

Application of machine learning algorithms for predicting internal carotid artery stenosis and comparing their value to duplex Doppler ultrasonography criteria

İnternal karotid arter darlığını tahmin etmede makine öğrenme algoritmalarının kullanımı ve öngörüm başarısının dubleks Doppler ultrasonografi kriterleriyle karşılaştırılması

Pınar Çeltikçi, Önder Eraslan, Mehmet Ali Atıcı, Işık Conkbayır, Onur Ergun, Hasanali Durmaz, Emrah Çeltikçi

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Abstract

Purpose: There is a discrepancy between duplex Doppler ultrasonography (DUS) and digital subtraction angiography (DSA) for determining internal carotid artery (ICA) stenosis. We aim to train machine learning algorithms (MLAs) with DUS velocity values for predicting ICA stenosis and comparing their success to DUS criteria.

Materials and methods: DUS values (peak systolic velocity (PSV) and end-diastolic velocity of the common carotid artery (CCA) and ICA) and DSA studies of 159 ICA stenoses were reviewed retrospectively. Stenoses were classified as <50%, 50-69%, ≥70% by each modality. Linear regression models with descriptive and predictive analysis and MLAs; LightGBM, XgBoost, KNeighbors, Support Vector Machine (SVM), Decision Tree, Random Forest were trained with DUS values for predicting DSA stenosis.

Results: Predicted values of regression models have a linear relationship with DSA stenosis between 0-60%. LightGBM and SVM achieved the highest classification accuracy (69%), while all algorithms failed in the 50-69% interval. DUS criteria outperformed all MLAs in predicting DSA stenosis of ≥70% (sensitivity:0.91). Both MLAs and DUS criteria were unsuccessful in the 50-69% interval where DUS mostly overestimates and MLAs underestimate. MLAs using ICA PSV/CCA PSV ratio had higher accuracy for predicting DSA stenosis <50%.

Conclusion: DUS criteria could be considered as the sole diagnostic tool for ICA stenosis over 70%. Improved DUS criteria or wider training datasets for MLAs are warranted to detect 50-69% stenosis accurately.

Key words: Carotid artery, duplex Doppler ultrasonography, digital subtraction angiography, machine learning, stenosis.

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Öz

Amaç: İnternal karotid arter (İKA) darlığını belirlemede, dubleks Doppler ultrasonografi (DUS) ile dijital subtraksiyon anjiyografi (DSA) arasında tutarsızlık bildirilmiştir. DUS hız değerleri ile eğitilmiş makine öğrenme algoritmalarının (MÖA), İKA darlığını tahmin etme performansını araştırmayı amaçlıyoruz.

Gereç ve yöntem: İKA darlığı olan 159 karotid bifurkasyonunun, ortak karotid arter (OKA) ve İKA'dan elde olunmuş DUS hız değerleri (pik sistolik hız (PSH) ve diyastol sonu hızı) ve DSA tetkikleri retrospektif olarak incelendi. Darlık derecesi her modaliteye göre <50%, 50-69, ≥70 olarak sınıflandırıldı. Tanımlayıcı ve kestirimci analizler içeren doğrusal regresyon modelleri ve çeşitli MÖA'lar (LightGBM, XgBoost, KNeighbors, Support Vector Machine (SVM), Decision Tree, Random Forest) DSA'da saptanan darlık derecesini tahmin etmek için DUS hız değerleri ile eğitildi.

Bulgular: Regresyon modellerinin tahmin ettiği darlık değerleri ve asıl DSA darlık değerleri, %0-60 arasında doğrusal bir ilişkiye sahipti. MÖA'lar arasında LightGBM ve SVM en yüksek sınıflandırma doğruluğunu (%69)

Pınar Çeltikçi, M.D. Department of Radiology, Ankara Bilkent City Hospital, Ankara, Turkey, e-mail: drpınarceltikci@gmail.com (<https://orcid.org/0000-0002-1655-6957>) (Corresponding Author)

Önder Eraslan, M.D. Department of Radiology, Erbaa State Hospital, Tokat, Turkey, e-mail: ondereraslan@gmail.com (<https://orcid.org/0000-0001-8904-1412>)

Mehmet Ali Atıcı, M.S. Department of Computer Engineering, Gazi University Faculty of Engineering, Ankara, Turkey, e-mail: machinelearningdynamics@gmail.com (<https://orcid.org/0000-0002-0673-5724>)

Işık Conkbayır, M.D. Prof. Department of Radiology, University of Health Sciences, Diskapi Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey, e-mail: iconkbayir@yahoo.com (<https://orcid.org/0000-0003-2768-4871>)

