一定幅を確保することは有用である．同じDPCコードでも実際に得られる収入は医療機関係数Ⅱによって異なるため，どのレベルで比較するかは選択の余地はあるが，まずは現状の収入を基本とするのが妥当だろう．パスは工程管理であり，対象となる症例数も多いであろうから，パスが適用される疾患において逆ザヤとなっていては工程管理としては失敗であろう．計画的な医療介入ができるパスで対応する疾患で一定規模の利益を確保し，パスが適用できない難しい疾患の持ち出しをカバーするのが病院経営の基本である．DPC/PDPSでは1例1例の利益を求めるのではなく，一年を通じて全体で利益を求めるものであるので，パス適用部分のパフォーマンスは重要である．

他院とのベンチマーク分析

自院のDPCデータと他院のDPCデータとを直接比較することができれば，さらに詳細な改善へのアプローチが可能である．いくつかのITベンダーでは，DPCデータの分析環境の提供をビジネスとして展開し，他院とのベンチマークの機能も備えている．次項で述べる公開データではDPC14桁レベルのデータは公開されていないので，DPC14桁レベルで症例数や平均在院日数の比較をしたい場合は，これらのサービスは有用であろう．

ITベンダーの提供するベンチマークシステムでは，原則として医療機関名は匿名であり，臨床現場からすると直接の比較は難しい．その医療機関がどのような性格なのか，病院規模はどうなのか，立地はどうなのかがわからなければ，数値の比較は難しいからである．自院の名称を全体に公開してもよいという医療機関も稀にはあるが，多くは特定医療機関グループ内での閉じた世界での名称公開である．

ベンチマークで有用なのは診療内容の比較であろう．パスが適用されている疾患なのかそうではないのかはDPCデータでは把握できないが，症例数が多く在院日数のバラつきが少ない疾患ではパスが適用されていると考えてよいだろう．もし，自院の平均在院日数が目標とする医療機関の在院日数よりも長いのであれば，どのようにすれば短くできるのか，比較対象の医療機関の診療プロセスを精査する．また，平均在院日数は同じであるのに，包括・出来高差額が大きく異なる場合，診療内容の何が違うのかを精査する．行われている検査項目や数量が異なるのか，用いられている抗菌薬の単価や日数が異なるのか，チェックすべきポイントは多数ある．ただし，元々の基礎係数，暫定調整係数，医療機関係数Ⅱで包括点数は異なるため，差額の比較には限界があることも認識しておこう．

また，包括・出来高比較による出来高換算点数は，医科点数表上の価格であり，原価そのものではない．造影剤を用いないCTやMRIなどは，マシンタイムが空いているのであれば実質的なコストはゼロに近く，削減すべき項目とは言えない．これはむしろ医師が納得するまで使ってもらうのがよいだろう．ベストプラクティスであることが何よりも重要である．実際のコストを想像し，改善点を探ってゆくことが重要である．薬剤や材料，検査はコストに直結するが，最も高価なものは人件費である．このことも経営改善には忘れてはならないポイントである．

「DPC導入の影響評価に係る調査」の公開データの活用

年に一度，厚生労働省から「DPC導入の影響評価に係る調査（退院患者調査）」として，いわゆるDPC公開データが公表される．平成26年度分については先の平成27（2015）年11月16日の第7回DPC評価分科会において公開された[1]．このデータはDPCの導入により平均在院日数や効率性，複雑性，救急車搬送の数，全身麻酔の件数などがどのように変化してきたのか，医療機関の名称入りで経年の変化が記載されている．

公開データにおけるDPCコードの粒度は14桁そのものではなく，手術に関しては詳細であるが，手術・処置1あるいは手術・処置2については有無別であり，少し丸めた範囲となっている．定義副傷病の有無による区別もない．また個人情報保護の観点から，10例以下の症例数の場合はマスクされている．そのような制約はあるものの，医療機関の名称入りで症例数と平均在院日数が示されており，地域における自院の立ち位置を把握するには貴重なデータである．

このデータの活用としては，まず前項で述べた他院

とのベンチマークにおいて，比較対象とすべき医療機関名がわかっていることが貴重である．すなわち同じような病院規模，あるいは同じような専門性を持つ医療機関との比較が可能である．

次に，地域における自院の役割，立ち位置の把握のため，近隣の医療機関との各MDCあるいは各DPCのシェア，救急車による搬送などのシェアを把握する，あるいは経年的な変化を把握することが重要である．東京医科歯科大学の伏見教授がDPC導入当初から示しているSWOT分析において，自院の強みと弱み，機会と脅威を把握する上で，公開データの活用は重要であろう．また，MDCの構成割合の変化を見ることで，診療科の集約あるいは新設で医療機関の性格が変わりつつあるのかどうかも把握できる．

複雑性，効率性の指標も経営指標として重要であり，稼働率確保のために効率性を犠牲にしていないかどうかも把握できる．公開データの重要性は，院内利用のみでなく，厚生労働省のホームページで一般公開されていることで第三者による自院の評価として見ることができる点にある．例えば効率性の低さがあるとすれば，あるいは救急車の受け入れ台数が減っているとすれば，それはなぜなのか，院内・院外への丁寧な説明が必要である．いくつかの新聞社ではこの公開データを使用して記事化する動きが進んでおり，独自アンケートによる病院ランキングよりは信頼のできるデータソースともなっている．

DPCデータ分析における留意点

DPCデータを病院マネジメントの改革に使用することは一定程度進んできたと思われる．独力で生のDPCデータを分析することは容易ではないが，そのための商用の分析システムもあり，多くの医療機関で使用しているだろう．重要なことは単に表やグラフを作ることではなく，分析結果に分析担当者の視点，伝えたいメッセージが込められていることである．そのためには，分析担当者は院内の課題を収集し，自院の目標を理解し，制度を含む外的環境の変化に目を配り，病院経営の改善に資する資料を作成し説明することが求められる．

その過程において留意すべき事項は多数あるが，正しいDPCデータが作成されていることが基本である．アップコーディングやコーディングミスなどで正しいデータが作成されていないのであれば，まずそれを正すことから始めなければならない．また，臨床的な分類と支払分類は必ずしも同一ではないことにも留意しなければならない．例えば，現行のDPCでは心筋梗塞におけるPCIは手術が97にコーディングされるため，その他の手術と区別されない．短期の入院であれば他の手術が行われることは少ないであろうが，入院が長期化すれば他の手術により97となることもあるだろう．あるいは結腸癌の手術においては，開腹と腹腔鏡の手術コードは同じ01となる．当然ながら開腹と腹腔鏡ではパスが異なり，平均在院日数や抗菌薬の使用日数も異なる．2つの手技を合わせてしまった分析では臨床現場の感覚にそぐわない．次回改定ではCCPマトリックスの一部導入により，臨床分類と支払分類の現場感覚の違いが拡大する場合があるので，支払分類を使用したパスの分析では留意が必要であろう．

短期滞在手術等基本料3の拡大が次回改定でも予定されている．短期滞在手術等基本料3は医科点数表における1入院包括払いであり，DPC除外となる．今回の公開データではDPCコードを付与されて従前と同じ扱いになっているが，自院においても短期滞在手術等基本料3として別に分析をするのか，DPC対象外ではあるがDPCコードを付与して分析するのか，基本方針を固める必要もある．

おわりに

以上，DPCデータの活用による病院マネジメントの概略を示したが，ここに書かれているのはボトムラインであり，さらに先を行く活用も多くの医療機関でなされていると推察する．DPC/PDPSにおける病院経営の本質は，量から質への転換である．入院後の合併症でさえも医業収入となった出来高払いとは異なり，少ない合併症，少ない院内感染症，より洗練された診断と治療で入院診療のパフォーマンスが改善するほど健全経営に寄与する．ここでは“賢い医療”が求められる．

DPCデータを活用した医療マネジメントの改革に

向けて，各医療機関の創意工夫が大いに期待される．DPCの本質は包括支払いにあるのではなく，診断群分類に基づく全国統一基準のデータセットが作成され，活用されることにある．少子高齢化の中で財政上の厳しさは増すが，地域になくてはならない医療機関としてますますの活躍を期待して本稿を終える．

文献

1）厚生労働省　平成27年度 第7回 診療報酬調査専門組織・DPC評価分科会　http://www.mhlw.go.jp/stf/shingi2/0000104146.html（2015年11月18日確認）

Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.12987

GASTROENTEROLOGY

Diagnosis of *Helicobacter pylori*-induced gastritis by serum pepsinogen levels

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Key words
gastritis, *Helicobacter pylori*, pepsinogen.

Accepted for publication 12 April 2015.

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Declaration of conflict of interest: The authors declare no conflict of interests.

Abstract

Background and Aim: Gastric cancer develops due to atrophic gastritis induced by *Helicobacter pylori* (*H. pylori*) infection. Serum levels of pepsinogen (PG) are known to be excellent markers for evaluating the degree of atrophic gastritis. We investigated whether chronic gastritis could be diagnosed by evaluating serum PG levels.

Methods: A total of 4483 patients (average age, 49.7 years; 2879 men) were included in this study. Fasting serum samples were collected and anti-*H. pylori* antibody and PG levels were evaluated. We evaluated the endoscopic atrophy grade or histological extent of gastritis, and calculated the diagnostic capability of this serum marker.

