Turkish Journal of Thoracic and Cardiovascular Surgery 2022;30(1):8-10
http://dx.doi.org/doi: 10.5606/tgkdc.dergisi.2022.40073

***Biostatistician's Eyes** / Biyoistatistikçi Gözünden*

"Relationship between right atrial pressure and the Model For End-Stage Liver Disease (MELD) score in patients with advanced heart failure": Correlation analysis and ROC curve method

İleri evre kalp yetmezliği hastalarında sağ atriyum basıncı ile Son Dönem Karaciğer Hastalığı Modeli (MELD) skoru arasındaki ilişkinin değerlendirilmesi: Korelasyon analizi ve ROC eğrisi yöntemi

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Researchers may examine the variables related to the events one by one, or they may have a desire to explain and understand the relationship between the variables. Correlation analysis is a statistical method that reveals the direction, degree, and importance of the relationship between variables. The coefficient indicating the direction and degree of the relationship is called the correlation coefficient and is denoted by *"r"*. The correlation coefficient takes values between "-1" and "+1". If the r value is close to -1, it indicates a negative relationship between the variables, and if it takes values close to +1, there is a positive relationship. As the correlation coefficient value goes toward "0", the relationship between the two variables would be weaker. If the value is near ± 1, then there is a perfect correlation: as one variable increases, the other variable tends to also increase (if positive) or decrease (if negative). If the coefficient value lies between ± 0.50 and ± 1, there is a strong correlation. If the value lies between ± 0.30 and ± 0.49, it refers to a medium correlation. When the value lies below 0.29, there is a small correlation. When the value is zero, there is no correlation. Four types of correlations are used in statistical analysis: Pearson correlation, Kendall Rank correlation (Kendall's tau), Spearman Rank correlation (Spearman's rho) and the Point-Biserial correlation. In particular, studies using the Pearson and Spearman correlation coefficients are frequently encountered. Pearson's correlation coefficient is the test statistics that measures the statistical relationship between two continuous variables. Pearson *"r"* correlation is the most widely used correlation statistic to measure the degree of the relationship between linearly related variables. For the Pearson *"r"* correlation, both variables should be normally distributed (normally distributed variables have a bell-shaped curve). Other assumptions include linearity and homoscedasticity. Linearity assumes a straight-line relationship between each of the two variables and homoscedasticity assumes that data is equally distributed about the regression line. Spearman rank correlation is a non-parametric test that is used to measure the degree of association between two variables and it is the non-parametric version of the Pearson correlation coefficient. The Spearman rank correlation test does not carry any assumptions about the distribution of the data and is the appropriate correlation analysis, when the variables are measured on a scale that is at least ordinal. If one or both of the variables do not fit the normal distribution, Spearman's rank correlation is used to determine the direction and degree of the relationship between the variables. It is not correct to comment on the cause-effect relationship while interpreting the correlation coefficient. As the correlation shows the direction and degree of the

Received: January 10, 2022 *Accepted*: January 10, 2022 *Published online*: January 28, 2022

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Cite this article as:
Yay M. "Relationship between right atrial pressure and the Model For End-Stage Liver Disease (MELD) score in patients with advanced heart failure": Correlation analysis and ROC curve method. Turk Gogus Kalp Dama 2022;30(1):8-10

relationship between two variables, while it does not give information about the cause-effect relationship. It is also desired to include explanations that are thought to be guiding for studies in which Kendal's rank correlation and point biserial correlation analyzes are planned to be used. The Kendal's tau coefficient, which is usually smaller than Spearman's rank correlation, is insensitive to errors in the data. However, "p" values are more accurate with smaller sample sizes. In most cases, the interpretations of Kendall's tau and Spearman's rank correlation coefficient are very similar and, thus, invariably lead to the same inferences. The point biserial correlation coefficient is a special form of the Pearson correlation coefficient and it is used to measure the strength and direction of the association that exists between one continuous variable and one dichotomous variable. There should be no outliers for the continuous variable for each category of the dichotomous variable and continuous variable should be approximately normally distributed for each category of the dichotomous variable. In this study, the Pearson correlation coefficient between the right atrial pressure (RAP) and Model for End-Stage Liver Disease (MELD) scores of the patients was obtained as r=0.510 and a strong correlation was detected between the variables. By using the correlation coefficient, it is possible to test the null hypothesis stating that there is no relationship between the two variables (r=0). If the obtained "p" value is less than the alpha significance level, the null hypothesis is rejected and the existence of a relationship between the variables is mentioned. In this study, the p value for the correlation coefficient between RAP and MELD score was obtained as "0.001" and considering that the study was conducted at the 0.05 significance level, the null hypothesis of "no relationship" was rejected. In other words, there is a relationship between RAP and MELD variables.

