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Review Article

Meta-analysis of risk factors for gastrointestinal bleeding in patients with acute coronary syndrome

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Abstract: Objective: The data of risk factors associated with acute coronary syndrome (ACS) complicated with gastrointestinal bleeding were screened and meta-analyzed to provide theoretical basis for the clinical diagnosis, treatment and prognosis of the complication. Methods: Four databases, including China National Knowledge Infrastructure (CNKI), VIP Database (VIP), China Biology Medicine disc (CBM), Baidu Scholar, Scopus (Elsevier), Embase and Ovid were used to search for observational studies of ACS and gastrointestinal bleeding. Data extraction (computer exclusion and manual exclusion) was conducted to remove the papers that were not associated with ACS and gastrointestinal bleeding. Ten articles with randomized controlled trial (RCT) were included in this study. Revman5.3 was adopted to analyze the data. Odds Ratio (OR) was used to evaluate the influence of relevant risk factors on the complication. Results: The following indices, including age, hypertension, smoking, unstable coronary atherosclerotic plaque, diabetes and abnormal glucose tolerance, were identified as the independent risks factor leading to ACS complicated with gastrointestinal bleeding with significant difference ($P < 0.05$). Conclusion: In the clinic treatment of gastrointestinal bleeding in patients with ACS, nursing interventions should be customized to risk factors such as age, hypertension, smoking, unstable coronary atherosclerotic plaque, diabetes and abnormal glucose tolerance, so as to improve the prognosis and the quality of life of patients.

Keywords: Acute coronary syndrome, gastrointestinal bleeding, risks factor, meta-analysis

Introduction

Acute coronary syndrome (ACS) is a common and frequent cardiovascular disease, which is not infectious, but is a serious threat to the life of patients [1]. Studies focusing on ACS indicated that although China has established a relatively efficient treatment system for acute stage of ACS and improved the curative effect of ACS, there were still many issues far from standardization and normalization in many aspects, such as precaution, diagnosis, treatment, prognosis and long-term management after discharge from hospital. Moreover, the overall levels of health awareness and self-management of Chinese residents are poor, which is the main cause of death, and the incidence and mortality of ACS and relevant complications are still on the rise [2]. In the clinic treatment, ACS and gastrointestinal bleeding are reciprocal causation, leading to therapeutic difficulty. Whether the anticoagulating therapy should be used in the treatment of ACS complicated with gastrointestinal bleeding has been a controversial issue in the cardiovascular field. Meta-analysis was first developed in 1976. Its main purpose is to summarize the previous research results more objectively and comprehensively, which can avoid the limitation of small sample size of clinical trials and obtain more accurate, reliable and comprehensive medical information [3]. Meta-analysis is one of the main contents and means of evidence-based medical research. Although the pathogenic factors and risk factors of ACS complicated with gastrointestinal bleeding are extremely sophisticated, there is little high-quality evidence for the clinical treatment of ACS with gastrointestinal bleeding, especially the paper about meta-analysis. In order to investigate the correlation between relevant risk factors and ACS with gastrointestinal bleeding, 10 papers based on randomized controlled trial (RCT) were adopted for meta-analysis.

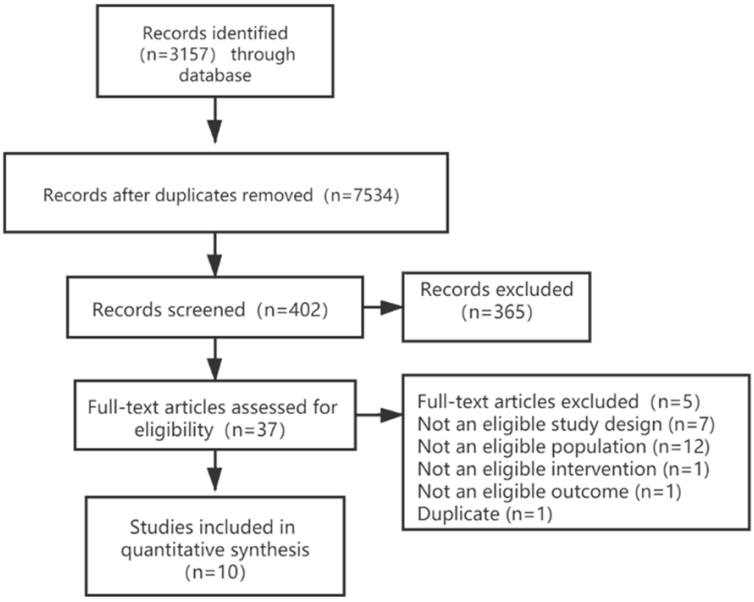

Figure 1. The flow chart of the literature screening.

