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Preoperative Prediction of Infection Stones Using Radiomics Features From Computed Tomography

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ABSTRACT Preoperative prediction of infection stones from CT images could provide additional information for treatment planning. We developed a radiomics algorithm that could apply data from non-contrast-enhanced CT images to distinguish infection stones from non-infection stones. This retrospective study included 98 patients with clinically confirmed infection kidney stones and 59 patients with non-infection kidney stones. Fifty-four radiomics features extracted from CT images were reduced to 27 key features by the LASSO algorithm, for which a radiomics signature was built with ensemble learning based on bagged trees. Multivariable logistic regression analysis was then used to develop a radiomics nomogram incorporating the radiomics signature and independent clinical factors. The radiomics signature, which consisted of morphological features and textural features, was significantly associated with infection kidney stones. Ensemble learning based on bagged trees could differentiate infection kidney stones from non-infection kidney stones with 90.7% accuracy, 85.81% sensitivity, 93.96% specificity, a 91% positive predictive value and a 91% negative predictive value. Predictors incorporated into the individualized prediction nomogram included the radiomics signature, white blood cell count and urine culture. Decision curve analysis demonstrated that the radiomics nomogram had potential clinical application for infection stone prediction.

INDEX TERMS Kidney stones, CT, multivariate analysis, nomograms, radiomics.

I. INTRODUCTION

Urolithiasis is a common, painful urological disease responsible for substantial health problems. In addition to painful recurrence, urolithiasis is also a risk factor for bone fractures [1], cardiovascular disease [2]–[4], and chronic kidney disease [5], [6]. Increasing evidence suggests that the incidence and prevalence of kidney stones are steadily increasing worldwide [7], [8], especially among adolescents [9], [10] and women [11]–[15].

Stones can be classified into infection, non-infection, genetic defects and drug stones by aetiology [16]. Infection stones are complex aggregates of crystals amalgamated in an organic matrix that are strictly associated with urinary

tract infections. Therefore, preoperative prediction of infection stones could provide additional information for clinical management [17]. In clinical practice, the urine pH, urinary crystals, prior stone history, the presence of urea-splitting organisms and plain radiography are factors currently used to determine stone types. However, thus far, stone composition has only been accurately determined by in vitro methods after surgery, such as infrared spectroscopy or chemical analysis [18].

At present, abdominal computed tomography CT has become the reference imaging standard for urolithiasis [19]. Many in vivo metrics such as Hounsfield unit HU (Hounsfield unit) values [20], absolute HU [21], mean HU [22] and 3D HU [23] have been investigated to predict stone composition from CT images. Moreover, dual-energy CT also demonstrated high sensitivity to predict uric acid stones [24].

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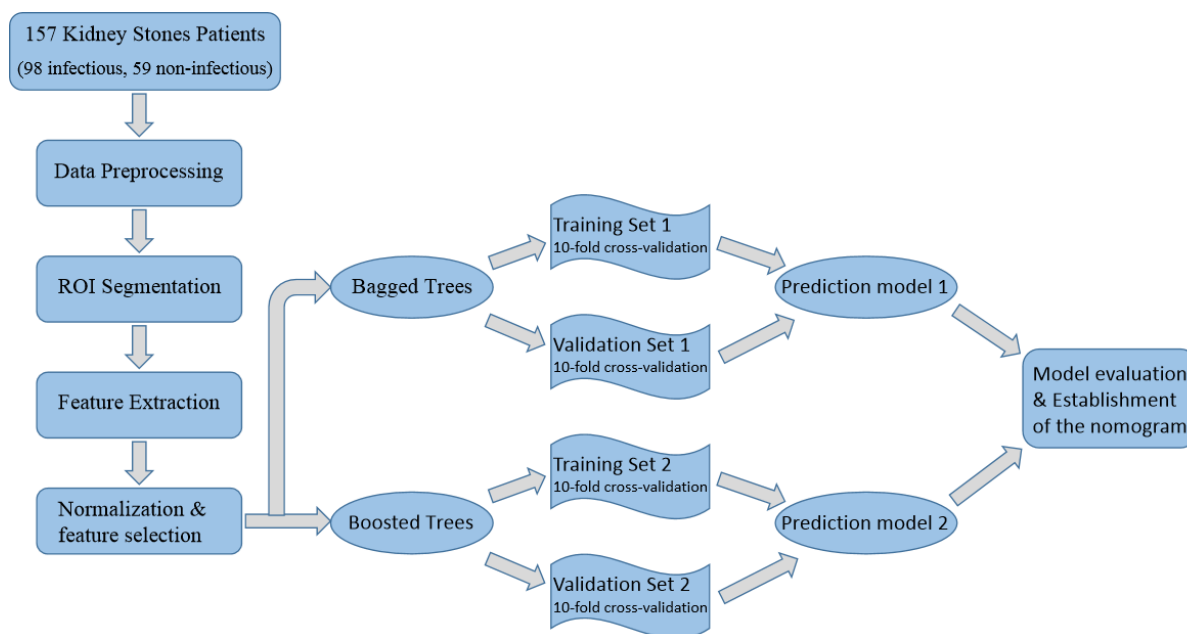


