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COMPREHENSIVE ANALYTICAL STUDY ON VITAMIN D DEFICIENCY PREDICTIVE MODELS

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Abstract

The majority of the human population presently suffers from a deficiency of Vitamin D. The rich diet and exposure to sunlight is the key source and the deficiency more frequently affects people during the winter season. Several disorder progressions linked with Vitamin D deficiency include Cancer, Multiple sclerosis, hypertension, rheumatoid arthritis, muscle weakness, and diabetes. The study reviews the prediction of Vitamin D deficiency on Various methods including conventional methods, statistical methods, and Machine Learning approaches by investigating the results in recent years. The main objective of the review is to analyze the methods of vitamin D prediction in various studies and the comparison of Machine Learning algorithms such as K-nearest neighbor's(KNN), Decision Tree(DT), Random Forest(RF), Adaboost, Stochastic gradient descent(SGD), Support Vector Machine(SVM), Multilayer Perceptron(MLP), Naïve Bayes(NB), etc and to estimate the performance metrics of the algorithms includes accuracy, precision, F1-score, sensitivity, specificity, mean absolute error, mean square error were compared to identify the best-fit model and to overview the non-invasive method of prediction with Vitamin D biomarkers such as tear fluid, saliva, hair mineral and skin impedance. A Deep learning approach is also an excellent criterion to be emphasized. Concepts of wearable devices on the prediction and continuous monitoring and their contribution to non-invasive prediction are discussed. The review findings help to avoid the limitations of high cost in Vitamin D testing and aid the clinicians in providing the best treatment at the required time.

Keywords: vitamin D, Machine learning, Chronic diseases, non-invasive, Machine Learning, Prediction methods

INTRODUCTION

Vitamin D plays a key role in the maintenance of bone metabolism and calcium. Diseases such as cancer, rickets in children, diabetes, and cardiovascular diseases are linked with the deficiency. Skin synthesizes ergocalciferol (Vitamin D2) and Cholecalciferol (vitamin D3) Liver circulates the major form of vitamin D (25 hydroxy vitamin D). Kidney hydrolyses 1 alpha,25-dihydroxy

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vitamin D(1,25(OH)2D). The small intestine takes the circulating 1,25(OH)2D and the calcium absorption in the intestine is enhanced. The osteoblasts were stimulated by 1,25 dihydroxycholecalciferols to form osteocalcin and produce alkaline phosphatase activity in the bone[1][2][3]. Healthy skeleton maintenance and development is from the effect of Ultraviolet B (UVB) radiation in the sunlight. Other tissues and cells in the body along with kidneys produce CYP27B1. The Parathyroid hormone (PTH) and fibroblast growth factor-23(FGF-23) also regulate the CYP27B[4][5][6]. Chronic Diseases can be prevented or diagnosed prior with the help of Vitamin D deficiency prediction. The frequent method of prediction is carried out with the blood sample. The recommended guidelines for serum 25-hydroxyvitamin D (25(OH)D) concentrations are stated as more than the value of 50 nmol/L(20ng/mL). Concentrations of serum 25(OH)D below 25-30nmol/L(10-12ng/ml) must be noted and clinical help should be provided to prevent Chronic diseases[7][8]. Vitamin D fortification in food is very much needed to improve public health. It is necessary to reduce the cost of Vitamin D testing and to avoid the harmful effects of over-supplementation [9][10]. The data indication availability shows that this deficiency is a major health issue in public mainly in MiddleEasterncountries[11]. The intake of Vitamin D from Fortified foods is also a source of Vitamin D[12]. Blood sample testing provides accurate results in various health management [13]. TheLifestyle, socio-demographic, and dietary determinants were examined in a cohort of 6-year-old children in the Netherlands to describe the status of vitaminD[14].Sunlight exposure plays a vital role in the consumption of Vitamin D[15]. The risk factors affecting the status of vitamin D were found in premenopausal females in Karachi. By considering the confounding factors this deficiency prevailsover one-fourth of the Australian population leading to obesity, Season, and life activity[16][17]. The study focuses on comparing the data analysis performance and predicting Vitamin D deficiency using the different algorithms of Machine Learning [18,114].

PHYSIOLOGY OF VITAMIN D

Amongst the Vitamins defined Vitamin D is fourth in sequence and plays a vital role in healthy metabolism. The two main isoforms are Vitamin D3 (Cholecalciferol) and Vitamin D2(ergocalciferol). Ultraviolet -B Induces Vitamin D production in the skin about 80% of vitamin D is from the above source and the remaining is from the intake of Vitamin-rich foods like eggs, fish, and, Fortified food with Vitamin D[19]. From the different sources of vitamin D supplements variations can be obtained related to genetic, environmental, and lifestyle factors[20][21]. The liver hydroxylases vitamin D which produces the serum 25(OH)D a strong bio-marker to determine the status of vitamin D. The active vitamin D is termed as 1,25dihydroxyvitamin D(1,25(OH)2D) or Calcitriol. The renal hydroxylases 25(OH)D and produce 1,25(OH)2D and rely on the mineral metabolism regulators. These regulators are Parathyroid hormone (PTH), Phosphate, and Fibroblast growth factor-23(FGF-23). metabolites of vitamin D in circulation bound to Vit-D Binding protein (DBP)with a small value to lipoproteins and albumin less than 1%. Along with

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Megalin -Cubilin very few tissues accept DBP-bound vitamin D and protrude through the membrane of the cell to get way to VDR which is intracellularly located. The metabolites of Vit D from 24-hydroxylation initiate the catabolism of vitamin D and finally, the bile and urine excrete [22][23]. Vitamin D is the photochemical product where isomerization is carried out in the skin to produce vitamin D and it is taken by hepatic cells where vitamin D is hydroxylase by CYP2R1. Mucous cells in the intestine are accompanied by dietary fat and absorb dietary vitamin D. Triacylglycerols, phospholipids, and cholesterol along with vitamin D enter the mucosal cell membrane. The two metabolic processes are carried out in hepatocytes at the same time. They are 25-hydroxylation and chylomicron lipids to triglyceride and cholesterol, VLDL. Liver cells bound this to DBP in blood [24]. Intestinal calcium absorption is the main function of vitamin D and Clinical support should be provided for the low status observed in the test[25][26].24,25-dihydroxy vitamin D3(24,25(OH)2D3) stimulates bone mineralization, secretion of parathyroid hormone, and development of embryonic maintenance C-24 hydroxylation and modifications of other side chains are catabolic and maintain the homeostasis of vitamin D [27][28].

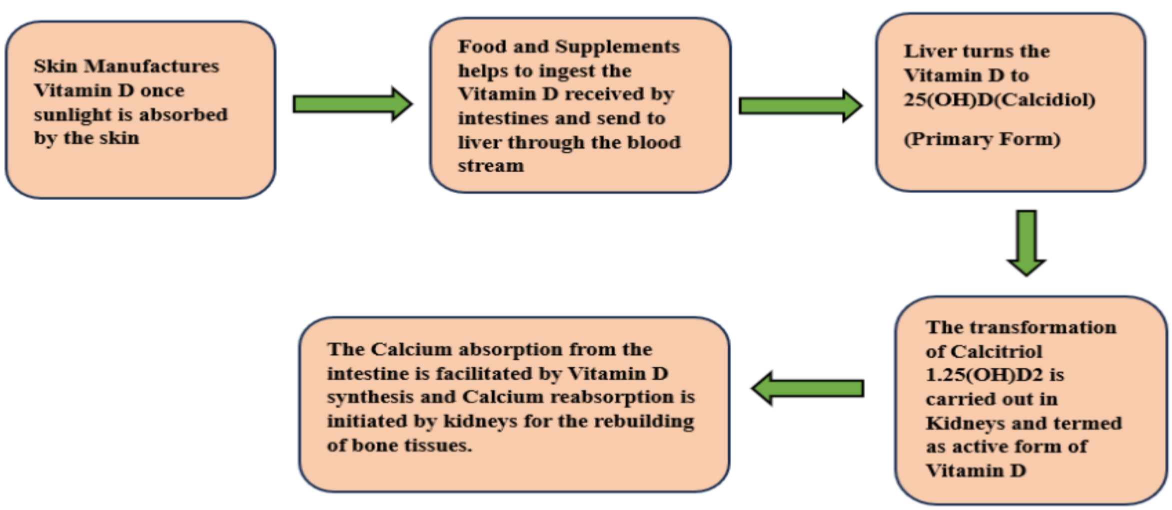

Figure 1. **Metabolism of Vitamin D in the Human Body**

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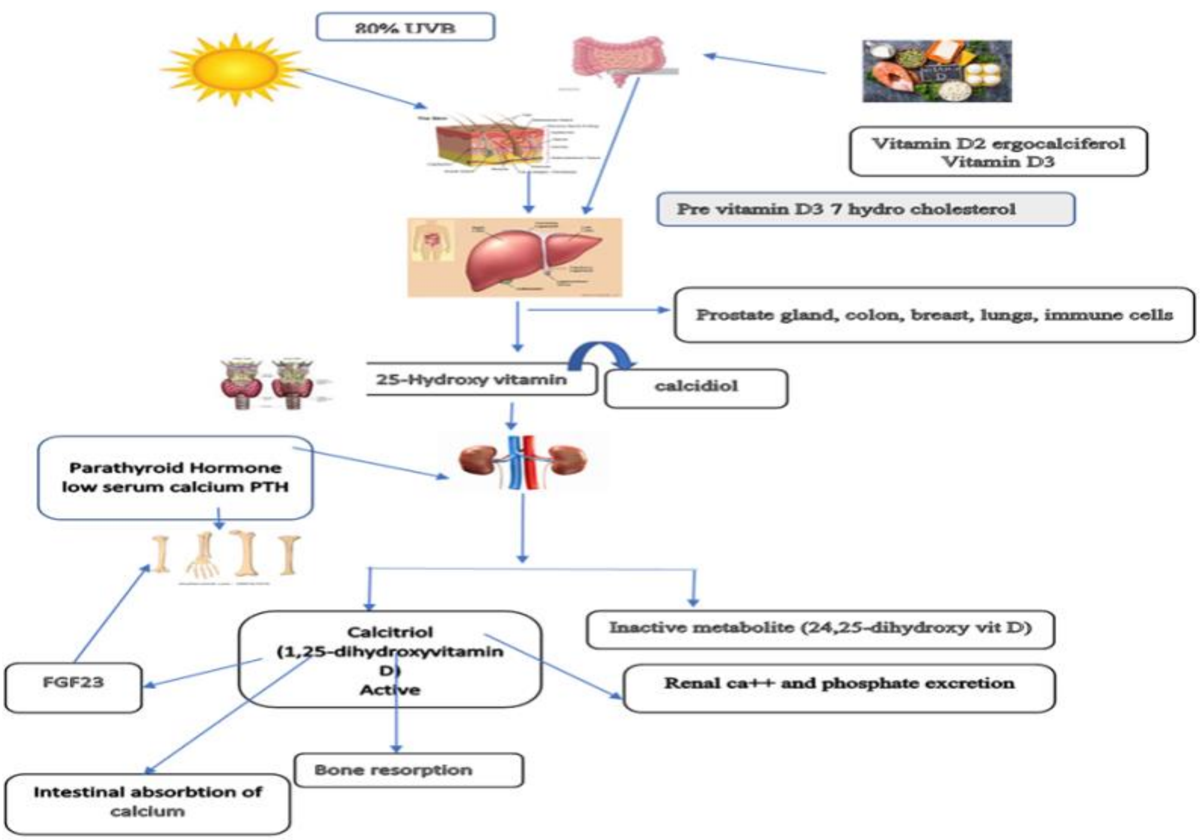

Figure 2.Pictorial representation of Vitamin D Signalling pathways

Figure 1,2 represents the Metabolism of Vitamin D in the Human Body and the signaling pathways. The Vitamin D is Converted to 25(OH)D serum by the Liver and the Serum is again Converted to 1,25(OH)2D and 24,25(OH)2D by the Kidney.

