ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2020 June 6; 8(11): 2066-2407

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Semimonthly Volume 8 Number 11 June 6, 2020

REVIEW

2066 Tumor circulome in the liquid biopsies for digestive tract cancer diagnosis and prognosis
Chen L, Chen Y, Feng YL, Zhu Y, Wang LQ, Hu S, Cheng P

2081 Isoflavones and inflammatory bowel disease
Wu ZY, Sang LX, Chang B

MINIREVIEWS

2092 Cytapheresis for pyoderma gangrenosum associated with inflammatory bowel disease: A review of current status
Tominaga K, Kamimura K, Sato H, Ko M, Kawata Y, Mizusawa T, Yokoyama J, Terai S

2102 Altered physiology of mesenchymal stem cells in the pathogenesis of adolescent idiopathic scoliosis
Ko DS, Kim YH, Goh TS, Lee JS

2111 Association between liver targeted antiviral therapy in colorectal cancer and survival benefits: An appraisal
Wang Q, Yu CR

2116 Peroral endoscopic myotomy for management of gastrointestinal motility disorder
Feng Z, Liu ZM, Yuan XL, Ye LS, Wu CC, Tan QH, Hu B

ORIGINAL ARTICLE

Case Control Study

2127 Clinical prediction of complicated appendicitis: A case-control study utilizing logistic regression
Sasaki Y, Komatsu F, Kashima N, Suzuki T, Takemoto I, Kijima S, Maeda T, Miyazaki T, Honda Y, Zai H, Shimada N, Funahashi K, Urita Y

2137 Clinical application of ultrasound-guided selective proximal and distal brachial plexus block in rapid rehabilitation surgery for hand trauma
Zhang J, Li M, Jia HB, Zhang L

2144 High flux hemodialysis in elderly patients with chronic kidney failure
Xue HY, Duan B, Li ZJ, Du P

2150 Determination of vitamin D and analysis of risk factors for osteoporosis in patients with chronic pain
Duan BL, Mao YR, Xue LQ, Yu QY, Liu MY

Retrospective Study

2162 Differences in parents of pediatric liver transplantation and chronic liver disease patients
Akbulut S, Gunes G, Saritas H, Aslan B, Karipkiz Y, Demyati K, Gungor S, Yilmaz S

2173 Epidemiological investigation of *Helicobacter pylori* infection in elderly people in Beijing
Zhu HM, Li BY, Tang Z, She J, Liang XY, Dong LK, Zhang M

2181 Application of a pre-filled tissue expander for preventing soft tissue incarceration during tibial distraction osteogenesis
Chen H, Teng X, Hu XH, Cheng L, Du WL, Shen YM

2190 Evaluation of clinical significance of claudin 7 and construction of prognostic grading system for stage II colorectal cancer
Quan JC, Peng J, Guan X, Liu Z, Jiang Z, Chen HP, Zhuang M, Wang S, Sun P, Wang HY, Zou SM, Wang XS

2201 Choice and management of negative pressure drainage in anterior cervical surgery
Su QH, Zhu K, Li YC, Chen T, Zhang Y, Tan J, Guo S

2210 Risk scores, prevention, and treatment of maternal venous thromboembolism
Zhang W, Shen J, Sun JL

2219 Role of Hiraoka's transurethral detachment of the prostate combined with biopsy of the peripheral zone during the same session in patients with repeated negative biopsies in the diagnosis of prostate cancer
Pan CY, Wu B, Yao ZC, Zhu XQ, Jiang YZ, Bai S

2227 Efficacy of thoracoscopic anatomical segmentectomy for small pulmonary nodules
Li H, Liu Y, Ling BC, Hu B

Observational Study

2235 Attitudes, awareness, and knowledge levels of the Turkish adult population toward organ donation: Study of a nationwide survey
Akbulut S, Ozer A, Gokce A, Demyati K, Saritas H, Yilmaz S

2246 Metabolic biomarkers and long-term blood pressure variability in military young male adults
Lin YK, Liu PY, Fan CH, Tsai KZ, Lin YP, Lee JM, Lee JT, Lin GM

2255 Cytokines predict virological response in chronic hepatitis B patients receiving peginterferon alfa-2a therapy
Fu WK, Cao J, Mi NN, Huang CF, Gao L, Zhang JD, Yue P, Bai B, Lin YY, Meng WB

SYSTEMATIC REVIEWS

2266 Utilising digital health to improve medication-related quality of care for hypertensive patients: An integrative literature review
Wechkunanukul K, Parajuli DR, Hamiduzzaman M

Contents

World Journal of Clinical Cases

Volume 8 Number 11 June 6, 2020

META-ANALYSIS

2280 Role of *IL-17* gene polymorphisms in osteoarthritis: A meta-analysis based on observational studies
Yang HY, Liu YZ, Zhou XD, Huang Y, Xu NW

CASE REPORT

2294 Various diagnostic possibilities for zygomatic arch pain: Seven case reports and review of literature
Park S, Park JW

2305 Extensive multifocal and pleomorphic pulmonary lesions in Waldenström macroglobulinemia: A case report
Zhao DF, Ning HY, Cen J, Liu Y, Qian LR, Han ZH, Shen JL

2312 Lung cancer from a focal bulla into thin-walled adenocarcinoma with ground glass opacity – an observation for more than 10 years: A case report
Meng SS, Wang SD, Zhang YY, Wang J

2318 Pyogenic discitis with an epidural abscess after cervical analgesic discography: A case report
Wu B, He X, Peng BG

2325 Clinical characteristics, diagnosis, and treatment of COVID-19: A case report
He YF, Lian SJ, Dong YC

2332 Paraplegia after transcatheter artery chemoembolization in a child with clear cell sarcoma of the kidney: A case report
Cai JB, He M, Wang FL, Xiong JN, Mao JQ, Guan ZH, Li LJ, Wang JH

2339 Macrophage activation syndrome as a complication of dermatomyositis: A case report
Zhu DX, Qiao JJ, Fang H

2345 Serial computed tomographic findings and specific clinical features of pediatric COVID-19 pneumonia: A case report
Chen X, Zou XJ, Xu Z

2350 Myxofibrosarcoma of the scalp with difficult preoperative diagnosis: A case report and review of the literature
Ke XT, Yu XF, Liu JY, Huang F, Chen MG, Lai QQ

2359 Endoscopic pedicle flap grafting in the treatment of esophageal fistulas: A case report
Zhang YH, Du J, Li CH, Hu B

2364 Hemophagocytic syndrome as a complication of acute pancreatitis: A case report
Han CQ, Xie XR, Zhang Q, Ding Z, Hou XH

2374 Reduced delay in diagnosis of odontogenic keratocysts with malignant transformation: A case report
Luo XJ, Cheng ML, Huang CM, Zhao XP