FIGURE 1. Flow chart of the experiment.

However, most methods were only based on the cut-off density of CT images, which are not sufficiently accurate for specific cases with ambiguous values [25].

As the attenuation value of X-rays is different for different substances, a radiomics [26] approach can provide more detailed features of stones [27]. Recently, Mannil *et al.* [28] demonstrated that three-dimensional texture analysis with machine learning can provide incremental predictive information for successful shock wave lithotripsy in patients with kidney stones. With this knowledge, we sought to create a multivariate statistical model based on radiomics features (morphological features and textural features) to quantitatively distinguish between infection stones and non-infection stones. Furthermore, a radiomics nomogram [29] incorporating radiomics signatures and clinical factors was developed to conveniently and non-invasively facilitate individualized preoperative prediction of infection stones.

II. MATERIALS AND METHODS

A. PATIENTS

This study was approved by the Ethics Committee of the First Hospital of China Medical University. A total of 157 clinical patients were included in this retrospective study, including 98 patients diagnosed with infection kidney stones and 59 patients diagnosed with non-infection kidney stones. We retrospectively identified patients in our stone registry treated for pure infection (including magnesium ammonium phosphate or carbonate apatite) or non-infection (including calcium oxalate, calcium phosphate or uric acid) stones from April 2016 to May 2018 who had at least 1 non-contrast-enhanced CT image prior to stone analysis. The stone composition was analysed by Fourier transform infrared

spectrometry immediately after acquisition, and a stone was considered pure if it was composed of 70% or more of a single compound. Stones were retrieved after PNL (percutaneous nephrolithotomy), URS (ureteroscopy), extracorporeal shockwave lithotripsy SWL (extracorporeal shockwave lithotripsy) or by the patient after spontaneous passage, and the composition was determined. If multiple unilateral or bilateral stones were present, and the retrieved fragment could not be clearly distinguished by the operative report or preoperative imaging, the patient was excluded from analysis.

B. ANALYSIS WORKFLOW

As shown in Figure 1, the prediction workflow includes data preprocessing, region of interest (ROI) segmentation, radiomics feature extraction, normalization and feature selection, prediction model generation, prediction performance evaluation and establishment of the nomogram.

C. STATISTICAL ANALYSIS

Statistical analysis was performed with R software (version 3.3.4; <http://www.Rproject.org>). Measurement data (e.g., age) are expressed as the mean \pm SD and were compared using two-tailed Student's t-tests. Count data are expressed as percentages (%), and differences were evaluated for statistical significance with the chi-square test ($P < 0.05$).

D. CT DATA ACQUISITION AND PREPROCESSING

Over the inclusion period, non-contrast-enhanced abdominal CT images were acquired on three different CT scanners: a Philips Brilliance CT, a Toshiba Aquillion 64 and a GE Optima CT680. The preprocessing of CT images including total number of stones, location of stones and ROI labelling

was implemented by a senior radiologist (with 10 years of experience). All imaging tomography including kidney stones was marked with ROIs, which were slightly larger than the peripheries of stones, providing a scientific standard for subsequent image segmentation. To unify the experimental standards and according to the actual situation of kidney stones, we used the most central 5 layers for the subsequent radiomics feature extraction of all images containing stones.