FACTORS TRIGGERING VITAMIN D DEFICIENCY

The major source of cholecalciferol is the skin and it is produced due to the ultraviolet B (UVB) radiation from the sun. Low UVB reduces the production of vitamin D in the skin and depends on the season, air pollution, etc. Numerous chemicals and toxins were dispersed by the industries continually into the environment. Tobacco smoke was exposed to a fraction of the population. The factors triggering vitamin D deficiency are the source of air pollution exposure, chemicals in the

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environment, tobacco smoke leading to a decline in serum level, and metabolites which are considered as the main factor including calcifediol 25(OH)D and 1alpha, (1,25(OH)2D 25-dihydroxy vitamin D (calcitriol) [29]. Minimal activity outdoors, and blockage of UVB photons lead to the deficiency. VD homeostasis involves in shortage of Cholecalciferol and less intake of VD in the intestine gene modulation. In polluted areas, vitamin D deficiency is more prevalent and this leads to lower bone alkaline phosphatase. Greater than 5000mg/week intaking calcium gives protection against pollution[30]. This study provides information on atmospheric pollution reducing the ground level UVB. The study was carried out in highly polluted areas (Tehran) and low-polluted areas (Ghazvin) [31].Vitamin D deficiency and obesity are associated with each other leading to risk factors. The air pollutants avoid UVB radiation and reduce exposure to the sun resulting in low vitamin D in the skin, combined with an unfair lifestyle.

The hypothesis can be framed by stating that an unhealthy diet, lifestyle, use of sunscreen, and pollution can cause low serum resulting in obesity by affecting adipose tissue and increasing metabolic rise [32][33][34].The association between patient-specific parameters like teeth numbers,25(OH)D level, gender, smoking history, and Low-density lipoprotein (LDL-C) isanalyzed. Particularly periodontitis and radiographic bone loss were familiar with Vit D deficiency. The experiment was carried out in mice whether cigarette smoke for deficiency in Vit D creates a risk in skeletal muscle hypertrophic response[35][36]. Compensatory overload causes plantar hypertrophy and the data shows that not only relying on two factors exposure to CS and Vitamin D deficiency changes the response of hypertrophic with overloadedmuscles but is also associated with cigarette smoking. Chain smoking causes ischemic stroke with a high rate of depression resulting in low vitamin D levels[37][38][39].

AVAILABLE METHODS OF PREDICTING VITAMIN D DEFICIENCY

4.1Principle of vitamin D measurement on existing methods

The metabolite 25(OH)D present in blood indicates that (OH) is bound to the 25th carbon of vitamin D. It is necessary to conduct blood tests through blood sampling to measure this serum. This is the frequently used methodology. Vitastiq is one of the existing devices for vitamin D measurement. Based on the electro-acupuncture methodology an electronic device is activated to find the status of vitamin D with a pen-like structure with a free vitastiq app to indicate the level. Another way of identifying the status is the Cue math tracker by collecting blood samples from the body or body fluids. Thedevice measures the status of vitamins with stick-like products placed in a cue box. One of the advanced technologies used in tracking vitamin D statusisthe use of a smartphone. It’s like a credit card reader associated with a smartphone. The levels of cholesterol and vitamin D can be measured with this device attached to a smartphone camera with the use of a drop of blood. The test strips were used to have a response from the blood and the levels were indicated in the display. The next two methods were an Impedance principle-based quantum

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analyzer to measure the body's metabolic function and an enzyme-linked immunoassay (ELISA) (Enzo, ADI-900-215) analysis on vitamin D [40]. Several serious health issues are related to the deficiency of Vitamin D and it is also included in pregnancy and considered a major public health concern. The issues related to pregnancy include Pre-eclampsia, gestational diabetes, fetal growth restriction, cesarean section, etc. The statistical method is used to analyze the relationship between serum 25(OH)D maternal and neonatal outcomes. The statistical methods including the Proportions, odds ratio, means, and medians, were obtained. Meta-analysis was also done meta-regression was used for predictive effect and heterogeneity variables[41]. The cohort study was carried out to evaluate the serum associated with neonatal pregnancy and adverse maternal outcomes. The sample of blood collected from each woman and the serum levels were estimated using ELISA. The continuous variables were described with mean and standard deviation. The analyses of categorical data were carried out with the chi-squared test and Fisher's exact test[42] The review was conducted on the analysis of vitamin D globally. The problem is higher in Middle Eastern countries and there was a lack of data regarding children, adolescents, and most of the countries in South America and Africa, the indication of this report specifies that deficiency of vitamin D is a global health problem[43].New food sources were introduced in Canada and the USA to have vitamin D-rich food, so the fortification of food led to Bio-addition staples by adding vitamin D-rich content in animal feed, and food manipulation on pre-processing**.** Many studies concentrated on demographic and anthropometric data to analyze Vitamin D status [44][45]. The Vitamin D screening tool visualization is an important criterion.The friendly usage and feedback response on the status of vitamin D is based on the respectivevalues[46][47].The Various methods for Vitamin D measurement are given in the traditional approach.

Table 1.Vitamin D status with analysis of serum 25(OH)D

Deficiency	<10ng/mL	(0-25nmol/L)
Insufficiency	10-30ng/mL	(25-75nmol/L)
Sufficiency	30-100ng/mL	(75-250nmol/L)
Toxicity	>100ng/mL	(>20nmol/L)

Table 2. Methods of Vitamin D Measurement

HPLC	High-PerformanceLiquid Chromatography
RLA	Radioimmunoassay
ELIZA	Enzyme-linked immunosorbent assay
ICMA	Immuno Chemiluminometric assay
UVA	UV absorption

Table 1,2 clarifies the status of vitamin D and the methods of Vitamin D measurement to analyze serum 25(OH)D.

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4.2Literature Survey on Vitamin D Deficiency Prediction Using Statistical Methods

Table 3: Literature survey on Statistical method for prediction of Vitamin D Deficiency

Author year	Region and Population	Age mean +-SD	Statistical Method	25(OH)D level nmol/l+-SD	Limitations
Trudy Voortman etal.2022 [48]	Netherlands 4167 children	6yrs median 64nmol/L	Multivariable model	6.2%<25nmol/L 23.6%deficient (25 to 50 nmol/L) 36.5%sufficient (50 to <75nmol/L) 33.7% optimal>=75nmol/L)	Nodata available on vitamin D intake for 6yrs children
V. FONSECA et al. 2011 [49]	Saudi Arabia 31	Median 45 yrs. Range (22-65)	Mann-Whitney U-test	Village/rural 7-5 <2-18 Apartment 4<2-15 >30minsun exposure 8 <2-18 <30 min 5 <2-8	Limited data
Aysha Habib Khan et al.2012 [50]	Karachi Pakistan 305	31.97±8yrs 25.06±5.6kg/m 88.42±13.3cm	Chi-square test ANOVA Multiple Linear Regression	91.50%vitaminD deficient. Females <50nmol/L Insufficient 5.2% Sufficient 4.3%	No data on genetic determinants of vitamin D

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Gill, Tiffany K. et al. 2014 [51]	South Australia 2413	Male 49.6±16.2 Female 51.5+-16.9	T-tests Chi-square tests Anova	22.7%<50nmol/L High-level 25(OH)D insummer and in autumn. 25% lower in the case of obesity. Low serum found in smokers' criteria.	Information self-reporting health risk factors was limited
Lubna I. et al. 2017 [52]	Saudi women 87	18-32 years	Multiple linear Regression model	7(8%) sufficient 8(9.0%) insufficient 52(59%) deficient	A large study needed to examine hypovitamino sis
T. Merlijn et al. 2018 [53]	Noord-Holland 2689	65-90 yrs	Logistic regression with backward selection	10.1%25(OH)D concentration 61.5nmol/L 9.9% 36nmol/L	Toxic levels of serum not shown

Table 3 explains the literature survey on Vitamin D deficiency with statistical methods and elucidates the limitations of the survey.

4.3Machine Learning in Vitamin D Prediction, Diagnosis, Decision Making and Analysis

Machine Learning is the concept of making machines learn from the experience adopted. Most versatile machine learning methodologies are named as supervised learning, Semi-supervised,unsupervised learning, and Reinforcement learningwith algorithms including large sets. It obtains excellent performance and can be applied in various areas for processing and analysis of data[54][55]. The classification ofthe supervised learning method is explained with differentiation.The techniques are based on the logic that deals with a Decision tree and a set of learning rules. whereas techniques based on perceptron deal with perceptron having single, multi,and RBF networks.The techniques of statistical learning havea Naïve Bayes classifier and Bayesian network.The learning based on instance has KNN and SVM provides high accuracy in problem classification[56]. The diagnostic performance on older patients showed high accuracy with ML algorithms and the RF model exceeds the logistic regression in identifying peripheral

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arterial disease[57].Risk factors and Insulin Resistance prediction in chronic kidney disease is carried out by ML and the output confirms that RF proved to have high accuracy with good AUC and SHAP differentiation in value[58].Machine learning models were developed to get accuracy and scores of precisions greater than 90% for prediction severity levels indiseasesthat attained 95.5% precision, 94.8% F1score, acc-95%,and AUC-94%.Thisprediction showed that serum levels of calcium can be used for COVID-19 severity assessment with automation[59]. Auto ML for prediction of risk and assessment in behavior were used in decision-making and trajectory motion planning of vehicles which is autonomous[60]. Machine Learning has many applications particularly most versatile is Data mining. The classification techniques used in this analysis are Decision Tree, BayesianNetwork-Nearest Neighbor, SVM,etc. The advantages and disadvantages of Machine Learning were discussed with big data[61]. Parameters fine-tuning is needed for classification in Machine Learning and for a particular set of data the learning algorithm can be the bestbut it is not sure for another set of data. SVM, NB, and RF algorithms of Machine Learning provide greater precisionand accuracy.Processing environments with distributed conditions should be included for huge datasets[62]. Machine Learning combined with cloud computing was used to predict the spread of COVID-19 with high efficiency.

