Université de Poitiers
Faculté de Médecine et Pharmacie

ANNÉE 2018

THÈSE
POUR LE DIPLÔME D'ÉTAT
DE DOCTEUR EN MÉDECINE
(décret du 16 janvier 2004)

Présentée et soutenue publiquement
Le jeudi 6 septembre 2018 à Poitiers
Par Monsieur Pierre-Henri BERNARD

Performance of pre-contrast CT-derived radiomics for non-invasive cholegallstone depiction

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Madame le Professeur Catherine CHEZE-LE REST

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UNIVERSITE DE POITIERS

Faculté de Médecine et de Pharmacie

Le Doyen,

Année universitaire 2018 - 2019

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REMERCIEMENTS

A Madame le Professeur Catherine CHEZE-LE REST, Présidente du jury,

Vous me faites l'honneur de présider le jury de cette thèse. Mes plus sincères remerciements pour votre aide, votre encadrement, votre disponibilité et votre expertise sur ce travail.

A Monsieur le Professeur Jean-Pierre TASU,

Je vous remercie de l'intérêt que vous portez à ce travail. Merci pour votre soutien et votre enseignement durant toute ma formation.

A Madame le Professeur Christine SILVAIN,

Je souhaite vous exprimer ma gratitude pour avoir accepté de participer à ce jury de thèse et de vous être rendue disponible. Veuillez trouver dans ce travail l'expression de ma reconnaissance et de mon profond respect.

A Monsieur le Docteur Guillaume HERPE, Directeur de thèse,

Un grand merci Guillaume pour m'avoir proposé ce sujet, et m'avoir encadré du début à la fin. Merci pour ta disponibilité durant tous ces mois et pour tes qualités humaines. Tes connaissances, idées et conseils, forcent le respect. Ce fut un réel plaisir de travailler avec toi.

A Monsieur le Docteur Taman UPADHAYA,

Thank you for your help on the statistical analysis and the writing of the article.

A Monsieur Moustapha NDIAYE,

Merci pour votre aide sur l'analyse statistiques des résultats de notre étude.

A Madame Anaïs CHALANT,

Merci pour votre aide sur notre étude.

REMERCIEMENTS

A mes parents,

Tout d'abord, je souhaite vous remercier, maman et papa, pour votre éducation, votre amour et votre soutien indéfectible qui m'ont permis d'arriver jusqu'à ce jour.
Je vous suis extrêmement reconnaissant d'avoir cru en moi et de m'avoir encouragé à chaque étape de ma vie pour devenir l'homme que je suis aujourd'hui.

Maman, merci pour tes encouragements quotidiens et pour m'avoir transmis ta pugnacité et ton envie de se dépasser pour réussir.

Papa, merci pour tous tes conseils avisés, ta force tranquille et ta passion de la musique que tu m'as transmise.

Je vous aime énormément.

A mon frère Jean-Philippe,

Merci d'être le meilleur frère que l'on puisse avoir. Tous ces moments partagés ensemble dans notre maison à Bordeaux et au cours des nombreux voyages avec les parents ont grandement contribué à ma réussite. Tu as su toi aussi faire les efforts et les sacrifices pour devenir très bientôt chirurgien orthopédiste.
Nous sommes tous très fier de toi, je t'aime.

A mes grands-parents maternels,

Merci papi et mamie pour votre éducation et tous ces moments partagés lors de mon enfance à Carreire. Que de bons et chaleureux souvenirs ! J'aurais souhaité que vous soyez présents aujourd'hui, vous me manquez, je pense à vous.

A mes grands-parents paternels,

Merci papi Lucien et mamie Anne-Marie pour votre éducation et votre gentillesse. Je vous suis très reconnaissant, je pense à vous.

A Dominique et tata Marie-Louise,

Vous êtes malheureusement parties trop tôt. Je vous remercie toutes les deux pour ce que vous m'avez apporté durant mon enfance et mon adolescence. Aujourd'hui je pense beaucoup à vous deux.

A Clarisse,

La plus belle rencontre de ma vie et le tournant de mon internat à Poitiers.
Que j'ai été chanceux ce jour-là ! Chaque jour ton amour, ton soutien et ta bienveillance m'accompagnent et me rendent heureux. Grâce à toi, j'ai réussi à surmonter mes craintes, gagner en confiance et être un homme comblé.
Je te remercie pour tous ces fous rires partagés ensemble, l'apprentissage de la chorégraphie de SL, les séances de karaoké véhiculés, et les dimanches Netflix and chill si agréables.
Je suis convaincu qu'aujourd'hui, avec le petit gris, tu es mon exceptionnel quotidien, je t'aime.

A mes amis,

A Alexis,

Difficile ici de résumer toute la reconnaissance et l'amitié que j'ai pour toi. Que de bons et chers moments passés au cours de nos nombreuses escapades à Bordeaux, Paris, New York, Londres, Cuba, La Réunion… Le Pete's Tavern, le Zoo bar et le Titi Twister en sont témoins ! Je te remercie également pour ton soutien inébranlable notamment avant l'ECN qui m'a permis de choisir cette belle spécialité qu'est la radiologie.
D'autres aventures nous attendent, au cours desquelles nous leur laisserons, on demandera des 12 aux chauffeurs de taxi, on salura Lamar, on fera du ski de fond urbain, on refera le carrelage et on s'appellera Maurice.
Je te suis très reconnaissant d'avoir fait tant de chemin pour venir à ma thèse, et je sais qu'on pourra toujours compter l'un sur l'autre jusqu'au bout de l'histoire !

