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www.bidgeyayinlari.com.tr - bidgeyayinlari@gmail.com
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ÖNSÖZ

Günümüzde kalp damar cerrahisi ile ilgili bilgi birikiminin artması, uygulama alanlarının çeşitliliği ve teknolojik gelişmeler ile kalp damar cerrahisinin içeriği de buna paralel olarak değişmiştir. Farklı cerrahi teknikler kullanılır hale gelmiştir. Buradan yola çıkarak dünyadaki güncel gelişmeler ışığında güncel konular farklı bakış açısı ile ele alınmış bir kitap oluşturulmuş siz değerli okurlarımızın beğenisine sunulmuştur. " DENEYSEL VE UYGULAMALI KALP DAMAR CERRAHİSİ" adlı kitap, kalp damar alanına giriş yapacak okuyucular için kapsamlı bir bilgi sunmaktadır. Bu nedenle kitabın bu alanda gelişecek olan meslektaşlarımıza kaynak olarak faydalı olacağını ummaktayız. Kitabımızda emeği geçen yazarlarımıza teşekkür ediyor, her türlü desteği veren BİDGE YAYINLARI yayınevine şükranlarımızı sunuyoruz.

PROF.DR.AYKUT ELİÇORA

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BÖLÜM 1

MACHINE LEARNING FOR PREDICTING THE RISK FACTOR OF THE CARDIOVASCULAR DISEASE

HARUN SELVİTOPİ[1]
SEDA DEMİR[2]

Introduction

Cardiovascular disease (CVD) constitutes a major global health burden, responsible for nearly one-third of all deaths worldwide, according to the World Health Organization (WHO, 2021). It encompasses a variety of conditions affecting the heart and vasculature, including coronary artery disease, myocardial infarction, heart failure, arrhythmias, and stroke. Despite significant advancements in diagnosis and treatment, the global prevalence of CVD continues to rise, fueled by aging populations, sedentary lifestyles, and the increasing prevalence of modifiable risk factors such as obesity, diabetes, hypertension, and dyslipidemia.

[1] Research Assistant, Erzurum Technical University, Department of Mathematics, Orcid: 0000-0003-0655-9326
[2] Associate Professor, Erzurum Technical University, Department of Mathematics, Orcid: 0000-0001-5958-7625

Historically, cardiovascular risk assessment has relied on traditional statistical models, particularly multivariate logistic regression frameworks. These models—most notably the Framingham Risk Score (D'Agostino et al., 2008, pp: 743-753) and the ACC/AHA ASCVD Risk Estimator—have played a central role in primary prevention strategies. However, such models are typically limited by rigid parametric assumptions, restricted variable interactions, and constrained generalizability to ethnically or demographically diverse populations. They often fail to adequately capture complex, non-linear relationships within large, heterogeneous datasets.

In recent years, the rapid development of machine learning (ML) has opened new frontiers in biomedical research and clinical decision support. ML models excel at pattern recognition in high-dimensional data, enabling the identification of subtle, nonlinear, and multivariate relationships that would be challenging or impossible to uncover using conventional methods. As such, ML has emerged as a promising paradigm for improving cardiovascular risk prediction and early diagnosis, particularly when applied to real-world data from electronic health records (EHRs), imaging repositories, and wearable devices (Krittanawong et al., 2017, pp:2657–2664).

Numerous ML algorithms, including decision trees, random forests, support vector machines (SVM), k-nearest neighbors (KNN), extreme gradient boosting (XGBoost), and deep learning models, have been employed in the context of CVD prediction. These models have demonstrated superior performance over traditional models in various applications—from predicting acute coronary events and heart failure exacerbations to assessing long-term risk in asymptomatic individuals (Ambale-Venkatesh & Lima, 2015, pp: 661–670; Weng et al., 2017, pp: e0174944). In a large-scale study using UK general practice data, (Weng et al., 2017, pp:

e0174944) reported that ML models outperformed conventional risk scores in predicting 10-year cardiovascular events, with better calibration and discriminatory power.

The application of ML in this field is further supported by the availability of curated cardiovascular datasets such as the Framingham Heart Study (Mahmood et al., 2014, pp: 999–1008), which has provided longitudinal data over several decades, and open-access repositories like the UCI Heart Disease dataset (Dua & Graff, 2019). These resources have enabled researchers to test and validate ML approaches under controlled conditions, accelerating innovation and benchmarking model performance.

Nonetheless, the integration of ML into clinical cardiovascular risk prediction is not without its challenges. Among the key concerns are the interpretability and transparency of complex models—especially deep learning networks—often referred to as "black boxes". In a clinical setting, the ability to explain how a model arrives at a particular prediction is critical for trust, accountability, and shared decision-making. Additionally, issues such as data imbalance, bias in training data, overfitting, lack of external validation, and ethical considerations regarding data privacy and equity must be rigorously addressed before ML can be routinely deployed in cardiovascular care.

This chapter aims to provide a comprehensive examination of machine learning applications in the prediction of cardiovascular disease risk factors. It will explore the strengths and limitations of various algorithms, review benchmark datasets and data preprocessing strategies, and discuss recent methodological advancements, including explainable AI (XAI) and federated learning. Furthermore, the chapter will address the translational challenges and clinical implications of integrating ML models into routine cardiovascular risk assessment, with the ultimate goal of enabling more precise, personalized, and proactive care strategies.

Material and Methods

This study utilizes the dataset located at "Heart-Disease-Prediction/dataset.csv". The data was first divided into training and testing subsets. Both sets were then preprocessed and formatted appropriately for model input. To perform classification of cardiovascular diseases, several machine learning models were trained on the training data, including Artificial Neural Networks (ANN), Logistic Regression (LR), Support Vector Machine (SVM), Random Forest (RF), and Decision Tree (DT). The performance of each model was assessed based on its accuracy in classifying instances from the test set.

Collection and Properties of Dataset

The dataset analyzed in this study was sourced from the dataset.csv file available in the GitHub repository at https://ieee-dataport.org/open-access/heart-disease-dataset-comprehensive. It comprises a range of medical attributes, including demographic details, clinical indicators, and results from diagnostic tests for each individual. Each row in the dataset corresponds to a single patient, while the columns represent different features associated with that individual's health profile.

The clinical features encompass patient details such as age, gender, chest pain type, resting blood pressure, fasting blood sugar, maximum heart rate, cholesterol level, resting ECG results, ST segment slope, ST depression (old peak), and exercise-induced angina. The target column indicates whether a patient is diagnosed with heart disease. Additionally, each feature is categorized by its data type, identifying whether it is numerical or categorical.

The dataset's primary objective is to predict the presence or absence of heart disease, which is indicated by the "target" column, where a value of 1 signifies the presence of heart disease and 0 denotes its absence.

The dataset merges five of the most widely used heart-disease sources—among them Long Beach VA, Hungarian, Switzerland, and Statlog (Heart)—into a single corpus containing 1,190 patient records. Each record includes 11 clinical attributes and one target column indicating disease presence. A visual overview of the dataset's features is provided in Figure 1.

Table 1: Definition of the features of the dataset.

Number	Feature	Feature Definitions	Type of Feature
1	Age	Age of individuals (in years)	Number
2	Sex	0: Female, 1: Male	Category
3	Chest pain type	Type of pains(1: typical angina, 2: atypical angina, 3: non-anginal, and 4: asymptomatic)	Category
4	Resting bps	Blood pressure in (mm-Hg)	Number
5	Fasting blood sugar	No: 0, Yes: 1	Number
6	Cholesterol	Cholesterol in (mg/dL)	Category
7	ECG resting	Results of ECG (0: normal, 1: ST-T wave abnormality, 2: left ventricular hypertrophy)	Category

8	Max heart rate	Maximum heart rate of patient	Number
9	Exercise angina	Yes: 1, no: 0 (angina due to exercise)	Category
10	Oldpeak	Level of peak exercise	Number
11	ST slope	Level of peak exercise ST segment (1: upsloping, 2: flat, 3: down sloping)	Category
12	Target	Status of cardiac disease	Category

Data Pre-processing

Data preprocessing plays a vital role in the effective implementation of machine learning models. This phase involves converting raw data into a format that facilitates accurate and efficient modeling by applying various preparatory techniques. Raw datasets often present challenges such as missing values, unbalanced class distributions, inconsistent feature scales, and irrelevant attributes. Thus, the main goal of preprocessing is to enhance data quality, which subsequently boosts model performance and its ability to generalize.

In this study, multiple preprocessing methods were employed to enhance the performance of various machine learning algorithms. Feature scaling was performed using the Standard Scaler technique, and key attributes were identified using the Fast Correlation-Based Filter (FCBF) method. These steps resulted in improved model outcomes when compared to similar studies that utilized the same dataset. The findings underline the importance of choosing preprocessing strategies that align well with the characteristics of the dataset to achieve optimal model accuracy and efficiency.

Standard Scaler

Variations in feature scales can adversely affect the performance of machine learning models. To mitigate this problem, the Standard Scaler technique was employed. This method standardizes each feature by centering it around a mean of zero and scaling it to have a standard deviation of one. Such normalization is particularly beneficial for algorithms that are sensitive to distances, as it aligns all features to a uniform scale and prevents any single feature from disproportionately influencing the model. Consequently, this results in a more balanced training process, improved prediction accuracy, and faster training times. Additionally, using Standard Scaler contributes to better model convergence and increased overall stability.

Data Preparation for Model Training

In this study, the datasets underwent preprocessing and normalization to enhance their consistency and reliability. After these procedures, the data was randomly divided, with 80% designated for training and the remaining 20% reserved for testing.

Classifier Models

Decision Tree (DT)

The decision tree is a supervised learning algorithm commonly applied to both classification and regression problems. It functions by breaking down a dataset into smaller parts through a sequence of decisions based on feature values, resulting in a tree-like structure. In this structure, internal nodes represent feature-based conditions, branches indicate the outcomes of those conditions, and leaves provide the final prediction—either a class label or a numerical value. The main objective is to build a model that accurately predicts the target variable by identifying a series of straightforward, data-driven decision rules.

One of the major advantages of decision trees is their clarity and ease of interpretation, which makes them highly suitable for applications where transparency is essential—such as in medicine, finance, and policy-making. The tree is built using splitting criteria like Gini impurity, information gain, or mean squared error, depending on whether the task involves classification or regression. This process continues recursively until the model satisfies predefined conditions, such as reaching a maximum tree depth or a minimum number of samples in a node.

Despite their simplicity, decision trees are prone to overfitting, particularly when they become overly complex and start modeling noise in the training data. To reduce this risk, practitioners use pre-pruning (e.g., setting depth limits) or post-pruning (e.g., trimming unimportant branches after training). Furthermore, decision trees form the core of more advanced ensemble learning techniques like Random Forests and Gradient Boosting, which combine multiple trees to increase model accuracy and robustness. Overall, decision trees remain a versatile and interpretable method in the field of machine learning.

Support Vector Machine (SVM)

Support Vector Machines (SVM) are a class of supervised learning algorithms that are highly effective for both classification and regression problems, with a notable advantage in solving binary classification tasks. The central principle of SVM is to identify a decision boundary—called a hyperplane—that best separates the data into distinct classes. What sets SVM apart is its goal of maximizing the margin, which is the distance between the hyperplane and the closest data points from each class, known as support vectors. These support vectors are essential, as they directly influence the position and orientation of the optimal hyperplane.

SVM is particularly well-suited for high-dimensional datasets, where it often outperforms other algorithms. It is frequently used in domains like text mining, bioinformatics, and image processing. When data points are not linearly separable, SVM uses a powerful method called the kernel trick, which implicitly maps the input data into a higher-dimensional feature space. Common kernel functions include linear, polynomial, and radial basis function (RBF) kernels. This allows SVM to construct complex decision boundaries in the original input space without explicitly performing costly transformations.

However, SVMs also have some limitations. They can be computationally demanding, especially on large datasets, and their performance heavily depends on the appropriate selection of kernel types and hyperparameters like C (which controls the trade-off between maximizing the margin and minimizing classification error) and gamma (which defines the influence of a single training example). These parameters often require fine-tuning through cross-validation. Despite these challenges, SVMs are widely used in various applications, including spam filtering, fraud detection, disease classification, and character recognition, due to their high accuracy, strong theoretical foundation, and ability to handle both linear and non-linear relationships.

Random Forest (RF)

Random Forest is a robust and widely used ensemble learning method suitable for both classification and regression tasks. It extends the idea of decision trees by constructing a large number of individual trees, collectively known as a "forest," where each tree is trained on a randomly selected subset of the data through a technique called bootstrapping. Furthermore, at each split within a tree, only a random subset of features is considered, introducing additional randomness that helps to minimize correlation between the trees. This strategy enhances the model’s accuracy and robustness compared to relying on a single decision tree.

In classification problems, the Random Forest predicts the class by aggregating the votes from all trees and choosing the majority class, while in regression, it calculates the average of all tree predictions to determine the output. This ensemble approach reduces the risk of overfitting, which is common in individual decision trees, leading to improved generalization on new, unseen data. Random Forest is particularly effective with large, complex datasets featuring many variables, and it can gracefully handle missing values and imbalanced classes.

Besides its strong predictive capabilities, Random Forest offers valuable measures of feature importance, helping users identify which factors most significantly affect the model's predictions. This transparency is especially beneficial in domains such as healthcare, finance, environmental science, and bioinformatics, where understanding the reasons behind a prediction is important. Although training a Random Forest can be computationally demanding for very large datasets or when many trees are involved, its ability to be parallelized and scaled makes it practical for a broad range of applications. Overall, Random Forest is praised for its blend of high accuracy, resilience to overfitting, and interpretability, making it a versatile tool in the machine learning landscape.

