Clinical difference between acute appendicitis and acute right-sided colonic diverticulitis

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Abstract
Background: The clinical presentations of acute appendicitis (AA) and acute right-sided colonic diverticulitis (ARCD) are similar, but the usual treatment for each disease differs between surgical and conservative management. This study aimed to identify the clinical differences between AA and ARCD.

Method: We performed a single-center retrospective case-control study on adult patients with AA and ARCD confirmed by computed tomography who had visited an emergency department between March 2018 and February 2019. The clinical variables, including past medical history, presented symptoms and signs, and laboratory findings were compared between the two groups. We subsequently performed a logistic regression analysis for differentiating ARCD from AA based on the results of univariate analyses.

Results: A total of 222 (79%) and 59 (21%) patients were enrolled in the AA and ARCD groups, respectively. Logistic regression analysis revealed that factors associated with ARCD were a past history of diverticulitis [OR 141.691 (95% CI: 12.222 – 1642.601), p < 0.001], ketonuria [OR 0.268 (95% CI: 0.099 – 0.726), p = 0.010], anorexia [OR 0.037 (95% CI: 0.007 – 0.207), p < 0.001], and neutrophilia [OR 0.179 (95% CI: 0.062 – 0.519), p = 0.002].

Conclusion: Anorexia, neutrophilia, and ketonuria were predictors of AA and a history of diverticulitis was a predictor of ARCD.

1. Introduction
Acute appendicitis (AA) and acute right-sided colonic diverticulitis (ARCD) are inflammatory diseases that occur at near anatomical locations and the clinical presentations are similar and not easy to differentiate.[1–3] However, the current standard treatment for each disease is different. Surgical appendectomy is needed for AA and non-operative conservative treatment, such as bowel rest and/or antibiotics is usually used for uncomplicated diverticulitis.[4–7] Nevertheless, ARCD is often misdiagnosed as AA and was revealed during invasive surgery.[3, 8] Computer tomography (CT) or ultrasound can be used as a diagnostic imaging tool to avoid unnecessary surgical exploration or for ARCD mimicking AA, but it has the disadvantage of radiation exposure and cost.[9, 10] Episodes of
diverticulitis are reported to recur in about 30% of the cases, where abdominal image testing for each episode to differentiate between the two diseases can be a burden on the patient.[6, 11] In this respect, only a few studies have verified the clinical differences between the two diseases.[12, 13] The purpose of this study was to reveal the different factors between AA and ARCD.

2. Materials And Methods
2.1. Study design and population
This single-center retrospective review case-control study was conducted in consecutive Asian patients, aged 18 years old or older, diagnosed with AA or acute colonic diverticulitis confirmed by one radiologist though an abdominal CT scan, and who had visited the emergency department of a tertiary university hospital between March 2018 and February 2019 in the Republic of Korea. Patients with diverticulitis not included in the right side of colon or those transferred for admission to another facility were excluded.

2.2. Study variables
Clinical data obtained from the electronic medical records included age, sex, body mass index (BMI), the time from symptom onset to visiting the emergency room, a past medical history of previous diverticulitis or chronic diseases (diabetes, hypertension), gastrointestinal symptoms and signs (right lower quadrant [RLQ] pain, migrated pain to the RLQ, anorexia, nausea and vomiting, diarrhea), physical exam (initial body temperature, RLQ tenderness, rebound tenderness), laboratory findings (complete blood count, serum alanine transaminase [ALT], serum creatinine [Cr], serum C-reactive protein [CRP], urine ketone), Alvarado score and its components, and outcomes (need of hospitalization, length of stay, need of surgical treatment, and mortality).

2.3. Study Definition
ARCD was defined as diverticulitis originating from primary inflammation of diverticulosis sited at the cecum or ascending colon. A history of diverticulitis was defined in patients who were previously diagnosed with any sited colonic diverticulitis before the study period. Elevated ALT was defined as serum ALT over the upper limit of the normal value of 33 IU/L for males or 25 IU/L for females.[14] Elevated Cr was defined as serum Cr over the upper limit of the normal value of 1.29 mg/dL for males or 1.1 mg/dL for females.[15] Elevated CRP was defined as serum CRP concentration over 1.0 mg/dL,
indicating significant inflammation.[16] Ketonuria was defined by a positive urine ketone dipstick test. The Alvarado score, a 10-point clinical scoring system, was calculated by adding each score to each clinical factor listed in Table 1[17].

2.4. Statistical Analysis
We compared the study variables of the AA and ARCD groups. Continuous variables are presented as median values (interquartile range, IQR) and were compared by the Mann-Whitney test. Nominal data were calculated as percentages based on the frequency of occurrence and compared using chi-squared or Fisher's exact test, as appropriate. Multivariate logistic regression was used to correlate the single variables with ARCD. The resulting odds ratios (ORs) are presented with 95% confidence intervals (95% CIs). A two-sided p-value of less than 0.05 was considered statistically significant.

Analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) software version 24.0 (SPSS, Inc., Chicago, IL, USA).

3. Result
During the study period, 231 AA and 74 acute colonic diverticulitis cases were diagnosed by abdominal CT scans of adult patients admitted to the emergency department. Among them, 14 were other-side diverticulitis and 10 patients (9 AA and 1 ARCD) were transferred to another hospital for admission. Finally, 222 (79%) and 59 (21%) patients were enrolled in the AA and ARCD groups, respectively.

Patient characteristics, including the clinical factors associated with each disease group and outcome, are shown in Table 2. The AA group had a higher percent of neutrophils [78.8 (70.2–84.8) vs. 73.8 (67.1–77.0), p < 0.001] and higher Alvarado scores [6 (4–7) vs. 5 (3–6), p < 0.001] than the ARCD group. The ARCD group had more past histories of diverticulitis (22% vs 0.9%, p < 0.001) than the AA group. The AA group had more RLQ pain (96.4% vs. 86.4%, p = 0.044), ketonuria (40.0% vs. 20.4%, p = 0.013), migration pain (20.3% vs. 8.5%, p = 0.036), anorexia (36.5% vs. 8.5%, p < 0.001), RLQ tenderness (98.2% vs. 88.1%, p = 0.002), rebound tenderness (40.1% vs. 25.4%, p = 0.048), neutrophilia (62.6 vs. 35.6, p < 0.001), admission care (100% vs. 44.1%, p < 0.001), and surgical treatment (98.6% vs. 1.7%, P < 0.001) than the ARCD group. The ARCD group had longer onset-to-
visit intervals [24 (13–48) vs. 11 (3–25) hours, p < 0.001] and higher percentage of lymphocytes [18.5(13.9–24.6) vs. 14.1(9.2–21.6), p = 0.001] than the AA group. There was no difference between the two groups in other single clinical variables.

Multivariate analysis revealed that the factors predictive of ARCD were a past history of diverticulitis [OR 141.691 (95% CI: 12.222–1642.601), p < 0.001], ketonuria [OR 0.268 (95% CI: 0.099–0.726), p = 0.010], anorexia [OR 0.037 (95% CI: 0.007–0.207), p < 0.001], and neutrophilia [OR 0.179 (95% CI: 0.062–0.519), p = 0.002] (Table 3).

4. Discussion

In the Asian population, diverticulosis affects approximately 25.1% of the population, accounting for 87.9% of the colonic diverticulosis cases involving the right side, which is significantly higher than in Western countries.[18] ARCD is reported to occur at a relatively young age and the overall prevalence of diverticulitis is 75% in the Asian population.[19, 20] This study population was limited to Asians and 81.1% of colonic diverticulitis cases were ARCD.

Our results showed that more surgical treatment was provided for AA, whereas conservative management was provided for ARCD, consistent with a previous study.[7] Therefore, distinguishing the two diseases will be important for determining a therapeutic plan and avoiding unnecessary surgery for ARCD patients. A classical tool for distinguishing appendicitis from other abdominal diseases is the Alvarado scoring system.[17] However, even appendicitis can show equivocal Alvarado scores and some studies revealed that ARCD patients had a higher or broader range of Alvarado scores.[21–23] Therefore, it may not be enough to use this scoring system as a tool to distinguishable between these diseases. Although the Alvarado scores showed a difference between the two groups in our single variable analysis, with a 6-point median value in AA and a 5-point median value in ARCD, it would be difficult to assign clinical meaning because scores of 5 to 6 have an equivocal probability for appendicitis.[24] Currently, few studies have reported clinical differences in the symptoms and signs (such as longer symptom duration associated with ARCD and nausea or vomiting, anorexia, migration pain, and RLQ pain associated with AA) between AA and ARCD.[12, 13, 21] Much of the differences in the symptoms are hypothesized to be due to the different pathophysiology and
elapsing course of the two diseases. Although both diseases have similar final symptoms due to localized peritonitis, appendicitis has a sequential reaction with prodromal symptoms due to the blockage and dilatation of the appendix first, then the increased intraluminal pressure results in wall necrosis.[25] Each subjective indicator might have a risk of bias by clinicians or patients. Otherwise, there are few studies that reported some objective factors (such as neutrophilia and high CRP) associated with AA than ARCD.[12, 13] Like most previous studies, we consistently found that a previous history of diverticulitis was a predictor of ARCD and anorexia and neutrophilia were predictors of AA.

An insufficient number of studies has reported the usefulness of leukocytosis for differentiating the two diseases and thus, it remains controversial.[21, 26] Shin et al.[12] reported that an elevated proportion of lymphocytes and a near-normal proportion of segmented neutrophils was seen in ARCD, even though no hypothesis was suggested to explain this phenomenon. Our results supported the relationship between neutrophilia and AA and higher fractions of lymphocytes were also related to ARCD. Sasaki et al. [13] categorized high serum CRP as > 3.0 mg/dL and reported that high serum CRP was associated with ARCD. However, our result did not support that finding. There was no statistical difference in our results between the AA and ARCD groups, even when serum CRP values over 3.0 mg/dL were used as criteria, as in the other study (39.0% vs 34.7%, p = 0.544). Serum CRP is known to peak after 48 hours due to its response to inflammation.[27] Our study and the study by Sasaki differed in the time interval from onset-to-visit in the ARCD patients (24 h vs. 48 h) and this could affect the blood sample collection time after infection. Therefore, it may not be appropriate to compare the two studies. Moreover, it has been revealed that serum CRP levels increase over time in appendicitis, questioning whether high CRP levels are more relevant to AA than ARCD if the confounding time factors related to the CRP increase are not removed.[28]

Our results revealed that ketonuria was one of the objective predictors of AA. We presented a boxplot for the distribution of urine ketone values between the two groups in Fig. 1. A few studies reported that ketonuria was seen in 12–45% of the AA cases, but there have been no comparative studies between AA and ARCD.[29, 30] Ketones are known as the end-product of fatty acid metabolism and
ketonuria indicates that the body is excessively using fat over carbohydrates as the major source of energy.[31] Ketonuria could arise from dietary conditions, such as fasting, nausea and vomiting, and anorexia, and metabolic conditions, including type-1 diabetes, fever, and pregnancy.[32] In our study, there were no patients with type-1 diabetes or pregnant women and there was no difference in body temperature between the two groups. Therefore, we could suggest that the probable cause of ketonuria in appendicitis is related to dietary conditions such as anorexia because these conditions were found more in the AA group than in the ARCD group. When we made a simple rule for predicting ARCD that included objective clinical factors, such as no ketonuria and no neutrophilia and the presence of a history of diverticulitis, the calculated positive predictive value (PPV) was 87.5%, the negative predictive value (NPV) was 82.6%, and the specificity was 99.5%. Thus, this rule might be a useful tool for distinguishing ARCD from AA.

This study had some limitations. First, this study was conducted at a single center in an Asian population in the Republic of Korea. Therefore, the results may not represent all races and nations. However, the presentation of diverticulitis in the Asian population is unusual because it most commonly involves the right side of the colon and the exact pathological mechanism of diverticular disease is unclear, although several theories related to genetics, diet, motility, and microbiome that may be affected by individual races and cultures have been presented.[33] Therefore, this study had some clinical implications because not many studies have been reported in an Asian population.

Second, because this study was a retrospective study rather than a confirmative study, data or cases might be missing. Specifically, for subjective symptoms and signs, it is difficult to accurately describe the intensity or presence without a proper prospective protocol. Third, ketonuria is roughly correlated with serum ketone concentrations, but the absence of ketonuria does not mean the absence of blood ketone bodies. However, we could not obtain the serum ketone concentrations to distinguish between AA and ARCD as that analysis was not included in the routine ER blood tests because it is more expensive than urine analysis and has not been proven useful in the diagnosis of these diseases.

Further studies quantitative analyzing these factors should be conducted.

5. Conclusion
Our results suggest that anorexia, neutrophilia, and ketonuria are useful predictors of AA, but not ARCD. Conversely, a history of diverticulitis was a useful predictor of ARCD, but not AA. If a history of diverticulitis is present and there is no neutrophilia or ketonuria, then the PPV is 87.5% and the specificity is 99.5% for ARCD. We suggest using our findings for the differential diagnosis between AA and ARCD to reduce unnecessary additional imaging studies for ARCD.

Declarations
Ethics approval and consent to participate: This study was approved by the Institutional Review Board of Dongguk University Ilsan Hospital, Dongguk University (2018-11-007). Informed consent was waived by the IRB.

Consent for publication: Not applicable.

Availability of data and materials: All datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Authors’ contributions: JH Song participated in the data collection, drafting the article. S Lee participated study design, data collection, data analysis. HH Do participated in the study design, data collection, and revising draft critically for important intellectual contents. JS Seo participated study design, and revising draft critically for important intellectual contents. JH Lee participated study design and revising draft critically for important intellectual contents. SC Lee participated study design and revising draft critically for important intellectual contents. YW Kim participated conception and design of the study, statistical analysis, drafting the article, and final approval of the version. All authors read and approved the final manuscript.

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Tables
### Table 1. Alvarado score

| Components                                        | Score |
|---------------------------------------------------|-------|
| Anorexia                                          | 1     |
| Nausea or vomiting                                | 1     |
| Migrating pain to RLQ                             | 1     |
| RLQ tenderness                                    | 1     |
| Rebound tenderness                                | 2     |
| Elevated temperature (> 37.3°)                    | 1     |
| Leukocytosis > 10,000/mm³                         | 2     |
| Neutrophilia > 75%                                | 1     |
| **Total**                                         | 10    |

RLQ, right lower quadrant

### Table 2. General characteristics

| Parameters                                        | Total N=281 | AA group N=222 (79.0%) | ARCD group N=59 (21.0%) | p-value |
|---------------------------------------------------|-------------|-------------------------|--------------------------|---------|
| Age (yr)                                          | 41(31-52)*  | 41(31-54)*              | 41(32-47)*               | 0.759   |
| Male gender, no. (%)                              | 132(47.0)*  | 113(50.9)*              | 24(40.7)*                | 0.188   |
| BMI (kg/m²)                                       | 23.3(20.7-26.0)* | 23.3(20.8-25.9)*       | 22.8(20.7-26.2)*         | 0.718   |
| Onset-to-visit interval (hr)                       | 16(4-48)*   | 11(3-25)*               | 24(13-48)*               | <0.001  |
| Past medical history                              | -           | -                       | -                        |         |
| Diabetes, no. (%)                                 | 11(3.9)     | 8(3.6)                  | 3(5.1)                   | 0.704   |
| Hypertension, no. (%)                             | 20(7.1)     | 14(6.3)                 | 6(10.2)                  | 0.390   |
| History of diverticulitis, no. (%)                | 15(5.3)     | 2(0.9)                  | 13(22.0)                 | <0.001  |
| Symptoms and Signs                                |             |                         |                          |         |
| Body temperature(°C)                              | 36.8(36.6-37.3)* | 36.8(36.5-37.3)*       | 36.8(36.5-37.2)*         | 0.516   |
| RLQ pain, no. (%)                                 | 261(92.9)   | 210(96.4)               | 51(86.4)                 | 0.044   |
| Diarrhea, no. (%)                                 | 49(17.4)    | 35(15.8)                | 14(23.7)                 | 0.176   |
| Constipation, no. (%)                             | 9(3.2)      | 5(2.3)                  | 4(6.8)                   | 0.096   |
| Laboratory findings                               |             |                         |                          |         |
| WBC                                               | 11,470(9,200-14,310)* | 11,740(9,118-14,543)*  | 11,160(9,090-13,170)*    | 0.277   |
| Absolute neutrophil count                         | 8,960(6,400-11,700)* | 9,270(6,410-11,890)*   | 7,960(6,220-9,960)*      | 0.067   |
| Neutrophil (%)                                    | 77.5(69.2-83.3)* | 78.8(70.2-84.8)*       | 73.8(67.1-77.0)*         | <0.001  |
| Lymphocyte (%)                                    | 14.8(9.9-22.7)* | 14.1(9.2-21.6)*        | 18.5(13.9-24.6)          | 0.001   |
| Hb (g/dL)                                         | 13.9(12.6-14.9)* | 13.9(12.8-15.0)*       | 13.9(12.3-14.7)*         | 0.551   |
| Measure                      | AA                          | ARCD                        | ARCD                        | p-value |
|------------------------------|-----------------------------|-----------------------------|-----------------------------|---------|
| Hct (%)                      | 40.8 (37.3-43.8)*           | 40.7 (37.6-43.8)*           | 41.0 (36.9-44.0)*           | 0.809   |
| Elevated ALT, no. (%)        | 40 (14.2)                   | 34 (15.3)                   | 6 (10.2)                    | 0.404   |
| Elevated Cr, no. (%)         | 6 (2.1)                     | 5 (2.3)                     | 1 (1.7)                     | 1.000   |
| Elevated CRP, no. (%)        | 161 (57.3)                  | 129 (58.1)                  | 32 (54.2)                   | 0.657   |
| CRP (mg/dL)                  | 1.7 (0.4-4.8)               | 1.5 (0.3-4.8)               | 2.4 (0.8-4.8)               | 0.181   |
| Ketonuria, no. (%)           | 94/259 (36.3)               | 84/210 (40.0)               | 10/49 (20.4)                | 0.013   |
| Alvarado score and components|                             |                             |                             |         |
| Alvarado score               | 6 (4-7)                     | 6 (4-7)                     | 5 (3-6)                     | <0.001  |
| Migration pain, no. (%)      | 50 (17.8)                   | 45 (20.3)                   | 5 (8.5)                     | 0.036   |
| Anorexia, no. (%)            | 86 (30.6)                   | 81 (36.5)                   | 5 (8.5)                     | <0.001  |
| Nausea or vomiting, no. (%)  | 92 (32.7)                   | 78 (35.1)                   | 14 (23.7)                   | 0.119   |
| RLQ tenderness, no. (%)      | 270 (96.1)                  | 218 (98.2)                  | 52 (88.1)                   | 0.002   |
| Rebound tenderness, no. (%)  | 104 (37.0)                  | 89 (40.1)                   | 15 (25.4)                   | 0.048   |
| Body temperature ≥37.3°C, no. (%) | 77 (27.4)            | 63 (28.4)                   | 14 (23.7)                   | 0.516   |
| Leukocytosis, no. (%)        | 190 (67.6)                  | 150 (67.6)                  | 40 (67.8)                   | 1.000   |
| Neutrophilia, no. (%)        | 160 (56.9%)                 | 139 (62.6)                  | 21 (35.6)                   | <0.001  |
| Outcomes                     |                             |                             |                             |         |
| Admission care, no (%)       | 248 (88.3)                  | 222 (100)                   | 26 (44.1)                   | <0.001  |
| Hospital days                | 6 (4-6)*                    | 5 (4-7)*                    | 5 (4-6)*                    | 0.508   |
| Surgical treatment, no. (%)  | 220 (78.3)                  | 219 (98.6)                  | 1 (1.7)                     | <0.001  |
| Mortality, no. (%)           | 1 (0.4)                     | 1 (0.5)                     | 0                           | 1.000   |

*Median(interquartile range); AA, acute appendicitis; ARCD, acute right-sided colonic diverticulitis; BMI, body mass index; RLQ, right lower quadrant; WBC, white blood cell; Hb, hemoglobin; Hct, hematocrit; LDH, lactate dehydrogenase; ALT, alanine transaminase; Cr, creatinine; CRP, C-reactive protein.
| Predictors of acute ARCD                  | Odds ratio | 95% CI       | p-value |
|-------------------------------------------|------------|--------------|---------|
| Onset-to-visit interval (hr)              | 1.000      | 0.999-1.001  | 0.784   |
| History of diverticulitis                 | 141.691    | 12.222-1642.601 | <0.001 |
| RLQ pain                                  | 1.595      | 0.184-13.906 | 0.673   |
| Ketonuria                                 | 0.268      | 0.099-0.726  | 0.010   |
| Migration pain                            | 0.295      | 0.083-1.049  | 0.059   |
| Anorexia                                  | 0.037      | 0.007-0.207  | <0.001 |
| RLQ tenderness                            | 0.154      | 0.023-1.049  | 0.056   |
| Rebound tenderness                        | 0.408      | 0.162-1.028  | 0.057   |
| Neutrophilia                              | 0.179      | 0.062-0.519  | 0.002   |

CI, confidence interval; ARCD, acute right-sided colonic diverticulitis; AA, acute appendicitis; RLQ, right lower quadrant

Figures
Boxplot showing urine ketone values from the dipstick test in acute appendicitis and acute right-sided colonic diverticulitis patients.