A Guillaume,

Mon ami d'enfance. Depuis les bancs du collège Alain Fournier et du lycée François Magendie, tu m'accompagnes depuis tout ce temps ! Tous ces souvenirs de guitares, de concerts, de voyages et de soirées me permettent d'avancer chaque jour.
Malgré les difficultés, tu as su les affronter et arriver à ton objectif. Je suis fier de toi Guillaume.
Je te remercie de ton soutien dans chaque étape importante de ma vie et je sais que tu resteras là quoi qu'il advienne.

Rock and Fn'Roll !

Aux chefs et internes du service,

Je remercie l'ensemble des chefs, manipulateurs et secrétaires que j'ai pu rencontrer au cours de mon internat avec mention spéciale à Yannick, Claire, Anne-Charlotte, Nadeem, Cédric, Nicolas, Remy, Cassandre, Pierre-Victor, Benoît, Sami, Pierre, Victor, Philippe, Ines, Simon, François, Ronan, Margaux, Raphaël, Karim.

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LIST OF ABBREVIATIONS

AUC : Area under the curve

BMI : Body Mass Index

CI : Confidential Interval

CT : Computed Tomography

FOV : Field Of View

MRI : Magnetic Resonance Imaging

ROC : Receiver Operating Characteristic

ROI : Region Of Interest

ABSTRACT

Objectives

To investigative the accuracy of radiomics features to cholegallstone depiction from pre-contrast computed tomography (CT).

Background and objectives

Standard abdominal CT is the first step imaging modality for acute abdominal pain. It is not sensitive for cholegallstones depiction. From the seventies, texture analysis has tried to provide a quantitative assessment of density heterogeneity by analyzing the distribution and relationship of pixel or voxel gray levels in the image. In liver imaging, there are numerous potential applications of this technique, often called “radiomics”, such as tumor grading, fibrosis assessment or evaluation of tumor response. However, to date, there is no available data on the potential interest of pre-contrast CT radiomics analysis in biliary gallstones depiction. Our hypothesis is that non radio-opaque lithiasis might provide density changes only depicted with radiomics analysis.

We would like to evaluated the accuracy of radiomics features in cholegallstone depiction from pre-contrast computed tomography. MRI was used as gold standard method.

Methods

We included patients admitted to our University Medical Center between March 2014 and March 2017 who had abdominal CT and MRI within 45 days. Twenty-two patients were excluded due to a small gallbladder (less than 1cm in axial diameter - threshold for our in house software).

A senior radiologist with 10 years experiment reviewed T2W sequences of abdominal MRIs.

Pre-contrast CT images were blindly and independently reviewed by a 7 years experiment radiologist and a junior fellow. For the discordants cases, a third review was realised by an independent radiologist.

Furthermore, an inter observer agreement of pre-contrast CT reports was assessed using a kappa test.

Blindly to MRI, the gallbladders contents were segmented with the software 3DSlicer® for each patient and a radiomics analysis was performed on the volume of interest by an in-house software.

810 radiomics features were generated for each patient.

The ability of the radiomics features to differentiate patients with or without gallstone were established using receiver-operating characteristics (ROC) curve. Area under curve (AUC) has been calculated. A univariate and a multivariate analyses were performed.

Association between radiomics features and gallstone were explored using all cohort as well as separating cohort into training (60%) and testing (40%). Receiver operating characteristics (ROC) curve was used to evaluated accuracy to the radiomics features.

Results

Using MRI analysis, 39 patients had cholelithiasis and 61 not.

Using visual CT analysis, 24 patients had cholelithiasis and 76 not. The sensitivity, specificity and AUC were respectively 56.4% [39.6 – 72.2; CI 95%], 96.7% [88.6 – 99.6; CI 95%] and 0.77 [0.67 – 0.84; CI 95%].

Using pre-contrast CT-derived radiomics features, in univariate analysis, the highest AUC of 0.8 were obtained. In multivariate analysis, AUC of 0.87 were obtained using all dataset. Whereas, in multivariate analysis, in training AUC of 0.87, sensitivity 93% and specificity 80% were obtained and AUC of 0.76 in validation.

Radiomics features were independent predictor for cholegallstone depiction, which could successfully categorize patients with or without gallstone. They improved the performance compared to classical visual assessment of pre-contrast CT.

Conclusion

Radiomics features seems to help the detection of gallbladder gallstone using pre-contrast CT compared to classical visual assessment of CT.

INTRODUCTION

Biliary gallstones are a very common diseases associated in USA with more than one million hospitalizations, 750,000 cholecystectomies and a global cost estimed over $6 billion per year (1). To diagnose biliary gallstones, transabdominal ultrasound examination (US) should be the imaging modality of choice because of its high sensitivity (95%) and specificity (95%) (2). However, in clinical routine, computed tomography (CT) is commonly performed in cases of acute abdominal pains. However, although CT can easily detect calcified or gas content gallstones, cholesterol gallstone, the most frequent form in western countries, are commonly missed (3); for all types of biliary gallstones, CT sensitivity varies between 39% and 75% (2).

From the seventies, texture analysis has tried to provide an objective, quantitative assessment of density heterogeneity by analyzing the distribution and relationship of pixel or voxel gray levels in the image (4). In liver imaging, there are numerous potential applications of this technique, often called radiomics, such as tumor grading, fibrosis assessment or evaluation of tumor response (5). However, to date, there is no available data on the potential interest of pre-contrast CT radiomics analysis in biliary gallstones depiction.

For this study, we made the hypothesis that radiomics features extracted from pre-contrast CT could detect density heterogeneities due to biliary gallstones whatever their content. Therefore, the aim of this study was to evaluated the accuracy of radiomedics features to detect gallbladder gallstone. MRI was used as gold standard method.

