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ARTIFICIAL INTELLIGENCE APPROACH IN OPTIMISATION OF HEPARIN DOSING IN POST COVID-19 PATIENTS DURING HEMODIALYSIS

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Abstract :

INTRODUCTION:

Hemodialysis patients have a higher risk of thrombo-embolic events and hence they require anti-coagulation therapy throughout the dialysis procedure. Post COVID patients undergoing hemodialysis experience an increased risk for dialysis circuit clotting compared to others. This study aims to optimize heparin dosing for post COVID-19 patients during hemodialysis using machine learning (ML).

METHODS:

A prospective observational study, conducted at Dialysis unit, PSG hospitals, Coimbatore for a duration of 6 months. 136 samples were collected and the data included age, gender, BMI, DM-2, hypothyroidism, ionized calcium, serum creatinine, serum albumin, clotting history, COVID-19 infected and vaccine doses which was fed into Machine Learning to optimize heparin dosing. We used decision tree algorithm for ML model.

RESULTS:

In this study, a prototype model of Machine Learning was developed and optimization of heparin dose during hypercoagulation was done. A sample data was validated in the model which gave a promising performance with a sensitivity score of 0.86. Other factors such as serum albumin, ionized calcium, anemia, body mass index and hypothyroidism were found to influence the clotting risk in hemodialysis patients.

CONCLUSION:

Heparin dose optimization was carried out using the prototype model. A variation of 24.39% is observed for heparin dose given based on the protocol and the model predicted dose. This model has to be fine tuned to improve sensitivity score and model accuracy, to analyze further other influencing factors for clotting and to predict heparin dosing for more complex data.

I. INTRODUCTION

INTRODUCTION

Chronic kidney disease (CKD) has come out as leading public health problem as well as causes of mortality worldwide1. The prevalence of CKD globally is between 11.7-15.1% and ESRD patients in need of renal replacement therapy is estimated between 4.902 and 7.083 million. The rise in the prevalence of DM, HT, obesity and aging mainly direct the rise in the prevalence of CKD2. CKD is defined as the abnormalities in the structure or function of the kidney (GFR <60ml/min/1.73m^2) for 3 months or longer with implications for health3.Both modifiable and non-modifiable factors predisposing to CKD are age, gender, race and ethnicity, family history, drug use, smoking, and socioeconomic status; and concurrent diseases, such as hypertension and diabetes which are related with CKD4. Hemodialysis is procedure which uses dialyzer for extracorporeal circulation of a patient's blood to exchange solute therapeutically. When the conservative medical therapy fails to reduce the progression of morbidity and mortality of renal failure, hemodialysis should be initiated5. Blood tubing carries the blood from vascular access to the dialyzer and purified blood returns back to the body. Blood tends to clot when it moves through the blood tubing. Clotting in the dialysis circuit is triggered by both the extrinsic and the intrinsic pathways at the same time but to different degrees depending on the composition of the dialysis membrane and design and composition of the lines. Platelets become activated in by contact and in response to turbulent flow and high shear stress of blood in dialysis machine. Platelets can contribute in differing degrees to the triggering of or

