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Development and validation of a mobile application based on a machine learning model to aid in predicting dosage of vitamin K antagonists among Indian patients post mechanical heart valve replacement

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ABSTRACT

Patients who undergo heart valve replacements with mechanical valves need to take Vitamin K Antagonists (VKA) drugs (Warfarin, Nicoumalone) which has got a very narrow therapeutic range and needs very close monitoring using PT-INR. Accessibility to physicians to titrate drugs doses is a major problem in low-middle income countries (LMIC) like India. Our work was aimed at predicting the maintenance dosage of these drugs, using the de-identified medical data collected from patients attending an INR Clinic in South India. We used artificial intelligence (AI) - machine learning to develop the algorithm. A Support Vector Machine (SVM) regression model was built to predict the maintenance dosage of warfarin, who have stable INR values between 2.0 and 4.0. We developed a simple user friendly android mobile application for patients to use the algorithm to predict the doses. The algorithm generated drug doses in 1100 patients were compared to cardiologist prescribed doses and found to have an excellent correlation.

1. Introduction

Patients who undergo mechanical heart valve replacements essentially need oral anticoagulant (OAC) drugs, mostly Vitamin K antagonists (VKA) to prevent blood clotting. The dosage of VKA drugs which has a very narrow therapeutic range are monitored by physicians by observing PT-INR (Pro-thrombin Time – International Normalised Ratio) values. Since even dietary pattern of the patient can modify the drug effects, monitoring of VKA therapy is pretty complex and will normally require the services of a physician.

Patients from low-middle income (LMIC)countries like India faces difficulties in getting PT-INR testing and dose adjustment by the physician/cardiologist periodically. This forces the patient to skip the tests and physician visits, which can lead to bleeding[1] or thrombosis,[2] which can be catastrophic. In a recent study the TTR (time in therapeutic range) was only 60% as reported from Chhattisgarh.[3]

Of late, the PT-INR test is widely available even in small clinical laboratories in villages and also point-of-care (POC) devices[4] is being marketed widely. If we can predict the warfarin dosage from the PT-INR values obtained from either of the above methods, using a software or computer application installed in a handheld device or a mobile phone, it will help patients to avoid physician visits for optimizing VKA antagonist therapy.

Currently there are no mobile applications/devices which is developed for Indian patients.

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2. Background and methods

Computer based systems have been used in the management of patients on VKA therapy and found to be useful.[5] They were mainly PC based systems used in hospital computers managed by physicians or trained health workers.

Smart phone based, patient operated applications have been used successfully in the management of chronic diseases.[6 7] Machine learning based algorithms developed by Sharabiani et al[8] used relevance vector machines and found to be accurate in dose prediction. Another system used two machine learning algorithms to predict the doses.[9] The usefulness of such systems have been tested with mixed method approach[10] and education status of the patient was found to be one of the predictive factors.[11]

Our idea was to develop a very simple algorithm which can be used by patients through simple mobile phone interface. The algorithm was trained to derive the dose based on previous and current INR values and the last drug dose, in the background of demographic factors and the indications.

2.1. Data collection, analysis and preprocessing

This project was done in collaboration with National Institute of Technology Calicut (NITC) and SCTIMST. SCTIMST provided the de-identified data of Indian patients who are attending the INR Clinic of SCTIMST to NITC. The study was initiated after signing an MOU with the two Institutions and after obtaining ethics clearance from the Institutional Ethics Committee of SCTIMST. The data model parameters are described in Table 1. Initially a dataset of 109 patients were used to develop the ML model and the algorithm. The model was refined and tested using additional 300 patients' data to increase accuracy. Dataset was split into 70% training and 30% test data.

2.2. Dataset analysis

A preliminary analysis was conducted on the dataset to figure out patterns and possible biases in the data. Frequency distribution of parameters was plotted to figure out shortcomings in dataset. Data distribution in relation to gender and procedure type were analyzed. AVR and MVR procedures were represented well, but there was a shortage of data from AF and DVR categories.

Patients with age varying from 12 to 94 years were present in the dataset. Most of the patients were in the age group 40 to 70. Old INR values were ranging from 1.7 to 5.5 and new INR between 1.6 and 5.5.

2.3. Data pre-processing

Data preprocessing was done to improve the accuracy of the model. Drug is usually prescribed either as daily dosage for some patients and as dosage sequence for other patients. The dosage sequence varies from fixed single daily dose or sequential dosing (two-day sequence to four-day sequence eg. 2 mg, 3 mg for the next two days or 2, 3, 3 mg for the next three days or 2,3,3,3 mg for the next 4 days and this cycle repeats every two - four days.

