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The relationships between sites of abdominal pain and the organs involved: A prospective observational study

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Abstract

Objectives: Abdominal pain is one of the most frequent chief complaints in primary care settings. The aim of the present study was to determine the positive and negative likelihood ratios of the relationships between the sites of abdominal pain and the organs involved.

Design: Prospective observational study.

Setting: A single tertiary center, a university hospital in Japan.

Participants: A total of 2591 new outpatients visited the Department of General Medicine at a university hospital from April 2017 to March 2018. Of these, 326 patients aged ≥20 years with abdominal pain were enrolled.

Results: Sites of abdominal pain were classified into 11 categories including 9 different abdominal sections, "generalized abdomen", and "site-indeterminate". The positive likelihood ratios between "right subcostal" and "liver and biliary tract"; between "right subcostal" and "musculoskeletal" ;between "epigastric" and "esophagus, stomach, and duodenum"; between "right or left flank" and "urinary tract"; between "left flank" and "dermatological"; and between "mid-lower" and "intestinal" ranged from 2.17 to 4.14. The positive likelihood ratios between "epigastric" and "urinary tract"; between "mid-lower" and "liver and biliary tract"; between "periumbilical" and "urinary tract"; and between "generalized abdomen" and "esophagus, stomach, and duodenum" were low, ranging from 0.17 to 0.25. The negative likelihood ratios ranged 0.5–1.5 excluding the relationship

between “left flank” and “dermatological.”

Conclusion: The presence of pain at right subcostal, epigastric, right or left flank, and mid-lower sites might be useful for identifying the organs involved. Additionally, the presence of pain at mid-lower, epigastric, periumbilical, and generalized abdominal sites might be helpful for denying the involvement of some organs. Some sites of abdominal pain can be indicative of the organs involved.

Keywords: abdominal pain site, organ involved, positive likelihood ratio, negative likelihood ratio, prospective observational study

Strengths and limitations of this study

- This was a prospective observational study about the relationships between the sites of abdominal pain and the organs involved.
- No prospective studies similar to the present study have been published since 1997.
- Some sites of abdominal pain may be useful for elucidating the organs involved.
- This was a single-center observational study, and the setting may have resulted in some sampling bias.

Introduction

Abdominal pain is one of the most frequent chief complaints in primary care settings, accounting for 5%–10% of visits to emergency departments.[1-4] Diseases causing abdominal pain range from mild conditions cured by conservative medical treatments alone to severe acute diseases requiring emergency surgery.[1,5-7] Given the possibility of severe disease requiring urgent treatment, it is vital that physicians make accurate and expeditious diagnoses.[8] In the process of making a diagnosis, history taking and physical examinations can prove decisive and crucial to the prognosis. The sites of abdominal pain can be extremely important because some are significantly associated with potentially serious diseases, such as McBurney's point pain with acute appendicitis and right subcostal pain with acute cholecystitis.[9,10]

To our knowledge, no studies focusing on the relationships between the sites of abdominal pain and the organs involved have been published since 1997.[1] However, it is certain that our capability to make an accurate diagnosis of abdominal pain has remarkably improved because of marked advancements of medical technologies such as imaging modalities including computed tomography (CT) and magnetic resonance imaging (MRI) in the last two decades.[11,12] In addition, in Japan, the epidemiology of conditions causing abdominal pain has changed in conjunction with aging of the population, as well as westernization of lifestyles.[13-15] Therefore, it makes strategic sense to examine current

relationships between the sites of abdominal pain and the organs involved two decades after the most relevant previous study.[1] In the present study, the relationships between the sites of abdominal pain and the organs involved in the underlying condition were investigated using positive likelihood ratios (PLRs) and negative likelihood ratios (NLRs).

Methods

Study design and patients

The present investigation was a single hospital-based prospective observational study conducted from April 2017 to March 2018. All new outpatients aged ≥20 years were enrolled, who visited the Department of General Medicine at Saga University Hospital in Japan with abdominal pain as a chief complaint or other symptoms excluding the chief complaint. They were initially seen by general physicians working in the department. Consenting patients were included regardless of whether they presented during the day or outside normal office hours, (*i.e.*, the emergency room for walk-in patients), but patients who utilized emergency service systems such as an ambulance or medical helicopter were excluded from the study. Comparative incidences of abdominal pain were evaluated, and then the organs and causative conditions involved were assessed. Statistical relationships between the sites of abdominal pain and the organs involved were then calculated. The present study was registered at https://www.umin.ac.jp as UMIN000037686. The design was assessed using a reporting checklist based on the Standards for Reporting of Diagnostic Accuracy (STARD) guidelines. [16]

Setting

The study was conducted at the Department of General Medicine at Saga University

Hospital in Saga prefecture, which is located in southern Japan and which has a population of 800,000. The hospital is open during the day and outside normal office hours (as an emergency room for walk-in patients).

Data and data sources

Physicians who initially saw the patients completed a document template containing survey items designed and prepared in advance. Survey items recorded at the first patient visit included age, sex, the date and time (daytime or outside normal office hours) of the visit, residence status (alone or without housemates), referral from another doctor (yes or no), sites of abdominal pain, characteristics of abdominal pain (intermittent or persistent pain, levels of abdominal pain, presence or absence of peritoneal signs), the types of examinations, and management decided at the first visit. Patients who lived in nursing-care facilities were included in the "with housemates" group. Sites of abdominal pain were classified into 11 categories including 9 different abdominal sections (right or left subcostal, right or left flank, right or left lower, epigastric, periumbilical, and mid-lower), "generalized abdomen", and "site-indeterminate". The types of examinations included blood and/or urinary tests, blood gas analysis, chest or abdominal X-ray including kidney ureter bladder (KUB), ultrasonography (US), CT, MRI including magnetic resonance cholangiopancreatography (MRCP), electrocardiography, esophagogastroduodenoscopy (EGD), and colonoscopy (CS). At the

"more than 3 months after the initial visit" time point, the final diagnoses and the organs involved were determined according to the gold standard.

Gold standard for making definitive diagnoses or identifying the organ involved

Two physicians independently made diagnoses for individual patients based on the classification of the International Statistical Classification of Diseases and Related Health Problems-10 using all information in the health records after more than 3 months from their first visits, including onset, symptoms, time course, underlying diseases, past history, vital signs, characteristics of abdominal pain, and findings of laboratory or imaging studies. Malignant diseases were diagnosed using the findings of imaging studies or pathological findings including cytology, as well as data from histopathological examinations of specimens acquired via biopsy or surgery. When the same diagnosis was made by both physicians, the diagnosis was set as the final diagnosis. When different diagnoses were made, the final diagnosis was determined through discussion among three physicians, including the aforementioned two physicians plus a third physician from our department. In cases in which the final diagnosis was unknown because the patient had only visited the department once without a definitive diagnosis being reached on that date, phone calls were made to the patients themselves or their family members more than 3 months after their first visit to ascertain the course of symptoms, visits to another hospital, and/or the results of examinations at other

hospitals and diagnoses made there. When the patients could not be reached by telephone, the final diagnosis was determined through discussion among the three physicians. The organs involved, which could overlap with more than two other organs, were determined on the basis of the final diagnoses. We classified the final diagnoses into 11 categories: "Esophagus, stomach, and duodenum", "Liver and biliary tract", "Pancreas", "Intestinal", "Urinary tract", "Gynecological", "Musculoskeletal", "Respiratory", "Cardiovascular", "Dermatological", and "Other" disease. "Other" disease consisted of "without definitive diseases", "unknown", "psychological", and "organ-indeterminate diseases".[1]

Investigations such as laboratory and imaging studies used in making the diagnosis and treatments of subjects were as follows. These investigations were not necessarily performed on all patients, especially those without higher positive pretest probabilities. Diseases of the esophagus, stomach, and duodenum system were diagnosed using complete blood cell count (CBC), blood chemistry analysis, abdominal X-ray, abdominal CT, and EGD. Intestinal diseases were diagnosed using CBC, blood chemistry analysis, abdominal X-ray, abdominal US, abdominal CT, and CS. Diseases of the urinary tract system were diagnosed using CBC, blood chemistry analysis, urinalysis, abdominal X-ray including KUB, abdominal US, and abdominal CT. Diseases of the liver and biliary tract were diagnosed using CBC, blood chemistry analysis, abdominal US, abdominal CT, and MRCP. Musculoskeletal diseases were diagnosed using CBC, blood chemistry analysis, X-ray of bones, chest and abdominal CT, and

MRI. Gynecological diseases were diagnosed using CBC, blood chemistry analysis, urinary human chorionic gonadotropin measurements, abdominal US, and transvaginal US. Pancreatic diseases were diagnosed using CBC, blood chemistry analysis, abdominal US, abdominal CT, and MRCP. Respiratory diseases were diagnosed using CBC, blood chemistry analysis, rapid immunoassay of influenza A and B nucleoprotein antigens, chest X-ray, and chest CT. Cardiovascular diseases were diagnosed using CBC, blood chemistry analysis, electrocardiography, and chest and abdominal CT. Dermatological diseases were diagnosed via macroscopic inspection and histopathological studies.

Data analysis

IBM SPSS (version 25) and Excel 2016 software were used to analyze the data using the chi-squared test, and $p < 0.05$ denoted statistical significance. We calculated sensitivity, specificity, PLRs, NLRs, and 95% confidence interval of the relationships between the sites of abdominal pain and the organs involved. In cases in which there were multiple sites of abdominal pain or multiple organs involved, we classified and analyzed all of them. Missing values were removed from applicable data in each test. The sample size of the present study was calculated based on 2 previous studies performed in our hospital, which were a prospective observational study reported in 1997 and a retrospective study reported in 2019.[1,17] On the hypothesis that there is no relationship between "Epigastric" and "Esophagus,

stomach, and duodenum", the smaller group size ranged from 18 to 165 patients.

