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Research Article

Linear Combination of Leukocyte Count and D-Dimer Levels in the Diagnosis of Patients with Non-traumatic Acute Abdomen

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Abstract

Aim: Rapid intervention is required in patients with non-traumatic acute abdominal pain. It is very important to distinguish between surgical and non-surgical pathologies during this intervention. This study aimed to increase the diagnostic accuracy by combining the leukocyte count and D-dimer levels used in this evaluation with linear combination methods.

Materials and Methods: Logistic regression, scoring, min-max, minimax, Su & Liu, Pepe & Thompson, Pepe, Cai & Langton, and Todor & Saplacan methods were used as linear combination methods. The data set was divided into 70% training set and 30% test set. Parameter optimization was performed on the training data by 5 fold cross-validation method using 10 repeats. The area under the ROC curve, sensitivity, selectivity, accuracy, positive and negative predictive value, and positive and negative likelihood ratio statistics were used in the performance evaluation.

Results: The area under the ROC curve statistic for D-dimer level and log-transformed leukocyte count variable were obtained as 0.71 and 0.70, respectively. The accuracy rate was 0.69 for the D-dimer level and 0.73 for log-transformed leukocyte count. For the linear combination methods, the area under the ROC curve was between 0.77 and 0.81, and the accuracy statistics were between 0.72 and 0.79. The best performance was obtained with the min-max method.

Conclusion: In patients with non-traumatic acute abdominal pain, leukocyte count and D-dimer levels can be evaluated together by using linear combination methods in differentiating surgical and non-surgical pathologies. The obtained results showed that the diagnostic performance of the combined results with the min-max procedure was higher than the leukocyte count and D-dimer levels.

Keywords: Abdominal pain, D-dimer level, linear combination, nontraumatic acute abdomen

INTRODUCTION

Patients with acute abdominal pain constitute a significant portion of patients admitted to the emergency department. Therefore, it is very important to determine whether there is an urgent need for surgery in these patients and to determine the follow-up period for those who do not need urgent surgery. A delay in diagnosis will increase the mortality of the patients (1-3).

Patient history and complete physical examination are compulsory for immediate therapy. In addition, methods such as laboratory tests, ultrasonography, computed tomography, and magnetic resonance imaging (MRI) contribute to this evaluation. However, the reason that the ultrasonography method does not have high sensitivity for all conditions and is recommended for use in right upper quadrant pains; allergic reactions, renal insufficiencies, and technical problems for computed tomography, and the high cost and lack of immediate availability of the MRI method increase the need for new diagnostic tests (3,4).

Akyıldız et al. (3) performed measurements of leukocyte counts and D-dimer levels in patients with this symptom. As a result of the study, the authors stated that D-dimer levels performed better in the differential diagnosis of patients with acute abdominal pain than the leukocyte count. In another study, using the same study data, Zararsiz et al. (4) combined these two tests using various machine learning methods. The built machine-learning models outperformed the performances of individual markers. Although high accuracy results are obtained with machine learning models, interpretation of the estimated results is very difficult since most models are based on the black-box concept. Especially in medical applications, there is a need to interpret the models to confirm the results, apart from obtaining highly accurate results (4,5).

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Another approach for combining diagnostic tests is the linear combination methods. These methods combine the results of two or more diagnostic tests with the help of linear models and aggregate them into a single variable. The performance of the combined diagnostic test is calculated on this newly generated variable. One of the most important advantages of linear combination methods is that they can increase diagnostic performance compared to individual diagnostic tests and produce simple and interpretable results (6-8).

In this study, we applied and assessed the performance of eight linear combination methods to increase the diagnostic accuracy of nontraumatic acute abdomen.

MATERIAL AND METHOD

Dataset

In our study, we used the data of previously published studies (3,4). This data contains 225 patients who applied to Erciyes University Hospital with acute abdominal pain. The patients were divided into two groups based on their medical history, prompt diagnostic modalities, physical examination, and laboratory test results. The first group included 110 patients who needed immediate laparotomy, while the second group included 115 patients without the need for immediate laparotomy. The data includes leukocyte count and D-dimer levels markers. D-dimer concentrations were measured with the quantitative immunofiltration assay method (MDA® D-dimer, bioMérieux Inc., Durham, NC, USA). Due to its highly skewed distribution and discrete count nature, a logarithmic transformation was applied (base 10) to leukocyte counts.

