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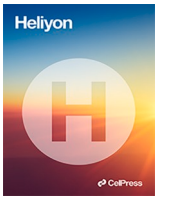

Parsimonious clinical prediction model for the diagnosis of complicated appendicitis

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ABSTRACT

Objective: To develop a logistic regression model that combines clinical and radiological parameters for prediction of complicated appendicitis.
Methods: 248 patients with histologically proven uncomplicated (n = 214) and complicated (n = 34) acute appendicitis were analyzed retrospectively. All patients had undergone a presurgical abdominal and/or pelvic computed tomography (CT) scan, assessed by two radiologists. A model using univariate and multivariate logistic regression analyses was developed, and the strength of association between independent predictors and complicated acute appendicitis was evaluated by adjusted odds radio. Clinical parameters were gender, age, anorexia, vomiting, duration of symptoms, right lower abdominal quadrant (RLQ) tenderness, rebound tenderness, body temperature, white blood cell (WBC) count, and neutrophil ratio. Radiological parameters were appendix diameter, appendicolith, caecal wall thickening, mesenteric lymphadenopathy, extraluminal air, abscess, fat stranding, and periappendicular fluid.
Results: Four features (body temperature > 37.2 °C, vomiting, appendicolith, and periappendiceal fluid) were included in the logistic regression model, and yielded an area under the curve (AUC) of 0.87 (95% confidence interval (CI), 0.80–0.93), sensitive of 88%, and specificity of 74%.
Conclusion: The logistic regression model makes an accurate and simple prediction of complicated appendicitis possible.

1. Introduction

Acute appendicitis (AA) is one of the most frequent causes of abdominal emergencies worldwide, with a rate of about 11 patients per 100,00 inhabitants per year and an estimated lifetime risk of approximately 7–8% [1,2]. It is classified as complicated AA and uncomplicated AA based on histopathological results. Complicated appendicitis includes gangrene, perforation, and local abscess formation. Uncomplicated appendicitis is defined as intraluminal inflammation, mucosal/submucosal inflammation, suppurative appendicitis, which is based on the depth and layer of neutrophil infiltration into the appendiceal wall [2–4]. These two different

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subtypes can be treated differently. Recent clinical trials [5–8] suggested a conservative treatment is effective and safe in uncomplicated AA, avoiding surgery related morbidity, and possible periprocedural complications. Accordingly, accurate differentiation between complicated and uncomplicated AA is important for treatment planning.

Multidetector computed tomography (MDCT) is the modality of choice in diagnosing AA in adolescent and adult patients because of its excellent diagnostic accuracy [9–11], which is better than uitrasound (US) [12–14]. The CT parameters [15–20] and clinical findings [21–23] have been used to distinguish complicated/perforated from complicated/unperforated. In recent studies, researchers have established logistic regression model to predict complicated AA, however, Eddama M [24] and Sasaki Y [25] only include clinical parameters into the model, most believe that a clinical diagnosis alone is insufficient for the diagnosis [26], and Kim HY [27] used contrast-enhancement CT, which is too time-consuming for emergency patient.

To improve the ability to differentiate between complicated and uncomplicated AA, we aimed to develop a logistic regression model that combines clinical and imaging features to predicted complicated AA.

2. Material and methods

2.1. Patients

The medical ethics review board approved this retrospective study (protocol No. K-2022-064-01), and informed consent from patients was waived because of its retrospective nature. 282 patients with clinically suspected AA who had undergone CT scan of the abdomen and/or pelvis were identified retrospectively. Study data were collected from our urban academic hospital from January 2017 to June 2021. Patient data were anonymized. We included patients with histopathological proven AA, for whom radiological and clinical parameters were available. These clinical parameters were obtained on admission and included demographic data (gender, age), clinical symptoms (anorexia, vomiting, duration of symptoms, RLQ tenderness, rebound tenderness, body temperature), and laboratory tests (WBC count, neutrophil ratio), this clinical symptoms and laboratory tests are easily accessible in daily routine. Those who had no signs of AA (n = 20), lacked of complete clinical data (n = 6), and had no histopathological proof of AA (including did not have surgery after admission) (n = 8) were excluded from the study. A total of 248 patients were ultimately included in our study (Fig. 1).