Results: A total of 4483 patients, were diagnosed as being positive (4160) or negative (323) for *H. pylori*-induced gastritis. In patients with *H. pylori*-induced gastritis, the PG II levels were higher and the PG I/II ratios were lower than among those without *H. pylori* gastritis. A cut-off values of (i) PG I/II ≤ 5; (ii) PG II ≥ 10 or PG I/II ≤ 5; (iii) PG II ≥ 12 or PG I/II ≤ 4.5 showed high sensitivity and accuracy (over 90%) for diagnosing *H. pylori*-induced gastritis. Moreover, in a mass screening of healthy subjects, a cut-off value of PG I/II ≤ 4.5 might be better for diagnosing the presence of gastritis because of a sensitivity and specificity > 80%.

Conclusions: The presence of *H. pylori*-induced gastritis can be evaluated using serum PG levels.

Introduction

Gastric cancer is a common neoplasm in Japan. The deaths due to gastric cancer rank second and third among the causes of cancer death in Japanese men and women, respectively.[1] *Helicobacter pylori* (*H. pylori*) infection is an important risk factor for gastric carcinogenesis, and many gastroenterologists believe that gastric cancer could be prevented using an *H. pylori* eradication therapy.[2] In a prospective study, Uemura *et al.* demonstrated that gastric cancer did not develop in *H. pylori*-negative patients.[3] We also recently reported that the incidence of *H. pylori*-negative gastric cancer was low among Japanese patients.[4] Moreover, Fukase *et al.* demonstrated that the development of metachronous gastric cancer was inhibited by *H. pylori* eradication therapy.[5] These results indicate the possible beneficial effect of eradication therapy for gastric cancer prevention in healthy subjects.[6]

In February 2013, the Japanese Ministry of Health, Labour and Welfare approved the eradication therapy for patients with *H. pylori*-associated gastritis, meaning that all *H. pylori*-positive patients can receive eradication therapy covered by the national health insurance system. This was a great step for establishing a national program to prevent gastric cancer deaths in Japan.[7] However, an upper gastrointestinal endoscopy examination is necessary to apply for the health insurance coverage; therefore, younger patients are less likely to be involved in the endoscopic test and treatment system. On the other hand, eradication therapy is well known to be more beneficial in younger patients than in older patients.[8]

More effective cancer prevention should be performed in the younger segment of the Japanese population. A previous paper reported that eradication therapy among younger patients (< 30 years) could completely prevent gastric cancer development, whereas the effect on elderly patients was limited.[8] However, endoscopic examinations for younger patients seem inadequate because the main reason for an endoscopic examination is cancer screening. To establish more effective gastric cancer prevention through eradication therapy, a nonendoscopic means of diagnosing *H. pylori*-associated gastritis is needed.

Many studies have clarified the significance of serum markers for identifying gastric inflammation.[9] Miki established a serum screening system using pepsinogen (PG) levels, which correlate with the degree of corpus atrophy.[10] Previously, we reported that

PG levels correlated with the histologic status of gastric inflammation.[11] In the present study, we conducted a retrospective, cross-sectional study involving a large patient population in our hospital. We investigated the possibility that serum PG levels can be a diagnostic of *H. pylori*-associated gastritis in Japanese patients.

Methods

Patients. We enrolled 11 609 patients who underwent endoscopic examination and evaluation of serum markers in the Hiroshima University Hospital between 1992 and 2010. Duplicated data were excluded in the first step, leaving 9034 patients eligible for inclusion. In the second step, 584 patients with factors that may have influenced their PG levels (proton pump inhibitor use, prior successful eradication therapy, postgastrectomy, severe hepatorenal dysfunction, Zollinger–Ellison syndrome, autoimmune gastritis, and patients with PG levels over the scale) were excluded. Of the remaining 8450 patients, the *H. pylori* status of 5188 could be identified (Table 1). Finally, patients with several diseases (peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, gastroesophageal reflux disease, and idiopathic thrombopenic purpura) were excluded because of the possible administration of proton pump inhibitors or eradication therapy. Finally, 4483 patients (mean age, 49.7 years; 2879 males) were included in the study. The 4483 patients consisted of 2519 with gastritis, 984 with gastric cancers, 144 with gastric adenomas, 141 with gastric hyperplastic polyps, 193 with normal gastric mucosas, and 502 with other diseases. The ethics committee of Hiroshima University Hospital approved the study and waived the requirement for informed consent because of the retrospective nature of the study.

Evaluation of serum PG levels. Fasting blood samples were obtained from the participants, and serum samples were stored at –20°C until use. Serum PG I and II levels were measured by radioimmunoassay (RIA; Abbott, Tokyo, Japan)[12] (1992–1999), chemiluminescent immunoassay (CLIA; Abbott) (1999–2001), enzyme immunoassay (EI; E-plate test; Eiken, Tokyo, Japan) (2001–2003), and a latex agglutination test (LA; L-Z test; Eiken)[13] (2003–2010) in 1371, 310, 279, and 2523 patients, respectively. Each method of evaluating serum PG levels was selected according to the period as noted above.

Table 1 Characteristics of all enrolled patients with serum pepsinogen test and endoscopic examination

Method	Patients		Enrolled patients			
	n	*H. pylori* (+)	*n*	Sex	Age	
				M/F	mean ± SD	range
RIA	2307	1635	1371	807/564	54.5 ± 48.7	20–89
CLIA	524	359	310	203/107	47.0 ± 38.2	20–91
EI	554	353	279	188/91	53.5 ± 47.3	20–87
LA	5065	2840	2523	1681/842	47.0 ± 38.2	20–95
Total	8450	5187	4483	2879/1604	—	—

CLIA, chemiluminescent immunoassay; EI, enzyme immunoassay; *H. pylori*, *Helicobacter pylori*; LA, latex agglutination test; RIA, radioimmunoassay.

Definition of* H. pylori*-induced gastritis status. Serum anti-*H. pylori* antibodies were evaluated by ELISA (Eiken). The atrophic gastritis status of each patient was evaluated using an endoscopic evaluation, according to the Kimura–Takemoto classification,[14] or a histological evaluation of gastritis, according to the updated Sydney system.[15] The definition of a negative *H. pylori*-induced gastritis (*H. pylori*-negative) status was as follows: (i) negative for serum anti-*H. pylori* antibodies and no endoscopically visible atrophic changes in the gastric corpus (C-0 or C-1 in Kimura–Takemoto's classification), or (ii) negative for serum anti-*H. pylori* antibodies and no histologically evident gastritis in either the gastric corpus or the antrum (no activity/metaplasia and none-to-mild atrophy/inflammation).[16] The remaining patients were judged to have *H. pylori*-induced gastritis (*H. pylori* positive).

Statistical analysis. Statistical analyses for comparing values were performed using Mann–Whitney *U*-test, as appropriate. A *P*-value of < 0.05 was considered statistically significant. JMP statistical software (SAS Institute, Cary, NC, USA) was used for all calculations.

Results

Status of* H. pylori*-induced gastritis and PG levels by each method. All enrolled patients were subclassified into two groups, *H. pylori*-positive and *H. pylori*-negative groups, according to the criteria described in the Methods section. The *H. pylori*-positive group included 1234, 291, 270, and 2365 patients, in the RIA, CLIA, EI, and LA test groups, respectively. The average levels of PG I, PG II, and PG I/II are summarized in Table 2. The mean titer of these parameters differed between the four groups. The titer of PG I was uncertain between those in gastritis-positive and -negative groups. However, the PG II titer was higher and PG I/II was lower in *H. pylori*-positive patients than in *H. pylori*-negative patients. This tendency was preserved across all four test groups. The distribution of PG II and PG I/II was plotted as shown in Figure 1. In the *H. pylori*-negative group, low PG II and high PG I/II levels were characteristic compared with the gastritis-positive group, in which the PG distribution was diffuse.

Receiver operating characteristic curve for the diagnosis of* H. pylori*-induced gastritis by each parameter. We also analyzed the receiver operating characteristic (ROC) curve for diagnosis of the presence of *H. pylori*-induced gastritis using each serum marker. High area under the curve (AUC) values were obtained when we used the PG II or PG I/II levels; higher AUCs were obtained when using PG I/II as the test parameter. Each AUC value is shown in Table 3.