To attain uniformity in dataset, the sequence was averaged out to daily dosage by dividing the sum of sequence by the number of days. Patients were prescribed either warfarin or acenocoumarol (Acitrom), Warfarin dosage is converted to Acitrom dosage by dividing by a factor of two based on already published clinical data.[12]

The categorical parameters present in the dataset (gender and procedure type) are encoded using one-hot encoding scheme. One hot encoding scheme encodes categorical parameters using binary representation to remove any extra weight assigned to higher integer value of categorical label in the schema.[13] Gender is encoded with two binary variables and procedure type is encoded with four binary variables.

2.4. Statistical analysis

2.4.1. Machine learning models

It was decided to use new INR values between 2 and 4 to get processed in the application. Patients who had INR values below 2 and above 4 were referred to physician for management as he/she may need urgent medical help.

A general procedure of random splitting dataset to 70% training data and 30% testing data was followed and a set of machine learning models was applied to detect accuracy. The accuracy of regression models was compared using R square value. The best possible value for R is 1.0.

The details of the machine learning processes are detailed in http://arxiv.org/abs/2004.11460. (Further reading reference 1)

Many methods were tried out as listed below.:-

1. Linear Regression
2. Support Vector Regression
3. Logistic Regression
4. Multi Layer Perceptron

Support Vector Machines are models which are trained under the condition that an optimal hyperplane exists which separate the dataset into different classes.[14] The Support Vector Regression Model (SVR) with five simple baseline variables and using the linear kernel gave the lowest mean square error value of 0.41 and R2 of 0.955.

2.5. Weekly dosage prediction algorithm

Warfarin tablets are available only in doses of milligrams (1,2,3 and 5 mg). Hence, an algorithm was designed to convert the daily decimal dosage (in mg) to a weekly sequence of integers. The algorithm takes predicted daily dosage and sequence length to

Table 1
Data Parameters description.

Sl.No	Parameter	Description
1	Age	Age of the patient
2	Gender	Gender of the patient (M/F)
3	Old INR Value	Basal INR value of patient.
4	New INR Value	New INR value of patient after PT-INR test
5	Old Dosage	Old Warfarin/Nicoumalone dosage of the patient (in mg)
6	Procedure type	Type of procedure the patient had under-gone. It can be MVR, DVR, AVR or AF.
7	New Dosage	New warfarin dosage prescribed by the doctor after the INR test (in mg)

MVR - Mitral Valve Replacement, AVR - Aortic Valve Replacement, DVR - Double Valve Replacement, AF - Atrial Fibrillation, INR - International Normalised Ratio.

produce best possible sequence with given sequence length and minimal error from predicted daily dosage.

2.6. Output

Various machine learning models are compared and linear SVM Regression model with coefficients given in Fig. 3 gave the best variance score and accuracy. Regression models with linear base generally outperforms other models in prediction. The daily dosage predicted by the server is stable and useable in case of stable INR value range of two to four. The weekly prediction model also provides reasonable accuracy with one-off errors in boundary cases. A variance score of 0.955 was obtained for daily prediction with mean square error of 0.41.

2.7. Smartphone client application

The application was developed in the Android platform. Since the app is going to be used by the common man, care was taken to make it simple and user friendly. Initially, when the mobile application is loaded, the user has to authenticate with username and password. This will guide them to the main page. This main page will have fields namely patient's age, gender, old INR value, new INR value and old dosage, which the user must enter. The first entry is planned to be done by hospital staff (which will be stored) and the patient needs to enter only the old INR value, new INR value and old dosage subsequently. When the user clicks the "Predict" button, if the values entered by the user are all valid, then the user is directed to the output page which shows the warfarin dosage of the patient for the next week (Fig. 1).

The initial version of the app was pilot tested in the heart failure clinic of SCTIMST and based on the feedback, some modifications were done in the app. The window to enter three consecutive day doses and the provision to enter the drug acenocoumarol/nicoumalone (Acitrom) were added. The current version of the app, displays the drug doses for a week starting from the date of entry not in descending order as before (3 mg, 3 mg, 2 mg, 2 mg, 2 mg, 2 mg, 2 mg) but varying doses interspersed (eg 2 mg, 3 mg, 2 mg, 3 mg, 2 mg, 2 mg, 2 mg).

2.8. Pre-testing and fine tuning the algorithm

The application was pretested using a different set of 300 physician assigned values for INR prediction in the INR Clinic of SCTIMST. It was found that the application predicted the values accurately in lower INR ranges, but towards the higher range (3.5–4 range of INR), there was variation compared to physician assigned values in the tune of upto 5 mg in weekly doses. This indicated the need for further refinement of the algorithm, by re-training the algorithm.

