

# Evaluation of symptomatic reflux esophagitis in proton pump inhibitor users

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**Abstract.** The aim of the present study was to evaluate symptomatic reflux esophagitis (RE) in proton pump inhibitor (PPI) users. The present study conducted a hospital-based, retrospective cross-sectional study of consecutive RE cases in PPI users at Juntendo University Hospital recruited between 2008 and 2016. Eligible patients were PPI users with a complete patient profile, who completed the Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (FSSG) questionnaire, and who underwent upper gastrointestinal endoscopy for the examination of RE, hiatal hernia (HH) and endoscopic gastric mucosal atrophy (EGA). The patients with RE who were administered PPIs were divided into two groups: Those with symptomatic RE (FSSG $\geq$ 8) and those with non-symptomatic RE (FSSG $<$ 8). The present study investigated the risk factors for symptomatic RE among the patients with RE patients who were administered PPIs. Of the 13,052 cases who underwent patient profiling, the FSSG questionnaire and upper gastrointestinal endoscopy, a total of 2,444 PPI users were eligible. Of the PPI users, 206 cases (8.4%) had RE. Among the 206 patients with RE, 115 (55.8%) had symptomatic RE. The profile of the symptomatic and non-symptomatic RE groups were as follows: A total of 45 females (39.1%) vs. 32 females (35.2%; non-significant); mean  $\pm$  standard deviation age, 54.8 $\pm$ 13.5 vs. 62.9 $\pm$ 11.1 years (P $<$ 0.01); mean body mass index, 23.5 $\pm$ 3.3 vs. 23.2 $\pm$ 3.8 (non-significant); severe RE, 12 (10.4%) vs. 2 (2.2%; P $<$ 0.05); HH, 70 (60.9%) vs. 40 (44.0%;

P $<$ 0.05); and mean score of EGA, 1.2 $\pm$ 1.8 vs. 1.8 $\pm$ 2.1 (P $<$ 0.05). Multivariate analysis revealed that a younger age [odds ratio (OR)=0.94; 95% confidence interval (CI): 0.92-0.97, P $<$ 0.01] and HH(+) (OR=2.37; 95% CI: 1.30-4.34, P $<$ 0.01) were associated with symptomatic RE among patients with RE who were administered PPIs. In conclusion, a younger age and HH were associated with symptomatic RE in patients with RE who were administered PPIs.

## Introduction

In the background of the westernization of eating habits and decrease in the infection rate for *Helicobacter pylori* (*H. pylori*) (1), gastric acid secretion in the Japanese population has increased in previous years (2) and the number of patients diagnosed with gastro-esophageal reflux disease (GERD) in Japan has increased annually (3).

Proton pump inhibitors (PPIs), which profoundly suppress acid secretion, are used to treat gastric acid-associated diseases globally (4). Numerous previous studies have demonstrated that PPI therapy is superior to histamine-2 receptor antagonist therapy in the inhibition of gastric acid secretion (5,6); therefore, in Japanese GERD treatment guidelines, a PPI is considered to be the first-line drug to use for GERD therapy (7). However, it has been reported that there are patients with reflux esophagitis (RE) who are resistant to PPI treatment (8). Few reports have investigated patients who have symptomatic RE despite PPI use. Japanese GERD guidelines also report that self-administered questionnaires including the Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease (FSSG) questionnaire are useful for the diagnosis and evaluation of the therapeutic efficacy of PPIs in patients with GERD (9).

The aim of the present study was to evaluate the risk factors for symptomatic RE among patients with RE who were administered PPIs by using the FSSG questionnaire.