Sensitivity and specificity of each serum marker for diagnosing gastritis. We calculated the sensitivity and specificity of the serum markers to diagnose *H. pylori*-induced gastritis at various cut-off levels. Out of four tests, we selected the

Table 2 Serum pepsinogen levels in *H. pylori*-positive and -negative group by each test

Method		*n*	PG I (ng/mL)		PG II (ng/mL)		PG I/II ratio	
			mean ± SD	range	mean ± SD	range	mean ± SD	range
RIA	*Hp* (+)	1234	55.2 ± 39.5*	1.0–293.4	19.8 ± 12.7*	0.5–84.6	3.14 ± 2.14*	0.08–31.5
	Hp (–)	137	45.0 ± 21.0	6.2–154.4	8.6 ± 8.2	2.5–76	6.08 ± 1.75	0.47–10.2
CLIA	*Hp* (+)	291	58.3 ± 40.5	0.9–258.7	23.7 ± 15.3*	3.2–110	2.65 ± 1.61*	0.19–10.7
	Hp (–)	19	55.3 ± 36.1	7.9–168.9	9.1 ± 3.7	4.3–17.9	5.95 ± 1.99	0.81–9.4
EI	*Hp* (+)	270	51.8 ± 35.5*	2.5–176.3	22.5 ± 14.4	2.2–81.1	2.44 ± 1.34*	0.19–7.9
	Hp (–)	9	55.4 ± 22.6	36.9–106.5	9.4 ± 3.4	5.5–14.5	6.12 ± 1.59	3.51–7.9
LA	*Hp* (+)	2365	55.6 ± 42.9*	2.0–295.5	22.4 ± 15.1*	1.0–169.5	2.66 ± 1.68*	0.17–21.5
	Hp (–)	158	64.3 ± 34.7	25.8–256.3	11.2 ± 5.6	3.6–33.1	5.97 ± 1.79	3.09–15.6

*$P < 0.05$ versus *Hp* (–), Mann–Whitney *U*-test.

CLIA, chemiluminescent immunoassay; EI, enzyme immunoassay; *H. pylori*, *Helicobacter pylori*; LA, latex agglutination test; PG, pepsinogen; RIA, radioimmunoassay.

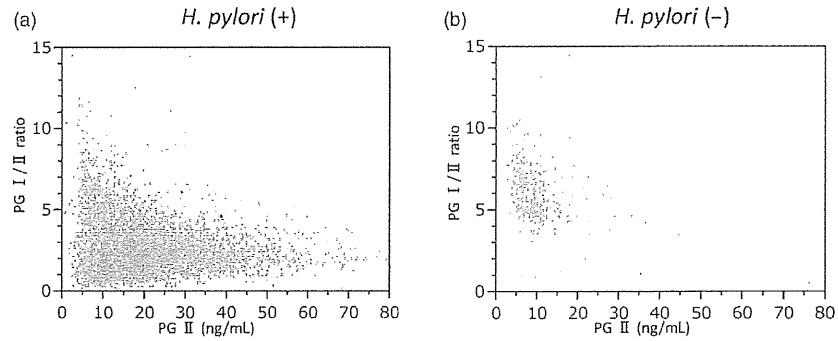

Figure 1 The distribution of serum pepsinogen (PG) II levels and PG I/II ratios in patients in (a) *H. pylori*-positive and (b) *H. pylori*-negative group.

Table 3 AUC values of ROC curve for diagnosing the *H. pylori-induced gastritis* by each serum markers

Method	PG I (ng/mL)	PG II (ng/mL)	PG I/II ratio
RIA	0.565	0.838	0.877
CLIA	0.514	0.854	0.898
EI	0.569	0.855	0.955
LA	0.604	0.770	0.934

AUC, area under the curve; CLIA, chemiluminescent immunoassay; EI, enzyme immunoassay; *H. pylori*, *Helicobacter pylori*; LA, latex agglutination test; PG, pepsinogen; RIA, radioimmunoassay; ROC, receiver operating characteristic.

CLIA and LA tests, because these two tests are currently used in clinical practice in Japan. The results are summarized in Table 4. We set the cut-off levels for PG II at ≥ 10 ng/mL, ≥ 12 ng/mL, or ≥ 15 ng/mL, and those for PG I/II at ≤ 4, ≤ 4.5, or ≤ 5 to diagnose gastritis in each test. For the diagnosis of patients with *H. pylori*-induced gastritis, cut-off values of PG I/II ≤ 5 showed the best sensitivity and accuracy. Further, we combined two parameters, PG II and PG I/II, for diagnosis of *H. pylori*-induced gastritis. A cut-off values of "PG II ≥ 10 or PG I/II ≤ 5" and "PG II ≥ 12 or PG I/II ≤ 4.5" showed high sensitivity and accuracy (over 90%) for diagnosing *H. pylori*-induced gastritis. The highest sensitivity (more than 95%) was obtained when we set the cut-off levels at "PG II ≥ 10 ng/mL or PG I/II ≤ 5" for diagnosing the presence of gastritis (Table 5). On the other hand, in the practical mass screening of healthy subjects, both sensitivity and specificity may be important. Therefore, in a mass screening of healthy subjects, a cut-off value of PG I/II ≤ 4.5 might be better for diagnosing the presence of gastritis because of a sensitivity and specificity > 80%. When we set the cut-off level as PG I/II ≤ 4.5, the sensitivity and specificity were, respectively, 88.3 and 84.2 in the CLIA test, and 88.3 and 84.8 in the LA test (Table 4). As above, the sensitivity and specificity were 80.8 and 86.9 in the RIA test, and 91.1 and 77.8 in the EI test (data not shown). In addition, the number of gastric cancers for (i) PG I/II ≤ 5, (ii) PG II ≥ 10 or PG I/II ≤ 5, (iii) PG II ≥ 12 or PG I/II ≤ 4.5 was (i) 933 (94.8%), (ii) 955 (97.1%), (iii) 933 (94.8%), respectively.

Discussion

Control of chronic inflammation is known to be a key step in the suppression of human carcinogenesis, including of gastric cancer. Prior to treatment, an accurate diagnosis of chronic inflammation is an important first step. Indeed, in the Japanese health insurance system, the diagnosis of chronic gastritis (*H. pylori*-induced gastritis) is essential before undergoing *H. pylori* eradication therapy. In the present situation, an endoscopic examination is recommended for each patient to diagnose chronic gastritis prior to undergoing *H. pylori* eradication therapy. However, a recent Japanese multicenter study demonstrated that the accuracy of endoscopic diagnosis of *H. pylori* infection was approximately

Table 4 Sensitivity and specificity to diagnose gastritis by each serum marker

method	CLIA						LA					
	PG II (ng/ml)			PG I/II ratio			PG II (ng/ml)			PG I/II ratio		
cut off line	10	12	15	4	4.5	5	10	12	15	4	4.5	5
sensitivity	82.1	76.6	66	81.8	88.3	92.8	80.4	73.0	63.8	83.4	88.3	91.6
specificity	68.4	84.2	89.5	89.5	84.2	68.4	53.8	72.2	82.9	92.4	84.8	68.4
accuracy	81.3	77.1	67.4	82.3	88.1	91.3	78.8	72.9	65.0	83.9	88.1	90.1

Table 5 Sensitivity and specificity to diagnose gastritis by combined two parameters

method	CLIA				LA			
cut off line	PGII ≧ 10 and I/II ratio ≦ 5	PGII ≧ 10 or I/II ratio ≦ 5	PGII ≧ 12 and I/II ratio ≦ 4.5	PGII ≧ 12 or I/II ratio ≦ 4.5	PGII ≧ 10 and I/II ratio ≦ 5	PGII ≧ 10 or I/II ratio ≦ 5	PGII ≧ 12 and I/II ratio ≦ 4.5	PGII ≧ 12 or I/II ratio ≦ 4.5
sensitivity	78.0	96.9	70.8	94.2	76.1	95.9	68.4	92.9
specificity	89.5	47.4	94.7	73.7	77.2	44.9	94.3	62.7
accuracy	78.7	93.9	72.3	92.9	76.1	92.7	70.0	91.0

80%.[17,18] On the other hand, the use of serum markers offers objective and reproducible results, which are important for clinical application. In the present study, the accuracy of a chronic gastritis diagnosis using serum markers seems to be similar or superior to that of an endoscopic examination. Furthermore, in cases where the patient may be hesitant to undergo an endoscopic examination, such as in younger patients, a serological diagnosis of gastritis should be considered instead of an endoscopic examination.

Several test methods have been established and used in clinical practice, necessitating an evaluation of the concordance of the test results. We examined four test methods (RIA, CLIA, EI, and LA) in the present study, and confirmed that the between-test difference in assayed PG levels is an important issue. Previously, Miki and Fujishiro reported a difference in serum PG levels between Western and Eastern tests.[19] Even within domestic tests, certain differences may exist. Unfortunately, we did not evaluate the same samples using different methods in this study; therefore, we could not directly compare the differences. Although the degree of difference was not crucial, normal ranges or cut-off values should be determined for each test.

The effects of age and gender may also be problematic. PG levels may be influenced by a patient's age or sex. Hormonal alterations or renal dysfunction in elderly patients may also affect PG levels. Recent changes in Japanese lifestyle, especially regarding food and standard physical condition, may also influence the basal gastric conditions in *H. pylori*-negative subjects.[20]

This study that the PG I/II value showed the highest ROC–AUC value, and cut-off levels of PG I/II ≤ 5 had the highest sensitivity and accuracy for diagnosing *H. pylori*-induced gastritis. However, higher specificities and sensitivities should be guaranteed before the practical application of these biomarker tests. Therefore, we concluded that a cut-off level of PG I/II ≤4.5 may be better, because the sensitivity and specificity were over 80%. These observations were consistent for both tests (CLIA and LA). We tried to combine the two cut-offs (for PG II and PG I/II) to obtain higher sensitivity. We found that the highest sensitivity (more than 95%) was obtained when we set the cut-off levels at "PG II ≥ 10 ng/mL or PG I/II ≤ 5" for diagnosing the presence of gastritis. The combination of two parameters may be beneficial for accurate diagnosis of *H. pylori*-induced gastritis.