progressive activation of the clotting cascade leading to thrombosis in the dialysis circuit6. Heparin is an essential anti-thrombotic drug for hemodialysis which is most widely used worldwide7. Systemic anticoagulation during hemodialysis (HD) reduces the risk of extracorporeal circuit clotting. Decades of medical experience with unfractionated heparin (UFH) and safety profile enhanced by its short half-life made UFH the most common anticoagulant employed for HD8. For hemodialysis, UF heparin can be administered as a loading dose bolus followed by either an infusion or repeat bolus at 2–3 hours duration. The loading dose bolus may be 500 units or 1000 units and infusion may vary from 500 units hourly to 1000 units hourly, depending on whether it is 'low dose heparin' or 'normal heparin'. Heparin administration is usually stopped at least 1 hour before the end of dialysis as to prevent further bleeding risk after cessation of hemodialysis6. Heparin is a narrow therapeutic drug. In sub-therapeutic doses of heparin it can lead to occlusion of dialyzer by forming clots; in case of overdose it can cause bleeding. In order to achieve a therapeutic range, optimal dose of heparin should be given. Coronavirus disease 2019 (COVID-19) appears to be associated with increased arterial and venous thromboembolic disease. These presumed abnormalities in hemostasis have been associated with filter clotting during continuous renal replacement therapy (CRRT). Clotting of the CRRT filter is a major limitation to care, as it leads to inefficient dialysis, causes blood loss, and depletes limited resources (CRRT filters)9. In recent times, after 2nd wave of COVID-19, post COVID patients undergoing hemodialysis experience an increased risk for dialysis circuit clotting compared to others. This reduces the dialyzer life which substantially increase the overall cost for hemodialysis18. This issue is not solved until now. Our study deals with this issue by providing dose adjustment by machine learning. Artificial intelligence is potential to exploit meaningful relationship within a data set can be used in the diagnosis, treatment and predicting outcome in many clinical scenarios10. One of the prime branches of AI is called machine learning (ML). ML can be defined as a set of algorithms that have the ability to learn and improve from experience, without being explicitly programmed for a specific task11. Computing optimal drug administration strategies for hypercoagulation in dialysis is a sequential decision-making problem in which the goal is to find the best sequence of drug doses12. Machine learning algorithms that learn from input/output pairs are called supervised learning algorithms. If your application can be formulated as a supervised learning problem, and you are able to create a dataset that includes the desired outcome, machine learning will likely be able to solve your problem13. This study aims to optimize heparin dosing in post COVID-19 patient during hemodialysis based on machine learning to provide individualized therapy for better treatment outcome.

NEED OF THE STUDY.

In recent times, after 2 nd wave of COVID-19, post COVID patients undergoing hemodialysis experience an increased risk for dialysis circuit clotting compared to others. This reduces the dialyzer life which substantially increase the overall cost for hemodialysis. This issue is not solved until now. For treating dialysis circuit clotting, Heparin dose has been increased. But this doesn't produce a permanent solution. Our study deals with this issue by providing dose adjustment by machine learning.

3.1Population and Sample

STUDY DESIGN: Prospective observational study
STUDY POPULATION: ESRD patients on hemodialysis.
SAMPLE SIZE: Sample size was calculated using RAO software. At confidence interval of 99% and margin of error is 0.5%, the sample size is found to be 136 hemodialysis patients.
SELECTION OF STUDY SUJECTS: • The subjects were selected for the study based upon inclusion and exclusion criteria.
INCLUSION CRITERIA: • Patients above 18 years of age • CKD – stage 5 on hemodialysis. • Post COVID – 19 patients, COVID vaccinated.
SAMPLE JUSTIFICATION: In order to train the ML model, Post COVID – 19, COVID vaccinated, non-COVID and non-vaccinated patients were included in this study.
EXCLUSION CRITERIA: • Patients on peritoneal dialysis. • Patient not willing to participate, patient death and patient went outside.

3.2 Data and Sources of Data

STUDY LOCATION: PSG Hospitals (Dialysis unit)
STUDY TOOL: • Data collection form. • Machine learning (Decision tree algorithm).
STUDY DURATION: The study was conducted for a period of six months (March 2022 – August 2022).