2.2. CT acquisition

All CT images were obtained on a 16-slice MDCT (Light Speed16, GE Medical Systems; USA) or a 320-slice MDCT (Aquilion ONE, Toshiba Medical Systems; Japan). Scan slice thickness and slice interval were set to 7 mm for 16-MDCT (120 kVp, 280–380 mAs,

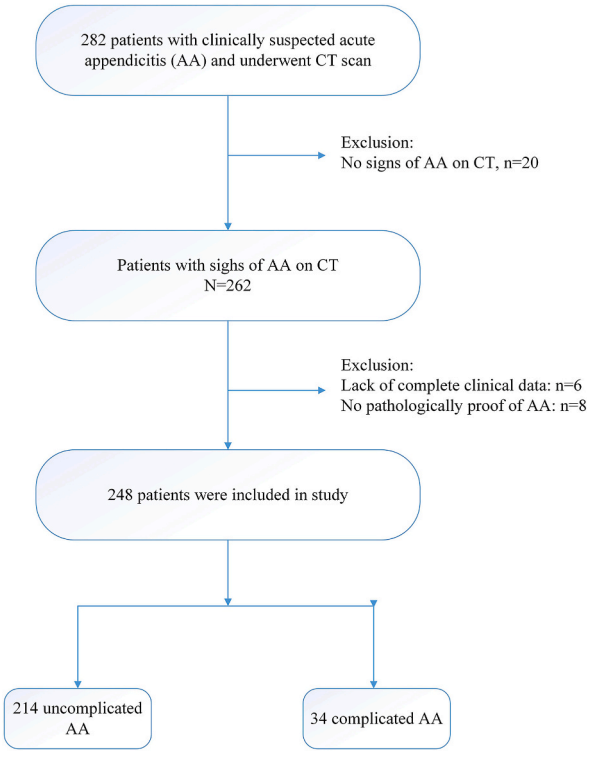

Fig. 1. Flowchart of selection of study patients. CT, computed tomography; AA, Acute appendicitis.

matrix, 512 × 512, collimation, 1.25 mm) or 3 mm for 320-MDCT (120 kVp, 100 mAs, matrix, 256 × 256, rotation time, 0.6s), respectively, covering from diaphragm to pubic symphysis. Coronal and sagittal images were all reformatted with a slice thickness of 3 mm. None of the patients received contrast agents.

2.3. Image analysis

All CT images including axial, coronal and sagittal reformatted images were independently analyzed by two abdominal radiologists (with 2 years and 6 years of experience, respectively) in Picture Archiving and Communication System (PACS) workstation (GE Advantage Windows Workstation, version 3.0; GE Medical Systems). Both observers were blinded to the clinical data and final histopathological results of AA. Cases in which there was disagreement between the two radiologists were resolved by a third radiologist with 20 years of experience in abdominal imaging. Radiological parameters, including appendix diameter, appendicolith, caecal wall thickening, mesenteric lymphadenopathy, extraluminal air, abscess, fat stranding, and periappendicular fluid, were evaluated. Mesenteric lymphadenopathy was defined as the right lower quadrant lymph node having a short diameter larger than 1.0 cm, or a cluster of four or more lymph nodes [18]. Fat stranding is manifested by blurred spots and streaks in the fat around the appendix. Periappendiceal fluid is defined as extraluminal fluid collections surrounding the appendix [28].

2.4. Statistical analysis

Categorical variables such as gender were expressed as number (percentage) and analyzed using the Chi-square test. Continuous variables are presented as mean ± standard deviation. We used *t*-test for distributed normally continuous variables otherwise Mann-Whitney *U* test to evaluate the differences between the complicated AA and uncomplicated AA groups. The normal distribution of data was assessed by the Kolmogorov-Smirnov test. The area under the curve (AUC), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) , cutoff values, sensitivity, specificity, accuracy as well as corresponding 95% confidence interval (95% CI) were calculated for all parameters with $p < 0.05$ to assess the performance in differentiating complicated from uncomplicated AA. The Youden index was used to obtained the optimal cut-off points of temperature, duration of symptoms, neutrophil ratio, and appendix diameter.

Univariate and multivariate logistic regression analyses were performed to evaluate the association between clinical/radiological factors and complicated AA. For factors that showed statistical significance ($p < 0.05$) in univariate logistic regression, a stepwise backward approach ($p = 0.1$) was used to enter multivariate logistic regression to obtain the final model. The odds ratio (OR) for independent predictors was obtained by logistic regression analysis. The discriminative performance for the logistic regression model was assessed by measuring AUC with 95% CI. The calibration of the model was assessed by the Hosmer-Lemeshow test. The collinearity of independent factors from the logistic regression model was tested by calculating the variance inflation factor (VIF). The agreement between interobserver for was estimated by intraclass correlation coefficients (ICCs) for continuous data or by Cohen's kappa (*k*) for

Table 1
Patient characteristics. RLQ, right lower abdominal quadrant; WBC, white blood cell; CT, computed tomography.