Onur Ergun, Assoc. Prof. Department of Radiology, University of Health Sciences, Diskapi Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey, e-mail: onurergun@yahoo.com (<https://orcid.org/0000-0002-0495-0500>)

Hasanali Durmaz, M.D. Department of Radiology, University of Health Sciences, Diskapi Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey, e-mail: dr.hasan.ali.durmaz@hotmail.com (<https://orcid.org/0000-0003-1140-6666>)

Emrah Çeltikçi, M.D. Department of Neurosurgery, Gazi University Faculty of Medicine, Ankara, Turkey, e-mail: drceletikci@gmail.com (<https://orcid.org/0000-0001-5733-7542>)

elde ederken, tüm algoritmalar %50-69 darlık aralığında başarısız oldu. DUS kriterleri, ≥ 70 'lik DSA darlığını tahmin etmede tüm MÖA'lerden daha iyi performans gösterdi (duyarlılık:0,91). Hem MÖA'lar hem de DUS kriterleri %50-69 darlık aralığında başarısız olup, DUS darlığı olduğundan fazla, MÖA'lar darlığı olduğundan az olarak tahmin etti. İKA PSH/OKA PSH oranını kullanan MÖA'lar, < 50 DSA darlığını öngörmeye daha yüksek doğruluğa sahipti.

Sonuç: DUS kriterleri, %70'in üzerinde İKA darlığı için tek tanı aracı olarak kabul edilebilir. Geliştirilmiş DUS kriterleri veya MÖA'lar için daha geniş eğitim veri setleri sağlanması, %50-69 darlık aralığının daha yüksek doğrulukla tespit edilmesini sağlayabilir.

Anahtar kelimeler: Darlık, dijital subtraksiyon anjiyografi, dupleks Doppler ultrasonografi, karotid arter, makine öğrenmesi.

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Introduction

Detection and accurate quantification of extracranial internal carotid artery (ICA) stenosis is of great importance in order to prevent morbidity and mortality by secondary cerebrovascular ischemic events [1, 2]. Main goal is to detect carotid artery atherosclerotic disease and determine the stenosis degree, so that patients are selected either for conservative treatment or surgery. Patients with stenosis rates exceeding 70% have shown to benefit from endarterectomy [3]. Digital subtraction angiography (DSA) is the gold standard method for estimating stenosis percentage. However, DSA is an invasive and expensive procedure which requires access to an angiography suite, trained personnel, as well as exposure to ionizing radiation and administration of iodinated contrast agent which might compromise renal function. Computed tomography angiography and magnetic resonance imaging angiography are less invasive options, which also entail contrast media administration and/or radiation exposure nevertheless.

Duplex Doppler ultrasonography (DUS) is a non-invasive, rapid, safe, and low-cost technique, therefore considered as the first line of choice for evaluating patients with suspected carotid atherosclerotic disease. The value of DUS for the detection and classification of the atherosclerotic disease of the carotid arteries is widely investigated. There are various DUS parameters and criteria proposed in the literature [4-6]. Overall high rates of performance parameters were reported for the Society of Radiologists in Ultrasound Consensus Conference criteria. However, the precise determination of ICA stenosis rate with DUS and the agreement between DUS and

DSA are still a matter of debate in the current literature [7-14].

Machine learning algorithms are increasingly utilized for detecting possible relationships and patterns in the medical field. To the best of our knowledge, machine learning classifier algorithms have never been utilized to predict DSA stenosis rates of extracranial ICA stenosis following training with velocity data in comparison to DUS criteria. Here, we aim to investigate the correlation between DUS and DSA for the classification of ICA stenosis, and to train multiple machine learning algorithms with DUS velocity values in order to reveal their success in predicting DSA stenosis and compare them to DUS criteria.

Materials and methods

Prior to the study, the Local Ethics Committee approval and informed written consent from all patients were obtained.

Patient selection

All patients that were referred to the Vascular Ultrasonography Unit of the fourth listed institution, for carotid artery DUS examination, between March 2013-November 2018 and diagnosed with ICA stenosis were considered for this retrospective study. Following the elimination of vessels without a DSA study followed by the DUS evaluation, 198 patients underwent further evaluation of DUS examination reports and DSA studies. The average time interval between DUS and DSA examinations were 26 days. Exclusion criteria were; previous history of carotid artery surgery, occlusion and near occlusion, suboptimal image quality. Following exclusion, 159 ICAs of 123 patients constituted the study cohort.