Materials and methods

Search strategy

Keywords and subject terms were entered the databases. "Acute coronary syndrome", "gastrointestinal hemorrhage" and "meta-analysis" were included in keywords, and "acute coronary syndrome" and "gastrointestinal bleeding" were included in subject terms. Articles published before 5/22/2020 were considered for inclusion.

Inclusion and exclusion criteria

Studies included should be eligible for inclusion in the meta-analysis and fulfill the following criteria: (1) Inclusion criteria: ① reported ACS complicated with gastrointestinal bleeding in Chinese, English, Latin, French and other languages; ② included more than 30 patients with surgical treatment and drug treatment; ③ included subjects with complete clinical data (fatality rate, mechanical ventilation duration, paper onset and publication time, place, study population, signed informed consent) from RCT; (2) exclusion criteria: ① animal experiment; ② studies, reviews, letters, reviews related ACS complicated with gastrointestinal bleeding without RCT, or not associated with the prognosis; ③ cases, repea-ted reports and papers with insufficient data; ④ the number of subjects was less than 30. The inclusion and exclusion criteria were based on "Guidelines for rapid diagnosis and treatment of acute coronary syndrome (2019 Edi-tion)" and "the 10th chapter of Meta-analysis series: criteria for eligibility" [4, 5].

Data extraction

The papers were extracted from the following databases: China National Knowledge Internet (CNKI), China Biology Medicine disc (CBM), VIP Database (VIP), Baidu Scholar, PubMed, Scopus (Elsevier), Embase and Ovid. The following information was extracted from each eligible study: first author's surname, data of ACS patients complicated with gastrointestinal bleeding (sample size, group information, therapeutic method, disease course, intervention duration and curative effect), year of publication, and included database. All procedures conform to the principle of Declaration of Helsinki. Search strategy: Chinese terms for "Acute coronary syndrome" and "risk factors for gastrointestinal bleeding" and "segmentectomy" or "pulmonary wedge resection" or "lobectomy" or "partial lobectomy" were searched in Chinese database; English terms for "Acute coronary syndrome" or "ACS" and "Gastrointestinal bleeding" or "bleeding" and "risk" were searched in English database. The included literature included both Chinese and English literature, and animal experiments were excluded. References were also searched (**Figure 1**).

Quality assessment

The data were collected, sorted, screened, analyzed and included in this study independently by two trained investigators. In case of dispute, a third researcher was consulted. Data were evaluated by the criteria of Cochrane 5.1.0 brochure. The final results were discussed and completed.

Statistical analysis

We adopted Revman5.3 to analyze the data. Logarithmic standard errors were analyzed

Table 1. Basic information of literature search and screening results

	Years	Sample size		Duration of treatment (month)		Gastrointestinal bleeding rate (%)	
		Experiment	Control	Experiment	Control	Experiment	Control
Cao Zhongnan [6]	2019	165	95	12	12	1.21	16.84
Jiang Shubin [7]	2011	134	132	12	12	2.24	15.15
Wang Jianning [8]	2010	51	126	< 1	< 1	3.92	33.11
Wang Hao [9]	2017	194	280	< 1	< 1	40.93	59.07
Liu Weitai [10]	2010	120	235	< 1	< 1	6.70	19.80
Xue Haiwei [11]	2012	80	83	< 1	< 1	7.50	22.90
Wang Baoping [12]	2014	25	25	< 1	< 1	0.76	12.88
Li Yang [13]	2014	155	147	< 1	< 1	0.65	0.68
Zheng ruolong [14]	2014	127	125	12	12	2.36	4.80
Tao Yuting [15]	2014	35	32	1	1	2.86	21.88