Ethics considerations

An explanatory pamphlet detailing the study was provided to all patients or their family members during the first visit, and it included all relevant information pertaining to the ways in which their individual information would be utilized. We obtained consent from all subjects via the comprehensive agreement method in the hospital, and anonymity of the patients was protected. The study was approved by the Ethics Committee of Saga University Hospital (file number 20170108) and was conducted in accordance with the guidelines of the 1975 Declaration of Helsinki.

Patients and public involvement

No patient involved.

Results

A total of 2591 new outpatients visited the Department of General Medicine at Saga University Hospital during the study period, 2265 of whom were excluded because abdominal pain was not present or they were less than 20 years of age. All 326 (14.4%) of the remaining patients consented to participation in the study, and they were enrolled (Figure 1). The characteristics of the subjects are shown in Table 1. The mean patient age was 51.7 ± 20 years, and 141 patients (43.3%) were men. Forty-six (14.1%) of the patients lived alone. Of the total number of patients included in the study, 126 (38.6%) were referred to the department either by another facility or by another department within Saga University Hospital. Of these 126 referred patients, 93 (73.8%) were referred by another hospital, 28 (22.2%) were referred by another department of Saga University Hospital, and 5 (4.0%) were referred by general practitioners working at community health centers. A total of 209 (64.1%) patients visited during the daytime, 18 (8.6%) of whom visited during a national public holiday and who were thus considered "outside normal office hours" patients in accordance with Saga University Hospital procedures. Attempts were made to reach 81 of the 326 patients in the study by telephone (24.8%), and 22 of these patients (6.7% of the total study sample) could not be reached.

The types of examinations planned at the first visit, which were also performed at the last visit to facilitate diagnosis and treatment, included CBC and blood chemistries in 281

patients (86.2%), blood gas analysis in 86 patients (26.4%), chest or abdominal X-ray in 222 patients (68.1%), abdominal US in 118 patients (36.2%), abdominal CT in 155 patients (47.5%), and MRI in 9 patients (2.8%). Follow-up and admission decisions made at first visits were classified as "follow-up unnecessary but condition apparently mild" (65; 19.9%), "follow-up at the Saga University Hospital Outpatient Clinic" (112; 34.4%), "follow-up at outpatient clinics of other Saga University Hospital departments" (34; 10.4%), "follow-up at outpatient clinics of other hospitals" (42; 12.9%), "admission to the Department General Medicine at Saga University Hospital" (33; 10.1%), "admission to other departments at Saga University Hospital" (41; 12.6%), and "admission to other hospitals" (4; 1.2%).

Including cases in which multiple sites of abdominal pain were individually identified, a total of 576 sites of abdominal pain were recorded. The most frequent complaint was epigastric pain (95/576; 16.5%), followed by periumbilical pain (72; 12.5%), mid-lower pain (66; 11.5%), and right-lower pain (62; 10.8%) (Figure 2). In the 326 patients included in the study, the total number of organs identified as being involved was 354. The fact that the number of organs identified as involved was greater than the number of patients in the study was partly because cases of acute gastroenteritis (28/326; 8.6%) were doubly classified into both the "intestinal" and "esophagus, stomach, and duodenum" categories. The most frequently involved organ category was "intestinal" (125/354; 35.3%), followed by "esophagus, stomach, and duodenum" (58; 16.4%), "urinary tract" (38; 10.7), and "liver and

biliary tract" (25; 7.1%). Detailed diagnostic data, putative diagnoses of conditions causing abdominal pain, and the organs involved are shown in Table 2.

Relationships between the sites of abdominal pain and the organs involved are shown in Table 3. Relationships between the sites of abdominal pain and causative organs with $p < 0.05$ as determined via the chi-squared test and PLR ≥ 2 were as follows: "right subcostal" and "liver and biliary tract" ($p < 0.001$, PLR = 3.59); "right subcostal" and "musculoskeletal" ($p < 0.001$, PLR = 2.34); "epigastric" and "esophagus, stomach, and duodenum" ($p < 0.001$, PLR = 2.24); "right flank" and "urinary tract" ($p < 0.001$, PLR = 2.84); "left flank" and "urinary tract" ($p = 0.008$, PLR = 2.17); "left flank" and "dermatological" ($p = 0.019$, PLR = 4.14); and "mid-lower" and "intestinal" ($p < 0.001$, PLR = 2.47). Relationships between "epigastric" and "urinary tract" ($p = 0.002$, PLR = 0.25), "mid lower" and "liver and biliary tract" ($p = 0.035$, PLR = 0.19), "periumbilical" and "urinary tract" ($p = 0.008$, PLR = 0.22), and "generalized" and "esophagus, stomach, and duodenum" ($p = 0.034$, PLR = 0.17) yielded $p < 0.05$ in the chi-squared and PLRs < 0.5. NLRs ranged from 0.5 to 1.5, with the exception of the relationship between "left flank" and "dermatological" ($p = 0.020$, PLR = 0.40).

Discussion

Moderate but statistically significant relationships between some sites of abdominal pain and the organs involved were identified in the current study. Although it has been reported that PLRs ranging from 2 to 4 increase the probability that an organ causes abdominal pain at a related site by 15%–30%,[18] in the present study, PLRs between "right subcostal" and "liver and biliary tract"; between "right subcostal" and "musculoskeletal" ; between "epigastric" and "esophagus, stomach, and duodenum"; between "right or left flank" and "urinary tract"; between "left flank" and "dermatological"; and between "mid-lower" and "intestinal" ranged from 2.17 to 4.14 ($p < 0.05$). Therefore, the presence of abdominal pain at the aforementioned sites may increase post-test probability when other information such as medical history is factored into calculations, and there may be important associated indications with regard to identifying the organs involved.

Relationships between "right subcostal" and "liver and biliary tract" and between "epigastric" and "esophagus, stomach, and duodenum", which were significant at $p < 0.05$ and PLR ≥ 2 in both the present study and that reported 20 years ago,[1] may be particularly useful in the context of identifying the organs involved in cases of abdominal pain, given the apparent reproducibility of the results. Whereas it has been reported that PLRs ranging from 0.1 to 0.2 reduce the probability that an organ is involved in abdominal pain at a related site by 30%–45%,[18] in the present study, the PLRs between "epigastric" and "urinary tract";

between “mid-lower” and “liver and biliary tract”; between “periumbilical” and “urinary tract”; and between “generalized abdomen” and “esophagus, stomach, and duodenum” were low, ranging from 0.17 to 0.25 ($p < 0.05$). Although information about the sites of abdominal pain is considered useful for identifying organs that are involved and/or making accurate diagnoses on that basis, such information may also be useful for discounting the involvement of some organs. Notably, all NLRs excluding that between “left flank” and “dermatological” ranged from 0.5 to 1.5. It has been suggested that NLRs in this range only reduce the probability of the involvement of certain organs in abdominal pain at some sites by 15% or less.[18] Therefore, it is impossible to discount the involvement of some organs because of the absence of abdominal pain at a site generally considered to be significantly clinically associated, such as “epigastric” and “heart disease” or “right subcostal” and “acute cholecystitis”.

The causes of abdominal pain and the distributions of the organs involved have changed markedly since Yamamoto et al.’s[1] study was conducted more than 20 years ago. Although the most commonly involved organs in the present study were “intestinal” (35.3%), “esophagus, stomach, and duodenum” (16.4%), and “urinary tract” (10.7%), their corresponding frequencies of involvement in the previous study were 24.3, 38.9, and 4.1%, respectively, reflecting increases in the rates of “urinary tract” and “intestinal” diseases and reductions in the frequencies of diseases of the “esophagus, stomach, and duodenum.”

Increases in the frequencies “urinary tract” and “intestinal” diseases and decreases in the frequencies of diseases of the “esophagus, stomach, and duodenum” are considered to be related.

It has recently become possible to diagnose conditions involving the urinary tract and intestines more accurately because of advances in medical technology, particularly imaging modalities. Of the urinary tract conditions investigated by both Yamamoto et al.[1] and the present study, urinary tract stones exhibited the biggest increase in frequency, increasing from 2.5% of cases to 9.2% of cases. Whereas urinary tract stones were typically diagnosed via urinalysis, abdominal US, or intravenous pyelography in the study by Yamamoto et al.,[1] abdominal CT, which is now widely available in Japan, has become the major imaging modality for definitively diagnosing the condition. CT makes it possible to accurately diagnose extremely small urinary tract stones, which were difficult to detect 20 years ago, resulting in ambiguous diagnoses such as “gastritis” attributed to the presence of digestive complaints such as nausea or vomiting.[1] Notably, CT was used as a definitive diagnostic modality in approximately 80% of cases diagnosed as urinary tract stones in the present study.

Similar considerations as those applicable to urinary tract stones are also applicable to intestinal diseases. It is essential to monitor changes in the frequencies of different types of intestinal diseases beyond simply monitoring the collective incidence of such conditions as a

group. In the present study, the most highly represented category of intestinal conditions was "other intestinal diseases" (40.8%), followed by constipation (15.2%), hyperperistalsis (3.2%), acute enteritis (2.4%), and irritable bowel syndrome (2.4%). Their corresponding frequencies in the study by Yamamoto et al.[1] were 10.1, 27.7, 24.4, 24.4, and 13.4%, respectively, suggesting a substantial relative increase in the frequency of "other intestinal diseases" over time. "Other intestinal diseases" include various conditions such as colon diverticulitis, large intestinal diverticulum bleeding, ischemic enteritis, intestinal membrane panniculitis, or non-obstructive intestinal membrane ischemia, most of which can usually be definitively diagnosed via CT.[19-22] In Yamamoto et al.[1] these conditions were typically diagnosed via blood tests, urinary tests, or US, usually without abdominal CT, and this may be relevant to the discrepancy in the incidence of "other intestinal diseases" between Yamamoto et al.[1] and the present study.