DUS evaluation

DUS studies were performed by two radiologists with 10+ and 20+ year experience, using an Aplio™ 500 ultrasound machine (TUS-A500) (Toshiba Medical Systems, Otawara, Japan) with 6-12 MHz linear array transducers. All DUS studies were performed prior to angiography. Common carotid artery (CCA), bifurcation, ICA and external carotid arteries of both sides were evaluated. Gray-scale imaging in longitudinal and axial planes, color mode and spectral imaging were utilized in all cases. Gray-scale examination included evaluation of arterial walls and lumens and measurement of atherosclerotic plaques. Angle-adjusted spectral DUS images were obtained from CCA approximately 2 centimeters proximal to the bifurcation and at the ICA stenosis. Highest peak systolic velocity (PSV) and end-diastolic velocity (EDV) measured of both CCA and ICA were recorded. Stenosis percentage was calculated according to Society of Radiologists in Ultrasound Consensus Conference criteria and classified as <50%, 50-69% and ≥70% [6].

DSA evaluation

DSA studies were performed by a 15+ year experienced interventional radiologist using an Artis zee floor interventional angiography system (Siemens, Germany). Omnipaque 350@ (Iohexol, GE Healthcare, Milwaukee, WI, USA) was utilized as contrast agent in all examinations. Unilateral or bilateral carotid arterial system was examined through femoral artery puncture. At least two orthogonal views of ICA and CCA at bifurcation were acquired following selective catheterization. DSA studies were evaluated by the same interventional radiologist blinded to DUS results and clinical information. ICA stenosis percentage was calculated according to The North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria and then categorized as <50%, 50-69% and ≥70% [1].

Data analysis

Both linear regression model with descriptive and predictive analysis, and machine learning algorithms were employed for data analysis. Python Sci-kit Learn (<https://scikit-learn.org/stable/>), Numpy (<https://numpy.org/>), Pandas (<https://pandas.pydata.org/>), Matplotlib (<https://matplotlib.org/>) and Seaborn (<https://seaborn.pydata.org/>) libraries were utilized. For descriptive analysis, Pearson correlation matrix is calculated. Pearson correlation coefficient measures the linear relationship between random variables and takes values between -1 and +1 such that 0 means no relation whereas -1 and +1 means perfect association. The values between 0.5 and 0.8 indicates a moderate relationship between the variables whereas the values between -0.2 and +0.2 point out weak association [15]. In predictive analysis, simple linear regression was applied. Dependent variables were predicted by the predictor variable. Linear regression model was trained for predicting the DSA stenosis value (%) from ICA PSV and ICA EDV separately. Training was on basis of k-fold cross validation (k=5).

Second, machine learning algorithms were trained for classifying the DSA stenosis intervals from ICA PSV, ICA EDV, CCA PSV and CCA EDV values. For this, DSA stenosis values in the dataset were divided into 3 classes as; class 1: <50%, class 2: 50-69%, class 3: ≥70%. We also trained classifiers that takes only ICA PSV/CCA PSV ratio as the input. In experiments, 6 different machine learning algorithms (LightGBM, XgBoost, K Neighbors, Support Vector Machines (SVM), Decision Tree and Random Forest) were implemented for classification. Training was on basis of k-fold cross validation (k=19). Performance of the classifiers have been evaluated by accuracy, precision, recall and F1-measure metrics calculated according to confusion matrix are elaborated in Table 1.

Table 1. Confusion Matrix

	Predicted Negative	Predicted Positive
Actual Negative	True Negative (TN)	False Positive (FP)
Actual Positive	False Negative (FN)	True Positive (TP)

Accuracy, precision, sensitivity and F1-measure can be formally calculated as; Precision=TP/(TP+FP), Recall=Sensitivity=TP/(TP+FN), Accuracy=(TP+TN)/(TP+FN+TN+FP) and F1-measure=2/((1/precision)+(1/recall))

Results

A total of 159 carotid artery bifurcations constituted the study cohort. Stenosis percentage ranged from 0- 91% by DSA. PSV measurement ranged from 62-720 cm/s in ICA and 18-110 cm/s in CCA. EDV measurement ranged from 10-390 cm/s in ICA and 5-30 cm/s in CCA. The ratio of ICA/CCA PSV ranged from 1.2-20.

Pearson correlations matrix with pairwise Pearson correlation coefficient calculations of ICA PSV, ICA EDV, CCA PSV, CCA EDV and DSA stenosis percentage were presented in Figure 1. There is a moderate correlation between DSA stenosis percentage and both

ICA PSV and ICA EDV according to Pearson correlation coefficient calculations; which are 0.66 and 0.58 respectively. On the other hand, there is weak association between DSA stenosis percentage and CCA PSV, CCA EDV values.

