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KIDNEYS, URETERS, BLADDER, RETROPERITONEUM

Longitudinal follow-up of incidental renal calculi on computed tomography

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Abstract

Rationale and objectives Measuring small kidney stones on CT is a time-consuming task often neglected. Volumetric assessment provides a better measure of size than linear dimensions. Our objective is to analyze the growth rate and prognosis of incidental kidney stones in asymptomatic patients on CT.

Materials and methods This retrospective study included 4266 scans from 2030 asymptomatic patients who underwent two or more nonenhanced CT scans for colorectal screening between 2004 and 2016. The DL software identified and measured the volume, location, and attenuation of 883 stones. The corresponding scans were manually evaluated, and patients without follow-up were excluded. At each follow-up, the stones were categorized as new, growing, persistent, or resolved. Stone size (volume and diameter), attenuation, and location were correlated with the outcome and growth rates of the stones.

Results The stone cohort comprised 407 scans from 189 (M: 124, F: 65, median age: 55.4 years) patients. The median number of stones per scan was 1 (IQR: [1, 2]). The median stone volume was 17.1 mm^3 (IQR: [7.4, 43.6]) and the median peak attenuation was 308 HU (IQR: [204, 532]. The 189 initial scans contained 291stones; 91 (31.3%) resolved, 142 (48.8%) grew, and 58 (19.9) remained persistent at the first follow-up. At the second follow-up (for 27 patients with 2 follow-ups), 14/44 (31.8%) stones had resolved, 19/44 (43.2%) grew and 11/44 (25%) were persistent. The median growth rate of growing stones was 3.3 mm^3/year, IQR: [1.4,7.4]. Size and attenuation had a moderate correlation (Spearman rho 0.53, $P < .001$ for volume, and 0.50 $P < .001$ for peak attenuation) with the growth rate. Growing and persistent stones had significantly greater maximum axial diameter (2.7 vs 2.3 mm, $P = .047$) and peak attenuation (300 vs 258 HU, $P = .031$)

Conclusion We report a 12.7% prevalence of incidental kidney stones in asymptomatic adults, of which about half grew during follow-up with a median growth rate of about 3.3 mm^3/year.

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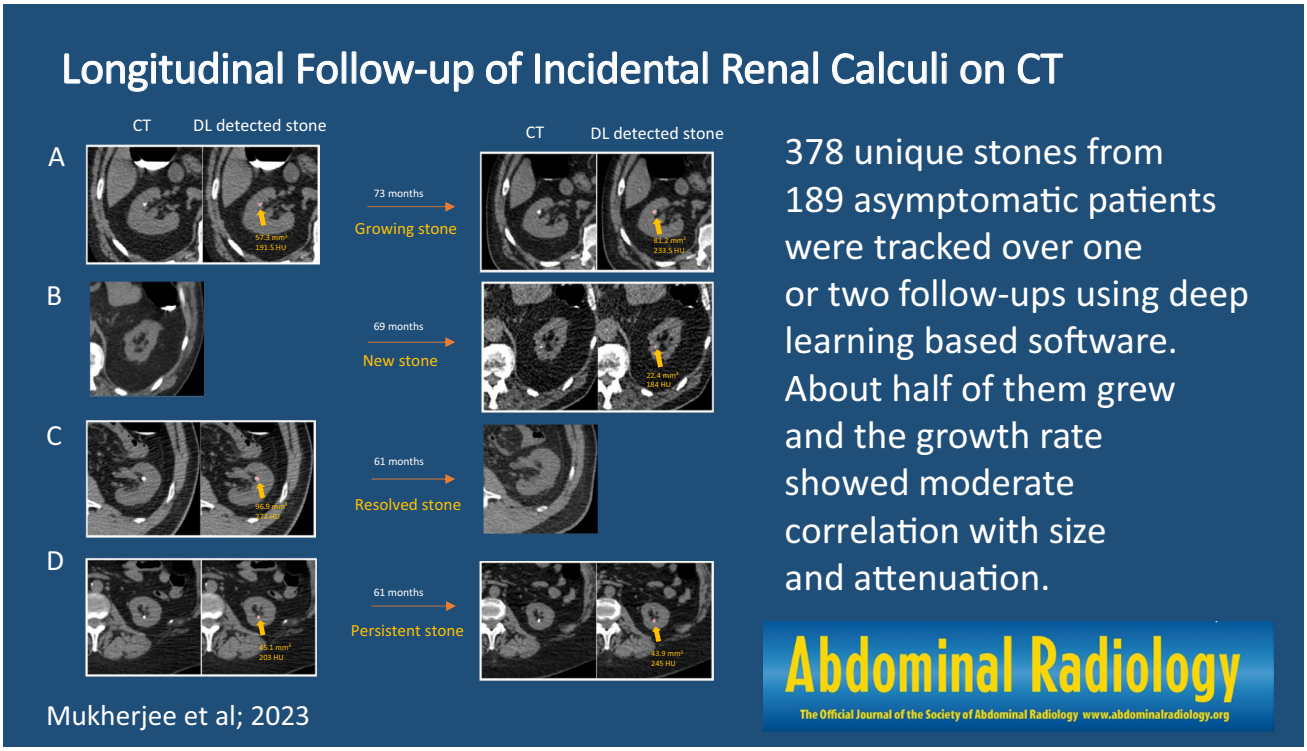
Graphical Abstract