MATERIAL AND METHODS

Patients

This study was performed in a single academic medical institution and was approved by the Local Committee for Medical Ethics.

From the local Picture Archiving and Communication System (Mc Kesson, Vancouver, Canada), all patients who underwent an upper abdominal CT and a biliary MRI examination within 45 days between March 2014 and March 2017 were potentially includable. Clinical exclusion criteria were; patients aged less than 18 years or more than 90, any history of gallbladder and/or biliary surgery, any history of biliary disease and/or main biliary duct gallstone and pregnancy. In case of gallbladder less than 1 cm in axial diameter and or in case of cholegallstone, patients were also excluded because radiomics analysis cannot be reliably performed on small structure due to the small number of voxel involved. For the same reason, patients with gallstone under 1cm in diameter were also excluded.

The following risk factors of gallbladder gallstone were collected: age, gender and body mass index (BMI).

A follow-up of the potential complications of gallbladder gallstone (acute cholecystitis, angiocholitis) has been done over one year after CT and MRI was performed.

CT protocols

CT examinations were performed on one of the following devices: three MDCT (64-slice Toshiba Aquilion One® Tokyo Japan; 64-slice Siemens Somatom®, Erlangen, Germany and 40-slice Philips B40®, Amsterdam, Netherlands) and one 320-slice MDCT (Toshiba Aquilion One Genesis® Tokyo, Japan). For each system, acquisitions were performed using the following parameters; a submillimeter slice, a pitch of 0.65 to 1.406, a 300 mm field of view (FOV), a 512^2 matrix and a 1 mm reconstruction slice

thickness with standard abdominal filtering. Voltage ranged between 110 and 120 kV. An automatic exposure control, which takes the body mass index into consideration, was applied to optimize the current (mA) relative to body attenuation; accordingly, tube current was between 90 and 370mA. Only abdominal pre-contrast CT phase was considered for this study.

MRI protocols

MRI examinations were performed on one of the 3 following devices; two 3T magnets (Siemens Verio®, and Siemens Skyra®, Siemens Healthcare, Erlangen Germany), and two 1.5 T (Siemens Area®, Siemens healthcare, Erlangen Germany and General Electric MR450®, General Electric medical, Milwaukee, USA). A liver dedicated phase array torso coil was used;16x2 on Siemens Verio, 18 on Siemens Skyra and Area, 48 on General Electric MR450. Axial T2-weighted images were obtained using the following parameters: TR and TE ranges respectively, 1500ms–1700ms and 95–111ms; 5 mm slice thickness and 2 mm gap, a 210×384 or 168x320 matrix and a field of view adapted to the patient. The following parameters were used to obtain MR cholangiogram respectively for 2 dimensional (2D) and 3D images;

Image analysis

MRI

MRI, associated T2 weighted imaging and MR cholangiogram was used in this study as the gold standard to diagnose biliary gallstone (6). A 10-year experienced senior involved in abdominal imaging reviewed all MR examinations. Homogeneous hyper intense T2 gallbladder was considered without gallstone. Area of low signal on T2 and or on MR cholangiogram located in dependent position, outlined by markedly hyper intense bile within gallbladder was considered as biliary gallstone. In doubtful abnormality, pre and post enhanced contrast phases were reviewed to withdraw a

polyp or a gallbladder mass. Gas in the gallbladder was identified as an T2 hypo intense area, round or linear, floating over the biliary liquid sometime associated with a gas-liquid level.

According to MRI report, patients were classified in 2 subgroups, with or without gallstone.

In case of gallstone, 3D fast spoiled gradient-echo T1-weighted sequences was used to characterize the gallstone content according to a previous published study (7); compared with the signal intensity of the gallbladder bile, an hyperintense gallstone was defined as pigmentary, an hypointense as cholesterol and sludge was identified as hypointense liquid-liquid level in the gallbladder.

CT

Pre-contrast CT images were blindly and independently reviewed by a 7 years experiment radiologist and a junior fellow using the following criteria;

- A biliary gallstone was defined as a mass of increased density into the gallbladder, compared to the surrounding liquid content. Presence of gas in gallstone was recorded.
- An empty gallbladder was defined as a homogenous liquid content.

For the discordants cases, a third review was realised by an independent radiologist.

Furthermore, an inter observer agreement of pre-contrast CT reports was assessed using a kappa test.

Radiomics analysis

For the texture analysis, all gallbladders measuring more than 1cm in axial diameter were segmented on pre-contrast CT images (*Fig 1-2)* using an automatic method (3D slicer(8)).

