REVIEW PAPER

WILEY

Applications of artificial intelligence for hypertension management

Kelvin Tsoi PhD[1,2] ⓘ | Karen Yiu MSc[1] | Helen Lee BSc[2] | Hao-Min Cheng MD, PhD[3,4,5,6] | Tzung-Dau Wang MD, PhD[7,8] | Jam-Chin Tay MBBS[9] | Boon Wee Teo MB, BCh[10] | Yuda Turana MD, PhD[11] | Arieska Ann Soenarta MD[12] | Guru Prasad Sogunuru MD, DM[13] | Saulat Siddique MBBS[14] | Yook-Chin Chia MBBS[15,16] | Jinho Shin MD[17] | Chen-Huan Chen MD[3] | Ji-Guang Wang MD, PhD[18] | Kazuomi Kario MD, PhD[19] | the HOPE Asia Network

[1]SH Big Data Decision and Analytics Research Centre, Shatin, Hong Kong

[2]JC School of Public Health and Primary Care, The Chinese University of Hong Kong, Shatin, Hong Kong

[3]Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

[4]Faculty of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan

[5]Institute of Public Health and Community Medicine Research Center, National Yang-Ming University School of Medicine, Taipei, Taiwan

[6]Center for Evidence-based Medicine, Department of Medical Education, Taipei Veterans General Hospital, Taipei, Taiwan

[7]Cardiovascular Center and Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei City, Taiwan

[8]Division of Hospital Medicine, Department of Internal Medicine, National Taiwan University Hospital, Taipei City, Taiwan

[9]Department of General Medicine, Tan Tock Seng Hospital, Singapore, Singapore

[10]Division of Nephrology Department of Medicine, Yong Loo Lin School of Medicine, Singapore, Singapore

[11]Department of Neurology, School of Medicine and health Sciences, Atma Jaya Catholic University of Indonesia, Indonesia

[12]Department of Cardiology and Vascular Medicine, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia

[13]Department of Cardiology, MIOT international hospital, Chennai, India

[14]Punjab Medical Center, Lahore, Pakistan

[15]Department of Medical Sciences, School of Healthcare and Medical Sciences, Sunway University, Bandar Sunway, Malaysia

[16]Faculty of Medicine, Department of Primary Care Medicine, University of Malaya, Kuala Lumpur, Malaysia

[17]Faculty of Cardiology Service, Hanyang University Medical Center, Seoul, Korea

[18]Department of Hypertension, Centre for Epidemiological Studies and Clinical Trials, The Shanghai Institute of Hypertension, Shanghai Key Laboratory of Hypertension, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

[19]Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

Correspondence
Kelvin KF Tsoi, JC School of Public Health and Primary Care, Prince of Wales Hospital, Shatin, Hong Kong.
Email: kelvintsoi@cuhk.edu.hk

Abstract

The prevalence of hypertension is increasing along with an aging population, causing millions of premature deaths annually worldwide. Low awareness of blood pressure (BP) elevation and suboptimal hypertension diagnosis serve as the major hurdles in effective hypertension management. The advent of artificial intelligence (AI), however, sheds the light of new strategies for hypertension management, such as remote supports from telemedicine and big data-derived prediction. There is considerable

evidence demonstrating the feasibility of AI applications in hypertension management. A foreseeable trend was observed in integrating BP measurements with various wearable sensors and smartphones, so as to permit continuous and convenient monitoring. In the meantime, further investigations are advised to validate the novel prediction and prognostic tools. These revolutionary developments have made a stride toward the future model for digital management of chronic diseases.

1 | INTRODUCTION

Hypertension constantly presents as a public health challenge due to its high prevalence with intimate relationship to cardiovascular diseases (CVD) and the complexity of pathophysiology and pathogenesis. Around 1.13 billion people worldwide are hypertensive population, most of whom are unaware of their status.[1]

Standard treatment protocol for hypertension management is available, but control rate for hypertension remains unsatisfactory worldwide. Controlled hypertension is only seen in 43.5% of patients in the United States,[2] while in just one-fourth in Japan[3] and even a mere 13.8% in China.[4] Foreseeing an exacerbating aging population, where the number of elderly people would increase by 66% in Asia over the next 15 years,[5] alternative strategies are urgently required to reduce the health care burden posed by hypertension.