E. RADIOMICS SIGNATURE BUILDING AND PREDICTIVE MODEL DEVELOPMENT

In this study, all image processing methods were implemented using an in-house MATLAB script (version 2017a; MathWorks, Natick, MA). Greyscale normalization of the images was performed using the “1-99%” method to distribute the greyscale values of pixels between 0 and 255 to avoid insufficient image contrast (unbalanced image pixel brightness distribution). Image scaling refers to the process of adjusting the sizes of images. Due to the inconsistent size of the CT images used in the study, processing the images later in the analysis was problematic. Therefore, the image matrices were adjusted to a size of 512×512 pixels. Subsequently, a region-based image segmentation technique [30], the Otsu algorithm, was used to extract the stone ROIs. The segmentation results were then re-checked by the radiologist.

Morphological and textural features were extracted from ROIs of stones. Morphological features included 16 descriptors of the tumour region, including area, perimeter, roundness, centroid, and so on. Textural features are visual characteristics that reflect the homogeneity phenomenon of images and the arrangement of properties that change slowly or periodically on the body surface. These features are represented by the greyscale distribution of the neighbourhood of the pixel and its surrounding space. In the paper, textural features included mainly six types: the grey-level co-occurrence matrix (GLCM), the grey-level run-length matrix (GLRLM), the grey-level-gradient co-occurrence matrix (GLGCM), the neighbouring grey-level dependence matrix (NGLDM), greyscale histogram features, and Tamura features. Overall, 16 morphological features and 38 textural features per ROI were computed.

The least absolute shrinkage and selection operator (LASSO) [31] method was used to select the most useful predictive features from the primary dataset. The basic aim of the LASSO method is to minimize the residual square sum under the constraint that the sum of the absolute values of the regression coefficients is smaller than a constant so that some regression coefficients that are strictly equal to zero can be generated. The “glmnet” package (MATLAB version) was used to implement the LASSO logistic regression analysis.

Ensemble learning based on bagged trees and boosted trees was used to distinguish infection stones from non-infection stones. The bagging (bootstrap aggregating) algorithm adopts randomly selected training data to construct a classifier. By performing random sampling N times, N sample sets are obtained. N weak learners are learned independently, and

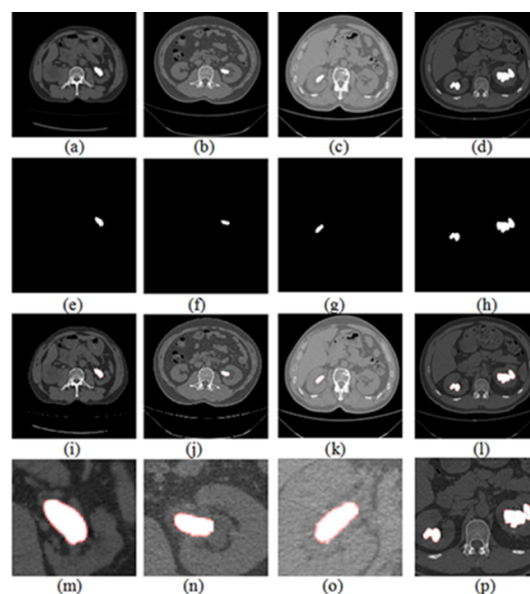


FIGURE 2. Segmentation results. (a) - (d) original images; (e) - (h) segmentation results from the threshold segmentation algorithm; (i) - (l) approximate outlines of the segmentation results (red); (m) - (p) enlarged views of the segmentation results (red).

then strong learners are obtained by combining strategies. The boosting algorithm first trains a base learner from the initial training set, then adjusts the training sample distribution according to the performance of the base learner (giving more weight to the wrong samples), and then trains the next learner based on the adjusted distribution of samples, which is repeated until the specified value is reached.

To reduce the overfitting, to a certain extent, and to obtain as much valid information as possible from limited data, a 10-fold cross-validation was used to determine the robustness of the classifiers for variation in the training data. The accuracy, area under the curve AUC (area under the curve), sensitivity, specificity, PPV (positive predictive value) and NPV (negative predictive value) were calculated as metrics to assess the quantitative discrimination performance of the model.