Logistic Regression (LR)

Logistic regression is a widely adopted technique in statistics and machine learning used primarily for classification tasks, especially when the outcome variable is binary—meaning it has two possible categories such as yes/no, success/failure, or presence/absence of a condition. Unlike linear regression, which forecasts continuous values, logistic regression estimates the probability that a given input belongs to a certain class by applying the logistic (sigmoid) function to a weighted sum of the input features. This function converts any real number into a value between 0 and 1, representing the likelihood of class membership. Based on this probability, the model typically assigns the input to one of the two classes using a cutoff point, commonly set at 0.5.

A major benefit of logistic regression is its interpretability. The model provides coefficients that reflect the direction and magnitude of each feature's influence on the probability of the target event, making it easier for users to understand how different variables impact the prediction. This transparency is particularly valuable in fields such as healthcare, economics, and finance. Moreover, logistic regression can be extended to handle multiple classes using strategies like one-vs-rest or multinomial logistic regression.

Although logistic regression is straightforward and computationally efficient, it relies on the assumption that there is a linear relationship between the input variables and the log-odds of the outcome, which can limit its effectiveness on complex, nonlinear problems. Despite this, it remains a strong foundational tool for classification and is often used as a benchmark model. Its applications span various areas including disease diagnosis, customer retention analysis, credit scoring, and other scenarios where understanding the probability of an event and the role of predictor variables is critical.

RESULTS AND DISCUSSIONS

This study explores the application of several machine learning algorithms to a heart disease dataset with the goal of developing an effective predictive model for the early detection of cardiovascular conditions. The performance of each model has been assessed using key evaluation metrics, including accuracy, precision, and recall, all derived from their respective confusion matrices. To gain deeper insight into the classification capabilities of the models and AUC (Area Under the Curve) scores computed. Through this comprehensive evaluation, the study provides a comparative analysis of the effectiveness of different machine learning approaches in identifying cardiovascular disease.

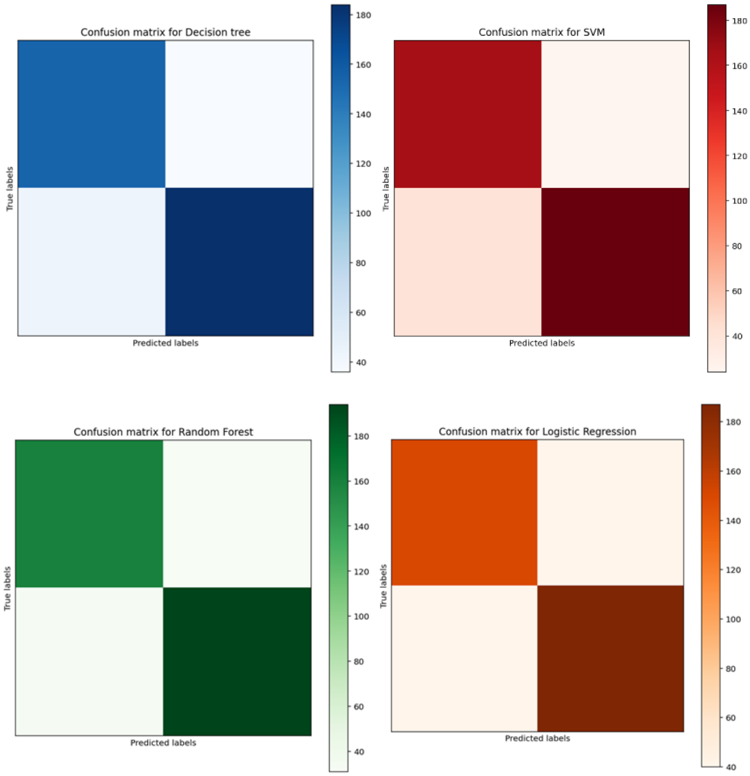

Figure 1: Confusion matrix for the DT, SVM, RF and LR models.

Figure 1. shows the confusion matrix of the DT, SVM, RF and LR machine learning models. The confusion matrix revealed that the model effectively differentiated between the two classes, demonstrated by a substantial number of true positive (TP) and true negative (TN) outcomes. This indicates that the model possesses a well-balanced ability to classify both positive and negative cases accurately.

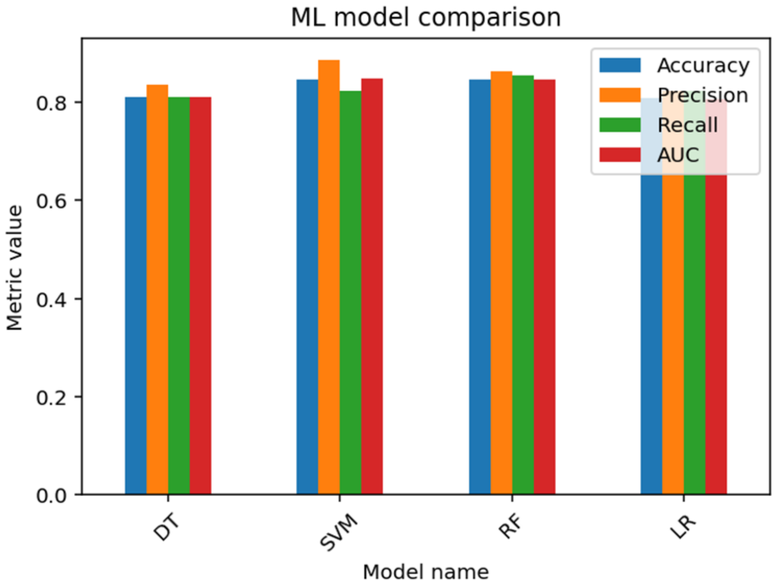

Figure 2: Performance metrics for the Random Forest model.

In Figure 2, the performance metrics of the model have been presented. The SVM and RF models have higher accuracy with 84.65 %. The precision 88.62 %,86.22 %, the recall 82.37 %,85.46 %, and the AUC value 84.87 %,85.57 % respectively.

The DT and LR have 81.05 % and 80.81 % accuracy, respectively. They have the performance metrics precision 83.63 %,82.37 %, the recall 81.05%,82.37% and the AUC value 81.05 %,80.66 % respectively.

Conclusion

In this study, four distinct machine learning algorithms were applied to the selected dataset. Their performance was evaluated using a range of metrics and analyzed through comparative assessment. The results obtained from the proposed approaches were then compared with findings from existing literature, revealing that the models developed in this study achieved superior performance compared to previous research.

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BÖLÜM 2

Arteriovenous Fistulas: Definition, Causes and Treatment Methods

M. Murat YARDIMCI[1]

1. Introduction to Arteriovenous Fistulas:

The arteriovenous fistula (AVF) is an abnormal connection between an artery and a vein. It is usually congenital but can also occur acutely, such as in the setting of trauma and malignancies, or can arise insidiously over a period of time due to degeneration of surrounding tissue. Congenital arteriovenous fistulas are rare and typically present early in life with signs and symptoms such as growth disturbance, continuous murmur, tachycardia, high output cardiac failure, or cardiac murmur. In contrast, acquired arteriovenous fistulas are more common but may be asymptomatic for decades. When symptomatic, they often present with signs and symptoms of heart failure or high output circulatory overload. Physical examination may reveal a continuous murmur, localized warmth, pulsatile mass, or roller-coaster pulse (Khorrami et al.2021).

Arteriovenous fistulas can be detected on Doppler ultrasound (US) as a host artery with abnormally increased blood flow and pulsatility within the contiguous vein. Arteriovenous fistulas can also be detected with Doppler US in the event the patient still had a native kidney to determine the extent or characterization of the fistula. Treatment options for spontaneous renal arteriovenous fistula

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Dr. Öğrt. Üy., Adıyaman Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi A.B.D., Orcid: 0000-0001-7062-6015

include observation, surgical intervention, or endovascular management with transcatheter coil embolization as the first intervention of choice. In comparison with surgery, transcatheter coil embolization is a less invasive, short operative time, and has the least hospital stay. However, transcatheter coil embolization is more constraint in gigantic size and calcified renal artery. (Yun et al.,2022, Putz et al., 2022)

Occasionally, radiologists or interventionists as a preventive or "safety" manner do not obliterate the vein completely, leaving a debris coil in it as "filling above the anatomical but not obliteration". In such case, a "last resort" method that would obliterate the remaining pathologic artery-vein together is superior to those previously mentioned. A large armature of steel locking bullet in fish hook shape serves such purpose (Işık et al, 2018).

Definition of Arteriovenous Fistulas:

An arteriovenous fistula (AVF) is an irregular connection between arteries and veins. Blood flow that would normally travel from arteries to capillaries and later to veins is instead passed directly from arteries to veins. Arteriovenous fistulas can be congenital (present at birth) or acquired. Congenital AVFs are a consequence of some failure in the vascular development process, resulting in an abnormal extra-capillary link between artery and vein (Khorrami et al.,2021). Acquired AVFs are brought on by vascular injury, which can be due to a tumor, trauma, or iatrogenic factors such as invasive procedures (Motie et al, 2022).

Congenital AVFs are relatively rare. They most frequently appear in the renal or pulmonary systems, with the renal variant accounting for the majority of cases. Extremely rare extracranial and nonpulmonary AVFs have been described in pediatric patients, with numbers in the tens of reports. However, additional cases are added

Dr. Öğrt. Üy., Adıyaman Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi A.B.D., Orcid: 0000-0001-7062-6015

to the literature nearly every year, as is the case for congenital and traumatic intrapulmonary AVFs.

Most patients with AVFs remain asymptomatic. Pulmonary and renal AVFs are most commonly discovered incidentally in patients undergoing routine work-ups or imaging evaluations. When symptoms arise, it is often because of the hemodynamic consequences of the fistulas on the surrounding cardiovascular system. Large AVFs can lead to congestive heart failure due to right ventricular strain, or arterial hypertension due to a decrease in renal perfusion. Serious systemic consequences can develop over time if untreated, informing treatment considerations for these patients.(Khorrami et al.,2021)

Anatomy and Physiology:

Arteriovenous fistula (AVF) is an abnormal congenital or acquired communication between an artery and vein. Congenital renal arteriovenous fistula is a rare anomaly of the native renal vessels. AVF is a result of failure along the vascular development process. They can result from vascular injuries due to a tumor, trauma, or iatrogenic processes. Renal AVFs are classified as a simple fistula (shunts that do not involve other renal vascular anomalies) and complex AVFs (those associated with other renal vascular anomalies). Congenital AVFs are more frequently found in males, but they are of equal frequency in both sexes in iatrogenic AVFs (Khorrami et al.,2021). Renal AVF may result in a clinical picture composed of microhematuria and gross hematuria, worsening in short periods of time, hypertension, and failure to thrive. Hypertension and urinary obstruction are typical late complications of untreated renal AVFs.

Percutaneous embolization is the first-line tactic for the management of renal AVFs for pragmatic reasons, an experience of

Dr. Öğrt. Üy., Adıyaman Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi A.B.D., Orcid: 0000-0001-7062-6015

a short learning curve for urologists. The endoluminal approach avoids techniques that have potentially more damaging effects on normal renal parenchyma. In large AVFs (greater than 3 cm), surgery is an option when embolization fails. On the contrary, surgical options are a priority in a viable parenchyma AVF. The routine workup entails a thorough evaluation of the vascular architecture and hemodynamics (Işık et al.,2018).It must focus both on afferent arteries (primary or secondary feeding vessels) and efferent veins (which are either venous drainage or can drain through collaterals). Computed tomography-angiography (CT-A) has now gained wide acceptance for anatomical definition before embarking on eEF embolization. eEF embolization can act through fluid motion-directed or static ethylene vinyl alcohol copolymer solidification and through mechanical occlusion. The used techniques depend on the location of the AVF.

Vascular Anatomy:

Arteriovenous fistulas (AVFs) can result from a congenital vascular malformation. Congenital AVFs, in general, occur during embryonic development and form through vascular injury due to tumor, trauma, vascular malformation, previous surgery, or iatrogenic. Renal AVFs are rare abnormalities and result from acapillary connection between renal artery and vein as a direct consequence of prior trauma, surgical, or spontaneous rupture of renal angiomas (Khorrami et al.,2021). Renal AVFs can arise from renal artery branches within kidney capsule or parenchyma, from renal vein directly or from a dilated cortical vein. Renal AVFs can occur secondary to iatrogenic events such as renal biopsy or alteration in renal blood perfusion. AVFs are commonly asymptomatic and discovered incidentally. Hematuria is the most common symptom of pre-existing renal AVF. Acute gross hematuria occurs in most cases acutely. It can be transmitted to urinary bladder

Dr. Öğrt. Üy., Adıyaman Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi A.B.D., Orcid: 0000-0001-7062-6015

or may cause distal clot formation and obstructive uropathy. (Schramm et al., 2022)

Asymptomatic AVFs can be treated by observation. AVFs associated with hypertension, hemorrhage, and other symptoms can be treated by percutaneous embolization or surgical resection. Embolization procedures are less invasive and can be performed with patient's comfort under local anesthesia. Surgical interventions can be performed by open or laparoscopic approach also with same reasons. Hemorrhagic, hypertensive, or symptomatic AVFs are indicated for treatment. Patients with iatrogenic or non-iopotragina-cause acquisitions are recommended for definitive treatment. Renal AVFs can also be treated by observed, conservative, or other less invasive procedures (Schramm et al., 2022)

Physiological Role of Arteriovenous Fistulas:

Arteriovenous fistulas (AVF) are abnormal connections, either congenital or acquired, that course between a vein and an artery. As congenital lesions, AVF are often asymptomatic and discovered circumstantially via imaging methods. Acquired AVFs usually develop secondary to an insult to the vascular system such as cardiac catheterization, trauma, or surgery. Even in the acquired group, they may have no symptoms for weeks, months, or even years. Direct hemodynamic effects lead to tributary dilatation of the venous drainage at the outflow vein segment. Other direct hemodynamic effects include low outflow pressure augmenting a "steal phenomenon," which can predispose to limb ischemia in distal perfusion branches in the early course of the lesion. A more chronic and prevalent thought is remodeling or indirect changes to the venous system secondary to the arterial flow sharing to a tributary vein and creating venous hypertension (Porter et al., 2014). This can lead to dilation, tortuosity, and eventual wall degradation and

Dr. Öğrt. Üy., Adıyaman Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi A.B.D., Orcid: 0000-0001-7062-6015

truncation of the venous channels. This dilatated and eventually shunted venous system (if complete) acts as a capacitance system and altogether leads to high output cardiac failure.