	Total number n = 248	Uncomplicated appendicitis n = 214 (86%)	Complicated appendicitis n = 34 (14%)	*p* value
Clinical findings				
Male, n (%)	147 (59)	126 (59)	21 (62)	0.95
Age (years)				
< 35	21.5 ± 7.8	21.8 ± 7.8	18.9 ± 7.7	0.15
35-50	42.3 ± 4.5	42.2 ± 4.6	42.9 ± 4.5	0.60
> 50	63.6 ± 9.1	62.3 ± 8.8	68.0 ± 9.0	0.07
Anorexia, n (%)	127 (51)	109 (51)	18 (53)	0.83
Vomiting, n (%)	144 (58)	118 (55)	26 (76)	< 0.05
Duration of symptoms (h)	32.7 ± 37.0	31.5 ± 38.3	39.9 ± 26.2	< 0.05
RLQ tenderness, n (%)	245 (99)	212 (99)	33 (97)	0.32
Rebound Tenderness, n (%)	224 (90)	195 (91)	29 (85)	0.24
Temperature (°C)	37.0 ± 0.8	36.9 ± 0.7	37.6 ± 1.0	< 0.001
WBC (%)	14.7 ± 4.6	14.6 ± 4.5	15.8 ± 5.3	0.16
Neutrophil ratio (%)	82.9 ± 8.8	82.4 ± 9.0	86.3 ± 6.3	< 0.05
CT findings				
Appendix diameter (mm)	11.8 ± 2.9	11.6 ± 2.9	13.1 ± 3.0	< 0.05
Appendicolith, n (%)	132 (53)	103 (48)	29 (85)	< 0.001
Caecal wall thickening, n (%)	46 (19)	32 (15)	14 (41)	< 0.001
Mesenteric lymphadenopathy, n (%)	94 (38)	75 (35)	19 (56)	< 0.05
Fat stranding, n (%)	219 (88)	186 (87)	33 (97)	0.09
Periappendiceal fluid, n (%)	98 (40)	71 (33)	27 (79)	< 0.001

Table 2
Diagnostic performance of clinical and CT parameters to identify patients with complicated acute appendicitis. AUC, area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; CT, computed tomography.

	AUC (95% CI)	Cutoff	Sensitivity	Specificity	Accuracy	PPV	NPV	PLR	NLR
Clinical findings									
Temperature (°C)	0.70 (0.64–0.76)	> 37.2	58.8 (40.7–75.4)	76.6 (70.4–82.1)	74.2 (68.7–79.7)	28.6 (21.6–36.7)	92.1 (88.6–94.6)	2.5 (1.7–3.7)	0.5 (0.4–0.8)
Duration of symptoms (h)	0.64 (0.58–0.70)	> 15	85.3 (68.9–95.0)	36.9 (30.4–43.8)	43.5 (37.3–49.8)	17.7 (15.3–20.3)	94.0 (87.3–97.3)	1.4 (1.1–1.6)	0.4 (0.2–0.9)
Vomiting	0.61 (0.54–0.67)	> 0	76.5 (58.8–89.3)	44.9 (38.1–51.8)	49.2 (42.9–55.5)	18.1 (15.0–21.6)	92.3 (86.5–95.7)	1.4 (1.1–1.7)	0.5 (0.3–1.0)
Neutrophil ratio (%)	0.64 (0.57–0.70)	> 85.1	67.7 (49.5–82.6)	60.3 (53.4–66.9)	61.3 (55.2–67.4)	21.3 (16.9–26.5)	92.1 (87.7–95.1)	1.7 (1.3–2.3)	0.5 (0.3–0.9)
CT findings									
Appendix diameter (mm)	0.64 (0.57–0.70)	> 13	44.1 (27.2–62.1)	76.6 (70.4–82.1)	72.6 (67.0–78.2)	23.1 (16.1–32.0)	89.6 (86.4–92.2)	1.9 (1.2–3.0)	0.73 (0.5–1.0)
Appendicolith	0.69 (0.62–0.74)	> 0	85.3 (68.9–95.0)	51.9 (45.0–58.7)	56.5 (50.2–62.7)	22.0 (18.8–25.5)	95.7 (90.7–98.1)	1.8 (1.5–2.2)	0.3 (01–0.6)
Caecal wall thickening	0.63 (0.57–0.69)	> 0	41.2 (24.6–59.3)	85.1 (79.6–89.5)	79.0 (73.9–84.1)	30.4 (20.8–42.2)	90.1 (87.2–92.4)	2.8 (1.6–4.6)	0.7 (0.5–0.9)
Mesenteric lymphadenopathy	0.60 (0.54–0.67)	> 0	55.9 (37.9–72.8)	65.0 (58.2–71.3)	63.7 (57.7–69.7)	20.2 (15.1–26.4)	90.3 (86.2–93.2)	1.6 (1.1–2.3)	0.7 (0.5–1.0)
Periappendiceal fluid	0.73 (0.67–0.79)	> 0	79.4 (62.1–91.3)	66.8 (60.1–73.1)	68.5 (62.7–74.4)	27.6 (22.7–32.9)	95.3 (91.3–97.5)	2.4 (1.9–3.1)	0.3 (0.2–0.6)