Study Limitation

Concerning potential limitations, the present study was performed at a tertiary medical center at a university hospital. Although patients can visit the hospital without a referral, the study setting may have resulted in some sampling bias. Ideally, a prospective study including both primary and secondary medical centers will be conducted in the near future.

Conclusion

Our results differed from previous results reported more than 20 years ago by our institute, which could be attributable to the marked advancement of medical science and technology during this period. Determining the site of abdominal pain could be useful for identifying the organs involved or excluding them as targets of detailed examination to make a diagnosis.

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Contributors

SY, MT and NEK conceived the study. SY, MT, NEK, and TMN collected the data. SY, MT, and NEK determined the final diagnoses and the organs involved. SY and TMN analyzed the data. MT, NEK, and SI-Y reviewed the data analysis. SY wrote the initial manuscript. MT, NEK, and SI-Y reviewed the manuscript.

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Competing Interests

None declared

Patient consent for publication

Not required

Provenance and peer review

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Not available

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Table 1: Patient characteristics

Characteristic	N = 326
Age in years; mean (standard deviation)	51.7 (20.0)
Male	141 (43.3%)
Living with	
Housemates	261 (80.1%)
Alone	46 (14.1%)
Unknown	19 (5.8%)
Referral letter	126 (38.6%)
Time of visit	
Day time (9:00 a.m. to 5:00 p.m.)	209 (64.1%)
Outside of normal office hours (5:00 p.m. to 9:00 a.m.)	117 (35.9%)
Required telephone communication†	81 (24.8%)
Did not require telephone communication†	22 (6.7%)
Examination at the first visit	
Blood test	281 (86.2%)
Chest or abdominal x-ray	222 (68.1%)
Computed tomography	155 (47.5%)
Ultrasonography	118 (36.2%)
Electrocardiography	91 (27.9%)
Blood gas	86 (26.4%)
Magnetic resonance imaging	9 (2.8%)
Other	31 (9.5%)
Management decided at the first visit	
Follow-up unnecessary	65 (19.9%)
SUH Department of General Medicine outpatient clinic	112 (34.4%)
Outpatient clinic of another hospital	42 (12.9%)
Outpatient clinic of another SUH department	34 (10.4%)
Admission to another SUH department	41 (12.6%)
Admission to SUH Department of General Medicine	33 (10.1%)
Admission to another hospital	4 (1.2%)

SUH, Saga University Hospital (Saga prefecture, Japan)

†We telephoned patients (or their relatives) whose final diagnoses were unknown

because they only visited our department once and did not receiving a definitive diagnosis during their first visit. After being informed of the course of their condition with or without visiting another hospital, and/or the results of examinations at other hospitals, definitive diagnoses were determined.

Table 2: Classifications of organs and detailed diagnoses of patients with abdominal pain.

Organs involved	Detailed diagnosis
Intestinal (*n* = 125)	Gastroenteritis (28) Enteritis (20) Constipation (19) Ileus (9), colon diverticulitis (9) Acute appendicitis (6) Ischemic enteritis (5) Hyperperistalsis (4) Irritable bowel syndrome (3), Crohn's disease (3), intestinal membrane panniculitis (3), large intestinal diverticulum bleeding (3) Hereditary angioedema (2) Sigma volvulus (1), toxic megacolon (1), inguinal hernia (1), postoperative adhesion (1), familial Mediterranean fever (1), allergic purpura (1), ulcerous colitis (1), colon ulcer (1), non-obstructive intestinal membrane ischemia (1), drug-induced abdominal pain (1), celiac artery compression syndrome (1)
Esophagus, stomach, and duodenum (*n* = 58)	Gastroenteritis (28) Reflux esophagitis (12), Barrett's esophagus (12) Gastritis (9) Functional dyspepsia (4) Gastric ulcer (2) Duodenum ulcer (1), exogenous material in duodenum (1), bleeding gastric ulcer (1)
Urinary tract (*n* = 38)	Urinary tract or kidney stone (30) Urinary retention (3) Benign prostatic hyperplasia (1), urinary tract inflammation (1), hemorrhagic cystitis (1), acute bacterial prostatitis (1), acute pyelonephritis (1)
Liver and biliary tract (*n* = 25)	Cholecystitis (8) Cholangitis (5) Choledocholithiasis (4) Cholecystolithiasis (2), biliary colic (2), acute obstructive suppurative cholangitis (2), gallbladder cancer (1), acute alcoholic hepatitis (1)
Musculoskeletal (*n* = 12)	Bruise (4) Postoperative pain (3)

	Myalgia (2) Metastatic bone tumor (1), abdominal penetrating wound (1), femoral neuralgia (1)
Gynecological (*n* = 10)	Ovarian cancer (2) Endometriosis (1), adhesion of uterine appendages (1), atypical genital bleeding (1), pregnancy (1), ovarian cystoma (1), tubo-ovarian abscess (1), uterine cancer (1), ovarian tumor (1)
Pancreas (*n* = 9)	Pancreatitis (7) Pancreatic carcinoma (1), caput pancreatic cancer (1)
Respiratory (*n* = 5)	Pleural pneumonia (3) Influenza virus (1), cough (1)
Cardiovascular (*n* = 4)	Celiac artery dissection (2) Acute aortic dissection (1), superior mesenteric artery dissection (1)
Dermatological (*n* = 3)	Subcutaneous abscess or granuloma (2) Herpes zoster virus (1)
Other (*n* = 55)	Unknown (39) Psychological problem (8) Without definitive disease (7) Peritoneal cancer (1)

Table 3: Relationships between sites of abdominal pain and diagnoses

Sites of pain	Organs involved	Sensitivity %	Specificity %	LR+ (95% CI)	LR- (95% CI)
Left-flank	Dermatological	66.7	83.9	4.14 (1.27–5.92)	0.40 (0.07–0.95)
Right-subcostal	Liver and biliary tract	56.0	84.4	3.59 (2.23–5.08)	0.52 (0.32–0.76)
Right-flank	Urinary tract	39.5	86.1	2.84 (1.71–4.42)	0.70 (0.53–0.87)
Mid-lower	Intestinal	32.0	87.1	2.47 (1.60–3.83)	0.78 (0.70–0.88)
Right-subcostal	Musculoskeletal	41.7	82.2	2.34 (1.05–4.0)	0.71 (0.39–0.99)
Epigastric	Esophagus, stomach, and duodenum	53.4	76.1	2.24 (1.60–2.99)	0.61 (0.46–0.79)
Left-flank	Urinary tract	31.6	85.4	2.16 (1.23–3.57)	0.80 (0.63–0.96)
Epigastric	Urinary tract	7.9	68.1	0.25 (0.08–0.66)	1.35 (1.15–1.44)
Periumbilical	Urinary tract	5.3	75.7	0.22 (0.06–0.72)	1.25 (1.08–1.31)
Mid-lower	Liver and biliary tract	4.0	78.4	0.19 (0.33–0.92)	1.22 (1.02–1.27)
Generalized	Esophagus, stomach, and duodenum	1.7	89.5	0.17 (0.03–0.90)	1.10 (1.01–1.12)

LR, likelihood ratio; CI, confidence interval

Figure legends

Figure 1. Diagnostic flow chart of abdominal pain.

A total of 2591 new outpatients visited the Department of General Medicine at Saga University Hospital in Japan during the study period, 2265 of whom were excluded because of a lack of abdominal pain or an age of less than 20. All 326 patients were enrolled. After more than 3 months from their first visits, the final diagnoses were determined by 2 physicians.

Figure 2. Classification of sites of abdominal pain.

Sites of abdominal pain were classified into 11 categories, including 9 different abdominal sections (right or left subcostal, right or left flank, right or left lower, epigastric, periumbilical, and mid-lower), generalized abdomen, and site-indeterminate. When patients had multiple sites of pain or multiple organs involved, classification and analysis of all sites and organs were performed. A total of 576 sites of abdominal pain were identified in the 326 subjects in the study. The most frequent complaint was epigastric pain (95/576; 16.5%), followed by periumbilical pain (72; 12.5%), mid-lower pain (62; 10.8%), and right-lower pain (61; 10.6%).

