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Review

Theranostic roles of machine learning in clinical management of kidney stone disease

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ABSTRACT

Kidney stone disease (KSD) is a common illness caused by deposition of solid minerals formed inside the kidney. The disease prevalence varies, based on sociodemographic, lifestyle, dietary, genetic, gender, age, environmental and climatic factors, but has been continuously increasing worldwide. KSD is a highly recurrent disease, and the recurrence rate is about 11% within two years after the stone removal. Recently, machine learning has been widely used for KSD detection, stone type prediction, determination of appropriate treatment modality and prediction of therapeutic outcome. This review provides a brief overview of KSD and discusses how machine learning can be applied to diagnostics, therapeutics and prognostics in clinical management of KSD for better therapeutic outcome.

Contents

1. Introduction

In routine clinical practice, kidney stone disease (KSD) can be detected by laboratory tests such as urinalysis, X-ray, ultrasonography, and/or computerized tomography (CT) scan [1]. Disease management depends on type and size of the stones. Most of KSD patients (or stone formers) are asymptomatic and may require no specific treatment [2,3]. In complicated KSD, extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PNL), ureteroscopy (URS) and other surgical procedures are the common therapeutic procedures to remove kidney stones [4–6].

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Nevertheless, there is a high recurrence rate following the stone removal [7–9].

Machine learning has been used in medicine for diagnostics and therapeutics for quite some time. The use of artificial intelligence (AI) has been increasing in several aspects of biomedical areas. Using training dataset, machine learning algorithms can create models, identify underlying patterns, and then make predictions based on the best-suited model [10,11]. Development of image and speech recognition is one of the significant advancements in this field. The use of machine learning in medical imaging, such as ultrasound elastography (UE), CT scan and magnetic resonance imaging (MRI), improves diagnostic accuracy and reduces the possibility of human errors across a wide range of medical areas [12]. This approach has been also used in urology to diagnose urological disorders, to design appropriate treatment modality, and to predict therapeutic outcome [13,14]. Deep learning, a branch of machine learning, has a potential to be used as an innovative method for diagnosis of chronic kidney disease (CKD) [15] and predicting the decline of renal function [16], renal dysfunction [17], and diabetic nephropathy [18].

In KSD, machine learning has been employed for over two decades [19]. Recently, it has been widely used for stone detection [20], stone type prediction [21], determination of appropriate management option, and prediction of therapeutic outcome [22]. This review provides a brief overview of KSD and discusses how machine learning can be applied to diagnostics, therapeutics and prognostics in clinical management of KSD for better therapeutic outcome.

2. Brief overview of KSD

2.1. Epidemiology and risks

KSD, also known as urolithiasis, nephrolithiasis and renal calculi, is a common illness caused by deposition of solid minerals formed inside the kidney [23]. It is one of the oldest diseases that has caused human suffering for over millennia with evidence in Egyptian mummies [24,25]. The worldwide disease prevalence and incidence vary based on sociodemographic, lifestyle, dietary, genetic, gender, age, environmental and climatic factors [26,27]. The prevalence of KSD is greater in the Western hemisphere as compared with the Eastern (7–13 %, 5–9 % and 1–5 % in North America, Europe and Asia, respectively) [26]. KSD is a highly recurrent disease, of which recurrence rate is approximately 11 %, 20 % and 31 % within two, five and ten years, respectively, after the stone removal [28]. The evidence also indicates the continuously increasing prevalence and incidence around the globe [26,29–31]. In addition to genetic and geographical backgrounds, which are environmental risk factors [26], some systemic diseases, including obesity, diabetes mellitus, hypertension, metabolic syndrome and gout, are also considered as the risks for KSD development [26].