Table 2. Stratified heterogeneity test

Factor	Literature	Q test		I^2 (%)	*H* (95% CI)	*OR* (95% CI)
		Q value	*P* value			
Age	8	6.527	0.007	54.271	1.428 (2.51~0.84)	2.510 (1.82~3.27)
Hypertension	2	6.014	0.098	83.679	2.512 (3.45~1.25)	3.715 (3.12~4.53)
Smoking	5	9.815	< 0.01	28.471	1.572 (3.15~1.87)	2.781 (2.86~3.76)
Dyslipidemia	3	5.628	0.401	48.716	2.243 (3.25~1.256)	3.014 (2.62~4.00)
Diabetes and impaired glucose tolerance	6	4.213	0.238	38.975	2.012 (2.87~1.43)	3.824 (3.01~4.52)

by subgroup analysis. Heterogeneity between studies was evaluated using fixed effect model (I^2 < 25.0% standing for low, 25.0% < I^2 ≤ 50.0% standing for medium, I^2 > 50.0% standing for high). When I^2 > 50.0%, random effect summaries were employed. Continuous variable was evaluated by Mean Difference (MD). Dichotomous variables were evaluated by Odds Ratio (OR).

Result

Characteristics and screening of studies

A total of 3157 relevant papers were obtained by searching the subject terms and keywords. Among them, 402 papers were dropped after the exclusion by EndnoteX7 and after reading the titles and abstracts, 37 papers were retained. Finally, 10 full-text articles were selected based on RCT [6-15]. A total of 2366 subjects were enrolled in the 10 RCTS, including 1086 (45.90%) in the experimental group and 1280 (54.10%) in the control group. The rate of gastrointestinal bleeding was 6.91% in the experimental group and 20.71% in the control group. The bleeding rate in the experimental group was significantly lower than that in the control group (**Table 1**).

Results of quality assessment

According to the evaluation of Cochrane, all baseline information from 10 RCTs were comparable, including 4 RCTs of random sequence generation [7-10], 3 RCTs of detection bias [6, 11, 13], 4 RCTs of random assignment hiding [9, 11, 14, 15], 5 RCTs of reported deviation [7-9, 12, 15], and 2 RCTs of loss bias [10, 13].

Heterogeneity test of factors on the ACS complicated with gastrointestinal bleeding

If *P* < 0.05 stood for high heterogeneity among groups, age and lesion region were analyzed by random effects model (D-L). If *P* > 0.05 stood for low heterogeneity among groups, GCS scores, instability of coronary atherosclerotic plaque, and history of digestive tract disease were analyzed by fixed effect model (Peto) (**Table 2**).

Meta-analysis of risk factors for gastrointestinal bleeding with ACS

Age: The heterogeneity was manifested by heterogeneity test among 5 studies (*P* < 0.46, I^2=0%), and the fixed effect model showed that the gastrointestinal bleeding rate of ACS patients over 60 years old is 1.95 times com-

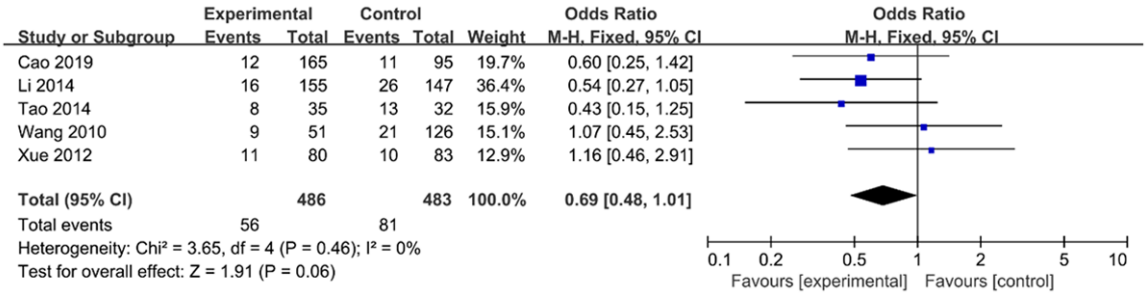

Figure 2. Comparison of the incidence of ACS complicated with gastrointestinal bleeding in patients aged > 60 years and ≤ 60 years.

