Original Article

Decline incidence in upper gastrointestinal bleeding in several recent years: data of the Japan claims database of 13 million accumulated patients

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This study was to examine the recent trends in upper gastrointestinal bleeding in Japan using a large-scale real-world database. The incidence of upper gastrointestinal bleeding was evaluated in the Japan Medical Data Center claims database of 13,019,713 patients aged 20 to 74 years with traceability for 3 months from 2009 to 2014. The incidence was compared with peptic ulcers and gastroesophageal reflux disease. The prescription of medications was also evaluated. The incidence of bleeding was 0.137%, 0.121%, 0.113%, 0.106%, 0.099%, and 0.105% during 2009 to 2014 with a time-dependent decline ($p<0.001$). Peptic ulcers (>10 times higher than the incidence of bleeding) decreased with time ($p<0.001$), whereas gastroesophageal reflux disease increased ($p = 0.006$). Upper gastrointestinal bleeding was higher in male patients and older patients (60–74 years old) ($p<0.001$ respectively). The prescription rate of antithrombotic medications and proton pump inhibitors increased from 2009 to 2014 ($p<0.001$ respectively). The incidence of upper gastrointestinal bleeding decreased from 2009 to 2014 in this relatively large-scale real-world database in Japan, concomitant with the decrease in peptic ulcers. The decreased incidence might have been due to changes in the disease structure and therapeutic strategies over time.

***Key Words*: antithrombotic, gastroesophageal reflux disease, JMDC, peptic ulcer, proton pump inhibitor**

Upper gastrointestinal (GI) bleeding is a serious and lethal condition especially in older patients, and endoscopic hemostasis and/or radiological intervention are widely applicable therapeutic approaches.[1–8] Upper GI bleeding can be induced by lesions of the esophagus, stomach, and duodenum, including gastroduodenal ulcers induced by *Helicobacter pylori* (*H. pylori*) infection, nonsteroidal anti-inflammatory drugs (NSAIDs), and antithrombotic agents; Mallory–Weiss tears; and gastroesophageal varices.[1,2,9–12] The Japan Medical Data Center (JMDC) claims database is a real-world database in Japan that has been available for research purposes since 2005. The JMDC consists of data for approximately 3.7 million people, including data from health insurance providers for company employees and their families.[13–16]

Although the incidence of upper GI bleeding is influenced by several risk factors and therapeutic approaches, the time transition of the incidence of the GI bleeding evaluated by large amounts of data in a real-world database has not been clearly reported in Japan. The present study was performed to i) examine the time course of the incidence of upper GI bleeding in several recent years (2009–2014) using the relatively large-scale JMDC claims database; ii) compare the incidence of upper GI bleeding, peptic ulcers, and gastroduodenal reflux disease (GERD); and iii) examine the time course of the medications prescribed from 2009 to 2014 in the JMDC claims database.

Methods

The JMDC claims database (Japan's real-world healthcare database) has retained cumulative data for 3.7 million people since 2005 (around 2.5% of the Japanese population). This database contains integrated medical and pharmacy claims data, including data for inpatients and outpatients from >90 health insurance providers for company employees and their family members as previously described.[13–16] The JMDC claims database consists of data from relatively younger and more homogeneous populations than the general population in Japan, and patients aged ≥75 years are not included. The database includes data on demographics, diagnoses, examinations, and drugs prescribed, including days of supply and dosage information. Diagnoses for insurance claims are coded by the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Drugs are coded according to the Anatomical Classification of Pharmaceutical Products of the European Pharmaceutical Market Research Association. In the present study, all personal data were converted to a unique numerical code to avoid identifying the individual patients in the JMDC claims database, and informed consent was not required according to the local ethical guidelines for epidemiological research. The present study protocol was approved by the Saga University Medical Science Ethics Committee.