2.2. Types of kidney stones and mechanisms of the stone formation

Kidney stones can be classified into five major types based on the stone composition, including calcium oxalate (CaOx), carbonated apatite or carbapatite (CA), urate, struvite or magnesium ammonium phosphate, and cystine or drug-induced stones [32–34]. Kidney stone formation is a prerequisite process initiated by urinary supersaturation of ions of the stone composition, leading to their transformation from liquid phase to solid phase, the mechanism that is called crystallization or crystal nucleation [35,36]. Thereafter, the loosely formed stone crystals can enlarge by adding free ions from the supersaturated urine, resulting in crystal growth [37]. Additionally, individual crystals can form crystal aggregates that further enlarge the crystalline particles [37,38]. Moreover, the formed crystals can adhere onto apical surfaces of renal tubular cells via affinity between crystals and their receptors on the cell surfaces [39]. Crystal growth, aggregation and adhesion altogether slow down the elimination rate of the formed crystals through intratubular luminal segments with small size, resulting in crystal retention [35,36]. These processes are known as the "free-particle model" of kidney stone formation (the stone forms inside renal tubule) [35,40].

In another model of kidney stone formation namely "fixed-particle model" [35,41], the stone develops on the preformed plaque firstly described by Alexander Randall in 1937 [42]. Randall's plaque comprises mainly calcium phosphate that forms at interstitial compartment of the renal papilla and then serves as an anchor for stone formation [43,44]. Several studies have shown histopathological evidence indicating that the majority of idiopathic CaOx stones are associated with Randall's plaque [43,44]. And basement membrane of the thin loop of Henle is the main locale that plaque arises and expands to the nearby interstitial space under the urothelium [43,44]. After affecting the integrity of urothelium, the plaque is unmasked and exposed to the urine rich with calcium and oxalate ions. Thereafter, the supersaturated urine reacts with the emerging plaque to forms layers of the CaOx crystals on the Randall's plaque by repeated coating, crystallization and growth [43,44].

2.3. Diagnosis and management in current clinical practice

Although most of the stone formers are mainly asymptomatic and do not require specific treatment or surgical intervention, they are suggested to attend the follow-up program annually or at least every 2–3 years to evaluate the disease progression [2,3]. Symptomatic stone formers typically have acute renal colic or flank pain (originating over the costovertebral angle and extending towards the inguinal area), nausea and/or vomiting [2,45]. Clinical presentations may also include hematuria, low urinary flow, hydronephrosis, and secondary urinary tract infection (UTI) [3,23].

Diagnosis and disease management usually start with confirmation of the presence of the stone [3]. The gold standard method for stone detection, size measurement and localization is non-contrast CT (NCCT) scan of the kidneys, ureters, and bladder [2,3,46]. NCCT scan is a highly sensitive and highly accurate method for stone imaging, which is very helpful for further selecting appropriate disease management [46]. Ultrasonography has lower sensitivity as compared with CT scan. However, it is more suitable for some stone formers, e.g., children, pregnant women and patients with frequent episodes of KSD [46]. MRI is used as a second-line modality for pregnant stone formers, who do not meet the criteria for ultrasonography [46]. Besides imaging modality, history taking, physical examination and laboratory tests (e.g., urinalysis and blood chemistry) are also required [2,3].

Based on the guidelines for management of KSD by the European Association of Urology (EAU), non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as the first-line analgesics for renal colic management [3,47]. Spontaneous passage is recommended for the cases with stones <5 mm, whereas medical expulsive therapy (MET) using α-blockers is recommended for those with stones >5 mm in the distal ureter [47]. In the cases with stones >20 mm, PNL is recommended as the first-line treatment [47]. Note that when the patients do not meet the criteria for PNL, retrograde intrarenal surgery (RIRS) or ESWL is recommended [47]. More details and the updated version of the guidelines for disease management are available on the EAU Guidelines Office website (https://uroweb.org/guidelines/urolithiasis).

3. Roles of machine learning in KSD diagnostics

Imaging is a crucial diagnostic tool and the first step for selecting the most appropriate treatment modality in KSD management. De Perrot et al. [48] have reported how well radiomics features and a machine learning classifier can distinguish KSD from phleboliths using low-dose CT. Li et al. [49] have employed the unenhanced abdominopelvic CT scans and deep learning segmentation networks to exclude false positive areas from kidney stones. Parakh et al. [20] have shown the efficacy of cascading convolutional neural network (CNN) for detecting urinary stones. Using this approach, the urinary tract is detected by the first CNN model, whereas the stones are detected by the second CNN model [20]. Additionally, a total of six models have been designed and deployed using CT image datasets of kidney stones, cysts and tumors [50]. Both deep learning techniques (VGG16, Inceptionv3 and Resnet50) and Visual Transformer variants (EANet, CCT and Swin transformer algorithms) can be applied to differentiate KSD from renal cysts and tumors with 99.30 % accuracy achieved by Swin transformer-based model [50]. Caglayan et al. [51] have examined the efficacy of a deep learning model for identifying kidney stones in unenhanced CT images in various planes based on stone size. The sagittal plane has provided the best sensitivity and specificity as compared with other planes [51]. Längkvist et al. [52] have created a computer-aided detection (CAD) algorithm that can detect a ureteral stone in a CT scan. Similarly, Sudharson et al. [53] have developed a CAD algorithm using support vector machine (SVM)-based machine learning classifier to identify kidney abnormalities of multiple classes, such as kidney stones, cysts and tumors, by ultrasonography.

