. When the data were re-examined, excluding patients with missing or unknown information, the results remained unchanged.

All patients had been examined by an emergency room physician and/or a medical resident, and the decision to request a chest x-ray had been made by the examining staff. All patients received standard posteroanterior and lateral chest films and none had portable films.

Demographic information sought included age, gender, and nationality. Symptoms included the presence or absence, within the previous 24 hours, of cough, sputum (white or colored), chills, fever by history, pleuritic chest pain, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and wheezing. Signs included oral temperature for documentation of fever ($\geq$ 38°C) as measured by an ordinary thermometer; respiratory rate; pulse rate; systolic and diastolic blood pressures; mental status; and the presence or absence of cyanosis, decreased thoracic expansion, dullness to percussion, decreased intensity of breath sounds, bronchial breathing, egophony, rales, rhonchi, wheezing, and pleural friction rub. Also documented were coexisting medical conditions such as bronchial asthma, chronic obstructive pulmonary disease, cardiac disorders, diabetes mellitus, sickle cell disease, underlying neoplasm, etc. Detailed drug history was also included in the database. Arterial blood gases were not routinely requested and, therefore, were not included among the tested variables.

Chest roentgenograms were reviewed by one radiologist (FAM) who was blinded from all demographic and clinical data, as well as from the previously released reports or the final diagnosis. The results were classified into one of four categories: no pneumonia, if the roentgenogram was normal or showed radiologic abnormalities other than pneumonia; possible pneumonia, if the roentgenogram showed "possible" or "questionable" pneumonic infiltrates and the radiologist was unable to exclude pneumonia in describing the radiologic finding(s); probable pneumonia, if the chest x-ray showed an abnormality that "most likely" represented a pneumonic infiltrate; or definite pneumonia, if there was an unequivocal pneumonic infiltrate. Concordance for this classification with the original report was measured by kappa statistics for reliability. Lack of concordance was resolved by open discussion with the radiologist who released the original report or by seeking the opinion of a third senior radiologist.

Data Analysis. Only patients with a chest roentgenogram that showed definite or probable pneumonia were included among the cases of pneumonia, and only patients with a chest roentgenogram that showed no pneumonic infiltrates were included among the cases with no pneumonia. Patients with possible pneumonia were excluded from further analysis. Patients with probable pneumonia were then included first among the pneumonia group and then among the nonpneumonia group, and the discriminatory functions of the resulting prediction rules were compared with those of rule derived by excluding these indeterminate cases.

Comparisons of proportions of categorized variables were made using chi-square tests with the

Table 1 - Patients characteristics and the unadjusted predictors of pulmonary infiltrates (derivation set).

Predictor	95 Patients with Pulmonary Infiltrates No. (%)	95 Patients without Pulmonary Infiltrates No. (%)	P Value
Sex			
Males	65 (68)	304 (66)	
Females	30 (32)	158 (34)	
Absence of bronchial asthma	80 (84)	322 (70)	0.006
History of COPD	4 (4)	30 (7)	0.54
History of malignancy	0 (0)	5 (1)	0.68
Cough	94 (99)	433 (94)	0.07
Whitish sputum	20 (21)	156 (34)	0.02
Colored sputum	57 (60)	164 (36)	<0.0001
Chills	7 (7)	9 (2)	0.01
Dyspnea	28 (30)	204 (44)	0.01
Fever by history	67 (71)	181 (39)	<0.0001
Documented fever	62 (55)	151 (33)	<0.0001
Tachypnea	16 (17)	63 (14)	0.51
Tachycardia	39 (41)	144 (31)	0.08
Dullness to percussion	10 (11)	7 (2)	<0.0001
Decreased chest expansion	11 (12)	40 (9)	0.37
Decreased breath sounds	30 (32)	98 (21)	0.04
Bronchial breathing	10 (11)	9 (2)	0.0001
Egophony	1 (1)	2 (0.4)	1
Rales	42 (44)	83 (18)	<0.0001
Rhonchi	31 (33)	195 (42)	0.1
Pleural rub	0 (0)	2 (0.4)	0.34

Yates correction for continuity where appropriate, or by using Fisher's exact test, and the analysis of variance was used to compare means. Within the derivation set, all variables with a univariate significance level of (0.1 were entered into a stepwise logistic regression procedure with forward selection to develop a subset of variables that were independent predictors of pneumonia. Step selections were based on an asymptotic covariance approximation to maximum likelihood.[11] Interactions between variables were not tested. The accuracy of the logistic model in discriminating patients with and without pulmonary infiltrates in the derivation set was evaluated using the area under a receiver operating characteristic (ROC) curve,[12] determined by the method of maximum likelihood.[13] The standard error of each curve was calculated using the methods of Hanley and McNeil.[14,15] The ROC plots the model's sensitivity (true-positive rate) against 1-specificity (false-positive rate) as the cutoff criterion (operating point) between a positive and negative result is altered. The ROC, thus, illustrates how the choice of a cutoff criterion changes the proportions of correct and incorrect classifications.