As previously demonstrated,[13] data of patients aged 20 to 74 years with traceability for at least 3 months from the JMDC claims database during the 6-year period from January 2009 to December 2014 were selected. The total number of patients was 13,019,713

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(1,098,882 in 2009, 1,600,201 in 2010, 2,070,139 in 2011, 2,168,695 in 2012, 3,148,442 in 2013, and 2,933,354 in 2014). The upper GI mucosal injuries evaluated in this study were upper GI bleeding [ICD10 codes: K22 (K228), K25 (K250, 252, 254, 256), K26 (K260, 262, 264, 266), K28 (K284), K29 (K290), and K92 (K922)], peptic ulcers [ICD10 codes: K25 (K250–257, 259), K26 (K260–267, 269), K27 (K270, 277, 279), and K28 (K284, 285, 287, 289)], and GERD [ICD10 codes: K21 (K210, 219) and K22 (K221)]. These diseases were identified in patients who were diagnosed with any upper GI injury and underwent upper GI endoscopy in the diagnosed month or ±1 month. Recurrence was defined as that occurring within a 3-month interval. Patients who were prescribed proton pump inhibitors (PPIs) and/or type 2 histamine (H2)-receptor antagonists were not excluded because whether the prescription of these drugs occurred before or after endoscopy was not specified in the JMDC claims database. The incidence of upper GI bleeding in each year was evaluated in a time-dependent manner from 2009 to 2014, and these data were compared with the data for peptic ulcers and GERD.

Use of high-risk drugs with the potential to induce upper GI mucosal injuries, including NSAIDs, selective cyclooxygenase-2 (COX-2) inhibitors, low-dose aspirin, antiplatelet medications (except low-dose aspirin), and anticoagulants, was detected within 3 months before diagnosis of upper GI mucosal injuries. Data for NSAIDs were evaluated for >28-day prescriptions. Data were not adjusted for PPI and/or H2-receptor antagonist therapy administered immediately before upper GI endoscopy because related detailed endoscopic findings were not available from the JMDC claims database. The influence of *H. pylori* was not evaluated because of the limited number of diagnoses of *H. pylori* infection in the JMDC database.

Data were evaluated by analysis of variance, and all analyses were performed using SPSS 24 (IBM Corp., Armonk, NY) and SAS software ver. 9.2 (SAS Institute Inc., Cary, NC). *P* value of <0.05 was considered statistically significant.

Results

The changes in the incidence of upper GI bleeding over time detected from the JMDC claims database from 2009 to 2014 are indicated in Fig. 1A. The incidence of upper GI bleeding significantly decreased in a time-dependent manner: 0.137% in 2009, 0.121% in 2010, 0.113% in 2011, 0.106% in 2012, 0.099% in 2013, and 0.105% in 2014 ($p<0.001$). Figure 1B shows that similar to GI bleeding, the incidence of peptic ulcers decreased in a time-dependent manner: 1.67% in 2009, 1.66% in 2010, 1.60% in 2011, 1.56% in 2012, 1.41% in 2013, and 1.38% in 2014 ($p<0.001$). The incidence of upper GI bleeding was less than one-tenth the incidence of peptic ulcers. In contrast to upper GI bleeding and peptic ulcers, the incidence of GERD was exacerbated over time, as shown in Fig. 1C: 0.361% in 2009, 0.425% in 2010, 0.506% in 2011, 0.632% in 2012, 0.561% in 2013, and 1.11% in 2014 ($p = 0.006$).

The incidence of upper GI bleeding was two times higher in male than female patients, as indicated in Fig. 2A ($p<0.001$). The incidence of peptic ulcers was also higher in male than female patients, as shown in Fig. 2B ($p<0.001$). No sex-related difference in the incidence of GERD was observed in the present study (Fig. 2C). As indicated in Fig. 3A, the incidence of upper GI bleeding increased with aging ($p<0.001$), and the incidence in 60 to 74 year-old patients was markedly higher than that in the other generations ($p<0.001$ respectively). This indicated that the time-dependent decline in upper GI bleeding was mainly due to the decline in the 60 to 74 year-old patients in the JMDC claims database. An increased incidence with aging was observed for both peptic ulcers (Fig. 3B) and GERD (Fig. 3C) ($p<0.001$ respectively), and the incidence of peptic ulcers and GERD was higher in 60 to 74 year-old patients than in younger generations