## Materials and methods

**Study design.** The present study conducted a hospital-based, retrospective cross-sectional study of consecutive PPI

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**Key words:** symptomatic reflux esophagitis, proton pump inhibitor, gastro-esophageal reflux disease, reflux esophagitis, Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease, potassium-competitive acid blocker

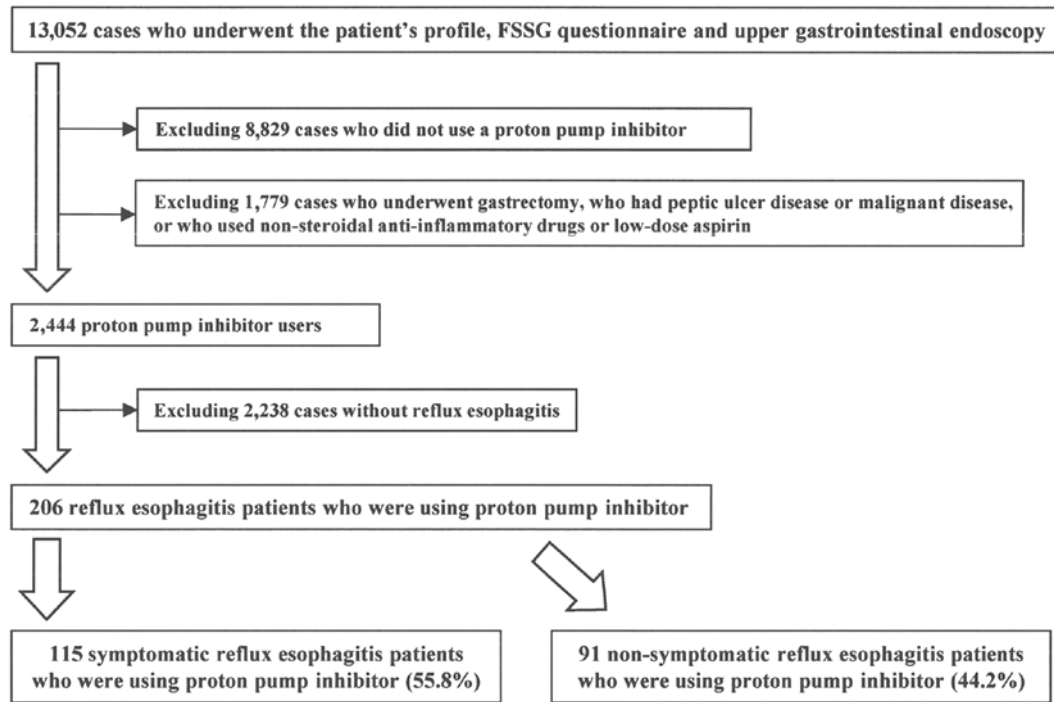


Figure 1. Flowchart of patient selection process. Of the 13,052 cases who underwent patient profile completion, the FSSG questionnaire and upper gastrointestinal endoscopy, 8,829 cases who did not use PPI and 1,779 cases who had undergone a gastrectomy, had peptic ulcer disease, had gastric or esophageal malignant disease or were users of NSAIDs or low-dose aspirin were excluded. A total of 2,444 PPI users were eligible for further analysis. Among the 2,444 PPI users, 206 (8.4%) cases had RE. Among the 206 patients with RE who were administered PPIs, the proportion with symptomatic RE was 55.8% (115/206). FSSG, Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; RE, reflux esophagitis.

users [n=206; aged  $\geq 20$  years, mean age  $58.4 \pm 13.1$  years (20-87 years); male:female 129:77] who were diagnosed with RE in the Department of Gastroenterology, School of Medicine, University of Juntendo Department of Gastroenterology at Juntendo University Hospital between April 2008 and August 2016. The following patients who were administered PPI treatment were eligible for the present study: Patients for whom a complete patient profile was obtained [age, sex and body mass index (BMI)]; patients who completed the FSSG questionnaire (9); and patients who underwent upper gastrointestinal endoscopy and were examined for RE, hiatal hernia (HH) and endoscopic gastric mucosal atrophy (EGA). The collection of patient profile data, FSSG questionnaire and upper gastrointestinal endoscopy were performed at the same time. In terms of exclusion criteria, amongst all patients in this department for whom a patient profile, FSSG questionnaire and upper gastrointestinal endoscopy were completed, cases who did not use PPI were excluded. Then, patients with the following were excluded: Patients who had undergone gastrectomy, patients with peptic ulcer disease, patients with gastric or esophageal malignant disease and patients who use non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin. Furthermore, among the PPI users, patients who did not have RE were excluded. The patients with RE among the PPI users were divided into two groups according to their FSSG score: The symptomatic RE group had a FSSG score  $\geq 8$  and the non-symptomatic RE group had a FSSG score  $< 8$ . The present study evaluated the proportion of patients with RE who had symptomatic RE despite using PPIs. The patient profiles and results of the upper gastrointestinal endoscopy

between the symptomatic RE and non-symptomatic RE groups were compared using bivariate analysis. Additionally, risk factors for symptomatic RE among patients with RE who were administered PPIs were investigated using multivariate logistic regression analysis.