categorical data. The p value was set at 0.05 for assessing statistical significance. SPSS Statistics 18 (IBM SPSS, Armonk, NY, USA) software and MedCalc 18.2 (MedCalc Software, Ostend, Belgium) were utilized for statistical calculations.

3. Results

3.1. Patients

248 patients (214 uncomplicated AA, 34 complicated AA) were included in the final study group. There were no significant differences in age and gender ($p > 0.05$) between the uncomplicated and complicated groups. Patients with complicated AA were more likely to have evidence of vomiting than patients with uncomplicated AA. Duration of symptoms, temperature, and neutrophil ratio were significantly different, with these parameters all being significantly higher in complicated AA than uncomplicated AA. Most of the CT findings, such as appendix diameter, appendicolith, caecal wall thickening, mesenteric lymphadenopathy, extraluminal air, abscess, and periappendiceal fluid were significantly different between complicated and uncomplicated AA (Table 1).

3.2. Primary analysis

Table 2 summarizes the diagnostic performances for all statistically significant parameters between the groups ($p < 0.05$). Among all clinical parameters, body temperature outperformed all other parameters in terms of AUC (0.70; 95% CI, 0.64–0.76), specificity (76.6%; 95% CI, 70.4–82.1%), accuracy (74.2%; 95% CI, 68.7–79.7%), PPV (28.6%; 95% CI, 21.6–36.7%), and PLR (2.5; 95% CI, 1.7–3.7). However, the sensitivity was the smallest of all clinical findings (58.8%; 95% CI, 40.7–75.4%). The highest sensitivity (85.3%; 95% CI, 68.9–95.0%) and NPV (94.0%; 5% CI, 87.3–97.3%) were recorded for the duration of symptoms. Among all CT parameters, periappendiceal fluid revealed the highest AUC of 0.73 (95% CI, 0.67–0.79), appendicolith revealed the highest sensitivity of 85.3% (95% CI, 68.9–95.0%) and NPV of 95.7% (95% CI, 90.7–98.1%), and caecal wall thickening revealed the highest accuracy of 79.0% (95% CI, 73.9–84.1%). Extraluminal air and abscess both show the highest specificity with 100%.

3.3. Prediction of complicated appendicitis

Univariate and multivariate logistic regression analyses were performed in two sessions. In univariate logistic analysis, seven factors that showed a statistically significant ability to distinguish patients with complicated AA from uncomplicated AA were body temperature (> 37.2 °C), duration of symptoms (> 15 h), vomiting, appendicolith, caecal wall thickening, mesenteric lymphadenopathy, and periappendiceal fluid ($p < 0.05$), entering the multivariate logistic analysis. A stepwise regression approach (backward procedure) indicated that duration of symptoms (> 15 h), caecal wall and mesenteric lymphadenopathy could be removed. Details are provided in Table 3.

3.4. Interobserver agreement

The interobserver agreement was assessed for CT findings (appendix diameter, appendicolith, caecal wall thickening, mesenteric lymphadenopathy, extraluminal air, abscess, fat stranding, and periappendicular fluid) between two radiologists with the k value of 0.66–0.91 (appendicolith, 0.69, caecal wall thickening, 0.82, mesenteric lymphadenopathy, 0.91, fat stranding, 0.67, periappendicular fluid, 0.85, extraluminal air 0.79, abcess, 0.66), ICC value of 0.89 (appendix diameter, 0.89).

3.5. Collinearity

All VIF values of each independent predictor in the final model were ranged from 1.02 to 1.04 (<5) (temperature, 1.05, vomiting, 1.02, appendicolith, 1.02, appendicolith, 1.04), indicating no collinearity. The discriminatory ability of the model is credible.

Table 3
Univariable and multivariable analyses of candidate predictors. OR, odds ratio; CI, confidence interval.