There are some limitations to this study. We analyzed the serum from patients who visited our hospital due to some symptom or disease. To apply our data as a cancer prevention strategy, an analysis using healthy subjects is essential. The sample size in this study was another limitation, especially with respect to the small number of gastritis-negative patients. This may influence the results by causing unstable specificity. In Japan, the prevalence of *H. pylori* is gradually decreasing. *H. pylori*-negative subjects can be enrolled in the next study, especially when enrolling healthy subjects.[6] The main problem lies in the criteria for diagnosing *H. pylori*-induced gastritis. In the present study, endoscopic evaluation was used for some subjects. We excluded patients with a history of previous eradication therapy, as some subjects might have received unexpected eradication, making the atrophic border difficult to diagnose endoscopically. In Japan, broad-spectrum antibiotics are used more widely than in other countries, and this is a cause of the natural disappearance of *H. pylori*. In our previous study, we reported that about 10% of patients with gastric neoplasms represented cases of natural disappearance of *H. pylori*.[13] In our *H. pylori*-induced gastritis-positive patients, two groups were included, those with actual *H. pylori* infections and those with prior *H. pylori* infections. Because the risk of gastric cancers is different, it is important to distinguish between these two groups.[5] Although it is difficult to distinguish between current infection and past infection (including natural disappearance) of *H. pylori*, it might be possible by setting a new cut-off value of serum PG level for distinguishing current and past infection. The next study should investigate these two groups. The last limitation

is the study design, which was a single-center, retrospective evaluation. A multicenter prospective study will yield stronger results.

In summary, we demonstrated that chronic gastritis, identical to *H. pylori*-infected status, could be demonstrated using a serum marker evaluation. The method for diagnosing gastritis should shift from an endoscopic examination to a serological test. This may contribute to the widespread use of eradication therapy, followed by gastric cancer prevention, not only in Japan but also worldwide.

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Helicobacter

Helicobacter ISSN 1523-5378
doi: 10.1111/hel.12210

LETTER TO THE EDITOR

Rate of Unintended *Helicobacter pylori* Eradication in the Vietnamese

To the Editor,

Many studies have indicated that *Helicobacter pylori* (*H. pylori*) infection and gastric mucosal atrophy, which is induced by *H. pylori* infection, are important factors for the development of gastric cancer [1]. We have reported that the incidence of true *H. pylori*-negative gastric cancer, without gastric mucosal atrophy, is quite low [2].

Helicobacter pylori infection is prevalent, and the incidence of gastric cancer is high in both Vietnam and Japan. Recently, a combination panel using serum anti-*H. pylori*-antibody titers (measured with enzyme-linked immunosorbent assay) and serum pepsinogen (PG) levels (measured with radioimmunoassay), called the ABC system, has been applied to evaluate the individual risk for gastric cancer in Japan but not in Vietnam. In this system, subjects with negative anti-*H. pylori* antibody and high PG levels are classified into Group A, indicating a very low risk for gastric cancer [3]. However, when subjects with severe gastric mucosal atrophy, which is a high-risk state for gastric cancer, receive successful *H. pylori* eradication treatment, they are classified as Group A by the system [4]. *H. pylori* eradication can reduce the development of gastric cancer by one to two-thirds, but it cannot reduce the risk to zero. Therefore, subjects with unintended eradication would be assigned an incorrect risk evaluation by the system.

In Japan, the rate of unintended *H. pylori* eradication has been reported to be 10–14% of patients with gastric cancer, a population with few true *H. pylori*-negatives [3,5]. To apply the ABC method in Vietnam, knowledge of the rate of unintended *H. pylori* eradication is crucial. If the rate might be quite high, the system would show frequent incorrect risk assessments. Because there are no reports on the rate of unintended *H. pylori* eradication in Vietnamese, we examined this rate.

We enrolled 200 consecutive patients without previous *H. pylori* eradication treatment who underwent upper gastrointestinal endoscopy at University Medical Center in Ho Chi Minh City, Vietnam, between October 2012 and December 2012. Details of the patients' characteristics were reported previously [6]. *H. pylori* status was examined with a rapid urease test (PyloriTek; Serim Research Co., Elkhart, IN, USA), urinary *H. pylori*-antibody test (Rapirun *H. pylori* Antibody Stick; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan), and histologic examination. Patients with at least one positive test of the three tests were regarded as those with a present *H. pylori* infection. Glandular atrophy is quite rare in patients with true non-infection and is associated with infection [1]. Therefore, patients with negative results from all of the three tests and the presence of glandular atrophy by histologic examination were regarded as those with unintended eradication, that is, past infection. Patients with all the three tests negative and no glandular atrophy were regarded as those with true non-infection.

The results showed that 120 (60%) subjects had present *H. pylori* infection, 58 (29%) had true non-*H. pylori* infection, and 22 (11%) had unintended *H. pylori* eradication. The characteristics of the subjects are shown in the Table 1. GERD without peptic ulcer was observed significantly more frequent in the subjects with true non-infection than in those with present infection (prevalence ratio 0.3, 95% confidence interval (CI): 0.1–0.8, $p = .012$). Peptic ulcer without GERD was seen significantly more frequent in subjects with present infection than in those with true non-infection (prevalence ratio 9.7, 95% CI: 1.2–70.3, $p = .002$). These data suggest that the association between *H. pylori* infection and ulcer disease may be stronger than that with GERD.

The rate of unintended *H. pylori* eradication in the Vietnamese was similar to that in Japanese [3,5]. This could be because antibiotics such as penicillin, macrolide, and quinolone are used for other infectious diseases not only in Japan but also in Vietnam. In addition, metronidazole is commonly used for parasites in Vietnam. Another possibility is that it may be caused by misunderstanding of patients concerning previous eradication treatment or by insufficient explanation from their physicians.

Can the ABC method be applied to select subjects at high-risk for gastric cancer in Vietnam? Taking into account the current medical conditions in Vietnam, our answer is yes. The number of endoscopy and other medical resources is limited in Vietnam, and the rate

Table 1 *Helicobacter pylori* infection states in the Vietnamese population

	Present infection (n = 120)	Unintended eradication (n = 22)	True non-infection (n = 58)	Total (n = 200)
Mean age in years (range)	35.6 (18–62)	36.7 (20–76)	36.6 (18–58)	36.0 (18–76)
Sex (male/female)	54/66	8/14	22/36	84/116
Diagnosis				
Normal/gastritis/duodenitis	92	17	47	156
Gastric ulcer	4	0	1	5
Duodenal ulcer	16	1	0	17
GERD	6	4	10	20
GERD + peptic ulcer	2	0	0	2

GERD, gastroesophageal reflux disease.

of unintended *H. pylori* eradication is not so high in the present study. Selecting high-risk subjects is a useful strategy to make the most of the medical resources. Of course, we should explain the merits and limitations of the system to the subjects who take the examination. We should also monitor the rate of unintended eradication to help revise the strategy for gastric cancer screening in Vietnam. We believe that early application of the ABC system as a mass screening method can reduce the mortality rate of gastric cancer in Vietnam.

Acknowledgements and Disclosures

Competing interests: the authors have no competing interests.

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Award Report 上原*H. Pylori*賞—最優秀賞—

本邦における40年間の*H. pylori*感染率および組織学的胃炎の推移

鎌田智有[1]、春間 賢[2]、井上和彦[3]、伊藤公訓[4]、吉原正治[5]、塩谷昭子[1]

はじめに

胃粘膜に*H. pylori*感染が起こると急性胃炎を発症し、その後持続感染が成立すると慢性活動性胃炎に進行する。すなわち、胃粘膜固有層に好中球やリンパ球および形質細胞などを主体とする炎症細胞浸潤、間質の浮腫、腺窩上皮細胞の過形成性変化が慢性的に起こり、次第に固有胃腺が減少・消失した萎縮性胃炎、さらには萎縮の進行した腸上皮化生へと進展する[1,2]。通常、この変化は幽門腺領域から始まり、加齢とともに小彎を中心として胃底腺領域まで拡大する。このような萎縮性胃炎や腸上皮化生を背景として、消化性潰瘍、過形成性ポリープ、胃癌などが発生するため、*H. pylori*感染状態とともに萎縮、腸上皮化生などの組織学的胃炎の有無とその程度を診断することは胃癌のリスクを評価する上で重要である[3~6]。また、*H. pylori*感染率は出生時の環境に左右され、近年の衛生・社会環境の改善や核家族化に伴い*H. pylori*感染率は低下していることが指摘されている[7]。このような近年の*H. pylori*感染率の低下傾向は胃粘膜における組織学的胃炎に何らかの変化をもたらしていることが予測されるが、これまでに長期間に渡る*H. pylori*感染率および組織学的胃炎の推移を検討した報告は国内外でも少なく、これらの変化が胃癌発症にどのように影響するかも明らかではない。

本稿では、過去40年間（1970～2010年代）における*H. pylori*感染率および組織学的に評価した胃粘膜萎縮と腸上皮化生の推移について検討した成績[8]を中心に概説する。