Clinicians would take great benefit from a deep learning system that is automated and can segment data automatically. Several previous studies have tried using automated machine learning to detect kidney stones. For example, Yildirim et al. [54] have applied a deep learning model to automatically detect and localize kidney stones from coronal CT scans. Cui et al. [55] have also reported automated detection of kidney stones in NCCT images using deep learning and S.T.O.N.E. nephrolithometry scoring method. To deal with noisy CT, Elton et al. [56] have employed CNN (U-Net model) for automated detection and volume quantification of small stones in coronal CT images. Babajide et al. [57] have analyzed the efficacy of a machine learning method to detect and characterize kidney stones automatically compared with manual diagnosis. The data have shown that the machine learning algorithm more accurately approximates the stone boundary with both sensitivity and specificity of 100 % [57].

Most of kidney stone studies on diagnostics use various medical imaging methods, including X-ray, CT scan and MRI. Nevertheless, only few studies have used clinical characteristics to assist KSD diagnostics. Using clinical and gut microbiota traits, one can predict the development of CaOx KSD [58]. Recently, Kavoussi et al. [59] have used 24-h urine and clinical data to predict urinary abnormalities. Age, gender and body mass index are the three variables that have the most impact on training the prediction models

Table 1
Summary of studies using machine learning in KSD diagnostics.

Study/Reference	Year	Objective	Input	Method(s)	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC
Längkvist et al. [52]	2018	Detecting kidney stone in CT images	CT images	Deep learning (CNN)	n/a	100.00	n/a	0.997
Parakh et al. [20]	2019	Detecting ureteral stone in CT images	CT images	Deep learning (CNN)	95.00	94.00	96.00	0.954
De Perrot et al. [48]	2019	Differentiating kidney stones and phleboliths in low-dose CT (LDCT) images	Radiomics features extracted form LDCT	Machine learning (AdaBoost)	85.10	91.70	78.30	0.902
Cui et al. [55]	2021	Detecting and scoring kidney stone score based on S.T.O.N.E. nephrolithometry	Non-contrast CT (NCCT) images	Deep learning (CNN) & Machine learning (3D U-Nets)	n/a	95.90	n/a	n/a
Sudharson et al. [53]	2021	Detecting kidney abnormalities from noisy ultrasound images	Ultrasound images	Machine learning (SVM) & Deep learning (CNN)	87.31 at noise level = 0.02	n/a	n/a	n/a
Yildirim et al. [54]	2021	Detecting kidney stone using coronal CT images	CT images	Machine learning (XResNet50)	96.82	95.76	97.00	n/a
Xiang et al. [58]	2021	Predicting calcium oxalate kidney stone	Patients and microbiota characteristics	Machine learning (RF)	n/a	n/a	n/a	0.940
Elton et al. [56]	2022	Detecting kidney stone using coronal CT images	CT images	Deep learning (CNN) & Machine learning (3D U-Nets)	n/a	86.00	n/a	n/a
Islam et al. [50]	2022	Detecting kidney tumors, cysts, and stones using CT scan of the entire abdomen and urogram	CT and urogram images	Machine learning (Swin transformers)	99.30 for stone	98.90 for stone	n/a	0.99975 for stone
Kavoussi et al. [59]	2022	Predicting 24-h urine abnormalities for KSD using electronic health record-derived data	Patient characteristics and 24-h urine data	Machine learning (XGBoost)	98.00 for urine volume	n/a	n/a	0.590 for urine volume
Li et al. [49]	2022	Detecting kidney stone in CT images	CT images	Machine learning (Res U-Net)	99.95	96.61	99.97	n/a
Babajide et al. [57]	2022	Detecting kidney stone and measuring stone features in CT images	CT images	Machine learning	n/a	100.00	100.00	n/a
Caglayan et al. [51]	2022	Detecting kidney stone in CT images with different planes	CT images	Machine learning (XResNet50)	93.00 for stone sizes >2 cm	n/a	n/a	n/a

AUC = area under the curve; n/a = not available.