	Univariate analysis		Multivariate analysis	
	OR	95% CI	Adjusted OR	95% CI
Temperature (> 37.2 °C)	4.67	2.21–9.95	3.90	1.65–9.18
Duration of symptoms (> 15 h)	3.39	1.26–9.12	(removed)	
Vomiting	2.64	1.15–6.11	2.17	0.85–5.56
Neutrophil ratio (> 85.1%)	1.55	0.75–3.20		
Appendix diameter (> 13 mm)	1.66	0.77–3.57		
Appendicolith	6.25	2.33–16.76	6.89	2.35–20.21
Caecal wall thickening	3.98	1.83–8.68	(removed)	
Mesenteric lymphadenopathy	2.35	1.13–4.89	(removed)	
Periappendiceal fluid	7.77	3.23–18.70	7.94	3.08–20.47

4. Discussion

The main objective of this study was to predict complicated AA by building a logistic regression model that combined clinical and radiological parameters. We used univariate and multivariate logistic regression analyses to get four independent predictors of complicated AA, including temperature (> 37.2 °C), vomiting, appendicolith, and periappendiceal fluid ($p < 0.05$). The body temperature (> 37.2 °C), appendicolith, and periappendiceal fluid had a significantly high ORs, which contribute to promote complicated AA, and vomiting is not shown to be an independent factor since the 95% CI crosses one (Table 2). The logistic regression model was built by incorporating these four predictors. Based on our model, if a patient with AA has all the factors of the model, he/she is 20.9 times more likely to have complicated AA than patients without these factors. Furthermore, we compared the model with each independent predictor, and found that the logistic regression model had the highest predictive ability (Fig. 2). Our model show a good calibration ($p > 0.05$), and contributed to complicated AA with an amount of 34.1% (Nagelkerke's R2).

As we hypothesized, the predictive ability in the model yielded an AUC of 0.87, which is higher than Kim et al. [27], who developed a diagnostic model produced an AUC of 0.81. That model [27] included one clinical feature (neutrophil ratio) and five CT features (appendiceal diameter, fat stranding, extraluminal air, abscess and contrast-enhancement defect of the appendiceal wall). Nevertheless, the present of periappendiceal fluid was not evaluated, although Foley TA et al. [18] shows this CT finding has strong association with appendiceal perforation and the length of hospital stay. Moreover, they [27] used contrast-enhancement CT in study, which is too time-consuming for emergency patient. Eddama M et al. [24] and Sasaki Y et al. [25] used clinical parameters to build logistic regression model for differentiation between complicated AA and uncomplicated AA that produced AUC of 0.862 and 0.74 (Model 1), respectively, which is lower than our study. This is because CT features combined into the model can achieve a better predictive ability of complicated AA. Besides, Sasaki Y et al. [25] also built Model 2 with AUC of 0.87. Surprisingly, the AUC of Model 2 is equal to our study. However, unlike our study, C-reactive protein (CRP) was the only significant predictive factor of complicated AA in Model 2, so the result is debatable.

Appendicolith had the highest sensitivity and NPV, which is much higher than previously reported [28]. Moreover, in contrast to Iamwat J et al. [28], the presence of an appendicolith in our study showed statistical significance both in univariate and multivariate logistic regression analyses, suggesting that an appendicolith is significantly associated with complicated AA. Bertrand et al. [5] also showed that antibiotic treatment for patients with an appendicolith is more likely to fail. This suggests that operative management may be appropriate for AA with appendicolith. The sensitivity and NPV of periappendiceal fluid were higher than Avanesov et al. [29], which has strong association with appendiceal perforation [18], suggesting that conservative treatment may be not suitable for AA with periappendiceal fluid. Although the extraluminal air and abscess has extremely high specificity, which is similar with Bixby SD et al. [30], these CT findings have no statistical significance in logistic regression analysis, so we did not include these factors in our model. Our cut-off for body temperature of > 37.2 °C is closely related to another study that used a temperature of ≥37.4 °C [4]. The lower value of the temperature cut-off in our study may be due to the fact that the patients in our study were younger (mean age, 33 years vs 44.5 years [4]). Circulating levels of elevated pro-inflammatory mediators are associated with increasing age [31] and contribute to increased body temperature. It also may be the patients have been able to take antipyretics or analgesics before their arrival at the emergency department. This is also why the sensitivity of temperature (> 37.2 °C) was relative low in study. Vomiting were more significantly found in the complicated AA, which is similar with previous study [32]. The sensitivity and NPV of vomiting and body temperature are not much high in clinical parameters. However, when clinical parameters and radiological parameters are combined into the model, high sensitivity is achieved. In order to prudently select treatment planning, sensitivity should be prioritized over specificity in diagnosing complicated AA. This is because a high sensitivity and NPV can be helpful in ruling out complications. A false-positive rate in diagnosing complicated AA may lead to serious complications such as peritonitis, sepsis, whereas a false-positive rate in diagnosing uncomplicated AA would only lead to an appendectomy.