RESEARCH METHODOLOGY

A Prospective observational study was conducted in dialysis unit of a tertiary care hospital PSG Hospitals, Coimbatore for a duration of 6 months from March – August 2022. Our project was approved by PSG hospital's human ethics committee. The data was collected from primary source - patient's medical file. Consent was obtained from the participants. Codes were assigned for the participants to ensure their privacy and confidentiality. The collected data was stored for a period of 3 years at Department of Pharmacy Practice, PSG College of Pharmacy in a confidential manner under authorized persons use only in a locked cabinet. Patients above 18 years of age, CKD on hemodialysis, Post COVID – 19 patients, COVID vaccinated were included in this study. Patients on peritoneal dialysis, patients not willing to participate were excluded from this study. The dialysis parameters like blood flow, ultrafiltration and type of access are mentioned below. The blood flow during hemodialysis was fixed as 200 ml/min for all patients. The ultrafiltration goal varies from 0 – 4 Liters was fixed based on the weight gain of the patient and the ultrafiltration rate is determined by the Fresenius dialysis machine. The pump is then activated by the sensor according to the ultrafiltration rate and the total duration of hemodialysis is 4 hours. Type of access used is AV fistula. Serum albumin, serum creatinine, BUN and ionized calcium values were collected. All these lab parameters were collected before hemodialysis session. Since, lab investigations before hemodialysis will be abnormal which determines the possibility of clotting during hemodialysis. Patient's COVID-19 status, Vaccination status, BMI and comorbid conditions like Hypertension, Diabetes, Hypothyroidism, Anemia and CVD data were collected. Clotting frequency data (Clotting history) during hemodialysis was collected from a specified period of 5 months from

January 2022 to May 2022. Vitamin K and protein diet of patients was considered as they influence the coagulation cascade. Based on the patient requirement, the nutrition chart were framed from which the data was collected.

Statistical Analysis:

Descriptive, chi square correlation, Pearson correlation and odds ratio were used for statistical analysis to identify the correlation between the parameters (Table 2) and to assess the significance. SPSS version 26 was used for statistical analysis. To assess the model's performance, we show it new data (data that it hasn't seen before) for which we have labels. This is usually done by splitting the labelled data we have collected into two parts. One part of the data is used to build our machine learning model, and is called the training data. The rest of the data will be used to assess how well the model works; this is called the test data. Scikit-learn contains a function that shuffles the dataset and splits it: the train test split function. This function extracts 70% of the rows in the data as the training set, together with the corresponding labels for this data. The remaining 30% of the data, together with the remaining labels, is declared as the test set13.

Decision tree classifier:

Decision tree is a supervised ML algorithm that uses a set of rules to make decisions. Here, the descriptive attributes are continuously split according to a certain parameter. The tree can be explained by two factors, such as decision nodes and leaves. The leaves are the final outcomes and the decision nodes are where the data is split. Compared with other learning methods (eg., Artificial neural network, support vector machine, naïve Bayesian classifier), decision tree learning is easy to interpret. Decision tree algorithm is preferable for dose optimization16 and medical diagnosis17. Decision classification tree was preferred because it easily identifies significant attributes for analysis and can handle categorical variables. The ML dataset consists of 21 features. Among these, numerical features are age, BMI, BMI category, clotting history, Ionized calcium, Serum creatinine, Serum albumin, Blood urea nitrogen (BUN), Total protein and vaccine doses and Categorical features are gender, anemia, bone disorders, DM, Hypothyroidism, HT, CVD, protein rich intake, vitamin K rich intake, Post COVID history, vaccine doses, present heparin dose. The total 136 data samples were taken. We carried out the preprocessing steps which include getting the dataset, importing libraries and datasets, missing data was found and filled using mean average, categorical data were encoded and outliers were removed. Exploratory data analysis (EDA) is the key to the development of high-yield data models. Using EDA, we will have a solid set of features that can be used for data modelling. For data visualization libraries, we used Python: Matplotlib, Seaborn, and Plotly. Feature selection involves selecting the features that are important for the model. To develop our dose adjustment algorithm, we partitioned 70% (95) patients into training set and 30% (41) of the patients into testing set and evaluated. The proportions were chosen in the study to have enough cases in the testing set to run statistical analysis. Domain expertise was done using CART algorithm16 on the training set to generate decision tree based on the variables know to influence the heparin dosage such as gender, age, BMI, anemia, bone disorders, clotting history, DM, hypothyroidism, ionized calcium, serum creatinine, serum albumin, post COVID history and vaccine doses. We used 5-fold cross-validation to assess the accuracy of the model by comparing the predicted heparin dose given by the decision tree with present heparin dose (as per protocol) from our dataset. As our sample size is small, we used 5-fold cross validation and got better results. Algorithms were developed using python language via jupyter notebook to generate decision tree and perform statistical validation. According to the results, heparin dose was altered to 7500 U for patients with higher risk and 5000 U for patients with low or no risk. The hyperparameters used for this model training were criterion='gini', splitter='random', max_depth=None, min_samples_split=2, min_samples_leaf=1, min_weight_fraction_leaf=0. 0, max_features=None, random_state=None, max_leaf_nodes=None, min_impurity_decrease=0.0, class_weight=None, ccp_alpha=0.0.

