Upper Gastrointestinal Complications and Cardiovascular/Gastrointestinal Risk Calculator in Patients with Myocardial Infarction Treated with Aspirin

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Abstract

Background: Aspirin is widely used for the prevention of cardiovascular and cerebrovascular diseases for the past few years. However, much attention has been paid to the adverse effects associated with aspirin such as gastrointestinal bleeding. How to weigh the benefits and hazards? The current study aimed to assess the feasibility of a cardiovascular/gastrointestinal risk calculator, AsaRiskCalculator, in predicting gastrointestinal events in Chinese patients with myocardial infarction (MI), determining unique risk factor(s) for gastrointestinal events to be considered in the calculator.

Methods: The MI patients who visited Shapingba District People's Hospital between January 2012 and January 2016 were retrospectively reviewed. Based on gastroscopic data, the patients were divided into two groups: gastrointestinal and nongastrointestinal groups. Demographic and clinical data of the patients were then retrieved for statistical analysis. Univariate and multiple logistic regression analyses were used to identify independent risk factors for gastrointestinal events. The receiver operating characteristic (ROC) curves were used to assess the predictive value of AsaRiskCalculator for gastrointestinal events.

Results: A total of 400 MI patients meeting the eligibility criteria were analyzed, including 94 and 306 in the gastrointestinal and nongastrointestinal groups, respectively. The data showed that age, male gender, predicted gastrointestinal events, and *Helicobacter pylori* (HP) infection were positively correlated with gastrointestinal events. In multiple logistic regression analysis, predicted gastrointestinal events and HP infection were identified as risk factors for actual gastrointestinal events. HP infection was highly predictive in Chinese patients; the ROC curve indicated an area under the curve of 0.822 (95% confidence interval: 0.774–0.870). The best diagnostic cutoff point of predicted gastrointestinal events was 68.0‰, yielding sensitivity and specificity of 60.6% and 93.1%, respectively, for predicting gastrointestinal events in Chinese patients with MI.

Conclusions: AsaRiskCalculator had a predictive value for gastrointestinal events in Chinese patients with MI. HP infection seemed to be an independent risk factor for gastrointestinal events caused by long-term aspirin treatment in Chinese patients with MI, and it should be included in the risk calculator adapted for Chinese patients.

Key words: Aspirin; Cardiovascular/Gastrointestinal Risk Calculator; Gastrointestinal Events; Myocardial Infarction

INTRODUCTION

Myocardial infarction (MI) is defined as necrosis of the heart muscle secondary to prolonged lack of oxygen supply.[1] In 2010, there were estimated 8.1 million patients with MI in China. The World Bank predicted this number to reach 23 million by 2030.[2] In 2010, myocardial ischemia was the second cause of death in China (948,700 deaths, 95% uncertainty intervals: 774,500–1,024,600).[3] This points to an already high and steadily increasing disease burden of MI in China.

Aspirin (acetylsalicylic acid) is an effective, safe, and inexpensive early treatment for MI, with few administrative barriers; it is of significant importance in areas with underdeveloped health-care infrastructure and limited resources.[4] Several

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international guidelines recommended long-term use of low-dose aspirin (75–150 mg/day) as an effective antiplatelet agent for patients with cardiovascular disease, unless contraindicated.[5,6] A meta-analysis of randomized controlled trials demonstrated that low-dose aspirin is protective in most patients at increased risk of occlusive vascular events, including those with acute MI, ischemic stroke, stable or unstable angina, peripheral artery disease, and atrial fibrillation.[7] Low-dose regimens of aspirin have become a standard treatment for the secondary prevention of cardiovascular outcomes.[8]

While the benefits of low-dose aspirin in MI prevention are undeniable, adverse events are inevitable. A previous meta-analysis showed that use of low-dose aspirin is associated with several adverse effects, among which the most clinically relevant are major extracranial bleeding events, especially gastrointestinal bleeding.[9] For secondary prevention of cardiovascular disease, the studies of Western countries collectively proposed that the absolute benefits of aspirin far outweigh its absolute risks of major bleeding events.[7] Individuals with a history of cardiovascular events discontinuing low-dose aspirin are at an increased risk of nonfatal MI compared with those who continue treatment of low-dose aspirin.[10] However, the risk of gastrointestinal events in Chinese patients using low-dose aspirin as secondary MI prevention remains unclear.