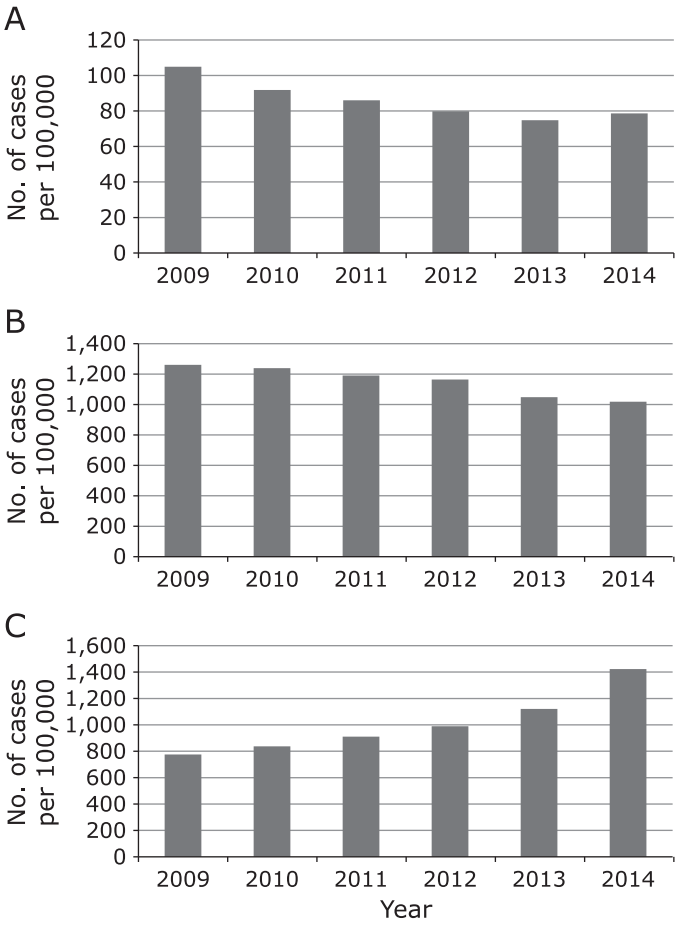

Fig. 1. Incidence from 2009 to 2014: data from the Japan Medical Data Center claims database of 13 million accumulated patients. (A) Upper gastrointestinal bleeding. (B) Peptic ulcers. (C) Gastroesophageal reflux disease. The incidence decreased in a time dependent manner in (A) ($p<0.001$) and (B) ($p<0.001$), whereas the incidence in (C) increased in a time dependent manner ($p = 0.006$).

($p<0.001$ respectively).

The relationship between the prescribed medications and the incidence of disease is shown in Fig. 4A (upper GI bleeding) and Fig. 4B (peptic ulcers). The rate of complications in patients with prescriptions for NSAIDs and COX-2 inhibitors (around 2%) was not different between patients with upper GI bleeding and controls or between patients with peptic ulcers and controls (all). The complication rate in patients with upper GI bleeding and peptic ulcers was about 10% higher in patients with prescriptions for antithrombotic medications, including aspirin, antiplatelet medications, and anticoagulants. As indicated in Fig. 5A, prescription of COX-2 inhibitors increased in a time-dependent manner ($p<0.001$), whereas prescription of COX-2 inhibitors was much more limited that of NSAIDs in Japan. Figure 5A indicates that the rate of prescribing antithrombotic medications increased in a time-dependent manner during the examined period (2009–2014). Prescription of H2-receptor antagonists slightly decreased from 2009 to 2014 ($p<0.001$), and prescription of PPIs doubled during the examined period in Japan ($p<0.001$) (Fig. 5B).

Discussion

The present study using a relatively large real-world database showed that the incidence of upper GI bleeding decreased in a time-dependent manner during several recent years (2009–2014)