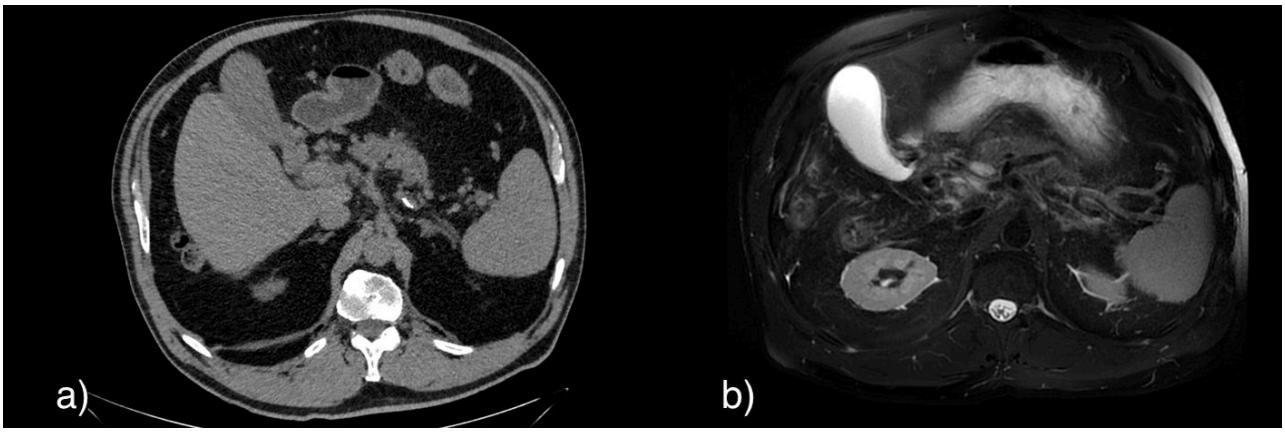

Fig 1. ***Pre-contrast CT, MRI and segmented cholegallstone gallbladder***

a) Empty gallbladder with the pre-contrast CT visual analysis
b) Sludge with the MRI analysis

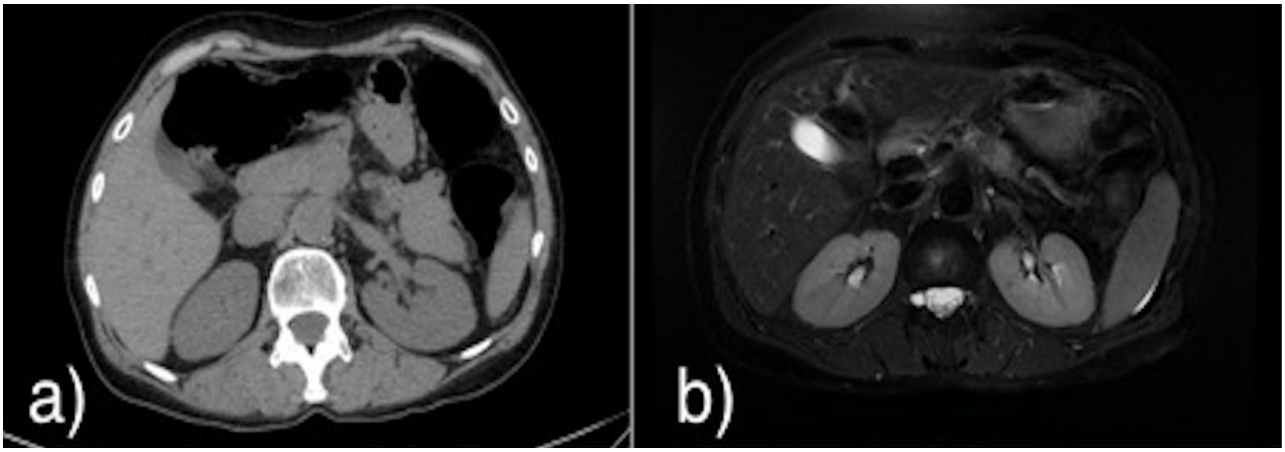

Fig 2. **Pre-contrast *CT, MRI and segmented empty gallbladder***

a) Empty gallbladder with the pre-contrast CT visual analysis
b) Empty with the MRI analysis

From this region of interest, a total of 90 radiomics features *(Annexe 1)* were extracted by using an in-house implemented software following the guidelines defined by the Image Biomarker Standardization Initiative (IBSI) (9,10) (see within for feature calculation formula). Each of the 90 textural features were calculated using 3 different methods: linear, fix-bin and histogram equalization and 8 different grey levels, a

process defined as “texture optimization” there by creating different “variants” for each textural feature. As results, 810 radiomics features per CT examination were obtained. The annexe 1 gives the radiomics features studied.

Statistical analysis

Patient characteristics were expressed as mean ± SD as they were normally distributed. They were described as number (percentage). Inter observer agreement of pre-contrast CT reports was assessed using a kappa test.

Clinical data and radiomics features were compared in subgroups of patients with or without gallstone using the independent-samples Student’s *t* test, and χ^2 as appropriate. A p value less than 0.05 was considered as statistically significant.

Following statistical analyses were performed using R (version 2.3.1). In univariate analysis the ability of the radiomics features to differentiate patients with or without gallstone were established using receiver-operating characteristics (ROC) analysis. The optimal cutoff threshold values were graphically determined as corresponding to the maximal vertical distance between the ROC curves and the diagonal lines (11). In multivariate analysis, first, only those radiomics features with area under curve (AUC) above 0.58 were considered as predictive and subjected to further analysis. Then correlation coefficient between each pair of features was calculated. Among feature pairs with correlated coefficient ≥ 0.90 the more prognostic features were retained and the others removed. Finally, the remaining features were selected and ranked based on binomial logistic regression with forward feature selection (FFS) and backward feature elimination (BFE) technique to build the final predictive model with optimal radiomics features. This procedure was applied on the whole initial cohort as well after dividing the cohort into a training (60%) and a validation (40%) dataset using random stratified sampling. Training and validation dataset are commonly used in radiomics

analysis in order to create algorithms that can learn from and make prediction on data (12–14).

RESULTS

Clinicopathologic characteristics of patients

One hundred and twenty-two patients were eligible *(Fig 3).* Twenty-two patients were excluded due to a small gallbladder (less than 1cm in axial diameter). Remaining 100 patients (36 women and 64 men) were included in the analysis. The mean age was 61y± 11.2, and the mean BMI was 26.2 $kg.m^{-2}$± 5.2, respecting a normal distribution.