Keywords Renal calculi · Outcomes · Longitudinal follow-up · Deep learning · Volumetric measurements

Abbreviations

CTC	Computed tomography colonography
DL	Deep learning
IQR	Interquartile range
NA	Not available

Introduction

The prevalence of kidney stones in the United States is increasing. An analysis of the National Health and Nutrition Examination Survey (NHANES) data from 2007-2010 put the prevalence of kidney stones at 8.8% [1]. A more recent study based on the NHANES data from 2015 to 2018 reported the prevalence to be 11.0% [2]. The same study reported 12-month incidence of kidney stones to be 2054 stones per 100,000 adults. The incidence of kidney stones has also risen over the past few decades: a Minnesota population-based study reported that between 1984 and 2012, the incidence of symptomatic kidney stone formers increased from 51 to 217 per 100,000 person-years in women and from 145 to 299 per 100,000 person-years in men [3]. This rise can be partially explained by the increased detection of asymptomatic incidental stones which, in part, may be attributed to higher utilization of computed tomography (CT) [3]. The cost of caring for patients with kidney stones in 2000 was estimated to be $2 billion in the United States and is expected to rise to $5 billion by 2030 [4, 5].

Nonenhanced CT is a widely used method to accurately diagnose and quantify kidney stones [6], is generally considered as the gold standard, and can now be performed with a very low radiation-dose technique [7]. Similarly, CT colonography (CTC) is a nonenhanced low-dose CT of the abdomen and pelvis for detecting colorectal polyps. A previous study on a large asymptomatic cohort undergoing CTC scans found the prevalence of kidney stones to be 8% [8]. Although these opportunistically-detected kidney stones are considered a less significant finding, patients with asymptomatic kidney stones are known to be at increased risk for future symptomatic stone events [9].

Kidney stones are often not reported [10], not measured [11], or measured differently depending on the reader or CT window level [12, 13]. Semi-automated or fully automated measurement of the stone volume would increase the detection rate and decrease the inter-reader size difference [14–17]. Prior work developed a fully automated deep learning (DL) based kidney stone detector that detects and measures the volume of kidney stones at unenhanced CT

(AUC of 0.95) [18]. The current work applies this software to asymptomatic adults undergoing serial CT scans to analyze the growth rate and prognosis of kidney stones found at CTC screening. Additionally, it also serves as additional validation of the results obtained in [18].

Materials and Methods

Patient population

This retrospective cohort study was HIPAA-compliant and was approved by the Institutional Review Board. The need for additional signed informed consent was waived.