In our study, the average of patients is 33 years, since most children chose US firstly. All patients performed surgery as soon as

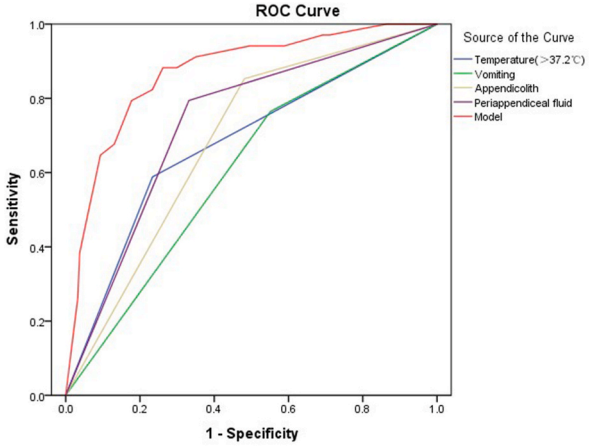

Fig. 2. ROC curve analysis with 95% confidence interval (CI) to predict complicated appendicitis.

possible after admission. Appendicectomy has been the method of choice to treat acute appendicitis for over a century. Although the surgical technique has shifted from open to laparoscopic, appendicectomy continues to have risks, including surgical site and intra-abdominal infections, incisional herniae, and peritoneal adhesions [33]. A logistic regression model can improve the ability to predict complicated AA, thus helping clinicians choose treatment planning.

There are several limitations to our study. First and foremost, our model is limited by retrospective study design and lacks appropriate external validation. Appropriate external validation studies are needed to clarify the generalizability of the model. Besides, some previously reported important information, such as CRP could not be collected. Since there were few subjects with CRP, which limits the multivariate analysis. And this study can not collect correctly many variables in a standardized way, like if there was or was not vomiting or the exact duration of the onset of symptoms. Secondly, the number of patients is relatively low, especially complicated AA, this may decrease the statistical reliability of logistic regression model; a larger number of patients, should be included in further study. Dual-energy CT with low keV and iodine overlay images have been proven useful in diagnosing complicated AA [20]. We can incorporate these two factors in our model in further studies.

5. Conclusions

In conclusion, in the present study, we found that four factors (temperature (>37.2 °C), vomiting, appendicolith, and peri-appendiceal fluid) are useful in preoperatively predicting complicated AA. Combining these predictors in a logistic regression model achieves better predictive ability, with AUC of 0.87, sensitive of 88%, and specificity of 74%. This finding may be helpful in facilitating decisions regarding emergency surgery and providing better patient management and care.

Author contribution statement

Jia-hui Cai: Conceived and designed the experiments, Performed the experiments, Analyzed and interpreted the data, Wrote the paper. Hui Zhou, Dan Liang and Qiao Chen: Contributed reagents, materials, analysis tools or data. Ye-yu Xiao: Analyzed and interpreted the data. Guang-ming Li: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Data availability statement

The data that has been used is confidential.

Additional information

No additional information is available for this paper.

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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References