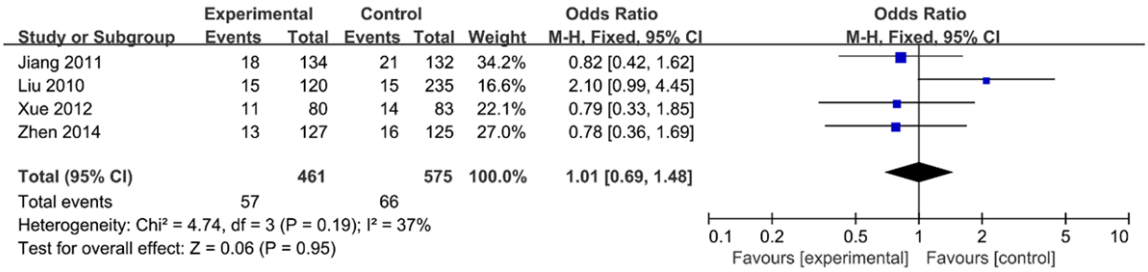

Figure 3. Comparison of abnormal blood lipid in patients with ACS complicated with gastrointestinal hemorrhage.

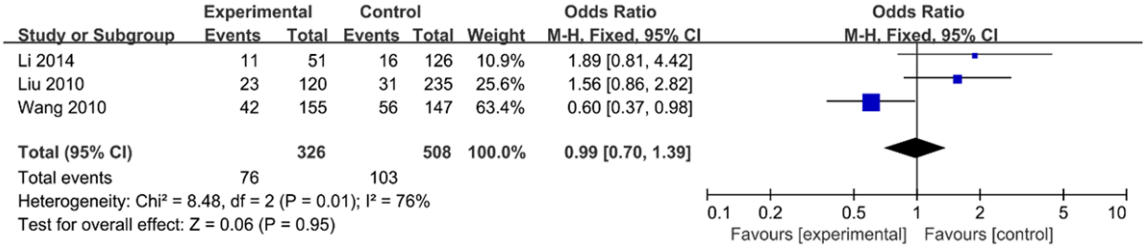

Figure 4. Comparison of hypertension in patients with ACS complicated with gastrointestinal hemorrhage.

pared to patients under 60 years old, with significant difference ($P < 0.05$) (**Figure 2**).

Dyslipidemia: The heterogeneity was analyzed by heterogeneity test among 4 studies ($P < 0.19$, I^2=37%), and the fixed effect model revealed that the gastrointestinal bleeding rate of ACS patients with dyslipidemia is 6.36 times compared to patients without dyslipidemia, with significant difference ($P < 0.05$) (**Figure 3**).

Hypertension: The heterogeneity was demonstrated by heterogeneity test among 3 studies ($P < 0.01$, I^2=76%), and the fixed effect model discovered that the gastrointestinal bleeding rate of ACS patients with hypertension is 7.21 times compared to patients without hypertension, with significant difference ($P < 0.05$) (**Figure 4**).

Diabetes and abnormal glucose tolerance

The heterogeneity was evaluated by heterogeneity test among 3 studies ($P < 0.2$, I^2=33%), and the fixed effect model discovered that the gastrointestinal bleeding rate of ACS patients with diabetes and abnormal glucose tolerance is 0.19 times compared to patients without diabetes and abnormal glucose tolerance, with significant difference ($P < 0.05$) (**Figure 5**).

Smoking: The heterogeneity was manifested by heterogeneity test among 5 studies ($P < 0.2$, I^2=33%), and the fixed effect model showed that the gastrointestinal bleeding rate of ACS patients with smoking is 2.84 times compared to patients without smoking, with significant difference ($P < 0.05$) (**Figure 6**).