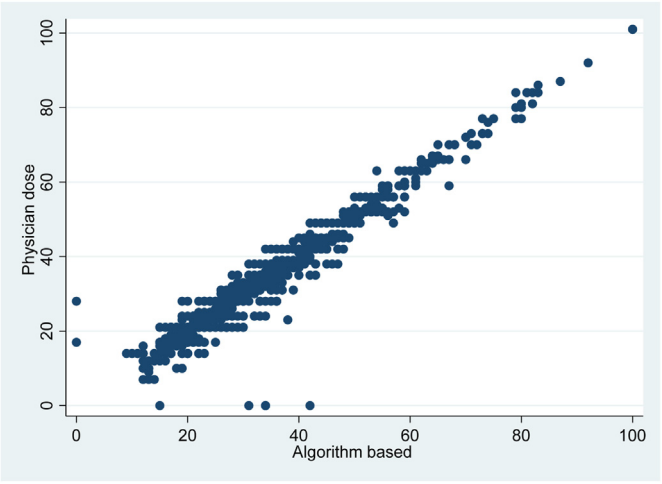

Fig. 2. Scatter plot showing the correlation between algorithm derived and cardiologist predicted dosages.

Re-training was done and three more models were developed and tested with different datasets of 100 physician derived values and finally we identified the model with best accuracy. The correlation of the same is given in Fig. 3.

We gave the same set of data to two experienced physicians who is managing the INR clinic of SCTIMST and averaged the doses prescribed by them and used for comparison and we found the Algorithm 3 to be having a very good correlation (Fig. 2).

We also tested the accuracy of the algorithm in INR ranges 2–2.5, 2.5–3, 3–3.5 and 3.5–4 and found that the best correlation was between 2.5 and 3.5. This information was used in predicting the date of next PT-INR test. If the value of both old INR and new INR is within 2.5–3.5 range, the patient will be prompted to re-test in 2–3 weeks. If either of the values are between 2 -2.4 and 3.6–4.0, the patient will be prompted to re-test in a weeks' time.

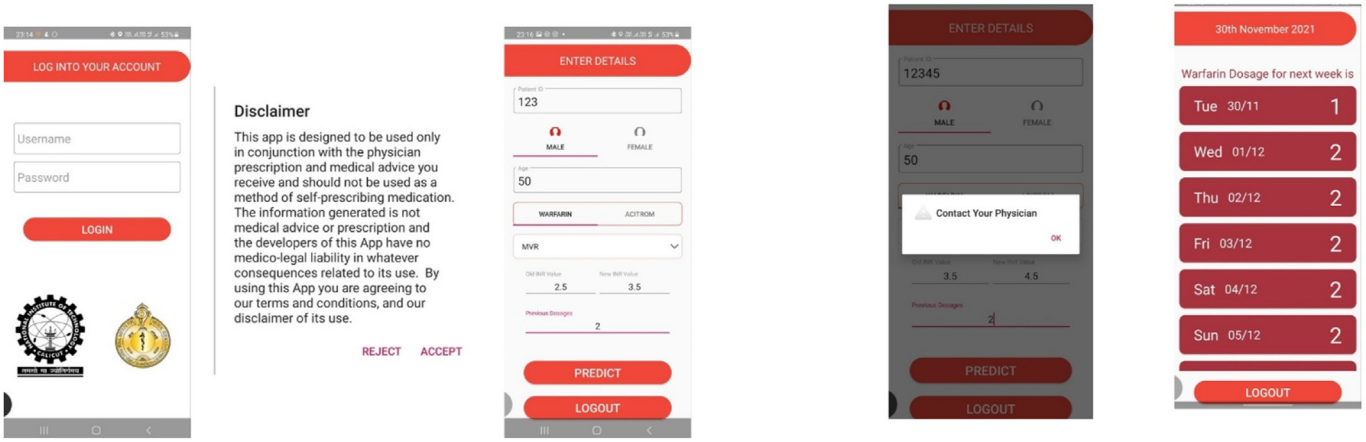

Fig. 1. Screenshots of the client application.

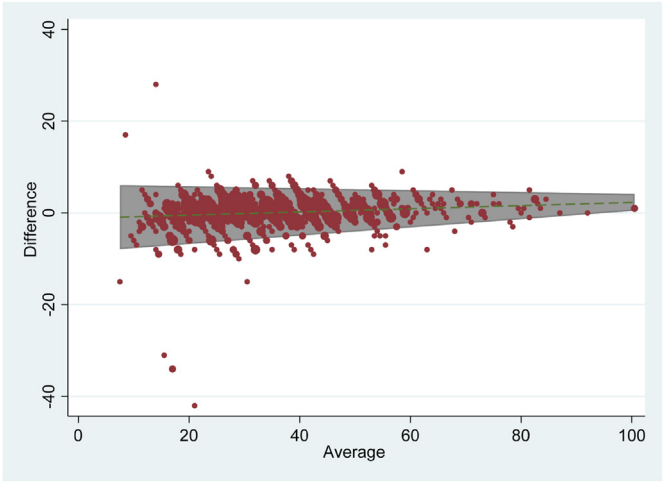

Fig. 3. Bland-Altman (B&A) plot shows that the difference between predicted and actual dosage is low.