The primary output of the study is the patient's need for immediate laparotomy (0: not needed, 1: needed). The used biomarker measurements were D-dimer levels and the leukocte counts on log scale. We did not find any information about randomization or blinding in the study where the data was taken (3,4). As far as we can see, no power analysis has been carried out. For this reason, we decided to make an evaluation with the power analysis performed at the end of the study.

Considering an inequality test for two ROC curves, we calculated post-power statistics using the area under ROC curves of the D-dimer level, leukocyte counts and min-max linear combination model. In our hypothesis, which is the subject of post power analysis, we evaluated whether the AUC value obtained as a result of combining with the min-max model was found to be significantly higher than the AUC of D-dimer level and log (leukocyte count). For this purpose, we used Hanley and McNeil approach to compute the effect sizes. For type-I error rate of 5%, the post power statistics for the two hypothesis were computed as 0.953 and 0.971. Power Analysis and Sample Size Software, version 11.0. (PASS, NCSS Statistical Software, Kaysville, UT, USA: https://www.ncss.com/software/pass/).

The study was approved by the local ethics committee in accordance with the Declaration of Helsinki (2022/703). Since the study was designed as retrospective, no informed consent was obtained from participants.

Linear Combination Methods

We used eight linear combination methods to combine leukocyte count and D-dimer levels. In this section, we describe the background of these methods. Let x_1 and x_2 the quantitative values of the first and second markers, respectively. Then, a combination score (s) can be obtained using linear combination methods as follows:

Logistic regression: A binary logistic regression model is fitted using the maximum-likelihood method. The combination score will be the posterior probabilities obtained from the following logistic regression model:

$$s = \frac{e^{\beta_0 + \beta_1 x_1 + \beta_2 x_2}}{1 + e^{\beta_0 + \beta_1 x_1 + \beta_2 x_2}}$$

Scoring based on logistic regression: The same binary logistic regression model is used. However, this time, for a more straightforward interpretation, slope values are rounded to a given digit number, and the combination score is computed as follows:

$$s = \beta_1 x_1 + \beta_2 x_2$$

Pepe & Thompson's method (9): This method is a ranking score-based approach that does not include any distribution assumptions in determining the linear combination of diagnostic tests. The combination score is obtained as follows:

Control group: $C_i = (C_{1i}, C_{2i}), i = 1,2,\ldots,n,$

Disease group: $D_j \leq (D_{1j}, D_{2j}), j = 1,2,\ldots,m,$

$$maximize\ W(\lambda) = \frac{1}{mn}\sum_{j=1}^{m}\sum_{i=1}^{n} I[D_{1j} + \lambda D_{2j} \geq C_{1i} + \lambda C_{2i}]$$

$$s = x_1 + \lambda x_2$$

Pepe, Cai & Langton's method (10): Pepe, Cai, and Langton combination score is obtained by using AUC as the parameter of a logistic regression model:

Control group: $C_i = (C_{1i}, C_{2i}), i = 1,2,\ldots,n,$

Disease group: $D_j <= (D_{1j}, D_{2j}), j = 1,2,\ldots,m,$

$$maximize\ W(\lambda) = \frac{1}{mn}\sum_{i=1}^{n}\sum_{j=1}^{m} I(D_{1j} + \lambda D_{2j} > C_{1i} + \lambda C_{2i}) + \frac{1}{2} I(D_{1j} + \lambda D_{2j} = C_{1i} +$$

$$s = x_1 + \lambda x_2$$

Su & Liu's method (11): Su and Liu's combination score is obtained by using Fisher's discriminant function under the assumption of a multivariate normal distribution model and proportional covariance matrices. Let μ the mean vector, Σ the covariance matrix for the corresponding group, and σ^2 unknown scaling factor. Then, the combination score is calculated as follows:

Control group: $C \sim N(\mu_c, \Sigma)$

$$\text{Disease group: } D \sim N(\mu_D, \sigma^2 \Sigma)$$

$$\text{Fisher' s discriminant coefficient: } (\alpha,\beta)\alpha(\mu_D-\mu_C)^T \Sigma^{-1}$$

$$s = \alpha x_1 + \beta x_2$$

Minimax method (12): Minimax method is an extension of Su & Liu's method. In this case, the combination score is obtained with the minimax procedure:

$$\text{Control group: } C_i = (C_{1i}, C_{2i}),\ i = 1,2,\ldots,n,$$

$$\text{Disease group: } D_j = (D_{1j}, D_{2j}),\ j = 1,2,\ldots,m,$$

$$(b_1, b_2) = [t\Sigma_D + (1-t)\Sigma_C]^{-1} (\mu_D - \mu_C)$$

$$s = b_1 x_1 + b_2 x_2$$

In this formula, t is a constant which takes values between 0 and 1. This value can be optimized by maximizing the AUC from the combination score by trial and error method.

Min-Max method (13): This method linearly combines the minimum and maximum values of the markers by finding a parameter λ that maximizes the corresponding Mann-Whitney statistic.

$$\text{Control group: } C_i = (C_{1i}, C_{2i}),\ i = 1,2,\ldots,n,$$

$$\text{Disease group: } D_j = (D_{1j}, D_{2j}),\ j = 1,2,\ldots,m,$$

$$\text{maximize } W(\lambda) = \frac{1}{mn}\sum_{i=1}^{n}\sum_{j=1}^{m} I(D_{j,max} + \lambda D_{j,min} > C_{i,max} + \lambda C_{i,min})$$

$$s = x_{max} + \lambda x_{min}$$

Todor & Saplacan's method (14): Todor and Saplacan's method uses trigonometric functions to calculate the combination score. The combination score is obtained by the θ value that optimizes the corresponding AUC.

$$s = \sin(\theta) x_1 + \cos(\theta) x_2$$

Statistical Analysis

Histogram, q-q plots, and Shapiro-Wilk's test were performed to test data normality. In addition, the Levene test was used to assess variance homogeneity. To compare the distribution of leukocyte counts and D-dimer levels in patients with or without need of immediate laparotomy, a two-sided Mann-Whitney U test was applied. Analyses were conducted using TURCOSA (Turcosa Analytics Ltd. Co., Turkey, www.turcosa.com.tr) statistical software. A p-value less than 5% was considered statistically significant.

Model Building and Performance Assessment

The data was split into training (70%) and test (30%) sets. All model-building steps were conducted in training data, while the performances of each model were assessed in test data. The training data included 158 (immediate laparotomy needed 77, immediate laparotomy not needed 81) patients. The test data included the data of the remaining 67 (immediate laparotomy needed 33, immediate laparotomy not needed 34) patients. In training data, five-fold cross-validation was performed with 10 repeats to optimize the model parameters. Logistic regression, scoring, min-max, minimax, Su & Liu, Pepe & Thompson, Pepe, Cai & Langton, and Todor & Saplacan methods were used as linear combination methods. The combination scores for each method were calculated as described in the previous section. Performances of the built models were assessed using the area under the ROC curves. Moreover, the Youden index was used to identify the optimal cut-points, sensitivity, selectivity, accuracy, positive and negative predictive value, and positive and negative likelihood ratio statistics were also calculated for performance assessment. All analyses were conducted using R programming language 4.2.0 (www.r-project.org) with self-generated R scripts.

RESULTS

The distribution of leukocyte counts, as well as D-dimer levels, were found to be statistically higher in patients who need immediate laparotomy (p<0.05) (Table 1, Figure 1). These markers were combined using linear combination models described in the Material and Methods section. The model parameters were optimized, and the detected optimal parameters are given in Table 2.

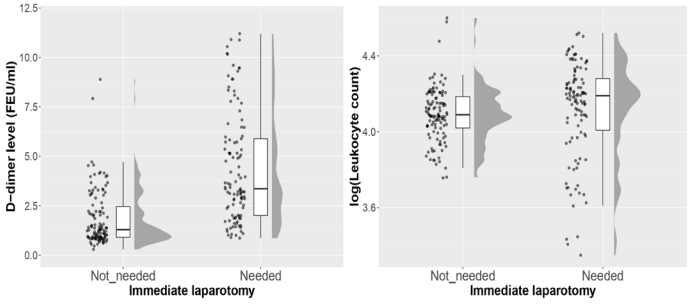

Figure 1. Raincloud plots displaying the distribution of D-dimer levels and leukocyte counts on a logarithmic scale in patients with and without the need for immediate laparotomy