A summary of the study plan is illustrated in Fig 1. The initial cohort included asymptomatic patients who came for initial CTC screening with follow-up CTC scans between 2004 and 2016 at one medical center. A detailed description of the indications for the initial CTC can be found in [19]. The inclusion criteria were (a) patients who had at least one follow-up CT scan and (b) nonenhanced scans with slice thickness less than 2 mm. The exclusion criteria were: patients that had stone intervention such as extracorporeal shock wave lithotripsy (ESWL) between the scans. We then ran an automated kidney stone detector on these scans. A radiologist with 13 years of experience (SL) manually reviewed the results of the kidney stone detector to exclude false-positive results, and to link the same stones in follow-up scans. For each patient with at least one true stone, the first scan containing a true stone was considered the "initial scan" and all subsequent scans were considered "follow-up" scans. Patients with the initial and at least one follow-up scan comprised the final cohort.

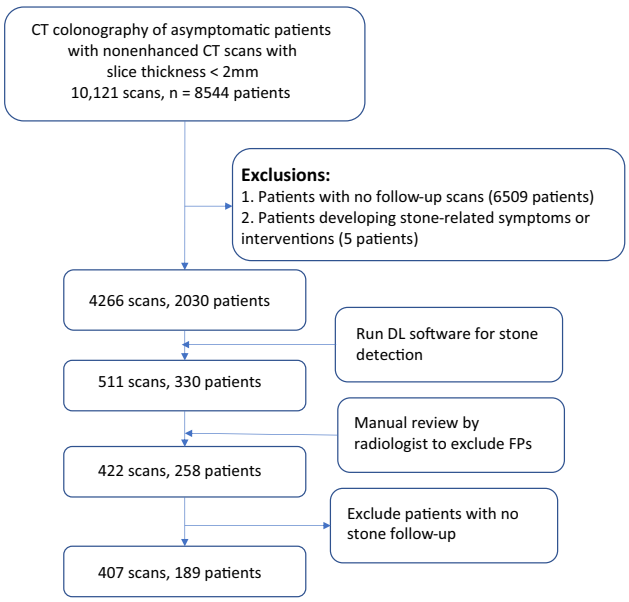


Fig. 1 Cohort selection

The patient cohort used in this study has been previously published to demonstrate automated measurements of the abdominal aorta, muscle, visceral and subcutaneous fat, liver, bone [20], and pancreas [21]. Unlike these other works, in this paper the dataset was used to show automated measurements of renal calculi. The cohort also overlaps, in part, with the cohort used in [8], which comprised patients undergoing CTC between 2004 and 2008, and did not require follow-up scans. Finally, this cohort overlaps with the one used to develop an automated method for tracking kidney stones over scans from multiple time points [22].

Scan protocol and preprocessing

CTC scanning was performed on multi-channel CT scanners (GE Healthcare) with 1.25 mm slice thickness, a reconstruction interval of 1 mm, and scanner settings of 120 kVp and modulated mA to achieve a low-dose scan noise index of 50. Axial nonenhanced supine series that included the entire kidney were selected from each study. The follow-up scans had varying slice spacings (median 1 mm, IQR: [0.75, 1]). All scans were resized to 1 mm slice spacing, if required, and reformatted into 3D NIfTI files before applying the kidney detector algorithm.

Kidney stone detector algorithm

The deep learning-based software (DL) trained on 91 manually-marked CTC scans with kidney stones and 89 CTC scans without stones was developed and validated in prior work [18]. The deep learning software segmented the kidneys using a 3D U-Net, and then performed gradient-based anisotropic denoising, thresholding (130 HU), connected components analysis, and region growing to detect and segment "candidate" stones (Supplementary Fig. 1). A CNN-based classifier then predicted if the "candidate" was a stone. The software outputs the volumetric size (mm^3), location (XYZ coordinates, upper/lower pole, left/right kidney), attenuation (mean, median, standard deviation, maximum Hounsfield unit, HU), and center coordinate of kidney stones. A segmentation of both kidneys was generated and stone detections outside the kidney segmentation were removed. A detailed description of the software is found in Ref. [18].