BMI was calculated as the body weight divided by the body height in meters squared ( $\text{kg}/\text{m}^2$ ). The FSSG, which is a self-administered questionnaire developed by Kusano *et al* (9), has been validated for the assessment of upper abdominal symptoms in clinical trial settings. The FSSG comprises 12 items. Each response is assigned a score for the frequency of each symptom, as follows: 0, never; 1, occasionally; 2, sometimes; 3, often; and 4, always. With a cut-off score of 8 points, the FSSG exhibited a sensitivity of 62% and specificity of 59% for RE based on endoscopic examination. FSSG score was calculated as a total number of points accumulated from the FSSG questionnaire. Patients who used any one of the four types of PPIs (rabeprazole, omeprazole, lansoprazole or esomeprazole) daily for  $> 4$  weeks were defined as PPI users. Regarding the results of the upper gastrointestinal endoscopy, HH was defined as an apparent separation of the esophago-gastric junction and diaphragm impression by  $> 2$  cm. Patients with RE were defined as patients who had results indicating RE of grade A, B, C or D according to the Los Angeles Classification system (10); grade A and grade B were classified as mild RE, and grade C and grade D as severe RE. Grade A is defined as one or more mucosal breaks confined to the mucosal folds, each no longer than 5 mm. Grade B is defined as at least one mucosal break  $> 5$  mm long confined to the mucosal folds but not continuous between the tops of two mucosal folds. Grade C

Table I. Clinical characteristics of RE among proton pump inhibitor users (n=206).

Characteristics	Value
Patient profile	
Age (years)	58.4±13.1 <sup>a</sup>
Sex	
Female	77 (47.4) <sup>b</sup>
Male	129 (62.6) <sup>b</sup>
Body Mass Index (kg/m <sup>2</sup> )	23.4±3.5 <sup>a</sup>
Upper gastrointestinal results	
RE	
Grade A	140 (68.0) <sup>b</sup>
Grade B	52 (25.2) <sup>b</sup>
Grade C	10 (4.9) <sup>b</sup>
Grade D	4 (1.9) <sup>b</sup>
Hiatal hernia	
No	96 (46.6) <sup>b</sup>
Yes	110 (53.4) <sup>b</sup>
Endoscopic gastric mucosal atrophy	
1.5±2.0 <sup>a</sup>	
C-0	109 (52.9) <sup>b</sup>
C-1	22 (10.7) <sup>b</sup>
C-2	24 (11.7) <sup>b</sup>
C-3	14 (6.8) <sup>b</sup>
O-1	12 (5.8) <sup>b</sup>
O-2	9 (4.8) <sup>b</sup>
O-3	16 (7.8) <sup>b</sup>

RE, reflux esophagitis. <sup>a</sup>Mean ± standard deviation, <sup>b</sup>Number (%).

is defined as at least one mucosal break continuous between the tops of two or more mucosal folds but not circumferential. Grade D is defined as a circumferential mucosal break. EGA was classified as C-0 (normal), C-1, C-2, C-3, O-1, O-2 or O-3 using the Kimura-Takemoto classification system (11), which identifies the location of the endoscopic atrophic border. Overall, the EGA was scored as 0 for C-0 type, 1 for C-1 type, 2 for C-2 type, 3 for C-3 type, 4 for O-1 type, 5 for O-2 type and 6 for O-3 type. In symptomatic RE and non-symptomatic RE groups, the EGA score was calculated as the mean of the score.