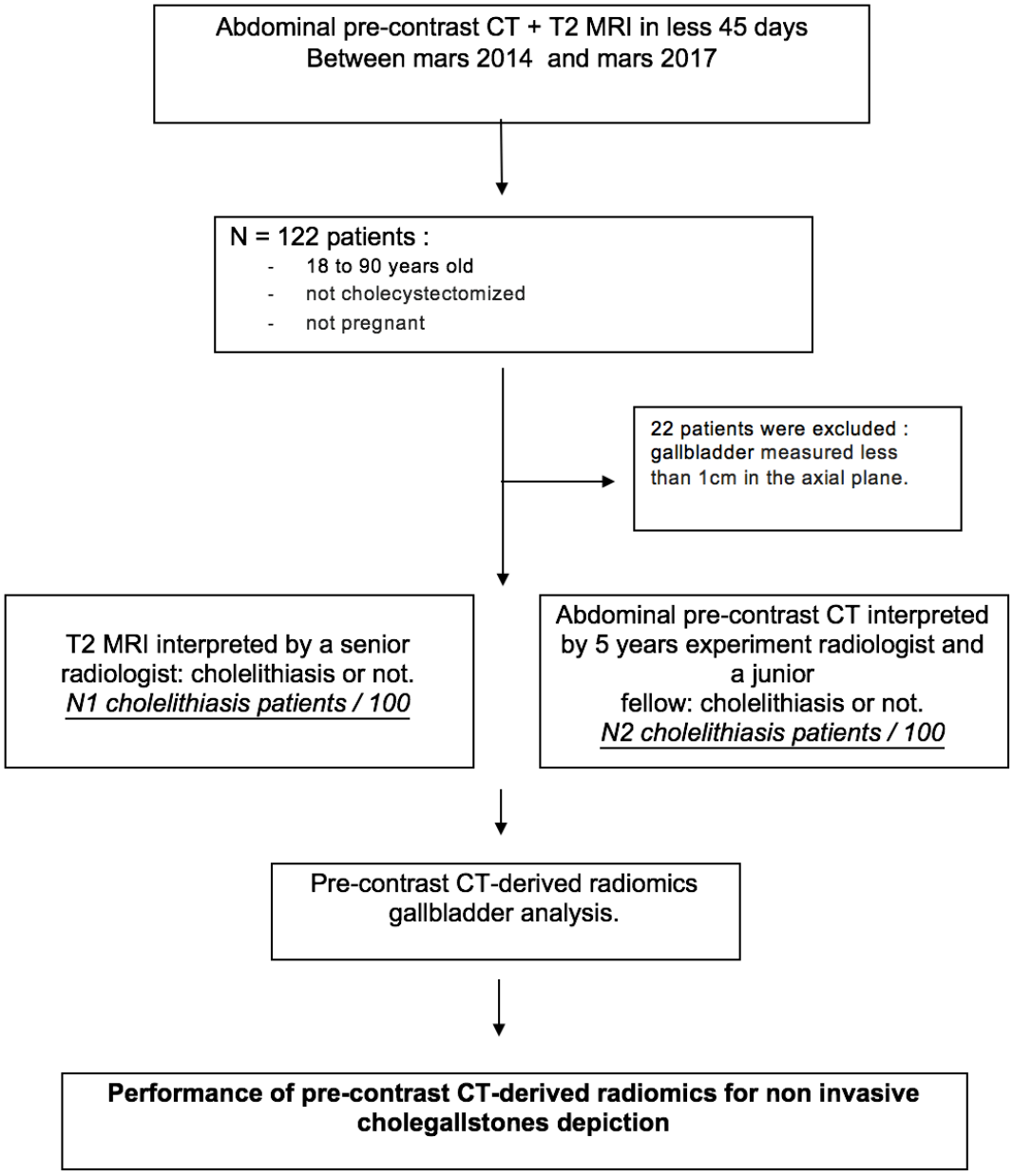

Fig 3. Flowchart

CT analysis

The CT and MRI examinations mean interval time was 13.4 days± 20 (range 0-45).

In this retrospective study, CT were initially performed for different indications: carcinoma staging (57%), acute abdominal symptoms (17%), intra-abdominal infection or bleeding (9%), cirrhosis follow-up (7%), characterization of liver/pancreatic masses (5%), intestinal obstruction (3%), post-abdominal surgery (2%).

Based on CT, gallstone was diagnosed in 24 patients. The inter-observer agreement was very good (k=0.81).

The sensitivity, specificity and AUC for the diagnosis of gallbladder gallstone were respectively 56.4% [39.6 – 72.2; CI 95%], 96.7% [88.6 – 99.6; CI 95%] and 0.77 [0.67 – 0.84; CI 95%].

Seventeen false negative were observed because of low density gallstone (5 patients) and sludge (12 patients) only visible on MRI. In the following, five of them had cholecystitis.

MRI analysis

Nearly all MRI examinations (95/100) were performed using a 1.5T magnet and only 5 with 3T. MRIs were performed for characterization of liver/pancreatic masses with/without cancer history (55%), carcinoma staging (18%) follow-up of cirrhosis (15%), investigation of bile duct (12%).

Based on MRI examinations, gallbladder gallstones were diagnosed in 39 patients and gallbladder was empty in the remaining 61 patients. The gallgallstones were predominantly classified as pigment gallstone (24, 62%), 6 as cholesterol gallstone (15%), while 9 patients had sludge (23%).