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*H. pylori*感染率および組織学的胃炎の推移

本研究は過去40年間（1970～2010年代）の*H. pylori*感染率および組織学的胃炎の程度について胃生検組織を用いて後向きに検討を行った。対象は消化器症状または胃癌検診のスクリーニング目的にて上部消化管内視鏡検査を受けた患者のうち、*H. pylori*感染や胃炎の組織学的検査を胃生検により行う必要があると消化器内科医が判断した患者または、検査を自ら望んだ患者1,381例である。1975～1978年に広島大学病院で採取された289例（70s群；平均年齢44.9歳）、1991～1994年の787例（90s群；同44.2歳）に加え、2010～2013年に川崎医科大学附属病院で採取された305例（2010s群；同44.2歳）の生検組織の記録を後向きに評価した。上部消化管内視鏡検査施行時に前庭部小彎から2カ所および胃体部前後壁から各1カ所の計4点生検を採取し、*H. pylori*感染の診断はギムザあるいはヒメネス染色にて、萎縮と腸上皮化生の程度はUpdated Sydney Systemに準じた。また、腸上皮化生のフェノタイプを評価するため、一部の*H. pylori*感染者では粘液染色（MUC5AC、MUC6、MUC2、CD10、CDX-2）を施行した。

その結果、*H. pylori*感染率は70s群74.7%、90s群53.0%、2010s群35.1%と経年的に有意な低下が見られ（70s群 vs. 90s群；$p<0.05$, 90s群 vs. 2010s群；$p<0.05$, 70s群 vs. 2010s群；$p<0.001$）（図1）、年齢別に検討すると、これらの感染率の低下は若年者世代において特に顕著であった（図2）。胃粘膜萎縮と腸上皮化生のスコアは*H. pylori*感染率の低下に呼応するかのように低下し、2010s群では劇的な低下が見られた（図3、4）。また、*H. pylori*感染者における前庭部および胃体部における萎縮の頻度は2010年代ではそれぞれ33%および19%であり、1970年代（98%、82%）および1990年代（80%、67%）のそ

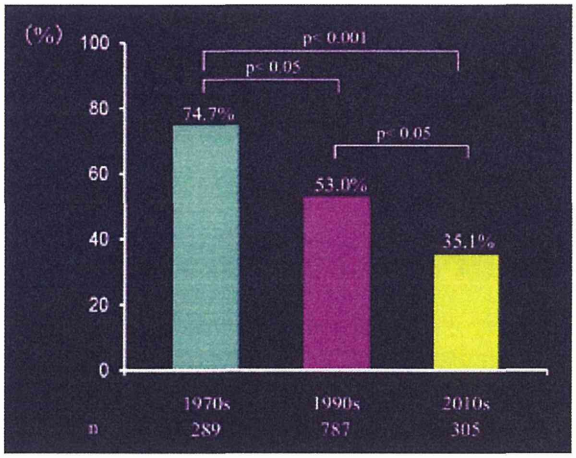

図1　1970年代から2010年代までの*H. pylori*感染率の推移

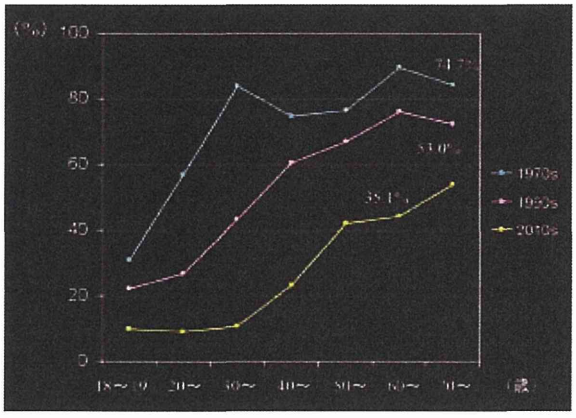

図2　1970年代から2010年代までの*H. pylori*感染率～年齢別の比較～

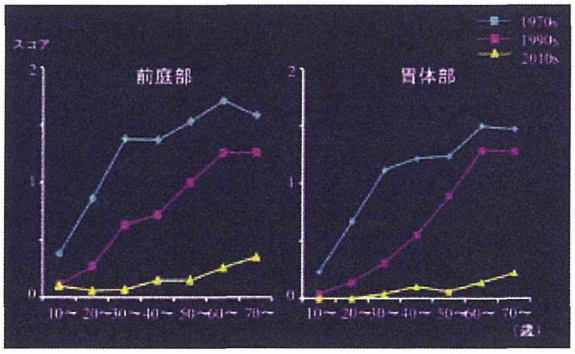

図3　1970年代から2010年代までの胃粘膜萎縮の推移

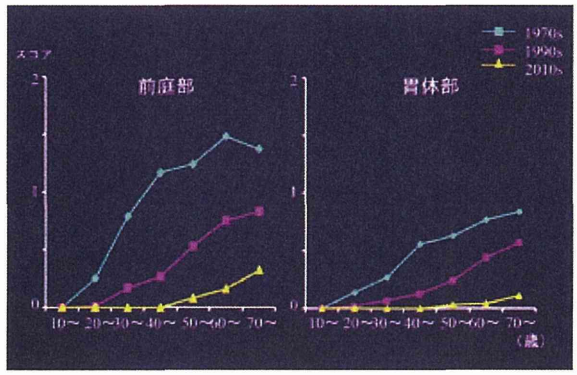

図4　1970年代から2010年代までの腸上皮化生の推移

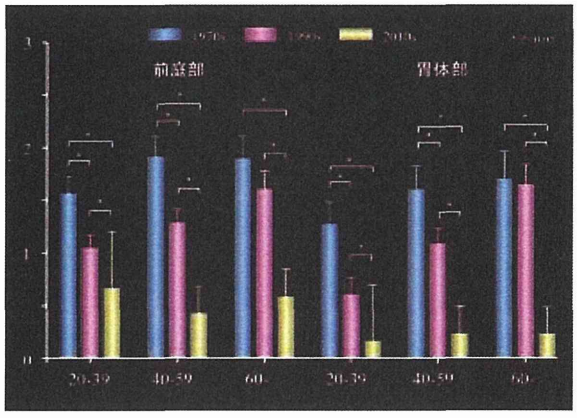

図5　*H. pylori*陽性者における過去40年間の萎縮の推移

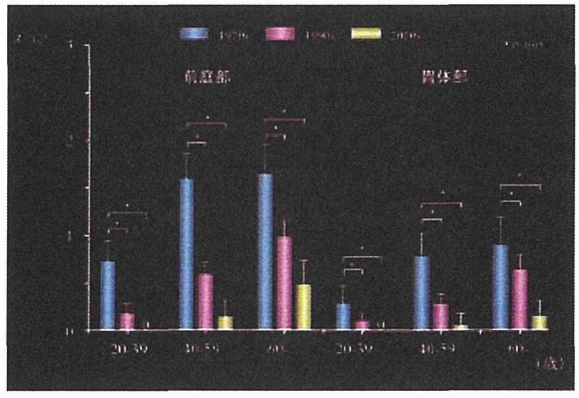

図6　*H. pylori*陽性者における過去40年間の腸上皮化生の推移

れらと比較して有意に低率であり（$p<0.001$）、腸上皮化生についても同様の結果であった。

一方、*H. pylori*感染者のみをこの40年間で比較した胃粘膜萎縮・腸上皮化生のスコアも経年的に低下が見られ、特に2010s群で劇的な低下が認められ（図5、6）、胃炎の分布も胃体部優勢胃炎から前庭部優勢胃炎へと近年変化していた（図5）。さらに、完全型と不完全型の2つのフェノタイプが分けられる腸上皮化生は不完全型でよりがん化しやすいことが以前から知られており、一部の*H. pylori*感染例における腸上皮化生のフェノタイプの割合を70s群（10例）と2010s群（20例）で比較検討した。その結果、70s群に比べ2010s群では完全型腸上皮化生の割合が有意に増加しており（図7）、腸上皮化生は

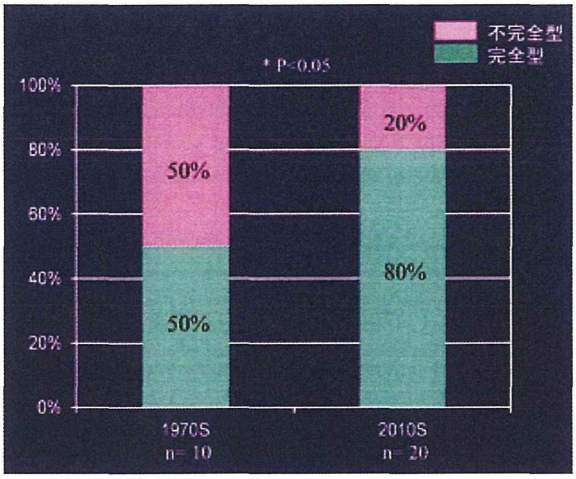

図7 ***H. pylori*陽性者における粘膜形質からみた腸上皮化生の変化**

がん化しにくい質の良いものに近年変化していることが示唆された。

上記の本研究では過去40年間の*H. pylori*感染率の低下のみならず、*H. pylori*感染者での組織学的胃炎の軽減、胃体部優勢胃炎から前庭部優勢胃炎への変化、さらには腸上皮化生のフェノタイプの変化を明らかとし、胃癌の発症頻度の低下が*H. pylori*感染率の低下よりも今後早く起こることが予測された。