F. ESTABLISHMENT OF THE NOMOGRAM

To provide clinicians with a quantitative tool for the preoperative prediction of infection stones, multivariable logistic regression analysis was used to develop a radiomics nomogram [31] incorporating the radiomics signature and independent clinical factors. The selection criterion of clinical factors was the chi-square test ($P < 0.05$).

Decision curve analysis was conducted to determine the clinical usefulness of the nomogram by quantifying the net benefits at different threshold probabilities.

III. RESULTS

A. CLINICAL CHARACTERISTICS

The clinical characteristics of the patients are summarized in Table 1. The results showed that sex, white blood cell (WBC) count and urine culture (UC) were significantly

TABLE 1. Clinical characteristics of the patients.

Characteristic	Infection (n=98)	Non-infection (n=59)	χ^2	P
Age, mean±SD, years	53.25±1.67	51.20±5.77	1.092	0.277
Sex, No. (%)				
Male	44(44.9)	43(72.9)	10.96	<0.001***
Female	54(55.1)	16(27.1)		
WBC count				
<20	29(29.6)	33(55.9)	9.620	<0.01**
≥20	69(70.4)	26(44.1)		
UC				
Positive	43(43.9)	12(20.3)	8.364	<0.01**
Negative	55(56.1)	47(79.7)		
CRP level				
<5	65(66.3)	42(72.4)	0.3760	0.540
≥5	33(33.7)	16(27.6)		
PH				
Positive	16(16.3)	7(11.9)	0.284	0.594
Negative	82(83.7)	52(88.1)		

NOTE. P-values are derived from the univariate association analyses between each clinical characteristic of the patients and infection stones.

* P-value < 0.05; ** P-value < 0.01; *** P-value < 0.001.

Abbreviations: WBC: white blood cell; UC: preoperative urine culture; PH: preoperative haemogram; CRP: C-reactive protein.

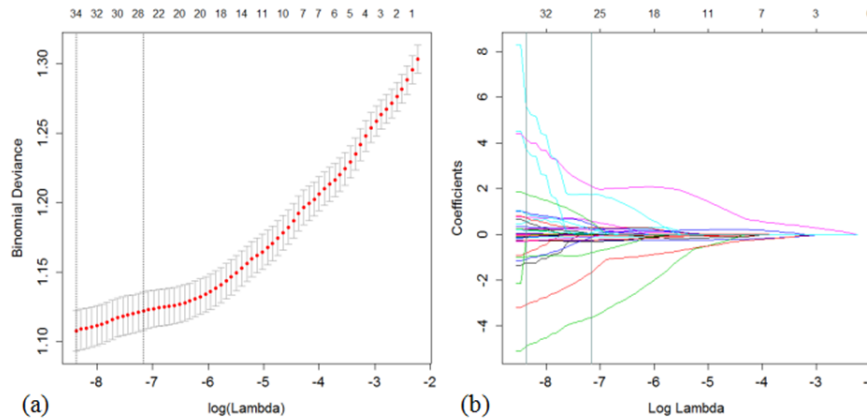


FIGURE 3. LASSO logistic regression for feature selection. (a) Selection of the parameter (λ) in the LASSO model by 10-fold cross-validation based on minimum criteria. The y-axis indicates binomial deviances. The lower x-axis indicates the $\log(\lambda)$. Red dots indicate the average deviance values for each model with a given λ , and vertical bars through the red dots show the upper and lower values of the deviances. The vertical black lines define the optimal values of λ , for which the model provides the best fit of the data. A λ value of 0.00077 was chosen. (b) LASSO coefficient profiles of the features. The dotted vertical line was plotted at the value selected using 10-fold cross-validation, where an optimal λ resulted in 27 non-zero coefficients.

associated with infection kidney stones ($P < 0.05$). No significant differences were found in other clinical characteristics.

B. IMAGE SEGMENTATION AND RADIOMICS SIGNATURE BUILDING

Kidney stones may be present in the left kidney, right kidney, or both kidneys. Therefore, for each patient, we examined ROIs in both kidneys. The segmentation results are shown in Figure 2. All of the segmentation results were reviewed by the doctor, all met the standard and could be accurately divided.