Table 1. Comparison of leukocyte count and D-dimer levels in patients with or without need of immediate laparotomy

Marker	Immediate laparotomy		p-value
	Not needed (n=115)	Needed (n=110)	
Leukocyte count	12200 (10400-15400)	15500 (9900-19100)	0.003
D-dimer level (µg FEU/mL)	1.29 (0.90-2.53)	3.39 (2.01-5.98)	<0.001

Values are expressed as median(1st-3rd quartiles). Significant p values are shown in bold characters

Table 2. The optimal parameters were detected with the linear combination models

Linear combination models	Parameters
Logistic regression	β_0 = -15.069, β_1= 0.563, β_2 = 3.195
Scoring based on logistic regression	β_1 = 0.640, β_2 = 2.690
Pepe & Thompson	λ = 0.651
Pepe, Cai & Langton	λ = 0.382
Su & Liu	α = 0.225, β = 1.382
Minimax procedure	b_1 = 0.558, b_2 = 1.627
Min-max	λ = 0.772
Todor & Saplacan	sin(θ)= 0.330, cos(θ) = 0.944

The area under ROC curves for D-dimer levels and leukocyte counts on the logarithmic scale were 0.706 and 0.699, respectively. The area under the ROC curves for linear combination models was between 0.770 and 0.810 (Table 3). The highest performance was achieved using the min-max method. The ROC curve generated with the combination score from the min-max model, D-dimer levels, and leukocyte count markers were given in Figure 2. It is seen that the min-max method made a significant improvement between 14.7% and 15.9% in AUC statistics as compared to D-dimer level and leukocyte counts, respectively.

The optimal cut-off values for both markers and linear combination models are identified, and classification tables are generated for each marker and model. These cut-off values and the observed frequencies in each table are given in Table 4. For each table, statistical diagnostic measures are calculated with 95% confidence intervals and given in Table 5.

Table 3. Area under the curves of markers and combined score

Markers and models	AUC (95% CI)	z	p-value
Markers			
D-dimer level	0.706 (0.582-0.831)	3.24	<0.001
log (Leukocyte count)	0.699 (0.561-0.838)	2.82	<0.001
Linear combination models			
Logistic regression	0.781 (0.666-0.895)	4.80	<0.001
Scoring based on logistic regression	0.779 (0.665-0.893)	4.78	<0.001
Pepe & Thompson	0.782 (0.666-0.898)	4.76	<0.001
Pepe, Cai & Langton	0.770 (0.655-0.885)	4.61	<0.001
Su & Liu	0.786 (0.671-0.902)	4.86	<0.001
Minimax procedure	0.773 (0.661-0.884)	4.79	<0.001
Min-max	0.810 (0.698-0.922)	5.43	<0.001
Todor & Saplacan	0.772 (0.658-0.886)	4.68	<0.001

AUC: Area under the ROC curve. Significant p values are shown in bold characters

Table 4. Classification tables obtained for each marker and linear combination model

Markers and models	TP	TN	FP	FN
Markers				
D-dimer level (>1.74 µg FEU/mL)	27	19	15	6
log (Leukocyte count) (>4.27)	17	32	2	16
Linear combination models				
Logistic regression (>0.38)	27	23	11	6
Scoring based on logistic regression (>12.72)	26	23	11	7
Pepe & Thompson (>0.33)	26	25	9	7
Pepe, Cai & Langton (>0.29)	23	26	8	10
Su & Liu (>6.32)	27	25	9	6
Minimax procedure (>7.56)	24	24	10	9
Min-max (>0.42)	26	27	7	7
Todor & Saplacan (>4.93)	23	26	8	10

TP: True positive, TN: True negative, FP: False positive, FN: False negative

Table 5. Statistical diagnostic measures with 95% confidence intervals calculated for each marker and linear combination model