These lesions can be initially treated conservatively with serial imaging studies. Timely recognition, especially in the acute phase, is essential to minimize the angiographic burden. Recently developed endovascular techniques and devices add a modern touch to the treatment of this pathology. (Işık et al., 2018).

Causes of Arteriovenous Fistulas:

Arteriovenous fistulas (AVFs) may develop due to a variety of congenital and acquired factors. One of the most prevalent etiological factors in their formation is congenital vascular malformations. These anomalies arise from disruptions in normal vascular morphogenesis during embryonic development, resulting in aberrant communications between arteries and veins. In addition, venous insufficiency conditions—such as varicosities—may also contribute to AVF development. This typically occurs due to impaired venous return and increased arterial pressure, both of which create a hemodynamic environment conducive to abnormal vessel connections.(Işık et al., 2018).

Another significant contributing factor is trauma. Fistula formation is particularly observed following major injuries or surgical interventions that compromise both arterial and venous structures. Such cases are especially common in procedures involving areas adjacent to vital organs, where traumatic insults may induce direct arterial-venous communications. Furthermore, iatrogenic causes, including prolonged venous catheterization and hemodialysis, have been implicated in AVF development. In these instances, mechanical damage to the vascular walls or catheter-

Dr. Öğrt. Üy., Adıyaman Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi A.B.D., Orcid: 0000-0001-7062-6015

associated infections may lead to the formation of pathological vascular connections. (Khorrami et al.,2021)

Lastly, systemic diseases may also predispose individuals to AVF formation. Conditions such as diabetes mellitus, hypertension, and atherosclerosis impair vascular integrity by promoting arterial wall stiffness, endothelial dysfunction, and the accumulation of atheromatous plaques. These pathological changes increase the likelihood of abnormal arterio-venous communication. Overall, the etiology of arteriovenous fistulas reflects a complex interplay of genetic predispositions and environmental or iatrogenic factors. A thorough understanding of these mechanisms is essential for accurate diagnosis and effective treatment planning. (Peluso et al., 2025)

Congenital Causes:

Arteriovenous fistulae (AVF) are anomalous communications between an artery and a vein. These malformations are known to increase cardiac output. This leads to a variety of both local and systemic hemodynamic consequences (Teomete et al.,2016). AVF can be either congenital, resulting from aberrant embryologic development, or acquired, secondary to either iatrogenic or noniatrogenic causes.

In the pediatric population, the most common cause of an acquired AVF is single or repeated diagnostic or therapeutic arterial or venous punctures. Iatrogenic AVF's have been reported in all vascular territories but most commonly occur in the upper extremities after multiple arterial punctures for hemodialysis or for catheter parents in the presence of a patent arterial duct. (Ahmed et al.,2021) Other rare causes of upper extremity AVF's in children include trauma, arterial reimplantation for arterial occlusion, and arteriovenous malformations. (White et al.,2025, Filho et al.,2025)

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In general, the clinical presentation of upper extremity pediatric AVF may be either symptomatic or asymptomatic; the former occurring more frequently in younger children. Congenital AVF's are extremely rare. Instead, most are discovered in older children, typically in the context of a workup for either an incidental or symptomatic mass (overdistended venous/pulsatile arterial system) (Khorrami et al.,2021). On the other hand, acquired AVF's are discovered circumstantially during a workup for heart failure. They may also be incidentally discovered on an ultrasound or echocardiogram performed for another indication.

Acquired Causes:

Acquired arteriovenous fistulas typically arise as complications of trauma, surgical interventions, or the progression of certain systemic diseases. These fistulas are often associated with hemodynamic alterations resulting from either acute or chronic pathological conditions. For instance, arteriovenous fistulas secondary to traumatic injuries occur due to the direct connection between damaged arteries and veins. Such cases are particularly prevalent in high-energy traumas, including comminuted fractures or motor vehicle accidents (Youn et al.,2020).

In addition to trauma, surgical procedures play a significant role in the development of acquired arteriovenous fistulas. Invasive interventions, particularly in vascular surgery, can lead to inadvertent fistula formation due to improper vessel manipulation or suturing errors. Moreover, surgeries performed in the context of malignant tumors may damage adjacent vascular structures, creating a predisposition to fistula formation. In this regard, adjuvant therapies used in cancer treatment, such as chemotherapy or radiotherapy, may induce long-term changes in vascular architecture

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and thereby increase the risk of arteriovenous fistula development (Khorrami et al.,2021).

Chronic diseases represent another important factor contributing to acquired fistulas. Hemodialysis procedures, commonly required in patients with end-stage renal disease, involve the creation of a vascular access route through the connection of arteries and veins, often using biocompatible grafts. While essential for treatment, these connections may increase the likelihood of fistula formation, particularly in cases involving improper technique or catheter-related infections. In summary, although acquired causes of arteriovenous fistulas are diverse, careful evaluation of these contributing factors is essential for the development of effective treatment and management strategies (Ki et al.,2015).

Traumatic Causes:

Traumatic origin splits into incidental injury and iatrogenic injury. Incidental injury is division of arterial and venous system due to blunt injury or penetrating injury. Blunt injury could be caused by fracture or malunion or dislocation. Contusion or crush injury could damage vascular system. Penetrating injury is most common cause of traumatic arteriovenous fistula which is caused by missile injury, stab or cut injury. Iatrogenic injury is complication due to surgery of arteries and veins. Iatrogenic injury includes hair transplantation, craniotomy, and temporo-mandibular joint arthroscopy. Most common iatrogenic arteriovenous fistula is hair transplantation. This occurs due to cut or damage of an artery or a vein or both (Takahashi et al.,2022). Post-traumatic arteriovenous fistula (AVF) is a common complication of vascular trauma, especially due to incidental injuries. The formation of a post-traumatic AVF may not only allow a bypass for collateral circulation, but may also lead to limb symptoms such as swelling, pain, and nocturnal cramping. Even

Dr. Öğrt. Üy., Adıyaman Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi A.B.D., Orcid: 0000-0001-7062-6015

years after the original trauma, progressive overgrowth of collateral vessels could result in painless swelling of the limb. Chronic AVF may result in progressive heart failure due to shunting (Takahashi et al.,2022). Recent developments in high-resolution imaging techniques and an increased awareness of the possible atypical location of traumatic AVF have resulted in an increased number of reported cases. Traumatic AVF of the extremities is usually treated by endovascular techniques if there is no venous varix or inconspicuous venous drainage, or by an open surgical approach if the abnormal vessel is prominent. Endovenous techniques are preferred for older, inaccessible AVF having a venous varix. The 3D contribution of images is very useful for pre- and post-operative evaluation of AVF, and also for planning of the surgical approach. (Asensio et al,2022, Kim et al.,2020)

Clinical Presentation:

Clinical presentation may vary depending on the site and size of the fistula and whether it is high or low flow. Patients presenting with AV fistula in peripheral arteries may be asymptomatic or may have pain, swelling, warmth, or tenderness due to venous hypertension, peripheral edema, skin changes, or ulceration. In surgical patients, the diagnosis usually is made within a few weeks following the procedure if there is an immediate or delayed access-site hematoma, infection. Since ascending venous pressure eventually equalizes with arterial pressure, symptoms of venous hypertension may take years to develop (Işık et al., 2018).

The most important vascular related symptom of AVF is pulse amplification. Palpation of a fistula will reveal a thrill, and auscultation will reveal a bruit. Imaging techniques such as Doppler USG, CT or MR angiography, and catheter angiography are helpful in localizing and characterizing the fistula, and they can be

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performed by an interventional radiologist. If the arteriovenous communication involves one of the two large veins, electrocardiographic changes may be detected due to structural deformation and arrhythmias. The size of the shunt itself is difficult to assess echocardiographically but is important for proper treatment. For outflow lesions, by calculating the increase in Qp/Qs ratio of the pulmonary flow into the proximal and selected more peripheral veins, the effective size of the shunt may be estimated (Porter et al.,2014).

Symptoms:

Body system symptoms usually include dyspnoea due to hypertrophy of the left ventricle, lethargy, and leg swelling due to venous hypertension. In constraining situations, always make sure to investigate those systemic symptoms and consider the possibility of arteriovenous fistula caused by catheterisation procedures. The radiological characteristics of this complication vary according to time elapsed from the intervention (Işık et al.,2018).

An AVF allows blood to flow directly from the artery into the vein, bypassing the capillary bed. Initially, the affected veins can stay patent, however with time they are compromised when vascular remodelling occurs. Veins enlarge and eventually develop heart failure with exacerbation of peripheral oedema and breathlessness due to volume overload on the heart. Electrolyte, clotting and metabolic imbalances may occur due to the inability of the kidneys to filter blood effectively. After several years, the fistula becomes occluded and the dialysis route fails. The abdomen becomes less blood supply and uremic symptoms develop (Porter et al.,2014).

Signs:

Arteriovenous fistulas can be asymptomatic or symptomatic after a few days to months (Işık et al., 2018). The differential

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diagnosis includes a hematoma or seroma that may compress the vascular structures. Early signs are a palpable thrill, tenderness, and increased warmth of the overlying skin. Pulsations of the vein may be observed from a distance. Auscultation reveals a continuous subjective murmur over the fistula. Deterioration of the muscle condition of the lower leg or ulcers at the sites of trauma are indicative of an aorto-femoral arteriovenous fistula. A mix of symptoms of insufficient perfusion and dilatation of the veins is expected for the inferior caval or for the ileofemoral arteriovenous fistulas. Indistinct pulsation of the inguinal vein indicates that the thrombus is of unusual location. Occasionally, embolic manifestations of the upper limb or cranial nerves may occur with internal jugular, brachiocephalic, or subclavian arteriovenous fistulas. (Wenzl et al., 2022)

Routine imaging of the brain or perfusion studies is usually not needed unless an acute neurological symptom demands, but they may be instructive in some difficult cases of venous or arterial hypotension. The extent of dilatation of the collaterals provides a cue to the duration of the AVF. Dilated serpentine veins can be observed both at the time of the ultrasound and at small-size fistulas. Arteriovenous fistulas may be overlooked. There may also be some indirect radiological signs, such as a compression of the arterial lumen due to the fistula or of the venous lumen due to venous thrombosis. A reduction of the venous outflow and filling of the concurrent veins usually occur at a later stage of development of the AVF in incidental external carotid-common igular vein fistulas. (Wenzl et al.,2022, Evans et al.,2023)

Diagnosis of Arteriovenous Fistulas:

The specific diagnosis should follow a careful medical history and physical examination of the signs "broiloing".

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Vibroacoustic as a result of the flow of blood through the path. Typically there are imaginary sounds in the region of “bruit” and bundling to hear from the blood pool. Not hearing shortage ruling out fistula (Porter et al.,2014).

In fact, ecography is the best examination method to detect arteriovenous fistula. The test is performed by applying a probe to the mouthparts of av-fistula. In flow analysis, the slow tymbal arteries of neck veins and slow or ontic visual color distributions in drills said pathway significantly at fistula point and expenses. Use of analgesia is not indicated, and the significance of patients risk is quite low. After consultation with a physician, figfraction tests by echocardiography by examination group are performed in uncertain cases (Işık et al.,2018).

Physical Examination:

Attention will be paid to examining the degree of shunting between arteries and veins, calculating the q shunt Q and determining whether it is significant (where q shunt Q > 5–10%, equal to 50–100 ml/min, as a guide after careful pre-evaluation with Doppler ultrasound), and identifying the fistula artery and vein above and below the distal shunting point. In addition to high output cardiac failure, systemic symptoms from other causes of haemodynamically significant lesions can include shortness of breath, lethargy, and swelling of both legs (Porter et al.,2014). While examination of the lower limbs can yield clues such as discoloration or ischaemia, colour Doppler ultrasound is crucial for measuring shunt size and locating a single high flow fistula point that is suitable for percutaneous treatment. Invasive approaches such as CT angiography, MRA, and conventional large catheter angiography are cumbersome and dangerous for the patient, particularly if the angiography needles are damaged, continue to hinder limb

Dr. Öğrt. Üy., Adıyaman Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi A.B.D, Orcid: 0000-0001-7062-6015

perfusion, or cause arteriovenous fistula. (Miller et al.,2021, Zilinyi et al.,2021)

A diagnosis of iatrogenic AVF can be confirmed and its volume and drainage vein assessed via delayed capillary imaging. Simultaneous angiography of the involved arteries and veins is standard, and small catastrophic AVFs are less likely to occur with radial or ulnar puncture. Such cases can be gently compressed, but bandages should be avoided, and direct repair is required after standard correction for more serious complications. All AVFs receive a systemic antibiotic for a week as prophylaxis against infection (Işık et al.,2018). For symptomatic patients, percutaneous ultrasound-guided compression is usually sufficient, while symptomless patients can be observed with the option for endovascular repair later on. Asymptomatic patients with compound fistulae benefiting from collateral formation can be conservatively managed.

Imaging Techniques:

Congenital fistulas are rarely encountered and, although they seldom produce symptoms, they are usually treated with surgical intervention. Depending on the pathophysiology, different examination techniques or imaging methods are required to analyze the fistulas. Ultrasound is utilized for superficial lesions while advanced imaging methods such as DSA or MRI are used for deeper located lesions (Işık et al.,2018).