The cardiovascular/gastrointestinal risk calculator, AsaRiskCalculator, is a tool to estimate cardiovascular and gastrointestinal risks to facilitate the clinical decision-making process. Gastrointestinal risk ratio estimation and the incidence of gastrointestinal events are based on different risk factors, including age, gender, a history of complicated and uncomplicated ulcer, dyspepsia, and concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin/ dicumarinics, or clopidogrel.[11,12] The aim of this study was to assess the feasibility of AsaRiskCalculator in predicting gastrointestinal events in Chinese MI patients, determining unique risk factor(s) to gastrointestinal events in Chinese patients that should be considered in the calculator. Our findings should better equip physicians for therapeutic decision-making and minimize the risks of aspirin-induced gastrointestinal events in Chinese patients with MI.

Methods

Ethical approval
The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Research and Ethics Committee of Shapingba District People's Hospital. Patient consent was waived by the Ethics Committee due to the retrospective nature of this study.

Patients and study design
The MI patients who visited Shapingba District People's Hospital between January 2012 and January 2016 were retrospectively reviewed. All patients should meet the following eligibility criteria: (1) patients with a history of MI who underwent gastroscopy at the time of study; (2) treated with enteric-coated aspirin (ECA) at the time of study; (3) patients without malignant tumor or hepatocirrhosis.

The patients were diagnosed with gastrointestinal events if either gastric ulcer or acute erosive gastritis was detected. Based on gastroscopic data, the patients were divided into two groups: gastrointestinal and nongastrointestinal groups. Predicted gastrointestinal and cardiovascular events were assessed based on demographic and clinical characteristics of the patients using AsaRiskCalculator.[11] The risk of gastrointestinal bleeding was calculated using the patient's history of gastrointestinal bleeding.

Patients' data were collected at the time of consultation, including age, gender, smoking status, blood pressure (systolic and diastolic), cholesterol levels (total cholesterol, high-density lipoprotein [HDL], and low-density lipoprotein), comorbidities (hypertension, diabetes mellitus, hyperlipidemia, MI, and stroke), and concomitant drugs (clopidogrel, other antiplatelet drugs, other NSAIDs, and proton pump inhibitor [PPI]). The patients were also tested for *Helicobacter pylori* (HP) infection using a rapid urease test kit (Shenzhen Zhonghe Headway Bio-Sci and Tech Co., Ltd., China).

Statistical analysis
Continuous variables with normal distribution were presented as mean ± standard deviation and assessed by Student's t-test. Nonnormally distributed continuous variables were presented as median (range) and assessed by the Mann-Whitney U-test. The Chi-square test was used to analyze categorical variables. In simple logistic regression, covariates that affected gastrointestinal events with $P < 0.1$ were included in multiple logistic regression analysis. Backward elimination was then used for factors that contributed to gastrointestinal events through multiple logistic regression. All statistical analyses were performed using the SPSS statistical software version 19.0 (SPSS Inc., Chicago, IL, USA). A $P < 0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics of patients
A total of 400 MI patients meeting the eligibility criteria were analyzed, including 94 and 306 in the gastrointestinal and nongastrointestinal groups, respectively. Demographic and clinical characteristics of the patients are listed in Table 1. There were more males than females in the gastrointestinal group compared with the nongastrointestinal group ($P < 0.001$). The mean age of gastrointestinal group was 71.7 ± 6.1 years (range: 54–80 years), which was older than the mean age of the nongastrointestinal group (67.9 ± 6.9 years, range: 42–80 years; $P < 0.001$).