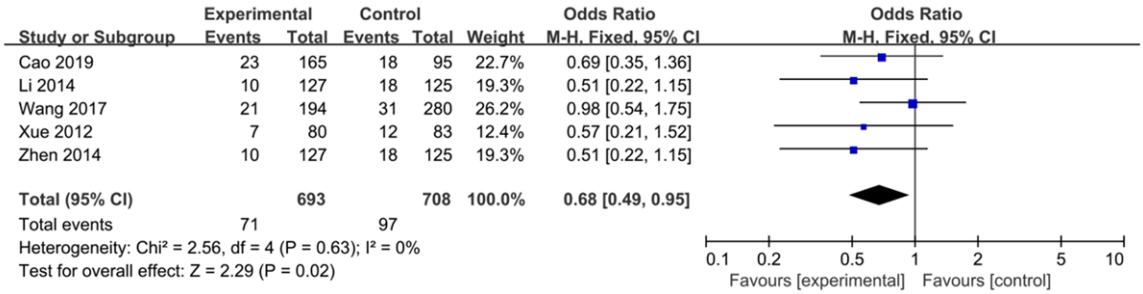

Figure 5. Relationship between diabetes mellitus and impaired glucose tolerance and gastrointestinal bleeding in patients with ACS.

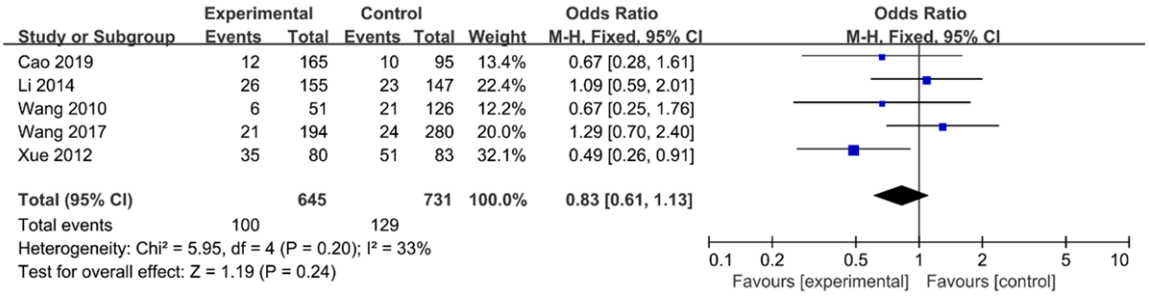

Figure 6. The relationship between smoking and gastrointestinal bleeding in patients with ACS.

Deviation of risk factors: There were missing corners in the funnel plots of risk factors like age, hypertension, smoking, unstable coronary atherosclerotic plaque, diabetes and abnormal glucose tolerance, which were missed in the right corner. The reasons for that might be related to small sample size, insufficient data, and unpublished negative results.

Discussion

According to statistics, the mechanism of gastrointestinal bleeding is unclear [16]. However, tremendous clinical studies have shown that the occurrence of the complication is associated with unstable gastric mucosal ischemia, leading to the impaired stress response, barrier damage and ischemia of gastric mucosa. Some studies have demonstrated that the death rate of ACS patients with gastrointestinal bleeding is significantly higher than that of patients without complication. The reoccurrence rate of prognosis is also higher. Hence, it is necessary to identify risk factors of complication in early stage. Precaution measures are required to be carried out to reduce the fatality rate and improve the quality of prognosis.

The paper manifested that there are tremendous risk factors underling ACS complicated with gastrointestinal bleeding. The fatal factors are age, hypertension, smoking, unstable coronary atherosclerotic plaque, diabetes and abnormal glucose tolerance. The reason why age leads to the escalation is the artery sclerosis of gastric mucosal in the patients over 60 years old, resulting in ischemia of local tissue [17-19]. Owing to artery sclerosis, the regeneration of epithelium and mucus releasing are slower than before, and coupled with decreased vascular elasticity and increased vascular brittleness, the frequency of gastrointestinal bleeding in ACS patients is raised [17, 20]. In general, hypertension is highly correlated with ACS. In previous studies, approximately 60.0 to 70.0% of patients with coronary atherosclerosis suffered from hypertension, and the probability of gastrointestinal bleeding in ACS patients with hypertension was 3 to 4 times of that in non-hypertension patients. This study found that the incidence of ACS complicated with gastrointestinal bleeding in hypertensive patients was 7.21 times of that in non-hypertensive patients ($P < 0.05$). Due to small sample size and insufficient data, the incidence was higher than previous studies [21-23]. The comparison of smoker and non-smoker showed that the former incidence of the complication is 2.84 times to the latter, and was correlated