The scattered plots of these values against DSA stenosis percentages supports the findings from the correlation matrix. There is a linear relationship between DSA stenosis percentage and ICA PSV and ICA EDV to some extent (Figure 2A and Figure 2B). However, randomly scattered values do not provide an evidence for linear relationship between DSA stenosis percentage and CCA PSV or CCA EDV (Figure 2C and Figure 2D).

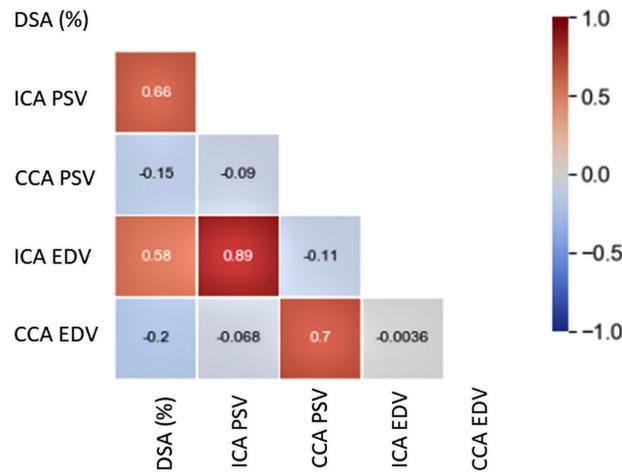


Figure 1. Pearson correlations matrix with pairwise Pearson correlation coefficient calculations of internal carotid artery peak systolic velocity (ICA PSV), internal carotid artery end-diastolic velocity (ICA EDV), common carotid artery peak systolic velocity (CCA PSV), common carotid artery end-diastolic velocity (CCA EDV) and digital subtraction angiography (DSA) stenosis percentage

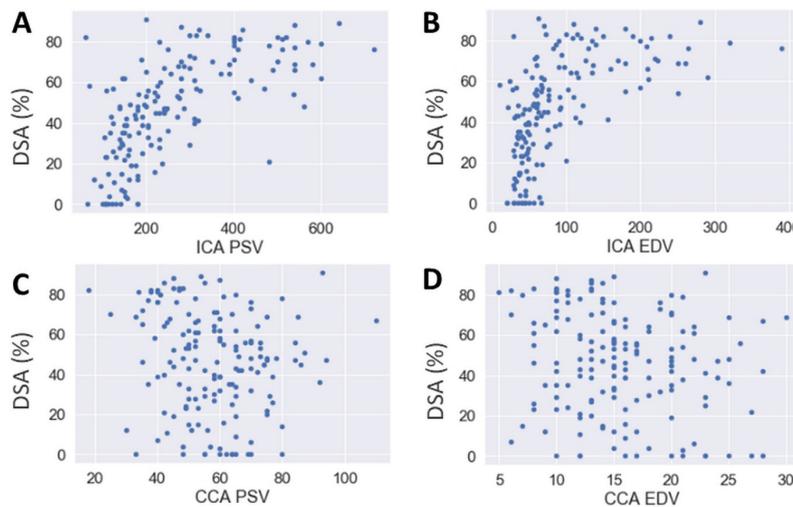


Figure 2. The scattered plots of internal carotid artery peak systolic velocity (ICA PSV), internal carotid artery end-diastolic velocity (ICA EDV), common carotid artery peak systolic velocity (CCA PSV), common carotid artery end-diastolic velocity (CCA EDV) values against digital subtraction angiography (DSA) stenosis percentages

Two linear regression models were trained for predicting DSA stenosis percentage from ICA PSV and ICA EDV. These two values were utilized due to the fact that there was a moderate correlation according to Pearson correlation coefficient calculations. The achieved R^2 scores (*coefficient of determination*), which equals to square of Pearson correlation coefficient for each trained model of ICA PSV and ICA EDV was 0.43 and 0.33, respectively. In accordance with descriptive analysis results, these results indicate that ICA PSV has more impact for predicting DSA stenosis percentage than ICA EDV. The scattered plots of predicted DSA stenosis percentage against actual percentage is demonstrated in Figure 3. The predicted values of trained regression models have a linear relationship with actual DSA stenosis percentages to some extent but there is some corruption above 60% and around 0% values.

Confusion matrices for each machine learning classifier trained with both ICA PSV and CCA PSV are given in Figure 4.

Performance metrics of the classifiers are given in Table 2. Results in Table 2 indicate that LightGBM and SVM algorithms achieved the highest classification accuracy which is 69%. LightGBM achieved the highest sensitivity for DSA stenosis 50-69% interval when compared to other algorithms. It is clear that all algorithms fail for classification of 50-69% interval. This result is demonstrated on the 2D scattered plots of data samples in reduced dimension by Linear Discriminant Analysis (LDA). Samples for 50-69% interval are scattered across the both of clusters of other classes (Figure 5).