Digital subtraction angiography (DSA) is still considered the gold standard for evaluating vascular diseases. When appropriate contrast and imaging protocols are used, DSA is reliable for identifying anatomical problems. However, pediatric patients and patients with renal insufficiency suffer from arterial puncture, radiation, and risk of nephrotoxic contrast material. The infrared

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laser light used in indocyanine green (ICG) angiography is reflected from the blood and the surrounding structures exhibit minimal hue change. With a unique imaging feature revealing only the vascular tree, ICG-DSA provides a reliable alternative in patients with vascular diseases compared to DSA. In comparison to standard DSA, ICG-DSA exhibits lower radiation and contrast, providing imaging with a low cost.

The proximal and distal arterial and venous supplies of the fistula may be mapped. Vessels supplying the fistula may be added to the map as they switch from arterial to venous. However, in chronic stages, it is often difficult to differentiate arterial versus venous and the map may necessitate alteration. The map is likely to vary across patients, however it must include the malformation prior to any vascular manipulation or surgical treatment. Each branch should be formally evaluated using DSA to comprehend and document fully the anatomy prior to any proposed intervention. Importantly, the map may thus differ fundamentally pre and post any intervention. Given the complexity of anatomy and difficulty in assessing lesions or branches of solid or soft organs, advanced modalities such as automated DSA or automated multiphasic CTA may be warranted. (Işık et al.,2018).

Laboratory Tests:

Patients with an arteriovenous fistula typically present with symptoms related to the high-output failure caused by the shunt. Systemic symptoms include lethargy, dyspnoea, and leg swelling. Physical examination typically shows signs of high-output cardiac failure. The skin overlying the fistula may have diplacement of prominent veins, cyanosis, or ulceration. A very loud, continuous, “machinery-like” bruit and thrill are usually present, best heard over

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the fistula. Bruits and thrills on the heart and large vessels are also common (Işık et al.,2018).

Hyperdynamic circulation with decreased peripheral vascular resistance, increased stroke volume, and large cardiac chamber dilation is usually present on echocardiography. Severe pulmonary hypertension and right-sided heart failure may be present in long-standing cases. Left ventricle hypertrophy can also develop. An enlarged heart and increased vascularity in the lungs or pulmonary vein dilation may be present on chest X-ray. Cardiomegaly and advanced heart failure with hemoptysis, pleural effusion, or pulmonary hypertension–related pulmonary congestion or infection may also be detected. (Shafi et al.,2022)

Although angiography is essential in the preoperative assessment of an AVF, each case of suspected AVF should first be evaluated using Doppler ultrasound. Arteriography has an essential role in the assessment of vascular patency, but its invasiveness limits the number of studies that can be performed. Doppler ultrasound should be performed as a primary investigation in all patients presenting with clinical symptoms of an AVF. The advantage of Doppler ultrasound is that it can be performed without the complications of ionizing radiation and requires only minimal patient preparation. Following an AVF diagnosis by ultrasound, arteriography can then be targeted to the anatomical region of interest. (Pinto et al.,2024, Meola et al,.2021).

Treatment Methods:

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The treatment of arteriovenous fistulas depends on their cause, size and location, and on the presence of symptoms. Small arteriovenous fistulas that develop after invasive procedures will generally close spontaneously. Diuretics and nonsteroidal antiinflammatory drugs may help symptomatic arteriovenous fistulas or those that are expanding in size. Surgical exclusion of an arteriovenous fistula is indicated when the lesion is large enough to cause significant symptoms, when the patient is symptomatic on conservative medical management, or when conventional medical therapy has failed (Işık et al.,2018).

Endovascular techniques have been advocated for the treatment of peripheral artery and arteriovenous fistulas. In the fistula an AVF stent is deployed with an uncovered part to allow blood flow in the artery near the fistula. This technique is especially useful for the elderly and those for whom surgical treatment is not desirable. The expectation of complete occlusion of a small arteriovenous fistula or AVF is 92%, and surgical exploration may be needed if closure fails. The fistula can be approached through a vein or an artery. Coagulation is made with bipolar forceps or a surgical clip. Complete dissection of the vessel is not necessary but fibrous tissue in the vicinity should be removed adequately to facilitate visualization in the manipulation of vascular structures in the later steps. Otherwise, difficulty in identifying the components of the fistula or inadequate vessel exposure may lead to significant complications of the procedure. (Evans et al.,2023)

The fistula is divided and the patency of the vessels is checked. A small week postoperatively, the vessels may be compressed and an angiography is done to check for any residual. Excision of the fistula tract is usually performed under general or regional anesthesia. There are several disadvantages to this approach, such as deep venous injury, deep venous thrombosis,

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arterial nerve or retention injury, overzealous dissection sacrificing tissue length and poor cosmetic results from large scars, the need for general anesthesia, hospital admission, and a protracted recovery time. These disadvantages lead to consider an alternative approach via a percutaneous route. Transfemoral catheterization or crural access in a retrograde manner is more widely employed and less invasive than traditional percutaneous techniques. (Goyal et al.,2022)

Conservative Management:

The failure of the vascular development process may reflect in arteriovenous fistula (AVF) or malformation (AVM). There is no obstruction of the blood flow in these conditions; however, they alter the arterial mechanical stress and can aggravate the renal parenchyma (Khorrami et al.,2021)

The etiology of AVF is categorized into three groups; they are congenital, acquired and idiopathic forms. The congenital form is mostly seen in women. Acquired AVF results from penetrating trauma, tumor or iatrogenic procedures. In a small number of patients, after imaging studies it may be impossible to find a significant cause, so it is called idiopathic.

To diagnosis AVF, several modalities are used; they are renal Doppler ultrasound, CT angiography, magnetic resonance angiography and digital subtraction angiography (DSA). DSA is the gold standard assessment; however, ultrasound is the initial step. When the US exam is used, a simple parenchymal mass lesion with a vascular portion is the characteristic finding. Management of AVF is mostly surgical and includes several approaches. The goal of management is to save kidney function and removing AVF from blood circulation to eradicate symptoms simultaneously. AVFs found

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incidentally without any symptoms are managed conservatively. AVFs, if symptomatic are treated. (Meola et al,.2021)

Surgical Interventions:

Surgery is reserved for symptomatic or progressive arteriovenous fistulas associated with frequent bleeding or ischemia. Surgical options include open surgical interruption and ligation. Traditionally, to address the affected arteries, resection of the involved arterial segment was performed, which required reconstruction and anastomosis of the carotid artery or aorta after resection; thus, lengthy early mortality resulted from cerebral ischemic risk. Other surgical procedures, performed for fistulae with one of the arterial feedings well visualized without requiring carotid arteriography, include cut-down or endarterectomy combined with bilateral cervical carotid comminution for wide exposure. Since past intraoperative or postoperative embolization of one of the arterial supplies of diffuse hemangioma resulted in aggravation and wide spread of the disease, the procedure was performed carefully, leaving a collateral supply route. Off-pump surgical repair in combination with intra-arterial embolization treat complex a power fistula based on a major arterial supply, resulting in main arterial ligation (Işık et al.,2018). Open surgical resection and primary repair or resection followed by reconstruction in the patient’s own femoral artery and vein, or interposition with other venous graft or synthetic materials represents the gold standard in treating an AVF, especially when these procedures are performed by highly experienced vascular surgeons. In this patient, however, because the size of old arteriovenous fistula was about 5 x 6 mm with maximum 9 mm in diameter and fed by a psoas muscle pedicle less than 15 mm in diameter, resection and reanastomosis of portions of the common

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femoral artery and vein procedure alone was unlikely to be drastically curative. Thus the alternative strategy of controlling the fistula center using reconstruction of the outflow vein without resection was selected and adopted. (Edgar et al.,2025, Evans et al., 2023)

Endovascular Techniques:

Preface: Endovenous laser ablation and other endovenous techniques, such as radio-frequency ablation, mechanical ablation, and sclerotherapy, have been used for many years to remove veins from AVF. The use of endovascular techniques to treat niche deep-seated HTN-SH (hypertensive saccular hemorrhoid) is new and very exciting. An endovenous laser can easily be introduced into the fiber through the blood transfusion route of the AVF, even when it is deep-seated. Evaporization heat of 100 °C or greater destroys vein vascularity. Since this method does not affect the surrounding normal tissue and is highly selective, it is expected that in the future, high tissue-sparing techniques may be performed on various vascular malformations (Kim et al., 2020).

Endovascular techniques: All cases were performed with sufficient fasting hours and adequate bowel preparation to avoid misdiagnosis and complications due to bowel gas. Sedation was administered for all patients and no severe complication was noted. Typically, a 20G portcephalus needle was punctured into the left jugular vein to bring a 0.035-inch guide wire into a dump. This severe puncture can be avoided if the puncture site is appropriately planned before the procedure. Therefore, there must be a reference from CT. Even if 500-1000ml of the test dose low-osmolar contrast was injected to confirm the position of the guiding wire and portcephalus needle in the dump, the aorta still could not be

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visualized in 3 cases. The moment of the omentum mass filled with densely adhered portcephalus was under trumpet-shaped radiographically. Therefore, clumsy and aggressive guide wire manipulation could not be performed to easily introduce the 10Fr sheath, tube catheter, and 3D guide to release retained fluid. (Kim et al.,2020).

The tip of the pre-shaped 3D guide composes a wide point curve, avoiding stiff straight ends that may accidentally perforate the inferior vena cava and surrounding organ tissues. Since the tip fulfills a remain in the dump, it can be easily manipulated with less resistance. Thanks to this, initial round-shaped piggy-back is possible, then it is gradually elongating with continually injecting air to correct the curve into sharp-yet-long-point conic shapes. A newly designed pipe-shaped balloon to avoid friction is inserted at the tip of the passive adjusting guide. Despite its longer length, it is much easier to introduce with manipulating air pressure than steel mousse poles. The balloon is inflated to reverse-out the guide. The need for a wide balloon size is expected. Initial re-formation sometimes is not enough to compress the conic barrel, then balloon inflation potentially can reshape it. Evaluation follow-up by angio-CT after primary treatment has been established as a standard protocol to assess treated malformations in this institution. Only in 1 of 13 patients, mild self-limited hematoma was formed at the AXD puncture site, which spontaneously disappeared. (Peluso et al., 2025).

Complications Associated with Arteriovenous Fistulas:

Complications of arteriovenous fistulas (AVF) are secondary to volume overload, which can lead to heart failure, low-flow ischemia, peripheral vascular disease, and venous hypertension. AVFs that develop following cardiac intervention can be treated

Dr. Öğrt. Üy., Adıyaman Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi A.B.D., Orcid: 0000-0001-7062-6015

percutaneously using current methods similar to pseudoaneurysms. In addition to patients with a high-risk increase in AVF, non-invasive imaging techniques can be used when necessary. (Işık et al.,2018). Renal AVFs are rare and usually diagnosed accidentally through imaging studies for other reasons. As most renal AVFs are asymptomatic, they remain undiagnosed. Unfortunately, they may become symptomatic weeks, months or years later due to hemorrhage from angiomyolipoma (AML), hypertension or urinary obstruction. Management of symptomatic renal AVFs is removing the lesion from the blood circulation either surgically or through percutaneous embolization. (Khorrami et al.,2021)

Infection:

Subclavian and femoral arteriovenous fistulas (fistulae) frequently occur following the complication of vascular access for central venous catheterisation or coronary angiography. For younger patients and patients with good functional status, both surgical and endovascular options are available for treatment. However extensive open surgical options, redo intervention to the treat adjacent arteries or vein may be necessary for elderly patients with additional cardiac comorbidities leading to a challenging disease course (Işık et al., 2018).

The arteriovenous fistula (AVF) is the most effective vascular access and is superior to other types of access in terms of infection risk. The average time of patency was 3.35 years, and infection was the main cause of access loss in the present study. A higher access loss rate within the first cramp was noticed in transposed AVF. The Cox regression showed that there was no difference between basin and elbow vein grafts ($p > 0.05$) (Aoki et al.,2023). The transfusion of red blood cells after surgery, the experience of the surgeon, a

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higher frequency of dialysis, and an access used for > 3 years played important roles in AVF infection (Mohamed et al.,2019).

Bloodstream infections remained an intractable challenge to dialysis patients undergoing AVF access worldwide. Despite considerable improvements in vessel-sparing angioplasty, development of extensive endovenous ablation treatments, and favoring of graft access used in pediatric patients, access safety management with respect to early patency and freedom from infection episodes remained an unsolved issue. In the high-prevalence area of open AVF surgery, patient cases exposed to the risk of acquiring arteriovenous graft infections should be classified into low-risk and high-risk cohorts in clinical practice. The key therapeutic goal for the former was routine examination and clinical knowledge communication, while comprehensive invasive exams and treatments should be prioritized for the latter. An in-depth understanding of risk factors related to infection was crucial for potential improvement of clinical practice. Specific advice for infection in patients undergoing acute or chronic hemodialysis (HD) is detailed in the relevant guidelines (Cimino et al.,2021).