Manual screening and follow-up of the automatically detected stones

A board-certified radiologist (13 years of experience) manually reviewed the DL predictions to first confirm the automatically detected stones, exclude false-positives, and match

the same stones in follow-up scans. An in-house developed code to register and match stones between interval scans was used to increase the accuracy of this process [22], but the final determination of the match was made by the radiologist. Ureteral stones were not included. Stones that were recognized to have moved within the kidney were counted as persistent stones. The stone measurements of size, intensity and location were obtained from the segmentations provided by the DL software. To validate the quality of the automated stone segmentations, we randomly selected 30 stones and calculated the Dice Similarity Coefficient (DSC) between the automated and the radiologist's segmentations.

Stone growth class and location

For every patient, the first study that contained a true stone was considered the "initial" scan (for the purpose of stone follow-up); subsequent scans are considered "follow-up". At every follow-up, we consider the following four categories of stones: (1) "growing" stones, which have grown more than 10% in volume from the previous scan, (2) "persistent" stones, which were present in the previous scan, but are not growing stones, (3) "new" stones, which were not present in the previous scan, and (4) "resolved" stones which are stones that were present in the previous scan but are no longer present in the current scan. We allowed an error rate of 10% as partial volume averaging affects the volume measurement in small objects when using the thresholding method [23].

A relative location of each stone was calculated by:

(z coordinate of the stone centroid
−z coordinate of the lowermost point of the kidney segmentation)
/(z coordinate of the uppermost point of the kidney segmentation
−z coordinate of the lowermost point of the kidney segmentation)

All z coordinates (index of axial slices with the 3D image) were outputs of the software. The relative location ranged from 0 to 1. Numbers close to 1 represented a stone near the upper pole of the kidney, and numbers close to 0 represented a stone near the lower pole of the kidney.

Statistics

The maximum 3D and axial diameters (mm), volume (mm^3), peak_attenuation (maximum HU), median_attenuation (median HU), mean_attenuation (mean HU), std_attenuation (standard deviation of HU) and location (upper/lower pole, left/right kidney) of every stone were provided by the automated software along with the stone segmentation. If a stone was considered growing (or persistent or resolved) at a given follow-up scan, its measurements at the immediately preceding scan were considered to be the features of the stone. Wilcoxon *P* values, adjusted using Holm's method [24], were calculated to test for associations between the features and the stone group (growing or persistent or resolved). The following comparisons were made: resolved vs. persistent, resolved vs. growing, growing vs. persistent, resolved vs. not-resolved (comprising growing and persistent stones). Growth rate (mm^3/year) was calculated for the growing stones as (current volume − previous volume)/(follow-up interval in years). The volume (mm^3), median_attenuation, peak_attenuation, mean_attenuation, std_attenuation, and relative location were correlated to the growth rates using Spearman correlation. All statistics were done with Microsoft Excel (version 2112) and R (version 4.1.0).

Results

Cohort selection

Out of 4266 CTC scans in 2030 patients, DL found 883 stone candidates in 511 scans from 330 patients (Fig. 1). Manual review determined that there were 698 true kidney stones in 422 scans (9.9% of 4266) from 258 patients (12.7% of 2030). Of the 258 patients with true stones, 69 patients were excluded since all stones for these patients first appeared in their last available scan and no stone follow-up was available (Fig. 1). Ultimately, 189 patients with 407 scans (189 initial scans and 218 follow-ups) and 608 stones comprised our cohort—161 patients had a single follow-up scan, 27 patients had 2 follow-up scans and 1 patient had 3 follow-up scans. Patient characteristics are summarized in Table 1.