A total of 54 candidate radiomics features were extracted from ROIs of stones. The 54 features were divided into two types: morphological features and textural features.

To reduce complexity, 54 features (16 morphological features and 38 textural features) were reduced to 27 features (16 morphological features and 11 textural features) for potential predictors from 157 patients, and these features had non-zero coefficients in the LASSO logistic regression model. The feature selection process is shown in Figure 3.

C. VALIDATION OF THE PREDICTIVE MODEL

According to the 27 features selected by the LASSO analysis, the results of ensemble learning based on bagged trees and boosted trees are shown in Table 2. Considering the results comprehensively, the accuracy, sensitivity, and specificity of ensemble learning based on bagged trees for distinguishing infection stones were significantly better than those based

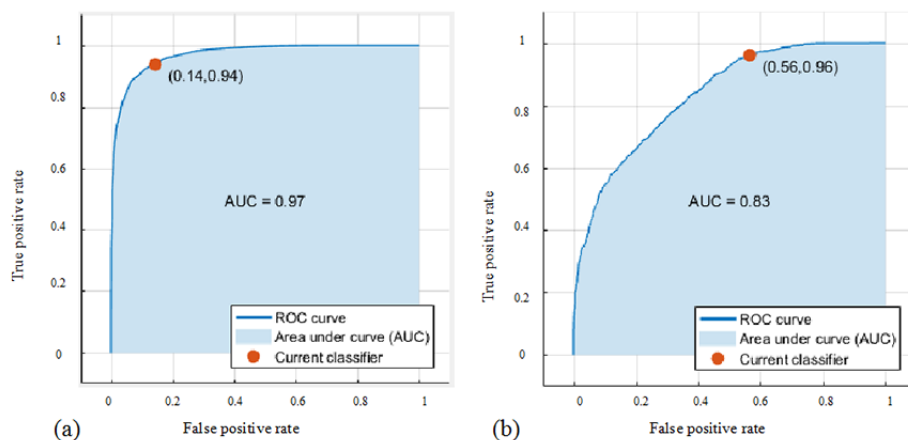


FIGURE 4. AUC of ensemble learning based on bagged trees (a) and boosted trees (b).

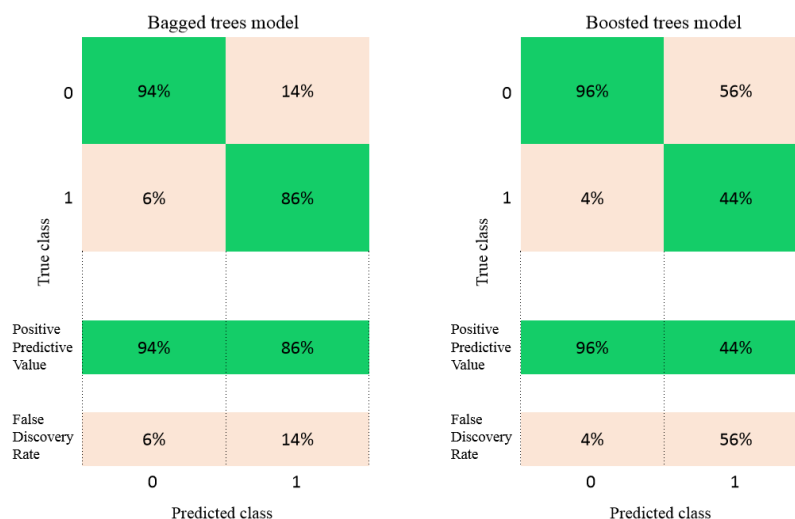


FIGURE 5. Confusion matrix for prediction results of infectious calculi based on integrated learning of bagged tree.

TABLE 2. Predictive value of ensemble learning based on bagged trees and boosted trees.