Gini = 1− n∑i=1(pi)2, where, 'pi' is the probability of an object being classified to a particular class.

The model performance was evaluated by Accuracy, precision, recall and F1 score.

Accuracy describes how many predictions are correct for all predictions.

Accuracy = (TP + TN) / (TP + FN + TN +FP) where TP and TN are true positive and negative respectively; FP and FN are false positive and negative respectively.

Precision is a measure of how many of the positive predications made are correct (TP).

Precision = TP / (TP + FP).

Recall / sensitivity is a measure of how many of the positive cases the classifier correctly predicted, over all the positive cases in the data.

Recall = TP / (TP + FN).

The F1 score is a measurement that combines accuracy with recall.

F1 score = 2 * {(Precision * Recall) / (Precision + Recall)}.

The model was tuned using hyper parameters and cross validation after which the accuracy was increased by 2%. In this prototype model, protocol -based heparin dose and the model predicted dose was compared, frequency of clotting were considered as the outcome measures and the results were concluded.

3.1 Results

Descriptive data analysis of 136 hemodialysis patients is mentioned in the Table-1.

Among the study population, patients with anemia (p value=0.020), obese (p value=0.003), Post COVID-19 (p value=0.024), COVID-19 vaccinated (p value=0.048), increased vitamin K intake and increased ionized calcium level had increased clotting history. Hypothyroidism patients (p value=0.047) and patients with low serum albumin (p value = 0.020) had decreased clotting history. On further analysis showed a significant relationship between COVID-19 vaccination and clotting (p = .049), (OR = 2.036). The risk of clotting is 2 times increased with COVID-19 vaccination. Correlation and risk values obtained for each observed parameter is mentioned in Table -2.

Among 136 samples 70% were used as training data and 30% were used as testing data (41 patients) which was randomly chosen. Present and predicted heparin doses were compared for the testing samples. Among 41 testing patients, variation was seen in 10 patients. Out of those 10 patients, 7 patients heparin dose was increased to 7500 U and 3 patients heparin doses was decreased to 5000 U based on the risk (Figure 3).

Accuracy, precision, sensitivity and F1 score for ML are expressed between 0 and 1. Accuracy obtained for our ML model is 0.80. Precision value for the model was 0.91 for 5000 U and 0.17 for 7500 U. Sensitivity obtained for 5000 U is 0.86 and for 7500 U is 0.25. F1 score for 5000 U is 0.89 and 7500 U is 0.20. The Macro average is the average precision, recall and F1 score between classes. Macro average doesn't take class imbalance into effort. Since we have class im-balance we take this into consideration. Macro average for F1 score is 0.54. According to the weighted average, weighted means each metric is calculated with respect to how many samples are there in each class. This metric will favor the majority class (high value for each class containing more samples). The weighted average for F1 score is 0.82. The values of the ML results obtained is mentioned in the Table-3.

IV. RESULTS

Table 1: Descriptive analysis data and the clotting history of the parameters.

	Patients with Clotting	Patients without clotting
Number of patients	72	64
Male gender, n (%)	27 (61.3)	17 (38.6)
Female gender, n (%)	45 (49.4)	46 (50.5)
HT, n (%)	68 (53.5)	59 (46.4)
Anemia, n (%)	35 (57.3)	26 (42.6)
CVD, n (%)	18 (62.1)	11 (37.9)
Hypothyroidism, n (%)	7 (41.2)	10 (58.8)
DM, n (%)	30 (56.6)	23 (43.3)
COVID-19 & Vaccination	14 (19.44)	9 (14.1)
COVID-19 & No vaccination	7 (9.72)	4 (6.25)
No COVID & Vaccinated	39 (54.16)	28 (43.7)
No COVID & not Vaccinated	13 (18.05)	22 (34.37)
Low serum Albumin, n (%)	25 (44.6)	31 (55.3)
High Ionised calcium, n(%)	2 (100)	0 (0)
Protein rich diet, n(%)	92 (71.3)	37 (28.6)
Vitamin K rich diet, n(%)	24 (72.7)	9 (27.2)