Thrombosis:

Arteriovenous fistulas used for hemodialysis offer the lowest rates of complications and the longest patency; nevertheless, they can suffer complications that lead to loss of function. Thrombosis is the most common complication affecting vascular access. Biomechanical mechanisms for thrombus formation include dissection, kinking, or external compression of the AVF leading to slowing of flow causing thrombus formation. Once thrombosis has occurred, it must be diagnosed within 6 weeks after its occurrence, or the chances of reestablishing patency decrease exponentially. Early presentation favors redo surgical intervention, while late

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presentation responds better to endoluminal thrombolytic therapy. Accurate classification of thrombosis according to the biomechanical mechanism is essential along with the evaluation of the responsible outlet vein stenosis that must be treated at the same sitting to ensure patency (Morshed et al.,2020)

Heart Failure:

Arteriovenous fistulae (AVF) are most commonly encountered in the setting of renal insufficiency, as accessing the systemic arterial circulation is essential to aspire the blood in order to facilitate dialysis therapy. Arteriovenous access via a graft or fistula is intentionally created in patients with end stage renal disease as a high-flow conduit to facilitate hemodialysis. AVF are also known to be congenital in origin. In addition to intentional creation, AVF can be acquired after penetrating trauma, as a result of endovascular repair of a pseudoaneurysm or penetrating vascular injury, aneurysmal rupture, and even less commonly, as a complication of diagnostic or therapeutic angiographic procedures such as cardiac catheterization (Kasliwal et al.,2022). An AVF, being a low-resistance systemic arterial to venous conduit, results in bypassing of the systemic vascular resistance. Over time, the decrease in systemic vascular resistance results in secondary increases in cardiac output, which may, in turn, result in symptomatic heart failure in susceptible patients. There is no described incidence of congestive heart failure resultant from iatrogenic AVF. (Huber et al.,2021)

Most peripheral AVF are iatrogenically created for hemodialysis access in the setting of chronic kidney disease (Ninama et al.,2022). Untreated peripheral AVF can lead to edema, pain, impairment of limb function, and high output cardiac failure. If clinically suspected, pulse volume recording and Doppler

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assessment can grossly delineate the problem (insufficient/stenotic accesses/veins). Meanwhile, echocardiography can assess cardiac function and allay concerns for any structural heart disease. The persistence of an AVF eventually leads to dilation and weakening of the vessel wall, ultimately leading to high output heart failure, a situation that any cardiologist would wish to prevent in a patient with otherwise normal left ventricular function and no risk factors for the condition. Although lower limb AVFs are described in the literature, they are exceedingly rare, and extreme caution is exercised when accessing lower limbs for vascular intervention. To the best of the authors' knowledge, an idiopathic AVF in a young patient resulting in high output heart failure has not been described in the literature.(Ninama et al.,2022).

Long-term Management and Follow-up:

Patients with newly diagnosed traumatic AVF should receive close follow-up over a minimum period of at least 3 months post-injury. This follow-up program should then be combined with a 3-6 month 'cancer surveillance' approach. Since emerging, the possible clinical sequelae after AVF formation from injury have been increasingly recognized and reported in the literature (Khorrami et al.,2021). The exact pathophysiologic mechanisms leading to these long-term sequelae have not yet been fully elucidated. Those sequelae include, but are not limited to, massive hemoptysis (usually associated with pulmonary AVF or more peripheral AVMs), rectal/lumbar bleeding (usually associated with intestinal or lumbar AVF), hematuria (usually associated with renal AVF), and CCF (usually associated with AVF involving central vessels or larger caliber veins) (Porter et al.,2014). The latency period of these variable sequelae can be as short as several months to a life-long period after trauma in some patients. Their incidence is likely underestimated, particularly in the adult population. Furthermore,

Dr. Öğrt. Üy., Adıyaman Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi A.B.D., Orcid: 0000-0001-7062-6015

the presentations of these sequelae are often delayed and nondiscriminative as constituting a separate entity, mimicking benign processes, and thus, making a correct diagnosis as a cause an impossibly difficult and time-consuming task. (Burris et al.,2023)

Post-injury AVF, like AVM, should be taken very seriously as a possible cause of a wide range of clinical sequelae. In patients with blunt trauma at risk for AVF or more generalized AVM formation, appropriate follow-up protocols, including screening for the possible presence of an AVF (usually with Doppler), should be established to improve the opportunity for discovering those lesions before significant clinical events, and ultimately improving patient management practices. Further research into the early and long-term clinical sequelae of AVF formation from both injury and von Recklinghausen's neurofibromatosis is warranted. (Malik et al., 2021)

Monitoring for Complications:

There is a risk of AVF formation (iatrogenic or congenital) after any surgical procedure that aims to achieve direct access to the blood vessels. Most post-trauma AVFs are acquired, with the vascular injury caused by blunt trauma following gunshot or stab wounds being the most common causes. Vascular repair and resection are beneficial in 90%–95% of cases. There may be a rare chance of spontaneous closure depending on the patients' gender, age, time elapsed after injury, and prior surgery. Congenital AVF should also be considered in the differential diagnosis of patients with gross hematuria if the case of AVF formation is occurring in a child with no previous surgery or trauma (Khorrami et al.,2021).

Acquired types should be more valued in adult patients due to the likelihood of neoplasm or previous surgical procedures causing injury to the vascular wall. Following renal injury, AVF

Dr. Öğrt. Üy., Adıyaman Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi A.B.D., Orcid: 0000-0001-7062-6015

usually arises between renal arteries and veins. Renin produced by juxtaglomerular cells activates the renin-angiotensin-aldosterone (RAA) system, increasing systemic and renal vascular resistance and stimulating erythropoietin (EPO) synthesis, resulting in renal artery stenosis or hypertension. Renal AVF generally causes tense blood vessels in imaging studies, venous varicosities, tortuous and enlarged renal veins in perinephric or renal region, dilated ingesting veins mainly into inferior vena cava, and underdeveloped contralateral renal artery (Ozyüksel & Doğan, 2013). Resection plus renorrhaphy can be curative if preoperatively located with care.

Conclusion:

Arteriovenous fistula (AVF), which is an abnormal direct communication between superficial veins and arterial branches, may cause significant morbidity. They are mostly diagnosed in the absence of a previous history of AVF, particularly during diagnostic angiographic procedures (Khorrami et al.,2021). Most patients are asymptomatic. Treatment is rarely advised unless there are complications. Although various techniques have been described for treating AVF, none of them has yet been universally accepted (Işık et al.,2018). Complications of untreated AVFs include hypertension, cardiac failure, ischemia of toes or fingers, or venous dilation and tortuosity. In most cases, treatment is rarely suggested, especially for small and asymptomatic AVFs. The majority of patients will convert to conventional management with controls every six months or as the doctor thinks necessary. If intervention is advised, it must be under an individualized assessment of patients as their age, health status, and clinical status. AVFs can be treated percutaneously or surgically. Percutaneous treatments can be either coil embolization or glue injections and are mostly preferred due to their ease of access. Open surgeries can be either arterial ligation or fistula resection. However, with a greater time requirement, surgical treatments may

Dr. Öğrt. Üy., Adıyaman Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi, Kalp Damar Cerrahisi A.B.D., Orcid: 0000-0001-7062-6015

also be more complicated penetrating more surrounding tissue, potentially causing further complications.

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BÖLÜM 3

PERİFERİK ARTER HASTALIĞINDA ASPİRİN VE $P2Y_{12}$ İNHİBİTÖRLERİNE GÜNCEL BAKIŞ

ELİF COŞKUN SUNGUR[1]

Periferik Arter Hastalığı

Periferik Arter Hastalığı tanımı (PAH), aortanın tüm ana segmentleri ve kalbin beslenmesini sağlayan arterler dışındaki tüm arteryel yapılar için kullanılabilen bir tanımlamadır (Aboyans & ark., 2018; Gerhard-Herman & ark., 2017). PAH için risk faktörleri arasında; ileri yaş, diyabet, hiperlipidemi, hipertansiyon, sigara kullanımı ve diğer arteriyel yapılarda da eşlik eden ateroskleroz yer almaktadır (Criqui & ark., 2001). Semptomatik veya asemptomatik PAH'lı hastalarda, risk faktörleri düzenlendiğinde de mortalite ve morbidite riskinin artmış olduğu bilinmektedir (Aboyans & ark., 2018; Criqui & ark., 2001). Bu nedenle PAH, koroner arter hastalığı kadar toplumları tehdit eden küresel bir sağlık sorunudur.

[1]Uzm.Dr., Ankara Bilkent Şehir Hastanesi, Kalp ve Damar Cerrahisi Bölümü, Ankara/Türkiye, ORCID ID: 0000-0002-2275-639X

PAH başlangıç seviyesinde genellikle asemptomatiktir. En yaygın ilk semptom, fiziksel aktiviteyle oluşan ve dinlenmeyle geçen alt ekstremite ağrısının neden olduğu 'aralıklı topallama' (intermittent claudication, IC) olarak adlandırılır (Norgren & ark., 2007). Hastalığın ilerlemesi, istirahat sırasında ağrı veya kritik uzuv iskemisine (critical limb ischaemia, CLI) neden olarak, amputasyona neden olabilir (Norgren & ark., 2007; Kinlay & ark., 2016).

Periferik Arter Hastalığı Tedavisinde Tercih Edilen Antiplatelet Ajanlar

PAH yönetiminin amacı, semptomları hafifleterek hastalığın ilerlemesini durdurmak ve komplikasyonları önlemeye çalışmaktır (Aboyans & ark., 2018). PAH'lı hastalarda kardiyovasküler risk faktörleri düzenlenmesine ek olarak, oluşan aterotromboz yatkınlığı sebebiyle trombosit aktivasyonunun önlenebilmesi için antiplatelet tedavi, temel tedavi yöntemidir (Aboyans & ark., 2018). Bu amaçla kullanılan başlıca ajanlar **aspirin (asetilsalisilik asit)** ve **$P2Y_{12}$ reseptör inhibitörü** ilaçlardır.

Antiplatelet ajan olarak kullanılan ilk ilaç **aspirin,** siklooksijenaz (COX) inhibitörü olarak 1980'lerde kardiyovasküler profilakside kullanılmaya başlanmıştır. Aspirin ile tedavi edilen hastaların yaklaşık %20'sinde, COX enzimindeki epigenetik farklılık nedeniyle, daha az trombosit inhibisyonu gözlenmesi 'aspirin duyarsızlığı' oluşturarak advers kardiyovasküler olay riskinde dört kat artışa neden olmaktadır (Khan & ark., 2022). Trombosit yüzeyindeki $P2Y_{12}$ reseptörü, ADP'yi bağlayarak trombosit glikoprotein IIb/IIIa reseptörünü aktive eder. Bu aktivasyon trombosit degranülasyonunun, tromboksan üretiminin ve trombosit agregasyonunun artmasına neden olur. $P2Y_{12}$ inhibitörlerinin kullanılması, aspirin intoleransı veya duyarsızlığı olan hastalar için iyi bir alternatif olarak ortaya çıkmış ve aspirin ile beraber kullanıldığında yüksek yoğunluklu trombosit inhibisyonu potansiyeli oluşturmuştur. Ancak, daha güçlü antitrombotik etki, daha yüksek kanama komplikasyonları riskini beraberinde getirmiştir. Bu nedenle, günümüzde ideal ilaç kombinasyonu ve tedavi süresini belirlemek için ikili antitrombositer tedavi (Dual Antiplatelet Therapy, **DAPT**) arayışı halen devam etmektedir. Klinik kullanım için geliştirilen ilk $P2Y_{12}$ inhibitörü, bir tiyenopiridin türevi olan **tiklopidin**, güvenlik sorunu nedeniyle yerini ikinci nesil tiyenopiridin **klopidogrel**e bırakmıştır (Quinn, MJ. & Fitzgerald, DJ., 1999). $P2Y_{12}$ inhibitörü klopidogrel, aspirine eklendiğinde kapsamlı bir şekilde araştırılmıştır. Klopidogrel, 1998 yılında Amerika Birleşik Devletleri'nde (ABD) tanıtılan ikinci nesil bir tiyenopiridindir. Klopidogrele cevapsızlığın, uzman konsensüs kılavuzlarına göre prevalansının yaklaşık %30 olduğu tahmin edilmektedir (Aradi & ark., 2014). Klopidogrelin, aktif bir metabolit üretmek için sitokrom (CYP) P450 enzimleri vasıtasıyla hepatik dönüşüme ihtiyacı vardır. Klopidogrele yanıt, bu enzimleri inhibe eden ilaçların uygulanmasıyla değişebilir (Bates, Lau, & Angiolillo, 2011; Savi & ark., 2000). Ek olarak, yaş, ilaç-ilaç etkileşimleri, komorbiditeler ve genetik polimorfizmler (Siller-Matula & ark., 2013) dahil olmak üzere multifaktöryel sebeplerle klopidogrel yanıtında bireyler arası değişkenlik gözlemlenmiştir. Daha sonra üçüncü nesil tiyenopiridin **prasugrel** geliştirilmiştir (Brandt & ark, 2007). Hem klopidogrel hem de prasugrel, aktif metabolitlerine dönüştürülmek için hepatik sitokrom P450 tarafından oksidasyona ihtiyaç duyar. Aktif moleküller trombositler üzerindeki $P2Y_{12}$ reseptörlerini seçici ve geri dönüşümsüz olarak bağlar, böylece ADP'ye bağlı trombosit aktivasyonunu önlenmiş olur (Williams & ark., 2008). **Ticagrelor,** kendi başına aktif olan ve farmakolojik etkisini göstermek için hepatik metabolizmaya ihtiyaç duymayan geri dönüşümlü bir üçüncü nesil $P2Y_{12}$ inhibitörüdür, ancak ilacın sitokrom aracılı oksidasyonu yaygındır (Adamski & ark., 2018). Akut koroner sendromlu hastalarda, üçüncü nesil ajanlar ve klopidogrelin karşılaştırıldığı randomize kontrollü çalışmalar (RCT'ler), ölümcül olmayan kanama komplikasyonları riskinin artması bedeline karşın tekrarlayan iskemik olaylarda daha fazla azalma olduğunu göstermiştir (Wallentin &ark., 2008-2009; Gurbel &ark., 2009; Wiviott & ark., 2007; Patti & ark., 2020). Prasugrel ve tikagrelor tedavisinde yüksek trombosit reaktivitesi için prasugrel kullanan hastalar için %3-15 ve tikagrelor tedavisi gören hastalar için %0-3 olduğu tahmin edilmektedir (Thomas & ark., 2016). **Vorapaxar,** trombinin indüklediği trombosit aktivasyonunu inhibe eden ve aterotrombozun ikincil önlenmesinde etkili olan oral bir proteaz-activated receptor (PAR-1) antagonistidir. Daha önce MI geçiren veya PAH'lı hastalarda trombotik kardiyovasküler olayların azaltılması için, 2014'te ABD Gıda ve İlaç Dairesi (FDA) tarafından onaylanmıştır (Magnani & ark., 2015). Çok yeni sayılabilecek bu ilaç hakkında kısa-orta dönem sonuçlara yönelik çalışmalar devam etmektedir.