The discriminatory function of the prediction rule was also analyzed by the cross-tabulation of the potential predictive finding and the outcome by means of a two-by-two contingency table and therefore the sensitivity, specificity, and the total error rate were calculated.[8] The accuracy of the prediction rule for predicting radiologic pneumonic infiltrate in the derivation set was also tested using a likelihood ratio formulation of Bayes' theorem.[16 17] Likelihood ratios were estimated using the formula:

L(X)=P(X\D)/P(X\D°), where L(X) is the likelihood ratio for a particular result X; P(X\D), the probability that a patient with pneumonic infiltrates will have result X; and P(X|D°), the probability that a patient without pneumonic infiltrates will have result X. The post-test probability for a positive chest rentogenogram for each subgroup of patients classified according to the prevalence of the derived prediction variables was calculated from the equation: P(D\X) = [L(X) x p] / [(1-p) + [L(X) x p]}, where p is the pre-test probability of having pulmonary infiltrates.[16]

The logistic rule was cross-validated using the "jackknife" technique on a randomly drawn population consisting of one-third of the original derivation set.[18] The procedure was repeated using different random samples drawn by the computer. Furthermore, the derived prediction rule was subsequently tested prospectively on a newer cohort population consisting of the first 100 adult patients with acute respiratory illness seen in the emergency room department of KFHU between January 1994 and March 1994 and for whom chest roentgenograms were requested and showed either definite pneumonia or no pneumonia. Adjusting for the difference in the prevalence of pneumonia between the derivation and the prospective validation sets was made by modifying the constant terms in the logistic equations using the correction factor:[10,19] $\log_e$ (πValidation) (1-πDerivation)/(1-πValidation) (πDerivation).

In all analyses, a two-sided P value of less than 0.01 was considered significant. The BMDP Statistical Software programs (P1D, P2D, P4F, P7M, and PLR) were used to analyze the data.[20]

Results. Between January 1993 and December 1993, a total of 1276 adult patients were presented to the emergency room department with acute respiratory illness and chest roentgenogram was requested for 557 (45%). Of the latter, chest x-films showed possible pneumonia in 6 patients and were therefore excluded from further analysis. Another 12 patients were also excluded from further analysis due to significantly deficient documentation of several important symptoms such as cough or fever together with poor reporting on signs such as bronchial breathing, etc. (10 had normal chest roentgenogram, 1 definite pneumonia, and 1 probable pneumonia). The remaining 557 patients constitute the derivation population. When the data were re-analyzed, excluding cases with a few missing symptoms, signs, or comorbidity data, the outcome remained essentially unchanged. Of this derivation group, chest roentgenograms showed definite pneumonia in 88 patients (16%), probable pneumonia in 7 (1%), and no pneumonia in the remaining 462 patients (83%). Concordance between this chest roentgenogram classification and the original reports was shown in 90 of the 95 (95%) patients with definite or probably radiologic infiltrates and in 455 of 462 (98%) of those who had no pneumonia (Kappa measure of reliability was 0.92; indicating strong agreement). The discordance in the remaining 12 chest roentgenogrphic studies was resolved by consensus agreement through an open discussion with the radiologist who reported the films initially or by seeking the opinion of a third senior radiologist.

The mean (SD age of the derivation population was 36.6 (19 years. Sixty-six percent of patients were males. Table 1 (see previous page) shows the demographic and clinical characteristics of those 557 patients, and the unadjusted predictors of pulmonary infiltrates where patients with definite and probable pneumonia were combined together. Absence of bronchial asthma, presence of cough, presence of whitish sputum, presence of colored sputum, presence of chills, presence of dyspnea, positive history of fever, documented fever, presence of tachycardia, dullness to percussion, decreased chest expansion, decreased intensity of breath sounds, presence of bronchial breathing, presence of egophony, presence of rales, and presence of rhonchi were each shown on unadjusted analysis to predict pneumonic infiltrates with P (0.1. Age tested as a categorized variable using different cutpoints has not been shown to predict pulmonary infiltrates. None of the other captured variables that were not shown in the table attained P value of $\leq$ 0.1.