In this study, patients with ischemic (37%) and non-ischemic cardiomyopathy were also examined within the scope of correlation analysis. Since both MELD score and RAP are continuous variables, the direction and degree of the relationship between these two variables are given with the Pearson correlation coefficient. The Pearson correlation coefficient requires both variables to be continuous and to fit a normal distribution. If the variables do not show a normal distribution, the correlation between the variables is expressed with the Spearman's rank correlation coefficient. In this study, both the RAP and MELD score variables fit the normal distribution, and both were continuous variables. The Pearson correlation coefficient of MELD score with patients with ischemic cardiomyopathy was obtained as r=0.569 and this coefficient was found to be statistically significant (p=0.001<0.05). The Pearson correlation coefficient of the MELD score with patients with non-ischemic cardiomyopathy was lower than those with ischemic disease (r=0.443). This coefficient was also statistically significant (p=0.001<0.05). In addition, the correlation coefficient between the RAP and the other variables used in the calculation of the MELD score was also examined in this study. Pearson correlation coefficients of the RAP variable with total bilirubin, international normalized ratio (INR) and creatinine and the significance of these coefficients were obtained as (r=0.521, p<0.001; r=0.358, p<0.001 and r=0.251, p<0.003), respectively.

In clinical studies, it is aimed to distinguish between patients with the disease and no disease by using various diagnostic methods. It is of utmost importance to identify how accurately a test can distinguish sick individuals from healthy patients. One of the methods used to determine the distinctiveness of the test in the medical decision-making process is the receiver operating characteristic (ROC) curve method. It is one of the most important evaluation metrics for checking any classification model's performance. The ROC curves are used when the dependent variable is dichotomous, whereas the independent variable to be used in decision making is continuous. The ROC curves show all possible cut-off points for this continuous variable and allow estimates to be made about the frequency of different outcomes -true positive (TP), true negative (TN), false positive (FP), and false negative (FN) at each cut-off point. In ROC curves, the x-axis has FPR (false positive ratio), while the y-axis has TPR (true positive proportion). The FPR and TPR values, that is, sensitivity and 1-selectivity values, are calculated for different threshold values. Both pairs form the ROC curve. The ROC curve is an increasing function between (0,0) and (1,1). The point nearest to the top-left on the ROC curve is the optimal cut-off to differentiate patient with disease from those without disease. This point, compared to other possible cut-offs, has the minimum value for $(1\text{-sensitivity})^2$+ $(1\text{-specificity})^2$. A simpler and more commonly used alternative is the use of cut-off with the maximum sum of sensitivity and specificity. It is calculated as the cut-off with maximum value of Youden's index, which is defined as (sensitivity + specificity - 1). Its values can vary between -1.0 and 1.0, and higher values indicate a test cut-off with higher discriminative ability. Desired result TPR is high while FPR is low that is. The point (0.1) as a coordinate indicates the best classification. It tells how much the model is capable of distinguishing between classes. The higher the area under the ROC curve (AUC), the better the model is at predicting 0 classes as 0 and 1 classes as 1. By analogy, the higher the AUC, the better the model is at distinguishing between patients with the disease and no disease. If the diagnostic test cannot distinguish between patients with the disease and no disease, it would be a useless test and the AUC is 0.5. In this study, ROC curve analysis was performed using the dichotomous dependent variable RAP (≤12 mmHg, >12 mmHg) and continuous dependent variable MELD score. The calculated AUC was 0.789 (95% confidence interval [CI]: 0.710-0.867, p<0.001). It indicates that there is a 78.9% chance that the model would be able to distinguish between positive class and negative class. The diagnostic power of the MELD score, in other words, the power to distinguish between patients with disease and no disease, is expressed by the AUC. As the AUC approaches 1, the diagnostic power increases. In this study, it is possible to mention that the diagnostic power of the MELD score is quite good. A statistically significant diagnostic test can be mentioned with the help of the confidence interval obtained for the AUC. If the "0.50 (no diagnostic ability)" value is outside the confidence interval, a statistically significant diagnostic value is mentioned. In this study, a 95% CI (0.710-0.867) was obtained for the AUC, and since the interval does not contain "0.50", the diagnostic value of the MELD score is stated to be statistically significant. The fact that the p value is less than 0.001 also supports this result. With the help of ROC analysis, it is possible to identify the optimal cut-off point value for the test as well as the diagnostic accuracy of the test. In this study, the cut-off value for the MELD score in the prediction of high RAP was 10.5 with 75% sensitivity and 73% specificity. On the other hand, the AUC values and its confidence intervals for total bilirubin, INR, and creatinine used in the MELD score were 0.765 (CI: 0.681-0.849), 0.696 (CI: 0.608-0.784) and 0.621 (CI: 0.524-0.717), respectively. It can be stated that the confidence intervals for the AUC do not contain the value of "0.5" and that the diagnostic values of the mentioned variables are statistically significant.