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Figure 1: Clotting in co-morbid condition

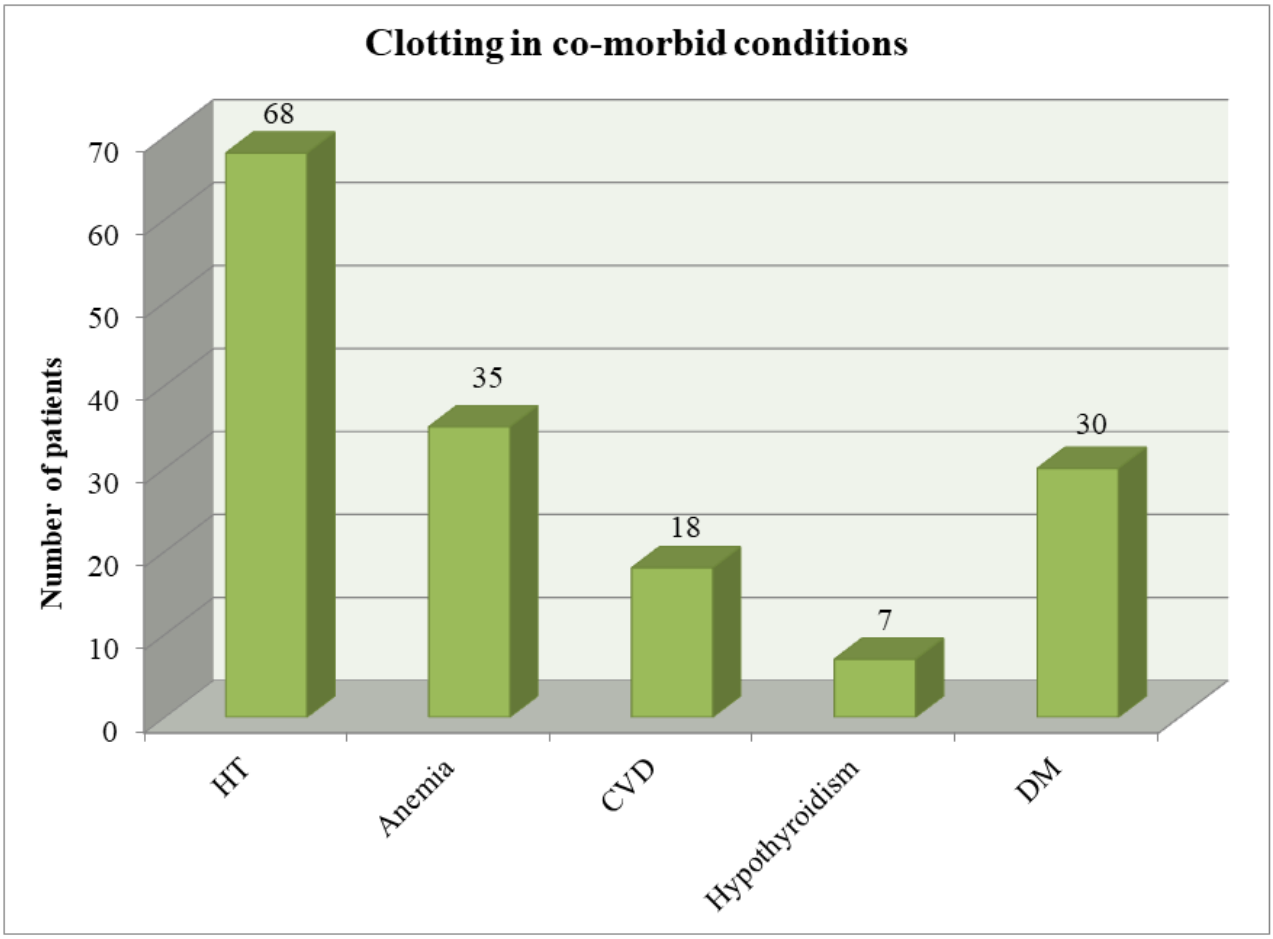
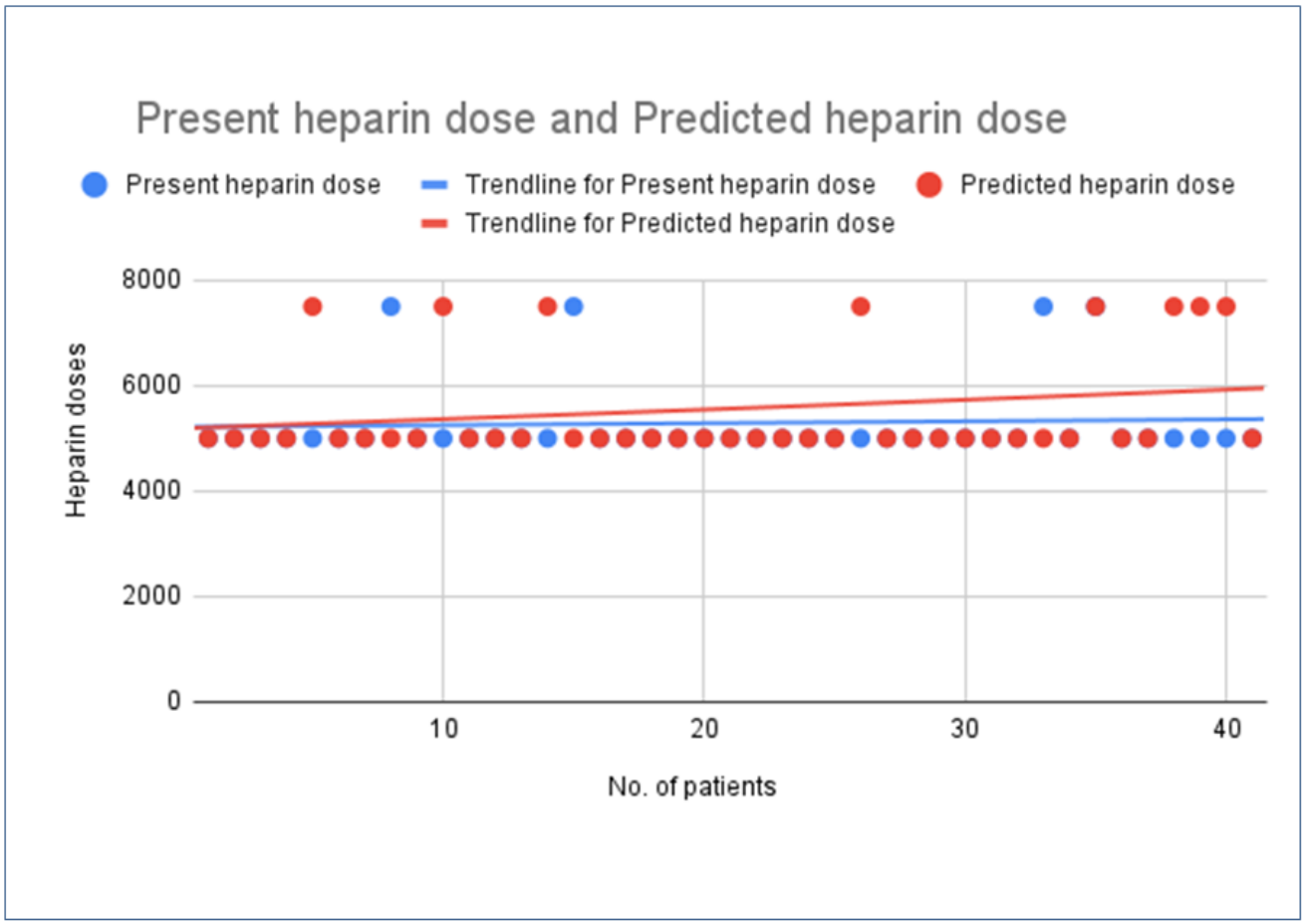