In the midst of a technological and information era, medical records are usually digitalized, and various sensors have been invented for the collection of vital signals. Therefore, artificial intelligence (AI) has been increasingly recognized as a data-derived computational approach in data analytics for clinical decision making.[6] Branches of AI tools, such as data mining, machine learning (ML), and deep learning (DL), have shown promises in a wide breadth of medical applications. Image processing for breast cancer screening,[7] pattern recognition on electrocardiogram (ECG) for detection of atrial fibrillation,[8] and data exploration of novel genotypes in cardiovascular conditions[9] are the typical examples. Therefore, its application in hypertension management emerges as an important research interest, either from a technical or clinical perspective.

In this review, we discuss current evidence and ground-breaking AI applications for hypertension management from three perspectives: incidence prediction, hypertension management, and application of technology.

2 | ARTIFICIAL INTELLIGENCE: BASIC CONCEPTS

Artificial intelligence is the all-encompassing concept referring to the means incorporating human intelligence to machines firstly mentioned in 1956.[10] ML and DL are the two subclasses of AI with predictive properties, while DL is a new concept of escalating the advances of AI to the next level. ML investigates the association among given training datasets with variables and subsequently performed prediction on newly seen datasets. DL has been widely applied on pattern recognition such as image analysis, given its robust computational power in analyzing data via intricate neural networks.[11]

Supervised and unsupervised learning are the ways of formulating the ML or DL algorithms. In supervised learning, labeled datasets are used to predict known outputs with selection of appropriate tools such as support vector machine and K-nearest neighbor. In unsupervised learning, unlabeled datasets are used to predict unknown outputs, that is, data exploration on formerly unidentified patterns or clusters.

In health care setting, these AI tools have the capability to predict, diagnose, suggest treatment protocols for hypertensive patients, as well as explore meaningful relationship between sophisticated datasets, for personalized treatment and care.

3 | PREDICTION FOR INCIDENCE HYPERTENSION OR ITS RELATED CLINICAL OUTCOMES

Health data provide valuable information for AI applications in assisting health assessment and disease prognosis. Current evidence has revealed AI's efficacy on identification of hypertensive status,[12-14] prediction for incidence,[15-17] and outcomes from hypertension.[18,19]

Masked hypertension, with a reported prevalence ranging from 9% to 30%[20,21] globally, persists as an obstacle for accurate hypertension diagnosis which mainly relies on elevated office blood pressure (BP) level. However, studies[22,23] have found the incremental risk of CVD caused by masked hypertension is similar to that by sustained hypertension. Thus, other than traditional way of diagnosing hypertension, which was primarily based on clinical BP, alternative methods for distinguishing hypertensive status are an urgent need for early treatment or intervention. Golino and colleagues[12] proposed a classification tree ML model for identifying hypertensive subjects with their anthropometric parameters. The data were acquired from 400 participants by three-dimensional body scanning. The proposed model showed limited capability with 58.4% of sensitivity and 69.7% of specificity. Similarly, Lopez-Martinez and colleagues[13] created an artificial neural network (ANN) model with anthropometric metrics to predict hypertension, with the addition of demographic and lifestyle parameters, from 24 434 adults. The model yielded high specificity (87.4%) but relatively low sensitivity (40.2%). Furthermore,

Soh and colleagues[14] introduced the features recognition of ECG signals in detecting the cases of hypertension, the trained k-nearest neighbors algorithm (kNN) on 21 ECG's features attained accuracy of 97.7%, which represented sensitivity of 98.9% and specificity of 89.1%. In comparison, ECG-derived model outperformed other estimations from anthropometric, demographic, and lifestyle parameters in terms of hypertension status. Such identification tools could assist physicians in detecting masked or white-coated hypertensive patients for better diagnosis.

Insights generated from the prognosis of hypertension could lead the ways in predictive approaches based on the individual's BP profiles and conditions. Völzke and colleagues[15] recruited 1605 normotensive subjects and predicted the incidence of hypertension with age, BP levels, and biochemical measurements via data mining of these predictors and subsequently using the identified parameters as the inputs in the Bayesian network model. The model gave an 0.77 (95% CI 0.74–0.80) in the area under curve (AUC) in the external validation cohort. While Ye and colleagues[16] capitalized on electronic medical records in predicting the incidence of hypertension within the next year with ML tool XGBoost, profiles of 1 504 437 subjects were recruited in the development of the model, with 823 637 in the retrospective cohort and 680 810 in the prospective cohort, resulting in AUC of 0.92 and 0.87, respectively. The capability of the model was also proven in a real-world setting as it has been adopted in Maine, the United States. Kanegae and colleagues[17] also investigated the utility of XGBoost by incorporating both body examination parameters and lifestyle factors in the model and yielded slightly improved prediction performance, with AUC of 0.97 upon training and 0.88 upon validation. These prognostic tools have the capacity in quantifying the risk of hypertension and outperforming the existing Framingham risk score for hypertension whose AUC is at around 0.80.