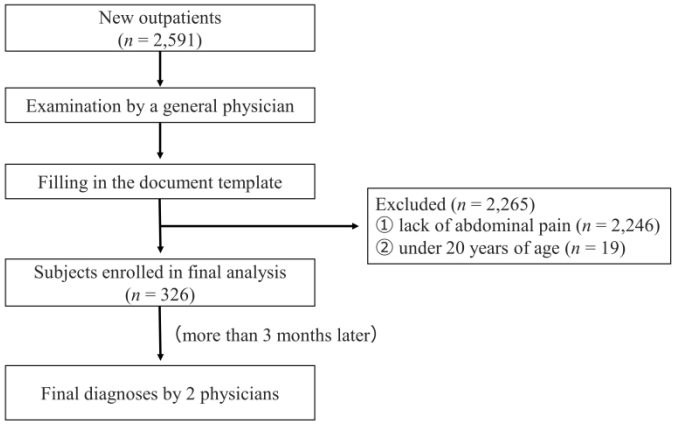

Figure 1

338x190mm (300 x 300 DPI)

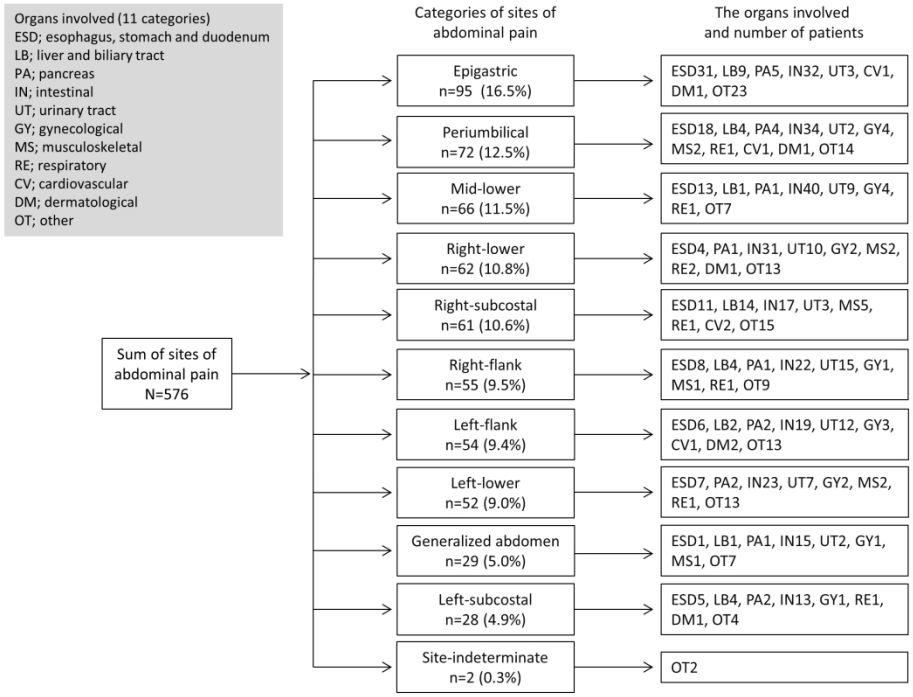

Figure 2

254x190mm (300 x 300 DPI)

Reporting checklist for diagnostic test accuracy study.

Based on the STARD guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STARDreporting guidelines, and cite them as:

Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, LijmerJG Moher D, Rennie D, de Vet HCW, Kressel HY, Rifai N, Golub RM, Altman DG, Hooft L, Korevaar DA, Cohen JF, For the STARD Group. STARD 2015: An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies.

Reporting Item	Page Number
Title or abstract	

	#1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2
Abstract			
	#2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2-3
Introduction			
	#3	Scientific and clinical background, including the intended use and clinical role of the index test	5
	#4	Study objectives and hypotheses	5-6
Methods			
Study design	#5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	7
Participants	#6	Eligibility criteria	7
Participants	#7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	7
Participants	#8	Where and when potentially eligible participants were identified (setting, location and dates)	7
Participants	#9	Whether participants formed a consecutive, random or convenience series	7

Test methods	#10a	Index test, in sufficient detail to allow replication	8
Test methods	#10b	Reference standard, in sufficient detail to allow replication	9-11
Test methods	#11	Rationale for choosing the reference standard (if alternatives exist)	10
Test methods	#12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	8
Test methods	#12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	9-11
Test methods	#13a	Whether clinical information and reference standard results were available to the performers / readers of the index test	8
Test methods	#13b	Whether clinical information and index test results were available to the assessors of the reference standard	9
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Analysis	#15	How indeterminate index test or reference standard results were handled	9
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Participants	#20	Baseline demographic and clinical characteristics of participants	13
Participants	#21a	Distribution of severity of disease in those with the target condition	n/a †
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Participants	#22	Time interval and any clinical interventions between index test and reference standard	13-14
Test results	#23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	15
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Test results	#25	Any adverse events from performing the index test or the reference standard	n/a † †
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	#28	Registration number and name of registry	7
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	#30	Sources of funding and other support; role of funders	21

<Short explanation>

†: As this study include multiple hypothesis, the distribution of severity and alternative diagnosis of all groups can not be described.

††: Because the present research is a prospective observational study, there are no adverse events.

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The relationships between sites of abdominal pain and the organs involved: A prospective observational study

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The relationships between sites of abdominal pain and the organs involved: A prospective observational study

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Abstract

Objectives: Abdominal pain is one of the most frequent chief complaints in primary care settings. The aim of the present study was to determine the positive and negative likelihood ratios of the relationships between the sites of abdominal pain and the organs involved.

Design: Prospective observational study.

Setting: A single tertiary center, a university hospital in Japan.

Participants: A total of 2591 new outpatients visited the Department of General Medicine at a university hospital from April 2017 to March 2018. Of these, 326 patients aged ≥20 years with abdominal pain were enrolled.

Results: Sites of abdominal pain were classified into 11 categories including nine different abdominal sections, "generalized abdomen", and "site-indeterminate". The positive likelihood ratios between "right subcostal" and "liver and biliary tract"; between "right subcostal" and "musculoskeletal" ;between "epigastric" and "esophagus, stomach, and duodenum"; between "right or left flank" and "urinary tract"; between "left flank" and "dermatological"; and between "mid-lower" and "intestinal" ranged from 2.17 to 4.14. The positive likelihood ratios between "epigastric" and "urinary tract"; between "mid-lower" and "liver and biliary tract"; between "periumbilical" and "urinary tract"; and between "generalized abdomen" and "esophagus, stomach, and duodenum" were low, ranging from 0.17 to 0.25. The negative likelihood ratios ranged 0.5–1.5 excluding the relationship

between “left flank” and “dermatological.”

Conclusion: The presence of pain at right subcostal, epigastric, right or left flank, and mid-lower sites might be useful for identifying the organs involved. Additionally, the presence of pain at mid-lower, epigastric, periumbilical, and generalized abdominal sites might be helpful for denying the involvement of some organs. Some sites of abdominal pain can be indicative of the organs involved.

Keywords: abdominal pain site, organ involved, positive likelihood ratio, negative likelihood ratio, prospective observational study

Strengths and limitations of this study

- This was the first prospective study published since 1997 regarding the relationships between sites of abdominal pain and the organs involved.
- This was the first study regarding sites of abdominal pain since computed tomography (CT) has become widely available, especially in Japan.
- The availability of CT is particularly high in Japan, which might not reflect its availability worldwide.
- CT or other diagnostic modalities were not used equally among all included patients, which could have influenced the diagnosis of abdominal pain.
- This was a single-center observational study, the setting of which may have contributed to some sampling bias.

Introduction

Abdominal pain is one of the most frequent chief complaints in primary care settings, accounting for 5%–10% of visits to emergency departments.[1-4] Diseases causing abdominal pain range from mild conditions cured by conservative medical treatments alone to severe acute diseases requiring emergency surgery.[1,5-7] Given the possibility of severe disease requiring urgent treatment, it is vital that physicians make accurate and expeditious diagnoses.[8] Computed tomography (CT) may be the most accurate imaging modality for assessment of abdominal pain, and is widely accepted as the first-line imaging modality for patients who present with this type of pain. However, it is necessary to select CT and other imaging tests (e.g., abdominal ultrasonography or magnetic resonance imaging [MRI]) based on pretest probability, because these tests cannot be performed for some patients with abdominal pain; moreover, unnecessary examination and hospitalization should be avoided.[9] History taking and physical examinations can influence pretest probability and prove crucial to the prognosis. In particular, the sites of abdominal pain can be extremely important because some are significantly associated with potentially serious diseases, such as McBurney's point pain with acute appendicitis and right subcostal pain with acute cholecystitis.[10,11]

To the best of our knowledge, no studies focusing on the relationships between the sites of abdominal pain and the organs involved have been published since 1997.[1] However, it is

certain that our capability to make an accurate diagnosis of abdominal pain has remarkably improved because of marked advancements of medical technologies such as imaging modalities including CT and MRI in the last two decades.[12,13] In addition, in Japan, the epidemiology of conditions causing abdominal pain has changed in conjunction with aging of the population, as well as westernization of lifestyles.[14-16] Therefore, it makes strategic sense to examine current relationships between the sites of abdominal pain and the organs involved two decades after the most relevant previous study.[1] In the present study, we investigated the influence of sites of abdominal pain on the pretest probability of organs involved using positive likelihood ratios (PLRs) and negative likelihood ratios (NLRs).

Methods

Study design and patients

The present investigation was a single hospital-based prospective observational study conducted from April 2017 to March 2018. All new outpatients aged ≥20 years were enrolled, who visited the Department of General Medicine at Saga University Hospital in Japan with abdominal pain as a chief complaint or other symptoms excluding the chief complaint. They were initially seen by general physicians working in the department. Consenting patients were included regardless of whether they presented during the day or outside normal office hours, (*i.e.*, the emergency room for walk-in patients), but patients who utilized emergency service systems such as an ambulance or medical helicopter were excluded from the study. Comparative incidences of abdominal pain were evaluated, and then the organs and causative conditions involved were assessed. Statistical relationships between the sites of abdominal pain and the organs involved were then calculated. The present study was registered at https://www.umin.ac.jp as UMIN000037686. The design was assessed using a reporting checklist based on the Standards for Reporting of Diagnostic Accuracy (STARD) guidelines. [17]

Setting

The study was conducted at the Department of General Medicine at Saga University

Hospital in Saga prefecture, which is located in southern Japan and which has a population of 800,000. The hospital is open during the day and outside normal office hours (as an emergency room for walk-in patients). Patients who visited our hospital with a referral letter during the daytime could directly see the appropriate medical specialists. Additionally, patients transferred by ambulance were usually treated by the Department of Emergency Medicine or other medical specialists, irrespective of their visiting time, without undergoing treatment by the Department of General Medicine.