Additionally, confusion matrices of classifier algorithms using ICA PSV/CCA PSV ratio as the input improves the classification accuracy up to 0.74 and sensitivity for DSA stenosis <50% cases up to 0.98 (Figure 6). However, general accuracy of DUS is too low when compared the machine learning classifiers (Table 3) which is 0.33; even worse than random guess. For subjects with DSA stenosis <50%, sensitivity (recall) is too low again and DUS overestimates

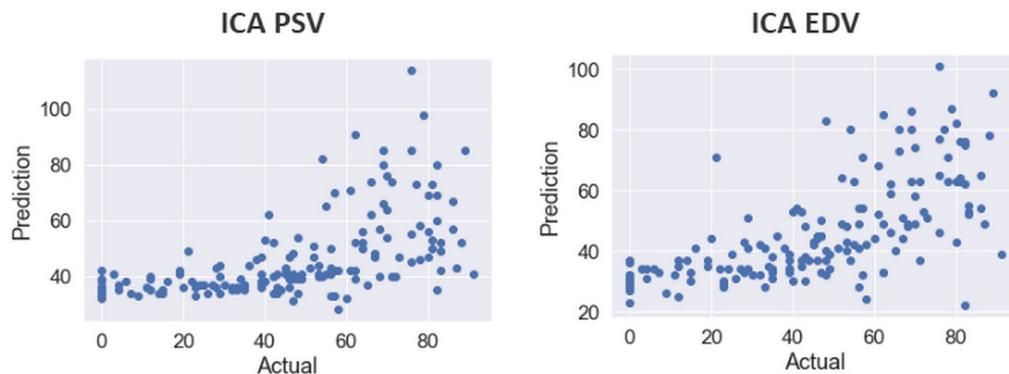


Figure 3. The scattered plots of predicted digital subtraction angiography (DSA) stenosis percentage against actual percentage; internal carotid artery peak systolic velocity (ICA PSV), internal carotid artery end-diastolic velocity (ICA EDV)

Table 2. Performance metrics of classifier machine learning algorithms trained with internal carotid artery peak systolic velocity and common carotid artery peak systolic velocity

Classifier	<50%			50-69%			>70%			General
	P (%)	R (%)	F1 (%)	P (%)	R (%)	F1 (%)	P (%)	R (%)	F1 (%)	Accuracy (%)
KNeighbors	76	87	81	23	15	18	44	44	44	60
Random Forest	76	91	83	36	21	26	63	65	64	68
SVM	72	94	82	43	15	23	67	65	66	69
Decision Tree	76	83	79	23	15	18	49	56	52	60
XGBoost	76	81	79	31	31	31	61	50	55	62
LightGBM	77	87	82	47	36	41	69	65	67	70