There was no significant difference between subgroups of patients with or without

lithiasis with respect to age, sex ratio or BMI *(Table 1).*

Predictive performance of the radiomics signature

The radiomics signature presented good performance for the discrimination of patients with or without lithiasis compared to visual report of CT. Univariate analysis yielded an AUC between (0.77 to 0.8), sensitivity 77% and specificity 74% (p<0,0001). Multivariate analysis yielded an AUC between (0.78 to 0.87), sensitivity 82% and specificity 83% (p<0,0001) when using all the 100 *(Table 2).* These predictive radiomics features were from second and high order statistic employing regional and local scale heterogeneity in images were predictive of patients with or without gallstone. In second set of experiment, the radiomics signature again presented good performance for the discrimination, which yielded an AUC of (0.81 to 0.87), sensitivity 93% and specificity 80% in the training dataset and in validation dataset yielded an AUC of (0.73 to 0.76) in multivariate analysis *(Table 3).*

The mean time required to obtain all quantitative CT parameters (including segmentation, preprocessing and radiomics analysis) for each patient was 5 min, (range 4,5-7).

DISCUSSION

Radiomics features seems to help the detection of gallbladder gallstone in pre-contrast CT examination by increasing the sensitivity from 56.4%, by a visual analysis, to 93%. To our knowledge, this has been never published before.

The limited sensitivity of 56.4% of visual analysis is also in accord with the literature (1,2,15). The same results were obtained with an experienced and a junior radiologist, as demonstrated with a very good inter-rater agreement (k= 0.81), pointing an intrinsic limitation of the CT approach in this indication.

In addition, those performances were not related to confounding biliary disease, since we didn't register any polyps or endoluminal masses in our population.

Radiomics analysis has already proven its interest in clinical applications such as renal masse characterization (16), pulmonary nodules risk stratification (17), pyelonephritis (18). Radiomics features CT image analysis may also improve detection performances as we have demonstrated in the current study. Pre-contrast CT-derived radiomics (Mean_hist, Skewness_hist, Kurtosis_hist, Variance_cooc_d1_r64 .000000_v1, Major_axis_length, Minor_axis_length …) provided a selection of new parameters which could help with the detection of biliary gallstone. However, in this study, 810 parameters were evaluated. The number of radiomics features could be expanded according to different filtrations or mathematics transformations (wavelet or Laplacian of Gaussian) (19); this leads to a various number of parameters, from (20) to more than 1000 (21). Actually, the majority of the studies describes between 100 and 200 radiomics features. A recent study from Berenguer et al (19) demonstrated that many parameters were redundant and non reproducible. According to this study, if all CT parameters are fixed except tube voltage, milliamperage and FOV, only 10 radiomics are enough because of redundancy. A further study is therefore required to determine which radiomics features are really significative.

The dual-energy spectral CT imaging is the other potential technique to detect cholesterol gallstones (22); virtual monochromatic imaging increased detectability of cholesterol gallstones as CT number of cholesterol was mostly negative at low photon energy and increased as the photon energy increased. In another hand, CT number of bile was mostly positive at low photon energy and decreased as energy increased. However, dual energy spectral CT is not available everywhere and most technologies require specific acquisition, associated with an increase of the patient dose.

Improvement of cholelithiasis detection is of great interest in different medical conditions. Acute abdominal pain is a common presenting symptom in emergency departments and outpatient medical pratices. It can reveal hepatic colic, cholecystitis, acute pancreatitis or cholangitis, all potentially related to gallstone presence.

Improvement of asymptomatic cholelithiasis detection is also of great interest since as many as 35% of patients with gallstones will ultimately become symptomatic and require cholecystectomy (23). In our study, five patients out of seventeen false negative visual CT reports presented effectively with a delayed acute cholecystitis. Moreover, cholelithiasis assessment can also be usefull in non urgent conditions, such as pre operative cholelithiasis assessment, chronic abdominal pain, pancreatitis aetiology.

In this study, we focused on individual radiomics feature as well as a panel of radiomics features as a signature. In univariate analysis, when considering only individual radiomics feature many radiomics feature were found to be predictive *(Table 4 and 5)* however, only few radiomics feature were superior to that of visual assessment of CT. In multivariate analysis, panel of radiomics features as a signature were able to achieve superior performance than visual assessment of CT. However, these results may be further improved using advance machine learning technique although large cohort is needed for these kinds of approach. Moreover, this study did not take into account reproducibility and robustness of the radiomics features as no multiple baseline scans and no multiple VOI which are necessary for this kind of study. Furthermore, radiomics feature from various quantization method were analyzed separately in multivariate analysis to make the analysis simple and due to less number of patients available for the study. Future work will be focused on adding larger cohort, mixing radiomics features from various quantization method, conducting robustness and reproducibility

study to further improve the predictive model. However, to date our study is the first one and the bigger ever published on this topic which shows a potential application not yet suggested.

There are some limitations of this study.

First, the retrospective design of the study may have an impact on patient selection. Indeed, included patients underwent radiological examinations for different medical indications. In addition, MRI referral were based on initial CT results. It will be interesting to confirm our results in a prospective study focusing on abdominal pain, which will make it possible to measure the therapeutic impact of improved detection. Future work will be focused on mixing radiomics features from various quantization method, conducting robustness and reproducibility study to further improve the predictive model. However, to date our study is the first one and the biggest ever published on this topic.

Second, diffferents MR magnets were used to perform biliary exploration used to establish the gold standard. However, it was shown that performances of biliary gallstone diagnosis from MRI are not modified with the field strength (24) .

Third, the use of different CT devices is likely to affect pixel values (signal and noise) and thus CT-derived radiomics. According to the literature (25), the most affected parameters are those of first order. In addition, recent quantitative analysis studies showed good reproducibility between different CT devices, suggesting that using different CT devices should not alter results (25–27). For gallstone smaller than 1cm in diameter were excluded in order to allow accurate quantification by radiomics. However, smaller gallstones are more likely to cause obstruction due to migration into the cystic and common bile ducts. Similarly, non-calcified gallstone within contracted gallbladders should also be detected, although they were excluded from this study, Further investigations are therefore needed to assess the diagnostic

performance of radiomics features in clinical practice, including clinically relevant gallbladder gallstone of all sizes. Lastly, chemical analysis of gallstone content was not performed, as this was not the primary focus of our study.