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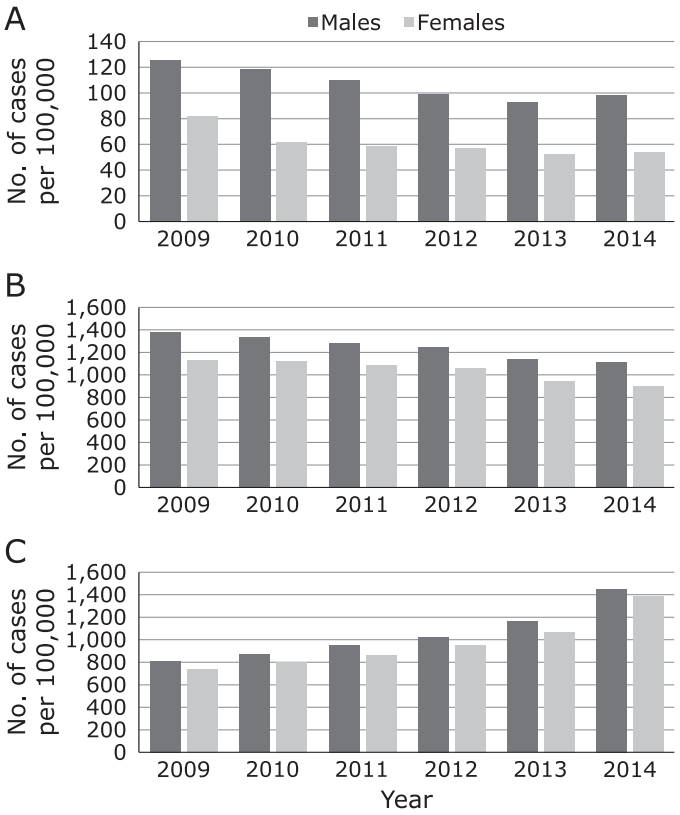

Fig. 2. Incidence in male and female patients from 2009 to 2014. (A) Upper gastrointestinal bleeding. (B) Peptic ulcers. (C) Gastroesophageal reflux disease. The incidence of upper gastrointestinal bleeding and peptic ulcer was significantly high in the male than female patients (p<0.001 respectively), and the incidence of gastroesophageal disease was not different between male and female patients.

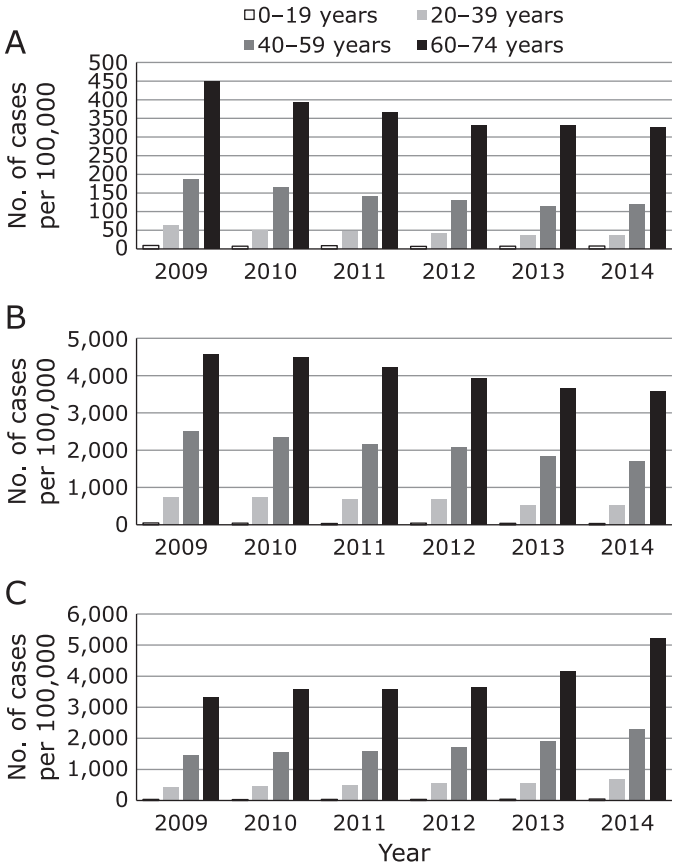

Fig. 3. Incidence in each generation from 2009 to 2014. (A) Upper gastrointestinal bleeding. (B) Peptic ulcers. (C) Gastroesophageal reflux disease. In the 3 evaluated diseases, the incidence increased with aging, and the incidence in 60- to 74-year-old patients was higher than that in other generations (p<0.001 respectively).

in Japan, as shown in Fig. 1A. The incidence of upper GI bleeding was affected by several factors, including peptic ulcers, gastroesophageal varices, GERD, Mallory-Weiss tears, and prescription of antithrombotic agents and NSAIDs, as previously demonstrated.[1,7,10–13,17–19]