P: precision, R: recall, F1: F1 measure, SVM: support vector machine

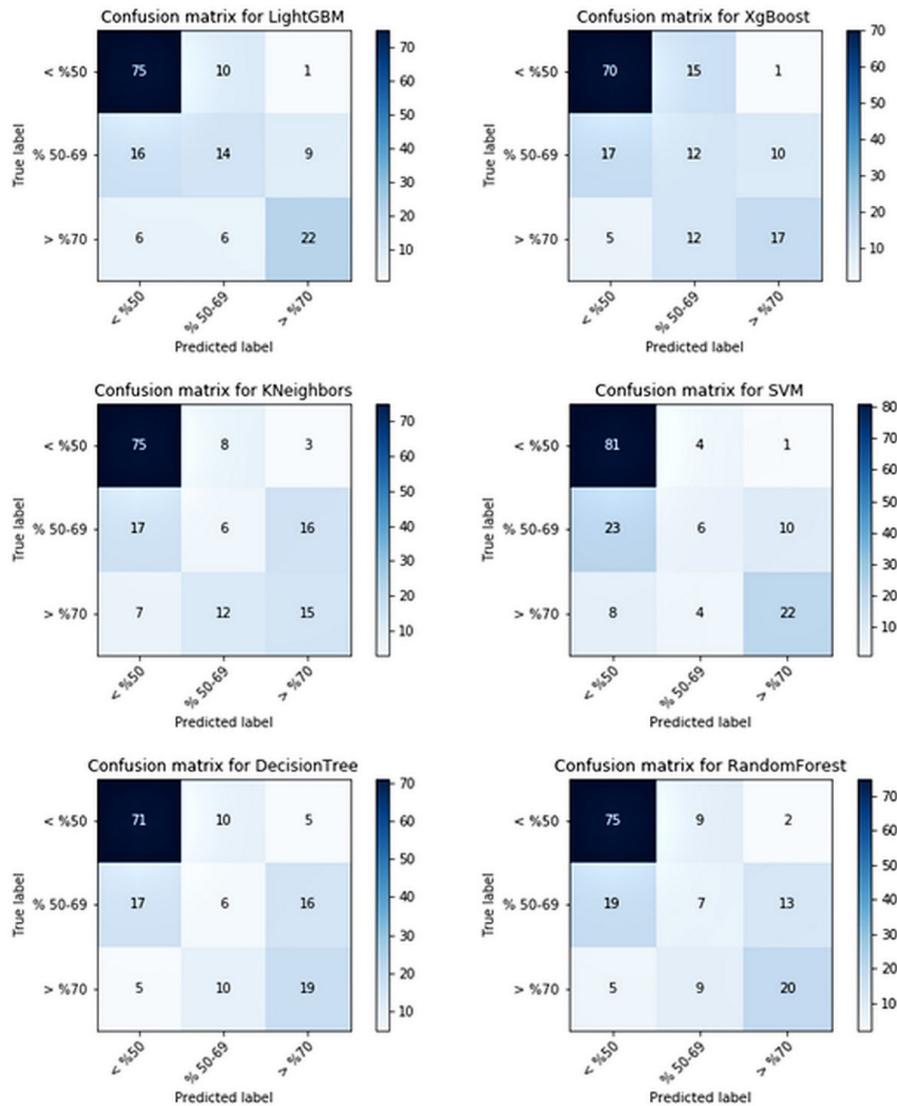


Figure 4. Confusion matrices for each machine learning classifier which are trained with internal carotid artery peak systolic velocity (ICA PSV) and common carotid artery peak systolic velocity (CCA PSV); LightGBM, XgBoost, KNeighbors, Support Vector Machine (SVM), Decision Tree, and Random Forest

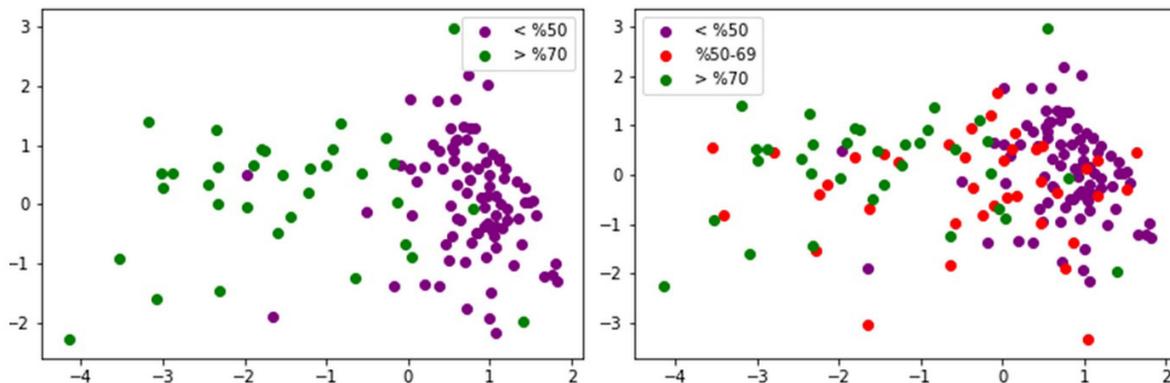


Figure 5. Linear Discriminant Analysis (LDA) scattered plots of data samples reveal that samples of <50% stenosis (purple dots) and samples of >70% stenosis (green dots) are almost distinguished from each other (left) forming mostly separate clusters. However, samples of 50-69% stenosis (red dots) are scattered across both clusters of other classes (right) which demonstrates the failure of machine learning classifiers in this stenosis range

Table 3. Performance metrics of classifier machine learning algorithms trained with internal carotid artery peak systolic velocity/common carotid artery peak systolic velocity ratio and duplex Doppler ultrasonography criteria

Classifier	<50%			50-69%			>70%			General
	P	R	F1	P	R	F1	P	R	F1	Accuracy
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
KNeighbors	75	88	81	42	26	32	67	63	65	68
Random Forest	78	87	82	47	39	43	61	54	58	69
SVM	72	98	83	40	11	17	62	57	60	68
Decision Tree	78	85	81	43	39	41	60	51	55	67
XGBoost	78	87	82	47	39	43	68	60	64	70
LightGBM	77	97	86	80	32	45	64	66	65	74
DUS	92	13	22	13	26	17	46	91	62	33

P: precision, R: recall, F1: F1 measure, DUS: Duplex Doppler Ultrasonography
SVM: support vector machine

almost 87% of the subjects. On the other hand, DUS is more successful than machine learning algorithms with respect to subjects with DSA stenosis $\geq 70\%$, whereas achieves 0.91 sensitivity. Both machine learning algorithms and DUS are unsuccessful for predicting DSA stenosis of 50-69%. One difference is that DUS mostly overestimates the incorrect predictions whereas machine learning algorithms underestimate. This may be related to both data set and the algorithm. For instance, confusion matrix of K Neighbors algorithm in Figure 6 indicates that numbers of overestimated and underestimated predictions are the same. When trained with a larger data set, machine learning algorithms may achieve higher sensitivity for DSA stenosis in the 50-69% interval.