**Statistical analysis.** Age, BMI and EGA were presented as the mean ± standard deviation. Bivariate analyses of patient profiles and results of the upper gastrointestinal endoscopy were performed using a  $\chi^2$  test and Student's t-test. No cutoff for age was used for patients  $\geq 20$  years old. All age data was used in multivariate analysis. Multivariate logistic regression analysis of the risk factors for symptomatic RE among patients with RE who were using PPIs was performed using a backward selection method (likelihood ratio). The odds ratio (OR) and 95% confidence intervals (CIs) were also used to identify the presence and strength of any associations. All statistical analyses were performed using the SPSS version 19

software (IBM Corporation, Armonk, NY, USA).  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**Clinical characteristics.** Of the 13,052 cases who underwent patient profile completion, the FSSG questionnaire and upper gastrointestinal endoscopy, a total of 8,829 cases who did not use PPIs and 1,779 cases who had undergone a gastrectomy, had peptic ulcer disease, had gastric or esophageal malignant disease or were users of NSAIDs or low-dose aspirin were excluded. Finally, 2,444 PPI users were eligible for further analysis [1,219 men (49.9%) and 1,225 women (50.1%); mean [ $\pm$  standard deviation (SD)] age 58.4±15.2 years and BMI 22.6±3.7]. Among the 2,444 eligible PPI users, 1,341 (54.9%) had an FSSG score  $\geq 8$ . Among the 2,444 PPI users, 206 (8.4%) cases had RE. Fig. 1 presents a flow chart of the study patient selection process.

The clinical characteristics of the 206 patients with RE who were administered PPIs [129 men (62.6%) and 77 women (47.4%); mean age 58.4±13.1 years old and mean BMI 23.4±3.5] are summarized in Table I. A total of 140, 52, 10 and 4 cases of RE had Los Angeles Classification grade A, B, C and D of RE, respectively. HH was observed in 110 cases (53.4%). Mean ( $\pm$  SD) EGA was 1.5±2.0. The number of cases with EGA of grades C-0, C-1, C-2, C-3, O-1, O-2 and O-3 were 109, 22, 24, 14, 12, 9 and 16 cases, respectively; Most cases of reflux esophagitis were of the mild type and most cases of EGA grade were mild type atrophy.

**Risk factors for symptomatic RE among patients with RE who were administered PPIs.** Among the 206 patients with RE who were using PPIs, the proportion with symptomatic RE was 55.8% (115/206). There were 45 females (39.1%) in the symptomatic RE group and 32 females (35.2%) in the non-symptomatic RE group [non-significant (ns)]. In the symptomatic and non-symptomatic groups, the mean age was 54.8±13.5 vs. 62.9±11.1 years old ( $P < 0.01$ ), and the mean BMI was 23.5±3.3 vs. 23.2±3.8 (ns). In the symptomatic RE group, 77, 26, 9 and 3 cases of RE had Los Angeles Classification grade A, B, C and D, respectively. In non-symptomatic RE group, 63, 26, 1 and 1 cases of RE had Los Angeles Classification grade A, B, C and D, respectively. The percentage of patients with severe RE was significantly higher in the symptomatic RE group compared with in the non-symptomatic RE group [12 (10.4%) vs. 2 (2.2%);  $P < 0.05$ ]. In the symptomatic RE group, the number of cases with EGA of grades C-0, C-1, C-2, C-3, O-1, O-2 and O-3 were 67, 12, 15, 5, 6, 4 and 6 cases, respectively. In the non-symptomatic RE group, the number of cases with EGA of grades C-0, C-1, C-2, C-3, O-1, O-2 and O-3 were 42, 10, 9, 9, 6, 5 and 10 cases, respectively. The percentage of patients with HH was also significantly higher in the symptomatic RE group [70 (60.9%) vs. 40 (44.0%);  $P < 0.05$ ], while the EGA score was significantly lower in the symptomatic RE group (1.2±1.8 vs. 1.8±2.1;  $P < 0.05$ ; Table II).

In the results of the multivariate analysis, a younger age (OR=0.94; 95% CI: 0.92-0.97;  $P < 0.01$ ) and HH(+) (OR=2.37; 95% CI: 1.30-4.34;  $P < 0.01$ ) were significantly associated with symptomatic RE among patients with RE who were administered PPIs (Table III).

Table II. Patient profiles and results of upper gastrointestinal endoscopy in symptomatic and non-symptomatic RE groups.