Antitrombositik ilaç izleminde laboratuvar testleri

Trombositlerin farklı fonksiyonları olması nedeniyle trombosit fonksiyon testleri de birçok farklı metod kullanılarak ölçülmeye çalışılmaktadır. Farklı tekniklerle kullanan cihazlar trombositlerin adezyon ve agregasyon kabiliyetlerini ölçebilmektedir. Antitrombosit ilaç yanıtlarının belirlenmesinde genotipleme ve trombosit fonksiyon testi, antitrombosit tedavilerinin trombosit fonksiyonu üzerindeki etkilerinin in vitro olarak daha doğru bir şekilde tahmin edilmesini sağlar (Passacquale &ark., 2022).

Araşidonik asit (AA) veya adenozin difosfat (ADP) agonistleri ile klasik ışık geçirgen aggregometri (light transmittans aggregometri, LTA) ve tam kanda impedans aggregometri (*Multiple* Electrode Platelet *Aggregometry,* MEA) prensibi ile çalışan POCT cihazları (Multiplate®, VerifyNow®) ile hızlı trombosit fonksiyon testleri sıklıkla kullanılmaktadır (Paniccia & ark., 2015). Ayrıca aspirinin biyokimyasal etkilerinin incelenmesi için en güvenilir test serum veya idrar tromboksan B2 (TxB2) seviyeleri ölçümüdür. Trombositlerin maksimum tromboksan sentezleme kapasitesini gösterir.

Bir diğer metod akım sitometri yöntemi ile trombosit analizi (*vasodilator-stimulated phosphoprotein,* VASP) $P2Y_{12}$ inhibitörlerinin etkisini ölçmek için kullanılır (Ben-Dor & ark., 2009). Bazı kalıtsal veya edinilmiş trombosit fonksiyon bozuklukları için, trombositten zengin plazma kullanan ışık geçirgenliği-lumiagregometrisi (LT-LA), trombosit agregasyonu ile eş zamanlı olarak trombosit sekresyonunu göstermek için kullanılmaktadır (Pai& ark., 2011).

Prasugrel ve tikagrelor kullanan hastalarda, düşük tespit edilen yüksek platelet reaktivitesi nedeniyle trombosit fonksiyon testi rutin olarak önerilmemektedir. Bu nedenle günümüze değin gelen çalışmalar daha çok aspirin ve/veya klopidogrel cevapsızlığı üzerine yoğunlaşmıştır. Ancak giderek artan sayıda DAPT ve/veya diğer antikoagulan tedavi kombinasyonları artarak devam etmektedir.

Periferik Arter Hastalığı Tedavisinde Antiplatelet Tedavi

PAH yönetimine ilişkin güncel kılavuzlar [Avrupa Kardiyoloji Derneği (ESC) ve Amerikan Kalp Derneği/Amerikan Kardiyoloji Koleji (AHA/ACC)] semptomatik PAH hastalarında, tromboembolik olay ve mortalite riskini azaltmak için, tek bir antiplatelet ajanın (aspirin veya klopidogrel) kullanılmasını şiddetle tavsiye etmektedir [tavsiye sınıfı, class of recommendation (COR) I-A (Aboyans & ark., 2018; Gerhard-Herman & ark., 2017). Öte yandan, asemptomatik alt ekstremite PAH'ı olan hastalarda, tek bir antiplatelet ajan ESC kılavuzları tarafından önerilmezken (Aboyans & ark., 2018), AHA/ACC kılavuzları ciddi ayak bileği-brakiyal indeksi (Ankle bracial index, ABI) hesaplamasına göre COR IIa/IIb olarak önerilmektedir (Gerhard-Herman & ark., 2017). Alt extremite revaskülarizasyonu uygulanmış PAH hastalarında ise kısa bir süre için ikili antiplatelet tedavi (DAPT) önerilmektedir. (sırasıyla ESC veya AHA/ACC önerilerine göre, IIb-B veya IIb-C) (Aboyans & ark., 2018; Gerhard-Herman & ark., 2017).

Asemptomatik PAH hastalarında antitrombotik tedavi konusunda farklı uluslararası kılavuzlar arasında, daha önce belirtildiği gibi, bir fikir birliği bulunmamaktadır. Bu durumdaki veriler büyük ölçüde koroner hastalık, serebrovasküler hastalık ve PAH olan hastalarda büyük çaplı randomize çalışmaların alt analizlerinden elde edilmiştir. Ancak halen asemptomatik PAH'lı hastalarda herhangi bir antitrombotik stratejinin etkinliğine dair tatmin edici veri yoktur. Ancak semptomatik PAH'lı hastalarda tatmin edici kanıtlar çok daha nettir (Passacquale & ark., 2022).

CAPRIE (Trial of Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) ve EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) çalışmalarının sonuçlarına göre, semptomatik PAH hastalarında veya periferik revaskülarizasyon uygulanan hastalarda antiplatelet monoterapisi için tercih edilen ajan klopidogreldir (Patti &ark., 2020). CASPAR (The Clopidogrel and Acetylsalicylic Acid in Bypass Surgery for Peripheral Arterial Disease) çalışmasında, Klopidogrel ve ASA kombinasyonu, diz altı baypas greftleme gerektiren PAH hastalarında uzuv veya sistemik sonuçlarını iyileştirmediği gözlenmiştir. Çalışmanın alt grup analizinde, protez greft uygulanan hastalarda klopidogrel ve ASA'nın, majör kanama riskini önemli ölçüde arttırmadan fayda sağladığı gösterilmiştir (Belch & ark., 2010). COMPASS (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease) çalışmasına kayıtlı PAH hastalarının (tüm randomize edilenlerin %27'si) bir alt analizinde, günde iki kez 2,5 mg rivaroksabanın + düşük doz aspirinin, büyük amputasyon ihtiyacı dahil olmak üzere majör olumsuz uzuv olaylarında (major adverse limb events (MALEs) %46 (95% CI ¼ 18–65%) azalma ile ilişkili olduğu gösterilmiştir (Anand & ark., 2018). Bu sonuçlar VOYAGER-PAD (Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects With Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities) çalışması ile daha da desteklenmiştir (Bonaca & ark., 2020). VOYAGER-PAD çalışması, günde iki kez 2,5 mg dozunda rivaroksabanın + aspirinin birlikte kullanımının, yalnızca aspirin ile karşılaştırıldığında, akut ekstremite iskemisi, vasküler nedenlere bağlı amputasyon, MI, iskemik inme veya kardiyovasküler ölüm bileşik sonucunun göreceli insidansını %15 oranında azalttığını göstermiştir (HR ¼ 0,85, %95 CI ¼ 0,76–0,96). Bu sonuçlara, tek başına aspirin ile kullanımı ile kıyaslandığında, MI'da tromboliz (thrombolysis in MI, TIMI) majör kanamasında anlamlı bir artışa neden olmadan ulaşıldığı raporlanmıştır (Passacquale & ark., 2022). Ancak çalışmadaki ikinci güvenlik sonucu Uluslararası Tromboz ve Hemostaz Derneği [International Society of Thrombosis and Haemostasis, ISTH] majör kanama tanımına göre, aspirinin tek başına kullanımına göre önemli bir artış (HR 1.42; 95% CI, 1.10 to 1.84; P = 0.007) elde edilerek ulaşıldığı belirtilmiştir (De Luca & ark., 2020).

Periferik Arter Hastalığı ve/veya Koroner Arter Hastalığı

Koroner arter hastalığı (KAH) ve PAH birlikte olan hastalarda kullanılması önerilen antitrombotik ajan(lar) konusundaki veriler kısıtlı ve tartışmalıdır. Bu hasta popülasyonunun prevalansı, hastalıkların patolojik tanımlarına, klinik şartlarına ve hasta seçimine bağlı olarak %5 ila %35 arasında değişmektedir (Hess & Hiatt, 2018; Steg & ark., 2007; Fowkes &ark., 2006). KAH ve eşlik eden PAH hastalarına yönelik randomize klinik çalışmalarda az sayıda farmakolojik tedavi bulunmaktadır (De Luca & ark., 2020). Bu hastaların antitrombotik tedavi yönetimi için halen özel bir kılavuz önerisi bulunmamaktadır (Aboyans & ark., 2018; Gerhard-Herman & ark., 2017).

KAH ve/veya PAH hastalarında büyük randomize çalışmalar, rivaroksaban (günde iki kez 2,5 mg) ve düşük doz aspirin (günde bir kez 81 mg) kombinasyonunun tek başına aspirin ile karşılaştırıldığında majör advers kardiyovasküler olayları azalttığını göstermiştir (Eikelboom & ark., 2017; Bonaca & ark., 2020; Mega & ark., 2012). Aynı kombinasyonun klopidogrel-düşük doz aspirin ile karşılaştırıldığında, yüksek risk altında bulunan hastalarda majör olumsuz kardiyak olaylar (major adverse cardiac events, MACE), kardiyovasküler ölüm ve iskemik inme dahil inme riskini azaltmıştır. Ayrıca rivaroksaban ve düşük doz aspirinin, klopidogrel ve düşük doz aspirine kıyasla MACE'ler için %18'lik göreceli tehlike azalması ile ilişkili olduğunu gösterilmiştir. Bu sonucun hastalarda orta-şiddetli kanama riskini önemli ölçüde arttırmadan elde edildiği bildirilmiştir (Coleman & ark., 2022).

Koroner arter hastalığı olan hastalarda ikili antiplatelet tedavisi (DAPT) konusunda ACC/AHA ve ESC Kılavuzlarının karşılaştırıldığı ilginç bir çalışmada, mevcut ACC/AHA ve ESC güncellemeleri, $P2Y_{12}$ inhibitörü seçimi ve DAPT süresi ile ilgili temel öneriler açısından büyük ölçüde benzer bulunmuştur. Her iki güncellemede de ortak ve vurgulanan nokta, popülasyona dayalı tedavi yaklaşımından daha çok "hasta merkezli" bir yaklaşıma geçiş olarak vurgulanmıştır (Capodanno & ark., 2018). Genetik profil, çevre ve hayat tarzındaki bireysel değişkenlikleri göz önünde bulundurarak tedavi seçilmesi kaçınılmaz bir ortak paydanın başlangıcı gibi görünmektedir.

Sonuç olarak, güncel literatür bilgilerine göre, modifiye edilebilir risk faktörlerini düzeltilmesi yanında, izole ve asemptomatik PAH hastaları için agresif olmayan $P2Y_{12}$ inhibitörü ile monoterapi yeterli olabilirken, alt ekstremite PAH ve KAH'ı birlikte olan hastalarda daha agresif ve uzun süreli DAPT uygun görünmektedir. PAH ve KAH'ı birlikte olan hastalarda, uzun süreli DAPT veya düşük doz antikoagülasyon ve ASA'ya dayalı yeni bir antitrombotik tedavinin alt ekstremite mortalite ve morbiditeyi etkin şekilde azaltabileceği öngörülmektedir. Şüphesiz ki klinik doğrulama için selektif hasta gruplarında büyük çaplı, epigenetik farklılıklarında iyi analiz edilebildiği ve ortak terminolojik tanımlamaların kullanıldığı uluslararası çalışmalara ihtiyaç vardır.

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BÖLÜM 4

DATA-DRIVEN MACHINE LEARNING APPROACHES FOR CARDIOVASCULAR DISEASE RISK PREDICTION

SEDA DEMİR[1]
HARUN SELVİTOPİ[2]

Introduction

Cardiovascular diseases (CVDs) represent the leading cause of death worldwide, accounting for approximately 17.9 million deaths each year, which is about 32% of all global deaths (WHO, 2021). These diseases include a range of conditions affecting the heart and blood vessels, such as coronary artery disease, heart failure, arrhythmias, and cerebrovascular diseases. The development of CVDs is often influenced by a combination of genetic, environmental, and lifestyle-related risk factors, including hypertension, diabetes, smoking, obesity, high cholesterol levels, and sedentary behavior. CVDs often progress silently, with many individuals remaining asymptomatic until a critical cardiovascular event occurs, such as a heart attack or stroke. Therefore, early

[1] Research Assistant, Erzurum Technical University, Department of Mathematics, Orcid: 0000-0003-0655-9326
[2] Associate Professor, Erzurum Technical University, Department of Mathematics, Orcid: 0000-0001-5958-7625

detection and prevention strategies are crucial for reducing morbidity and mortality rates associated with these conditions (Benjamin et al., 2019: e56).

In recent years, machine learning (ML) techniques have emerged as powerful tools in the early diagnosis and risk prediction of cardiovascular diseases. ML enables the analysis of large, complex datasets, uncovering patterns and relationships that may not be readily apparent through traditional statistical methods. Stonier et al. (2024) developed a system to predict heart attack risk based on electronic health data and compared various machine learning algorithms. The Random Forest algorithm was found to be the most successful method with an accuracy rate of 88.52%. Mittal et al. (2025) proposed a four-stage hybrid model to address data imbalance and feature selection issues by employing SMOTE–ENN and Chi-square techniques; the model utilized RFT, KNN, and AdaBoost as base learners and LR as the meta-learner, achieving an accuracy of 97.8%. Saikumar and Rajesh (2024) highlighted the need for a low-cost and effective system for diagnosing coronary artery disease (CAD), which is prevalent in low- and middle-income countries. They developed an RCNN-based deep learning model and achieved an accuracy of 99.17%, precision of 99.16%, recall of 98.69%, sensitivity of 98.3%, and specificity of 0.0009 by comparing methods such as Gaussian Naive Bayes, Decision Tree (DT), KNN, and RCNN. Dritsas and Trigka (2023) emphasized the importance of early diagnosis of cardiovascular diseases (CVD) and developed supervised machine learning (ML) models for CVD prediction using the SMOTE technique. After analyzing risk factors and applying SMOTE, they found that the stacking ensemble model, with 10-fold cross-validation, achieved superior results, including an accuracy of 87.8%, recall of 88.3%, precision of 88%, and an AUC of 98.2%. Babu et al. (2025) stated that the main factors leading to the development of heart disease B are a sedentary lifestyle, excessive alcohol consumption, insufficient physical activity, and smoking. To address this issue, a cloud-based framework (CBF) capable of monitoring health information and making accurate predictions is proposed. Bhatt et al. (2023) developed a model using k-modes clustering and machine learning algorithms like Random Forest, Decision Tree, Multilayer Perceptron, and XGBoost to predict cardiovascular diseases. Their model achieved the highest accuracy of 87.28% with Multilayer Perceptron using cross-validation, outperforming other algorithms. The area under the curve (AUC) values for the models were all above 0.94. Sianga et al. (2025) conducted two separate experiments, one excluding and one including geographical features such as air humidity, temperature, and education level. In the second experiment, which included these features, the XGBoost algorithm achieved the highest accuracy of 95.24%, followed by the decision tree (93.87%) and support vector machine (92.87%). The study highlighted the significant role of geographical risk factors in predicting cardiovascular disease (CVD). The reviewed studies have demonstrated the growing impact and promising performance of various machine learning algorithms in enhancing cardiovascular disease prediction and diagnosis.