Discussion

The results of this study indicate that DUS criteria and DSA show varying levels of discordance when calculating ICA stenosis, depending on the stenosis range, when a linear regression model and machine learning algorithms were applied. We believe the main reason behind this problem is the fact that, in each modality, a different indicator of stenosis is utilized. DUS criteria identifies stenosis via measurements regarding flow velocity, whereas catheter angiography measures the change in vessel calibration.

In our study, linear regression models showed ICA PSV value to be more predictive of the DSA stenosis rate with some corruption over 60%. Our results are compatible with

other studies from the literature which utilized regression models [16, 17]. However, with regression models, determining the success of DUS in predicting DSA stenosis, in each interval of <50%, 50-69% and $\geq 70\%$ as it classifies them, is not possible. After revealing the discordance between DUS criteria and DSA we trained machine learning algorithms with DUS data (both velocity values separately and ICA PSV/CCA PSV ratio), in order to see if they would perform any differently. Apart from a meta-analysis [18] which used a neural net algorithm to derive an equation relating ICA PSV/CCA PSV ratio to NASCET percent stenosis, our study is the only one in literature to apply multiple machine learning classifier algorithms on DUS velocity data for predicting DSA stenosis.

Machine learning algorithms are gaining wider recognition and application in the field of radiology. Currently, these methods are more commonly applied in image analysis and pattern recognition. Utilizing machine learning algorithms on numerical data such as flow velocity values is relatively uncommon. In our study, machine learning algorithms were more successful in predicting DSA stenosis rates below 50% than DUS criteria. This result is most likely due to the fact that, DUS criteria identifies stenosis by increased velocity which is not apparent in stenosis rates below 50%. Both DUS criteria and machine learning algorithms fail in the 50-69% range. In this range, success of DUS criteria is of debate and was shown to have discordance with statistical methods in various studies [11, 19, 20]. On the other hand,