Ensemble Learning	27 features extracted by LASSO			
	Accuracy	Sensitivity	Specificity	AUC
Bagged trees	0.907	0.858	0.940	0.97
Boosted trees	0.751	0.436	0.964	0.83

on bagged trees alone. Ensemble learning based on bagged trees performed well, with an accuracy of 90.7% and a sensitivity and specificity of 85.8% and 94.0%, respectively. The receiver operating characteristic (ROC) curve for the use of the proposed model to distinguish infection stones from non-infection stones is shown in Figure 4. Overall, ensemble learning based on bagged trees had a high predictive value for distinguishing infection stones from other stones.

Figure 5 shows the confusion matrix of the model. Green indicates that kidney stones could be correctly identified, while light orange indicates incorrect recognition of kidney stones. In Figure 5 (bagged trees model), the percentage of correct identification of infection stones was 86%, which indicates that the missed diagnosis rate was 14%, and the specificity for identifying other components of kidney stones was 94%, which indicates that the misdiagnosis rate was 6%. In Figure 5 (boosted trees model), the percentage of correct identification of infection stones was 44%. The result of this model was obviously not particularly ideal, not as good as that of the previous model. However, the specificity for identifying other components of kidney stones was 96%. Therefore, on the whole, the model was not perfect.

D. ESTABLISHMENT OF THE NOMOGRAM

A radiomics nomogram (Figure 6) was built using significant clinical characteristics (WBC and UC) and radiomics

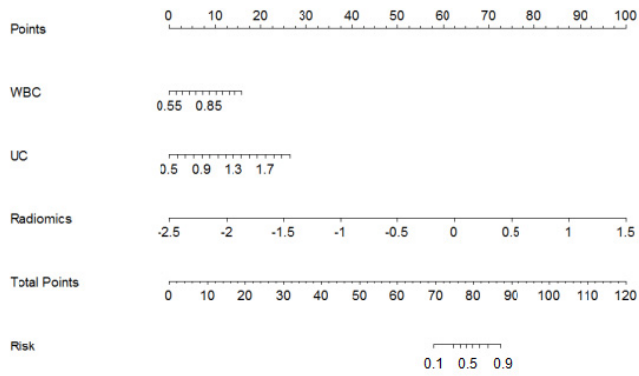


FIGURE 6. Nomogram for predicting the presence of infection kidney stones. The radiomics nomogram includes the radiomics features, WBC count and UC.

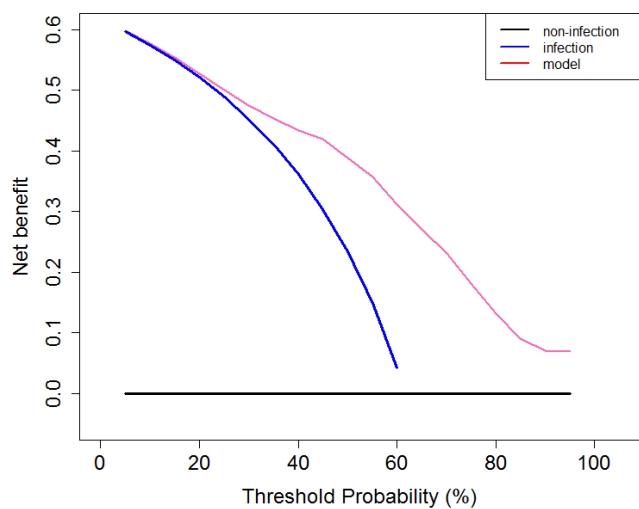


FIGURE 7. Decision curve analysis for the nomogram.

features with non-zero coefficients in the LASSO logistic regression. The nomogram set the scoring criteria according to the size of the regression coefficients of the clinical characteristics and radiomics features, and each independent variable was assigned a score. A total score could be calculated for each patient, and then the transfer function between the score and the probability of having infection kidney stones could be used to calculate the probability of infection kidney stones in each patient. The length of each factor was positively correlated with the presence of infection stones. Therefore, a significant relationship existed between infection stone components and the radiomics features of stones.

Figure 7 shows the decision curve analysis for the nomogram. The decision curve shows if the patient’s or physician’s threshold probability is greater than 18%, using the nomogram to predict the presence of infection and non-infection stones yields greater benefit than the “all infection” or “all non-infection” strategies. The threshold probability is where the expected benefit of treatment is equal to the expected benefit of avoiding treatment.