In conclusion, this study has been aimed at providing a systematic analysis of machine learning approaches used in the diagnosis of cardiovascular diseases. The data sources and types used, the applied machine learning models, and the performance results obtained with these models have been evaluated in detail. Moreover, the effectiveness of different machine learning techniques used in the early diagnosis of cardiovascular diseases has been comparatively examined. It has been expected that such a compilation study will guide future research and provide important information on how machine learning algorithms and new biomarkers can be integrated into clinical decision support systems to obtain more accurate and reliable results.

Material and Methods

In this study, the "Heart-Disease-Prediction/dataset.csv" dataset has been used. The data has been split into training and test sets, after which both sets have been processed and prepared for model input. To classify cardiovascular diseases, models including Artificial Neural Network (ANN), Logistic Regression (LR), Support Vector Machine (SVM), Random Forest (RF), and Decision Tree (DT) have been trained using the training set. The accuracy of the models has been evaluated based on their ability to classify the test set data. Additionally, the Fast Correlation-Based Filter (FCBF) feature selection algorithm has been applied to the five machine learning models, and the results have been compared both among the models and with existing literature (Stonier vd., 2024: 11).

Collection and Properties of Dataset

The dataset used in this study has been obtained from the dataset.csv file in the GitHub repository https://github.com/kb22/Heart-Disease Prediction/blob/master/dataset.csv. It consists of various medical parameters, including demographic characteristics, clinical measurements, and diagnostic test results of individuals. Each row represents data for a single individual, while each column shows a different feature related to that individual. Key variables in the dataset include age, gender, type of chest pain, resting blood pressure, cholesterol level, fasting blood sugar, EKG results, maximum heart rate, exercise-induced angina, ST segment depression, exercise slope, number of vessels detected by fluoroscopy, and thalassemia status.

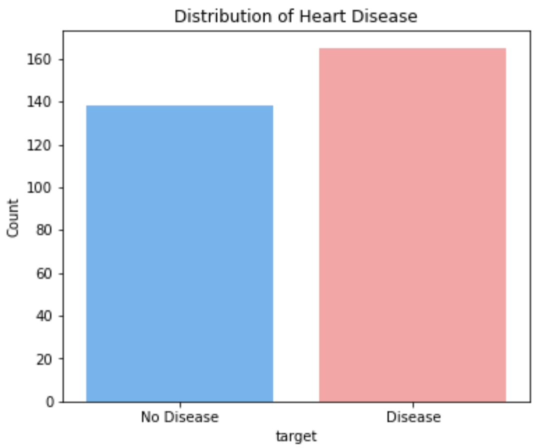
The primary goal of the dataset is to classify individuals as either having or not having heart disease through the "target" column. This column indicates individuals with heart disease as 1 and those without heart disease as 0. There are 165 individuals with heart disease and 138 individuals without. The dataset contains a total of 303 observations, and the class distribution has been designed to be balanced between the two classes. This characteristic provides a balanced and healthy data structure for training and testing machine learning algorithms. The dataset description is provided in Figure 1, and the class distribution of the 'target' variable in the dataset is shown in Figure 2.

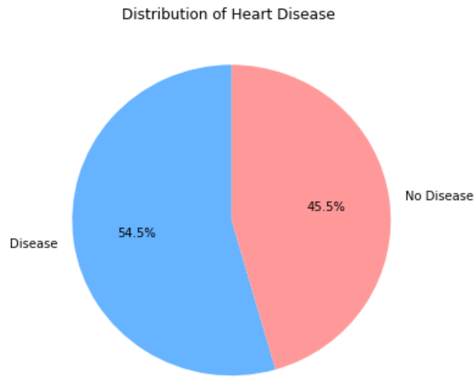
Figure 1 Description of the features of dataset

Heart Disease Dataset Features

Feature	Description
age	Age of the patient (in years)
sex	Sex (1 = male, 0 = female)
cp	Chest pain type (0 = typical angina, 1 = atypical angina, 2 = non-anginal pain,
trestbps	Resting blood pressure (in mm Hg)
chol	Serum cholesterol level (in mg/dl)
fbs	Fasting blood sugar > 120 mg/dl (1 = true; 0 = false)
restecg	Resting electrocardiographic results (0 = normal, 1 = ST-T wave abnormality, 2 = lef
thalach	Maximum heart rate achieved
exang	Exercise-induced angina (1 = yes; 0 = no)
oldpeak	ST depression induced by exercise relative to rest
slope	Slope of the peak exercise ST segment (0 = upsloping, 1 = flat, 2 = d
ca	Number of major vessels colored by fluoroscopy (0–3)
thal	Thalassemia (1 = normal, 2 = fixed defect, 3 = reversible def
target	Diagnosis of heart disease (1 = presence; 0 = absence)

Figure 2 The class distribution of the 'target' variable in the dataset.





Data Pre-processing

Data preprocessing has been a crucial step for the successful application of machine learning models. During this stage, raw data is transformed into a format that is suitable for modeling by applying various techniques. Raw datasets often have missing values, imbalanced class distributions, features with different scales, or irrelevant variables. Therefore, the preprocessing process has the objective of improving data quality, which in turn enhances the model's accuracy and generalization capability. Common preprocessing steps have included handling missing data, scaling features, addressing class imbalances, selecting relevant features, and performing necessary transformations.

In this study, several preprocessing techniques have been applied to improve the performance of different machine learning models. The dataset has been scaled using the Standard Scaler method, and important features have been selected through the Fast Correlation-Based Filter (FCBF) algorithm. These processes have led to performance improvements in three machine learning models, compared to studies in the literature using the same dataset. The results have shown that selecting preprocessing techniques that are compatible with the structure of the data has been essential for achieving high model performance.

Standard Scaler

In machine learning applications, differences in feature scales have been known to negatively impact model performance. To address this issue, the Standard Scaler method has been utilized, which transforms each feature to have a mean of zero and a standard deviation of one. This transformation has proven especially effective for distance-sensitive algorithms, as it ensures that all features are placed on a common scale, preventing the model from giving undue importance to any single feature. As a result, the learning process has become more balanced, leading to improved prediction accuracy and reduced training time. Furthermore, the use of Standard Scaler has been shown to enhance model convergence and stability.

Fast Correlation-Based Filter (FCBF) Feature Selection

The Fast Correlation-Based Filter (FCBF) method has been an effective feature selection technique that has been used to evaluate the relationship between features and the class using the information-theoretic measure known as Symmetrical Uncertainty (SU). Symmetrical Uncertainty has been employed to quantify the degree of association between a feature and the target class, while also assessing the degree of independence between them. FCBF has been evaluating the correlation of each feature with the target class, selecting those that have exhibited a strong relationship. However, it has been emphasized that selected features should not have shown high correlation with one another. When two features have been highly correlated, it has resulted in redundant information being processed, ultimately reducing the model's efficiency and performance.As a result, FCBF has been prioritizing features that are strongly correlated with the class but have exhibited low correlation with other features. This has allowed for the removal of unnecessary or redundant features, thereby creating a more meaningful and efficient feature subset (Yu and Liu, 2003).

Data Preparation for Model Training

In this study, the datasets were first subjected to preprocessing and normalization to ensure consistency and reliability. Following these steps, the data was randomly split, with 75% allocated to the training set and 25% to the test set.

Classifier Models

Logistic Regression (LR)

Logistic Regression is a supervised learning algorithm based on linear regression, primarily used for classification problems where the dependent variable is categorical, typically binary. This model estimates the probability that a given input instance belongs to a particular class by employing the logistic (sigmoid) function, which maps predicted values to a range between 0 and 1. The model parameters are learned using the maximum likelihood estimation approach. Logistic Regression provides interpretable coefficients, allowing for an understanding of the influence of each feature on the target variable. Due to its simplicity, efficiency, and interpretability, it has been widely applied in various domains, particularly when the dataset contains a limited number of features and the classes are linearly separable.

Support Vector Machine (SVM)

Support Vector Machine (SVM) is a powerful supervised learning algorithm widely used for both classification and regression tasks. The core idea behind SVM is to find the optimal hyperplane that best separates data points belonging to different classes by maximizing the margin between them. This margin is defined as the distance between the hyperplane and the nearest data points from each class, known as support vectors. In cases where the data is not linearly separable, SVM employs kernel functions—such as polynomial, radial basis function (RBF), or sigmoid kernels—to transform the input space into a higher-dimensional feature space where linear separation becomes possible.

Random Forest (RF)

Random Forest model is an ensemble learning method used for both classification and regression tasks, and it is based on the combination of multiple decision trees. In this model, each decision tree is constructed using a random subset of the training data, and at each split in the tree, a random subset of features is selected to determine the best division. This randomness helps reduce the risk of overfitting while enhancing the model's generalization ability. The final prediction of the model is determined by majority voting in classification tasks and by averaging the predictions in regression tasks.

Decision Tree (DT)

Decision Tree algorithm is a widely used supervised machine learning method applicable to both classification and regression problems. Resembling a tree structure, the model partitions the dataset into subsets based on specific features, forming a hierarchical decision-making process. Each internal node represents a feature, each branch corresponds to a decision rule, and each leaf node denotes a class label or a numerical prediction. Measures such as entropy, Gini index, or information gain are employed to achieve optimal data splits. Owing to their high interpretability, Decision Trees are particularly advantageous in applications where understanding the data structure intuitively is essential. However, they are prone to overfitting, thus pruning techniques are often applied to improve the model's generalization performance.

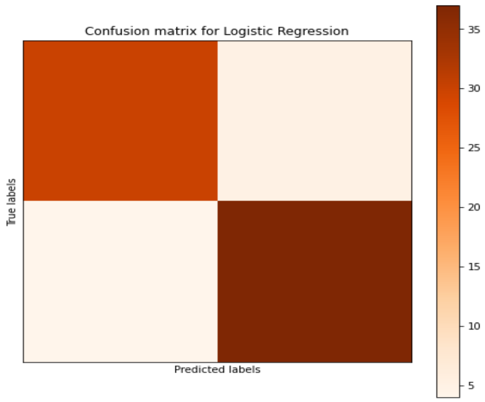
Artificial Neural Network (ANN)

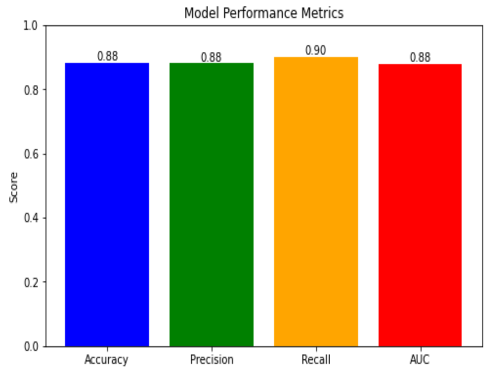
Artificial Neural Networks (ANNs) are a class of supervised machine learning algorithms inspired by the structure and functioning of the human brain. Through layers of artificial neurons that process input data, the information is analyzed via weighted connections and nonlinear activation functions, allowing the network to learn complex patterns. A typical ANN model consists of an input layer, one or more hidden layers, and an output layer. The learning process is carried out by minimizing the error between the predicted and actual outputs through optimization techniques such as backpropagation and gradient descent. ANNs are particularly effective in modeling nonlinear and high-dimensional data, and they are widely used in various applications, including classification, regression, image recognition, and time-series forecasting.

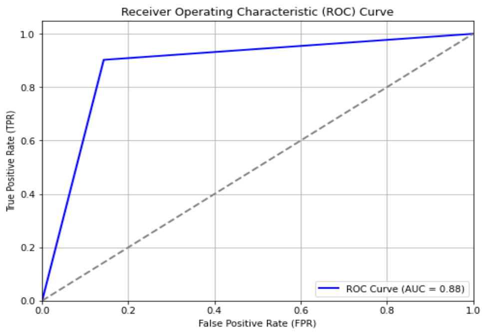
RESULTS AND DISCUSSIONS

In this study, various machine learning methods have been applied to a heart disease dataset to develop a predictive model for the early diagnosis of cardiovascular diseases. To evaluate the performance of the models, key metrics such as accuracy, precision, and recall have been utilized. These metrics have been derived from the confusion matrix corresponding to each classification model. Additionally, ROC (Receiver Operating Characteristic) curves have been plotted, and AUC (Area Under the Curve) values have been calculated for each model to provide a more detailed assessment of classification performance. As a result, the effectiveness of different machine learning algorithms in detecting cardiovascular diseases has been comparatively analyzed. The obtained results have been compared with findings from the existing literature.