AI techniques are also deployed in estimating the clinical events among hypertensive patients, particularly cardiovascular outcomes. Lacson and colleagues[18] examined the visit-to-visit blood pressure variability (BPV) and biochemical variables in 8799 subjects, for prediction model on CVD with the Random Forest (RF). The features of greatest relationship with CVD were age, urine albumin/creatinine ratio (CR), estimated glomerular filtration rate, serum CR, history of subclinical CVD, total cholesterol, a variable representing time-series SBP signals using wavelet transformation on high-density lipoprotein (HDL-C), the 90th percentile SBP, and triglyceride. The AUC for the model was 0.71 upon testing. Other than cardiovascular outcomes, Wu and colleagues[19] extended prediction from CVD to end-stage renal disease and all-cause mortality in 508 young patients, by using 11 clinical variables, including left atrial diameter, HDL-C, cholesterol, big endothelin-1, right arm diastolic BP, right leg SBP, left leg SBP, right leg diastolic BP, left arm SBP, mean nocturnal arterial oxygen saturation, past maximum SBP, and urea. Such modeling gave slightly better AUC performance, 0.76 (95% CI 0.66–0.85). Compared to the widely used method—Framingham Risk Score, which can achieve AUC of 0.858,[24] the accuracy of the current invented AI tools remains to be improved. However, it is sensitive to racial effects[25] and has a rather arbitrary scoring system. Thus, the significance of an AI model in CVD prediction is about its adaptability to dynamic values of the variables in projection, though the performance of the tools remains to be improved.

The development of prognostic tools that are applicable to different stages of hypertension (normal, elevated, hypertension) could, hence, allow individuals to know more about their BP conditions and the potential risks for CVD. When more health data are collected along the follow-up period, the accuracy of these AI models will continue to be improved. Non-pharmaceutical lifestyle modifications, namely reduction of sodium intake, weight loss, limited alcohol intake, and smoking cessation, are effective in BP control.[26] Physicians, with better understanding on individuals' risk through the AI models, could make early lifestyle modifications in prevention of hypertension.

4 | MANAGEMENT FOR HYPERTENSION

When proper lifestyle modifications have been in place, drug therapy remains unavoidable when BP remains uncontrolled. First-line medications include diuretics, angiotensin-converting enzyme, inhibitors or angiotensin receptor blockers, calcium channel blockers (CCB), and beta-blockers.[19] Standard medication therapy for hypertension is targeting a systolic blood pressure (SBP) level of <140 mmHg, while the SBP Intervention Trial (SPRINT) cohort demonstrated the benefits on non-fatal major cardiovascular events and mortality by targeting a lower SBP level to 120 mmHg with intensive treatment.[27]

Several studies evaluated constituents for successful treatment, Liu and colleagues[28] investigated the biomarkers related to drug effectiveness with the Ensemble model, among commonly used medications: Amlodipine, Felodipine, Irbesartan, Metoprolol, and Levamlodipine. A total of 14 582 subjects taking these five types of medications were analyzed with other clinical records, such as hemoglobin, serum creatinine, serum uric acid, and total cholesterol. Out of all biomarkers, serum creatinine was found to be the most significant indicator regardless of drug types and classes, while fasting blood glucose levels were the second important biometric for medication effectiveness in CCBs. Such findings are pivotal in leading to personalized medication in hypertension treatment and maximizing the possibility for successful BP control. Duan and colleagues[29] on the other hand also inspected heterogeneous treatment effects (HTEs) among individuals on intensive BP therapy along with prediction of 3-year CVD risks, with the use of X-learner ML meta-algorithms. Samples from two databases were studies, SPRINT (N = 9361) and ACCORD-BP (N = 4733), with extraction of demographics, medication, lifestyle, and physiological measurements. The resulting AUC was 0.60 (95% CI 0.58–0.63) for the prediction, surpassing that of traditional logistic regression with AUC 0.51 (95% CI 0.49–0.53). X-learner also observed that individual treatment effects upon intensive drug therapy were not always proportional to baseline CVD risk profiles, highlighting the importance of HTE risk estimation in clinical settings. In

addition, the authors also demonstrated the tool as guiding individualized therapy with satisfactory effects, where the recommendation given by X-learner extended the mean time to CVD events. Medication adherence is also a crucial concern for successful treatment, and Aziz and colleagues[30] examined and predicted adherence score with data from 160 hypertensive subjects using ANN, RF, and Support Vector Regression (SVR). The influential factors included marital status, educational level, occupation, ethnicity, religion, monthly income, and over-prescription of medications. ANN reported the least root-mean-square error (1.42) compared to those given by RF (1.53) and SVR (1.55). However, SVR achieved the highest accuracy to identify proportion of adherence among the three models.