Performance of the DL software

Manual review determined that 5/698 stones from 5 scans and 4 patients were missed by DL (false negatives), yielding a per-stone sensitivity of 0.993 (95% CI [0.987, 0.999]). The positive predictive values on a per-stone and per-scan basis were 693/883 (0.785, 95% CI [0.758, 0.812]) and 422/511 (0.826, 95% CI [0.793, 0.859]), respectively. Of

Table 1 Patient characteristics

Patients (n=189)	Male (n=124)	Female (n=65)
Age at first scan (years)	56.1 (51.4, 61.7)	54.4 (50.5, 57.9)
Mean weight (lbs)	195 (179, 225)	155 (125, 185)
Mean height (in)	70 (69, 72)	64 (62, 66)
BMI	28.1 (25.7, 31.3)	26.6 (22.5, 31.9)

Data are median (IQR), where IQR represents the interquartile range.
BMI body mass index, *IQR* interquartile range

the 190 false positive stone detections among 4266 scans, 80 (42.1%) were artifacts (e.g., beam hardening from surrounding oral contrast media in the colon or coarse-looking kidney parenchyma from low-dose images), 52 (27.4%) were due to renal artery calcified atherosclerotic plaque, 48 (25.3%) were due to cyst-related calcification, 5 (2.6%) were due to bowel content, 2 (1.0%) were spleen calcifications, 2 (1.0%) were due to contrast in a calyx, and 1 (0.05%) was due to milk of calcium (Supplementary Fig. 2). In the random sample that was manually segmented, the median DSC was 1.0 (1.0 in 29 stones and 0.941 in 1 stone).

Stone characteristics

Out of the 407 scans in our cohort, 353 of them had a stone. The median number of stones per scan was 1 (IQR: [1, 2], max: 12). The median stone volume was 17.1 mm^3 (IQR: [7.4, 43.6], max: 492.9). The median stone sizes, measured by maximum diameter and maximum axial diameter, were 3.5 mm (IQR: [2.5, 5.3], max: 15.6) and 2.8 mm (IQR: [2.0, 4.4], max: 15.4). The median peak_attenuation and median_attenuation was 309 HU (IQR: 204, 532]), and 178 HU (IQR: [155, 220], respectively. A histogram of peak attenuation for all stones is shown in Supplementary Fig. 3).

Stone follow-up

The 353 stone positive scans contained the longitudinal follow-up of 378 unique stones from 189 patients (Fig. 2). The median follow-up interval (including the intervals between two follow-up scans, if applicable) was 1868 days (IQR: [1653, 2092]). 161/189 patients had a single follow-up and the remaining 28 patients had two follow-up scans. Out of the 291 initial stones, 142 (48.8%) initial stones grew, 58 (19.9%) were persistent and 91 (31.3%) resolved at the first follow-up. At the second follow-up, 19/44 (43.2%) of stones grew, 11/44 (25%) were persistent and 14/44 (31.8%) resolved. Example images of growing, new, resolved, and persistent stones can be found in Fig. 3.

Associations with features

The median size of non-resolved (growing and persistent) stones were higher than that of the resolved stones, (maximum 3D diameter: 3.5 vs 3.2 mm, P =.055, maximum axial diameter: 2.7 vs 2.3 mm, P = .047, volume: 15.5 vs 12.4, P = .065). The non-resolved stones also had a significantly higher median peak_attenuation: 300 vs 258 HU, P = .031). For all results on the associations between the stone features and the stone groups, please see Table 2.

The median absolute growth rate of growing stones was 3.3 mm^3/year, IQR: [1.4, 7.4]. Size and attenuation had a moderate correlation (Spearman rho 0.53, P < .001 for volume and maximum axial diameter, 0.55, P < .001 for maximum 3D diameter, and 0.48, P < .001 for median_attenuation and 0.5, P < .001 for peak_attenuation) with the growth rate. The location had no significant correlation with the growth rate (Table 3).