To develop a framework iterative weighting for a generalized inverse Weibull distribution fitting model is used. To obtain high accuracy and prediction inreal-time, a platform of cloud computing is implemented**[**63]. A new method of topology is framed to improve the ideas of performance metrics and to enhance the work in regression algorithms handled in Machine Learning[64]. Much research was carried out on studies applied to a Supervised machine learning algorithm which is executed for more than one criterion on the same disease identifications, RF, and Naïve Bayes algorithms were used frequently and Random Forest showed higher accuracy. Various supervised learning algorithms' performance was measured on prediction [65]**.**Nearly 2 million people'sdata on electronic health records were used for the classification of patients diagnosed with incident atrial fibrillation for 6 months. Neural networks with a single layer showed excellent classification.Compared with logistic regression this model performed moderately on parameters like age,gender, and risk factors for fibrillation in atrial, and the output obtained showed the value of AUC-0.794 and F1 score-0.079.The values with incorrect test results and some elements of data were excluded,due to these limitations the model shows insufficiency inmedication on anticoagulation[66]**.** Health care system with smart applications based on IoT-Cloud is framed for the prediction of heart diseases using FIS (Fuzzy inference system) and Recurrent Neural network with LSTM (Long short-termmemory) which is bidirectional. The result shows the prediction with accuracy -98.85%, precision- 98.9%, Sensitivity, and specificity values are 98.9 and 98.89%, and F1 score -98.85%. Deep learning is the subset of Machine learning which shows higher efficiency by handling huge data at speed with exceptional criteria and solving critical problems[67]. The currently leading retinal disease Glaucomacreates a serious issue inthe eye due to Intraocular

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pressure. It can lead to loss of vision and damageto the Optic nerve head (ONH).Diagnosing manually takes more time and this problem can be rectified by using the Deep learning approach. Convolutional neural network (CNN) provides the higher-end result for this prediction of Glaucoma.Recurrent Neural Network (RNN), deep Belief Network (DBN), Restricted Boltzmann Machine (RBM), and Density-Based Spatial Clustering (DBSCAN) play a vital role in Deep Learning.

Two separate architectures of CNN were used to segregate the optic cup (OC) and optic disc (OD) to get the perfect disc[68]. Techniques on Machine learning provide an excellent prediction of problems with mental health in adolescence. A model can detectand compare many ML techniques provided like Random Forest, Neural network, Support Vector Machine, and XG Boost finally the output is examined and the algorithm outperforms the logistic regression. Amongst all Random forests showed high superiority with AUC-0.739[69]. Prediction of Chronic Kidney Disease Using Machine Learning provides an excellent output and the techniques used for feature selection are the Wrapper method, LASSO regression, and feature selection based on correlation. The classification algorithm included viz.C5.0, ANN, Logistic regression, SVM, KNN, and Random tree.

SMOTE technique is used for dataset balance and LSVM obtained 98.8% accuracy and Logistic regression showed poor performance[70].From 1647 patients with obesity and hypertension, a Supervised learning algorithm was developed to observe the risk factors, on the Threshold for type 2 diabetes mellitus (T2DM). K-Nearest neighbors showed 99% sensitivity,78% specificity and PPV of 96%, NPV of 94%. The main identification is regarding the patients whohave the chance of getting diabetes within the period of 2 years. The limitation of this concept is that other diseases cannot be generalized. It is not concluded whether the Homeostatic model Assessment for insulin (HOMA-IR), Body Mass Index (BMI), and insulin are the causes of T2DM[71]For neurologic and psychiatric diseases Deep learning is an excellent tool in recent identification and through the transformation, of a nonlinear function, the Deep learning models can able to learn the more complex representations[72].

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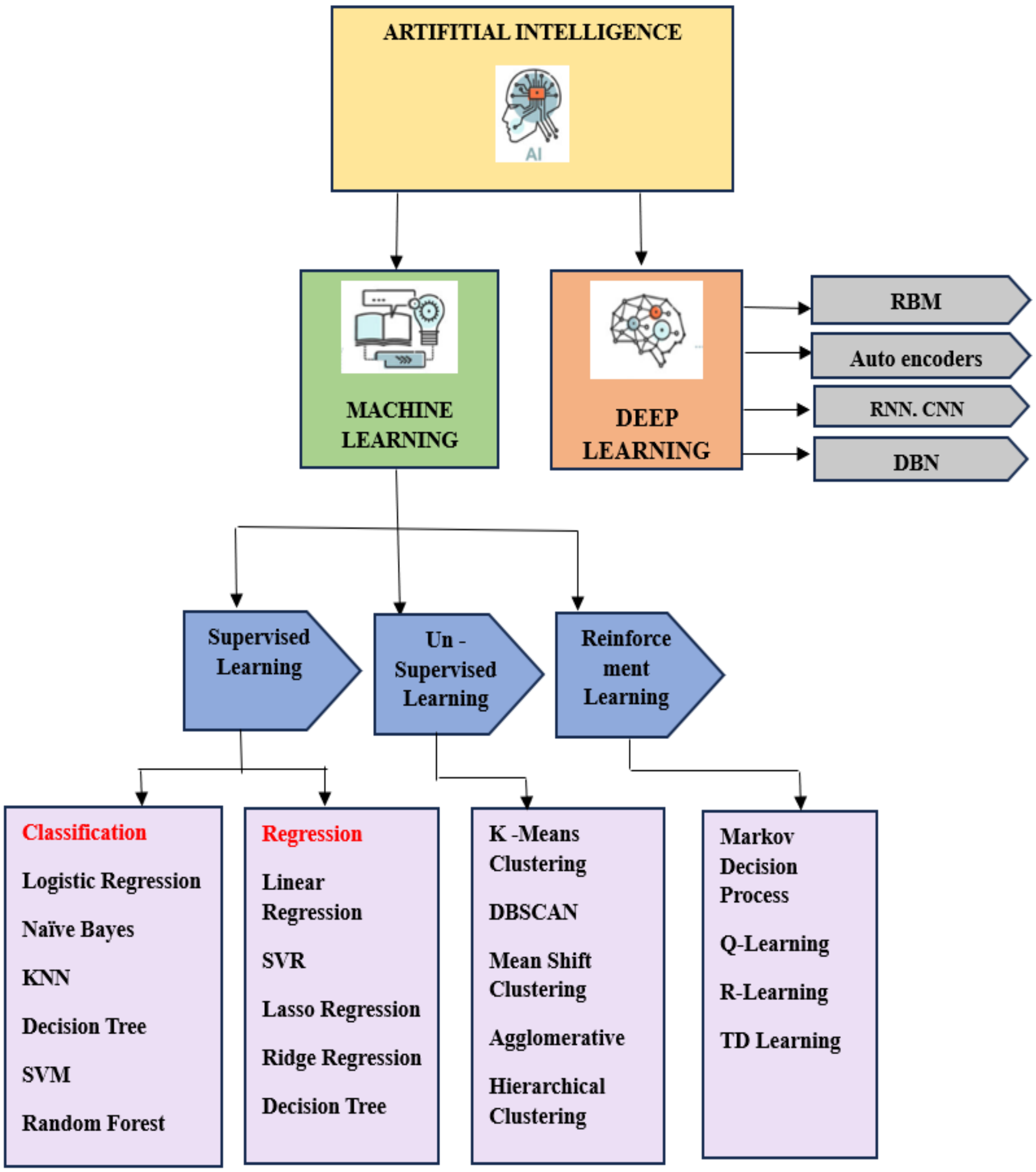

Figure 3.Types of Machine Learningand Deep Learning Methods

Figure 3 portrays the overview of Artificial intelligence, Machine Learning, and Deep Learning methods and algorithms to predict the severity.

4.3.1 Machine Learning Approach for Prediction of Deficiency using Dataset.

The work flow in Machine Learning approach elaborates the data usage and prediction to get higher end performance.

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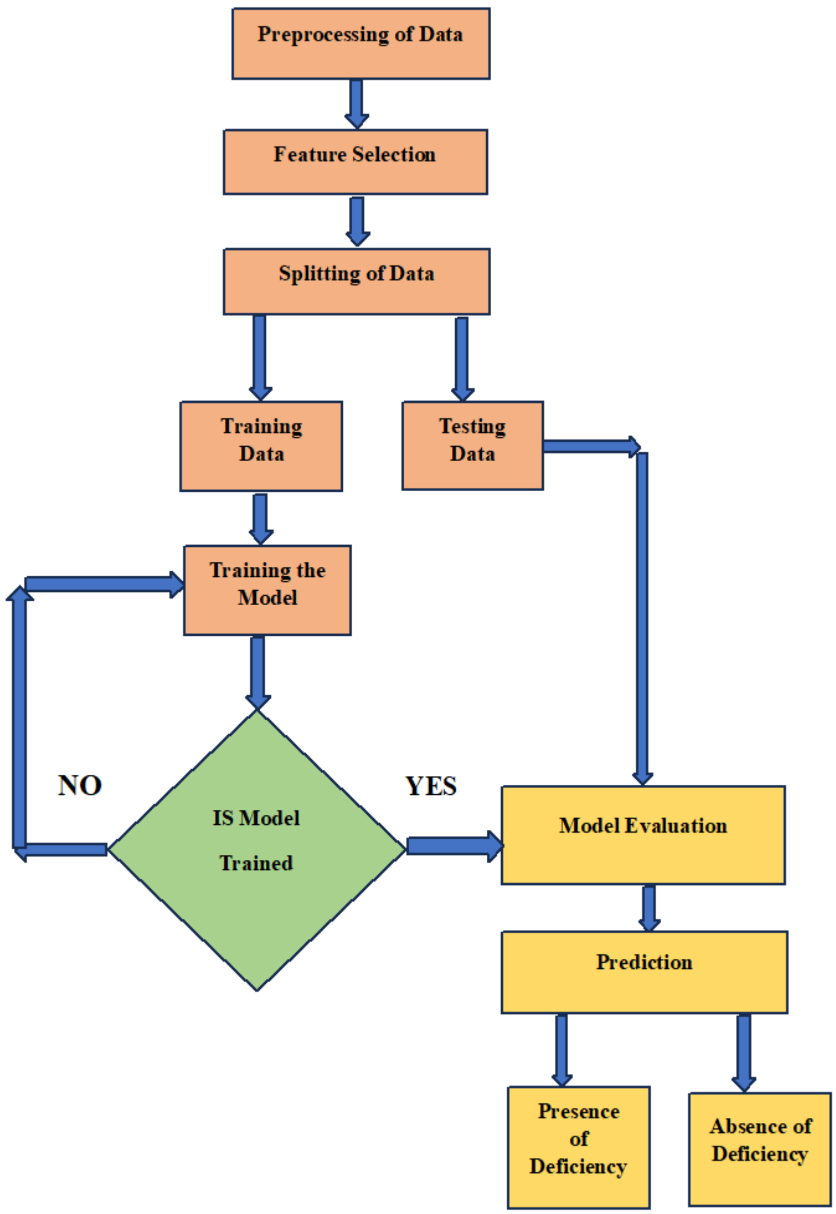