Evaluation of BP variability appears as another trend for guiding better BP management, for both people with and without medication intervention. Koshimizu and colleagues[31] showcased the feasibility of deep neural networks in prediction of mean value of BPV after 1–4 weeks from time-series data of 423 participants with standard deviation ratio of 0.67–0.70 and root-mean-square error of 5.04–6.65 mmHg. Meanwhile, Tsoi and colleagues[32] utilized ML techniques in stratifying individuals with different levels of BPV. The method was applied in two cohorts, SPRINT cohort from the United States and eHealth cohort from Hong Kong, with promising stability of 0.98 and 0.91, respectively. The study showed that around 1/7 population with high variability on BP are of higher risks for stroke and heart failure.

As such, AI has potential in rendering continuous evaluation on treatment efficacy and BP situation and hereby offers physicians with additional references for clinical judgments.

5 | PREDICTION FOR BLOOD PRESSURE LEVELS WITH NEW TECHNOLOGIES

Suboptimal BP control and unawareness of hypertension are the hurdles in combating hypertension burden, while routine self-monitoring of BP could allow early detection of hypertension for better BP control.[33] Although cuff-based BP measurement is invariably regarded as the gold standard, novel methods for BP monitoring from vital signals, or even speech analysis, have great potential to be embedded in wearable devices. Furthermore, fusion with smartphones for BP estimation appears as another trend, by taking advantage of the sound and image recording functions, with input of auscultatory waveforms and transdermal optical images.

Ankishan[34] proposed the prediction of BP values from speech recordings of /a/ vowel, owing to its accurate reflection of acoustic characteristics in a short period of time. The authors recorded the /a/ vowel for 10 s from 86 participants with a mobile application that allows 16-bit resolution and 44 100 Hz sampling rate, giving 230 audio records. The referencing BP was measured with a cuff-based BP monitor. A Convolutional Neural Network-Regression (CNN-R) with two groups was trained to predict the BP values, and promising experimental results were shown. The accuracy was up to 93.7% and the RMSE is 0.236.

Signal-derived BP measurement, such as photoplethysmogram (PPG) or ECG signals, is of particular research interest as well, because of the compatibility with wearable devices like smartwatches. Pulse wave velocity refers to the velocity at which the pressure propagates through the circulatory system and is a major parameter for BP, of which pulse transit time and pulse arrival time are the indicators. These indicators can be derived from PPG and ECG signals so as to allow instantaneous estimation for BP. Monte-Moreno and colleagues[35] has established a PPG-driven BP estimation ML model in year 2011 with preliminary success, where the model achieved a Grade B standard under protocol laid by the British Hypertension Society (BHS). Esmaelpoor and colleagues[36] further devised a multistage deep neural network model to estimate SBP and diastolic blood pressure (DBP) separately from PPG signals in year 2020. The authors first made use of two CNN for morphological features extraction, followed by long short-term memory (LSTM) for temporal dependencies capture. The model not only met the standard laid by the Association for the Advancement of Medical Instrumentation (AAMI), but also was certified for Grade A standard under BHS, with mean (SD) of deviation for SBP and DBP estimations of +1.91(5.55) mmHg and +0.67(2.84) mmHg, respectively.

Meanwhile, Miao and colleagues[37] utilized a mixture of ECG signals for continuous BP measurement, with a combination of residual network and LSTM. Again, the model was able to meet the AAMI standard for mean arterial pressure (MAP) and DBP estimation. MAP and DBP estimation achieved Grade A under BHS standard. These findings have illustrated the viability of using either PPG or ECG signals for BP estimation; thus, wearable devices could render viable BP estimation based on quality AI algorithms adoption.