Only variables that demonstrated P value of ($\leq$0.1 were included in the stepwise logistic regression procedure. The stepwise model identified documented fever ($\geq$38°C), rales, colored sputum, dullness to percussion, absence of asthma, and bronchial breathing as significant factors that independently predict pulmonary infiltrates (Table 2). The large P values for Hosmer-Lemeshow (0.57) and Brown's (0.443) goodness-of-fit tests indicate that the predicted values fit the model and the logistic

Table 2 - Multivariate predictors of pulmonary infiltrates

Predictor	Logistic Coefficient	Odd Ratio	95% CI*
Fever ($\geq$ 38°C)	1.533	4.6	2.40-6.20
Rales	1.218	3.4	1.03-8.20
colored sputum	0.782	2.2	1.40-3.50
Dullness	1.397	4.0	1.34-12.2
Absence of asthma	0.634	1.89	1.17-2.61
Bronchial breathing	1.066	2.9	2.10-5.50
Intercept	-1.582	0.21	0.16-0.26

*Confidence interval

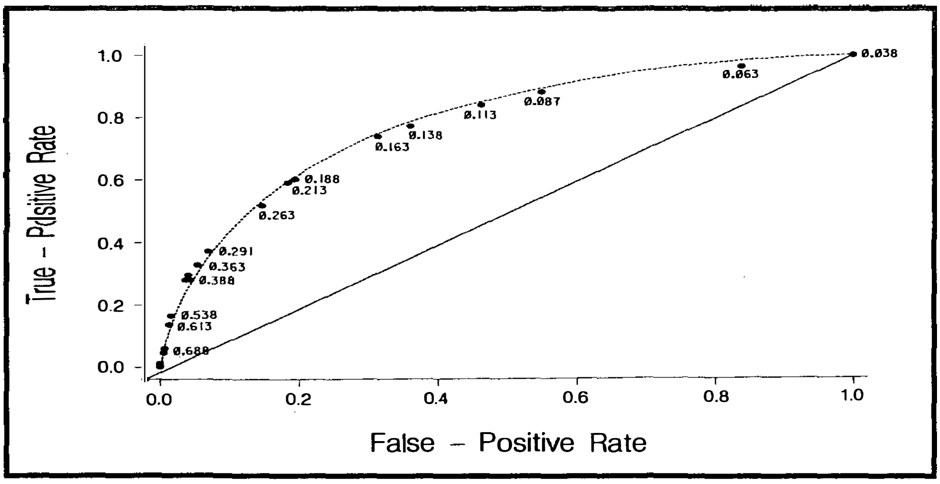

Figure 1 - Receiver operating characteristic curve of the logistic rule in the derivation set. Circles represent various cutoff points. Dashed diagonal line = no discrimination; solid line = smoothed curve.

model is appropriate for the data.[20] The same 6 variables were identified by the logistic regression when the 6 patients with probable pneumonia were considered as not having pneumonia and assigned to the no pneumonia group, or were excluded in entirety.

The LR program of the BMDP Statistical Software was used to construct the classification matrix and the table of correct and incorrect classification to a range of cutpoints. The latter data was utilized to construct the ROC curve (Fig. 1). The area under the ROC curve was 0.81 (95% CI, 0.77 to 0.85). On the other hand, the probability that the logistic rule would correctly identify a patient with pulmonary infiltrates was therefore 81%. To simplify the model,[21] the logistic equation was modified by rounding the coefficients to each of the six predictors and also the constant to the nearest 0.5 and doubling to form whole number. The simplified, modified logistic rule discriminated patients with and without pulmonary infiltrates with a ROC area of 0.83 (95% CI, 0.80 to 0.86).

Agreement between the predicted probability and actual frequency of pulmonary infiltrates was generally good and the overall sensitivity and specificity of the rule were 78% and 94%, respectively with a total error rate of 8.4%.

Using Bayes' theorem, the post-test probability incorporating the pre-test probability was estimated for each subgroup of patients (classified according to the prevalence of the prediction variables) to determine the discriminating power of the clinical prediction rule (Table 3).

The cross-validation technique using the "jackknife" method - done repeatedly on randomly selected test sets - has shown that the predicted rule achieved correct classification ratios that ranged from 78% to 93%.