Figure4.Workflow in the Machine Learning Approachfor DeficiencyPrediction

In Figure 4, The stages contain the cleaning of data, Selecting the required features from data by using the Feature selection algorithm, and the data is split into training data and test data, Various Machine Learning algorithms are applied, and the best-fit model is selected. The Machine Learning approach for the prediction of deficiency is elaborated with the Flow chart in Figure4.

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Table 4. Findings on Vitamin D prediction using Machine Learning approach.

Authors	Size of the Sample	Vitamin D cut-off value	Features related to cultural/ ethnic/area	Methods used	Observation and Results	Limitations
Shuyu Guo et al. [73]	494	<75nmol /L	Caucasian adults	Non-linear radial basis Function Support Vector Regression (RBF SVR)	RBFSVR is compared with MLR and showed high accuracy with PCC-0.74, MLR obtained PCC-0.51	The dataset for Validation is available with limited criteria.
Rafael Garcia-Carretero et al. [74]	221	Deficiency<20ng/mL	Mostoles University Hospital Madrid, Spain	Classical step-wise Logistic regression. LASSO (Least absolute shrinking selection operator) Elastic Net	In obese hypertensive patients, Vit D deficiency can be predicted using Penalized methods like LASSO and Elastic Net with AUC-0.74, and AUC-0.76.	A sample with a small size and potential confounders results in bias.
G. Sambasivam et al. [75]	3044 (18-21) years	Deficiency severe sufficiency In-sufficiency	Puducherry India	K-Nearest Neighbor (KNN) Decision Tree (DT) Random Forest (RF) Ada Boost (AB)	Identifies the best Machine learning classifier for predicting the severity of Vitamin D Deficiency.	Adequate datasets are not available for all age groups.

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				Bagging Classifier (BC) Extra Trees (ET) Stochastic Gradient Descent (SGD) Gradient boosting (GB) Support vector Machine (SVM) Multilayer perceptron (MLP)	Random Forest-94%accuracy Precision-0.96 Recall-0.96 F1 measure-0.96 ROC-0.8	
Rafael Garcia Carretero et al. [76]	1002 Hypertensive patients	NA	Spanish University hospital	Logistic Regression Support Vector Machine Random Forest Naïve Bayes	SVM exceeds all the other algorithms Sensitivity-98% NPV-71% Accuracy-73%	Higher error percentage can occur due to the selection of the wrong work
B. Padmaja et al. [77]	3000 People	0-sufficiency 1-in -sufficiency	NA	Support vector machine Random forest classifier	Decision tree classifier accuracy-56% Ada boost classifier accuracy-55%	All age groups were not added. For large differences, the dataset will be unbalanced.

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		2-deficiency 3-severe deficiency		K Neighbors classifier Logistic Regression MLP-ANN classifier SGD classifier Gaussian NB Extra tree classifier Gradient boosting classifier Ada boost classifier	Gradient boosting classfier-68% Extra tree classifier - 73,3% RF-72% The extra tree classifier exceeds another classifier with accuracy. The SMOTE technique is used to remove unbalanced data.	
Mohamed Choukri etal. [78]	124 9-87 years	NA	Oujda University Hospital Centre	Linear Regression Multivariate Adaptive Regression Spline (MARS) Random Forest (RF) Support Vector Regression (SVR)	The SVR model showed better results than the Random Forest	Weak correlations were observed between biomedical parameters like glucose and calcium and Vitamin D
Mali he Karamizadeh Akbar	201 Age 20 to	<30ng/mL	Shiraz, Iran	Conditional tree Conditional forest and	From the observation, conditional forest and	The nature of cross-sectional criteria

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Zadeh et al. [79]	40 years			Random Forest	random forest output declared that the vital concept was the intake of 50,000 IU Vit D3 as a monthly supplement.	reduces the ability to make causal inferences. The generalization of results is not framed for other people.

Mary Waterhouse et al. [80]	1788 Training 447 Testing	50,60 and 75 nmol/L	Older Australians	Boosted Regression tree model	D-health trial identifies a reduction in the rate of mortality and cancer prevention on vitamin D supplementation for 1788 datasets 10.5%<50nmol/L 23.1%<60 nmol/L 48.8%<75nmol<L.For 447 11.9%<50nmol/L 25.7%<60nmol/L 49.2%<75nmol/L	Errors remain due to the intervention of participants' lack of collection of data.
Sayed Sajjad Sharifm	99 ms patients	NA	Iran	Support vector Machine	The diagnostic model based on the support	Less number of datasets.

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onsavi et al. [81]	81 healthy people			algorithm (SVM) Decision tree (DT) K Nearest Neighbor.	vector machine method had high accuracy (98.89) %. Sensitivity (98.9) % and (98.98) %	
Carmen patino-Alonso et al. [82]	Ref population -43,946 Recruiter participants-501	Levels below 20ng/mL	Spanish people 35-75 years	Logistic regression Naïve Bayes Random forest	Considering gender, the efficiency of predicting Vitamin D varies. WC, WHtR, VAI, BMI, and BRI are highly useful for males in prediction, whereas CUN-BAE showed high usage in females.	The causal relationship between the anthropometric parameters and vitamin D was hindered**.** Many variables on confounding were not considered**.**
Otilia perichart-perera et al. [83]	192 Women	Adequate >30ng/mL	Mexico City Data from OBESO (Epigenetic and Biochemical origin of overweight and obesity)	Artificial Neural Network	An artificial Neural network model is used for SGA prediction and excellent output is obtained with an accuracy of 86% AUROC-0.8 Small gestational age can be	P-BMI self-reported was used which produces a bias in the classification of weight additional datasets are needed.

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					predicted early with the help of this model.	
Freshtehosmani et al. [84]	292 patients	NA	Iranian Society	Decision tree algorithm	Ageand BMI are the predictors independent of VDD.	Many factors influence vitamin D serum levels like food, lifestyle, etc.
Meng Ni et al. [85]	23,394 patients	<50nmol/L	Eastern coastal China	Logistic regression	Due to Vit D insufficiency, the Gestational Diabetes Mellitus(GDM) rate and Preeclampsia are greater and affected by intrauterine infection	It was not sure that maternal vitamin D with lower concentrations could lead torisk admission.
Fariba Aghajafari et al. [86]	1100	< 70nmol/L	NA	The statistical method is used to find the relationship between the 25(OH)D serum maternal and neonatal outcomes.	Several serious health issues were associated with vitamin D deficiency including in pregnancy and it is considered a major public health concern. The issues related to pregnancy	Dose-response relation cannot be visualized between outcomes and 25(OH)D levels. Insufficiency of data at high levels of 25(OH)D cut-off levels. There was no optimal quality

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					include pre-eclampsia, gestational diabetes, fetal growth restriction, cesarean section, etc.	of studies and it led to confounding factors in individual studies.
Ankana Ganguly et al. [87]	NA	<50nmol/L	NA	This paper defines the relationship between Vitamin D in early pregnancy and analysis was done to predict implantation and miscarriage.	Vitamin D receptor (VDR) and Cytochrome enzymes(CYP 27B1) expression of placental at early stages inform the importance of Vitamin D in the physiology of placental.	In Pregnancy, vitamin D supplementation trials are needed for women between 10 and 18 weeks of pregnancy.
WU. Yangian et al. [88]	41	<60nmol/L	NA	External validation Meta-analysis	The Proposed model identifies the risk of osteoporosis	To date, a small range of reports of vitamin D deficiency reported but this has to be expanded to achieve better results.

Table 4 illustrates the prediction of vitamin D using the Machine Learning approach with the algorithms used and performance measures for model evaluation.

4.4 Discussion on Non-invasive Methods of Finding Vitamin D Status.

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Table 5. Findings on vitamin D status for Non-Invasive methods

Authors	Methods used	Observation	Data set	Accuracy	Limitation
Iltaf Shah et al. [89]	Statistical Method	The Non-invasive concept and low risk of infection, with storage comfortability and sample transportation are the merits.	Sample collection	99%	Sample sizes are small, and different age groups, Populations, Variations in serum, and combinations of color.
Sahar Ajabshir et al. [90]	Multiple linear regression Analysis	To estimate 25(OH)D levels, non-invasive tools in indirect concept were used noted as skin color, exposure to the sun as well and intake of Vit D supplement.	Questionnaire	Insufficiency vit D for participants 77.6%	Huge portions of Vitamin D serum are unexplained.
Swaminathan Sethu et al. [91]	Statistical Methods	The observations from the current study suggest that 25-hydroxyvitamin D is present in tear fluid and its level was found to be higher than in the corresponding serum in humans	Chemiluminescent Immune Assay ELISA	3.3 and 27.5ng/ml mean±SEM 9.4±0.7ng/ml Median8.4ng/ml Higher value mean±SEM 17.0±1.6ng/ml	On analyzing the correlation between tear vit D and disease on the ocular surface the severity can be determined.

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				3.2-45.8ng/ml Median 16.3ng/ml Average of 2-fold(mean± SEM)1.9±0.2 Range 0.4-5.8 Median 1.7	
Elahe Allahyari et al. [92]	Artificial neural networks (ANNs) data mining analysis	Calculating the difference between levels of basal and post-supplementation the variation in Vit D level can be obtained. ANN model was used for the performance.	Questionnaire	For low values the sensitivity - 66 AUC-70.38% For moderate value The sensitivity-66% AUC-62.66% For low value Sensitivity-60 AUC-65.1%	There are no control group surroundings in the actual study and a lack of Consensus surrounding observing the no of hidden neurons.