胃炎の推移に関する国内外の主な成績

Uemuraら[5]の*H. pylori*感染の有無別に胃癌発症率を検討した前向き臨床研究では、*H. pylori*陰性群の0%に対し陽性群では2.9%と有意に高く、そのリスク因子として高度な萎縮性胃炎や腸上皮化生、胃体部優勢胃炎などが報告されている。胃炎の推移に関して、胃生検を用いて萎縮性胃炎の有病率の経年的な変化を検討した研究にはフィンランドのSipponenら[9]のものが古くにある。1977年から1992年の15年間で胃炎の頻度は有意に低下し、最も顕著な変化の認められた世代（20～49歳）では38%の低下が見られたと報告している。また、フィンランドの同一グループであるValleら[10]の研究では、32年間の経過で同一対象から胃生検を繰り返し採取し、胃体部の萎縮性胃炎の推移を後向きに検討している。*H. pylori*陽性85例では、その多くが正常→表層性胃炎→萎縮性胃炎へと経年的に進展することを示し、一方、*H. pylori*陰性17例ではその多くが時間経過に関わらず胃体部萎縮は進展しなかったことを報告した。腸上皮化生については1957～62年と1978～80年の約20年間にわたるImaiら[11]の研究があり、Grade2～3といった高度な腸上皮化生の有病率が、特に男性でこの期間で減少したと報告している。Harumaら[12]は*H. pylori*感染率の低下に加え、胃粘膜萎縮と腸上皮化生の減少を1970年代と90年代の20年間に見いだしている。今回の本研究はこのHarumaら[12]の研究に2010年代のデータを新たに加え、70年代から2010年代までの40年間という、これまでにない世界初の長期にわたる*H. pylori*感染率と胃炎の組織学的変化を検討したものになる。

近年の生活習慣の変化が胃炎の推移に影響しているか？

この40年間で*H. pylori*感染者における胃粘膜萎縮・腸上皮化生の程度が軽減した原因として、近年の生活習慣の変化、なかでも本邦における喫煙率や1日塩分摂取量の低下がその主な要因と考察している。すなわち、喫煙や塩分摂取が胃粘膜萎縮の進展に影響を与えることはすでに知られており、これらの因子の影響が経年的に低減することは胃粘膜萎縮の進展を抑制している可能性が考えられる。喫煙に関してNakamuraら[13]は、喫煙者および非喫煙者における胃粘膜萎縮の程度を組織学的に*H. pylori*感染別に検討をしている。その結果、*H. pylori*感染者において喫煙者は非喫煙者に比して有意に萎縮・腸上皮化生の程度が高いことを報告している。また、塩分摂取に関してShinozakiら[14]は、*H. pylori*感染スナネズミを用いて高塩分飼料が胃粘膜萎縮に与える影響を検討している。その結果、高塩分飼料は標準飼料と比較して*H. pylori*感染スナネズミにおいて胃粘膜萎縮を有意に発生させたことを報告している。

まとめ

近年の衛生・社会環境の改善や核家族化に伴う家族内感染リスクの減少により、*H. pylori*感染率が低下し、胃癌発症率が減少していることは広く知られている。今回我々の行った40年間という長期間に渡る組織学的胃炎の推移を検討した研究は国内外において初めての報告であり、将来の本邦における胃癌発生を考察する上でも意義深いと考えられる。Cag Aなどの菌株因子の検討は今回行っていない

が、本邦においてもこの40年間での喫煙率や塩分摂取量の低下は顕著であり、このような環境因子の変化が*H. pylori*感染者での萎縮や腸上皮化生の軽減に働いた因子と推察している。

本研究では過去40年間の*H. pylori*感染率の顕著な低下のみならず、感染者での組織学的胃炎の軽減、胃体部優勢胃炎から前庭部優勢胃炎への変化、腸上皮化生のフェノタイプの変化が示され、本邦における胃癌の発生頻度の低下が*H. pylori*感染率の低下よりも今後早く起こることが示唆された。

謝　辞

本研究内容が平成27年度日本ヘリコバクター学会上原*H. pylori*最優秀賞に選出されたのは、これまでに多くのご指導をいただきました春間 賢先生（川崎医科大学・川崎医療福祉大学特任教授・リオグランデドストール連邦大学国際研究部主任教授）、塩谷昭子先生（川崎医科大学　消化管内科学教授）、茶山一彰先生（広島大学大学院消化器・代謝内科学教授）、田中信治先生（広島大学大学院医歯薬保健学研究科 内視鏡医学教授）を初めとし、川崎医科大学消化管内科学並びに広島大学大学院消化器・代謝内科学の先生方、これまでに内視鏡診療に携わって頂いた医療スタッフの方々などのご協力の賜物とこの誌面を通じて深く感謝申しあげます。

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JNM
J Neurogastroenterol Motil, Vol. 21 No. 4 October, 2015
pISSN: 2093-0879 eISSN: 2093-0887
http://dx.doi.org/10.5056/jnm15016
Journal of Neurogastroenterology and Motility

Original Article

Validity and Reliability of the Japanese Version of the Rome III Diagnostic Questionnaire for Irritable Bowel Syndrome and Functional Dyspepsia

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Background/Aims

Reliable diagnostic instruments for measuring the presence of functional gastrointestinal disorders based on the Rome III criteria have been lacking in Japan. The aims of the present study were to translate and validate the Rome III diagnostic questionnaire which was widely used in Western countries.

Methods

The original version of Rome III diagnostic questionnaire was translated from English into Japanese through 3 independent forward translations, resolution, back translation and reconciliation of the differences. Forty-nine patients with irritable bowel syndrome (IBS), 32 patients with functional dyspepsia (FD) and 56 subjects without any current GI symptoms as controls were recruited from three hospitals located in different regions of Japan and completed the IBS and FD diagnostic modules twice within 14 days. Kappa statistic was used to assess test-retest reliability. The sensitivity and specificity of each diagnostic module for distinguishing IBS or FD patients from controls was tested.

Received: January 23, 2015 Revised: May 1, 2015 Accepted: May 5, 2015

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Financial support: This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan, and a Grant-in-Aid for Scientific Research from the Ministry of Health, Welfare, and Labor of Japan.

Conflicts of interest: The authors declare that they have no conflicts of interest except for Shin Fukudo, Douglas Drossman, William Whitehead, and Olafur Palsson. Professor Fukudo received a research grant from Kao and Astellas. He also received lecture fees from Abbott Japan, Dainippon-Sumitomo, and Astellas. Professor Drossman is a President of the Rome Foundation that created the Rome III criteria and he receives a stipend for this work. He also receives royalties for publication of the Rome III book. Professors Whitehead and Palsson received research grants from Ironwood Pharmaceuticals, Takeda Pharmaceuticals, and Salix Pharmaceuticals. Professor Whitehead is a consultant to Ono Pharma USA.

Author contributions: Motoyori Kanazawa participated in study design, data collection, data analysis, and preparation of the manuscript; Shigemi Nakajima participated in data collection; Tadayuki Oshima participated in data collection; William E Whitehead participated in study design and preparation of the manuscript; Ami D Sperber, Olafur S Palsson and Douglas A Drossman participated in preparation of the manuscript; Hiroto Miwa participated in study design and data collection; and Shin Fukudo participated as the guarantor of this paper, and he participated in study design, data collection, data analysis, and manuscript preparation.

ORCID: Motoyori Kanazawa, http://orcid.org/0000-0003-1953-3336.

Results
Median kappa statistics were 0.63 for the translated IBS diagnostic module and 0.68 for the FD module. The sensitivity, specificity, and positive predict value of the IBS module against physician diagnosis was 61.2%, 100%, and 100% and those of the FD module was 53.2%, 98.2%, and 94.4%, respectively. Meanwhile, IBS patients were significantly more likely to report blood in stools compared to controls (18.4% vs 1.8%, $P < 0.01$).

Conclusions
The IBS and FD diagnostic modules on the Japanese version of the Rome III diagnostic questionnaire are valid and reliable. Further studies are warranted to elucidate the diagnostic utility of the red flag questionnaire.
(J Neurogastroenterol Motil 2015;21:537-544)

Key Words
Dyspepsia; Functional gastrointestinal disorders; Irritable bowel syndrome; Japan; Questionnaire; Translations

Introduction

Rome III diagnostic criteria based on subjective gastrointestinal (GI) complaints are the most widely used criteria to diagnose functional gastrointestinal disorders (FGIDs).[1] Irritable bowel syndrome (IBS) and functional dyspepsia (FD) are the most common FGIDs both in the Western and the Eastern countries.[2,3] The Rome committee critically considered the available evidence, and multinational expert opinion, when they revised the former Rome II diagnostic criteria[4] and updated diagnosis and treatment recommendations.