[59]. All the information obtained from the aforementioned studies (also summarized in Table 1) indicate the important roles of machine learning in KSD diagnostics.

4. Roles of machine learning for stone type prediction

Specifying type of kidney stones is an important step for management of KSD to achieve satisfactory therapeutic outcome. There is a wide attention to predict type of kidney stones using clinical and imaging data. As such, machine learning-based text classification has been extensively used for this purpose. For example, data mining techniques have been used to extract useful information, such as stone types and compositions, from electronic health record [60]. In a study by Kazemi et al. [61], 42 features extracted from medical information record of patients have been used to build a model for predicting type of kidney stones. Similarly, Abraham et al. [62] have predicted stone composition by using XGBoost machine learning on 24-h urine data and clinical information. Interestingly, performance of the predictive model is improved by using 24-h urine data [62]. In another study, the microwave dielectric properties, which differ in various stone types, have been used to predict three types of kidney stones [63]. Moreover, the eight simple clinical parameters, including gender, age, body mass index, estimated glomerular filtration rate, urine pH, the presence of bacteriuria, the presence of gout, and the presence of diabetes mellitus, can improve uric acid stone prediction with an area under the curve (AUC) of 0.936 [64].

Additionally, the stone type can be predicted from appearance, texture and section of the stones shown in digital images, CT scans and digital videography. Grosse Hokamp et al. [65] have used dual-energy CT scan and machine learning to predict various compositions of the stones, including whewellite (CaOx monohydrate; COM), weddellite (CaOx dihydrate; COD), calcium phosphate, cystine, struvite, uric acid, and xanthine. Zheng et al. [66] have created a predictive model with radiomics signature based on NCCT images and independent clinical predictors for detecting infection stones with an AUC of 0.825. Recently, machine learning has been used to analyze high-quality digital images of a kidney stone, resulting in successful prediction of the stone type with high specificity [21]. El Beze et al. [67] have developed an automated stone detection technique to discriminate six types of stones from endoscopy by using surface and section of urinary calculi. Using a dataset of smartphone-based microscopic images, Onal et al. [68] have evaluated an image recognition system for categorizing four types of kidney stones in the rapid and precise manner. Likewise, Estrade et al. [69] have applied deep learning method on digital endoscopic video sequences to automatically detect stone morphology during the stone fragmentation process. All the aforementioned studies, including their goals, AI methods used and results, are summarized in Table 2.

5. Roles of machine learning for determination of appropriate treatment modality and prediction of therapeutic outcome

Significant technological advancements have been made for management of KSD. Parekattil et al. [70] have used information from 384 stone formers who had spontaneous passing stones or underwent intervention (stent, ureteroscopy or ESWL) to develop the model. The findings have shown that the cutoff at 6 mm of the stone dimension can accurately identify patients who may require intervention.

To prevent or minimize the problematic stone recurrence, many studies have employed machine learning to predict the therapeutic outcome of KSD. For this kind of research, most of the studies have applied artificial neural network (ANN) to predict the ESWL outcome. The clinical data and urine samples of patients who underwent ESWL are used as the parameters to predict the stone recurrence after ESWL [19,71]. In addition, radiographic images categorized by radiographic morphological patterns are used for prediction of stone clearance after ESWL with an accuracy of 92 % [72]. In addition, the most influential factors on prediction of the ESWL outcome are size and position of the stones, the usage of stents, and the stone width [73]. Moreover, combining three-dimension textual analysis features (3D-TA) derived from CT images with clinical variables can improve prediction of the ESWL success [74]. NCCT image analysis of stone formers who

Table 2
Summary of studies using machine learning for stone type prediction.