The decrease in the incidence of upper GI bleeding synchronized with the diminished incidence of peptic ulcers from 2009 to 2014, as indicated in Fig. 1B. The complication rate in patients with upper GI bleeding was <10% that in patients with peptic ulcers, and the complication rate did not change during the study period; this is similar to previous studies.[11,17] The main causes of peptic ulcers in Japan were *H. pylori* infection and treatment with NSAIDs and aspirin. The incidence of peptic ulcers caused by *H. pylori* infection has markedly decreased in Japan because eradication therapy for *H. pylori* has been widely accepted.[20–30] Additionally, the infection rate of *H. pylori* has markedly decreased in Japan,[20,31–33] especially in younger generations; the infection rate in junior high school students is <5%.[34] PPIs have recently become more frequently prescribed for secondary prevention of peptic ulcers and upper GI bleeding induced by NSAIDs and/or aspirin in Japan,[2,35–38] although the prescription of aspirin has increased in a time-dependent manner as demonstrated in Fig. 5B.

Prescription of antithrombotic agents is one of the main causes of upper GI bleeding.[1,2,4,7] Although prescription of antithrombotic agents gradually increased during the study period, as indicated in Fig. 5B, the incidence of upper GI bleeding decreased during the study period (Fig. 1A). The prescription of PPIs increased from 2009 to 2014 (Fig. 5C), which might have been due to an increased incidence of GERD and increased use of PPIs for prevention of peptic ulcers and upper GI bleeding.

Gastroesophageal varices are the baseline disease of upper GI bleeding.[39–41] The incidence of bleeding induced by gastroesophageal varices has decreased during the most recent decade in Japan because the prevalence of portal hypertension due to liver cirrhosis and/or hepatocellular carcinoma has decreased with the reduction in the prevalence of viral hepatitis and progress in therapeutic approaches to viral hepatitis.[42–45] Upper GI bleeding is a complication of GERD. The prevalence of GERD increased during the study period as shown in Fig. 1C. Severe complications such as bleeding and stenosis were not common in patients with GERD in Japan because most cases of GERD were minor illnesses, as previously demonstrated,[46–50] and prescription of PPIs for treatment of GERD was expanded, as indicated in Fig. 5C.[50–53]

The present study had several limitations. First, the JMDC database did not include data for patients aged >75 years, resulting in underestimation of the risk of upper GI bleeding. Second, the medical certificate of upper GI bleeding was not certified, although the performance of upper GI endoscopy was confirmed. Third, upper GI bleeding due to comorbidities was not distinguished from upper GI bleeding due to the adverse effects of the prescribed medications. Fourth, the influence of *H. pylori* was not evaluated, and the direct influence of PPIs and/or H2-receptor antagonists was not indicated. Finally, warfarin was the most frequently prescribed anticoagulant in the present study, and the