Compared with nongastrointestinal group, the gastrointestinal group had lower systolic and diastolic blood pressures, shorter length of ECA use, lower actual cardiovascular events, higher HP infection rate, increased risk of gastrointestinal events, and higher predicted gastrointestinal events (all $P < 0.05$).

Table 1: Demographic and clinical characteristics of patients with myocardial infarction in this study

Characteristics	GI group (n = 94)	Non-GI group (n = 306)	Statistical values	P
Gender, n (%)			18.089*	<0.001
Male	54 (57.4)	101 (33.0)		
Female	40 (42.6)	205 (67.0)		
Age (years), mean ± SD	71.7 ± 6.1	67.9 ± 6.9	−4.937†	<0.001
Total cholesterol (mmol/L), mean ± SD	4.18 ± 1.02	4.64 ± 1.30	−3.322†	0.001
HDL (mmol/L), mean ± SD	1.12 ± 0.33	1.16 ± 0.30	−1.895†	0.058
BP (mmHg), mean ± SD				
SBP	140.8 ± 15.2	145.0 ± 16.6	−2.195†	0.028
DBP	83.7 ± 9.8	86.5 ± 10.8	−2.284†	0.022
Diabetes mellitus, n (%)			0.123*	0.726
Yes	29 (30.9)	100 (32.7)		
No	65 (69.1)	206 (67.3)		
Smoking status, n (%)			3.287*	0.070
Yes	36 (38.3)	87 (28.4)		
No	58 (61.7)	219 (71.6)		
NSAIDs use				
Yes	0	0		
No	94 (100.0)	306 (100.0)		
Duration of ECA use (months), median (range)	10 (3–84)	12 (1–120)	−5.503‡	<0.001
Clopidogrel use, n (%)			3.836*	0.050
Yes	6 (6.4)	7 (2.3)		
No	88 (93.6)	299 (97.7)		
Predicted CV events (%), median (range)	26 (2–123)	21 (3–150)	−1.009‡	0.313
Actual CV events, n (%)			6.337*	0.012
Yes	4 (4.3)	42 (13.7)		
No	90 (95.7)	264 (86.3)		
Predicted GI events (%), median (range)	90 (24–360)	45 (10–324)	−8.988‡	<0.001
Risk of GI bleeding, n (%)			11.932*	<0.001
Yes	10 (10.6)	6 (2.0)		
No	84 (89.4)	300 (98.0)		
HP infection, n (%)			44.805*	<0.001
Positive	93 (98.9)	194 (63.4)		
Negative	1 (1.1)	112 (36.6)		
Anti-HP treatment, n (%)			0.102*	0.750
Yes	2 (2.1)	5 (1.6)		
No	92 (97.9)	301 (98.4)		
PPI therapy, n (%)			1.079*	0.299
Yes	8 (8.5)	38 (12.4)		
No	86 (91.5)	268 (87.6)		

*Chi-square value; †t values; ‡U value. HDL: High-density lipoprotein; BP: Blood pressure; SBP: Systolic blood pressure; DBP: Diastolic blood pressures; NSAIDs: Nonsteroidal anti-inflammatory drugs; HP: *Helicobacter pylori*; PPI: Proton pump inhibitor; ECA: Enteric-coated aspirin; GI: Gastrointestinal; CV: Cardiovascular; SD: Standard deviation.

Risk factors for gastrointestinal events

Univariate logistic regression was used to assess the effects of individual covariates on actual gastrointestinal events. Among these covariates, age, male gender, predicted gastrointestinal events, and HP infection were positively correlated with gastrointestinal events [all $P < 0.05$, Table 2], while total cholesterol level, HDL level, blood pressure (BP) (both systolic and diastolic BP), and the length of ECA use had negative impacts on actual gastrointestinal events (all $P < 0.05$). Notably, patients with HP infection had the highest probability of developing gastrointestinal events (odds ratio = 53.691, 95% confidence interval [CI]: 7.382–390.487, $P < 0.001$).