Study/Reference	Year	Objective	Input	Method(s)	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC
Kazemi et al. [61]	2017	Predicting kidney stone type	Patient and stone characteristics	Machine learning (Ensemble-based method)	97.10	n/a	n/a	0.996
Saclı et al. [63]	2019	Predicting kidney stone composition	Microwave dielectric properties of stone	Machine learning (K-nearest neighbors)	98.17	98.00	98.60	n/a
Grosse Hokamp et al. [65]	2020	Predicting the main component of pure and mixed kidney stones	CT images	Machine learning (Shallow neural network)	91.10	n/a	n/a	n/a
Black et al. [21]	2020	Predicting kidney stone composition	Digital photographs of stones	Machine learning (ResNet-101)	n/a	94.12 for uric acid stone	97.83 for uric acid stone	n/a
Zheng et al. [66]	2021	Identifying urinary infection stone *in vivo*	CT images	Machine learning (LASSO)	n/a	n/a	n/a	0.825
Abraham et al. [62]	2022	Predicting kidney stone composition	Demographic, clinical, and urine analyte data	Machine learning (XGBoost)	91.00	26.00	n/a	0.800
Chen et al. [64]	2022	Predicting uric acid component	Clinical parameters	Machine learning	n/a	100	91.20	0.936
El Beze et al. [67]	2022	Predicting kidney stone composition	Surface and section images of stone	Machine learning (Inception v3)	n/a	99.00 for COM	98.00 for COM	0.980 for COM
Onal et al. [68]	2022	Predicting kidney stone composition	Microscopic images of stone	Deep learning (CNN)	88.00	n/a	n/a	n/a
Estrade et al. [69]	2022	Predicting kidney stone composition	Endoscopic digital images and videos	Deep learning (CNN)	88 ± 6	80 ± 13	92 ± 2	n/a

AUC = area under the curve; n/a = not available.

Table 3
Summary of studies using machine learning for determination of appropriate treatment modality and prediction of therapeutic outcome.

Study/Reference	Year	Objective	Input	Method(s)	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC
Michaels et al. [19]	1998	Predicting stone regrowth after extracorporeal shock wave lithotripsy (ESWL)	Patient and stone characteristics	Deep learning (ANN)	91.00	91.00	92.00	0.964
Poulakis et al. [72]	2003	Predicting stone clearance in lower pole after ESWL	Patient and stone characteristics and radiographic images	Deep learning (ANN)	92.00	n/a	n/a	0.936
Gomha et al. [73]	2004	Predicting stone-free status after ESWL	Patient and stone characteristics	Deep learning (ANN)	77.70	77.90	75.00	n/a
Parekattil et al. [70]	2006	Predicting outcome and duration of passage for ureteral/renal calculi	Patient and stone characteristics	Deep learning (ANN)	88.00	n/a	n/a	0.900
Moorthy et al. [75]	2016	Predicting fragmentation of stones using non-contrast CT (NCCT) image of patients undergoing ESWL	NCCT images	Deep learning (ANN)	n/a	80.70	98.40	n/a
Aminsharifi et al. [79]	2017	Predicting different outcome variables of percutaneous nephrolithotomy (PNL)	Patient and stone characteristics	Deep learning (ANN)	98.20 need for SWL	98.00 need for SWL	n/a	n/a
Seckiner et al. [71]	2017	Predicting the stone-free rate after ESWL	Patient and stone characteristics	Deep learning (ANN)	85.48	n/a	n/a	n/a
Mannil et al. [74]	2018	Predicting stone-free status after ESWL	patient and stone characteristics and CT images	Machine learning (RF)	n/a	65.00	72.00	0.850
Choo et al. [76]	2018	Predicting treatment success after ESWL	Patient and stone characteristics, X-ray and CT images	Machine learning (Decision tree)	92.29	95.87	85.82	n/a
Shabaniyan et al. [80]	2019	Predicting postoperative outcome of PNL	Patient and stone characteristics and laboratory data	Machine learning (SVM)	94.80	100.00	88.90	n/a
Aminsharifi et al. [22]	2020	Predicting multiple outcomes after PNL	Preoperative and postoperative patient characteristics	Machine learning (SVM)	95.10 need for repeat PNL	n/a	97.00 need for repeat PNL	n/a
Yang et al. [77]	2020	Predicting stone-free success after ESWL	Patient and stone characteristics	Machine learning (LightGBM)	87.90 for stone-free	n/a	n/a	n/a
Hameed et al. [81]	2021	Predicting postoperative outcome of PNL	Preoperative and postoperative patient characteristics	Machine learning (RF)	81.00	n/a	n/a	0.810
Moghisi et al. [78]	2022	Predicting ESWL outcome to assist practitioners in their decision-making	Patient and stone characteristics	Machine learning (AdaBoost)	77.59	87.50	65.30	0.800