2380 Gastric pyloric gland adenoma resembling a submucosal tumor: A case report
Min CC, Wu J, Hou F, Mao T, Li XY, Ding XL, Liu H

2387 Ataxia-telangiectasia complicated with Hodgkin's lymphoma: A case report
Li XL, Wang YL

2392 Uterine incision dehiscence 3 mo after cesarean section causing massive bleeding: A case report
Zhang Y, Ma NY, Pang XA

2399 Optical coherence tomography guided treatment avoids stenting in an antiphospholipid syndrome patient: A case report
Du BB, Wang XT, Tong YL, Liu K, Li PP, Li XD, Yang P, Wang Y

LETTER TO THE EDITOR

2406 Macrophage activation syndrome as an initial presentation of systemic lupus erythematosus
Shi LJ, Guo Q, Li SG

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Consolato M Sergi, FRCP (C), MD, PhD, Professor, Department of Lab. Medicine and Pathology, University of Alberta, Edmonton T6G 2B7, Canada

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2019 Edition of Journal Citation Reports cites the 2018 impact factor for *WJCC* as 1.153 (5-year impact factor: N/A), ranking *WJCC* as 99 among 160 journals in Medicine, General and Internal (quartile in category Q3).

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Xia Xing*

Proofing Production Department Director: *Yun-Xiaojian Wu*

Responsible Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Semimonthly

EDITORS-IN-CHIEF
Dennis A Bloomfield, Bao-Gan Peng, Sandro Vento

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
June 6, 2020

COPYRIGHT
© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2020 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2020 June 6; 8(11): 2127-2136

DOI: 10.12998/wjcc.v8.i11.2127

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Case Control Study

Clinical prediction of complicated appendicitis: A case-control study utilizing logistic regression

Yosuke Sasaki, Fumiya Komatsu, Naoyasu Kashima, Takeshi Suzuki, Ikutaka Takemoto, Sho Kijima, Tadashi Maeda, Taito Miyazaki, Yoshiko Honda, Hiroaki Zai, Nagato Shimada, Kimihiko Funahashi, Yoshihisa Urita

ORCID number: Yosuke Sasaki (0000-0002-5290-4875); Fumiya Komatsu (0000-0003-3011-1089); Naoyasu Kashima (0000-0003-4650-432X); Takeshi Suzuki (0000-0002-5581-4779); Ikutaka Takemoto (0000-0002-3020-7972); Sho Kijima (0000-0001-9599-8405); Tadashi Maeda (0000-0002-9475-8909); Taito Miyazaki (0000-0001-7239-8677); Yoshiko Honda (0000-0002-9939-1587); Hiroaki Zai (0000-0002-2957-0213); Nagato Shimada (0000-0002-1482-9405); Kimihiko Funahashi (0000-0001-5158-9378); Yoshihisa Urita (0000-0003-1740-0572).

Author contributions: Sasaki Y designed the research, collected data, and wrote the manuscript; Komatsu F, Kashima N, and Suzuki T collected data with Sasaki Y; Takemoto I and Kijima S assisted in data collection; Maeda T and Miyazaki T advised on the discussion as experts of infectious diseases; Honda Y, Shimada N, and Funahashi K advised on the discussion as surgeons; and Urita Y supervised the research and advised on statistical analyses.

Institutional review board statement: The ethics committee of Toho University Medical Center Omori Hospital approved the study's protocol (M19023).

Informed consent statement: The center's ethics committee approved the waiver of individual informed consent subject to public

Yosuke Sasaki, Fumiya Komatsu, Naoyasu Kashima, Takeshi Suzuki, Ikutaka Takemoto, Sho Kijima, Tadashi Maeda, Taito Miyazaki, Yoshiko Honda, Nagato Shimada, Yoshihisa Urita, Department of General Medicine and Emergency Care, Toho University School of Medicine, Ota-ku, Tokyo 143-8541, Japan

Kimihiko Funahashi, Department of General and Gastroenterological Surgery, Toho University Omori Medical Center, Otaku, Tokyo 143-8541, Japan

Corresponding author: Yosuke Sasaki, MD, PhD, Assistant Professor, Department of General Medicine and Emergency Care, Toho University School of Medicine, Omori Hospital, 6-11-1 Omori-Nishi, Ota-Ku, Tokyo 143-8541, Japan. yousuke.sasaki@med.toho-u.ac.jp

Abstract

BACKGROUND

Since high-quality evidence on conservative treatment of acute appendicitis using antibiotics has increased, differentiation of patients with complicated appendicitis (CA) from those with simple appendicitis (SA) has become increasingly important. Previous studies have revealed that male gender, advanced age, comorbid conditions, prehospital delay, fever, and anorexia are risk factors of perforated appendicitis. Elevated serum C-reactive protein (CRP) level and hyponatremia have also been reported as predictive biomarkers of CA. However, confounding between various factors is problematic because most previous studies were limited to univariate analysis.

AIM

To evaluate non-laboratory and laboratory predictive factors of CA using logistic regression analyses.

METHODS

We performed an exploratory, single-center, retrospective case-control study that evaluated 198 patients (83.9%) with SA and 38 patients (16.1%) with CA. Diagnoses were confirmed by computed tomography images for all cases. We compared age, sex, onset-to-visit interval, epigastric/periumbilical pain, right lower quadrant pain, nausea/vomiting, diarrhea, anorexia, medical history (of previous non-surgically treated appendicitis, diabetes, hypertension, dyslipidemia, liver cirrhosis, hemodialysis, chronic lung diseases, malignant tumors, immunosuppressant use, and antiplatelet use), vital signs, physical

announcement of the research because of the retrospective and noninvasive study design.

Conflict-of-interest statement: None.

STROBE statement: The authors have read the STROBE Statement checklist of items, and the manuscript was prepared and revised according to the STROBE Statement.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: February 13, 2020
Peer-review started: February 13, 2020
First decision: April 1, 2020
Revised: April 8, 2020
Accepted: May 13, 2020
Article in press: May 13, 2020
Published online: June 6, 2020

P-Reviewer: Kristek J, Shiryajev Y
S-Editor: Wang JL
L-Editor: A
E-Editor: Liu MY

findings, and laboratory data to select the explanatory variates for logistic regression. Based on the univariate comparisons, we performed logistic regression for clinical differentiation between CA and SA using only non-laboratory factors and also including both non-laboratory and laboratory factors.

RESULTS

The 236 eligible patients consisted of 198 patients (83.9%) with SA and 38 patients (16.1%) with CA. The median ages were 34 years old [interquartile ranges (IR), 24-45 years] in the SA group and 49 years old (IR, 35-63 years) in the CA group ($P < 0.001$). The median onset-to-visit interval was 1 d (IR, 0-1) and 1 d (IR, 1-2) in the SA and CA groups, respectively ($P < 0.001$). Heart rate, body temperature, and serum CRP level in the CA group were significantly higher than in the SA group; glomerular filtration rate and serum sodium were significantly lower in the CA group. Anorexia was significantly more prevalent in the CA group. The regression model including age, onset-to-visit interval, anorexia, tachycardia, and fever as non-laboratory predictive factors of CA (Model 1) showed that age ≥ 65 years old, longer onset-to-visit interval, and anorexia had significantly high odds ratios. The logistic regression for prediction of CA including age, onset-to-visit interval, anorexia, serum CRP level, hyponatremia (serum sodium < 135 mEq/L), and glomerular filtration rate < 60 mL/min/1.73 m^2 (Model 2) showed that only elevated CRP levels had significantly high odds ratios. Under the curve values of receiver operating characteristics curves of each regression model were 0.74 for Model 1 and 0.87 for Model 2.

CONCLUSION

Our logistic regression analysis on differentiating factors of CA from SA showed that high CRP level was a strong dose-dependent predictor of CA.

Key words: Acute abdomen; Abscess; Appendicitis; C-reactive protein; Forecasting; Intestinal perforation

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Given few multivariate analyses on C-reactive protein (CRP) as a predictor of complicated appendicitis (CA), we performed a logistic regression analysis of 198 patients with simple appendicitis and 38 patients with CA. The regression model including non-laboratory factors of CA showed that age ≥ 65 years old, longer onset-to-visit interval, and anorexia had significantly high odds ratios. The logistic regression that additionally included laboratory data showed that only elevated CRP levels had significantly high odds ratios, which suggested that high CRP level can be a dose-dependent predictor of CA.

Citation: Sasaki Y, Komatsu F, Kashima N, Suzuki T, Takemoto I, Kijima S, Maeda T, Miyazaki T, Honda Y, Zai H, Shimada N, Funahashi K, Urita Y. Clinical prediction of complicated appendicitis: A case-control study utilizing logistic regression. *World J Clin Cases* 2020; 8(11): 2127-2136
URL: https://www.wjgnet.com/2307-8960/full/v8/i11/2127.htm
DOI: https://dx.doi.org/10.12998/wjcc.v8.i11.2127

INTRODUCTION

Emergent appendectomy has been the only standard form of management for acute appendicitis (AA). However, several well-organized, multi-center, randomized trials comparing conservative management with antibiotics to appendectomy have shown favorable or comparable results[1-4]. Based on these findings, a recent meta-analysis reported that conservative treatment can be considered an alternative to appendectomy[5]. Because conservative management of AA will become more popular thanks to this recent evidence, differentiation of high-risk patients with complicated appendicitis (CA) such as gangrenous appendicitis, perforated appendicitis, or cases complicated with intra-abdominal abscess from simple appendicitis (SA) has become

increasingly important. Many studies on predictive factors of CA in both pediatric and adult patients have revealed that male gender, advanced age, comorbid conditions, prehospital delay, fever, anorexia, leukocytosis, elevated serum C-reactive protein (CRP) level, and hyponatremia are risk factors for perforated appendicitis[6-11]. However, confounding between various factors is problematic because most previous studies were limited to univariate analysis[12-16]. Thus, the aim of the present study was to evaluate clinical predictive factors of CA including non-laboratory and laboratory data using logistic regression analyses.

MATERIALS AND METHODS

Design and patients

In this single-center, retrospective case-control study, we evaluated medical records from patients of the Toho University Medical Center Omori Hospital, which has 948 beds and is located in Tokyo, Japan. The center's ethics committee approved the study's protocol (M19023). We initially considered all patients who were ≥ 16 years old and hospitalized for AA between January 2012 and December 2016 from the discharge summary database of the hospital (Patients younger than 16 years old are treated by pediatricians in the hospital). Subsequently, the authors (Sasaki Y, Komatsu F, and Kashima N) reviewed the medical records of all the potential patients and manually collected pertinent data. We ultimately included only patients who were diagnosed as AA by computed tomography (CT) scans instead of surgical or pathological findings because of the low proportion of the patients treated with appendectomy according to the management policy of surgeons at our hospital as an advanced medical center (We will discuss the reason for the low proportion of operated patients in the Discussion section). We divided the enrolled patients into SA and CA groups based on the findings of the CT scan and ultrasound as follows: Patients were diagnosed with SA if they were clinically diagnosed with AA and had radiological/sonographical findings compatible with appendicitis catarrhalis or appendicitis phlegmonosa such as swelling of appendicitis and inflammatory findings of adjacent adipose tissue without any of the following findings of CA; patients were diagnosed with CA if they had gangrenous appendicitis, perforated appendicitis, or appendicitis complicated with an intra-abdominal abscess. All CT findings were reviewed by several different radiologists and surgeons. Gastroenterologists and surgeons reviewed all sonographic findings. These reviewing processes were timely or retrospectively performed within 48 h after the imaging studies.

Study variables

The patients' records were searched to collect data from their first visit, such as age, sex, time interval from the onset of symptoms until the time of the visit (onset-to-visit interval), epigastric/periumbilical pain, right lower quadrant pain, nausea/vomiting, diarrhea, anorexia, past medical history (of previous AA treated without appendectomy, diabetes, hypertension, hyperlipidemia, liver cirrhosis, hemodialysis, chronic lung diseases, malignant tumors, immunosuppressant use, and antiplatelet use), body temperature, blood pressure, heart rate, right lower quadrant tenderness, peritoneal signs, leukocyte count, glomerular filtration rate (GFR), serum CRP level, and serum alanine aminotransferase level, along with findings of CT scan and ultrasound at admission. We regarded clinical symptoms including pain, nausea/vomiting, diarrhea, and anorexia as positive if the patients complained of these symptoms at initial history taking.

Categorization of continuous variables

All continuous variables except for onset-to-visit interval were categorized for statistical analyses as follows: We defined patient as old if his/her age was ≥ 65 years according to previous researches[17]. Fever was defined as an axillary measured body temperature of ≥ 38.0°C based on a previous study on the diagnosis of acute appendicitis[18]. Shock was defined as systolic blood pressure < 12.0 kPa (< 90 mmHg)[19]. Tachycardia was defined as a heart rate ≥ 100 beats/minute. Leukocytosis was defined as a leukocyte count > 10000/mm^3 based on a previous study on the diagnosis of appendicitis[20]. Elevated liver enzyme was defined as alanine aminotransferase > 29 IU/L[21]. Renal dysfunction was defined as a GFR < 60 mL/min/1.73 m^2 based on the guidelines of chronic kidney diseases[22]. CRP level was categorized into the following three groups: 0.0 to 1.0 mg/dL, 1.1 to 5.0 mg/dL, and over 5 mg/dL, based on the distribution of CRP level of the participants and previous studies on the cut-off value of CRP[8,12,14,15,23,24]. Hyponatremia was defined as serum sodium < 135 mEq/L[25].

Statistical analyses

Univariate comparisons: We compared all evaluated patient characteristics with SA and CA to select candidates for independent variables of logistic regressions. The χ^2 test was used for all dichotomous/categorical variables, while the Wilcoxon rank-sum test was used for continuous variables because of their skewed distributions.

Logistic regression model: Logistic regression analysis was subsequently performed based on the results of the univariate analyses. As mentioned above, we converted all continuous variables, except for onset-to-visit interval, into categorized variables for logistic regression. To evaluate predictive factors of CA that were available prior to obtain laboratory results, we initially performed logistic regression using non-laboratory data including patient profiles, symptoms, and physical findings as explanatory variables (Model 1). Subsequently, we performed logistic regression using both laboratory factors and non-laboratory factors that were significant in Model 1 as explanatory variables (Model 2). We examined the variance inflation factors (VIF) to evaluate the multicollinearity of the regression models.

Discrimination, calibration, and internal validation of the regression model: We performed discrimination of the regression models by creating a receiver operating characteristic (ROC) curve. The differentiation abilities of the two regression models were compared using the methods described by DeLong *et al*[26]. We also calibrated the models using the Hosmer–Lemeshow (HL) goodness-of-fit test. Finally, we performed internal validation using bootstrap methods involving 100 samples tested five times.

All statistical analyses were performed using Stata/IC software (version 15.1; Stata Corp, United States). A P value < 0.05 was considered statistically significant. The statistical methods of this study were reviewed by Takuhiro Moromizato from the Internal Medicine Department, Renal and Rheumatology Division at the Okinawa Nanbu Medical Center and Children's Medical Center.

RESULTS

The 236 eligible patients consisted of 198 patients (83.9%) with SA and 38 patients (16.1%) with CA. Patient characteristics and the results of the univariate analyses are shown in Table 1. There were no patients with liver cirrhosis, receiving hemodialysis, and taking antiplatelets in either of the groups. Patients ≥ 65 years old were significantly prevalent in the CA group; the median ages were 34 years old [interquartile ranges (IR), 24-45 years] in the SA group and 49 years old (IR, 35-63 years) in the CA group (P < 0.001). The median onset-to-visit interval was 1 d (IR, 0-1) and 1 d (IR, 1-2) in the SA and CA groups, respectively (P < 0.001). Because even most cases with CA were conservatively treated with antibiotics in our hospital, appendectomy was performed in only 22/198 patients (11.1%) and 12/38 patients (31.6%) in the SA and CA groups, respectively (P = 0.001). Judgment on indication, reason, and selection of operated patients were based on the expert opinion of the surgeons on each individual case. In 34 operated patients, complications such as abscess formation, perforation, and wall necrosis (gangrenous appendicitis) were pathologically verified in 15/22 cases (68.2%) and 11/12 cases (91.7%) in the SA and CA groups, respectively. According to these results, sensitivity and specificity for differentiation of SA and CA based on the CT findings were 91.7% and 31.8%, respectively.

As shown in Table 1, heart rate, body temperature, and serum CRP level in the CA group were significantly higher than in the SA group (Table 1). On the other hand, GFR and serum sodium level were significantly lower in the CA group (Table 1). The prevalence of anorexia was significantly higher in the CA group compared to the SA group (Table 1).

Based on the results of univariate comparisons, we selected age, onset-to-visit interval, anorexia, tachycardia, and fever as non-laboratory predictive factors of CA and performed a logistic regression (Model 1). The regression model showed that advanced age (≥ 65 years old), longer onset-to-visit interval, and anorexia had significantly high ORs (Figure 1A). The logistic regression for prediction of CA including age, onset-to-visit interval, anorexia, serum CRP level, renal dysfunction (defined as GFR < 60 mL/min/1.73 m^2), and hyponatremia (defined as serum sodium < 135 mEq/L) showed that only elevated CRP levels had significantly high ORs (Figure 1B). The methods of DeLong *et al*[26] revealed that the area under the curve (AUC) values were 0.74 for Model 1 and 0.87 for Model 2 (Figure 2). Although the discrimination ability of Model 2 was better than that of Model 1, both models were considered moderately accurate because the AUC values were > 0.7.

The Model 1 regression showed good calibration (HL χ^2: 5.88, P = 0.437), and there

Table 1 Patient characteristics, *n* (%)

Characteristics	All (*n* = 236)	SA (*n* = 198)	CA (*n* = 38)	*P* value
Age ≥ 65 (yr)	17 (7.2)	10 (5.1)	7 (18.4)	0.001[a]
Age (yr)	35.5 (25-50.5)	34 (24-45)	49 (35-63)	< 0.00[a]
Male	129 (54.7)	105 (53.0)	24 (63.2)	0.251
Onset-to-visit interval (d)	1 (0-1)	1 (0-1)	1 (1-2)	< 0.001[a]
Epigastric/periumbilical pain	119 (50.4)	104 (52.5)	15 (39.5)	0.141
RLQ pain	171 (72.5)	141 (71.2)	30 (79.0)	0.328
Nausea/vomiting	123 (52.1)	106 (53.5)	17 (44.7)	0.32
Diarrhea	46 (19.5)	38 (19.2)	8 (21.1)	0.791
Anorexia	64 (27.1)	48 (24.2)	16 (42.1)	0.023[a]
Previous appendicitis	32 (13.6)	30 (15.2)	2 (5.3)	0.103
Diabetes mellitus	11 (4.7)	7 (3.5)	4 (10.5)	0.061
Hypertension	24 (10.2)	20 (10.1)	4 (10.5)	0.937
Dyslipidemia	21 (8.9)	16 (8.1)	5 (13.2)	0.314
Chronic lung diseases	2 (0.9)	1 (0.5)	1 (2.6)	0.19
Malignancy	1 (0.4)	1 (0.5)	0	0.661
Immunosuppressant use	1 (0.4)	1 (0.5)	0	0.661
Fever (≥ 38.0 °C)	34 (14.4)	23 (11.6)	11 (29.0)	0.005[a]
Body temperature (°C)	37.0 (36.7-37.5)	37.0 (36.6-37.4)	37.5 (37.1-37.9)	< 0.001[a]
Tachycardia	18 (7.6)	11 (5.6)	7 (18.4)	0.006[a]
Heart rate (beats/min)	78 (68-88)	76 (66-85)	85 (76-96)	< 0.001[a]
Shock	6 (2.5)	5 (2.5)	1 (2.6)	0.97
RLQ tenderness	230 (97.5)	192 (97.0)	38 (100)	0.277
Peritoneal signs	137 (58.1)	113 (57.1)	24 (63.2)	0.486
Leukocytosis	177 (75.0)	146 (73.7)	31 (81.6)	0.307
Leukocyte count ($10^3/mm^3$)	12.6 (10.1-15.2)	12.6 (10.0-15.2)	13.2 (10.8-15.4)	0.497
CRP (mg/dL)	1.1 (0.2-4.1)	0.7 (0.2-2.7)	8.8 (3.8-19.0)	< 0.001[a]
GFR < 60 mL/min/1.73 m^2	6 (2.5)	1 (0.5)	3 (13.2)	< 0.001[a]
GFR (mL/min/1.73 m^2)	120.7 (101.6-140.4)	123.8 (103.7-142.9)	105.1 (82.83-122.1)	0.007[a]
Serum sodium (mEq/L)	139 (137-140)	139 (138-140)	137.5 (136-139)	0.003[a]
Hyponatremia	9 (3.8)	5 (2.5)	4 (10.5)	0.019[a]
ALT > 29 IU/L	38 (16.1)	30 (15.2)	8 (21.1)	0.365
Appendectomy	34 (14.4)	22 (11.1)	12 (31.6)	0.001[a]

[a]*P* < 0.05. ALT: Alanine aminotransferase; CA: Complicated appendicitis; CRP: C-reactive protein; GFR: Glomerular filtration rate; RLQ: Right lower quadrant; SA: Simple appendicitis.

was no multicollinearity because the VIF of all explanatory variables was 1.2 or less and the mean VIF was 1.07. Optimism, as calculated by the bootstrap method, was 2.0 × 10^{-6}. Model 2 also showed good calibration (HL χ^2: 7.08, *P* value = 0.420) and there was no multicollinearity (all VIFs < 1.3, mean VIF = 1.12). Optimism was 0.0001.

Because CRP was the only significant predictive factor of CA in our regression model (Model 2), we additionally performed ROC analyses to evaluate the discrimination ability of serum CRP level for the prediction of CA, which revealed the AUC value was 0.85. The sensitivity and specificity of each serum CRP value were as follows: Sensitivity and specificity of 94.7% and 55.1 % when was CRP ≥ 1.0 mg/dL and sensitivity and specificity of 68.4% and 86.9% when was CRP ≥ 4.9 (Figure 3).

DISCUSSION

We performed a single-center, retrospective cohort study to evaluate clinical predictive factors of CA using univariate comparison and logistic regression. Univariate comparisons showed that advanced age, longer onset-to-visit interval, anorexia, tachycardia, fever, elevated CRP level, renal dysfunction, and hyponatremia were significantly more prevalent in the CA group than in the SA group. Logistic regression on non-laboratory factors of CA showed that advanced age (≥ 65 years

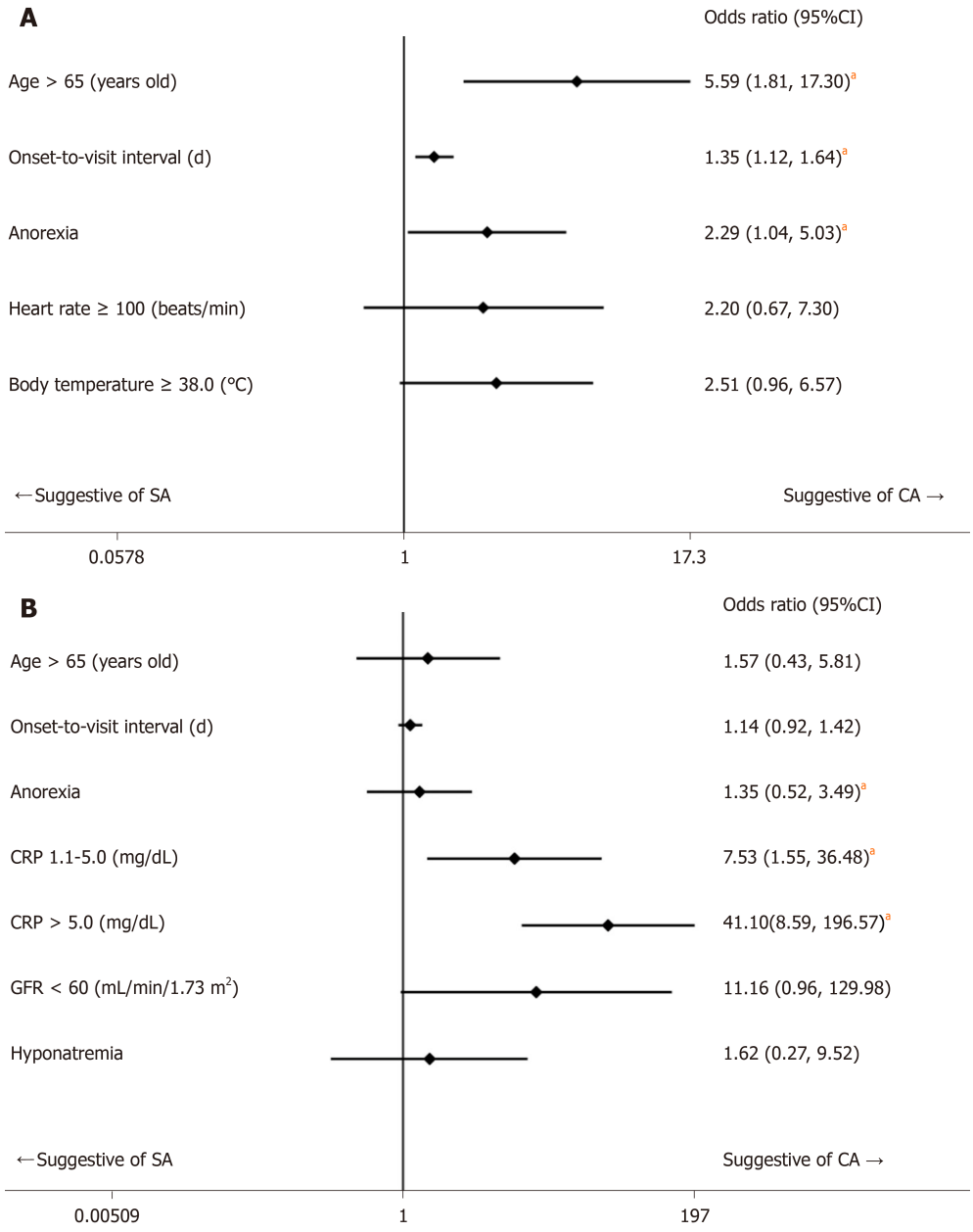

Figure 1 Forest plot of the logistic regression in Model 1 and Model 2. A: Model 1 (Non-laboratory factors only). [a]Age > 65 years old, longer onset-to-visit interval, and anorexia have significantly high odds ratios, which suggests that complicated appendicitis is more likely; B: Model 2 (including laboratory factors). [a]Only high CRP values have significantly high odds ratios, which suggests that complicated appendicitis is more likely. The odds ratio increases in proportion to the CRP value. CA: Complicated appendicitis; CI: Confidence interval; SA: Simple appendicitis; CRP: C-reactive protein; GFR: Glomerular filtration rate.

old), longer onset-to-visit interval, and anorexia had significantly high ORs (Model 1). Logistic regression including laboratory factors showed that only elevated CRP level had a significantly high OR (Model 2). Furthermore, the ORs increased in proportion to a rise in CRP level (Model 2).

In terms of the univariate analysis, our study showed that advanced age was a significant predictor of CA, which is compatible with the findings of previous studies[6]. On the other hand, male gender was not a significant predictor of CA in our study; nonetheless, male gender has been reported as a risk factor of CA[6,7]. The results of the significance of the preoperative interval as a predictor of CA are inconsistent. Some studies showed that longer durations before operation or admission are risk factors for perforation[7,8]. However, another high-quality study using logistic regression showed that the preoperative interval was insignificant[6]. In our study, the onset-to-visit interval was a statistically significant predictor of CA. However, because we could not evaluate the difference by the order of hours in this retrospective study and the medians were the same (1 d) in both the SA and CA groups, the clinical significance was limited. Although only a few studies have been conducted, hyponatremia has been reported as a predictor of CA[9,11]. We believe that

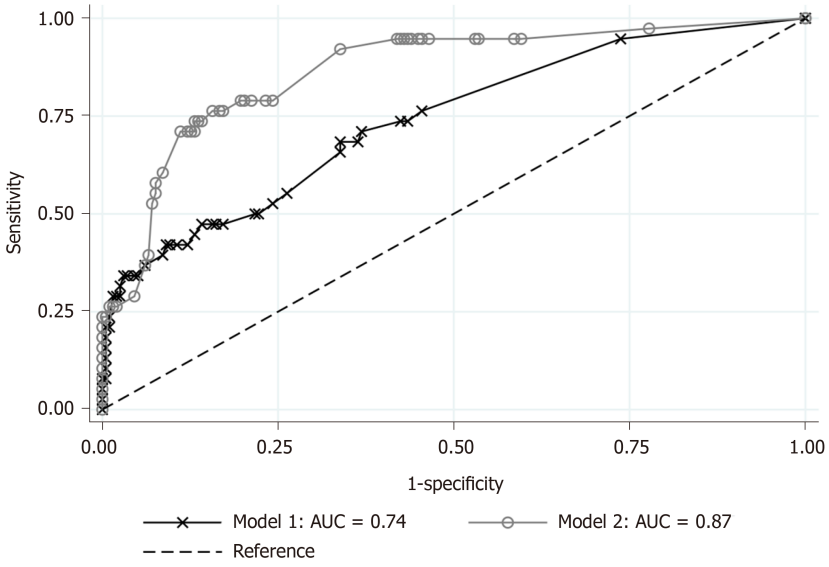

Figure 2 Comparison of the regression models for prediction of complicated appendicitis. The receiver operating characteristic curves are shown for Model 1 (explanatory variables: Age > 65 years old, onset-to-visit interval, anorexia, tachycardia, and fever) and Model 2 (explanatory variables: Age > 65 years old, onset-to-visit interval, anorexia, serum C-reactive protein level, renal dysfunction, and hyponatremia). Area under the curve of the receiver operating characteristic curve for Model 2 is superior to that of Model 1 (0.87 *vs* 0.74).

our study adds new evidence in support of these previous studies.

To the best of our knowledge, significant differences in anorexia, tachycardia, and renal dysfunction in our study are previously unreported findings because previous analyses on risk factors of CA were limited to patient profiles, underlying conditions, and inflammatory biomarkers[6-8].

Our study showed that CRP was the single significant predictor of CA in proportion to the value of serum CRP level. Furthermore, ROC analysis showed that serum CRP level had a high discrimination ability for the prediction of CA (AUC = 0.85). Our results are compatible with those of previous studies, which have shown that CRP is a useful predictor of CA[14-16,23,24,27]. Previously, the proposed cut-off values of CRP ranged among studies from 0.3 mg/dL to 5.1 mg/dL; one previous study revealed CRP > 0.3 mg/dL was associated with CA[15]. Other studies proposed a cut-off value of around 1.0 mg/dL[12,16]. Using logistic regression, another study showed that CRP > 5.1 mg/dL had an OR as high as 3.076[23]. In addition to these previous studies, our study revealed a dose-dependent increase of the OR predicting CA was associated with the CRP value. Our study also indicated that CRP > 1.0 mg/dL, a relatively low cut-off value, was useful for predicting CA. We believe that our study provides important knowledge on the usefulness of CRP for the clinical prediction of CA because a previous study using multivariate analysis that included both non-laboratory and laboratory factors was limited[23]. A previous multivariate analysis using logistic regression showed that male gender, age, comorbid conditions, and lack of insurance were significant predictors of perforated appendicitis. However, our logistic regression showed CRP elevation was a single significant predictor of CA. Given that previous studies did not include CRP as an explanatory variable, other risk factors are adjusted by CRP, a strong laboratory predictor, in the present study.

Our study has three major limitations. First, because the present study was a retrospective, case-controlled study using medical records, we could not collect some previously reported important information, such as migration of abdominal pain or other components of the Alvarado score[20]. As mentioned above, we also could not evaluate the precise onset-to-visit interval by the order of hours.

Second, despite the fact that most of the previous studies distinguished between CA and SA based on surgical or pathological findings, we differentiated CA from SA based on the findings of CT scan instead of pathological or surgical findings in the present study because our surgeons aggressively selected a combination of conservative therapy with antibiotics and subsequent elective appendectomy (interval appendectomy)[28] as a form of advanced medical care, and we could therefore not evaluate surgical and pathological findings of the resected appendix in most cases due to the low proportion of appendectomies, which were performed in only 11.1% and 31.6% of patients in the SA and CA groups, respectively. The discrepancy between

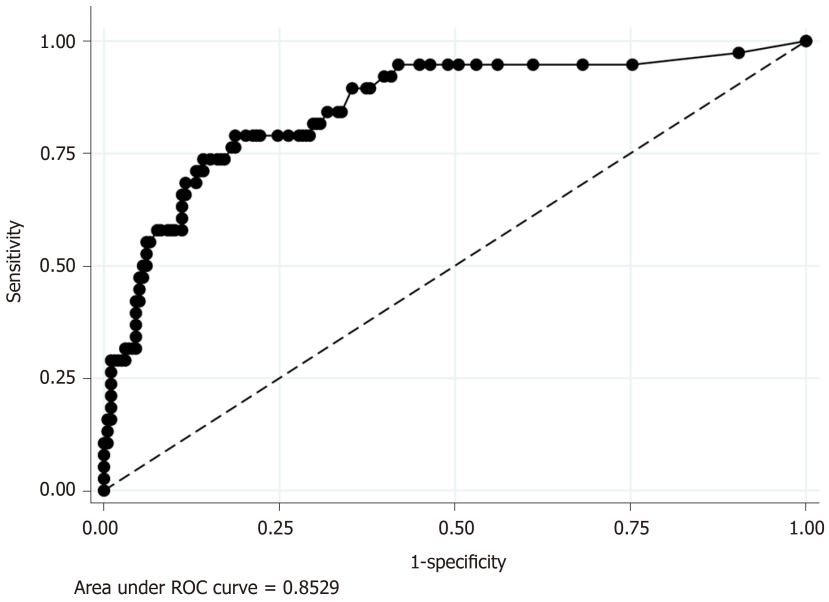

Figure 3 Receiver operating characteristic curve of serum C-reactive protein level for prediction of complicated appendicitis. Receiver operating characteristic curve of serum C-reactive protein (CRP) level for prediction of complicated appendicitis revealed an area under the curve value of 0.85. The sensitivity and specificity are 94.7% and 55.1% when CRP ≥ was 1.0 mg/dL and 68.4% and 86.9% when CRP was ≥ 4.9 mg/dL, respectively.

radiological findings and surgical/pathological findings diminished the reliability of the study although the sensitivity was as high as 91.7%. We should note that our study was conducted under somewhat unique circumstances: Conservative management for AA that we routinely performed in our hospital is not the global standard management of AA (*i.e.*, despite the fact that non-operative management of AA is increasingly accepted as an option of management of AA in some patents, such as those who prefer non-operative management or high-risk patients for operation[29], emergent or urgent appendectomy is still the global standard management in most cases)[5]. However, because the evidence on conservative management and interval appendectomy is increasing, as mentioned above, our differentiation of SA and CA based on radiological findings as a surrogate for surgical or pathological findings may become more clinically significant.

The third limitation is the small sample size, especially for cases with CA. This may decrease the statistical reliability of logistic regression models that include five explanatory variables.

In conclusion, our study, which utilized logistic regression analysis on differentiating factors of CA from SA, showed that high CRP level was a strong dose-dependent predictor of CA. Because of the scarcity of the studies using multivariate analysis on the prediction of CA, further study is needed to confirm our findings.

ARTICLE HIGHLIGHTS

Research background

Because evidence on conservative treatment of acute appendicitis has increased, differentiation of patients with complicated appendicitis (CA) from those with simple appendicitis (SA) has become increasingly important. Previous studies have revealed that male gender, advanced age, comorbid conditions, prehospital delay, fever, and anorexia are risk factors of perforated appendicitis. Elevated serum C-reactive protein (CRP) level and hyponatremia have also been reported as predictive biomarkers of CA.

Research motivation

Confounding between various factors is problematic because most previous studies were univariate analyses. Thus, we performed a study using logistic regression analyses.

Research objectives

The objective of the study was to evaluate non-laboratory and laboratory predictive factors of CA using logistic regression analyses using logistic regression analyses.

Research methods

We performed a single-center, retrospective case-control study that evaluated 198 patients

(83.9%) with SA and 38 patients (16.1%) with CA. Diagnoses were confirmed by computed tomography images for all cases. We compared age, sex, clinical symptoms, past medical history, vital signs, physical findings, and laboratory data. Based on the comparisons, we performed logistic regression for clinical differentiation between CA and SA using only non-laboratory factors and also including both non-laboratory and laboratory factors.

Research results

The 236 eligible patients consisted of 198 patients (83.9%) with SA and 38 patients (16.1%) with CA. The median ages were 34 years old in the SA group and 49 years old in the CA group. The median onset-to-visit interval was 1 d and 1 d in the SA and CA groups, respectively. Heart rate, body temperature, and serum CRP level in the CA group were significantly higher than in the SA group; glomerular filtration rate (GFR) and serum sodium were significantly lower in the CA group. Anorexia was significantly more prevalent in the CA group. The regression model including age, onset-to-visit interval, anorexia, tachycardia, and fever as non-laboratory predictive factors of CA (Model 1) showed that age ≥ 65 years old, longer onset-to-visit interval, and anorexia had significantly high odds ratios. The logistic regression for prediction of CA including age, onset-to-visit interval, anorexia, serum CRP level, hyponatremia, and glomerular filtration rate < 60 mL/min/1.73 m^2 (Model 2) showed that only elevated CRP levels had significantly high odds ratios.

Research conclusions

Our logistic regression analysis on differentiating factors of CA from SA showed that high CRP level was a strong dose-dependent predictor of CA.

ACKNOWLEDGEMENTS

We would like to acknowledge the excellent assistance of the staff of the Harvard Medical School Introduction to Clinical Research Training Japan and that of the Okinawa Asia Clinical Investigation Synergy (OACIS). Moreover, we would like to thank Dr. Takuhiro Moromizato (Internal Medicine Department, Renal and Rheumatology Division at the Okinawa Nanbu Medical Center and Children's Medical Center) for his assistance and review of the statistical analysis.

REFERENCES

1 **Eriksson S**, Granström L. Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis. *Br J Surg* 1995; **82**: 166-169 [PMID: 7749676 DOI: 10.1002/bjs.1800820207]
2 **Styrud J**, Eriksson S, Nilsson I, Ahlberg G, Haapaniemi S, Neovius G, Rex L, Badume I, Granström L. Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial. *World J Surg* 2006; **30**: 1033-1037 [PMID: 16736333 DOI: 10.1007/s00268-005-0304-6]
3 **Turhan AN**, Kapan S, Kütükçü E, Yiğitbaş H, Hatipoğlu S, Aygün E. Comparison of operative and non operative management of acute appendicitis. *Ulus Travma Acil Cerrahi Derg* 2009; **15**: 459-462 [PMID: 19779986]
4 **Hansson J**, Körner U, Khorram-Manesh A, Solberg A, Lundholm K. Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients. *Br J Surg* 2009; **96**: 473-481 [PMID: 19358184 DOI: 10.1002/bjs.6482]
5 **Wilms IM**, de Hoog DE, de Visser DC, Janzing HM. Appendectomy versus antibiotic treatment for acute appendicitis. *Cochrane Database Syst Rev* 2011; CD008359 [PMID: 22071846 DOI: 10.1002/14651858.cd008359.pub2]
6 **Drake FT**, Mottey NE, Farrokhi ET, Florence MG, Johnson MG, Mock C, Steele SR, Thirlby RC, Flum DR. Time to appendectomy and risk of perforation in acute appendicitis. *JAMA Surg* 2014; **149**: 837-844 [PMID: 24990687 DOI: 10.1001/jamasurg.2014.77]
7 **Sirikurnpiboon S**, Amornporncharoen S. Factors Associated with Perforated Appendicitis in Elderly Patients in a Tertiary Care Hospital. *Surg Res Pract* 2015; **2015**: 847681 [PMID: 26380377 DOI: 10.1155/2015/847681]
8 **Omari AH**, Khammash MR, Qasaimeh GR, Shammari AK, Yaseen MK, Hammori SK. Acute appendicitis in the elderly: risk factors for perforation. *World J Emerg Surg* 2014; **9**: 6 [PMID: 24428909 DOI: 10.1186/1749-7922-9-6]
9 **Kim DY**, Nassiri N, de Virgilio C, Ferebee MP, Kaji AH, Hamilton CE, Saltzman DJ. Association Between Hyponatremia and Complicated Appendicitis. *JAMA Surg* 2015; **150**: 911-912 [PMID: 26222325 DOI: 10.1001/jamasurg.2015.1258]
10 **Rentea RM**, Peter SDS, Snyder CL. Pediatric appendicitis: state of the art review. *Pediatr Surg Int* 2017; **33**: 269-283 [PMID: 27743024 DOI: 10.1007/s00383-016-3990-2]
11 **Pham XD**, Sullins VF, Kim DY, Range B, Kaji AH, de Virgilio CM, Lee SL. Factors predictive of complicated appendicitis in children. *J Surg Res* 2016; **206**: 62-66 [PMID: 27916376 DOI: 10.1016/j.jss.2016.07.023]
12 **Buyukbese Sarsu S**, Sarac F. Diagnostic Value of White Blood Cell and C-Reactive Protein in Pediatric Appendicitis. *Biomed Res Int* 2016; **2016**: 6508619 [PMID: 27274988 DOI: 10.1155/2016/6508619]
13 **Ozan E**, Ataç GK, Alişar K, Alhan A. Role of inflammatory markers in decreasing negative appendectomy rate: A study based on computed tomography findings. *Ulus Travma Acil Cerrahi Derg* 2017; **23**: 477-482 [PMID: 29115649 DOI: 10.5505/tjtes.2017.36605]
14 **Dal F**, Cicek Y, Pekmezci S, Kocazeybek B, Tokman HB, Konukoglu D, Şimşek O, Taner Z, Sirekbasan S, Uludağ SS. Role of Alvarado score and biological indicators of C-reactive protein, procalicitonin and neopterin in diagnosis of acute appendicitis. *Ulus Travma Acil Cerrahi Derg* 2019; **25**: 229-237 [PMID:

31135946 DOI: 10.5505/tjtes.2018.57362]
15 **Kim M**, Kim SJ, Cho HJ. International normalized ratio and serum C-reactive protein are feasible markers to predict complicated appendicitis. *World J Emerg Surg* 2016; **11**: 31 [PMID: 27330547 DOI: 10.1186/s13017-016-0081-6]
16 **Shogilev DJ**, Duus N, Odom SR, Shapiro NI. Diagnosing appendicitis: evidence-based review of the diagnostic approach in 2014. *West J Emerg Med* 2014; **15**: 859-871 [PMID: 25493136 DOI: 10.5811/westjem.2014.9.21568]
17 **Orimo H**, Ito H, Suzuki T, Araki A, Hosoi T, Sawabe M. Reviewing the definition of "elderly". *Geriatr Gerontol Int* 2006; **6**: 149-158 [DOI: 10.1111/j.1447-0594.2006.00341.x]
18 **Chen SC**, Chang KJ, Wei TC, Yu SC, Wang SM. Can cecal diverticulitis be differentiated from acute appendicitis? *J Formos Med Assoc* 1994; **93**: 263-265 [PMID: 7920071]
19 **Edelman DA**, White MT, Tyburski JG, Wilson RF. Post-traumatic hypotension: should systolic blood pressure of 90-109 mmHg be included? *Shock* 2007; **27**: 134-138 [PMID: 17224786 DOI: 10.1097/01.shk.0000239772.18151.18]
20 **Alvarado A**. A practical score for the early diagnosis of acute appendicitis. *Ann Emerg Med* 1986; **15**: 557-564 [PMID: 3963537 DOI: 10.1016/S0196-0644(86)80993-3]
21 **Kwo PY**, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol* 2017; **112**: 18-35 [PMID: 27995906 DOI: 10.1038/ajg.2016.517]
22 Chapter 1: Definition and classification of CKD. *Kidney Int Suppl (2011)* 2013; **3**: 19-62 [PMID: 25018975 DOI: 10.1038/kisup.2012.64]
23 **Yazar CKD**, Urfalioglu A, Bakacak M, Boran ÖF, Bülbüloğlu E. Efficacy of the Evaluation of Inflammatory Markers for the Reduction of Negative Appendectomy Rates. *Indian J Surg* 2018; **80**: 61-67 [PMID: 29581687 DOI: 10.1007/s12262-016-1558-y]
24 **Ahmed N**. C-Reactive Protein: An Aid For Diagnosis Of Acute Appendicitis. *J Ayub Med Coll Abbottabad* 2017; **29**: 250-253 [PMID: 28718241]
25 **Adrogué HJ**, Madias NE. Hyponatremia. *N Engl J Med* 2000; **342**: 1581-1589 [PMID: 10824078 DOI: 10.1056/NEJM200005253422107]
26 **DeLong ER**, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; **44**: 837-845 [PMID: 3203132]
27 **March B**, Leigh L, Brussius-Coelho M, Holmes M, Pockney P, Gani J. Can CRP velocity in right iliac fossa pain identify patients for intervention? A prospective observational cohort study. *Surgeon* 2019; **17**: 284-290 [PMID: 30309747 DOI: 10.1016/j.surge.2018.08.007]
28 **Perez KS**, Allen SR. Complicated appendicitis and considerations for interval appendectomy. *JAAPA* 2018; **31**: 35-41 [PMID: 30153202 DOI: 10.1097/01.JAA.0000544304.30954.40]
29 **Flum DR**. Clinical practice. Acute appendicitis--appendectomy or the "antibiotics first" strategy. *N Engl J Med* 2015; **372**: 1937-1943 [PMID: 25970051 DOI: 10.1056/NEJMcp1215006]

Published by Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2020 Baishideng Publishing Group Inc. All rights reserved.