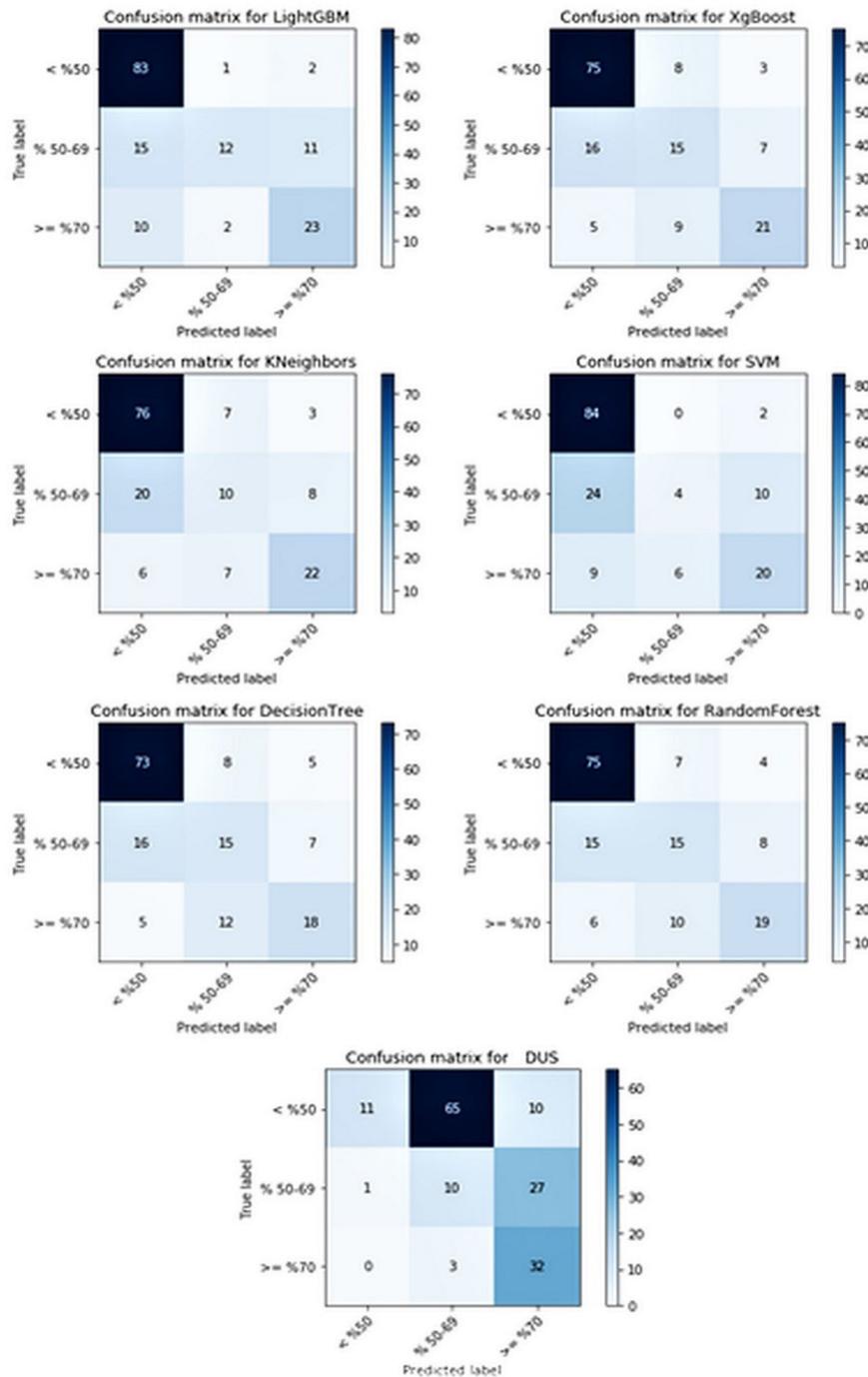


Figure 6. Confusion matrices of classifier algorithms; LightGBM, XgBoost, KNeighbors, Support Vector Machine (SVM), Decision Tree, and Random Forest, using internal carotid artery peak systolic velocity (ICA PSV)/common carotid artery peak systolic velocity (CCA PSV) ratio as the input

despite machine learning algorithms failed to successfully predict stenosis in our study, this could be simply due to lack of sufficient data. Future studies with wider datasets to train machine learning algorithms may produce more satisfactory results, that might even replace DUS criteria in this stenosis range. This could lead to integration of machine learning algorithms in ultrasound systems, which would provide unbiased clinical decisions.

DUS criteria predicted $\geq 70\%$ stenosis more successfully than all machine learning algorithms. Current guidelines recommend surgical or minimally invasive interventions such as carotid artery stenting, depending on the symptom status of patients with stenosis levels higher than 60%-70% [21, 22]. Therefore, we conclude that, as current DUS criteria are dependable for the detection of stenosis rates higher than $\geq 70\%$, with optimized and standardized equipment and

technique, this modality could be recommended as single preoperative diagnostic tool prior to intervention. Such diagnostic algorithm would prevent patients receiving unnecessary ionizing radiation and contrast media, as well as risks related to angiography procedure, shorten the diagnosis interval and hospitalization duration.

This study has several limitations. First, data utilized is retrospective. Second, study population is limited which might cause lower performance of classifier algorithms due to inadequate training. Our future perspective includes utilizing a multi-central big data analysis which would allow more accurate predictions.

In conclusion, DUS criteria can accurately detect ICA stenosis over 70%, when compared to machine learning algorithms, which might lead to utilization of this modality as sole diagnostic tool provided that equipment and technique is optimal. Concordance of DUS criteria with DSA is low for detecting stenosis rates under 70%, however, machine learning algorithms have substantially better performance in predicting DSA stenosis under 50%. Improved DUS criteria or wider training datasets for training machine learning algorithms in order to accurately detect 50-69% stenosis is warranted. Further studies with wider datasets would establish the value of the combined use of DUS criteria and machine learning algorithms in determining extracranial ICA stenosis, using velocity measurements, that might lead to alterations in diagnostic algorithm.

Conflict of interest: No conflict of interest was declared by the authors.

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Ethics committee approval: Prior to the study, the Local Ethics Committee approval was obtained from University of Health Sciences Ankara Diskapi Yildirim Beyazit Training and Research Hospital (date: 12 November 2018, issue number: 56/09). All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Authors' contributions

P.C., I.C. and O.E. conceived the idea. O.E. collected the data. M.A.A. performed the calculations, data analysis and created figures. P.C., M.A.A. and E.C. interpreted and discussed the results. E.C. and H.A.D. provided critical feedback. P.C. wrote the manuscript with input from all authors. All authors discussed the results, reviewed and commented on the manuscript.