Discussion

We used fully automated DL software to detect and measure kidney stones in CTC scans of an asymptomatic population. The performance of the DL software was excellent, with a sensitivity of 0.993 and per-scan positive predictive value of 0.826, serving as an additional validation of the model developed in the prior work [18]. After manual review to remove false positives and add missed stones, we found incidental kidney stones

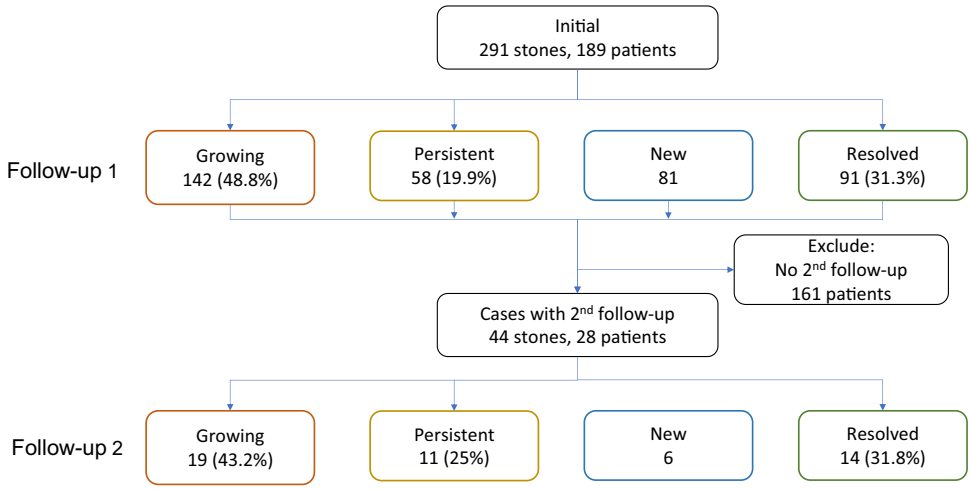


Fig. 2 Flowchart showing the trajectory of the tracked stones

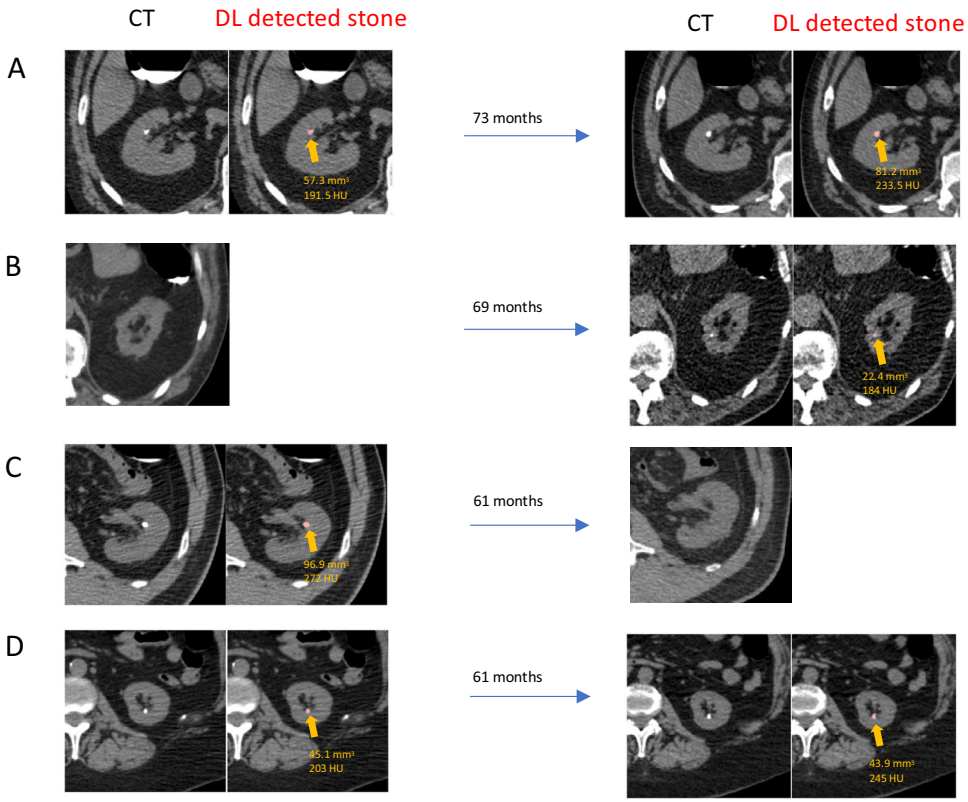


Fig. 3 Example growing, new, resolved, and persistent stones measured by DL software. **A** A 54-year-old male with a growing stone (top row). Growing stones represent stones that grew more than 10% in volume on the follow-up scan. **B** A 67-year-old male with a new appearing stone (second row). "New" stones represent stones that newly appeared on the follow-up scan compared to the initial scan. **C** A 60-year-old male with a passing stone (third row). Resolved stones represent stones that disappeared on the follow-up scan. **D** A 64-year-old female with a persistent stone (bottom row). Persistent stones represent stones that changed less than 10% in volume on the follow-up scan compared to the initial scan. Numbers on images represent the measured value (volume and median attenuation) of the stone measured by DL software

Table 2 Automatically measured kidney stone values and their outcomes

	Growing (G) (n=161)	Persistent (P) (n=69)	Resolved (R) (n=105)	*P* (adjusted)			
				G vs P	G vs R	P vs R	R vs (not R)
Stone size							
Volume (mm^3)	14.3 (5.8, 37.2)	21.8 (10.5, 45.1)	12.4 (5.7, 25.3)	0.420	0.400	0.007	0.065