Fourth, the technique described increased the sensibility of CT but is time consuming. The time required for the post-processing of images is at least 5 minutes including the manual segmentation of the gallbladder and the radiomics analysis. Even if it compatible with routine practice, a semi-automatic version of the segmentation process will be suitable and appreciated for a clinical routine practice.

Our study provides the basis for a larger prospective evaluation, as previously discussed, which may help for the implementation of such approach in commercial devices providing an innovative and useful help to clinicians. Furthermore, widespread clinical implementation, standardization of gallbladder segmentation, image filtration and post-processing techniques are required in addition to identification of key radiomics features among hundreds of potential candidates given by different softwares.

CONCLUSION

In conclusion, in our study, a radiomics signature was developed and validated to be a significant predictor for the discrimination of patients with and without gallstone. This newly developped radiomic's approach increased the accuracy of biliary gallstone depiction in the gallbladder using pre-contrast CT compared to classical visual assessment of CT. As a non invasive examination method and a potential imaging biomarker, radiomics signature provides a clinically valuable approach to identify individual characteristics to discriminate the patients with or without gallstone, which may serve as a complementary tool for the cholegallstone diagnosis.

ANNEX

List of the radiomics features studied

FIRST ORDER	
Min_hist	Minimum
Max_hist	Maximum
Mean_hist	Mean
Variance_hist	Variance
Standard_Deviation_hist	Standard deviation
Skewness_hist	Skewness
Kurtosis_hist	Kurtosis
Energy_hist	Energy
Entropy_hist	Entropy
AUC_hist	Area Under the curve
SECOND ORDER	
Max_cooc_d1_r5.000000_v1	Maximum
Average_cooc_d1_r5.000000_v1	Average
Variance_cooc_d1_r5.000000_v1	Variance
Entropy_cooc_d1_r5.000000_v1	Entropy
DAVE_cooc_d1_r5.000000_v1	Difference average
DVAR_cooc_d1_r5.000000_v1	Difference variance
DENT_cooc_d1_r5.000000_v1	Difference entropy
SAVE_cooc_d1_r5.000000_v1	Sum Average
SVAR_cooc_d1_r5.000000_v1	Sum Variance
SENT_cooc_d1_r5.000000_v1	Sum entropy
ASM_cooc_d1_r5.000000_v1	Angular Second Moment.
Contrast_cooc_d1_r5.000000_v1	Contrast
Dissimilarity_cooc_d1_r5.000000_v1	Dissimilarity
Inv_diff_cooc_d1_r5.000000_v1	Inverse Difference
Inv_diff_norm_cooc_d1_r5.000000_v1	Inverse Difference norm
IDM_cooc_d1_r5.000000_v1	Inverse difference moment
IDM_norm_cooc_d1_r5.000000_v1	Inverse difference moment norm
Inv_var_cooc_d1_r5.000000_v1	Inverse Difference variance
Correlation_cooc_d1_r5.000000_v1	Correlation
Autocorrelation_d1_r5.000000_v1	AutoCorrelation
Tendency_cooc_d1_r5.000000_v1	Tendency
Shade_d1_r5.000000_v1	Cluster Shade
Prominence_cooc_d1_r5.000000_v1	Cluster Prominence
IC1_d1_r5.000000_v1	Information Correlation 1
IC2_d1_r5.000000_v1	Information Correlation 2
Coarseness_vdif_d1_r5.000000	Coarseness
Contrast_vdif_d1_r5.000000	Contrast
Busyness_vdif_d1_r5.000000	Busyness
Complexity_vdif_d1_r5.000000	Complexity
Strength_vdif_d1_r5.000000	Texture Strength
HIGHER ORDER	
SRE_align_r5.000000	Short Run Emphasis (SRE)
LRE_align_r5.000000	Long Run Emphasis (LRE)
GLNU_align_r5.000000	Gray-Level Non Uniformity (GLNU)
RLNU_align_r5.000000	Run Length Non-Uniformity (RLNU)
RP_align_r5.000000	Run Percentage (RP)
LGRE_align_r5.000000	Low Grey-level Run Emphasis (LGRE)

HGRE_align_r5.000000	High Grey-level Run Emphasis (HGRE)
LGSRE_align_r5.000000	Short Run Low Grey level emphasis
HGSRE_align_r5.000000	Short Run High Grey-level emphasis
LGHRE_align_r5.000000	Long Run Low Grey-level Emphasis
HGLRE_align_r5.000000	Long Run High Grey-level Emphasis
GLNU_norm_align_r5.000000	Grey-level non Uniformity
RLNU_norm_align_r5.000000	Run length Non-Uniformity
GLVAR_align_r5.000000	Grey-level non Uniformity variance
RLVAR_align_r5.000000	Run length Non-Uniformity variance
Entropy_align_r5.000000	Entropy
SZSE_r5.000000	Short Zone Size Emphasis.
LZSE_r5.000000	Long Zone Size Emphasis.
LGLZE_r5.000000	Low Grey-level Zone Size Emphasis.
HGLZE_r5.000000	High Grey-level Zone Size Emphasis.
SZLGE_r5.000000	Short Zone Size Low Grey-level Emphasis
SZHGE_r5.000000	Short Zone Size High Grey-level Emphasis.
LZLGE_r5.000000	Long Zone Size Low Grey-level Emphasis.
LZHGE_r5.000000	Long Zone Size High Grey-level Emphasis.
GLNU_area_r5.000000	Gray-Level Non Uniformity
ZSNU_r5.000000	Zone Size Non-Uniformity.
ZSP_r5.000000	ZSP Zone Size percentage.
GLNU_norm_r5.000000	Gray-Level Non Uniformity.
ZSNU_norm_r5.000000	Zone Size Non-Uniformity.
GLVAR_area_r5.000000	Gray-Level variance
ZSVAR_r5.000000	Zone Size variance
SHAPE COMPLEXITY	
Entropy_area_r5.000000	Entropy area
Volume	
3D surface	
ratio 3ds_vol	
ratio 3ds_vol_norm	
Irregularity	
Compactness_v1	
Compactness_v2	
Spherical_disproportion	
Sphericity	
Asphericity	
Center_of_mass	
Max_3D_diam	
Major_axis_length	
Minor_axis_length	
Least_axis_length	
Elongation	
Flatness	