Table 2: Statistical analysis data

PARAMETERS	95% confidence interval	r value
Clotting history / Serum albumin	.02	-.50
Clotting history / Anemia	.02	.11
BMI category / Clotting history	.003	.22
Hypothyroidism / Clotting history	.04	-.14
Clotting history / Post COVID-19	.02	.19
Clotting history / COVID-19 vaccinated	.04	.15

Among 136 samples 70% were used as training data and 30% were used as testing data (41 patients) which was randomly chosen. Present and predicted heparin doses were compared for the testing samples. Among 41 testing patients, variation was seen in 10 patients. Out of those 10 patients, 7 patients heparin dose was increased to 7500 U and 3 patients heparin doses was decreased to 5000 U based on the risk (Figure 3).

Figure 3: Present heparin dose and predicted heparin dose



Accuracy, precision, sensitivity and F1 score for ML are expressed between 0 and 1. Accuracy obtained for our ML model is 0.80. Precision value for the model was 0.91 for 5000 U and 0.17 for 7500 U. Sensitivity obtained for 5000 U is 0.86 and for 7500 U is 0.25. F1 score for 5000 U is 0.89 and 7500 U is 0.20. The Macro average is the average precision, recall and F1 score between classes. Macro average doesn't take class imbalance into effort. Since we have class im-balance we take this into consideration. Macro average for F1 score is 0.54. According to the weighted average, weighted means each metric is calculated with respect to how many samples are there in each class. This metric will favor the majority class (high value for each class containing more samples). The weighted average for F1 score is 0.82. The values of the ML results obtained is mentioned in the Table-3.

Table 3: Machine learning reports

	PRECISION	RECALL	F1 SCORE
5000 U heparin dose	0.91	0.86	0.89
7500 U heparin dose	0.17	0.25	0.20
Macro average	0.54	0.56	0.54
Weighted average	0.84	0.80	0.82
Accuracy			0.80

3.1.DISSCUSSION:

In this study, we used a total of 136 hemodialysis patients under heparin treatment. Using AI-ML under decision tree classifier algorithm heparin optimization was initiated for HD patients with post COVID-19 status. As a result, a prototype model of ML was developed. Out of 41 testing samples, variation was seen in 10 samples (24.39%) when compared to conventional protocol for heparin dosing. The developed prototype model is advantageous over the conventional protocol. This is similar to the article12,14,15 in which an AI was developed using reinforcement learning for optimization of anemia treatment in HD patients.

Post COVID-19 patients, COVID-19 vaccinated patients, obese patients, patients with increased ionized calcium level, anemia patients, increased vitamin K intake involved in this study showed increased risk of clotting during hemodialysis. Patients with hypothyroidism, low serum albumin level had decreased risk of clotting during hemodialysis.

3.2.CONCLUSION AND FUTRUE WORK:

A Prototype model of ML was developed with a sensitivity score of 0.86 and the model accuracy was 0.80. The optimization of heparin dosing by ML provides promising performance. Heparin dose adjustment for ESRD patients during hemodialysis reduces the hypercoagulation related complications. This model is advantageous when compared to the conventional protocol. Patients with low serum albumin level and hypothyroidism shows reduced risk for clotting. Patients with increased ionized calcium level, obesity, anemia and vitamin K intake shows increased risk for clotting. The evidence from the research indicates that both vaccination and the post-COVID condition may be associated with an increased risk of clotting. It is essential to conduct further comprehensive studies to thoroughly examine and comprehend any potential connections between these factors. As a future work, this model has to be fine-tuned to improve the sensitivity score and the model accuracy (approximately 0.99), to analyse other influencing factors for clotting and to predict heparin dosing for more complex data. Based on the patient medical information, heparin dose can be calculated using automatization by machine learning at any time and could be accessed by authorized healthcare professionals in hospitals.

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