Through backward elimination in multiple logistic regressions, three covariates were identified as risk factors for gastrointestinal events, including the length of ECA use, predicted gastrointestinal events, and HP infection [Table 3]. Here also, HP infection showed strong positive correlation with gastrointestinal events ($\beta = 4.729$). In contrast, longer ECA use resulted in less gastrointestinal events, with a negative correlation coefficient (−0.034).

Receiver operating characteristic curve for analyzing the predictive value of AsaRiskCalculator

A receiver operating characteristic (ROC) curve was used to evaluate the sensitivity and specificity of AsaRiskCalculator.

Table 2: Simple logistic regression assessing individual factors that impact GI events in ECA patients after gastroscopy

Items	OR	95% CI	P
Gender (male vs. female)	2.740	1.707–4.398	<0.001
Age	1.096	1.053–1.141	<0.001
Total cholesterol	0.722	0.587–0.888	0.002
HDL	0.621	0.284–1.360	0.234
SBP	0.984	0.969–0.998	0.030
DBP	0.975	0.953–0.997	0.026
Diabetes mellitus (yes vs. no)	0.915	0.555–1.506	0.726
Smoking (yes vs. no)	1.562	0.963–2.536	0.071
Lengths of ECA use	0.939	0.913–0.967	<0.001
Clopidogrel use (yes vs. no)	2.912	0.954–8.891	0.060
Predicted GI events	1.045	1.034–1.057	<0.001
HP infection (yes vs. no)	53.691	7.382–390.487	<0.001

HDL: High-density lipoprotein; SBP: Systolic blood pressure; DBP: Diastolic blood pressures; HP: *Helicobacter pylori*; ECA: Enteric-coated aspirin; GI: Gastrointestinal; *OR*: Odds ratio; *CI*: Confidence interval.

Table 3: Multiple logistic regression assessing multiple factors that impact GI events in ECA patients after gastroscopy

Items	β	OR	95% CI	P
Length of ECA use	−0.034	0.966	0.940–0.993	0.014
Predicted GI events	0.040	1.041	1.029–1.053	<0.001
HP infection	4.729	113.235	5.496–2332.812	0.005

HP: *Helicobacter pylori*; ECA: Enteric-coated aspirin; GI: Gastrointestinal; *OR*: Odds ratio; *CI*: Confidence interval.

In the ROC curve, the area under the curve (AUC) was 0.822 (95% *CI*: 0.774–0.870, *P* < 0.001; Figure 1). The best diagnostic cutoff point of predicted gastrointestinal events was 68.0‰, yielding sensitivity and specificity of 60.6% and 93.1%, respectively, for predicting gastrointestinal events in Chinese patients with MI. The Youden index was 0.537.

Discussion

In the current study, we retrospectively analyzed the demographic and clinical data of 400 Chinese patients with MI. We found that age, male gender, predicted gastrointestinal events, and HP infection were positively correlated with gastrointestinal events. Multiple logistic regression analysis predicted that gastrointestinal events and HP infection were identified as significant risk factors for gastrointestinal events. HP infection was a high risk factor in Chinese patients; the ROC curve indicated a good test with AUC of 0.822. The best diagnostic cutoff point of predicted gastrointestinal events was 68.0‰ for predicting gastrointestinal events in Chinese MI patients.

The study aimed to analyze whether the AsaRiskCalculator is applicable to Chinese patients with MI in predicting gastrointestinal events. Predicted gastrointestinal events
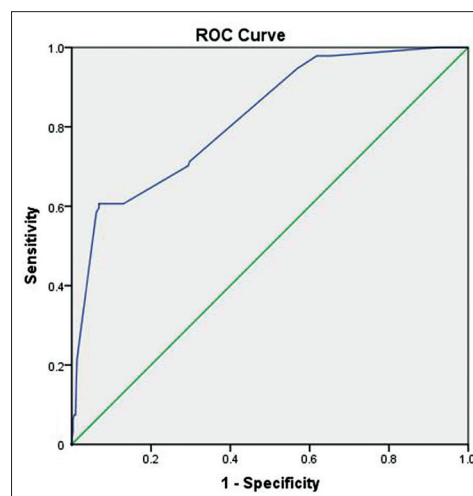