Characteristics	Symptomatic RE 115 (55.8%) <sup>a</sup>	Non-symptomatic RE 91 (44.2%) <sup>a</sup>	P-value
Patient profile			
Age (years)	54.8±13.5 <sup>b</sup>	62.9±11.1 <sup>b</sup>	<0.01
Sex			
Female	45 (39.1) <sup>a</sup>	32 (35.2) <sup>a</sup>	
Male	70 (60.9) <sup>a</sup>	59 (64.8) <sup>a</sup>	0.56
Body Mass Index (kg/m <sup>2</sup> )	23.5±3.3 <sup>b</sup>	23.2±3.8 <sup>b</sup>	0.55
Upper gastrointestinal endoscopy results			
RE			
Grade A	77 (67.0) <sup>a</sup>	63 (69.2) <sup>a</sup>	
Grade B	26 (22.6) <sup>a</sup>	26 (28.6) <sup>a</sup>	
Grade C	9 (7.8) <sup>a</sup>	1 (1.1) <sup>a</sup>	
Grade D	3 (2.6) <sup>a</sup>	1 (1.1) <sup>a</sup>	
Mild RE	103 (89.6) <sup>a</sup>	89 (97.8) <sup>a</sup>	
Severe RE	12 (10.4) <sup>a</sup>	2 (2.2) <sup>a</sup>	<0.05
Hiatal hernia			
No	45 (39.1) <sup>a</sup>	51 (56.0) <sup>a</sup>	
Yes	70 (60.9) <sup>a</sup>	40 (44.0) <sup>a</sup>	<0.05
Endoscopic gastric mucosal atrophy			
C-0	67 (58.3) <sup>a</sup>	42 (46.2) <sup>a</sup>	
C-1	12 (10.4) <sup>a</sup>	10 (11.0) <sup>a</sup>	
C-2	15 (13.0) <sup>a</sup>	9 (9.9) <sup>a</sup>	
C-3	5 (4.3) <sup>a</sup>	9 (9.9) <sup>a</sup>	
O-1	6 (5.2) <sup>a</sup>	6 (6.6) <sup>a</sup>	
O-2	4 (3.5) <sup>a</sup>	5 (5.5) <sup>a</sup>	
O-3	6 (5.2) <sup>a</sup>	10 (11.0) <sup>a</sup>	

RE, reflux esophagitis. <sup>a</sup>Number (%), <sup>b</sup>Mean ± standard deviation.

Table III. Risk factors for symptomatic RE among patients with RE who were using proton pump inhibitors (multivariate analysis).

Covariates	Standardized Coefficient	Odds ratio	(95% confidence interval)	P-value
Patient profile				
Age (years)	-0.06	0.94	(0.92-0.97)	<0.01
Sex				
Male		1.00	(Reference)	
Female	0.61	1.83	(0.96-3.49)	0.07
Body Mass Index (kg/m <sup>2</sup> )	-0.01	0.99	(0.90-1.08)	0.76
Upper gastrointestinal endoscopy results				
Hiatal hernia				
No		1.00	(Reference)	
Yes	0.86	2.37	(1.30-4.34)	<0.01
Endoscopic gastric mucosal atrophy	-0.08	0.92	(0.79-1.08)	0.32

RE, reflux esophagitis.

## Discussion

Of the 206 patients with RE who were administered PPIs, the proportion with symptomatic RE was 55.8% (115/206) and symptomatic RE was common in patients with RE who were using PPIs. Multivariate analysis revealed that a younger age and HH(+) were associated with symptomatic RE among patients with RE patients who were using PPIs.

Pilotto *et al* (12) reported that elderly patients with RE had less typical and more nonspecific symptoms compared with young or adult patients. Cho *et al* (13) also reported that asymptomatic erosive esophagitis in adults is strongly associated with old age ( $\geq 60$  years old) compared with symptomatic erosive esophagitis. This may potentially be due to the fact that gastrointestinal perception may decrease in elderly patients compared with younger patients. Since elderly patients with RE often have fewer reflux symptoms, unlike younger patients with RE (14), they may require more strict therapy compared with younger patients with RE.