[1] A. Petroianu, Diagnosis of acute appendicitis, Int. J. Surg. 10 (3) (2012) 115–119.
[2] A. Bhangu, K. Søreide, S. Di Saverio, J.H. Assarsson, F.T. Drake, Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management, Lancet 386 (10000) (2015) 1278–1287.
[3] N.J. Carr, The pathology of acute appendicitis, Ann. Diagn. Pathol. 4 (1) (2000) 46–58.
[4] Y. Imaoka, T. Itamoto, Y. Takakura, T. Suzuki, S. Ikeda, T. Urushihara, Validity of predictive factors of acute complicated appendicitis, World J. Emerg. Surg. 11 (2016) 48.
[5] M.M. Bertrand, J.Y. Lefrant, M. Prudhomme, A randomized trial comparing antibiotics with appendectomy for appendicitis, N. Engl. J. Med. 384 (9) (2021) 880–881, https://doi.org/10.1056/NEJMc2035865.
[6] P. Salminen, H. Paajanen, T. Rautio, P. Nordström, M. Aarnio, T. Rantanen, R. Tuominen, S. Hurme, J. Virtanen, J.P. Mecklin, J. Sand, A. Jartti, I. Rinta-Kiikka, J.M. Grönroos, Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial, JAMA 313 (23) (2015) 2340–2348.
[7] S. Di Saverio, M. Podda, B. De Simone, M. Ceresoli, G. Augustin, A. Gori, M. Boermeester, M. Sartelli, F. Coccolini, A. Tarasconi, N. De' Angelis, D.G. Weber, M. Tolonen, A. Birindelli, W. Biffl, E.E. Moore, M. Kelly, K. Soreide, J. Kashuk, R. Ten Broek, C.A. Gomes, M. Sugrue, R.J. Davies, D. Damaskos, A. Leppäniemi, A. Kirkpatrick, A.B. Peitzman, G.P. Fraga, R.V. Maier, R. Coimbra, M. Chiarugi, G. Sganga, A. Pisanu, G.L. De' Angelis, E. Tan, H. Van Goor, F. Pata, I. Di Carlo, O. Chiara, A. Litvin, F.C. Campanile, B. Sakakushev, G. Tomadze, Z. Demetrashvili, R. Latifi, F. Abu-Zidan, O. Romeo, H. Segovia-Lohse, G. Baiocchi, D. Costa, S. Rizoli, Z.J. Balogh, C. Bendinelli, T. Scalea, R. Ivatury, G. Velmahos, R. Andersson, Y. Kluger, L. Ansaloni, F. Catena, Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines, World J. Emerg. Surg. (2020), https://doi.org/10.1186/s13017-13020-00306-13013. Published online April 15.
[8] J. Martínez Carrilero, Safety an efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials, Rev. Clin. Esp. (2012), https://doi.org/10.1136/bmj.e2156. Published Online April 5.
[9] J.H. Park, Diagnostic imaging utilization in cases of acute appendicitis: multi-center experience, J. Kor. Med. Sci. 29 (9) (2014) 1308–1316.