Figure 1: Receiver operating characteristic curve analysis showing actual gastrointestinal events as the gold standard of diagnosis and predicted gastrointestinal events as diagnostic criteria (*P* < 0.001).

derived from AsaRiskCalculator showed a positive correlation with actual gastrointestinal events in both univariate and multiple logistic regression analyses, indicating that predicted gastrointestinal events might be an independent risk factor for actual gastrointestinal events. The ROC curve further confirmed that predicted gastrointestinal events assessed by AsaRiskCalculator could be a good predictor of gastrointestinal events in Chinese patients with MI, with the diagnostic cutoff point mentioned above. Assessing individual risk factors in aspirin-treated patients with MI, Lanas[13] reported that age, male gender, history of peptic ulcer, and concomitant use of NSAIDs, anticoagulants, or clopidogrel were major risk factors for upper gastrointestinal bleeding,[13] and included in the AsaRiskCalculator algorithm.[11] The findings of this study were consistent with the results of Lanas[13] with age, male gender, and clopidogrel use positively correlated with gastrointestinal events in simple logistic regression.

By logistic regression analysis, this study identified HP infection as an independent and significant risk factor for gastrointestinal events. This was consistent with previous findings. A meta-analysis assessing the prevalence of HP infection and NSAIDs use in patients with peptic ulcer bleeding revealed that HP infection increased the risk (3.53 folds) of peptic ulcer in NSAIDs-treated patients, in addition to the risk associated with the usage of NSAIDs.[14] Therefore, HP infection and NSAIDs use independently increased the risk of peptic ulcer and ulcer bleeding.[14] In other words, patients treated with PPI for HP eradication should be protected against gastrointestinal events. This suggested that Chinese patients may not be given PPI treatment consistently, possibly due to late diagnosis of HP infection, especially in areas with limited access to comprehensive health care. Therefore, HP infection itself should be considered a risk factor for predicting gastrointestinal events in Chinese patients, and standard clinical practice should include patients with MI in HP infection screening programs.

An important finding in this study was that the length of ECA use was negatively correlated with risk of gastrointestinal events. In addition, patients in the nongastrointestinal group had significantly longer ECA use than those of the gastrointestinal group, suggesting that some patients might be more resistant to gastrointestinal bleeding/events caused by aspirin. This could be due to differences in aspirin dosage, as a prospective study assessing 87,680 female aspirin users demonstrated that higher aspirin dosage was associated with higher risk of gastrointestinal bleeding in both short- and long-term users.[15] Therefore, patients should be prescribed the lowest effective dosage of aspirin in both long- and short-term treatment regimens.[15]

We acknowledged that the current study had limitations. First, it was a retrospective study, and the patients meeting the selection criteria were those able to keep aspirin treatment. We did not have data for patients who may have discontinued aspirin treatment due to adverse events, or those who had regimen or dosage change. Second, due to the retrospective nature of this study, medical treatment standards in the study cohort were inconsistent. For instance, PPI treatment might not have been timely given to MI patients with HP infection. Therefore, gastrointestinal risk reduction by PPI treatment reported by previous studies remains unclear based on the current cohort.

In summary, by retrospectively analyzing 400 Chinese patients with MI, this study found that AsaRiskCalculator had a predictive value for gastrointestinal events. More importantly, HP infection was identified as an independent risk factor for gastrointestinal events caused by long-term aspirin treatment in Chinese patients with MI. Therefore, Chinese researchers and clinicians should consider including HP infection in the AsaRiskCalculator algorithm for therapeutic decision-making in Chinese patients with MI.

Conflicts of interest
There are no conflicts of interest.

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