The Rome III diagnostic criteria for FGIDs provide a framework for symptom-based diagnosis. The Rome committee proposed that subtyping of IBS should be based on frequency and consistency of stools,[5] which can be assessed with the aid of the Bristol Stool Form Scale.[6] The committee also proposed that the newly defined entities of (1) meal-induced dyspeptic symptoms (postprandial distress syndrome, PDS), and (2) epigastric pain (epigastric pain syndrome, EPS) should be treated as subgroups of FD for pathophysiological and therapeutic research purposes.[3]

The Rome Foundation developed a questionnaire for the Rome III diagnostic criteria for FGIDs. They also validated the questionnaire to assess the test-retest reliability of the questionnaire for all diagnoses combined and for individual questions, and to test the sensitivity and specificity of the questionnaire for identifying medically diagnosed patients with FGIDs. The Rome III diagnostic questionnaire for IBS contains 10 items and the one for FD contains 18 items; answers to questions are on an ordinal scale with individual frequency thresholds for each question.[7] While "red flag" questions are not part of the diagnostic questionnaire, these features, if present, should prompt the clinician to consider further investigations to exclude other serious medical conditions. Briefly, the "red flag" questions include history for the past 3 months of fever, weight loss, cancer in family members, blood mixed with stool, anemia and change in bowel habit after age 50.[8] Red flags may be useful for identifying patients who require additional diagnostic evaluation in the clinical settings. However, it has been investigated that incorporating them into the Rome II criteria did not improve sensitivity and resulted in too many missed diagnoses of IBS.[8]

Previously, we have developed and validated the Japanese translated version of the Rome II modular questionnaire based on the former diagnostic criteria for IBS.[9] There are a few studies to investigate prevalence of FGIDs using the Rome III criteria in Japan.[10,11] However, reliable diagnostic instruments for measuring the presence of FGIDs based on the Rome III criteria, comparable to those used in Western countries, have been lacking in Japan. To make cross-cultural comparisons possible, it is indispensable to develop common diagnostic measures for FGIDs.[12] The aims of the present study were to translate the Rome III diagnostic questionnaire into Japanese and to validate them in Japanese patients with IBS and FD. In addition, we investigated whether the utility of red flag symptoms that can be incorporated into the Japanese instruments.

Materials and Methods

Translation

The Rome III diagnostic questionnaire was developed as a

diagnostic instrument for functional GI disorders according to the Rome III diagnostic criteria.[7] All answers in the Rome III diagnostic questionnaire were in ordinal scale with individual frequency thresholds except for 22 of 81 items which had a "yes" or "no" response. A score was given to each of the responses for ordinal scaled items (0, never; 1, sometimes; 2, often; 3, most of the time; and 4, always). There were 10 items for IBS diagnosis, 18 items for FD diagnosis, and 6 items for the "red flag" symptoms/conditions (blood in stools, unintended weight loss of over 10 pounds (4.5 kg), fever, symptom onset after age 50, and family histories of any GI cancer and inflammatory bowel disease) were used.

A group of the Japanese co-investigators (S.F. and M.K.) independently translated the English version of the Rome III diagnostic questionnaire into the Japanese language. Meanwhile, an investigator (S.N.) independently translated it in the same way to resolve the potential incongruity of the linguistic expressions between the Eastern and Western areas in Japan. After the descriptions of each item had been discussed with specialists, the Japanese version of the instruments was then counter-translated into English by a native speaker of English. This back-translated version was sent to the Rome Committee, compared with the original versions, and discussed to confirm that the Japanese-translated versions were comparable to the English versions of the Rome III diagnostic questionnaire. Then, the Japanese version of the instruments was approved by the authors of the original English versions.

Subjects

Forty-nine consecutive patients (21 females, mean age 40.9 years) clinically diagnosed by physicians as having IBS according to Rome III diagnostic criteria, and 32 patients with FD (26 females, mean age 53.8 years) diagnosed according to Rome III were enrolled from GI clinics in Tohoku University Hospital, Hyogo College of Medicine Hospital, and Japan Community Health care Organization Shiga Hospital, Japan. Clinical examinations including upper and/or lower GI endoscopy had been carefully performed and no abnormal findings to explain GI symptoms had been detected when diagnosed as FD or IBS. Fifty-six subjects (32 females, mean age 51.4 years) who visited at the same hospitals for an annual health check (n = 31) or treatment of mild hypertension/hyperlipidemia (n = 25) but did not have any current GI complaints and any past history of abdominal surgeries except for appendectomy were also recruited as controls. Control subjects were carefully diagnosed as not having any FGID by their physicians.

All the participants were Japanese and were 18 years of age or older. They did not have any organic GI diseases or any other severe physical or psychiatric complications. Informed consent was obtained from all the subjects. However, a study ID was assigned to insure that the investigators could not identify any subjects. This study was approved by the Ethics Committees of Tohoku University Graduate School of Medicine, Hyogo College of Medicine and Japan Community Health care Organization Shiga Hospital.

Severity of Irritable Bowel Syndrome Symptoms

The IBS symptom severity scale (IBS-SSS) was developed and is widely used in Western countries to assess the severity of lower GI symptoms and the degree to which the quality of life is impaired by IBS.[12] This instrument has five items, and the total score can range from 0 to 500. The IBS-SSS scores severity and frequency of abdominal pain, severity of abdominal distension, dissatisfaction of bowel movements, and the interference with life, with a 100-point scale (0, none and 100, worst) for each question. With the possible exception of the bowel dissatisfaction item, these symptom questions are appropriate for characterizing the severity of symptoms in FD as well as the severity of IBS. In the original English version, IBS is graded as mild (75-174), moderate (175-299), or severe (300-500) on the basis of clinical observations of IBS patients.[13] Our group previously developed the Japanese version of IBS-SSS and has confirmed the reliability and validity of this questionnaire.[9]

Procedure

Physician diagnosis for IBS, FD, and control was coded into numbers. The diagnostic code and a study ID were written on a cover page of the first questionnaire for each subject in advance. The first questionnaire containing all 81 questions on the original complete version plus the IBS-SSS was completed by each participant during a clinic visit. Fourteen days later, all subjects were asked to complete a second questionnaire and return it by post to test for reproducibility of answers. The follow-up questionnaire included only the modules for diagnoses of IBS (10 items, the IBS diagnostic module) and FD (18 items, the FD diagnostic module).

Statistical Methods

The test-retest reliability of the questionnaire was judged

with the use of the Kappa statistic to assess concordance between questionnaire responses on two separate occasions. The Pearson's chi-square tests were used to assess the agreement between a positive diagnosis by the Japanese version of Rome III diagnostic questionnaire and a clinical diagnosis assessed by their physicians. The sensitivity, specificity, and positive predictive value of the diagnostic questionnaire for discriminating IBS patients from controls, and for discriminating FD patients from controls were also analyzed. One-way analysis of variance (one-way ANOVA) was used to assess difference in the symptom severity scores between the clinical diagnostic groups. The discriminant validity was measured by comparing the grade of severity based on the IBS-SSS between subjects with Rome-positive and Rome-negative IBS using the nonparametric correlation coefficient, Kendall's tau-b. The proportion of each red flag symptom/condition was compared using the Fisher's exact test between the clinical diagnostic groups.

Results

No apparent modifications were required to resolve inconsistencies between the forward translations into the Japanese language. The translation prepared by S.F. and M.K. was primarily selected as the final version at this stage. When comparing the back translation to the original English version minor adjustments in the choice of words for "bothersome" (questions 26 and 39), "retching" (question 36), and "several" (question 79) were made in the Japanese translation. The Rome foundation board approved the completed translation in January 2010 (Supplementary Figure).

Characteristics of the sample are shown in Table 1. There was no difference in gender ratio among the groups. Patients with IBS were significantly younger in age compared with FD patients or control subjects. Each patient with IBS was subtyped as IBS with diarrhea (n = 28), IBS with constipation (n = 9), mixed IBS (n = 11), or unclassified IBS (n = 1) by their physician according to dominant stool consistencies. Each patient with FD was subtyped as postprandial distress syndrome (PDS, n = 25) or epigastric pain syndrome (EPS, n = 7) by their physician based on the upper GI symptoms. None of FD patients was diagnosed as overlap of PDS and EPS.

The total score on the IBS-SSS in patients with IBS was significantly higher than FD patients or control subjects ($P < 0.01$, respectively; Table 1). IBS patients also showed significantly

Table 1. Characteristics of Samples

	Controls	FD	IBS
Number (females)	56 (32)	32 (26)	49 (21)
Age (yr)	51.4 ± 2.2	53.8 ± 3.0	40.9 ± 2.3[a,c]
Number of subtypes of IBS			
Diarrhea	-	-	28
Constipation	-	-	9
Mixed	-	-	11
Unclassified	-	-	1
Number of subtypes of FD			
PDS	-	25	-
EPS	-	7	-
Number of types of non-GI controls			
Annual health check	31	-	-
Mild hypertension/hyperlipidemia	25	-	-
IBS-SSS total score	30 ± 7	192 ± 16[a]	252 ± 16[a,c]
Abdominal pain severity	1 ± 1	21 ± 4[a]	45 ± 4[a,c]
Abdominal pain frequency	0.1 ± 0.0	2.7 ± 0.6[a]	4.3 ± 0.5[a,b]
Abdominal bloating	2 ± 1	42 ± 6[a]	38 ± 5[a]
Bowel dissatisfaction	18 ± 4	55 ± 6[a]	65 ± 4[a]
Interference with life	8 ± 3	46 ± 6[a]	62 ± 4[a]

Characteristics of each group were shown.
FD, functional dyspepsia; IBS, irritable bowel syndrome; PDS, postprandial distress syndrome; EPS, epigastric pain syndrome; GI, gastrointestinal; IBS-SSS, IBS symptom severity scale.
Data were expressed as mean ± SEM, [a]$P < 0.01$ vs Controls; [b]$P < 0.05$, [c]$P < 0.01$ vs FD.

higher scores than FD patients on IBS-SSS items measuring the intensity and frequency of abdominal pain (Table 1). However, there was no difference in the scores for abdominal bloating, bowel dissatisfaction or interference with life on the IBS-SSS between IBS and FD groups. Control subjects had significantly lower symptom scores for all subscales and the overall symptom severity score on the IBS-SSS compared with IBS or FD patients ($P < 0.01$, respectively; Table 1).