Data and data sources

Physicians who initially saw the patients completed a document template containing survey items designed and prepared in advance. Survey items recorded at the first patient visit included age, sex, the date and time (daytime or outside normal office hours) of the visit, residence status (alone or with housemates), referral from another doctor (yes or no), sites of abdominal pain, intermittent or persistent pain, types of examinations, and management decided at the first visit. Patients who lived in nursing-care facilities were included in the "with housemates" group. When physicians could confirm the presence of pain on the patient's abdomen, whether by visual confirmation of the site of spontaneous pain or by physical examination of abdominal tenderness, the pain was recorded as abdominal pain. Sites of abdominal pain were classified into 11 categories including nine different abdominal sections

(right or left subcostal, right or left flank, right or left lower, epigastric, periumbilical, and mid-lower), "generalized abdomen", and "site-indeterminate". The types of examinations included blood and/or urinary tests, blood gas analysis, chest or abdominal X-ray including kidney ureter bladder (KUB), ultrasonography (US), CT, MRI including magnetic resonance cholangiopancreatography (MRCP), electrocardiography, esophagogastroduodenoscopy (EGD), and colonoscopy (CS). A correct diagnosis of abdominal pain could be elusive, difficult and time-consuming, especially when associated with psychiatric conditions that require exclusion of most major organic diseases. Furthermore, additional examinations performed at another visit, with or without improvement of abdominal pain, could aid physicians in making a correct diagnosis. Therefore, the period of 3 months (also used in our previous study[1]) was considered an appropriate duration for confirmation of the final diagnosis; we determined the final diagnoses and organs involved at more than 3 months after the initial visit, in accordance with the following gold standard.

Gold standard for making definitive diagnoses or identifying the organ involved

Two physicians independently made diagnoses for individual patients based on the classification of the International Statistical Classification of Diseases and Related Health Problems-10 using all information in the medical charts after more than 3 months from their first visits, including onset, symptoms, time course, underlying diseases, past history, vital

signs, characteristics of abdominal pain, and findings of laboratory or imaging studies. When the same diagnosis was made by both physicians, the diagnosis was set as the final diagnosis. When different diagnoses were made, the final diagnosis was determined through discussion among three physicians, including the aforementioned two physicians plus a third physician from our department. In cases in which the final diagnosis was unknown because the patient had only visited the department once without a definitive diagnosis being reached on that date, phone calls were made to the patients themselves or their family members more than 3 months after their first visit to ascertain the course of symptoms, visits to another hospital, and/or the results of examinations at other hospitals and diagnoses made there. When the patients could not be reached by telephone, the final diagnosis was determined through discussion among the three physicians. The organs involved, which could overlap with more than two other organs, were determined on the basis of the final diagnoses. We classified the final diagnoses into 11 categories: “Esophagus, stomach, and duodenum”, “Liver and biliary tract”, “Pancreas”, “Intestinal”, “Urinary tract”, “Gynecological”, “Musculoskeletal”, “Respiratory”, “Cardiovascular”, “Dermatological”, and “Other” disease. “Other” disease consisted of “without definitive diseases”, “unknown”, “psychological”, and “organ-indeterminate diseases”.[1]

The types of investigations (e.g., laboratory and imaging studies) used to make a diagnosis and identify the organ involved are described below (also listed in Supplement 1).

These investigations were not necessarily performed on all patients, especially those without higher positive pretest probabilities. Diseases of the esophagus, stomach, and duodenum system were diagnosed using complete blood cell count (CBC), blood chemistry analysis, abdominal X-ray, abdominal CT, and EGD. Intestinal diseases were diagnosed using CBC, blood chemistry analysis, abdominal X-ray, abdominal US, abdominal CT, and CS. Diseases of the urinary tract system were diagnosed using CBC, blood chemistry analysis, urinalysis, abdominal X-ray including KUB, abdominal US, and abdominal CT. Diseases of the liver and biliary tract were diagnosed using CBC, blood chemistry analysis, abdominal US, abdominal CT, and MRCP. Musculoskeletal diseases were diagnosed using CBC, blood chemistry analysis, X-ray of bones, chest and abdominal CT, and MRI. Gynecological diseases were diagnosed using CBC, blood chemistry analysis, urinary human chorionic gonadotropin measurements, abdominal US, and transvaginal US. Pancreatic diseases were diagnosed using CBC, blood chemistry analysis, abdominal US, abdominal CT, and MRCP. Respiratory diseases were diagnosed using CBC, blood chemistry analysis, rapid immunoassay of influenza A and B nucleoprotein antigens, chest X-ray, and chest CT. Cardiovascular diseases were diagnosed using CBC, blood chemistry analysis, electrocardiography, and chest and abdominal CT. Dermatological diseases were diagnosed via macroscopic inspection and histopathological studies. Malignant diseases were diagnosed using the findings of imaging studies or pathological findings including cytology, as well as data from histopathological examinations

of specimens acquired via biopsy or surgery.

Data analysis

IBM SPSS (version 25) and Excel 2016 software were used to analyze the data using the chi-squared test, and $p < 0.05$ denoted statistical significance. We calculated sensitivity, specificity, PLRs, NLRs, and 95% confidence interval of the relationships between the sites of abdominal pain and the organs involved. In cases in which there were multiple sites of abdominal pain or multiple organs involved, we classified and analyzed all of them. Missing values were removed from applicable data in each test. The calculated sample size of the present study, ranging from 18 to 165 patients, was based on two previous studies performed and reported by our institution: a prospective study reported in 1997 and a retrospective study in 2019 [1, 18].

Ethics considerations

An explanatory pamphlet detailing the study was provided to all patients or their family members during the first visit, and it included all relevant information pertaining to the ways in which their individual information would be utilized. We obtained consent from all subjects via the comprehensive agreement method in the hospital, and anonymity of the patients was protected. The study was approved by the Ethics Committee of Saga University

Hospital (file number 20170108) and was conducted in accordance with the guidelines of the 1975 Declaration of Helsinki.

Patients and public involvement

Two external members were present in the Institutional Review Board of our hospital. No other patients or members of the public were involved in the present research, including conceptualization of research questions, planning of study design, performance of the research, or analysis of the results.

Results

A total of 2591 new outpatients who visited our hospital were included in the initial cohort; all outpatients who had no abdominal pain or were <20 years of age were excluded. All 326 (14.4%) of the remaining patients consented to participation in the study, and they were enrolled (Figure 1). The characteristics of the patients are shown in Table 1. The mean patient age was 51.7 ± 20 years (age breakdown is shown in Supplement 2) and 141 patients (43.3%) were men. Of the 326 patients included in the study, 126 (38.6%) had been referred to our department either by another hospital (93; 73.8%), another department of our hospital (28; 22.2%), or by general practitioners working at community health centers (5; 4.0%). A total of 209 (64.1%) patients visited during the daytime, 18 (8.6%) of whom visited during a national public holiday and who were thus considered "outside normal office hours" patients in accordance with our hospital procedures. Attempts were made to reach 81 of the 326 patients in the study by telephone (24.8%), and 22 of these patients (6.7% of the total study sample) could not be reached. Of the types of examinations planned at the first visit in the present study, which might also be performed at the last visit to facilitate diagnosis and treatment, abdominal CT was performed in nearly half of the patients (155; 47.5%). One hundred forty-five patients (44.5%) were admitted to or followed up by the department of General Medicine; 75 patients (23.0%) were admitted to or followed up by other departments in our hospital; and 46 patients (14.1%) were admitted to or followed up by other hospitals.

The characteristics of patients that underwent CT examination are shown in Supplement 3.

Including cases in which multiple sites of abdominal pain were individually identified, a total of 576 sites of abdominal pain were recorded. The most frequent complaint was epigastric pain (95/576; 16.5%), followed by periumbilical pain (72; 12.5%), mid

-lower pain (66; 11.5%), and right-lower pain (62; 10.8%) (Figure 2). In the 326 patients included in the study, the total number of organs identified as being involved was 354. The fact that the number of organs identified as involved was greater than the number of patients in the study was partly because cases of acute gastroenteritis (28/326; 8.6%) were doubly classified into both the "intestinal" and "esophagus, stomach, and duodenum" categories. The most frequently involved organ category was "intestinal" (125/354; 35.3%), followed by "esophagus, stomach, and duodenum" (58; 16.4%), "urinary tract" (38; 10.7), and "liver and biliary tract" (25; 7.1%). Detailed diagnostic data, putative diagnoses of conditions causing abdominal pain, and the organs involved are shown in Table 2.

Relationships between the sites of abdominal pain and the organs involved are shown in Table 3. Relationships between the sites of abdominal pain and causative organs with $p < 0.05$ as determined via the chi-squared test and PLR ≥ 2 were as follows: "right subcostal" and "liver and biliary tract" ($p < 0.001$, PLR = 3.59); "right subcostal" and "musculoskeletal" ($p < 0.001$, PLR = 2.34); "epigastric" and "esophagus, stomach, and duodenum" ($p < 0.001$, PLR = 2.24); "right flank" and "urinary tract" ($p < 0.001$, PLR =

2.84); “left flank” and “urinary tract” ($p = 0.008$, PLR = 2.17); “left flank” and “dermatological” ($p = 0.019$, PLR = 4.14); and “mid-lower” and “intestinal” ($p < 0.001$, PLR = 2.47). Relationships between “epigastric” and “urinary tract” ($p = 0.002$, PLR = 0.25), “mid lower” and “liver and biliary tract” ($p = 0.035$, PLR = 0.19), “periumbilical” and “urinary tract” ($p = 0.008$, PLR = 0.22), and “generalized” and “esophagus, stomach, and duodenum” ($p = 0.034$, PLR = 0.17) yielded $p < 0.05$ in the chi-squared and PLRs < 0.5. NLRs ranged from 0.5 to 1.5, with the exception of the relationship between “left flank” and “dermatological” ($p = 0.020$, PLR = 0.40). Additionally, relationships between the sites of abdominal pain and the organs involved in patients who underwent CT, and in patients whose diagnoses were made solely on all the information in medical charts, are shown in Supplement 4 and 5, respectively.

Discussion

Moderate but statistically significant relationships between some sites of abdominal pain and the organs involved were identified in the current study. In the presence of pain at a given site, PLRs ranging from 2 to 4 can be interpreted as indicators of increased probability of disease in a certain organ, by approximately 15%–25%.[19] In the present study, PLRs between "right subcostal" and "liver and biliary tract"; between "right subcostal" and "musculoskeletal" ; between "epigastric" and "esophagus, stomach, and duodenum"; between "right or left flank" and "urinary tract"; between "left flank" and "dermatological"; and between "mid-lower" and "intestinal" ranged from 2.17 to 4.14 ($p < 0.05$). Therefore, the presence of abdominal pain at the aforementioned sites may increase post-test probability when other information such as medical history is factored into calculations, and there may be important associated indications with regard to identifying the organs involved.

Relationships between "right subcostal" and "liver and biliary tract" and between "epigastric" and "esophagus, stomach, and duodenum", which were significant at $p < 0.05$ and PLR ≥ 2 in both the present study and that reported 20 years ago,[1] may be particularly useful in the context of identifying the organs involved in cases of abdominal pain, given the apparent reproducibility of the results. PLRs ranging from 0.1 to 0.2 in the presence of pain at a given site can be interpreted as indicators of decreased probability of disease in a certain organ, by approximately 30%–45%.[19] In the present study, the PLRs between "epigastric"

and “urinary tract”; between “mid-lower” and “liver and biliary tract”; between “periumbilical” and “urinary tract”; and between “generalized abdomen” and “esophagus, stomach, and duodenum” were low, ranging from 0.17 to 0.25 ($p < 0.05$). Although information about the sites of abdominal pain is considered useful for identifying organs that are involved and/or making accurate diagnoses on that basis, such information may also be useful for excluding the involvement of some organs. Notably, all NLRs excluding that between “left flank” and “dermatological” ranged from 0.5 to 1.5. In the presence of pain at a given site, NLRs ranging from 0.5 to 1.0 can be interpreted as indicators of decreased probability of disease in a certain organ, by approximately 15% or less.[19] Therefore, it is impossible to exclude the involvement of some organs because of the absence of abdominal pain at a site generally considered to be significantly clinically associated, such as “epigastric” and “heart disease” or “right subcostal” and “acute cholecystitis”.

Major differences in patient characteristics between the present study and the study performed by Yamamoto et al. in 1997 were the mean patient age and the ratio of cases in which CT was used for diagnosis.[1] Notably, the mean patient age was higher in the present study than in the previous study (51.7 ± 20.0 years vs 44.4 ± 16.7 years[1]). Additionally, whereas CT was used as a definitive diagnostic modality in 47.5% of the patients in the present study, (including 80% of patients with urinary tract stone), CT was rarely used for diagnosis in the previous study[1]; this lack of CT use could have contributed to inaccurate

diagnosis. Therefore, it is important to discuss the different distributions of the causes of abdominal pain between the present study and the previous study.[1] The causes of abdominal pain and the distributions of the organs involved have changed markedly since Yamamoto et al.'s[1] study was conducted more than 20 years ago. Although the most commonly involved organs in the present study were "intestinal" (35.3%), "esophagus, stomach, and duodenum" (16.4%), and "urinary tract" (10.7%), their corresponding frequencies of involvement in the previous study were 24.3%, 38.9%, and 4.1%, respectively, reflecting increases in the rates of "urinary tract" and "intestinal" diseases and reductions in the frequencies of diseases of the "esophagus, stomach, and duodenum." Increases in the frequencies "urinary tract" and "intestinal" diseases and decreases in the frequencies of diseases of the "esophagus, stomach, and duodenum" are considered to be related.

It has recently become possible to diagnose conditions involving the urinary tract and intestines more accurately because of advances in medical technology, particularly imaging modalities. Of the urinary tract conditions investigated by both Yamamoto et al.[1] and the present study, urinary tract stones exhibited the biggest increase in frequency, increasing from 2.5% of cases to 9.2% of cases. Whereas urinary tract stones were typically diagnosed via urinalysis, abdominal US, or intravenous pyelography in the study by Yamamoto et al.,[1] abdominal CT, which is now widely available in Japan, has become the major imaging modality for definitively diagnosing the condition. CT makes it possible to accurately

diagnose extremely small urinary tract stones, which were difficult to detect 20 years ago, resulting in ambiguous diagnoses such as "gastritis" attributed to the presence of digestive complaints such as nausea or vomiting.[1] Notably, CT was used as a definitive diagnostic modality in approximately 80% of cases diagnosed as urinary tract stones in the present study.

Similar considerations as those applicable to urinary tract stones are also applicable to intestinal diseases. It is essential to monitor changes in the frequencies of different types of intestinal diseases beyond simply monitoring the collective incidence of such conditions as a group. In the present study, the most highly represented category of intestinal conditions was "other intestinal diseases" (40.8%), followed by constipation (15.2%), hyperperistalsis (3.2%), acute enteritis (2.4%), and irritable bowel syndrome (2.4%). Their corresponding frequencies in the study by Yamamoto et al.[1] were 10.1, 27.7, 24.4, 24.4, and 13.4%, respectively, suggesting a substantial relative increase in the frequency of "other intestinal diseases" over time. "Other intestinal diseases" include various conditions such as colon diverticulitis, large intestinal diverticulum bleeding, ischemic enteritis, intestinal membrane panniculitis, or non-obstructive intestinal membrane ischemia, most of which can usually be definitively diagnosed via CT.[20-23] In Yamamoto et al.[1] these conditions were typically diagnosed via blood tests, urinary tests, or US, usually without abdominal CT, and this may be relevant to the discrepancy in the incidence of "other intestinal diseases" between

Yamamoto et al.[1] and the present study.

In the present study, many organs involved were identified in multiple abdominal sites, potentially because sites of referred pain or minor non-specific pain were included, in addition to primary sites of abdominal pain. This is a potential limitation to diagnosis of abdominal disease based on the site of abdominal pain. In such instances, we attempted to clarify the accuracy of using sites of abdominal pain to identify the organs involved, which confirmed that some sites of abdominal pain could be used to identify the organs involved.

Study Limitation

Concerning potential limitations, the present study was performed at a tertiary medical center at a university hospital. Although patients can visit the hospital without a referral, the study setting may have resulted in some sampling bias. Ideally, a prospective study including both primary and secondary medical centers will be conducted in the near future. Nearly one-third of patients were left without any follow-up, or were admitted to or followed up (on outpatient basis) by other hospitals. There was no age or sex restrictions, except that patients were ≥20 years of age; this age criterion could have contributed to selection bias in our results. In addition, laboratory or imaging investigations may have differed among patients. Furthermore, final diagnoses of 81 patients were determined on the basis of phone calls to those patients, or through subsequent discussions among three physicians in our department, because they had only visited our hospital once and had not received a definitive diagnosis. These aspects of the study design could have caused biases in terms of both false negative and false positive results.

Conclusion

Our results differed from previous results reported more than 20 years ago by our institute, which could be attributable to the widespread acceptance and marked advancement of medical science and technology during this period. Some sites of abdominal pain could be

useful for identifying the organs involved or excluding them as targets of detailed examination to make a diagnosis. However, it is possible to make an inaccurate diagnosis of "esophagus, stomach, and duodenum" disease in patients with actual "intestinal" or "urinary tract" disease when CT is not used.

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Contributors

SY, MT and NEK conceived the study. SY, MT, NEK, and TMN collected the data. SY, MT, and NEK determined the final diagnoses and the organs involved. SY and TMN analyzed the data. MT, NEK, and SI-Y reviewed the data analysis. SY wrote the initial and revised manuscript. MT, NEK, and SI-Y reviewed the manuscript.

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Competing Interests

None declared

Patient consent for publication

Not required

Provenance and peer review

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Data sharing statement

Not available

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superior mesenteric vein at multidetector CT. Jpn J Radiol. 2013;31:737-743.

Table 1: Patient characteristics

Characteristic	N = 326
Age in years; mean (standard deviation)	51.7 (20.0)
Male	141 (43.3%)
Living with	
With housemates	261 (80.1%)
Alone	46 (14.1%)
Unknown	19 (5.8%)
Referral letter	126 (38.6%)
Time of visit	
Day time (9:00 a.m. to 5:00 p.m.)	209 (64.1%)
Outside of normal office hours (5:00 p.m. to 9:00 a.m.)	117 (35.9%)
Required telephone communication†	81 (24.8%)
Did not require telephone communication†	22 (6.7%)
Type of abdominal pain	
Intermittent	211 (64.7%)
Persistent	109 (33.4%)
Unknown	6 (1.8%)
Examination at the first visit	
Blood test	281 (86.2%)
Chest or abdominal x-ray	222 (68.1%)
Computed tomography	155 (47.5%)
Ultrasonography	118 (36.2%)
Electrocardiography	91 (27.9%)
Blood gas	86 (26.4%)
Magnetic resonance imaging	9 (2.8%)
Other	31 (9.5%)
Management decided at the first visit	
Follow-up unnecessary	65 (19.9%)
SUH Department of General Medicine outpatient clinic	112 (34.4%)
Outpatient clinic of another hospital	42 (12.9%)
Outpatient clinic of another SUH department	34 (10.4%)
Admission to another SUH department	41 (12.6%)
Admission to SUH Department of General Medicine	33 (10.1%)
Admission to another hospital	4 (1.2%)

Data are shown as number (%) unless otherwise indicated.