Table 1: Patient data

	Sub-group with lithiasis	***Sub-group without lithiasis***	***T-Test***	***Comparison of proportions***
Age	Average: 68 y.o Range: 30-83 SD : 2,3	Average: 57 y.o Range: 27-80 SD : 23,5	p=0,16	X
BMI	Average: 27.1kg.m^2 Range: 22-48 SD : 5,6	Average: 26,4kg.m^2 Range: 17-30 SD : 6,7	p=0,8	X
Sex-ratio	2,5	1,3	X	Difference=15%, χ^2=2,75 p=0,09

Table 2 ; Univariate and multivariate analysis of radiomics signature performance for the discrimination of patients with or without lithiasis compared to visual report of non-contrast CT. **P value <0.0001.**

	Variables & model	AUC	Sensitivity	Specificity	AUC (95%CI)
Univariate Analysis	**RLVAR**	**0,78**	**74%**	**72%**	**0.68-0.85**
	Max_cooc_1	**0,8**	**77%**	**74%**	**0.70-0.87**
	HGLRE	**0,79**	**85%**	**62%**	**0.69-0.86**
	LZHGE	**0,77**	**64%**	**84%**	**0.67-0.85**
	LZSE	**0,77**	**79%**	**66%**	**0.67-0.85**
	Max_cooc	**0,8**	**69%**	**85%**	**0.71-0.88**
	LZHGE	**0,77**	**64%**	**85%**	**0.70-0.87**
Multivariate Analysis	***Backward selection***				
	Linear 32	**0,78**	**69%**	**85%**	**0,69-0,78**
	Min_hist				
	Variance_hist				
	Busyness_vdif_d1_r32 .000000				
	HGSRE_align_r32 .000000				
	SZHGE_r32.000000				
	LZLGE_r32 .000000				
	ZSNU_norm_r32.000000				
	Volume				
	Lineaire 64	**0,84**	**61%**	**95%**	**0,76-0,84**
	Linéaire 128	**0,78**	**76%**	**77%**	**0,67-0,78**
	Fix bin 5	**0,82**	**74%**	**88%**	**0,74-0,82**
	Fix bin 10	**0,79**	**66%**	**88%**	**0,71-0,79**
	Histogram equalization 32	**0,87**	**76%**	**93%**	**0,80-0,88**
	Histogram equalization 64	**0,82**	**82%**	**83%**	**0,74-0,83**
	Histogram equalization 128	**0,85**	**84%**	**86%**	**0,77-0,86**
	Forward selection				
	Linear 32	**0,86**	**56%**	**98%**	**0,80-0,87**
	LGHRE_align_r32 .000000				
	LZHGE_r32.000000				
	Skewness_h i s t				
	Max_hist				
	Min_hist				
	SENT_cooc_d1_r32 .000000_v1				
	Lineaire 64	**0,75**	**59%**	**86%**	**0,66-0,76**
	Linéaire 128	**0,82**	**56%**	**95%**	**0,74-0,83**
	Fix bin 5	**0,85**	**59%**	**96%**	**0,78-0,86**
	Fix bin 10	**0,83**	**64%**	**93%**	**0,75-0,84**
	histogram equalization 32	**0,80**	**69%**	**88%**	**0,72-0,81**
	histogram equalization 64	**0,79**	**72%**	**85%**	**0,70-0,79**
	histogram equalization 128	**0,84**	**77%**	**90%**	**0,70-0,85**

Table 3: Training and validation dataset of radiomics signature performance for the discrimination of patients with or without gallstone compared to visual report of pre-contrast CT in multivariate analysis.

Variables & model	Testing dataset (40)			
	AUC	AUC (95%CI)	AUC	AUC (95%CI)
Backward selection	**0,8667**	**0.7792−0.9542**	**0,7344**	**0.6042 −0.8645**
RLVAR_align_r64 .000000				
Mean_hist				
Skewness_h i s t				
Kurtosis_hist				
Variance_cooc_d1_r64 .000000_v1				
IC1_d1_r64 .000000_v1				
SRE_align_r64 .000000				
RLNU_align_r64 .000000				
LGSRE_align_r64 .000000				
HGLRE_align_r64 .000000				
HGLZE_r64.000000				
SZHGE_r64.000000				
LZLGE_r64 .000000				
LZHGE_r64.000000				
ratio 3ds_vol				
Major_axis_length				
Minor_axis_length				
Forward selection	**0,817**	**0.7462−0.9325**	**0,7639**	**0.6134 −0.9144**
Max_hist				
Max_cooc_d1_r64 .000000_v1				
Major_axis_length				
Mean_hist				
RLNU_align_r64 .000000				
Variance_cooc_d1_r64 .000000_v1				

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UNIVERSITE DE POITIERS

Faculté de Médecine et de Pharmacie

SERMENT

En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses !
Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque !