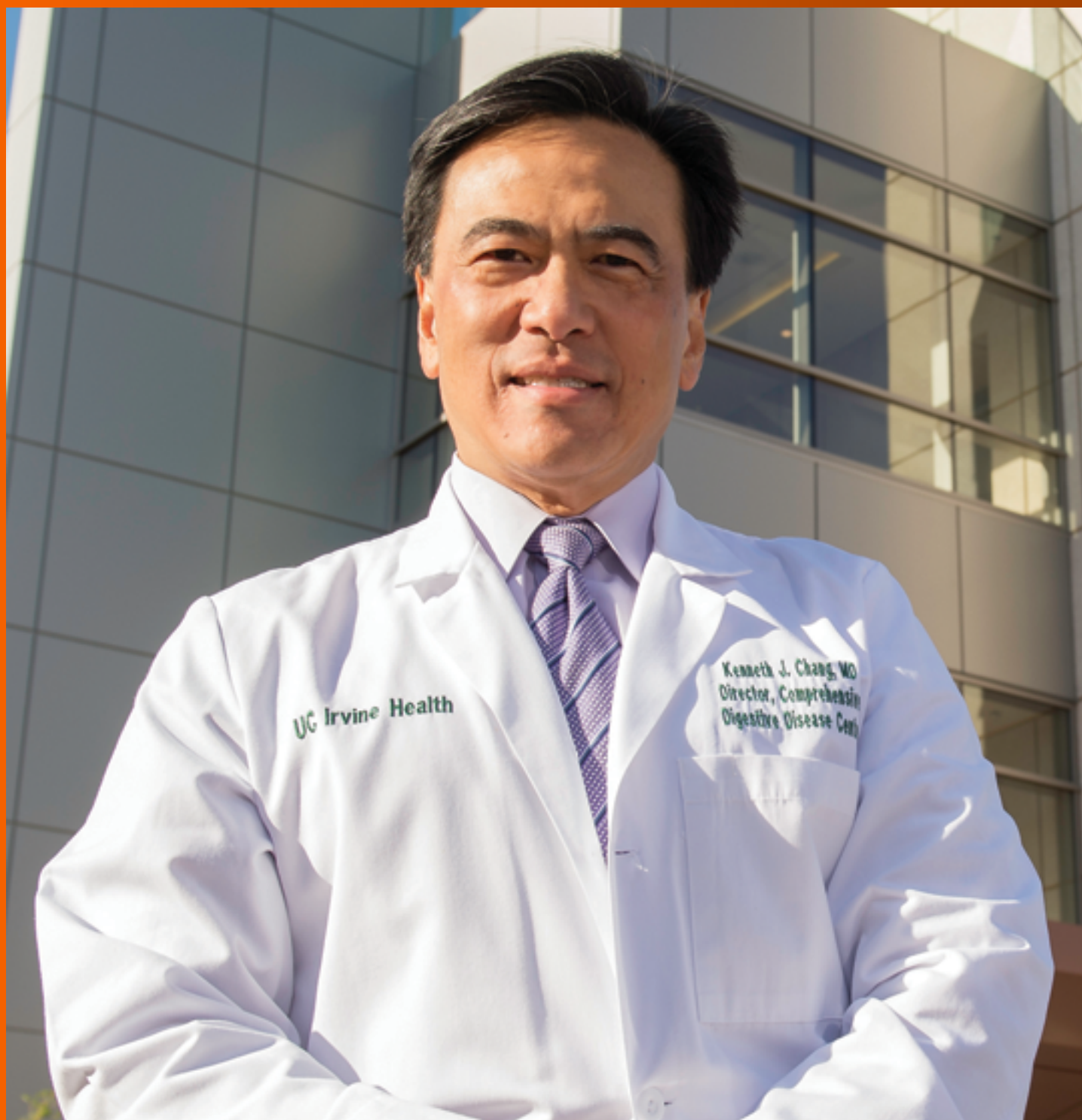


World Journal of *Gastroenterology*

World J Gastroenterol 2019 January 7; 25(1): 1-150



**FRONTIER**

- 1 Endoscopic foregut surgery and interventions: The future is now. The state-of-the-art and my personal journey
Chang KJ

REVIEW

- 42 Hepatitis C virus core protein modulates several signaling pathways involved in hepatocellular carcinoma
Mahmoudvand S, Shokri S, Taherkhani R, Farshadpour F

MINIREVIEWS

- 59 Role of surveillance imaging and endoscopy in colorectal cancer follow-up: Quality over quantity?
Liu SL, Cheung WY
- 69 Initial management for acute lower gastrointestinal bleeding
Aoki T, Hirata Y, Yamada A, Koike K

ORIGINAL ARTICLE**Basic Study**

- 85 Endoscopic trans-esophageal submucosal tunneling surgery: A new therapeutic approach for diseases located around the aorta ventralis
Xiong Y, Chen QQ, Chai NL, Jiao SC, Ling Hu EQ

Case Control Study

- 95 Autonomic functions and gastric motility in children with functional abdominal pain disorders
Karunanayake A, Rajindrajith S, de Silva HA, Gunawardena S, Devanarayana NM

Retrospective Study

- 107 Usefulness of urinary trypsinogen-2 and trypsinogen activation peptide in acute pancreatitis: A multicenter study in Japan
Yasuda H, Kataoka K, Takeyama Y, Takeda K, Ito T, Mayumi T, Isaji S, Mine T, Kitagawa M, Kiriya S, Sakagami J, Masamune A, Inui K, Hirano K, Akashi R, Yokoe M, Sogame Y, Okazaki K, Morioka C, Kihara Y, Kawa S, Tanaka M, Andoh A, Kimura W, Nishimori I, Furuse J, Yokota I, Shimosegawa T
- 118 Nomograms for predicting pathological response to neoadjuvant treatments in patients with rectal cancer
Ren DL, Li J, Yu HC, Peng SY, Lin WD, Wang XL, Ghoorun RA, Luo YX

Clinical Trials Study

- 138** Molecular detection of epithelial-mesenchymal transition markers in circulating tumor cells from pancreatic cancer patients: Potential role in clinical practice
Zhao XH, Wang ZR, Chen CL, Di L, Bi ZF, Li ZH, Liu YM

ABOUT COVER

Kenneth J Chang, MD, FACC, FASGE, Professor, Gastroenterology and Hepatology Division, H.H. Chao Comprehensive Digestive Disease Center, University of California, Irvine Medical Center, Orange, CA 92868, United States.

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, etc. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Report® cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35th among 80 journals in gastroenterology and hepatology (quartile in category Q2).

**RESPONSIBLE EDITORS
FOR THIS ISSUE**

Responsible Electronic Editor: Yan Huang

Proofing Editorial Office Director: Ze-Mao Gong

NAME OF JOURNAL*World Journal of Gastroenterology***ISSN**

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS<http://www.wjgnet.com/1007-9327/editorialboard.htm>**EDITORIAL OFFICE**

Ze-Mao Gong, Director

PUBLICATION DATE

January 7, 2019

COPYRIGHT

© 2019 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 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>



Retrospective Study

Usefulness of urinary trypsinogen-2 and trypsinogen activation peptide in acute pancreatitis: A multicenter study in Japan

Hiroaki Yasuda, Keisho Kataoka, Yoshifumi Takeyama, Kazunori Takeda, Tetsuhide Ito, Toshihiko Mayumi, Shuji Isaji, Tetsuya Mine, Motoji Kitagawa, Seiki Kiriya, Junichi Sakagami, Atsushi Masamune, Kazuo Inui, Kenji Hirano, Ryukichi Akashi, Masamichi Yokoe, Yoshio Sogame, Kazuichi Okazaki, Chie Morioka, Yasuyuki Kihara, Shigeyuki Kawa, Masao Tanaka, Akira Andoh, Wataru Kimura, Isao Nishimori, Junji Furuse, Isao Yokota, Tooru Shimosegawa

ORCID number: Hiroaki Yasuda (0000-0002-8346-9853); Keisho Kataoka (0000-0002-7227-3310); Yoshifumi Takeyama (0000-0002-8034-6997); Kazunori Takeda (0000-0002-0224-4848); Tetsuhide Ito (0000-0001-5381-0136); Toshihiko Mayumi (0000-0002-4462-9375); Shuji Isaji (0000-0002-7683-6328); Tetsuya Mine (0000-0001-6069-9747); Motoji Kitagawa (0000-0003-4431-9390); Seiki Kiriya (0000-0001-8163-8783); Junichi Sakagami (0000-0002-1219-4709); Atsushi Masamune (0000-0001-7184-7282); Kazuo Inui (0000-0002-0510-1412); Kenji Hirano (0000-0002-7348-892X); Ryukichi Akashi (0000-0002-9551-8720); Masamichi Yokoe (0000-0002-6186-887X); Yoshio Sogame (0000-0002-6919-5625); Kazuichi Okazaki (0000-0003-3424-3142); Chie Morioka (0000-0003-3088-9165); Yasuyuki Kihara (0000-0001-5453-8699); Shigeyuki Kawa (0000-0001-7870-9149); Masao Tanaka (0000-0003-0995-0494); Akira Andoh (0000-0001-8533-2669); Wataru Kimura (0000-0001-8761-3667); Isao Nishimori (0000-0003-4183-9243); Junji Furuse (0000-0003-0663-6117); Isao Yokota (0000-0001-6254-2225); Tooru Shimosegawa (0000-0003-1255-5444).

Hiroaki Yasuda, Keisho Kataoka, Junichi Sakagami, Yoshio Sogame, Department of Medicine, Division of Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, Kyoto 6028566, Japan

Keisho Kataoka, Department of Gastroenterology, Otsu Municipal Hospital, Otsu 5200804, Japan

Yoshifumi Takeyama, Department of Surgery, Kindai University Faculty of Medicine, Osakasayama 5898511, Japan

Kazunori Takeda, Department of Surgery, National Hospital Organization Sendai Medical Center, Sendai 9838520, Japan

Tetsuhide Ito, Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 8128582, Japan

Toshihiko Mayumi, Department of Emergency Medicine, University of Occupational and Environmental Health, Kitakyushu 8078555, Japan

Shuji Isaji, Department of Hepatobiliary-Pancreatic and Transplant Surgery, Mie University School of Medicine, Tsu 5148507, Japan

Tetsuya Mine, Department of Gastroenterology, Tokai University School of Medicine, Isehara 2591193, Japan

Motoji Kitagawa, Department of Nutritional Sciences, Nagoya University of Arts and Sciences, Nisshin 4700196, Japan

Seiki Kiriya, Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki 5038502, Japan

Atsushi Masamune, Tooru Shimosegawa, Division of Gastroenterology, Tohoku University Graduate School of Medicine, Sendai 9808575, Japan

Kazuo Inui, Department of Gastroenterology, Fujita Health University Bantane Hospital, Nagoya 4548509, Japan

Kenji Hirano, Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, Tokyo 1130033, Japan

Author contributions: All authors helped to perform the research; Yasuda H contributed to writing the manuscript and performing procedures and data analysis; Kataoka K contributed to writing the manuscript and drafting conception and design; Takeyama Y, Takeda K, Ito T, Mayumi T, Isaji S, Mine T, Kitagawa M, Kiriya S, Sakagami J, Masamune A, Inui K, Hirano K, Akashi R, Yokoe M, Sogame Y, Okazaki K, Morioka C, Kihara Y, Kawa S, Tanaka M, Andoh A, Kimura W, Nishimori I and Furuse J contributed to writing the manuscript; Yokota I contributed to writing the manuscript and reviewing the statistical method; Shimosegawa T contributed to writing the manuscript and drafting conception and design.

Institutional review board statement: The Institutional Review Board committee of each institution approved this study.

Informed consent statement: An informed written consent was obtained from all patients before inclusion.

Conflict-of-interest statement: The qualitative and quantitative analyses of urinary trypsinogen-2 were performed free of charge by Unitika Ltd. (Osaka, Japan). Mayumi T received research funding. The other authors declare no conflict of interest.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (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: Unsolicited manuscript

Received: October 19, 2018

Peer-review started: October 19, 2018

First decision: December 5, 2018

Revised: December 12, 2018

Accepted: December 19, 2018

Article in press: December 19, 2018

Published online: January 7, 2019

Ryukichi Akashi, Department of Healthcare Center, Kumamoto Regional Medical Center, Kumamoto 8600811, Japan

Masamichi Yokoe, General Internal Medicine, Japanese Red Cross Nagoya Daini Hospital, Nagoya 4668650, Japan

Kazuichi Okazaki, The Third Department of Internal Medicine, Division of Gastroenterology and Hepatology, Kansai Medical University, Hirakata 5731010, Japan

Chie Morioka, Third Department of Internal Medicine, Nara Medical University, Kashihara 6348521, Japan

Yasuyuki Kihara, Department of Gastroenterology, Kitakyushu General Hospital, Kitakyushu 8028517, Japan

Shigeyuki Kawa, Department of Internal Medicine, Matsumoto Dental University, Shiojiri 3990781, Japan

Masao Tanaka, Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka 8128582, Japan

Akira Andoh, Division of Gastroenterology, Department of Internal Medicine, Shiga University of Medical Science, Otsu 5202192, Japan

Wataru Kimura, Department of Gastroenterological, General, Breast and Thyroid Surgery, Yamagata University Faculty of Medicine, Yamagata 9909585, Japan

Isao Nishimori, Department of Gastroenterology and Hepatology, Kochi Medical School, Nankoku 7838505, Japan

Junji Furuse, Faculty of Medicine, Department of Medical Oncology, Kyorin University, Mitaka 1818611, Japan

Isao Yokota, Department of Biostatistics, Hokkaido University, Sapporo 0600808 Japan

Corresponding author: Hiroaki Yasuda, MD, PhD, Doctor, Senior Lecturer, Department of Medicine, Division of Gastroenterology and Hepatology, Kyoto Prefectural University of Medicine, 465 Kajii-cho Kawaramachi Hirokoji Kamigyo-ku, Kyoto 6028566, Japan. hiyasuda@koto.kpu-m.ac.jp

Telephone: +81-75-2515519

Fax: +81-75-2510710

Abstract

BACKGROUND

Rapid urinary trypsinogen-2 dipstick test and levels of urinary trypsinogen-2 and trypsinogen activation peptide (TAP) concentration have been reported as prognostic markers for the diagnosis of acute pancreatitis.

AIM

To reconfirm the validity of all these markers in the diagnosis of acute pancreatitis by undertaking a multi-center study in Japan.

METHODS

Patients with acute abdominal pain were recruited from 17 medical institutions in Japan from April 2009 to December 2012. Urinary and serum samples were collected twice, at enrollment and on the following day for measuring target markers. The diagnosis and severity assessment of acute pancreatitis were assessed based on prognostic factors and computed tomography (CT) Grade of the Japanese Ministry of Health, Labour, and Welfare criteria.

RESULTS

A total of 94 patients were enrolled during the study period. The trypsinogen-2 dipstick test was positive in 57 of 78 patients with acute pancreatitis (sensitivity, 73.1%) and in 6 of 16 patients with abdominal pain but without any evidence of acute pancreatitis (specificity, 62.5%). The area under the curve (AUC) score of urinary trypsinogen-2 according to prognostic factors was 0.704, which was highest in all parameter. The AUC scores of urinary trypsinogen-2 and TAP according to CT Grade were 0.701 and 0.692, respectively, which shows higher

than other pancreatic enzymes. The levels of urinary trypsinogen-2 and TAP were significantly higher in patients with extended extra-pancreatic inflammation as evaluated by CT Grade.

CONCLUSION

We reconfirmed urinary trypsinogen-2 dipstick test is useful as a marker for the diagnosis of acute pancreatitis. Urinary trypsinogen-2 and TAP may be considered as useful markers to determine extra-pancreatic inflammation in acute pancreatitis.

Key words: Acute pancreatitis; Trypsinogen activation peptide; Urinary trypsinogen-2 dipstick test

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: A total of 94 patients with acute abdominal pain were enrolled from 17 medical institutions in Japan from April 2009 to December 2012. The trypsinogen-2 dipstick test was positive in 57 of 78 patients with acute pancreatitis (sensitivity, 73.1%) and in 6 of 16 patients with abdominal pain but without any evidence of acute pancreatitis (specificity, 62.5%). The levels of urinary trypsinogen-2 and trypsinogen activation peptide (TAP) were significantly higher in patients with extended extra-pancreatic inflammation as evaluated by CT Grade. Urinary trypsinogen-2 and TAP may be considered as additional markers to determine extra-pancreatic inflammation in acute pancreatitis.

Citation: Yasuda H, Kataoka K, Takeyama Y, Takeda K, Ito T, Mayumi T, Isaji S, Mine T, Kitagawa M, Kiriya S, Sakagami J, Masamune A, Inui K, Hirano K, Akashi R, Yokoe M, Sogame Y, Okazaki K, Morioka C, Kihara Y, Kawa S, Tanaka M, Andoh A, Kimura W, Nishimori I, Furuse J, Yokota I, Shimosegawa T. Usefulness of urinary trypsinogen-2 and trypsinogen activation peptide in acute pancreatitis: A multicenter study in Japan. *World J Gastroenterol* 2019; 25(1): 107-117

URL: <https://www.wjgnet.com/1007-9327/full/v25/i1/107.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v25.i1.107>

INTRODUCTION

Acute pancreatitis is a common disease accompanied by acute abdominal pain. However, the early diagnosis of acute pancreatitis remains difficult, due to the difficulty of performing quick measurements of pancreatic enzymes in most clinics. Japanese guidelines for the management of acute pancreatitis in 2015 (JPN Guideline 2015)^[1] recommended the measurement of serum lipase instead of serum amylase for the diagnosis of acute pancreatitis because of its higher specificity for pancreas. In fact, serum amylase is more often measured than serum lipase in Japan, because only amylase can be rapidly measured in most of the emergency centers. Trypsinogen-2 is a pancreatic enzyme known to remain elevated longer in patients with acute pancreatitis, with higher levels in the urine than in serum, compared to the commonly measured pancreatic enzyme amylase^[2]. A rapid test strip for the detection of urinary trypsinogen-2 was developed in Finland and was reported to be useful for the diagnosis of acute pancreatitis^[3-8], and its accuracy and usefulness was also verified in Japan^[9].

Trypsinogen activation peptide (TAP) is the amino-terminus peptide released by the activation of trypsinogen. In experimental acute pancreatitis, the inappropriate activation of trypsinogen within the pancreas results in the release of TAP into the blood, urine, and peritoneum^[10,11]. The concentration of urinary TAP is thought to correlate directly with the severity of acute pancreatitis, reflecting the degree of trypsinogen activation in the pancreas^[12-14]. The concentration of urinary trypsinogen-2 has also been previously reported to be a candidate prognostic marker of severe acute pancreatitis^[6].

The criteria for severity assessment of acute pancreatitis was fully revised in Japan in 2008^[15], in which the diagnosis of severe acute pancreatitis can be made according to 9 prognostic factors and/or on computed tomography (CT) grading based on

contrast-enhanced CT. These criteria emphasize that the assessment of severity at the initial medical examination plays an important role in introducing adequate early treatment and the transfer of patients to a medical facility that is able to provide intensive treatment. However, CT has a problem for the radiation exposure and contrast-enhanced CT may cause worsening of renal dysfunction, often accompanied by severe acute pancreatitis. Therefore, the establishment of a simple marker and method in clinical practice is strongly warranted to diagnose severe acute pancreatitis.

In Japan, any examination or investigation without health insurance coverage is hardly performed, because we have national public health care system to cover them. We need clinical evidence of a useful marker to predict severity level of acute pancreatitis in order to be approved by and consider future inclusion under national health insurance system in Japan.

In the present study, in a multi-center study we performed rapid urinary trypsinogen-2 dipstick test to reconfirm its validity in the diagnosis of acute pancreatitis. In addition, we measured trypsinogen-2 and TAP levels in urine samples to evaluate their usefulness as possible prognostic markers of severe acute pancreatitis as assessed by Japanese criteria.

MATERIALS AND METHODS

Patients

Patients with acute abdominal pain were enrolled prospectively in this study. All patients who were seen in the emergency centers and hospitalized at 17 medical institutions in Japan from April 2009 to December 2012 were considered eligible for this study. The Institutional Review Board committee of each institution approved this study and an informed written consent was obtained from all patients before inclusion. This study was registered with the UMIN Clinical Trials Registry (reference no. UMIN000001622).

Study design

Urinary and serum samples were collected from all study participants twice, at enrollment and on the following day within 48 h after admission. These samples were frozen immediately and stored at -20 °C until analysis. The qualitative analyses of urinary trypsinogen-2 were performed using a dipstick test (Actim Pancreatitis, Medix Biochemica, Kauniainen, Finland). A quantitative immunoassay (Trypsinogen-2 Iema Test, Medix Biochemica) of urinary trypsinogen-2 was performed using commercially available kit of Unitika Ltd. (Osaka, Japan). The concentration of TAP in urine was measured by ELISA (Oriental Yeast Co. Ltd., Tokyo Japan). The urine and serum levels of amylase, lipase, and creatinine were measured by each institution or BML Inc. (Tokyo, Japan).

Acute pancreatitis was diagnosed according to the diagnostic criteria established by the Japan Ministry of Health, Labour, and Welfare (JMHLW) (2008)^[16]. These criteria are composed of 3 items: (1) acute abdominal pain and tenderness in the upper abdomen; (2) elevated levels of pancreatic enzymes in the blood or urine; and (3) findings of acute pancreatitis detected by ultrasonography (US), CT, or magnetic resonance imaging (MRI). Patients who presented with at least 2 of the above 3 manifestations and in whom other pancreatic and acute abdominal diseases had been ruled out were diagnosed as having acute pancreatitis.

The severity of acute pancreatitis within 48 h of entry was evaluated using the criteria established by the JMHLW (2008) for severity assessment of acute pancreatitis, in which patients were diagnosed as severe acute pancreatitis based on ≥ 3 of 9 prognostic factors and/or CT grading ≥ 2 based on contrast-enhanced CT scan (Table 1)^[15].

The primary outcome of this study was to find the association between the values of urinary trypsinogen-2 and TAP and the severity levels of acute pancreatitis. We investigated the relative accuracy of the urine trypsinogen-2 dipstick test for the diagnosis of acute pancreatitis and attempted to reconfirm its validity with published results.

Statistical analysis

In the qualitative evaluation of urinary trypsinogen-2 dipstick test for the diagnosis of acute pancreatitis, the sensitivity and of specificity with 95% confidence interval (CI), lower bound to upper bound were calculated. In the quantitative measurement of urinary trypsinogen-2 and TAP, data were expressed as median and lower and upper quartile. Their area under the curve (AUC) scores between severe and mild pancreatitis groups were calculated by logistic regression analysis. The relationship

Table 1 The severity scoring system of acute pancreatitis of the Japanese Ministry of Health, Labour and Welfare (2008)^[15]

Prognostic factors (1 point for each factor)	
Base excess ≤ 3 mEq/L or shock (systolic blood pressure < 80 mmHg)	
$\text{PaO}_2 \leq 60$ mmHg (room air) or respiratory failure (respirator management is needed)	
$\text{BUN} \geq 40$ mg/dL (or $\text{Cr} \geq 2.0$ mg/dL) or oliguria (daily urine output < 400 mL even after fluid replacement)	
$\text{LDH} \geq 2$ times of upper limit of normal	
Platelet count $\leq 100000/\text{mm}^3$	
Serum $\text{Ca} \leq 7.5$ mg/dL	
$\text{CRP} \geq 15$ mg/dL	
Number of positive measures in SIRS criteria ≥ 3	
Age ≥ 70 yr	
CT Grade by CECT	
Extra-pancreatic progression of inflammation	
Anterior pararenal space	0 point
Root of mesocolon	1 point
Beyond lower pole of kidney	2 points
Hypo-enhanced lesion of the pancreas	
The pancreas is conveniently divided into three segments (head, body, and tail).	
Localized in each segment or only surrounding the pancreas	0 point
Covers 2 segments	1 point
Occupies entire 2 segments or more	2 points
1 + 2 = total scores	
Total score = 0 or 1	Grade 1
Total score = 2	Grade 2
Total score = 3 or more	Grade 3
Assessment of severity	
(1) If prognostic factors are scored as 3 points or more, or (2) If CT Grade grade is judged as Grade grade 2 or more, the severity grading is evaluated to be as "severe".	
Measures in SIRS diagnostic criteria: (1) Temperature $> 38^\circ\text{C}$ or $< 36^\circ\text{C}$; (2) Heart rate > 90 beats/min; (3) Respiratory rate > 20 breaths/min or $\text{PaCO}_2 < 32$ torr; and (4) $\text{WBC} > 12000$ cells/ mm^3 , < 4000 cells/ mm^3 , or $> 10\%$ immature (band) forms.	

WBC: White blood cell; CT: Computed tomography; LDH: lactate dehydrogenase; CRP: C-reaction protein.

among 3 groups evaluated by scores of CT Grade was analyzed using ordinal logistic regression. Significance was defined by a *P* value of < 0.05 . All statistical analyses were performed using JMP® statistical software, version 8 (SAS Institute Inc., Cary, NC, United States).

RESULTS

A total of 94 patients with acute abdominal pain who were seen in the emergency centers and hospitalized at 17 medical institutions in Japan were included in this study. The mean age was 58.0 years (range: 25 to 92 years). Of these patients, 78 (82.9%) were diagnosed with acute pancreatitis and 16 (17.1%) with different diseases such as acute gastritis, biliary stones, and peptic ulcer. The characteristics of patients at enrollment are summarized in Table 2.

The results of the urinary trypsinogen-2 dipstick test were positive in 57 of the 78 patients with acute pancreatitis (sensitivity: 73.1%, 95%CI: 0.62-0.82). Dipstick results were also positive in 6 of 16 patients with abdominal pain but no evidence of acute pancreatitis (specificity: 62.5%, 95%CI: 0.39-0.82). The positive and negative predictive values of the trypsinogen-2 dipstick test for the diagnosis of acute pancreatitis were 90.5% and 32.3%, respectively.

When we distributed our data at enrollment based on prognostic factors of the JMHLW criteria, the median levels of urinary trypsinogen-2 were 2.87 and 6.49 mg/dL in patients with mild and severe pancreatitis and the AUC score was 0.704, which was highest among all parameters (Table 3). It was obvious that AUC score of

Table 2 The characteristics of patients at enrollment

	Acute pancreatitis (<i>n</i> = 78)	Other disease (<i>n</i> = 16)
Age, median (IQR), yr	57 (28)	61 (26)
Sex, <i>n</i> : male/female	50/26	9/7
Etiology of acute pancreatitis, <i>n</i> (%)		
Alcohol	26 (33.3)	
Gallstones	13 (16.7)	
Idiopathic	12 (15.4)	
Post-ERCP	5 (6.4)	
Others	22 (28.2)	
Prognostic factor score by JMHLW (2008) criteria (<i>n</i> = 78)		
Mean (SD)	0.9 (1.2)	
Severe acute pancreatitis (≥ 3), <i>n</i> (%)	9 (11.5)	
Score of CT Grade by JMHLW (2008) criteria (<i>n</i> = 70)		
Mean (SD)	1.0 (1.2)	
Severe acute pancreatitis (Score ≥ 2), <i>n</i> (%)	28 (40)	

serum creatinine was high, because it was one of prognostic factors.

The median levels of urinary trypsinogen-2 and TAP were 2.69 mg/dL and 2.07 ng/mL, respectively in patients with mild pancreatitis, and 14.68 mg/dL and 3.98 ng/mL, respectively in those with severe pancreatitis, according to CT Grade of the JMHLW criteria (Table 4). Their AUC scores were 0.701 and 0.692, respectively, which are higher than other pancreatic enzymes. The ratio of urinary trypsinogen-2 or TAP to urinary creatinine was calculated to correct the influence of dehydration. Their AUC scores of the urinary trypsinogen-2 and TAP to creatinine ratio were also high (Table 4). Compared with the levels of urinary trypsinogen-2 and TAP at enrollment, both of the levels on the following day and the values that subtracted the level at enrollment from that on the following day were not related to disease severity (data not shown).

The levels of urinary trypsinogen-2 and TAP showed significant differences between different scores of extra-pancreatic progression of inflammation, but no significant differences were observed between the different scores of hypo-enhanced pancreas lesions (Table 5). Furthermore, the levels of urinary trypsinogen-2 to creatinine ratio (trypsinogen-2/cre) and TAP to creatinine ratio (TAP/cre) also showed significant differences between different scores of extra-pancreatic progression of inflammation.

DISCUSSION

In this multi-center study, we reconfirmed the validity of performing urinary trypsinogen-2 dipstick test to isolate patients with acute pancreatitis who attends emergency clinics with acute abdominal pain. We also found that sensitivity and positive predictive value of this test in patients with acute pancreatitis is quite high and as such further strengthens its applicability in clinical practice. The frequency of acute pancreatitis diagnosed in patients with acute abdominal pain was reported to be approximately 5% in a previous Japanese multicenter study^[17]. This simple and easy laboratory procedure (urinary trypsinogen-2 dipstick test) may be able to make a quick decision for diagnosing patients with acute pancreatitis without diverging to measure other conventional pancreatic enzymes such as amylase, lipase, and trypsin, which needs laboratory technicians and/or expensive instruments.

In Japan, the present diagnostic criteria of acute pancreatitis as established by the JMHLW were revised in part in 2008^[16] and includes at least 2 of the 3 manifestations and exclusion of other diseases compatible with acute abdominal pain. In contrast, Revised Atlanta Criteria^[18] are composed of similar 3 items, strict in elevated levels of pancreatic enzymes and do not need to exclude other diseases. If the diagnosis of acute pancreatitis is established by abdominal pain and by increases in the serum pancreatic enzyme activities, a contrast-enhanced CT is not usually required for diagnosis. Therefore, Japanese Criteria seems to be more sensitive and specific than Revised Atlanta Criteria. The sensitivity and specificity of urinary trypsinogen-2 dipstick test in this study coincided with the findings of previous reports^[3-9,19].

Table 3 Urinary marker levels at enrollment in patients with severe and mild pancreatitis by prognostic factors according to the Japanese Ministry of Health, Labour and Welfare criteria (2008)^[15]

	Severity by prognostic factors				AUC
	Severe		Mild		
No. cases	9		69		
Prognostic factors: mean (SD)	2.89	(1.83)	0.57	(0.69)	
Age: median (LQ, UQ), yr	48.5	(45, 69.75)	58	(44, 72)	
Sex: male/female	5/2		45/24		
	Median (LQ, UQ)				AUC
Urinary trypsinogen-2, mg/ dL	6.49	(2.41, 208.76)	2.87	(0.22, 19.98)	0.704
Urinary trypsinogen-2/cre	11.2	(2.43, 214.05)	6.36	(0.31, 33.02)	0.592
Urinary TAP, ng/mL	2.68	(2.07, 5.22)	2.79	(1.25, 5.53)	0.458
Urinary TAP/cre, × 0.0001	6.7	(2.40, 11.50)	4.1	(2.25, 7.20)	0.631
Urinary amylase, × 1000 U/L	1.42	(0.50, 3.16)	1.01	(0.40, 2.68)	0.563
Urinary amylase/cre, U/mg	3.65	(0.38, 8.47)	2.22	(0.81, 4.00)	0.58
Urinary creatinine, × 10 mg/ dL	3.63	(3.16, 8.65)	6.09	(3.89, 10.24)	0.599
Serum amylase, × 100 U/L	11.37	(2.44, 23.37)	6.38	(3.46, 11.72)	0.581
Serum lipase, × 100 U/L	5.85	(4.41, 13.57)	6.95	(2.46, 16.71)	0.508
Serum creatinine, × 0.1mg/dL	9.7	(5.95, 19.65)	6.75	(5.83, 8.55)	0.676

Their area under the curve scores were calculated between severe and mild pancreatitis groups by logistic regression analysis. The cases with no available data were excluded from analysis. All data were showed by median, lower quartile, and upper quartile. AUC: Area under the curve; LQ: Lower quartile; UQ: Upper quartile; TAP: Trypsinogen activation peptide.

Mayumi *et al*^[9] reported in Japan for the first time that the urinary trypsinogen-2 dipstick test was able to diagnose or rule out most cases of acute pancreatitis, and the present results are in agreement with the clinical usefulness of the dipstick test despite the small number of patients. The urinary trypsinogen-2 dipstick test is based on the same rapid qualitative analysis method as was the rapid influenza diagnostic tests as well as the rapid panel tests for heart-type fatty acid-binding protein. However, the urinary trypsinogen-2 dipstick test is not widely utilized due to its relative unavailability compared to the rapid influenza and heart-type fatty acid-binding protein tests, which are already made available and approved under the national health insurance of Japan. We emphasize that our current findings will be helpful to achieve the national health insurance approval of the urinary trypsinogen-2 dipstick test as a diagnostic tool of acute pancreatitis.

In Revised Atlanta Criteria^[18], disease severity is classified as mild, moderate or severe. The prediction of severity levels of acute pancreatitis can be globally made by using scoring systems, the Ranson score, the Glasgow score, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score. In Japan, the criteria established by the Research Committee of Intractable Pancreatic Disease supported by the JMHLW in 2008^[15] was used for severity assessment of acute pancreatitis. As mentioned above, in the new Japanese criteria, the diagnosis of severe acute pancreatitis can be made according to 9 prognostic factors and/or CT grading based on contrast-enhanced CT^[15]. The new Japanese criteria predicted the mortality rate and were largely as useful as the old criteria, the Ranson Score and the APACHE II score for severity assessment^[15,20,21]. The present study examined whether the level of urinary trypsinogen-2, TAP, and amylase as well as serum amylase and lipase could be used as predicting markers of severe acute pancreatitis. The level of urinary trypsinogen-2 and TAP were higher in patients with severe pancreatitis by CT Grade, furthermore their AUC scores were higher than those of urinary amylase and serum pancreatic enzymes. In severe acute pancreatitis, the level of urinary creatinine is known to be elevated due to dehydration and renal dysfunction, and is one of prognostic factors according to the JMHLW criteria (2008). Subsequently, the urinary trypsinogen-2/cre ratio and TAP/cre ratio were evaluated to exclude the possibility of the elevation of urinary trypsinogen-2 and TAP due to dehydration, demonstrating that both the trypsinogen-2/cre ratio and the TAP/cre ratio were higher in patients with severe pancreatitis by CT Grade. Furthermore, the levels of urinary trypsinogen-2 and TAP were related to CT Grade, especially extra-pancreatic progression of

Table 4 Urinary marker levels at enrollment between patients with severe and mild pancreatitis by computed tomography Grade according to the Japanese Ministry of Health, Labour and Welfare criteria (2008)^[15]

	Severity by CT Grade				AUC
	Severe		Mild		
No. cases	28		42		
Score of CT Grade: mean (SD)	2.37 (0.69)		0.17 (0.38)		
Extra-pancreatic progression of inflammation (Score 0/1/2)	0/1/27		35/7/0		
Hypo-enhanced lesion of the pancreas (Score 0/1/2)	19/3/4		42/0/0		
Age: median (LQ, UQ), yr	53 (44, 67)		61 (47.5, 73.25)		
Sex: male/female, <i>n</i>	20/6		24/18		
		Median (LQ, UQ)			
Urinary trypsinogen-2, mg/dL	14.68	(2.10, 66.90)	2.69	(0.20, 17.11)	0.701
Urinary trypsinogen-2/cre	14.40	(4.29, 104.03)	6.36	(0.32, 17.94)	0.678
Urinary TAP, ng/mL	3.98	(2.20, 7.81)	2.07	(0.96, 3.87)	0.692
Urinary TAP/cre, × 0.0001	6.70	(4.15, 10.90)	3.10	(2.20, 6.00)	0.727
Urinary amylase, × 1000 U/L	1.94	(0.64, 3.62)	0.97	(0.47, 2.29)	0.615
Urinary amylase/cre, U/mg	3.54	(0.63, 5.88)	2.23	(0.88, 3.65)	0.588
Urinary creatinine, × 10 mg/dL	6.55	(3.54, 9.24)	5.54	(3.49, 10.47)	0.472
Serum amylase, × 100 U/L	9.28	(2.88, 15.22)	6.28	(3.91, 11.74)	0.588
Serum lipase, × 100 U/L	8.10	(1.82, 18.49)	6.95	(4.32, 15.73)	0.521
Serum creatinine, × 0.1 mg/dL	7.25	(5.40, 8.90)	6.90	(5.75, 7.95)	0.574

Their area under the curve scores were calculated between severe and mild pancreatitis groups by logistic regression analysis. The cases with no available data were excluded from analysis. All data were showed by median, lower quartile, and upper quartile. AUC: Area under the curve; LQ: Lower quartile; UQ: Upper quartile; CT: Computed tomography; TAP: Trypsinogen activation peptide.

inflammation, but not hypo-enhanced lesion of the pancreas, which may indicate that trypsinogen-2 and TAP generated in the pancreas did not release into blood, urine, and peritoneum in patients with hypo-enhanced lesion of the pancreas due to decreased pancreatic perfusion as reported by Takaoka *et al.* in the experimental acute pancreatitis^[11]. Furthermore, unlike amylase, only trypsin such as trypsinogen-2 and TAP was related to extra-pancreatic progression of inflammation, which may indicate that extra-pancreatic inflammation may be caused by the extra-pancreatic release of trypsin and not amylase. These results indicated that the level of urinary trypsinogen-2 and TAP may be useful for the determination of extra-pancreatic inflammation, particularly in cases who are not able to undergo CT examination and may be expected as predicting markers for severe acute pancreatitis. We expected urinary trypsinogen-2 and TAP as a marker, which can select the patients who should have CT examination, but they were not useful enough for the determination of hypo-enhanced lesion of the pancreas.

The main limitations of the present study are as follows: (1) small sample size and the indirect analysis; and (2) we measured urinary trypsinogen-2 and TAP levels as prognostic markers of severe acute pancreatitis but we did not compare them with morbidity/mortality or complications. Future large study may answer these unresolved issues.

In conclusion, we reconfirmed that urinary trypsinogen-2 dipstick test may be useful as a predictive marker to diagnose acute pancreatitis in emergency clinical setting. In addition, the levels of urinary trypsinogen-2 and TAP may be considered as suitable markers to determine extra-pancreatic inflammation in acute pancreatitis. Further studies with large number of samples may strengthen our current findings.

Table 5 Urinary marker levels at enrollment according to the score of computed tomography Grade by the Japanese Ministry of Health, Labour and Welfare criteria (2008)^[15]

Extra-pancreatic progression of inflammation					
Score of CT Grade		0	1	2	P value
n		32	8	24	
Urinary trypsinogen-2 (mg/dL)	Median	1.26	27.65	16.98	0.001 ^a
	(LQ, UQ)	(0.15, 11.20)	(2.67, 91.61)	(3.04, 71.25)	
Urinary trypsinogen-2/cre	Median	3.11	28.5	15.77	0.046 ^a
	(LQ, UQ)	(0.31, 13.17)	(6.70, 130.83)	(3.76, 106.64)	
Urinary TAP (ng/mL)	Median	1.97	2.7	4.19	0.001 ^a
	(LQ, UQ)	(0.95, 3.79)	(1.15, 4.73)	(2.55, 8.06)	
Urinary TAP/cre (× 0.0001)	Median	2.75	3.65	6.95	0.003 ^a
	(LQ, UQ)	(2.03, 6.53)	(3.10, 4.73)	(4.63, 11.20)	
Urinary amylase (× 1000 U/L)	Median	0.94	1.44	2.11	0.06
	(LQ, UQ)	(4.63, 17.14)	(3.13, 41.84)	(8.25, 36.65)	
Urinary amylase/cre (U/mg)	Median	2.22	2.02	3.72	0.22
	(LQ, UQ)	(0.85, 3.54)	(0.56, 4.36)	(0.91, 6.15)	
Urinary creatinine (× 10 mg/dL)	Median	4.68	6.5	6.7	0.94
	(LQ, UQ)	(3.48, 10.20)	(3.24, 10.14)	(3.95, 9.57)	
Serum creatinine (× 0.1 mg/dL)	Median	6.75	6.6	7.5	0.042 ^a
	(LQ, UQ)	(5.88, 8.33)	(4.95, 7.20)	(5.20, 9.00)	
Hypo-enhanced lesion of the pancreas					
Score of CT Grade		0	1	2	P value
n		55	3	4	
Urinary trypsinogen-2 (mg/dL)	Median	4.51	44.33	6.77	0.63
	(LQ, UQ)	(0.47, 30.35)	(1.78, 100.99)	(2.45, 14.81)	
Urinary trypsinogen-2/cre	Median	8.37	148.96	9.07	0.84
	(LQ, UQ)	(0.53, 40.84)	(2.27, 179.09)	(6.54, 15.45)	
Urinary TAP (ng/mL)	Median	2.61	3.07	5.88	0.45
	(LQ, UQ)	(1.33, 5.63)	(2.79, 5.22)	(1.04, 12.48)	
Urinary TAP/cre (× 0.0001)	Median	4.1	6.7	6.85	0.65
	(LQ, UQ)	(2.30, 7.20)	(4.90, 10.30)	(3.25, 11.80)	
Urinary amylase (× 1000 U/L)	Median	1.24	1.01	2.22	0.83
	(LQ, UQ)	(4.95, 28.55)	(7.87, 22.70)	(2.94, 35.16)	
Urinary amylase/cre (U/mg)	Median	2.59	3.39	2.21	0.72
	(LQ, UQ)	(0.88, 4.56)	(1.00, 4.03)	(0.46, 6.13)	
Urinary creatinine (× 10 mg/dL)	Median	6.37	5.64	7.47	0.56
	(LQ, UQ)	(3.70, 10.45)	(2.98, 7.85)	(3.11, 10.53)	
Serum creatinine (× 0.1 mg/dL)	Median	6.95	7.8	6.25	0.3
	(LQ, UQ)	(5.83, 8.60)	(4.90, 8.60)	(4.70, 7.88)	

Extra-pancreatic progression of inflammation: 0 = anterior pararenal space, 1 = root of mesocolon, 2 = beyond the lower pole of the kidney. Hypoenhanced lesion of the pancreas: The pancreas was divided into three segments. 0 = signal was localized in each segment or only the surrounding pancreas, 1 = covers two segments, 2 = entirely covered two or more segments. Data are expressed as the median (lower quartile, and upper quartile). Statistical significance is expressed as

^a*P* < 0.05 among the three groups by ordinal logistic regression analysis. LQ: Lower quartile; UQ: Upper quartile; CT: Computed tomography; TAP: Trypsinogen activation peptide.

ARTICLE HIGHLIGHTS

Research background

Rapid urinary trypsinogen-2 dipstick test and measurements of urinary trypsinogen-2 and trypsinogen activation peptide (TAP) has not covered by the national health insurance program in Japan. On the other hands, rapid urinary trypsinogen-2 dipstick spreads to Europe.

Research motivation

We would like to know how to diagnose acute pancreatitis earlier and estimate exacerbation risk of acute pancreatitis.

Research objectives

We would like to reconfirm the accuracy and accessibility of rapid urinary trypsinogen-2 dipstick test in a multicenter study in Japan for acceptance in the national health insurance program. Furthermore, we would like to verify usefulness of urinary trypsinogen-2 and TAP as prognostic factor of acute pancreatitis.

Research methods

This is a retrospective study by 17 medical institutions in Japan. Patients with acute abdominal pain were enrolled prospectively. Urinary and serum samples were collected twice, at enrollment and on the following day for measuring pancreatic enzymes. We investigated the association between the values of urinary and serum pancreatic enzymes and the severity levels of acute pancreatitis based on the JMHLW criteria (2008).

Research results

The sensitivity and specificity of the urinary trypsinogen-2 dipstick test were 73.1% and 62.5%, respectively. The area under the curve (AUC) score of urinary trypsinogen-2 according to prognostic factors of the JMHLW criteria was highest in all parameter. The AUC scores of urinary trypsinogen-2 and TAP according to computed tomography (CT) Grade of the JMHLW criteria were higher than other pancreatic enzymes. The levels of urinary trypsinogen-2 and TAP were significantly higher in patients with extended extra-pancreatic inflammation as evaluated by CT Grade of the JMHLW criteria.

Research conclusions

The levels of urinary trypsinogen-2 and TAP were significantly higher in patients with extended extra-pancreatic inflammation as evaluated by CT Grade, but not significantly higher in patients with hypo-enhanced pancreas lesions. Therefore, the measurement of urinary trypsinogen-2 and TAP could not select the patients who should have CT examination.

Research perspectives

We need a serum or urinary marker, which can select the patients who should have CT examination.

REFERENCES

- 1 Yokoe M, Takada T, Mayumi T, Yoshida M, Isaji S, Wada K, Itoi T, Sata N, Gabata T, Igarashi H, Kataoka K, Hirota M, Kadoya M, Kitamura N, Kimura Y, Kiriya S, Shirai K, Hattori T, Takeda K, Takeyama Y, Hirota M, Sekimoto M, Shikata S, Arata S, Hirata K. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. *J Hepatobiliary Pancreat Sci* 2015; **22**: 405-432 [PMID: 25973947 DOI: 10.1002/jhbp.259]
- 2 Kemppainen EA, Hedström JI, Puolakkainen PA, Sainio VS, Haapiainen RK, Perhoniemi V, Osman S, Kivilaakso EO, Stenman UH. Rapid measurement of urinary trypsinogen-2 as a screening test for acute pancreatitis. *N Engl J Med* 1997; **336**: 1788-1793 [PMID: 9187069 DOI: 10.1056/NEJM199706193362504]
- 3 Hedström J, Korvuo A, Kenkimäki P, Tikanoja S, Haapiainen R, Kivilaakso E, Stenman UH. Urinary trypsinogen-2 test strip for acute pancreatitis. *Lancet* 1996; **347**: 729-730 [PMID: 8602003 DOI: 10.1016/S0140-6736(96)90078-1]
- 4 Kylänpää-Bäck M, Kemppainen E, Puolakkainen P, Hedström J, Haapiainen R, Perhoniemi V, Kivilaakso E, Korvuo A, Stenman U. Reliable screening for acute pancreatitis with rapid urine trypsinogen-2 test strip. *Br J Surg* 2000; **87**: 49-52 [PMID: 10606910 DOI: 10.1046/j.1365-2168.2000.01298.x]
- 5 Kylänpää-Bäck ML, Kemppainen E, Puolakkainen P, Hedström J, Haapiainen R, Korvuo A, Stenman UH. Comparison of urine trypsinogen-2 test strip with serum lipase in the diagnosis of acute pancreatitis. *Hepatogastroenterology* 2002; **49**: 1130-1134 [PMID: 12143219]
- 6 Lempinen M, Kylänpää-Bäck ML, Stenman UH, Puolakkainen P, Haapiainen R, Finne P, Korvuo A, Kemppainen E. Predicting the severity of acute pancreatitis by rapid measurement of trypsinogen-2 in urine. *Clin Chem* 2001; **47**: 2103-2107 [PMID: 11719473]
- 7 Jin T, Huang W, Jiang K, Xiong JJ, Xue P, Javed MA, Yang XN, Xia Q. Urinary trypsinogen-2 for diagnosing acute pancreatitis: a meta-analysis. *Hepatobiliary Pancreat Dis Int* 2013; **12**: 355-362 [PMID: 23924492 DOI: 10.1016/S1499-3872(13)60056-9]
- 8 Kamer E, Unalp HR, Derici H, Tansug T, Onal MA. Early diagnosis and prediction of severity in acute pancreatitis using the urine trypsinogen-2 dipstick test: a prospective study. *World J Gastroenterol* 2007; **13**: 6208-6212 [PMID: 18069761 DOI: 10.3748/wjg.v13.i46.6208]
- 9 Mayumi T, Inui K, Maetani I, Yokoe M, Sakamoto T, Yoshida M, Ko S, Hirata K, Takada T; Urinary Trypsinogen-2 Dipstick for Acute Pancreatitis Study Group of Japanese Society of Abdominal Emergency Medicine (UtrAP Study Group). Validity of the urinary trypsinogen-2 test in the diagnosis of acute pancreatitis. *Pancreas* 2012; **41**: 869-875 [PMID: 22481290 DOI: 10.1097/MPA.0b013e3182480ab7]
- 10 Fernández-del Castillo C, Schmidt J, Rattner DW, Lewandrowski K, Compton CC, Jehanli A, Patel G, Hermon-Taylor J, Warshaw AL. Generation and possible significance of trypsinogen activation peptides in experimental acute pancreatitis in the rat. *Pancreas* 1992; **7**: 263-270 [PMID: 1375747]
- 11 Takaoka K, Kataoka K, Sakagami J. The effect of steroid pulse therapy on the development of acute pancreatitis induced by closed duodenal loop in rats. *J Gastroenterol* 2002; **37**: 537-542 [PMID: 12162412 DOI: 10.1007/s005350200083]
- 12 Neoptolemos JP, Kemppainen EA, Mayer JM, Fitzpatrick JM, Raraty MG, Slavin J, Beger HG, Hietaranta AJ, Puolakkainen PA. Early prediction of severity in acute pancreatitis by urinary

- trypsinogen activation peptide: a multicentre study. *Lancet* 2000; **355**: 1955-1960 [PMID: [10859041](#) DOI: [10.1016/S0140-6736\(00\)02327-8](#)]
- 13 **Tenner S**, Fernandez-del Castillo C, Warshaw A, Steinberg W, Hermon-Taylor J, Valenzuela JE, Hariri M, Hughes M, Banks PA. Urinary trypsinogen activation peptide (TAP) predicts severity in patients with acute pancreatitis. *Int J Pancreatol* 1997; **21**: 105-110 [PMID: [9209951](#)]
 - 14 **Huang W**, Altaf K, Jin T, Xiong JJ, Wen L, Javed MA, Johnstone M, Xue P, Halloran CM, Xia Q. Prediction of the severity of acute pancreatitis on admission by urinary trypsinogen activation peptide: a meta-analysis. *World J Gastroenterol* 2013; **19**: 4607-4615 [PMID: [23901239](#) DOI: [10.3748/wjg.v19.i28.4607](#)]
 - 15 **Takeda K**, Yokoe M, Takada T, Kataoka K, Yoshida M, Gabata T, Hirota M, Mayumi T, Kadoya M, Yamanouchi E, Hattori T, Sekimoto M, Amano H, Wada K, Kimura Y, Kiriya S, Arata S, Takeyama Y, Hirota M, Hirata K, Shimosegawa T. Assessment of severity of acute pancreatitis according to new prognostic factors and CT grading. *J Hepatobiliary Pancreat Sci* 2010; **17**: 37-44 [PMID: [20012329](#) DOI: [10.1007/s00534-009-0213-4](#)]
 - 16 **Kiriya S**, Gabata T, Takada T, Hirata K, Yoshida M, Mayumi T, Hirota M, Kadoya M, Yamanouchi E, Hattori T, Takeda K, Kimura Y, Amano H, Wada K, Sekimoto M, Arata S, Yokoe M, Hirota M. New diagnostic criteria of acute pancreatitis. *J Hepatobiliary Pancreat Sci* 2010; **17**: 24-36 [PMID: [20012328](#) DOI: [10.1007/s00534-009-0214-3](#)]
 - 17 **Otsuki M**, Kihara Y. The frequency of acute pancreatitis in acute abdomen. 2002; The Intractable Pancreatic Disease Investigation and Research Group of the Japanese Ministry of Health, Labour and Welfare 2003: 21-25
 - 18 **Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS; Acute Pancreatitis Classification Working Group.** Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102-111 [PMID: [23100216](#) DOI: [10.1136/gutjnl-2012-302779](#)]
 - 19 **Rompianesi G**, Hann A, Komolafe O, Pereira SP, Davidson BR, Gurusamy KS. Serum amylase and lipase and urinary trypsinogen and amylase for diagnosis of acute pancreatitis. *Cochrane Database Syst Rev* 2017; **4**: CD012010 [PMID: [28431198](#) DOI: [10.1002/14651858.CD012010.pub2](#)]
 - 20 **Matsuno S**, Takeda K, Kitagawa M, Ito T, Kataoka K, Takeyama Y, Hirota M, Otsuki M. The revision of the criteria for diagnosis and severity of acute pancreatitis. 2004; The Intractable Pancreatic Disease Investigation and Research Group of the Japanese Ministry of Health, Labour and Welfare 2005: 32-38
 - 21 **Matsuno S**, Takeda K, Ogawa M, Hirota M. CT staging of the severity of acute pancreatitis: Analysis of data collected by research committee for intractable disease of the pancreas in Japan. *Suizou* 2002; **17**: 93-99

P- Reviewer: Nishida T, Tantau A, Zhao JB

S- Editor: Ma RY **L- Editor:** A **E- Editor:** Huang Y





Published By Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