Abbreviation: SUH, Saga University Hospital (Saga prefecture, Japan)

†We telephoned patients (or their relatives) whose final diagnoses were unknown because they only visited our department once and did not receiving a definitive diagnosis during their first visit. After being informed of the course of their condition with or without visiting another hospital, and/or the results of examinations at other hospitals, definitive diagnoses were determined.

Table 2: Classifications of organs involved and detailed diagnoses of patients with abdominal pain.

Organs involved	Detailed diagnosis
Intestinal (*n* = 125)	Gastroenteritis (28) Enteritis (20) Constipation (19) Ileus (9), colon diverticulitis (9) Acute appendicitis (6) Ischemic enteritis (5) Hyperperistalsis (4) Irritable bowel syndrome (3), Crohn's disease (3), intestinal membrane panniculitis (3), large intestinal diverticulum bleeding (3) Hereditary angioedema (2) Sigma volvulus (1), toxic megacolon (1), inguinal hernia (1), postoperative adhesion (1), familial Mediterranean fever (1), allergic purpura (1), ulcerous colitis (1), colon ulcer (1), non-obstructive intestinal membrane ischemia (1), drug-induced abdominal pain (1), celiac artery compression syndrome (1)
Esophagus, stomach, and duodenum (*n* = 58)	Gastroenteritis (28) Reflux esophagitis (12), Barrett's esophagus (12) Gastritis (9) Functional dyspepsia (4) Gastric ulcer (2) Duodenum ulcer (1), exogenous material in duodenum (1), bleeding gastric ulcer (1)
Urinary tract (*n* = 38)	Urinary tract or kidney stone (30) Urinary retention (3) Benign prostatic hyperplasia (1), urinary tract inflammation (1), hemorrhagic cystitis (1), acute bacterial prostatitis (1), acute pyelonephritis (1)
Liver and biliary tract (*n* = 25)	Cholecystitis (8) Cholangitis (5) Choledocholithiasis (4) Cholecystolithiasis (2), biliary colic (2), acute obstructive suppurative cholangitis (2), gallbladder cancer (1), acute alcoholic hepatitis (1)
Musculoskeletal	Bruise (4)

(*n* = 12)	Postoperative pain (3) Myalgia (2) Metastatic bone tumor (1), abdominal penetrating wound (1), femoral neuralgia (1)
Gynecological (*n* = 10)	Ovarian cancer (2) Endometriosis (1), adhesion of uterine appendages (1), atypical genital bleeding (1), pregnancy (1), ovarian cystoma (1), tubo-ovarian abscess (1), uterine cancer (1), ovarian tumor (1)
Pancreas (*n* = 9)	Pancreatitis (7) Pancreatic carcinoma (1), caput pancreatic cancer (1)
Respiratory (*n* = 5)	Pleural pneumonia (3) Influenza virus (1), cough (1)
Cardiovascular (*n* = 4)	Celiac artery dissection (2) Acute aortic dissection (1), superior mesenteric artery dissection (1)
Dermatological (*n* = 3)	Subcutaneous abscess or granuloma (2) Herpes zoster virus (1)
Other (*n* = 55)	Unknown (39) Psychological problem (8) Without definitive disease (7) Peritoneal cancer (1)

Table 3: Relationships between sites of abdominal pain and diagnoses of patients in the present study

Sites of pain	Organs involved	Sensitivity %	Specificity %	LR+ (95% CI)	LR- (95% CI)
Left-flank	Dermatological	66.7	83.9	4.14 (1.27–5.92)	0.40 (0.07–0.95)
Right-subcostal	Liver and biliary tract	56.0	84.4	3.59 (2.23–5.08)	0.52 (0.32–0.76)
Right-flank	Urinary tract	39.5	86.1	2.84 (1.71–4.42)	0.70 (0.53–0.87)
Mid-lower	Intestinal	32.0	87.1	2.47 (1.60–3.83)	0.78 (0.70–0.88)
Right-subcostal	Musculoskeletal	41.7	82.2	2.34 (1.05–4.0)	0.71 (0.39–0.99)
Epigastric	Esophagus, stomach, and duodenum	53.4	76.1	2.24 (1.60–2.99)	0.61 (0.46–0.79)
Left-flank	Urinary tract	31.6	85.4	2.16 (1.23–3.57)	0.80 (0.63–0.96)
Epigastric	Urinary tract	7.9	68.1	0.25 (0.08–0.66)	1.35 (1.15–1.44)
Periumbilical	Urinary tract	5.3	75.7	0.22 (0.06–0.72)	1.25 (1.08–1.31)
Mid-lower	Liver and biliary tract	4.0	78.4	0.19 (0.33–0.92)	1.22 (1.02–1.27)
Generalized	Esophagus, stomach, and duodenum	1.7	89.5	0.17 (0.03–0.90)	1.10 (1.01–1.12)

LR, likelihood ratio; CI, confidence interval

Figure legends

Figure 1. Diagnostic flow chart of abdominal pain.

A total of 2591 new outpatients visited the Department of General Medicine at Saga University Hospital in Japan during the study period, 2265 of whom were excluded because of a lack of abdominal pain or an age of less than 20. All 326 patients were enrolled. After more than 3 months from their first visits, the final diagnoses were determined by 2 physicians.

Figure 2. Classification of sites of abdominal pain.

Sites of abdominal pain were classified into 11 categories, including 9 different abdominal sections (right or left subcostal, right or left flank, right or left lower, epigastric, periumbilical, and mid-lower), generalized abdomen, and site-indeterminate. When patients had multiple sites of pain or multiple organs involved, classification and analysis of all sites and organs were performed. A total of 576 sites of abdominal pain were identified in the 326 subjects in the study. The most frequent complaint was epigastric pain (95/576; 16.5%), followed by periumbilical pain (72; 12.5%), mid-lower pain (62; 10.8%), and right-lower pain (61; 10.6%).

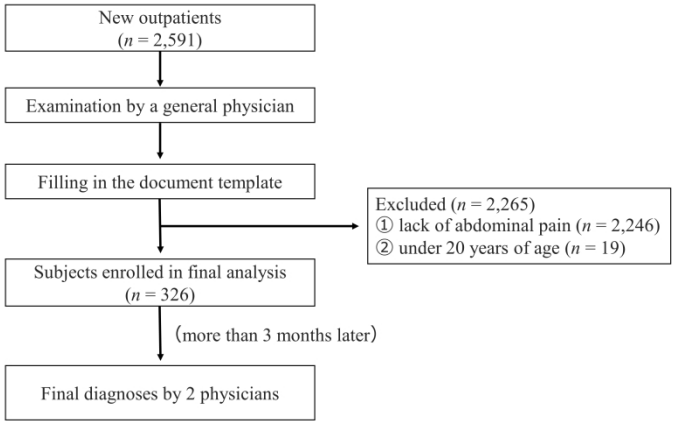

Figure 1

338x190mm (300 x 300 DPI)

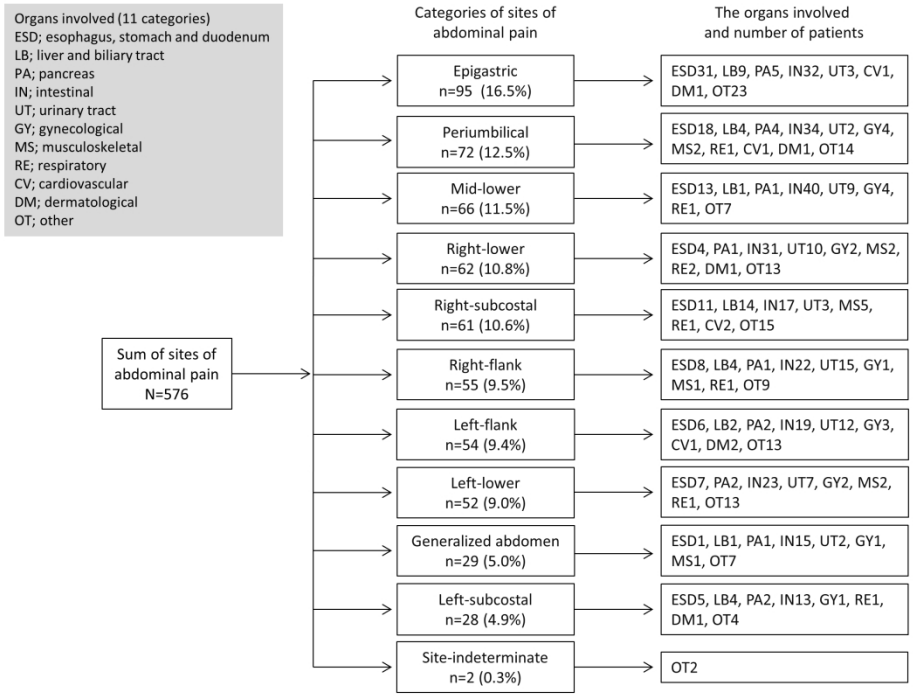

Figure 2

254x190mm (300 x 300 DPI)