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Haytham Eloqayli et al. [93]	ANN artificial neural networks (ANNs	To analyze whether Vitamin D and Ferritin are risk-modifiable factors using slandered statistics and ANN for chronic neck pain.	Questionnaire	The output of the ANN model reveals that 92 out of 108 samples were classified correctly with an accuracy of 85%	A limiting factor is the small sample size
Jin-Chul Heo et al. [94]	Statistical method	Noval Method of finding the status of vitamin D using bio-signals. The concentration of vitamin D is stated at a frequency in the body by skin impedance and correlated with body fat.	Anthropometric parameters	Impedance frequency measurement of 21.1 HZ reflected in blood and the Expected value of 75% of vitamin D in the body was confirmed	Throughdata acquisition continuation the reliability can be validated and further Research is needed.

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Hamidreza Abdolsamadi et al. [95]	Statistical method	Vitamin D serum levels and salivary levels were compared in high-blood-pressure patients	Saliva sample	An alternative method of finding vitamin D	There is no relation between the Vitamin D level serum, increased blood pressure, and salivary sample.
Sari, Dina Keumala et al. [96]	Statistical Method Spearman correlation test	The parameters included for the study were 25(OH)D and 1.25(OH)D levels in saliva and serum with vitamin D intake.	Saliva and serum 25(OH)D	56 members were included in the study and a deficiency of 78.6% in serum while evaluating saliva and 76.8% deficiency was noted while evaluating serum.	A poor correlation existed between 1.25(OH)D level and serum 25(OH)D.

Table 5 represents the findings on the Non-invasive method of Vitamin D deficiency prediction by using human bio-fluids and hair minerals to aid this novel method to clinicians for the best treatment for the patient.

PERFORMANCE EVALUATION AND COMPARISON

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Table 6. Performance evaluation of Machine Learning algorithms from the Survey on Diagnosis of Various diseases and Vitamin D prediction to find the best-fit model. (2020-2022)

Disease Prediction	Algorithm	Accuracy	Precision	F1-score	Support	AUROC	Sensitivity	Specificity
Insulin Resistance from Chronic Kidney Disease Patients. [58] 2022	Random Forest	0.77	0.77	-	-	0.77	-	0.81
Covid-19 Severity [59] 2022	Support Vector Machine	0.95	0.955	0.94	-	0.94	0.94	0.94
Incident Arterial Fibrillation [66] 2020	Fully Connected network	-	-	0.110	-	0.80	-	-
Chronic Kidney Disease [70] 2021	Linear Support Vector Machine, L2 Penalty	0.98	0.90	0.92	-	0.98	0.96	-
Type-2 Diabetes in obese hypertensive patients [71] 2020	Random Forest	0.99	0.76	-	-	-	0.99	0.97

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Vitamin D prediction in obese Hypertensive Population [74] 2020	Linear Absolute Shrinkage and Selection Operator (LASSO) Regression	-	-	-	-	0.76	-	-
Prediction of Vitamin D [75]2020	Random Forest Model	0.99	0.96	0.96	-	0.98	0.96	-
Vitamin D prediction in hypertensive patients [76]2021	Support Vector Machine with Recursive Feature Elimination (RFE)	0.73	-	-	-	-	0.98	-
Vitamin D Prediction [77]2021	Extra Tree Classifier	0.733	0.77	0.85	973	-	0.91	-
Multiple Sclerosis Diagnosis [81] 2020	Support Vector Machine with Radial Basis Function Kernal	0.98	0.98	-	-	-	0.98	-
Vitamin D Prediction [82]2022	Naïve Bayes with	0.60	0.85	-	-	0.54	0.66	0.11

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	Waist Circumference

Table 6 depicts the Performance Evaluation of Machine Learning algorithms used in various surveys from 2020-2022 to find the best-fit model for the prediction of diseases and deficiencies. Various performance measures were analyzed to find the best-fit model to predict the deficiency and provide the best treatment for patients without any high cost.

Based on the human body composition vitamin D is concentrated more which is mainly correlated with many chronic diseases and insufficient vitamin D levels affect children and causes Rickets, Risk for Osteoporosis, and weakness in the muscle, particularly in adults. It is very important to rule out the deficiency of vitamin D which causes the hectic emergency of health care**.** The parameters of the body associated with vitamin D are age, sex, body composition,muscle,fat, the ratio of water, etc.The main concern on the Vit D prediction in this review concentrated on the non-invasive techniques using biofluids like saliva, tears, sweat, and skin impedance as the biomarker. The correlation can be done using the various methods discussed.Vitamin D level is the key element in predicting diseases related to diabetes, cardiovascular diseases, bone diseases, chronic kidney diseases even cancer. It is very important to measure the levels of vitamin D in the human body and has to be rectified in case of any deficiency. Previous work related to the prediction of vitamin D mainly focuses on invasive methods and the main disadvantage of these techniques isthat are time-consuming, cost-effective, it's very delicate pain to the patient. The Impedance meter was developed to check the correlation between vitamin D and impedance. On the base of the impedance principle, the quantum analyzer was designed. The vitamin D is directly proportional to the impedance so the relationship is correlated. By using the portable sensor, data processing is done. In the background work, the amount of Vitamin D was calculated by using blood samples or with a product stick. An adequate amount of Vitamin D was absorbed by the diagnostic device to reduce the rate of vitamin D-related diseases. A Vitamin D measurement sensor module was developed and a quantum analyzer based on impedance was developed to note the changes caused by vitamin D. By this concept the vitamin D and the Impedance are correlated. In previous work, the deviceswere attached to the camera of the smartphone and measured the user's vitamin D levels and cholesterol in 2 min with a blood sample. This technology works on Non-invasive methods like the use of samples in hair, tear, saliva, and sweat[97][98][99].This approach leads to creating a comfortable prediction of vitamin D in the patients. The status of vitamin D is determined in tear fluid to examine the endocytic proteins and megalin, and cubulin, in glands such as lacrimal and Harderian [100].

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5.1 Graphical representation of Performance Evaluation of algorithms for the survey to find the best-fit model. (2020-2022)

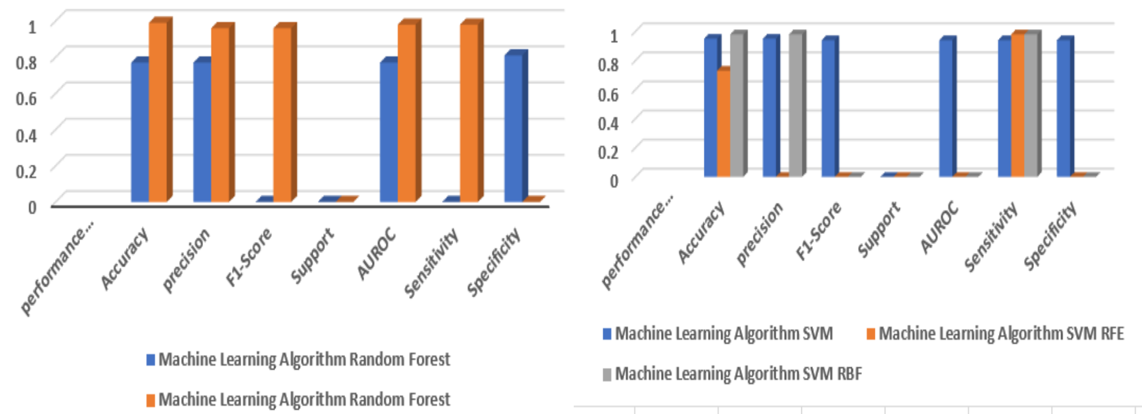

Figure5. Bar Chart Representation of Performance Evaluation by Random Forest and Support Vector Machine

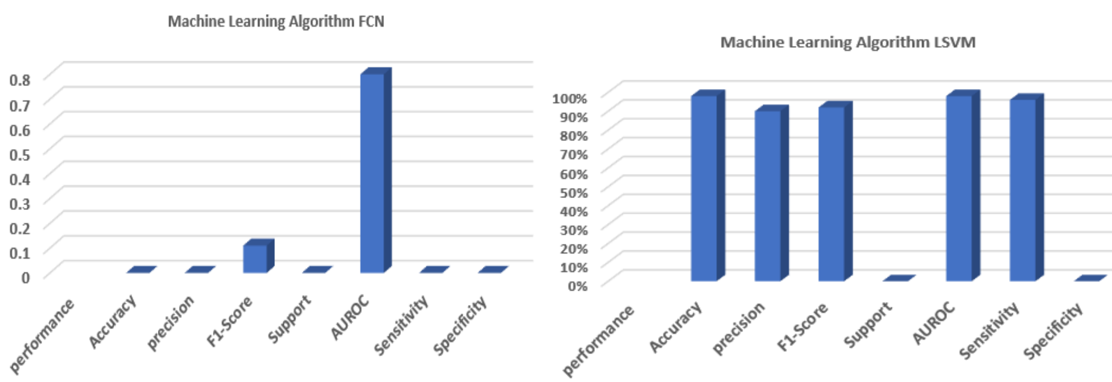

Figure6. Bar Chart Representation of Performance Evaluation by Fully Connected Network and LSVM

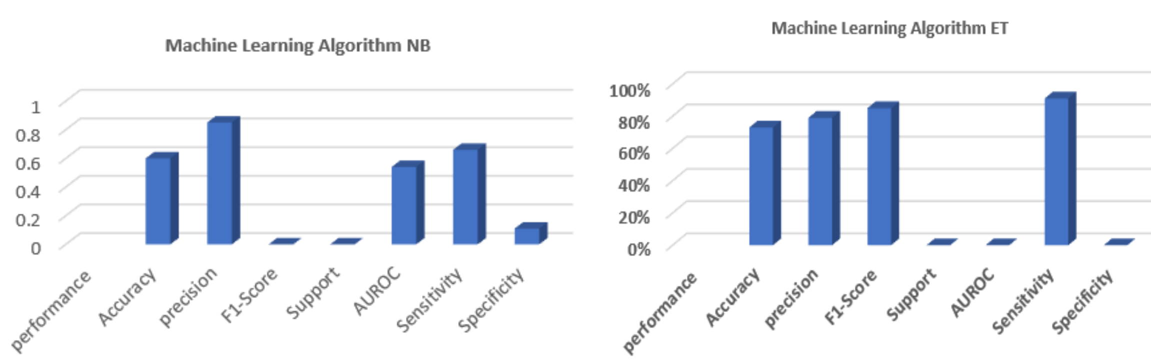

Figure7. Bar Chart Representation of Performance Naïve Bayes and Extra Tree Classifier.