Novel BP estimation strategies are increasingly being developed to permit compatibility with smartphones. Smartphone auscultatory BP kits were proposed and validated,[38,39] and Argha and colleagues[40] have further refined the methodology for more accurate BP estimation with LSTM and recurrent neural network (RNN). Cuff pressure and Korotkoff sounds are extracted from auscultatory sound for neural network building. The mean (SD) of deviation for SBP estimation is −1.5 (4.8) mmHg, such outcomes are classified as Grade A under BHS standard. Another seminal development in BP measurement is via the transdermal optical imaging technology, as advocated by Luo and colleagues[41] in 2019. The authors proposed that the subtle facial blood flow changes captured by a video with a smartphone camera could be used as the inputs for the ML model in estimating BP. Upon training, testing and validation with data collected from 1328 normotensive adults, the average measurement bias (SD) for SBP and DBP are +0.4 (7.3) mmHg and −0.2 (6.0) mmHg, respectively.

The advancements of cuff-less BP measurements may prove to be surrogates for cuff-based devices due to its high adaptability with wearable devices, in hopes of promoting self-monitoring habits. However, caution still must be taken regarding the clinical validity of measured values since there is no single cuff-less wearable device in the marketplace has been verified under International Validation Standard.[42]

TABLE 1 AI applications and new technology for hypertension management

Applications	AI Techniques	Benefits
Prediction:		
1) Identification of hypertension	Classification tree[12], Artificial neural network (ANN)[13], k-nearest neighbors algorithm (KNN)[14]	Precision diagnosis
2) Incidence prediction	Data mining with Bayesian Network[15], Extreme gradient boosting (XGBoost)[16,17]	Timely intervention
3) Clinical outcome prediction	Random Forest[18], XGBoost[19]	Treatment plan adjustment
Management:		
1) Treatment effectiveness	Ensemble Model[28], X-Learner[29], Support Vector Regression (SVR)[30]	Personalized treatment plan
2) Blood pressure variability	Deep neural network with gated recurrent unit[31], K-means clustering[32]	Pre-emptive interventions (eg lifestyle modifications) for normotensive people
New technology for blood pressure measurement	Convolutional Neural Network (CNN)[34], Random Forest[35], Long short-term memory (LSTM)[36,37], recurrent neural (RNN)[40], Advance machine learning algorithms[41]	Self BP monitoring for hypertension

Because hypertension is one of the most prevalent silent chronic conditions, while loosening patient motivation and adherence are the utmost challenges. AI could save tedious job and provide more free time for physicians to develop and to focus on patient motivation, empathy, and compassion. Such progress might improve systematic team approaches in adherence intervention and patient-centered medicine.[43,44]

6 | CONCLUSION AND FUTURE DIRECTIONS

Hypertension imposes a massive burden on medical resources, in terms of finance and manpower, costing $370 billion worldwide annually[45] alongside the demand-capacity gap on primary care physicians.[46] To date, the AI advancements have been seen in BP measurement, prognostic, and prediction tools, with promising results (Table 1). These solutions, when integrated appropriately with the health system, could contribute to hypertension prevention, prognosis, personalized therapy, and could also save time by avoiding unnecessary clinic visits.

In the transition to the era of "digital management" for hypertension, further actions are required before the official launch of AI applications for clinical practices. First, accuracy improvements on the AI techniques are necessary to reduce undiagnosed hypertension. Second, the AI techniques must be validated in real clinical settings with patients' participation. Therefore, large-scale clinical studies such as prospective cohort and randomized controlled trials should be conducted for further confirmation of the effectiveness of the AI applications. Last but not the least, transferring technical knowledge to the management of other chronic diseases is highly recommended, especially for those with complicated diseases along with hypertension, like diabetes mellitus and renal diseases. The

revolutionary inventions of the AI techniques have made a stride toward the future model of digital management for chronic diseases.

AUTHOR CONTRIBUTIONS
Kelvin Tsoi designed the content and drafted and revised the manuscript. Karen Yiu involved in literature review and draft the

manuscript. Helen Lee reviewed literature, prepared the tables, and drafted the manuscript. Hao-Min Cheng, Tzung-Dau Wang, Jam-Chin Tay, Boon Wee Teo, Yuda Turana, Arieska Ann Soenarta, Guru Prasad Sogunuru, Saulat Siddique, Yook-Chin Chia, Jinho Shin, Chen-Huan Chen involved in comment and revise the manuscript. Ji-Guang Wang and Kazuomi Kario lead the discussion on this paper and revised the manuscript.

ORCID

Kelvin Tsoi https://orcid.org/0000-0001-5580-7686

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.