Supplement 1: Investigations used in making final diagnoses or identifying the organs involved

Organs	Investigations										
	BC	CBC	CS	CT	ECG	EGD	MRI†	Urinalysis	US††	x-ray‡	Others*
ESD	+	+		+		+				+	
LB	+	+		+			+		+		
PA	+	+		+			+		+		
IN	+	+	+	+					+	+	
UT	+	+		+				+	+	+	
GY	+	+						+	+		
MS	+	+		+			+			+	
RE	+	+		+						+	+
CV	+	+		+	+						
DM											+

†: including magnetic resonance cholangiopancreatography

††: including transvaginal US

‡: including kidney ureter bladder or bone x-ray

*: including human chorionic gonadotropin measurements, rapid immunoassay of influenza A and B nucleoprotein antigens, macroscopic inspection, cytology, or histopathological studies

BC; blood chemistry analysis, CBC; complete blood cell count, CS; colonoscopy, CT; computed tomography, ECG; electrocardiography, EGD; esophagogastroduodenoscopy, MRI; magnetic resonance imaging, US; ultrasonography

ESD; esophagus, stomach and duodenum, LB; liver and biliary tract, PA; pancreas, IN; intestinal, UT; urinary tract, GY; gynecological, MS; musculoskeletal, RE; respiratory, CV; cardiovascular, DM; dermatological

Supplement 2. Breakdown of age groups in the present study

Age groups†	Total (n = 326)	Male (n = 141)	Female (n = 185)
20-29	37 (11.3%)	5 (3.5%)	32 (17.3%)
30-39	53 (16.3%)	25 (17.7%)	28 (15.1%)
40-49	58 (17.8%)	24 (17.0%)	34 (18.4%)
50-59	48 (14.7%)	19 (13.5%)	29 (15.7%)
60-69	54 (16.6%)	31 (22.0%)	23 (12.4%)
70-79	38 (11.7%)	18 (12.8%)	20 (10.8%)
80-89	36 (11.0%)	19 (13.5%)	17 (9.2%)
90-99	2 (0.6%)	N/A	2 (1.1%)

†: range in years

Supplement 3: Characteristics of patients who underwent computed tomography

Characteristic	N = 155
Age in years; mean (standard deviation)	57.5 (17.7)
Male	74 (47.7%)
Living with	
With housemates	131 (84.5%)
Alone	17 (11.0%)
Unknown	7 (4.5%)
Referral letter	63 (40.6%)
Time of visit	
Day time (9:00 a.m. to 5:00 p.m.)	81 (52.3%)
Outside of normal office hours (5:00 p.m. to 9:00 a.m.)	74 (47.7%)
Type of abdominal pain	
Intermittent	117 (75.5%)
Persistent	36 (23.2%)
Unknown	2 (1.8%)
Management decided at the first visit	
Follow-up unnecessary	20 (12.9%)
SUH Department of General Medicine outpatient clinic	39 (25.2%)
Outpatient clinic of another hospital	14 (9.0%)
Outpatient clinic of another SUH department	18 (11.6%)
Admission to another SUH department	36 (23.2%)
Admission to SUH Department of General Medicine	28 (18.1%)
Admission to another hospital	2 (1.3%)
Sites of abdominal pain	
Epigastric	43 (27.7%)
Right-subcostal	38 (24.5%)
Periumbilical	38 (24.5%)
Right- flank	32 (20.6%)
Mid-lower	30 (19.4%)
Right-lower	29 (18.7%)
Left- flank	23 (18.4%)
Left-lower	20 (12.9%)
Generalized abdomen	18 (11.6%)
Left-subcostal	13 (8.4%)
Site-indeterminate	2 (1.3%)

The organs involved	
Intestinal	53 (34.2%)
Urinary tract	27 (17.4%)
Liver and biliary tract	20 (12.9%)
Esophagus, stomach, and duodenum	14 (9.0%)
Pancreas	8 (5.2%)
Musculoskeletal	5 (3.2%)
Gynecological	4 (2.6%)
Cardiovascular	4 (2.6%)
Respiratory	2 (1.3%)
Dermatological	1 (0.6%)
Other	24 (15.5%)

Data are shown as number (%) unless otherwise indicated.

Supplement 4: Relationships between sites of abdominal pain and the organs involved in patients who underwent computed tomography (N=155)

Sites of pain	Organs involved	Sensitivity %	Specificity %	LR+ (95% CI)	LR- (95% CI)
Left- subcostal	Dermatological	100	92.2	12.83 (2.51-12.83)	0.00 (0.00–0.86)
Left- flank	Dermatological	100	85.7	7.00 (1.41-7.00)	0.00 (0-0.93)
Mid-lower	Intestinal	39.6	91.2	4.49 (2.29–9.03)	0.66 (0.56–0.80)
Right-subcostal	Musculoskeletal	80.0	77.3	3.53 (1.59–4.36)	0.26 (0.05–0.81)
Right-subcostal	Liver and biliary tract	65.0	81.5	3.51 (2.11–5.01)	0.43 (0.23–0.70)
Periumbilical	Gynecological	75.0	76.8	3.24 (1.25-4.22)	0.33 (0.06-0.92)
Right-lower	Intestinal	30.2	87.3	2.96 (1.31-6.69)	0.80 (0.67-0.95)
Left-flank	Urinary tract	29.6	88.3	2.53 (1.18–5.11)	0.80 (0.61–0.97)
Epigastric	Spleen	62.5	74.1	2.42 (1.14-3.50)	0.51 (0.19-0.95)
Generalized	Intestinal	18.9	92.2	2.41 (1.03-5.64)	0.88 (0.78-1.00)
Epigastric	Esophagus, stomach, and duodenum	57.1	75.2	2.30 (1.24–3.42)	0.57 (0.29–0.91)
Right-flank	Urinary tract	37.0	82.8	2.16 (1.13–3.80)	0.76 (0.55–0.97)
Epigastric	Intestinal	17.0	66.7	0.51 (0.26-0.94)	1.25 (1.02-1.44)
Right-subcostal	Intestinal	15.1	70.6	0.51 (0.25-1.00)	1.20 (1.00-1.37)
Epigastric	Urinary tract	11.1	68.8	0.36 (0.12–0.94)	1.29 (1.03–1.43)
Periumbilical	Urinary tract	7.4	71.9	0.26 (0.07–0.86)	1.29 (1.05–1.38)
Right-lower	Liver and biliary tract	0.0	78.5	0.00	1.27

	(0.00-0.76)	(1.06-1.27)

LR, likelihood ratio; CI, confidence interval

Supplement 5: Relationships between sites of abdominal pain and diagnoses in patients whose diagnoses were made solely on all the information in medical charts (N=245)

Sites of pain	Organs involved	Sensitivity, %	Specificity, %	LR+ (95% CI)	LR- (95% CI)
Left- flank	Dermatological	66.7	84.3	4.25 (1.29-6.11)	0.40 (0.07-0.94)
Right-subcostal	Liver and biliary tract	54.2	85.1	3.63 (2.16–5.40)	0.54 (0.34–0.76)
Mid-lower	Intestinal	35.2	87.9	2.91 (1.77–4.82)	0.74 (0.64–0.85)
Right-subcostal	Musculoskeletal	50.0	82.3	2.82 (1.17–4.66)	0.61 (0.26–0.96)
Right-flank	Urinary tract	40.0	85.2	2.71 (1.58–4.35)	0.70 (0.53–0.88)
Left-flank	Urinary tract	34.3	86.7	2.57 (1.42–4.37)	0.76 (0.58–0.92)
Epigastric	Spleen	55.6	75.8	2.30 (1.07-3.49)	0.59 (0.25-0.98)
Right-lower	Intestinal	26.1	86.6	1.95 (1.15-3.30)	0.85 (0.75-0.97)
Epigastric	Esophagus, stomach, and duodenum	41.7	77.5	1.85 (1.14–2.80)	0.75 (0.55–0.96)
Epigastric	Urinary tract	8.6	71.9	0.31 (0.10–0.82)	1.27 (1.06–1.37)
Periumbilical	Urinary tract	5.7	78.1	0.26 (0.07–0.87)	1.21 (1.03–1.27)
Mid-lower	Liver and biliary tract	4.2	77.8	0.19 (0.03-0.93)	1.23 (1.02-1.28)
Right-lower	Esophagus, stomach, and duodenum	2.8	79.4	0.14 (0.02-0.70)	1.22 (1.07-1.26)
Left- subcostal	Urinary tract	0.0	89.5	0.00 (0–0.96)	1.12 (1.00–1.12)
Right-lower	Liver and biliary tract	0.0	80.1	0.00 (0.00-0.70)	1.25 (1.07-1.25)
Left-lower	Liver and biliary tract	0.0	83.3	0.00 (0.00-0.83)	1.20 (1.03-1.20)

LR, likelihood ratio; CI, confidence interval

Reporting checklist for diagnostic test accuracy study.

Based on the STARD guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STARDreporting guidelines, and cite them as:

Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, LijmerJG Moher D, Rennie D, de Vet HCW, Kressel HY, Rifai N, Golub RM, Altman DG, Hooft L, Korevaar DA, Cohen JF, For the STARD Group. STARD 2015: An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies.

Reporting Item	Page Number
Title or abstract	

	#1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	2
Abstract			
	#2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2-3
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Test results	#23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	15
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<Short explanation>

†：As this study include multiple hypothesis, the distribution of severity and alternative diagnosis of all groups can not be described.

††：Because the present research is a prospective observational study, there are no adverse events.