Table 3 - Accuracy of the clinical rule in predicting pulmonary

		Prevalence of Pulmonary Infiltrates	
No of Predictors	**No of patients**	**Actual %**	**Estimated %**
0	65	5	2
1	161	4	2
2	179	15	20
3	111	33	35
5	34	50	57
5 or 6	7	71	79

Table 4 - The prevalence of the predictor variables in the validation set

Predictor	**95 Patients with Pulmonary Infiltrates No. (%)**	**95 Patients with Pulmonary Infiltrates No. (%)**	**P Value**
Absence of bronchial asthma	15 (83)	60 (73)	0.027
Colored sputum	10 (55)	21 (25)	0.015
Fever (> 38oC)	16 (89)	52 (63)	0.03
Dullness to percussion	3 (17)	1 (0.01)	0.018
Bronchial breathing	2 (11)	0 (0)	0.031

The prospective validation set of 100 adult patients (mean (SD age was 32.7 (15.3 years) included 56 males and 44 females. Definite radiologic evidence of pneumonia was shown in 18 patients (18%). The prospective validation set was, therefore, comparable to the derivation set as regards to the mean age, sex distribution, the prevalence of pneumonia, and the prevalence of the predictors (Table 4). For patients with 3 positive variables out of the 6 logistic predictors, the sensitivity and specificity of the rule in discriminating patients with pulmonary infiltrates were 76% and 97%, respectively with a total error rate of 7%. The performance of the simplified, modified model was further evaluated on the prospective validation sample using the ROC curve analysis. The area under the model's ROC curve adjusted for the prevalence of pulmonary infiltrates was 0.87 (95% CI, 0.82 to 0.92).

Discussion. Clinical prediction rules have been used to predict the presence of disease, or prognostic outcomes, among groups of patients. They are also intended to help physicians interpret clinical information, make more accurate estimates of disease likelihood, and assess the diagnostic values of various tests and procedures .[8]

Studies have shown that most physicians use probability thresholds when deciding to order chest x-rays, although the actual threshold probability may vary considerably from physician to physician.[21] In this study, the derived model identified documented fever (≥38(C), rales, colored sputum, dullness to percussion, absence of asthma, and bronchial breathing as significant factors that independently predict pulmonary infiltrates. The area under the ROC curve indicated that the probability that the logistic rule would correctly identify the patient with pulmonary infiltrates was therefore 81%. Simplification of the model, as well as, its cross- and prospective validation reaffirmed the robustness of the prediction rule.

Three of the 6 identified predictors in this study (documented fever, rales, and absence of asthma) were also identified as significant independent predictors of radiologically proved pneumonia in a derivation set of 1134 patients.[9] On assessing the reproducibility of the latter model, the same three predictors maintained their prediction ability and additional three variables (dullness to percussion, bronchial breathing, and egophony) were found significant in the replication samples.[10] Of these additional variables, dullness to percussion and bronchial breathing were among the predictors of our prediction rule. In other studies in patients from whom chest roentgenograms were obtained, production of sputum was identified - among other variables - as a significant predictor of pulmonary infiltrates.[23-24] Production of a colored and not a white sputum was the third most important variable in our model.

The absence of asthma shown in our study as a significant independent predictor of pulmonary infiltrates is an interesting finding that deserves further comments. As alluded to above, the same observation was identified in a recently reported model.[9,10] Despite an approximately equal prevalence of asthma among our derivation set (155 out of 557, 28%) as compared with other studies (21% to 28%),[9] the prevalence of pulmonary infiltrates among our asthmatics was higher (9.6% versus 1.9% to 4.6%).[7,9] Perhaps, adult patients with asthma presenting as acute respiratory illness and who clinically demonstrate some of the additional predictors may still require a chest roentgenogram. Conversely, the usefulness of a routine chest radiograph for children during acute first attacks of bronchial asthma is limited.[25]

Nevertheless, there are several pertinent factors that attribute to the lack of transportability of a prediction rule to classify patients as accurately as has been expected from the original report.[7-10] Among those factors, poor definition of the event to be predicted,[8] ill-defined predictive findings,[8] testing diagnostic criteria as predictors,[8] and non-blinding of the investigator who assigns a patient's diagnosis to the findings that are to be used as predictors,[8] are the most common attributing confounding factors. Other elements include failure to compensate for differences in disease prevalence,[17,26] and spurious association between predictors and outcome variables due to multiple comparisons,[27] etc. In the present study, the negative influence of those confounding variables was minimized and the model was validated. However, it still remains that the outcome variable "pneumonia" was defined as an infiltrate on chest roentgenogram that may represent a flawed criterion for making such definite diagnosis. Notwithstanding, radiological diagnosis of pneumonia will always remain as a clinically relevant yardstick.

In conclusion, this study showed that the derived, validated clinical prediction rule proved useful in classifying patients according to the risk of having pneumonia as demonstrated radiologically. With some knowledge of the prevalence of pneumonia in a given population, the model would be beneficial to physicians in predicting that an adult patient with acute respiratory illness has pulmonary infiltrates and therefore assists in the decision whether to order a chest roentgenogram.

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