[10] P.J. Pickhardt, E.M. Lawrence, B.D. Pooler, R.J. Bruce, Diagnostic performance of multidetector computed tomography for suspected acute appendicitis, Ann. Intern. Med. 154 (12) (2011) 789–796.
[11] A.S. Raja, C. Wright, A.D. Sodickson, R.D. Zane, G.D. Schiff, R. Hanson, P.F. Baeyens, R. Khorasani, Negative appendectomy rate in the era of CT: an 18-year perspective, Radiology 256 (2) (2010) 460–465.
[12] A.S. Doria, R. Moineddin, C.J. Kellenberger, M. Epelman, J. Beyene, S. Schuh, P.S. Babyn, P.T. Dick, US or CT for diagnosis of appendicitis in children and adults? A meta-analysis, Radiology 241 (1) (2006) 83–94.
[13] A. van Randen, S. Bipat, A.H. Zwinderman, D.T. Ubbink, J. Stoker, M.A. Boermeester, Acute appendicitis: meta-analysis of diagnostic performance of CT and graded compression US related to prevalence of disease, Radiology 249 (1) (2008) 97–106.
[14] K.A. Al-Khayal, M.A. Al-Omran, Computed tomography and ultrasonography in the diagnosis of equivocal acute appendicitis. A meta-analysis, Saudi Med. J. 28 (2) (2007) 173–180.
[15] H.Y. Kim, J.H. Park, S.S. Lee, W.J. Lee, Y. Ko, R.E. Andersson, K.H. Lee, CT in differentiating complicated from uncomplicated appendicitis: presence of any of 10 CT features versus radiologists' gestalt assessment, AJR Am. J. Roentgenol. (2020), https://doi.org/10.2214/AJR.2219.22405. Published Online May.
[16] C.E. Gaskill, V.V. Simianu, J. Carnell, D.S. Hippe, P. Bhargava, D.R. Flum, G.H. Davidson, Use of computed tomography to determine perforation in patients with acute appendicitis, Curr. Probl. Diagn. Radiol. 47 (1) (2018) 6–9.
[17] M. Ali, J. Iqbal, R. Sayani, Accuracy of computed tomography in differentiating perforated from nonperforated appendicitis, Taking Histopathology as the Gold Standard (2018), https://doi.org/10.7759/cureus.3735. Cureus (Published Online December 15.
[18] T.A. Foley, F.t. Earnest, M.A. Nathan, D.M. Hough, H.J. Schiller, T.L. Hoskin, Differentiation of nonperforated from perforated appendicitis: accuracy of CT diagnosis and relationship of CT findings to length of hospital stay, Radiology 235 (1) (2005) 89–96.
[19] W.D. Foley, CT features for complicated versus uncomplicated appendicitis: what is the evidence? Radiology 287 (1) (2018) 116–118.
[20] K.Y. Elbanna, M.F. Mohammed, T. Chahal, F. Khosa, I.T. Ali, F.H. Berger, S. Nicolaou, C.T. Dual-Energy, *In* differentiating nonperforated gangrenous appendicitis from uncomplicated appendicitis, AJR Am. J. Roentgenol. 211 (4) (2018) 776–782.
[21] E. Lietzén, J. Mällinen, J.M. Grönroos, T. Rautio, H. Paajanen, P. Nordström, M. Aarnio, T. Rantanen, J. Sand, J.P. Mecklin, A. Jartti, J. Virtanen, P. Ohtonen, P. Salminen, Is preoperative distinction between complicated and uncomplicated acute appendicitis feasible without imaging? Surgery 160 (3) (2016) 789–795.
[22] C.W. Yu, L.I. Juan, M.H. Wu, C.J. Shen, J.Y. Wu, C.C. Lee, Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin, C-reactive protein and white blood cell count for suspected acute appendicitis, Br. J. Surg. 100 (3) (2013) 322–329.
[23] C. García-Amador, V. Arteaga Peralta, R. de la Plaza Llamas, M. Torralba, A. Medina Velasco, J.M. Ramia, Evaluation of preoperative clinical and serological determinations in complicated acute appendicitis: a score for predicting complicated appendicitis, Cir. Esp. 99 (4) (2021) 282–288.
[24] M. Eddama, K.C. Fragkos, S. Renshaw, M. Aldridge, G. Bough, L. Bonthala, A. Wang, R. Cohen, Logistic regression model to predict acute uncomplicated and complicated appendicitis, Ann. R. Coll. Surg. Engl. 101 (2) (2019) 107–118.
[25] Y. Sasaki, F. Komatsu, N. Kashima, T. Suzuki, I. Takemoto, S. Kijima, T. Maeda, T. Miyazaki, Y. Honda, H. Zai, N. Shimada, K. Funahashi, Y. Urita, Clinical prediction of complicated appendicitis: a case-control study utilizing logistic regression, World J Clin Cases 8 (11) (2020) 2127–2136.
[26] B. Skjold-Ødegaard, K. Søreide, The diagnostic differentiation challenge in acute appendicitis: how to distinguish between uncomplicated and complicated appendicitis in adults, Diagnostics 12 (7) (2022).
[27] H.Y. Kim, J.H. Park, S.S. Lee, J.J. Jeon, C.J. Yoon, K.H. Lee, Differentiation between complicated and uncomplicated appendicitis: diagnostic model development and validation study, Abdom Radiol (NY) 46 (3) (2021) 948–959.
[28] J. Iamwat, W. Teerasamit, P. Apisarnthanarak, N. Noppakunsomboon, R. Kaewlai, Predictive ability of CT findings in the differentiation of complicated and uncomplicated appendicitis: a retrospective investigation of 201 patients undergone appendectomy at initial admission, Insights Imaging (2021), https://doi.org/10.1186/s13244-13021-01086-13243. Published Online October 21.
[29] M. Avanesov, N.J. Wiese, M. Karul, H. Guerreiro, S. Keller, P. Busch, F. Jacobsen, G. Adam, J. Yamamura, Diagnostic prediction of complicated appendicitis by combined clinical and radiological appendicitis severity index (APSI), Eur. Radiol. 28 (9) (2018) 3601–3610.
[30] S.D. Bixby, B.C. Lucey, J.A. Soto, J.M. Theysohn, A. Ozonoff, J.C. Varghese, Perforated versus nonperforated acute appendicitis: accuracy of multidetector CT detection, Radiology 241 (3) (2006) 780–786.
[31] L.A. van Vught, H. Endeman, S.C. Meijvis, A.H. Zwinderman, B.P. Scicluna, D.H. Biesma, T. van der Poll, The effect of age on the systemic inflammatory response in patients with community-acquired pneumonia, Clin. Microbiol. Infect. 20 (11) (2014) 1183–1188.
[32] S. Sirikurnpiboon, S. Amornpornchareon, Factors associated with perforated appendicitis in elderly patients in a tertiary care hospital, Surg Res Pract 2015 (2015), 847681.
[33] K.E. Rollins, K.K. Varadhan, K.R. Neal, D.N. Lobo, Antibiotics versus appendicectomy for the treatment of uncomplicated acute appendicitis: an updated meta-analysis of randomised controlled trials, World J. Surg. 40 (10) (2016) 2305–2318.