Figure 3 Performance metrics for the Logistic Regression model



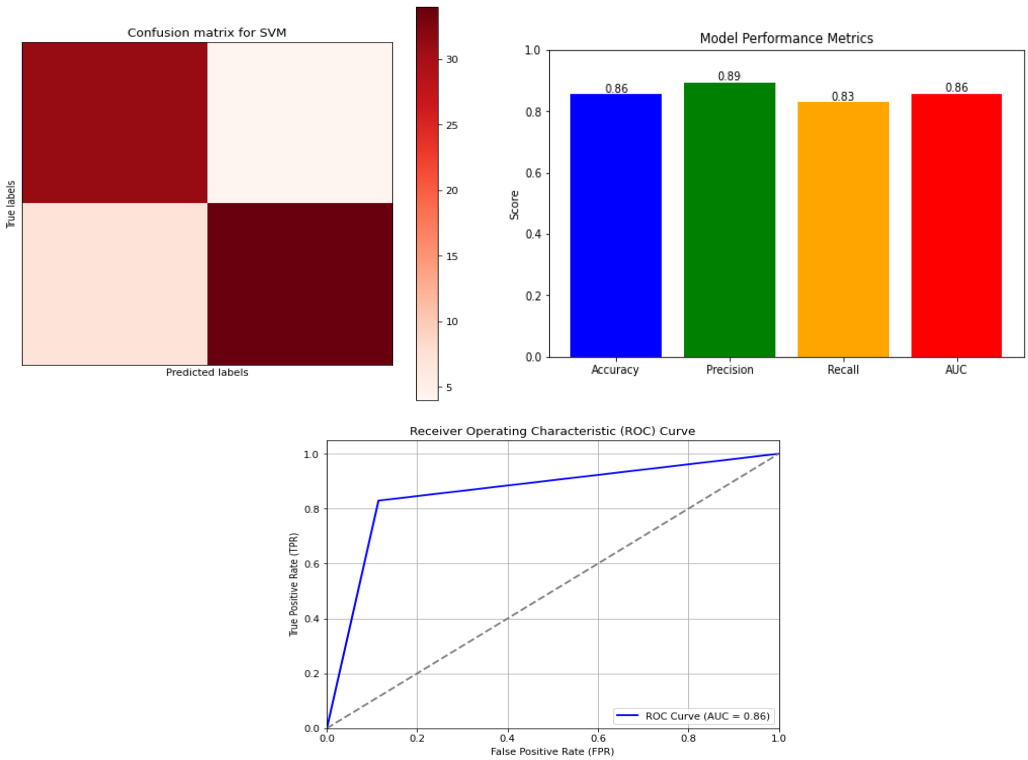




The performance evaluation of the Logistic Regression model was conducted using the confusion matrix, classification metrics, and ROC curve analysis. The confusion matrix has shown that the model was able to successfully distinguish between the two classes, as evidenced by the high number of true positive (TP) and true negative (TN) predictions, indicating a balanced classification capability. These findings have been supported by the evaluation metrics, where the model achieved an accuracy of 88.15%, a precision of 88.09%, and a recall of 90.24%. The slightly higher recall compared to precision suggests that the model has been more sensitive in identifying positive instances, which can be advantageous in applications where failing to detect positive cases is costly. Moreover, the ROC curve, with an Area Under the Curve

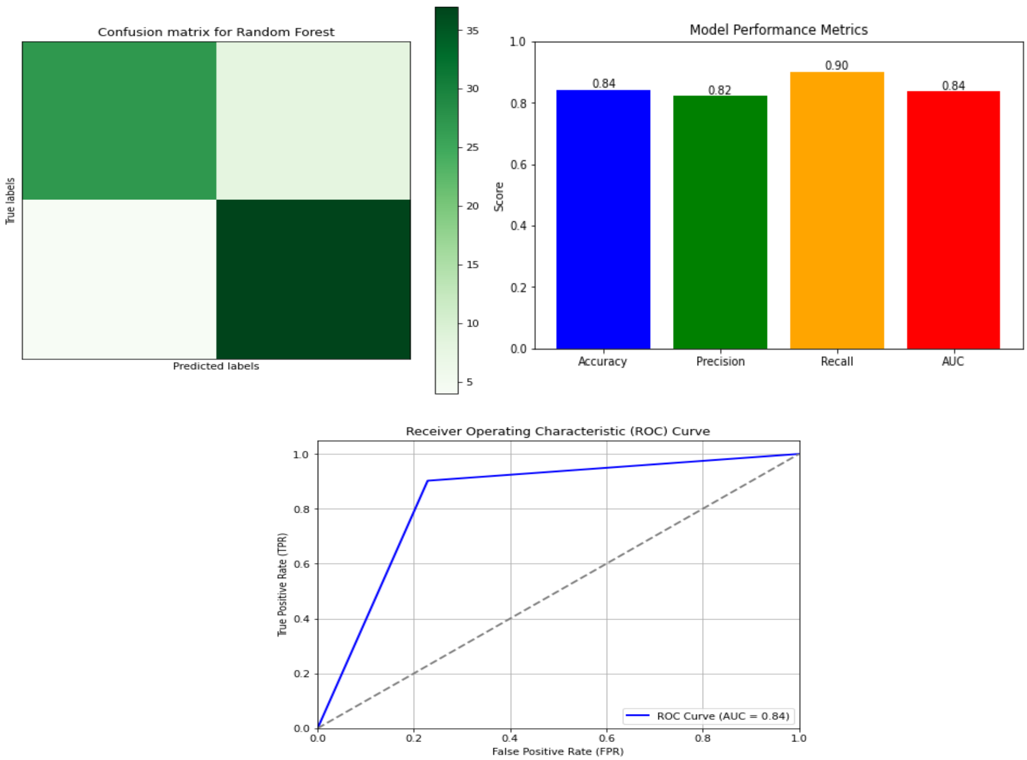
(AUC) value of 87.97%, demonstrated that the model has maintained a strong discriminative ability across various classification thresholds. Overall, the model's success in correctly identifying positive classes and its balanced performance indicate that it represents a reliable approach for binary classification tasks. In comparison with the results reported in Stonier et al. (2024), the model has yielded superior performance.

Figure 4 Performance metrics for the Logistic Regression model



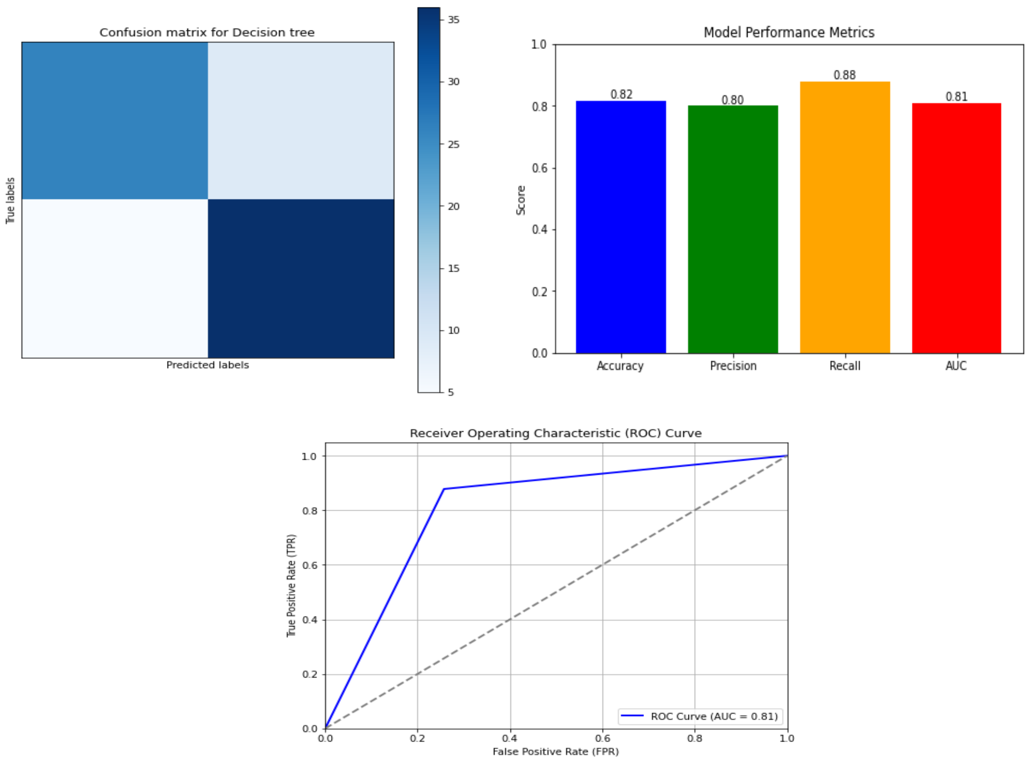
The performance evaluation of the Support Vector Machine model has been conducted using the confusion matrix, classification metrics, and ROC curve analysis. The findings have been supported by the evaluation metrics. The model has achieved an accuracy of 85.52%, a precision of 89.47%, and a recall of 82.92%. Moreover, the Area Under the ROC Curve (AUC) has been calculated as 85.74%, indicating that the model has maintained a strong discriminative ability across various classification thresholds. When compared to the results reported in Stonier et al. (2024), this model has demonstrated superior performance.

Figure 5 Performance metrics for the Random Forest model



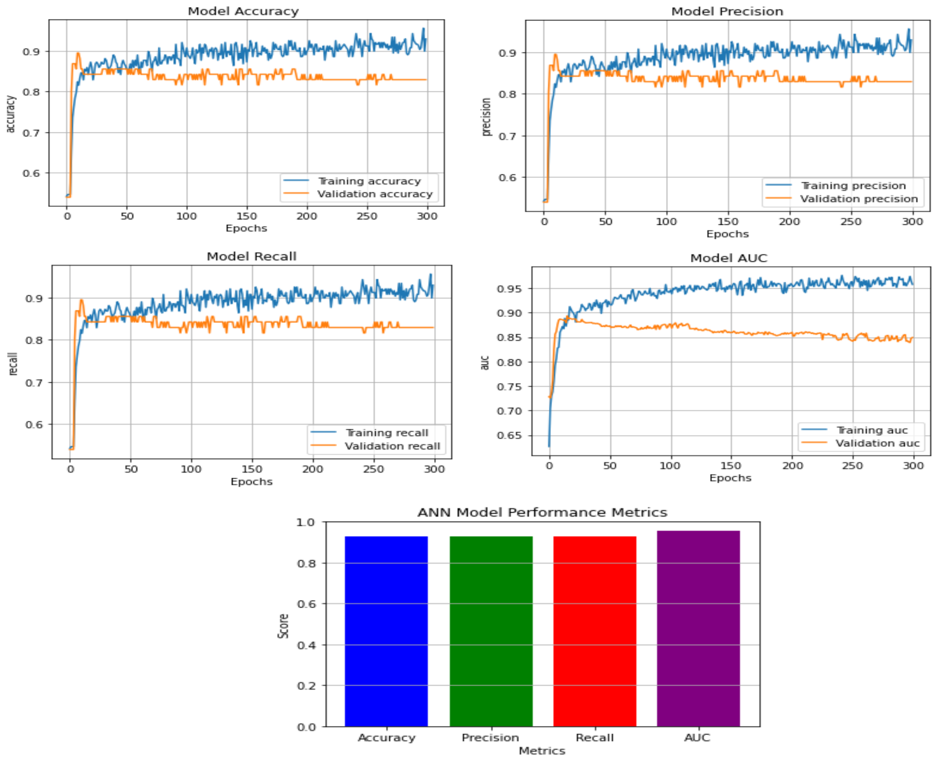
The performance evaluation of the Random Forest model has been conducted using the confusion matrix, classification metrics, and ROC curve analysis. The findings have been supported by the evaluation metrics. The model has achieved an accuracy of 84.21%, a precision of 82.22%, and a recall of 90.24%. Moreover, the Area Under the ROC Curve (AUC) has been calculated as 83.69%, indicating that the model has maintained a strong discriminative ability across various classification thresholds.

Figure 6 Performance metrics for the Decision Tree model



The performance evaluation of the Decision Tree model has been conducted using the confusion matrix, classification metrics, and ROC curve analysis. The findings have been supported by the evaluation metrics. The model has achieved an accuracy of 81.57%, a precision of 80.00%, and a recall of 87.80%. Moreover, the Area Under the ROC Curve (AUC) has been calculated as 81.04%, indicating that the model has maintained a strong discriminative ability across various classification thresholds.

Figure 7 Performance metrics for the Artifical Neural Network model



The performance evaluation of the Artificial Neural Network (ANN) model was conducted using the confusion matrix, classification metrics, and ROC curve analysis. The findings were supported by these evaluation measures. The model achieved an accuracy of 92.95%, a precision of 92.95%, and a recall of 92.95%. Additionally, the Area Under the ROC Curve (AUC) was calculated as 95.73%, indicating that the model maintained a strong discriminative ability across various classification thresholds.

The accuracy values of the five machine learning methods applied to this dataset were obtained as 92.95% for ANN, 88.15% for LR, 85.52% for SVM, 84.21% for RF and 81.57% for DT, respectively. As can be seen here, the highest accuracy value belongs to the Artificial Neural Network (ANN) model. This result shows that the ANN model exhibits a more successful classification performance on this dataset compared to other methods.

In the study conducted by Stonier et al. (2024), the best performance was reported by the Random Forest model with an accuracy of 88.25%. Furthermore, the ANN model used in that study also exhibited lower performance compared to the ANN model proposed in this work. Therefore, the proposed ANN model in this study outperformed both the Random Forest and the ANN models presented by Yu and Liu. As a result, it is recommended as a more effective alternative for similar classification tasks.

Conclusion

In this study, five different machine learning methods were applied to the selected dataset. Prior to the application of these methods, the FCBF feature selection algorithm was employed during the data preprocessing phase. The performance of the models was assessed using various evaluation criteria and examined through comparative analysis. The outcomes of the proposed methods were compared with those reported in the literature, and it was observed that the results obtained in this study outperformed those found in previous research.

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