AUC = area under the curve; n/a = not available.

underwent ESWL can create a model to predict fragmentation of stones and outcome of treatment [75]. Choo et al. [76] have utilized stone features from X-ray and CT scans to construct a decision support system (DSS) to forecast treatment success following ESWL with high accuracy, especially using the 15-factor model. Recently, Yang et al. [77] have also determined ability of DSS to predict the ESWL success rate with accuracy up to 88 % [77]. A more recent study has built a machine learning model that can predict the ESWL outcome to aid practitioners in decision making with a sensitivity of 87.5 % [78].

Machine learning has been also applied to predict the therapeutic outcome after nephrolithotomy. Aminsharifi et al. [79] have predicted postoperative outcome of PNL from preoperative and postoperative variables using ANN. The model can predict stone-free status or ancillary procedures with sensitivity and accuracy from 81.0 % to 98.2 % [79]. Moreover, machine learning technique classification software seems to provide better results as compared with the Guy's Stone Score (GSS) and the Clinical Research Office of Endourological Society (CROES) nomogram [22]. Machine learning has been also used to create the DSS for forecasting therapeutic success. In a study by Shabaniyan et al. [80] using four different classification methods to develop DSS, the PNL outcome can be predicted with a high degree of accuracy (94.8 %). Hameed et al. [81] have used Random Forest (RF)-based machine learning to develop a decision support system to predict stone-free status after PNL for staghorn calculi with an accuracy of 81 %. All the aforementioned studies, including their goals, AI methods used and results, are summarized in Table 3.

6. Summary and outlook

As evidenced by several studies, it becomes clear that machine learning plays essential theranostic roles in clinical management of KSD. Various machine learning algorithms, including XGBoost, CNN, ensemble-based method, k-nearest neighbors, ANN, SVM, RF and several other methods, have improved performance of the systems by increasing the accuracy and sensitivity of KSD diagnostics, prediction of stone type, prediction of therapeutic outcome and prognostics. The advantages of such computational-based approaches therefore serve as the other means for clinical management of KSD. These approaches may also lead to discovery of new therapeutic strategies, better therapeutic outcome, and more successful prevention of KSD.

The amount of available information on KSD has been growing exponentially as new generations of the biotechnology has continuously emerged. The recently emerging medical imaging technologies, like high-resolution 3D imaging and other new methods, have offered higher quality of imaging in terms of resolution and signal-to-noise ratio. These technologies together with improved machine learning algorithms have paved the way for more precise clinical diagnostics of KSD. Additionally, the well-developed texture analysis of stone images has dramatically improved the accuracy for prediction of kidney stone type. Such advances in these medical imaging technologies and machine learning are likely to be more extensively used in routine clinical management of KSD in the near future. However, there are still rooms for further improvements of machine learning algorithms to increase the sensitivity and specificity of automated classification methods, particularly for ureteroscopic kidney stone images. Furthermore, blood and urine chemistry laboratory tests should be also combined with clinical information and medical imaging to enhance the accuracy of machine learning in KSD theranostics.

Finally, establishment of an international network to construct a centralized kidney stone database for each type of the stones comprising patients' demographic and background information, urine/blood parameters and chemical analyses, imaging, all other laboratory tests, treatment modalities, therapeutic outcome, etc., should be considered. Such ideal database will definitely pave the way for development of the more robust machine learning algorithm towards precision medicine for KSD.

CRediT authorship contribution statement

Supatcha Sassanarakkit: Data curation, Formal analysis, Visualization, Writing – original draft. **Sudarat Hadpech:** Data curation, Formal analysis, Writing – original draft. **Visith Thongboonkerd:** Funding acquisition, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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