IV. DISCUSSION

With the advancement of minimally invasive surgical techniques, the performance of traditional open surgical methods for the treatment of urolithiasis has gradually decreased and been replaced by various types of minimally invasive surgical methods. SWL, URS and PNL are suitable treatment modalities for renal and ureteral calculi [25]. Determination of stone types can guide the clinical selection of appropriate treatment methods and provide a basis for cause analysis and the development of a reasonable surgical plan [19].

Infection stones, which are composed of magnesium ammonium phosphate, carbonate apatite or ammonium urate, are easily broken by SWL but can also cause systemic bacterial infection after lithotripsy. As many infection stones as possible should be removed during surgery to avoid residual stones. However, during the process of lithotripsy, various pathogenic bacteria are released, leading to the occurrence of infection. Effective antimicrobial therapy is an appropriate intervention for urinary tract infections and stone recurrence [32], [33]. This treatment not only prevents postoperative infections but also promotes the repair of renal tubular epithelial cells and reduces cellular debris and bacteria that form crystalline cores. Furthermore, the recurrence risk is higher in patients with residual fragments after treatment of infection stones than in those with other stones.

Non-infection stones, which are composed of calcium oxalate, calcium phosphate or uric acid, can be treated by conservative observational management if the stones are smaller than 6 mm and asymptomatic. Oral chemolysis is a treatment option for uric acid stones [17]. For acute disease, PNL and URS are more effective surgery options because non-infection stones are particularly hard.

In the present study, we employed a quantitative radiomics approach to preoperatively predict infection and non-infection stones. Our cohort included more infection stone patients (n = 98, 62.42%) than non-infection stone patients (n = 59, 37.58%), which supports the significance of this research. Fifty-four radiomics features (16 morphological features and 38 textural features) extracted from CT images were reduced to 27 key features (16 morphological features and 11 textural features) by the LASSO algorithm. Similar to the previous report [28], it was shown that the textural features were associated with stone compositions. In addition, compared with other methods of feature dimensionality reduction (such as PCA), LASSO regression can screen out the original features that have the most distinguishing value after feature dimensionality reduction – in other words, the features that still have physical significance. We also found that after LASSO regression, all of the morphological features were reserved, which indicated that the physical appearance of the stones can also be used to distinguish the infection stones from non-infection stones. One possible reason was that the lithogenesis of infection stones was heavily dependent on the interactions of bacteria with the various urinary components. Thus, the formation and physical characteristics of infection stones

differ substantially from those formed in the absence of bacteria [17].

Moreover, unlike previous studies [27], we used two ensemble learning methods to distinguish the stone types. This approach may improve the robustness of classification results. Our study showed that ensemble learning based on bagged trees can differentiate infection stones and non-infection stones with 90.7% accuracy, 85.81% sensitivity, 93.96% specificity, a 91% PPV and a 91% NPV.

Additionally, in an infected state, some pathogenic microorganisms can decompose urea in urine to form ammonia, which increases the pH of the urine [5]–[7]. Thus, the WBC count and UC, which were significantly associated with infection kidney stones, were used together to develop a radiomics signature based on a nomogram for individualized preoperative prediction of infection stones. The radiomics signature successfully stratified patients according to their risk of infection stones. Incorporating the radiomics signature and clinical risk factors into an easy-to-use nomogram facilitates individualized preoperative prediction of infection stones [31].

This study has certain limitations. First, only infection and non-infection stone patients were included in the analysis; stones due to genetic causes and drug use were excluded from analysis because of the small number of patients. Second, all subjects were patients from the First Hospital of China Medical University. The use of a multicentre dataset with different parameters may cause the model to behave differently. Large datasets from multiple centres should be studied to verify the robustness of our proposed radiomics model. Prediction of infection stones based on radiomics features requires further study.

In conclusion, we built a quantitative nomogram for preoperative prediction of infection stones. The model was easy to use for both clinicians and patients and may allow clinicians to preoperatively predict stone types more precisely, indicating that analysis of medical data using a radiomics method could be beneficial for clinicians.

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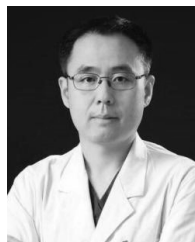
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