It was also revealed that HH is a risk factor for symptomatic RE among patients with RE who were using PPIs. Emerenziani *et al* (15) and Asaoka *et al* (16) reported that HH is likely to serve a function in the pathophysiology of gastro-esophageal reflux disease symptoms. Jones *et al* (17) reported that HH size was the dominant determinant of the presence of esophagitis. Since the presence of HH that causes the reflux of gastric acid to the esophagus may be the largest risk factor for GERD symptom generation, HH may be associated with symptomatic RE among patients with RE who use PPIs. However, the present study did not investigate data on the size of HH, despite the fact that a larger HH may be strongly associated with symptomatic RE in PPI users.

From the results of the bivariate analysis, there was a significantly greater percentage of patients with severe RE among patients with symptomatic RE compared with among those with non-symptomatic RE ( $P < 0.05$ ). Jung *et al* (18) reported that mild RE appeared to be more common among asymptomatic patients with RE compared with among symptomatic patients with RE. Increased reflux of gastric acid due to severe RE may cause GERD symptoms in symptomatic patients with RE compared with in non-symptomatic patients with RE.

Symptomatic patients with RE exhibited less endoscopic gastric mucosal atrophy compared with non-symptomatic patients. Generally, if there is less gastric mucosal atrophy, the quantity of gastric acid secretion increases (19). Increased gastric acid secretion may cause GERD symptoms in symptomatic patients with RE.

As for therapeutic agents for RE, PPIs have conventionally been used as the first-line treatment drug (7). However, it was reported that certain patients with RE are resistant to PPI treatment (8). As for the proposed underlying mechanisms for PPI failure, poor compliance (20,21), delayed gastric emptying (22) and visceral hypersensitivity (23) were noted as reasons for PPI failure. In symptomatic patients with RE who use PPIs, GERD may be associated with delayed gastric emptying and visceral hypersensitivity.

Since elderly patients often have severe HH due to kyphosis, PPI-resistant symptomatic patients with RE may increase in number in an aging society, for example in Japan (24).

Furthermore, elderly patients have fewer reflux symptoms, unlike younger patients, so elderly patients often are more at risk of severe esophagitis compared with younger patients. Previously, it was reported that a novel potassium-competitive acid blocker (P-CAB) may be a potential novel therapeutic drug for PPI failure in patients with RE (25). As a treatment strategy for symptomatic RE in PPI users, P-CAB may be a novel therapeutic drug.

The present study had a number of limitations. First, it was a hospital-based, single-center, retrospective study of PPI users who completed the FSSG questionnaire. Symptomatic patients with RE were defined as patients with RE with an FSSG score  $\geq 8$  among patients who were using PPIs for  $> 4$  weeks. Second, the present study was unable to investigate the treatment dose and duration of each PPI, drinking, smoking, *H. pylori* infection status, other medication history, other systematic diseases, dietary intake, waist circumference, visceral fat area, exercise, eating habits and sleep patterns, which may all affect upper abdominal symptoms. To clarify the risk factors of symptomatic RE in PPI users, further studies including these important data will be required in the future.

In conclusion, symptomatic RE was common among patients with RE who were using PPIs. Multivariate analysis revealed that a younger age and HH(+) were associated with symptomatic RE in patients with RE using PPIs. Further prospective multicenter trials are required to clarify symptomatic RE in PPI users.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Authors' contributions

DA and AN conceived and designed the study. DA analyzed the data. DA, TT, HS, YS, KM, HU, KM, KI, HK, YA, TO, MH and AN performed data collection. All authors contributed to the writing of the manuscript and reviewed and approved the final manuscript.

## Ethics approval and consent to participate

The present study was conducted in accordance with the tenets of the Declaration of Helsinki. The Juntendo University Ethics Committee ethically approved the study and the study protocol (reference no. 16-151). According to the Juntendo University Ethics Committee, the study patients were notified of the study

and permitted the opportunity to refuse participation in the study.

### Patient consent for publication

With regard to the informed consent of participants, the Juntendo University Ethics Committee made a decision based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects, which states that non-intervention studies are deemed exempt from patients' consent and, instead, researchers must notify the study subjects about the information regarding study contents on a home page, and guarantee an opportunity when the study subjects could refuse consent.

### Competing interests

The authors declare that they have no competing interests.

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