Variable	SEN (95% CI)	SPE (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)	ACC (95% CI)
Markers and models							
D-dimer level (>1.74 µg FEU/mL)	0.82 (0.65-0.93)	0.56 (0.38-0.73)	0.64 (0.48-0.78)	0.76 (0.55-0.91)	1.85 (1.23-2.80)	0.33 (0.15-0.71)	0.69 (0.56-0.79)
log (Leukocyte count) (>4.27)	0.52 (0.34-0.62)	0.94 (0.80-0.99)	0.89 (0.67-0.99)	0.67 (0.52-0.80)	8.76 (2.19-34.97)	0.52 (0.36-0.74)	0.73 (0.61-0.83)
Linear combination models							
Logistic regression (>0.38)	0.82 (0.65-0.93)	0.68 (0.49-0.83)	0.71 (0.54-0.85)	0.79 (0.60-0.92)	2.53 (1.52-4.22)	0.27(0.13-0.57)	0.75 (0.63-0.84)
Scoring based on LR (>12.72)	0.79 (0.61-0.91)	0.68 (0.49-0.83)	0.70 (0.53-0.84)	0.77 (0.58-0.90)	2.44 (1.45-4.09)	0.31 (0.16-0.63)	0.73 (0.61-0.83)
Pepe & Thompson (>0.33)	0.79 (0.61-0.91)	0.74 (0.56-0.87)	0.74 (0.57-0.88)	0.78 (0.60-0.91)	2.98 (1.65-5.36)	0.29 (0.15-0.57)	0.76 (0.65-0.86)
Pepe, Cai & Langton (>0.29)	0.70 (0.51-0.84)	0.76 (0.59-0.89)	0.74 (0.55-0.88)	0.72 (0.55-0.86)	2.96 (1.55-5.65)	0.40 (0.23-0.69)	0.73 (0.61-0.83)
Su & Liu (>6.32)	0.82 (0.65-0.93)	0.74 (0.56-0.87)	0.75 (0.58-0.88)	0.81 (0.63-0.93)	3.09 (1.73-5.54)	0.25 (0.12-0.52)	0.78 (0.66-0.87)
Minimax procedure (>7.56)	0.73 (0.54-0.87)	0.71(0.53-0.85)	0.71 (0.53-0.85)	0.73 (0.54-0.87)	2.47 (1.41-4.33)	0.39 (0.21-0.70)	0.72 (0.59-0.82)
Min-max (>0.42)	0.79 (0.61-0.91)	0.79 (0.62-0.91)	0.79 (0.61-0.91)	0.79 (0.62-0.91)	3.83 (1.93-7.58)	0.27 (0.14-0.53)	0.79 (0.67-0.88)
Todor & Saplacan (>4.93)	0.70 (0.51-0.84)	0.76 (0.59-0.89)	0.74 (0.55-0.88)	0.72 (0.55-0.86)	2.96 (1.55-5.65)	0.40 (0.23-0.69)	0.73 (0.61-0.83)

SEN: Sensitivity, SPE: Specificity, PPV: Positive predictive value, NPV: Negative predictive value, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, ACC: Accuracy rate, LR: Logistic regression

The sensitivity of the D-dimer level (0.82) was found to be higher than the sensitivity of log-transformed leukocyte counts (0.52). On the other hand, the specificity statistic was higher for log-transformed leukocyte counts (0.94) as compared to the D-dimer level (0.56). The diagnostic accuracy of log-transformed leukocyte counts was 0.73 and was higher than the accuracy of the D-dimer level, which was 0.69. After combining these markers with linear combination models, the accuracy of these models was obtained between 0.72 and 0.79. Higher accuracies were obtained with min-max, Su & Liu, Pepe & Thomson, and logistic regression models. There was no improvement in terms of accuracy statistics for scoring based on logistic regression; Pepe, Cai & Langton; minimax and Todor & Saplacan models. The best performance was achieved with the min-max model with a diagnostic accuracy of 0.79. For this best-performed model, sensitivity and specificity statistics were obtained as 0.79 as well. The final decision rule for the min-max model suggests an immediate laparotomy for patients with acute abdominal pain if the following condition is true:

$$_{max}(Ddimer, log_{10}(WBC)) + 0.772 *_{min}(Ddimer, log_{10}(WBC)) > 0.42$$

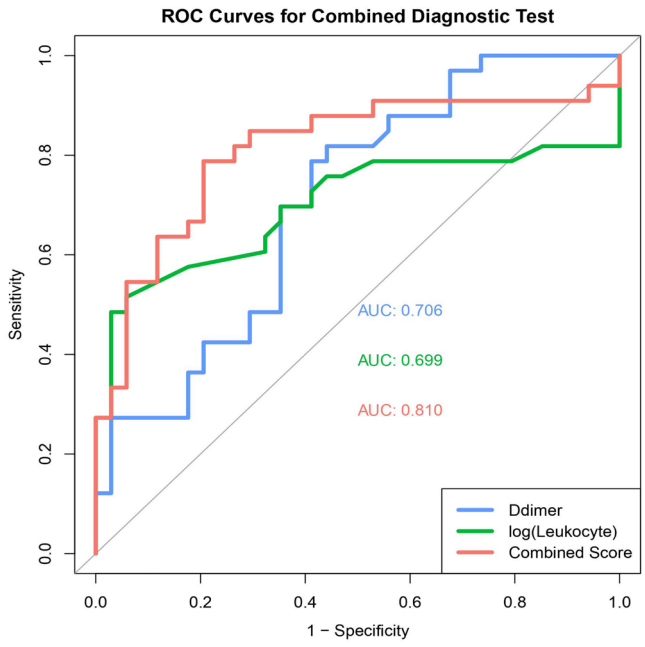

Figure 2. ROC curves for D-dimer levels, leukocyte counts on a logarithmic scale and, Min-max combined scores in diagnosing patients with nontraumatic acute abdomen

DISCUSSION

Rapid intervention is important in non-traumatic acute abdomen patients admitted to the emergency department. Increasing the diagnostic accuracy even at the level of 1% in clinical evaluation is vital for patients admitted to the emergency department with this symptom. In this study, we increased the diagnostic accuracy by combining leukocyte count and D-dimer levels with linear combination methods. The diagnostic accuracy of 79%, obtained with the best-performing min-max method, was found to be 8.2% higher than the leukocyte count marker and 14.5% higher than the D-dimer levels. In addition, the sensitivity of the D-dimer level marker and the specificity of the leukocyte count marker was found to be high. Using the min-max linear combination method, we obtained a high estimation of both sensitivity and specificity.

In the literature, there are studies in which the diagnostic test performance is increased using linear combination methods for different medical problems. Kyurkchiyan et al. (2021) combined the performance of miR-31-3p and miR-196a-5p transcripts using linear combination methods to diagnose advanced laryngeal squamous cell carcinoma (15). The AUC statistics for miR-31-3p and miR-196a-5p transcripts were 0.934 and 0.877, respectively, while the calculated AUC statistics for the combined test were 0.978. Huang et al. (2022) linearly combined ultrasound score and liver stiffness measurement of sound touch elastography in diagnosing liver fibrosis staging in patients with chronic hepatitis B (16). The combined score had the highest AUC in all fibrosis stages. Zhang et al. (2019) used three linear combination models and combined cerebrospinal fluid procalcitonin, lactate, interleukin-8, and interleukin-10 markers in differentiating between post-neurosurgical bacterial meningitis and aseptic meningitis (17). The AUC statistic was improved to 0.954 with the four marker model. Han et al. (2008) combined matrix metalloproteinase-9, N-acetyl-b-D-glucosaminidase, and kidney injury molecule-1 urinary biomarkers linearly in identifying acute kidney injury (18). The highest diagnostic performance was observed with the linear combination.

In a study using the same data in our study and combining D-dimer levels and leukocyte count markers with machine learning methods, the best diagnostic performance was obtained with the Naive-Bayes method with an accuracy of 78.57%. The diagnostic accuracy of the boosted and bagged logistic regression models was 78.12% (4). When performance comparisons are made, it can be said that the diagnostic accuracy of the min-max linear combination model was slightly better than machine-learning models. However, the sensitivity of the combined test was higher than the Naive-Bayes model, and the specificity was higher than the boosted and bagged logistic regression models. It is seen that high diagnostic accuracies are obtained with linear combination methods.

Moreover, the models obtained by linear combination methods are simple and clinically interpretable. In cases where more than one marker is evaluated in health studies, a common procedure is to compare the diagnostic performance of markers, and combining diagnostic tests is ignored in many studies. In the case of a single diagnostic marker, medical decisions can be made simply based on cut-off values. In many cases, combining multiple diagnostic tests with machine learning methods provides high diagnostic accuracies due to their strong mathematical infrastructures. The advantage of linear combination methods is that they may both increase diagnostic accuracies compared to single markers and provide simple and medically interpretable results. Therefore, clinicians may consider applying linear combination methods first and making a comparative evaluation based on the results, especially when making medical decisions based on a small number of diagnostic tests. In cases where similar accuracy performance is obtained with machine learning methods, linear combination methods can be used due to their simplicity and interpretability.

Although linear combination methods have many advantages, their absence in most statistical software limits their use. A further aspect of this work is developing a user-friendly web application in which linear combination methods can be applied.

CONCLUSION

In conclusion, the min-max linear combination model improved the diagnostic performance in differentiating between surgical and non-surgical pathologies in non-traumatic acute abdominal pain patients. Therefore, we suggest that D-dimer level and leukocyte counts should be evaluated together with the min-max procedure because of its higher diagnostic performance and simple interpretation.

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

Ethical approval: *Ethics committee approval is not required in this study.*

REFERENCES

1. Graff LG, Robinson D. Abdominal pain and emergency department evaluation. Emerg Med Clin North Am. 2001;19:123-36.
2. Yeniocak S, Turkmen S, Uzun O, et al. Analysis of Patients Presenting to the Emergency Department with Acute Abdominal Pain. J Acad Emerg Med. 2012;11:212-5.
3. Akyıldız HY, Sozuer E, Akcan A, et al. The value of D-dimer test in the diagnosis of patients with non-traumatic acute abdomen. Ulus Travma Acil Cer. 2010;16:22-26.
4. Zararsiz G, Akyildiz HY, Goksuluk D, et al. Statistical learning approaches in diagnosing patients with nontraumatic acute abdomen. Turk J Electr Eng Comput Sci. 2016;24: 3685-97.
5. Gohel P, Singh P, Mohanty M. Explainable AI: current status and future directions. arXiv: 2107.07045v1.

6. Kang L, Liu A, Tian L. Linear combination methods to improve diagnostic/prognostic accuracy on future observations. Stat Methods Med Res. 2016;25:1359–80.

7. Yin J, Tian L. Optimal linear combinations of multiple diagnostic biomarkers based on Youden index. Stat Med. 2014;33:1426-40.

8. Coolen-Maturi T. Predictive inference for best linear combination of biomarkers subject to limits of detection. Stat Med. 2017;36:2844-74.

9. Pepe MS, Thompson ML. Combining diagnostic test results to increase accuracy. Biostatistics. 2000;1:123–40.

10. Pepe MS, Cai T, Longton G. Combining predictors for classification using the area under the receiver operating characteristic curve. Biometrics. 2006;62:221–9.

11. Su JQ, Liu. Linear combinations of multiple diagnostic markers. Journal of the American Statistical Association. 1993;88:1350–5.

12. Sameera G, Vardhan RV, Sarma KVS. Binary classification using multivariate receiver operating characteristic curve for continuous data. JJ Biopharm Stat. 2016;26:421–31.

13. Liu C, Liu A, Halabi S. A min–max combination of biomarkers to improve diagnostic accuracy. Stat Med. 2011;30:2005–14.

14. Todor N, Todor I, Saplacan G. Tools to identify linear combination of prognostic factors which maximizes area under receiver operator curve. J Clin Bioinforma. 2014;4:1–7.

15. Kyurkchiyan SG, Popov TM, Shakola F, et al. A Pilot Study Reveals the Potential of miR-31-3p and miR-196a-5p as Non-Invasive Biomarkers in Advanced Laryngeal Cancer. Folia Med. 2021;63: 355-64.

16. Huang K, Li Q, Zeng W et al. Ultrasound score combined with liver stiffness measurement by sound touch elastography for staging liver fibrosis in patients with chronic hepatitis B: a clinical prospective study. Ann Transl Med. 2022;10:271.

17. Zhang G, Yang C, Kang X, et al. The combination of cerebrospinal fluid procalcitonin, lactate, interleukin-8 and interleukin-10 concentrations for the diagnosis of postneurosurgical bacterial meningitis: A prospective study. Ann Clin Biochem. 2019; 56:133-40.

18. Han WK, Waikar SS, Johnson A, et al. Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney Int. 2008;73:863-9.