With respect to the test-retest reliability for the Rome III diagnostic questionnaire, median kappa statistic for the IBS diagnostic module was 0.63. Median kappa statistic for the FD module was 0.68.

The instrument for the symptom-based IBS diagnostic questionnaire was in modest agreement with physician diagnosis; sensitivity of 61.2% and specificity of 100% for distinguishing IBS from health (Table 2). The positive predictive value (PPV) on the IBS module was 100%. When applied the functional bowel disorders (FBD) module on the Rome III criteria[1] instead of the IBS module, the sensitivity and specificity were 91.8% and 50.0%. PPV on the FBD module was 61.6%.

The FD module was also in modest agreement with physician diagnosis; sensitivity of 53.2%, specificity of 98.2% and PPV of 94.4% for distinguishing FD from health (Table 3). None of subjects with hypertension or hyperlipidemia (n = 25) was identified as IBS or FD. It is interesting to note that 19 of 49 (39%) patients with IBS were also diagnosed as FD when using the Rome III diagnostic questionnaire. On the other hand, 3 of 32 (9%) patients with FD were overlapping IBS.

When the score on the IBS-SSS for all the participants was graded as mild graded as mild (75-174), moderate (175-299), or severe (300-500),[13] subjects with Rome-positive IBS (n = 33) significantly had more severe symptoms compared to those who were not diagnosed as IBS (Rome-negative IBS, n = 100) using the diagnostic questionnaire (Kendall's tau-b = 0.45, $P < 0.001$; Table 4).

With respect to frequencies of the red flags, IBS patients were significantly more likely to report blood in stools (18.4% vs 1.8%, $P < 0.01$; Fisher's exact test) (Table 5), unintended weight loss (10.2% vs 0%, $P < 0.05$) and new bowel symptom onset after age 50 (40.0% vs 10.8%, $P < 0.05$) compared to controls. FD patients were more likely to report only unintended weight loss (12.5% vs 0%, $P < 0.05$) compared to controls. There was no significant difference in frequency of fever or fam-

Table 2. Agreement Between Physician Diagnosis and the Irritable Bowel Syndrome Diagnostic Module

Diagnosis	IBS	Controls	Total
Rome IBS (+)	30	0	30
Rome IBS (−)	19	56	75
Total	49	56	105

Sensitivity of the irritable bowel syndrome (IBS) diagnostic module was 61.2%, specificity (100%), and positive predict value (100%).
Data were expressed as number.

Table 3. Agreement Between Physician Diagnosis and the Functional Dyspepsia Diagnostic Module

Diagnosis	FD	Controls	Total
Rome FD (+)	17	1	18
Rome FD (−)	15	55	70
Total	32	56	88

Sensitivity of the functional dyspepsia (FD) diagnostic module was 53.2%, specificity (98.2%), and positive predict value (94.4%).
Data were expressed as number.

Table 4. Discriminative Validity With the Irritable Bowel Syndrome-Symptom Severity Scale in the Rome III Diagnostic Questionnaire (Adapted from Francis et al[13])

IBS-SSS Score	0-74	75-174	175-299	300-500	Total
Rome IBS (+)	0	7	15	11	33
Rome IBS (−)	49	22	20	9	100
Total	49	29	35	20	133

Score on the irritable bowel syndrome-symptom severity scale (IBS-SSS) was graded as mild (75-174), moderate (175-299), or severe (300-500). Subjects with Rome-positive IBS had more severe symptoms compared to those who were not diagnosed as IBS ($P < 0.001$).
Data were expressed as number.

Table 5. Frequencies of the "Red Flag" Symptoms

Frequency (%)	Controls (n = 56)	FD (n = 32)	IBS (n = 49)
Blood in stools	1.8	12.5	18.4[b]
Unintended weight loss	0	12.5[a]	10.2[a]
Fever	0	0	6.0
Bowel symptom onset after age 50	10.8	30.0	40.0[a]
Family history of any GI cancer	28.6	28.1	25.5
Family history of IBD	0	3.4	4.2

Frequencies of the self-reported symptoms or family histories which would suggest further evaluation to exclude organic gastrointestinal (GI) diseases were shown.
FD, functional dyspepsia; IBS, irritable bowel syndrome; IBD, inflammatory bowel disease.
[a]$P < 0.05$, [b]$P < 0.01$ vs Controls (Fisher's exact test).

ily history of any GI cancer or inflammatory bowel disease between the groups.

Discussion

The Rome III diagnostic questionnaire was translated into Japanese using the guidelines recommended by the Rome Foundation, and the translated instrument was reviewed and approved by the Rome Foundation. In this study we evaluated the validity of the Japanese-translated Rome III diagnostic questionnaire by examining the concordance between questionnaire based diagnoses and clinical diagnoses in patients with IBS and FD attending gastroenterology out-patient clinics in Japan. We found modest sensitivity for both the IBS questionnaire module (61.2%) and the FD module (53.2%). However, the specificity (100% for IBS, 98.2% for FD) and the PPV (100% for IBS and 94.4% for FD) were excellent. This suggests that clinician-diagnosed FD may be missed by the Japanese Rome III diagnostic questionnaire, but few subjects without FD will be incorrectly classified as IBS or FD cases.

We compared the sensitivity and specificity of the Japanese Rome III Diagnostic Questionnaire to the sensitivity and specificity of the Rome III Diagnostic Questionnaire in other languages. The original English language version of the questionnaire was tested in 328 patients with IBS diagnosed by gastroenterologists and 554 healthy controls, and sensitivity-defined as the proportion of medically diagnosed IBS patients identified by the questionnaire-was 71%, while specificity-defined as the proportion of healthy controls correctly classified as non-IBS-was 88%.[14] A translation of the Rome III questionnaire into the Malaysian language similarly showed a sensitivity of 81% and specificity of 100% for discriminating 31 clinically diagnosed IBS patients from 31 healthy controls.[15] A translation of the Rome III questionnaire into Portuguese discriminated medically diagnosed patients with FD from health controls with a sensitivity of 91% and specificity of 95%.[16] It has been reported that a sensitivity of the modified Rome III Diagnostic Questionnaire differs among the Asian countries,[17] suggesting that socio-cultural perspective and/or the linguistic nuances might be taken into account to translate the original questionnaire into different languages.

In studies which have tested the ability of the Rome III questionnaire to discriminate medically diagnosed IBS patients from patients with other gastrointestinal diagnoses such as inflammatory bowel disease or FD rather than discriminating them from healthy controls, performance has been more modest: In one study using the Rome II criteria, the questionnaire's sensitivity-defined as the ability to discriminate IBS patients from those with other gastrointestinal diagnoses-was 60% and specificity was 56%.[18] In a Norwegian study, which tested the discrimination of IBS from patients with other causes of abdominal pain, sensitivity was 39% and specificity was 63%.[19] On the other hand, using with the Korean version of the Rome III questionnaire, the sensitivity was 77.8% for the IBS module and 70.0% for the FD module and specificity was 81.6% and 63.0% when discriminated clinical IBS or FD patients from subjects who visited at gastroenterologists for any other reasons.[20] These data show that the sensitivity and specificity of the Japanese Rome III Diagnostic Questionnaire is as good as the English original and other translations of the Rome III questionnaire when similar methodologies are used to evaluate sensitivity and specificity. In this study, test-retest reliability over an interval of two weeks was acceptable with median kappa of 0.63 for IBS and 0.68 for FD. However, this is somewhat below the test-retest coefficient of 82% found for the English language version of the questionnaire.[14]

In the present study, frequencies of reporting "red flag" symptoms (eg, blood in stools and unintended weight loss) were concordant with previous reports.[8,21] It is not surprising that the frequency of family history of any GI cancer in our findings was relatively high in each group (25.5 to 28.6%, Table 5) since gastric and colon cancers are very common in the Japanese population.[22] Notably, the red flags are not automatically cause for alarm signs. A separate, benign problem (eg, rectal bleeding caused by hemorrhoids) is often found that explains them. In the present study, no organic abnormality had been detected in the colon for all of patients who were diagnosed as IBS with colonoscopy or barium enema despite the self-reported alarm symptoms on the red flag questionnaire. Whitehead et al[8] reported that patients with IBS or other functional bowel disorders are highly likely to report red flag symptoms, suggesting that these symptoms should not be incorporated into the symptom-based Rome criteria as exclusions. Therefore, the "red flag" questionnaires are not meant to be used for the discrimination of patients with FGIDs from patients who have any serious conditions but are used for identifying patients who may require further diagnostic testing to determine whether organic diseases are present.

A limitation of this and all other studies seeking to validate symptom based diagnostic criteria for FGIDs is that there is no biomarker to serve as a gold standard. The approach taken here of comparing questionnaire based diagnoses to medical diagnoses