Max 3D diameter (mm)	3.4 (2.2, 4.9)	3.7 (2.8, 5.5)	3.2 (2.2, 4.5)	0.062	0.320	0.009	0.055
Max axial diameter (mm)	2.6 (1.7, 3.9)	3.0 (2.2, 4.0)	2.3 (1.6, 3.3)	0.083	0.270	0.009	0.047
Stone attenuation							
Median attenuation (HU)	170 (151, 221)	182 (159, 219)	169 (149, 193)	0.200	0.290	0.060	0.088
Peak attenuation (HU)	269 (190, 478)	332 (224, 546)	258 (183, 364)	0.077	0.200	0.007	0.031
Mean attenuation (HU)	182 (154, 237)	195(167, 244)	174 (155, 209)	0.100	0.228	0.022	0.061
SD of attenuation (HU)	39 (18, 91)	54 (27, 102)	33 (18, 64)	0.085	0.200	0.010	0.034
Stone location							
Relative location	0.43 (0.23, .67)	0.43 (0.26, 0.60)	0.44 (0.27, 0.61)	1.00	1.00	1.00	0.83
Upper pole (count, %)	66 (41)	28 (41)	39 (37)				

Resolved stones are those that disappeared on the follow-up scan. Growing stones are those that grew more than 10% in volume on the follow-up scan. Persistent stones are those that grew less than 10% in volume on the follow-up scan. "Not resolved" includes growing and persistent stones. Relative location is a metric ranging from 0 (uppermost) to 1 (lowermost) representing the relative location of the stone on the kidney. Data are median (IQR), where IQR represents the interquartile range

HU Hounsfield unit

in 12.7% of the CTC screening population. The median stone volume was 17.1 mm^3 (equivalent to a sphere with a diameter of 3.2 mm) and the growth rate was 3.3 mm^3/year. Stones were more likely to grow (43.2 and 48.8%, at first and second follow-ups, respectively) than pass or resolve spontaneously (31.3 and 31.8%) or remain persistent (19.9 and 25%). New stones were also common—at first follow-up, 81 new stones were observed among 46 of

Table 3 Correlation between automatically measured values and growth rate in growing stones