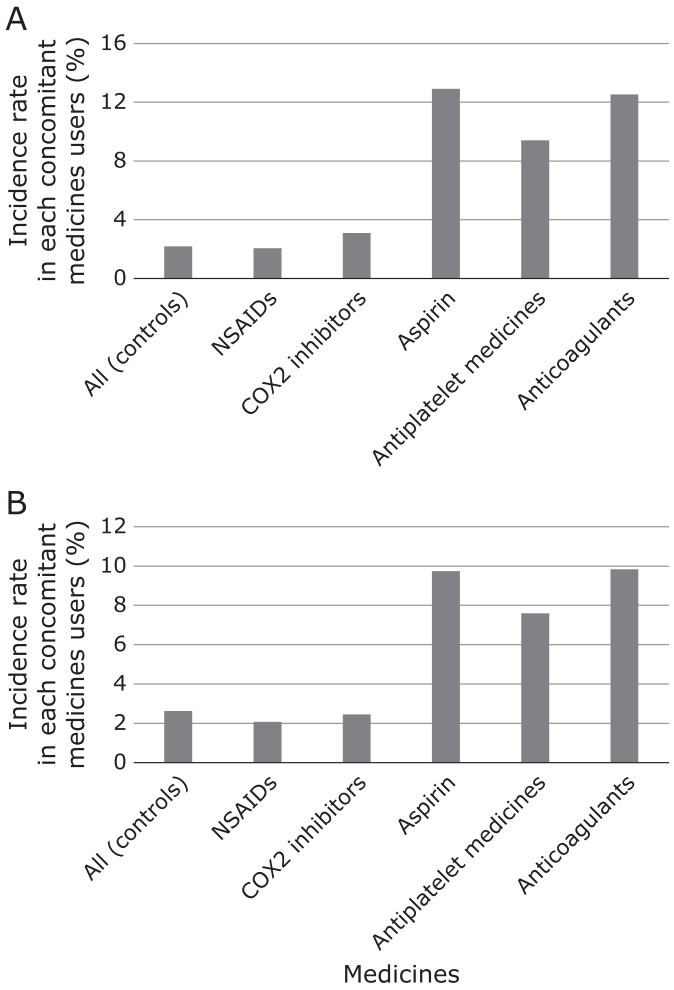

Fig. 4. Incidence rate in concomitant with the prescribed medications of upper gastrointestinal bleeding (A) and peptic ulcers (B). NSAIDs, nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2.

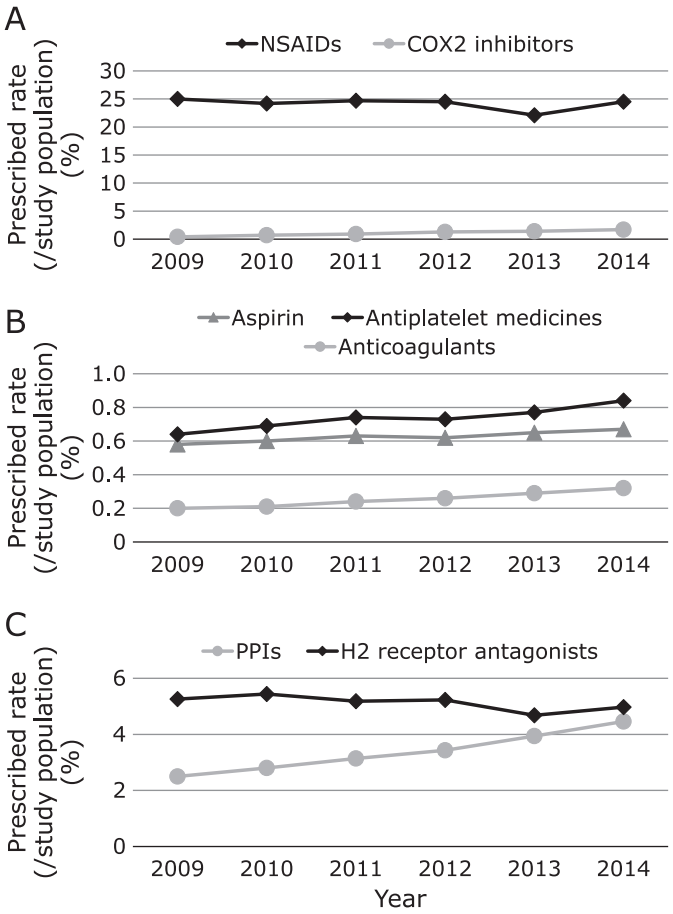

Fig. 5. Prescription rate from 2009 to 2014: data from the Japan Medical Data Center claims database of 13 million accumulated patients. (A) NSAIDs and COX-2 inhibitors. (B) Antithrombotic medicines. (C) Antacids. The prescription rate of COX-2 inhibitors increased with time (p<0.001). The prescription rate of COX-2 inhibitors was much lower than that of NSAIDs in Japan. The prescription rate of each antithrombotic medication increased from 2009 to 2014 (p<0.001 respectively). The prescription rate of PPIs increased in a time-dependent manner (p<0.001), whereas prescription of H2-receptor antagonists decreased (p<0.001). PPIs, proton pump inhibitors. H2, type 2 histamine.

number of prescriptions of direct oral anticoagulants was limited. The main strength of the present study was the synchronized evaluation of the prescribed medications for upper GI bleeding, peptic ulcers, and GERD within the same database.

In conclusion, the present clinical study involving large numbers of patients confirmed that the incidence of upper GI bleeding decreased from 2009 to 2014 in a time-dependent manner. This decrease might have been due to the change in disease structure and advances in medical therapy.

Author Contributions

SF wrote the initial draft of the manuscript. SF, NT, ME, AT, KN, KA, and KF contributed to analysis and interpretation of data, and assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript.

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Conflict of Interest

No potential conflicts of interest were disclosed.

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