2.9. Clinical validation

- Subsequently we tested the final version of the algorithm in 1092 patients and compared with cardiologist derived values. The correlation is shown by the scatter plot and the Bland Altman plot.
  The weekly average dose predicted
  Physician - 34.72 ± 14.6 mg,
  Algorithm - 34.55 ± 14.2 mg
- The **weekly average dose** difference
  0–1 mg in 522/1092 patients (47.8%)
  2–3 mg in 454/1092 patients (41.6%).
  < 3 mg - in 976/1092 patients (89.4%)
  < 5 mg – in 1020/1092 patients (93.5%)

2.10. Future research–clinical testing of the algorithm in patients

We are approaching the ethics committee of SCTIMST to test the efficacy and utility of this application in patients attending the INR clinic of SCTIMST.[15] Once the efficacy and utility are proven the application will be released to the public. We have derived a formula based on Machine learning model, we are in the process of incorporating it in a standalone device. This can be used without internet connection. We have filed an Indian patent application for that device. (No: 202,141,037,246 dated 17/08/2021. Title: A device with AI interface for predicting dosage of vitamin K antagonists for managing oral anti-coagulant drugs).

3. Discussion

Patients who require VKA therapy for various indications require very close monitoring of INR to remain in therapeutic range. Accessibility, availability and affordability issues and physical disabilities associated with the disease prevent patients from getting periodic titration of drug doses.

VKA antagonist therapy is usually in two phases. The first phase is identifying a stable dose of warfarin just after initiation of the drug. This is a tedious process which require supervision of a physician and usually done before the patient is discharged, for example after a valve replacement surgery.[16] The second phase is the maintenance phase of VKA therapy where patients whom we have identified a stable dose is managed on a long-term basis. Our work focused on predicting the maintenance dosage in patients who are on follow-up at home with stable INR readings for some time.

Anticoagulation management of patients on VKA using computer-aided systems[5 7] have shown good anticoagulation quality and reduced clinical adverse events in randomized trials like the APROAT[17] trial and few other studies.[18] This approach was found to be cost-effective also.[19]

But these studies used algorithms in personal computers mostly at anticoagulation clinics or hospitals or text messages were sent to physicians[20] and the decision on dosage alteration were done by physicians or trained hospital staff.

To circumvent the logistic issues faced by patients in LMIC, smart phone based applications may become useful as mobile phone penetration is high in countries like India. We developed this application to be simple and user friendly so that even lay people can use it. Many modifications were done based on the feedback received from patients and paramedics caring these patients.

This is the first algorithm developed using machine learning techniques from physician derived values in Indian settings. This will be more suited in the Indian conditions where physicians have to consider many factors like difficulty in frequent testing, accessibility and affordability issues.

This algorithm predicts values for both Nicoumalone and Warfarin, which are the two most common VKA drugs used in India.

The interface is very user friendly as the initial entry which is done in the hospital by the hospital staff get stored and the patient needs to enter only the subsequent INR values and the current dose in mg.

Patient safety is incorporated into this system as it is programmed to predict only those patients who have INR between 2 and 4. Values beyond this range will be prompted to seek help of a physician. The patient also will be prompted regarding the next test date based on the two INR values, if the values are between 2.5 and 3.5, it will request to test after 2 weeks, if beyond this range it will ask to test in a weeks' time. Both these features ensure safety.

This algorithm once tested in patients on VKA therapy and released to the public, it will be a useful for those who face challenges due to accessibility issues.

4. Conclusion

A warfarin/nicoumlaone dosage prediction algorithm was developed using data from South Indian patients who had a stable INR value of 2–4. Among the machine learning models tested, the support vector regression model was found to show better results with the lowest mean square error value of 0.41 and a variance value of 0.955. A mobile application was developed incorporating the model. It was tested in 1092 patents and was found to have to have very good correlation with physician prescribed doses. This is going to be clinically validated in a group of patients for ease of use and safety. More than half of the patients who are on the above oral anticoagulants from remote areas who have stable INR doses can use this application installed in their mobile phones and can avoid frequent physician visits.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Harikrishnan S. and all authors has applied for a patent #Indian Patent No. 202141037246 for a related device pending to SCTIMST, Trivandrum and NIT, Calicut.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2022.10.002.

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Further Reading

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