	Growing stones	
	Spearman rho	*P*
Stone size		
Volume (mm^3)	0.53	<0.001
Maximum 3D diameter	0.55	<0.001
Maximum axial diameter	0.53	<0.001
Stone attenuation		
Median attenuation (HU)	0.48	<0.001
Peak attenuation (HU)	0.50	<0.001
Mean attenuation (HU)	0.48	<0.001
SD of attenuation (HU)	0.50	<0.001
Stone location		
Relative location	0.09	0.25
Is in upper pole?		0.55*

Growing stones are those that grew more than 10% in volume on the follow-up scan. Relative location is a metric ranging from 0 (uppermost) to 1 (lowermost) representing the relative location of the stone on the kidney.

*Wilcoxon p value

189 (24.3%) patients. We also found that growing stones had higher volume and attenuation compared with stones that resolved. The volume and attenuation of the growing stones also had a moderate correlation with the growth rate.

The prevalence of kidney stones found among the CTC screening population in our study (12.7%) was higher than the previously reported 5-8% in CTC patients and kidney donors [8, 25–27]. This may be because the DL software will faithfully detect and report very small stones that might be ignored by human readers (median stone size of ours and the current literature: 3.5 mm vs. 5.7 mm [28]). Age distribution also affects stone prevalence [29].

The peak CT attenuation of stones in our study was lower than that previously reported [30]. This is likely due to the smaller stone size—mean axial diameter of 3.4 mm in our study vs 6.8 mm and 5.3 mm for uric acid and calcium oxalate stones, respectively in [30]—and partial volume averaging effects in our study.

Prior studies have shown that stones less than 5 mm diameter are more likely to pass spontaneously or resolve [28]. In our study, we found that the size of the stones that resolved was smaller on average than the stones that grew or persisted, particularly in terms of the maximum axial diameter for which the difference was significant ($P < .05$, Table 2). However, the fact that the observed differences in volume or maximum 3D diameter were not significant suggests that the stone size had a relatively limited impact on whether the stone resolved. We suggest this is because the majority of our stones were small—72% had a maximum 3D diameter of less than 5 mm.

The size of a kidney stone is usually measured by the maximal transverse diameter. However, this diameter is a poor indicator of the stone's volume particularly for larger stones which are rarely spheres [14–17, 31] and because the measurement varies between readers and window levels [13]. As symptomatic stone events are known to increase with the size and number of asymptomatic stones [32, 33], and over half of the asymptomatic stones tend to grow in size during follow up [28], we believe our fully automated detection and measurement would be a helpful, objective addition to nonenhanced CT scans that are taken for other purposes.

Some limitations should be noted. Partial volume averaging can affect the stone volume and attenuation measurement [34]; however, we used thin slice scans with (1 mm slice spacing) to mitigate this effect. The follow-up intervals were relatively long, and during this time a stone could have passed, and conceivably a new stone could have formed in the same spot, and later be mistaken as a stone with no change. Also, stone types (e.g. calcium oxalate/calcium phosphate and uric acid stones) can affect the peak attenuation of stones; however, we did not try to distinguish between stone types in this study [30]. This study was done using CTC from a single institution in the United States and may not reflect other regional or dietary factors that might affect the prevalence of kidney stones [29].

In summary, we used fully automated DL software to detect and measure kidney stones and observed the natural history of asymptomatic stones in CTC scans. We report a higher prevalence of incidental stones compared to other studies that relied on manual detection and measurement. We also found that almost half of asymptomatic stones grew in volume during follow-up with a growth rate of approximately 3.3 mm^3/year.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00261-023-04075-w.

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Declarations

Competing interests Author RMS receives royalties from iCAD, Philips, ScanMed, PingAn, MGB and Translation Holdings and has received research support from Ping An (CRADA). PJP is an adviser

or consultant for Zebra Medical Vision and Bracco Diagnostics, and shareholder in Cellectar, Elucent, and SHINE.

Ethical approval This study was approved by the Institutional Review Board. The need for additional signed informed consent was waived.

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