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Figure5,6,7 represents the bar graph for the performance evaluation of various Machine Learning algorithms to find the High-performance algorithm. Amongst Random Forest outperformed than others.

Hazardous wastes including masks, gloves, aprons, and sanitizer bottles are the major cause of plastic pollution in the COVID-19 pandemic. Database of Covid-19 spread from February 27, 2020, to October 10, 2021, were collected and various Machine Learning models such as Deep Neural Network, KNN, Decision Tree, RF, SVM, Gaussian Naïve Bayes, LR, Multilayer Perceptron were implemented to analyze the best-fit model.DNN over leads all other algorithms with low error rates follows Mean Square Error-0.024, Root Mean Square Error-0.027, Mean absolute Percentage error-0.025, AUC-0.929[101]. A Forecasting methodology has been accomplished during the COVID-19 outbreak since December 2019 with the invasion of Artificial intelligence. This study employed Short-term memory-based deep forecasting in time series. RNN, Seasonal autoregressive, integrated moving average, Holt Winter's, exponential smoothing, and moving averages were used to calculate the MAPE, MAE, and MSE were analyzed for the evaluation and the results proved that the LSTM model showed excellent results than other models [102]. The situation of COVID-19 infection in Iran is elaborated by using cluster data visualizations and a GIS mapping-based K-means algorithm. With the intrusion of datamining the pattern recognition in the Covid-19 infection spread can be recognised. The final decision concluded that Tehran city is responsible for the pattern spreading of diseases in Iran.[103]

Table7. Performance evaluation and Comparison of Machine Learning algorithms for Vitamin D prediction in Recent study. (2023-2024)

Recent work	Machine Learning Models used	High-performance Algorithm	Advantages
[104] 2023	Ordinal Logistic Regression (OLR) Elastic-net Ordinal regression (ENOR) SVM, RF	Random Forest	Avoids Multi Collinearity Problem
[105] 2023	Logistic Regression RF SVM (feature selection relief-f)	SVM RBF	Cost-effective and provides health care benefits.
[106] 2023	RF Stochastic gradient boosting (SGB)	Random Forest	Plasma Vitamin D levels can be identified in Chinese

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	Extreme gradient boosting (XGBoost)		pre-menopausal women.
[107] 2024	Gradient Boosting Machine (GBM) LR Neural Nets (NNet) RF SVM XGBoost	XG Boost Outperformed other algorithms.	Online web calculator constructed.
[108] 2024	Random Forest	Random Forest	Prediction of Maternal Vitamin D and continuous monitoring in pregnancy. Vitamin D changes during pregnancy on Maternal adverse events.

Table 7 explains the Recent studies on the application of Machine Learning in Predicting Vitamin D deficiency (2023-2024). Various algorithms were implemented and the best-fit model was identified in each study. After analysis, it is identified that Random Forest outperformed other models by providing high-performance metrics in the prediction of Vitamin D deficiency. The comparison of Machine learning algorithms was presented with relevant performance metrics including accuracy, Precision, sensitivity, specificity, F1-score, and AUC to obtain the best-fit model in recent studies from (2023-2024) are indicated in figures 8,9,10,11,12,13. Amongst all algorithms used Random Forest outperformed with high performance metrics.

5.2 Performance plots for Prediction of Vitamin D with Machine Learning approach and the comparison of algorithms in recent studies (2023-2024)

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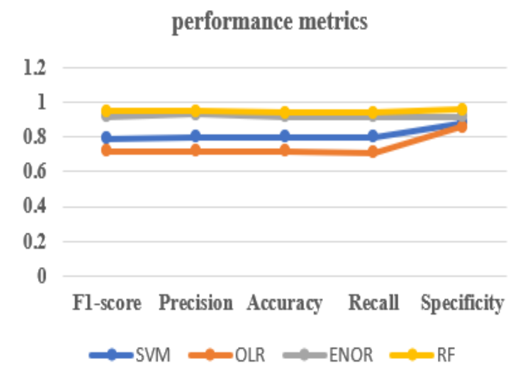


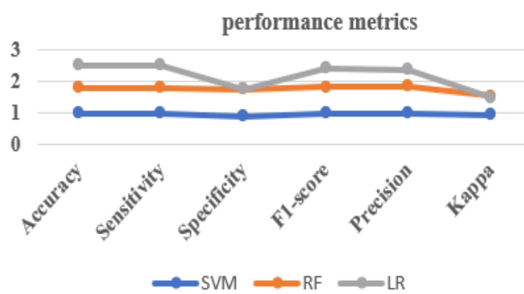
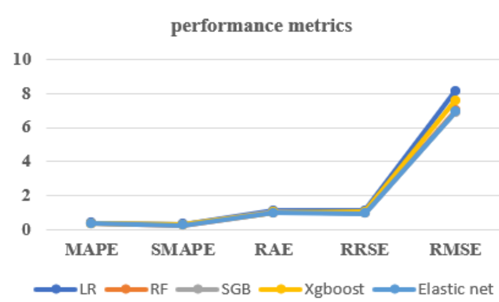


Figure 8. PE- SVM, OLR, ENOR and RF **Figure 9. PE- SVM, RF.LR**



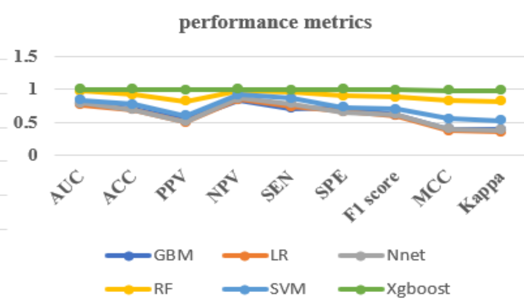
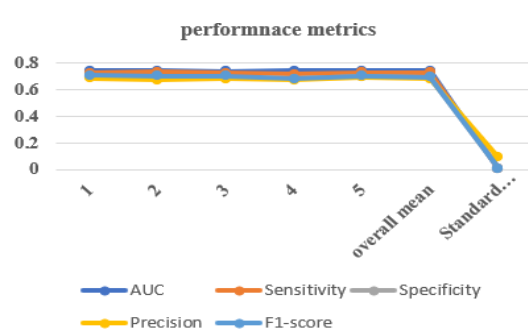


Figure 10. PE -LR, RF, SGB, XGboost, Elastic net Figure 11. PE-GBM, LR, Nnet, RF, SVM



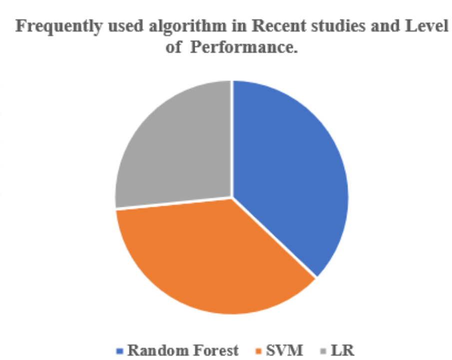


Figure 12. PE-Random Forest **Figure 13. Representation of High-performance algorithm**

The continuous real-time monitoring of health is highly dependent on the development of wearable devices and sensors. Physical activity monitoring devices and non-invasive devices are in the form of smart wristwatches, trackers on fitness, clothing with smart technology, and it is mainly used in glucose, blood pressure, and heartbeat monitoring, etc. Conventional wearable devices are heavy and rigid which leads to inaccurate measurements. The recent trends focus on the development of wearable sensors for non-invasive prediction without any difficulty for people. The novel ideas on

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wearable devices create reliability and durability to avoid the challenges with ordinary devices. smart contact lens with real-time application in tracking cortisol levels in tears by using smartphones. The measurement of skin impedance with a frequency of 21.1Hz indicates that 75% of Vitamin D concentration in blood is confirmed. Detection of Sweat metabolites using bio-sensors in non-invasive methods can identify the analytes to create high-quantity biofluid. The essential vitamins and amino acids can be traced using wearable electrochemical biosensors. Early detection of abnormal health conditions including hypertension, diabetes, and high Blood pressure can be obtained with the help of smart wearable devices and aids clinicians in improving patient monitoring. The future scope of wearable technology leads to the achievement of a 16% reduction in hospital costs and can attain high shipping of wearable devices worldwide.[109]

5.3 Classification of Algorithms

K-Nearest Neighbor's

K-Nearest Neighbor is one of the major Supervised Machine Learning algorithms implemented to bring the solution for Classification and Regression problems. It is mainly used for Classification tasks providing the application in Data mining, Pattern recognition, and intrusion detection. It is a non-parametric Classifier that uses vicinity to make predictions regarding the individual data point grouping. The complete training dataset storage is carried out during the training phase as a reference. The distance between the input data point and the training examples is calculated by using Euclidean distance as a distance metric. Easy output interpretation, time calculation and power of predictions are the added advantages of KNN.To avoid Overfitting or underfitting problems, the value of K needs to be chosen wisely. The optimal value of K can be selected with the help of cross-validation so that the performance can be improved.[110]

$$\textit{Euclidean} \quad \sqrt{\sum_{i=1}^{k}\left(\mathbf{x_i}-\mathbf{y_i}\right)^2}$$

$$\textit{Manhattan} \quad \sum_{i=1}^{k}\left|\mathbf{x_i}-\mathbf{y_i}\right|$$

$$\textit{Minkowski} \quad \left(\sum_{i=1}^{k}\left(\left|\mathbf{x_i}-\mathbf{y_i}\right|\right)^2\right)^{1/2}$$

Decision Tree

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In Practice, one of the commonly used models for prediction is the decision tree. Interpretation is easy and requires less effort for preparation of data. The requirement of linearity assumptions in the data is not required in Decision tree algorithm. The decision tree classifier is tree-structured and the features of the dataset are represented by internal nodes and the decision rules are indicated in branches whereas the outcome is denoted in each lead node. The decision-making is done by the decision node with many branches and the representation of output is carried out by the leaf node with no branches. Based on dataset features the performance of the test is intended. The problem and the solutions are represented in the form of a graph. The main reason for choosing the decision tree is the ability to make decisions and an easy understanding of decision logic. The terminologies of the decision tree include Root Node, Leaf Node, Splitting, Subtree, Pruning, and Parent/Child Node. By using Attribute selection measures such as information gain, and the Gini index the best attributes are picked. Information gain is the entropy changes in measurement. Entropy is the metric that measures the impurity of the given attribute.[110]

Information gain=Entropy(S)- [(Weighted Avg) *Entropy (each feature)]

Entropy(S)=-P(Yes)log2P(Yes)-P(no)log2P(no)

S-no of samples in total

P(Yes)-Probability of Yes

P(No)-Probability of No

Gini index -The impurity and purity measurement on the Decision Tree with Classification and Regression algorithm (CART).

Random Forest

Random Forest falls on the category of Supervised Machine Learning algorithm. It is a group of decision tree and the training in each tree is done with the random selection on data subset. In Classification and Regression task, the selection of features and the prime dataset variables are implemented using RF. The shorter training time, high accuracy, and efficient handling of big datasets make the RF overcome other algorithms with a high-performance rate. From a given dataset the samples are selected randomly and the algorithm builds a decision tree for each training data. The average of the decision tree is calculated for voting. The final result of the prediction is noted with high voted prediction result. Ensemble model is the fusion of multiple models with two methods including Bagging and Boosting.RF uses Bootstrap Aggregation also called Bagging and any random original data is arranged into Bootstrap samples. The Aggregation is process of obtaining different results by training models individually. In the end, the combination of results is achieved by the majority voting and decides the output.[110]

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Adaboost

It is an ensemble modeling used for binary classification issues. Many weak learners are converted to strong learners to get high prediction power. The idea of boosting algorithms first deals with model building in the training dataset and then builds a second model and corrects the faults in the first model. This concept repeats until the mistakes are reduced and the prediction of accuracy is obtained. The boosting algorithms are of three types including the Gradient descent algorithm, Xtreme gradient descent algorithm, and Adaboost algorithm, etc. Adaboost is mainly used to reduce overfitting, bias, and variance and also to improve accuracy in prediction and data complexity.[110]

Stochastic gradient descent

SGB classifier is one of the important tools in Machine Learning tool kit and data science for the classification problem. It is versatile and used in real-time monitoring ofbig data. The model parameters are updated iteratively to minimize the loss function. In each iteration, the training data contains the random subsets and by implementing mini-batches it is termed as 'stochastic'. With the advantages of regularization strategies and schedules of suitable learning rates, SGB is mostly preferred in ML algorithms. The Process of SGB includes the initialization of models randomly with default values. Then the training data is randomly shuffled with the help of recent examples on current model parameters so that the cost function gradient is computed. Model parameters are updated in negative gradient direction by the learning rate and the process is repeated for the number of iterations.[111]

Support Vector Machine

Support Vector Machine is the most versatile Supervised learning algorithm for Classification and Regression Problems, the n-dimensional space is segregated into classes by the decision boundary also called best-line. The hyperplane is created by choosing the extreme points/vectors by the SVM algorithm. These extreme points are called support vectors. The SVM is of two types they are Line SVM used for linearly separable data and Non-Linear SVM which is used for separated data with non-linear form. The support vectors are the vectors (or)data points that relyuponthe nearest point to the hyperplane. The main advantages of SVM include that the data can be used to avoid the linear functions difficulties, particularly in high-dimensional feature/space. To obtain the effortless separation of two classes SVM uses kernel functions for mapping input data points into high-dimensional space.[111]

Multilayer Perceptron (MLP)neural network

Multilayer Perceptron neural network is a part of Deep learning with fully connected multiple layers and uses Backpropagation for model training. The MLP is included in the class of feed-

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forward neural networks, with different layers of interconnected nodes. It contains the activation function, node's value, weights, and inputs for the calculation of output.MLP works in the forward direction with a connected network and the direction of passing the value to the forthcoming node is only with one direction. The Backpropagation increases the training model accuracy and the structure of MLP contains three layers input layer, hidden layer, and output layer. The features of the dataset are represented in the input node and it passes the input value to the hidden layer. The input variable is multiplied with the weight in the hidden layer and the values are summed to obtain the corresponding output. The active nodes are identified by the activation function and the output is streamed in the output layer. The difference between the predicted and actual output is calculated. The MLP can solve non-linear problems and can handle the tedious task with huge datasets. Quick prediction and high accuracy with minimal error can be achieved with the help of backpropagation.[111]

These algorithms are selected and they are suitable for the prediction of Vitamin D deficiency by considering several concepts, including the data characteristics, and features associated with deficiency of Vitamin D such as lifestyle, age, history of medications, test results, etc. In the case of the Classification problem, the deficient and non-deficient values are indicated whereas in the Regression task, the exact value of Vitamin D levels arepredicted. The selection of the algorithm depends on the prediction complexity. To obtain interpretability, simple algorithms can be used rather than the ensemble methods. These algorithms such as KNN, RF, SVM, Adaboost, and MLP are relevant to performance metrics to identify the problem accurately and can achieve good generalization while RF and boosting Models can able to handle the datasets effectively. By investigating the algorithms and their evaluation it is clear that it is suitable for the prediction of Vitamin D deficiency. Even Deep learning models including Conventional neural network (or)Recurrent neural networks are used for the prediction task.

5.4Performance MetricsUsed for Evaluation

The Performance metrics are the quantitative measures that help to investigate the effectiveness (or) performance of a Machine Learning model. It can able to validate the best model by comparing different models (or) algorithms. The ability to predict, the capability of generalization, and the quality are the major challenges in the case of evaluation. These aspects can be measured with the help of performance metrics and it depends on the data type, outcome, and problem domain. Precision, F1-score, AUROC, and accuracy fall on the metrics of Classification and Mean Absolute error, Mean Squared error belongs to Regression metrics.[112]

Precision

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he performance of the Machine Learning model can be indicated by Precision and the quality of the model's positive prediction can be stated. It refers to the ratio of true positives to the total number of positive predictions.

Precision=True positive/ (True positive+False Positive)

F1-Score

F1 Score (or)F-measure is the combination of precision and recall scores of a model. It ranges from 0-100%. The high F1 score represents the high-quality performance of a classifier and commonly it is used in Classification problems.

*F1 score=2*Precision*Recall*

Precision+ Recall

AUROC

The Area under the Receiver Operating Characteristics curve provides the performance of a model in binary Classification at different Classification thresholds in graphical form. Across different decision thresholds, the trade-off between the True Positive Rate (TPR) and False Positive Rate (FPR)is indicated with the help of the ROC curve. The overall performance can be achieved in binary classification and the value lies between 0 to 1. AUC of 0.5 indicates no discrimination and the patient's deionisation depends on the test.0.7 to 0.8-satisfactory,0.8 to 0.9-excellent and above 0.9 the output is outstanding.

Accuracy

The metric that measures the ability of the Machine Learning Model that predict the outcome correctly and it is used in the classification task.

Accuracy= (Total number of correct predictions)/ (Total number of predictions)

Mean Absolute Error

The mean absolute error is the magnitude of the difference between the observation's prediction and the observation's value. It is indicated as an L1 Loss function and used for the regression tasks. Here the learning problems are converted into optimization problems. It is less sensitive to outliers with high interpretability.

$MAE=(1/n) \sum (i= 1 \text{ to } n) |y_i-\hat{y}_i|$

n-no of observations in the dataset

y_i is the true value

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$\hat{y}$_i is the predicted value

Mean Squared Error

Mean squared error is the Squared difference average between the actual values and predicted values. This is highly sensitive to outliers due to the squaring. It has moderate interpretability and calculates the nearness of the regression line with a data point. By taking average, mean, and squared errors from data the MSE is calculated.

$MSE=(1/n) *\sum(actual\text{-}Forecast)^2$

$\sum$-sum, n-sample size, actual-data value, forecast-predictive value

The reason for the requirement of performance metrics in Machine Learning that are essential for assessing the reliability and accuracy of models is explained to achieve the evaluation objective to quantify the ability of the model in predictions, data classification, and tasks. The practitioners and researchers can have an idea of the best-performing model by comparing different models on the same dataset. The hyperparameters are fine-tuned to analyze the changes and to obtain optimization, better reliability, and accuracy. The strengths and weaknesses of the model are identified. The generalization of the model is a challenging task and it can be achieved through cross-validation the metrics play a vital role in assessing the accuracy and reliability of models by improving the comparison, optimization, strength weakness, and ability of generalization.

5.5Deep Learning approachto the overall accuracy and reliability of the models, key findings, and their implications

Deep neural networks (DNNs) have gained significant attention by considering them as the criterion for the prediction of Vitamin D. In Deep learning models the features are represented from the raw data and avoid manual feature engineering. It shows high reliability on complex data including images, anthropometric data, and Health records suitable for Vitamin D prediction. This prediction may involve in non-linear relationship between the status and the predictors which solves the problem through computation on multiple layers. Deep learning is another option as Machine Learning which can show excellence in prediction rather than traditional approaches, particularly in handling tedious tasks. Transfer learning and multi-model data integration seek the attention of Deep learning. Uncertainty in prediction can be estimated to achieve accurate decisions. The advancements in the model, optimization, regularization techniques, and methods of interpretability provide tremendous improvement of deep learning models and provide outstanding applications in health care including Vitamin D prediction. The application of deep learning for Vitamin D prediction and the key findings include the Learning on Automatic feature representation, accurate predictions, Multi-modal data integration, generalization and

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Regularization, etc. The implications are listed as prediction improvement, Robustness, Support Clinicians on decision making, ethical consideration,etc. [113]

Limitations or gaps in existing research and future solutions.

Predicting the levels of Vitamin D using the Machine learning approach has provided outstanding results despite there are some gaps and limitations in the research that need to be investigated. Due to the scarcity of a wide range of datasets, the models often meet the challenges of the success of accurate prediction. The datasets mostly lack Comprehensive information on the status of Vitamin D and influencing factors such as exposure to sunlight, intake of diet, predispositions on genetic concepts, and the conditions regarding health. The collection of data from various sources varies accordingly concerning consistency and quality due to the lack of these parameters in data the Robustness of prediction capacity of the model is disturbed. To improve the accuracy of predictions standardization and measurable indicators called biomarkers need to be incorporated effectively. The factors influencing the metabolism of vitamin D play a vital role in models leading to low accuracy in the prediction. Even the generalized models cannot able to withstand the issues of interindividual variability in the metabolism of vitamin D. Machine Learning models' ability to interpretability is reduced due to the misunderstanding of the factors that influence the prediction. There is a need for transparency in models to explore the features so that the reliability, trustability, and fitness of the model can be improved. Despite Machine learning's promising Vitamin D level prediction, the challenges of effective usage and decision guidelines in clinical aspects remain a problem. The patient outcomes on the effect of predictive models on the real-world scenario should be considered in future research. The stated limitations and gaps in recent research on the prediction of vitamin D using a Machine-learning approach can be addressed in future research. Incorporating Multiomic data, metabolomics, genomics, and proteomics helps to get a clear understanding of the metabolism of Vitamin D to obtain an accurate prediction. Wearable devices and sensors can be used to increase granularity and reliability. Sharing of data and collaboration among the practitioners, researchers, and health centers can acquire the diverse and large-scale dataset required for validating and training the models. The potential areas for future research can be expanded by adapting advanced ML techniques such as Deep learning, Ensemble methods, etc. To improve the generalizability the future ideas on the research rely on studies of varying demographic, socio socio-economic characteristics in diverse populations. The limitation of the proposed work is the limited data with 1958 Osteoporosis patients and the limited models were compared with only SHAP interpretation. The main goal of future research in the prediction of vitamin D deficiency is to contribute solutions for more realistic clinical predictive models to improve the health outcomes related to deficiency of Vitamin D and the associated diseases. The real-time data analysis is to be carried out with various ML models and interpretation with XAI such as Lime, Q5 lattice, etc.

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Scope of the research Specifying Machine Learning algorithms and biomarkers

Relating to the prediction, detection, and exploring the deficiency by using advanced techniques including Machine Learning and Deep Learning enhances the research. A clear understanding of physiological, biochemical, and the aspects of Vitamin D deficiency, symptoms, factors of risk, causes and the associated diseases can be identified. The Machine Learning approach and data analysis for prediction involves the selection implementation and the evaluation of algorithms for the application that can be retrieved. Classification can be carried out between individuals with and without vitamin D deficiency by using features such as medical history, demographic data, factors of lifestyle, and bio-markers. The likelihood estimation of the deficiency severity in individuals is estimated by considering the variations in season, habits of food intake, etc. Clustering and feature selection are taken into account for the determination of biomarkers in prediction. Analysis of time series and anomaly detection can be used to find the outliers and the irregular patterns that indicate health issues. The Bio-markers associated with the deficiency of vitamin D are stated as 25(OH)D serum 25-hydroxyvitamin D a biomarker to find the vitamin D status. (PTH) Parathyroid hormone, Levels of Calcium and Phosphorous, Bone turnover markers, markers on genes e.g. VDR, CYP27B1, C-reactive protein, pattern analyzation of metabolites in biological samples are the biomarkers related to the Vitamin D prediction. By Integrating and validating the clinical data and examining the performance metrics including the accuracy, sensitivity, and specificity of the models the ML proves to be the best criteria for the prediction of Vitamin D deficiency.

Table 8. Tabulation of Research Questions

Research Questions	References
RQ1.what are the factors that influence the Vitamin D Deficiency?	[29] to [39]
RQ2. What are the available methods of predicting Vitamin D Deficiency?	[40] to [96]
RQ3. Discuss the importance of Machine Learning in Medical field.	[56] to [72]
RQ4. What is the best-fit model in the prediction of Vitamin D Deficiency?	[58],[71],[75],[79],[104],[106],[108]

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RQ5. What are the Performance metrics used for the Evaluation of models?	[58],[59],[66],[70],[71],[74],[75],[76],[77],[81],[82],[104] to [108]
RQ6. Ellucidate the role of Deep Learning in prediction and detection of diseases.	[67],[68],[69],[72],[112]
RQ7. Explain the various ML algorithms.	[104] to [109] [110] to [112]
RQ7.1 Do Random Forest exceeds other ones.	

The motivation of this study is to provide the possible answers for the formulated research questions in order to obtain the knowledge on the Various Machine Learning roles in prediction of Vitamin D deficiency and to identify the limitations addressed in this study to focus on the future scope. The research questions and the relevant references are tabulated in table.8.

Table 9. Information on types of Datasets and Parameters used for the prediction.

References	Datasets and the Parameters
[73]	Ausimmune study 494 participants from control group. Examination of risk factors for multiple sclerosis. Questionnaire-Exposure to sunlight, Physical activity, history of smoking etc.
[74]	Collection of data from electronic records (2006-2017)221 patients from hypertension unit.
[75]	Datasets from Institute Ethical committee of Bharathidasan Govt-college for women, Puducherry India. A totalof 3044 college students participated, aged-(18-21) Features include Age, sex, weight, height, BMI, waist circumference, Body fat, Bone mass, Exercise, and exposure to sunlight.
[76]	1002 Hypertensive patients from Spanish university hospital
[77]	Real-time dataset
[78]	The biochemical database was collected from the hospital. A blood test was taken in the biochemistry lab. parameters-age, sex, uric acid, albumin, calcium, chlorine, cholesterol, Gamma-Glutamyl-Transferase GGT, Vitamin D and season, sodium, protein, etc

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[79]	201 healthy people age(20-40yrs) in shiraz Iran. A cross-sectional study with demographic details, supplements of vitamin D, sun exposure, concentration of serum, and food habits are gathered.
[80]	Data collection from the survey at baseline, annual survey, supplements off-trial, questionnaire on a blood sample, measurement of 25(OH)D concentration, and Ambient ultraviolet radiation. Parameters-Height, weight, BMI, Skin exposure to sunlight, lifestyle, alcohol consumption, and physical activity.
[81]	99 Multiple sclerosis patients and 81 healthy people. To determine selenium and Vitamins (B12, D3) atomic absorption spectroscopy and chemical autoanalyzer are used.
[82]	Data was collected from an urban population of 43,946 people in 5 health centers. Age-(35-75), sex,501-people selected within 100 patients,50-male, 50 females from June 2016-Nov 2017
[83]	Data obtained from Epigenetic and biochemical origin of overweight and obesity perinatal cohort Mexico City Voluntary participation.
[84]	Dataset from Khorasan Janoobi province random participation, 292-Chronic hepatitis patients 330-natural immunized persons.
[85]	Cross-sectional retrospective study.23,394, mother-infant pairs included. Neonatal and obstetric information is obtained from a database. Serum Vitamin D concentration is measured by chemiluminescence immunoassay.

References	Datasets and the Parameters
[86]	Data sources (1966 to Aug 2012), PubMed (2008 to Aug 2012), Embase (1980 to Aug 2012), CINAHL (1981 to Aug 2012) Cochrane Database of registered clinical trials.
[88]	Four databases including Pubmed, Embase, Cochrane Library, and Web of Science till 31stMay 2023.
[89]	70-Healthy Emirati students UAE University in Dec 2019, Age (18-35)
[90]	Cross-sectional study 76-adults, aged (18-36) participants in South Florida The criteriacolor obtained from the IMS smart probe 400 scanner, Vitamin D-ELISA, Sun exposure, and food intake are obtained from the questionnaire
[91]	48 healthy volunteers, observational cohort study, Parameters-tear fluid, Serum Vitamin D
[92]	608 participants, age-(12-19), Interventional study.

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[93]	54 patients with chronic neck pain. Data was collected from2016 to Aug 2016 at King Abdullah University and Hospital. Parameters-Height, weight, serum Vitamin D, Vitamin B12, Ferritin, Calcium, phosphorus, zinc.
[94]	26 participants, age-(20-60) yrs., Daegu city 2020.Parameters-Body composition measurement, Obesity level, Skeletal muscle fat.
[95]	Control survey, 40 blood pressure patients, 40 healthy individuals. Parameters-Saliva sample, Vitamin D serum.
[96]	Cross-sectional study, Healthy men and women with age (18-60) yrs. during Aug to Nov 2020, North Sumatra, Indonesia. Parameters-Saliva and Serum Vitamin D.
[99]	21 individuals without ocular disease, Blood test-electrochemiluminescence, Tear samples-Schimer test strips.

The information on the types of datasets used in the studies and the references are tabulated in Table9. The table summarizes the datasets used in the studies that are conducted for the detection and prediction of diseases and deficiencies.

CONCLUSION

This systematic review's main goal is to analyze various methods of predicting vitamin D status in the human body. Since Calcium absorption and bone metabolism are managed by vitamin D it is stated as steroid hormone. The deficiency of Vitamin D leads to health issues such as Diabetes, hypertension, Cancer, multiple sclerosis, and infertility conditions both in males and Females. Measurement of Vitamin D levels plays a vital role in the analysis of chronic diseases and helps in the treatment of patients. The Various methods of predicting the status of vitamin D were analyzed and the findings were compared with various diseases that are correlated to the serum 25(OH)D. Dietary issues, nutritional deficiency, and Sun exposure are the major causes of deficiency, and the level of serum 25(OH)D plays an important role in predicting the status of Vitamin D. This review states that the conventional method of predicting vitamin D leads to more discomfort and may spread the chronic diseases in a blood sample. This review mainly concentrates on the novel and Non-invasive method of predicting serum 25(OH), Artificial Intelligence assists professionals and it can provide services to people 24/7. The tools used to diagnose the problems can reduce the cost and improve the work production of healthcare providers.

Another innovative method is the Non-invasive which uses the bio-marker for the measurement. Tear fluid termed to be a non-invasive method contains huge proteins, metabolites, and peptides as the best bio-markers. Statistical analysis uses various methods to acquire the best accuracy, many investigations were carried on with Vitamin D to avoid Cardiomyopathy and thromboembolic risk with COVID-19. Various Supervised and Unsupervised learning methods

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comparisons were carried out to find the best methodology of Machine learning which provides a high level of accuracy. The deep learning part of the AI family was used in diagnosing image-based issues in health care. For cellular analysis, bio-sensors were used and the data obtained by bio-sensors were analyzed and classified using Machine learning and deep learning methods. Work related to bio-sensors was enhanced by SVM and ANN. The majority of newer publications were recently enriched due to these techniques. The non-invasive diagnostic technique is mostly considered to avoid the inconvenience of multiple readings on pricking the blood leads to spreading infectious diseases.

This study aims at investigation of grouping Non-invasive methods of machine learning to find the status of vitamin D and to avoid and predict the chronic diseases prevailing in human beings. It is found that with the survey of Machine Learning approach on Deficiency prediction during the year from 2020 to 2024, the best model for the prediction is the Random Forest algorithm with high-performance measures of 0.99 accuracies, Precision 0.96, F1-Score 0.96, AUROC 0.98 and Specificity 0.96. The Future ideas are enabling wearable devices to display the vitamin D level without any complications and IOT-based systems to be modeled for an easy way for health care and monitoring to provide the best medications for the patients.

Declarations

Review and/or approval by an ethics committee was not needed for this study because the paper explains the studies on various predicting methods of Vitamin D deficiency.

Data availability statement

No data was used for the research described in the article.

Declaration of interest statement

The author declares no conflict of interest

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