with the smoking counts. Many studies also demonstrated the high correlation between passive smoking and the complication [24-26]. ACS complicated with gastrointestinal bleeding is characterized by rapid onset, rapid progression and severe stress response. When affected by diabetes or abnormal glucose tolerance, the bleeding incidence may increase accordingly. In previous research, the incidence of the complication in patients with diabetes and abnormal glucose tolerance was higher than that of patients without diabetes and abnormal glucose tolerance [27]. This study demonstrated that the incidence of ACS complicated with gastrointestinal bleeding in patients with diabetes and abnormal glucose tolerance was 0.19 times higher than that in patients without diabetes and abnormal glucose tolerance ($P < 0.05$). The inconsistency between the two studies may lead to the bias in the papers [28]. Due to the complex mechanism in the complication with diabetes and abnormal glucose tolerance, there are still tremendous issues for further investigation.

In conclusion, age, hypertension, smoking, unstable coronary atherosclerotic plaque, diabetes and abnormal glucose tolerance are all the risk factors for ACS complicated with gastrointestinal bleeding. Therefore, the relevant treatment needs to be adopted, so as to improve the prognosis and the quality of life of patients.

Disclosure of conflict of interest

None.

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References

[1] Shalev A, Zahger D, Novack V, Etzion O, Shimony A, Gilutz H, Cafri C, Ilia R and Fich A. Incidence, predictors and outcome of upper gastrointestinal bleeding in patients with acute coronary syndromes. Int J Cardiol 2012; 157: 386-390.

[2] Yeh J, Wu B and Ho N. Su1097 acute coronary syndrome and risk of gastrointestinal hemorrhage: when is it safe to proceed? Gastroenterology 2015; 148: S-406.

[3] Wang N and Du Q. Risk factors of upper gastrointestinal hemorrhage with acute coronary syndrome: a nested case-control study. Am J Emerg Med 2018; 37:

[4] Zhang X, Yu X, Chen F and Zhu H. Guidelines for rapid emergency diagnosis and treatment of acute coronary syndrome (2019). J Clin Emerg 2019; 20: 6-15.

[5] Zeng X, Sun Z and Tang H. Ten Meta Analysis Series: formulation of qualification criteria. Chinese Journal of Evidence Based Cardiovascular Medicine 2013; 5: 6-9.

[6] Cao Z and Du X. The effect of Helicobacter pylori eradication on upper gastrointestinal hemorrhage in acute coronary syndrome. Chinese Journal of Nosocomial Infection 2019; 29: 2285-2288+2293.

[7] Jiang S, Li L and Parharti. Evaluation of pantoprazole on gastrointestinal protection in patients with acute coronary syndrome treated with tirofiban and aspirin. Chinese Journal of Circulation 2011; 026: 178-181.

[8] Wang J, Zhang Y, Xu C, She W, Zhai Q and Zhu Z. Combined application of pantoprazole and bismuth aluminate compound to prevent upper gastrointestinal bleeding after acute coronary syndrome. Chinese Modern Applied Pharmacy 2010; 027: 565-568.

[9] Wang H and Xu Y. Upper gastrointestinal hemorrhage after PCI in patients with acute coronary syndrome. Chinese and Foreign Medical Treatment 2017; 36: 65-66+72.

[10] Liu W. Omeprazole and pantoprazole in the prevention of gastrointestinal bleeding caused by antiplatelet therapy in patients with acute coronary syndrome. Chinese Journal of New Drugs and Clinical Medicine 2010; 29: 904-907.

[11] Xue H. A comparative study on the efficacy and safety of total and half dose tirofiban combined with coronary intervention in patients with non ST elevation acute coronary syndrome. Hebei Medical University 2012.

[12] Wang B, Cao W and Duan S. The efficacy and safety of pantoprazole sodium in the prevention of gastrointestinal bleeding after PCI in patients with acute coronary syndrome. Chinese Practical Medicine 2014; 149-150.

[13] Fan Y, Li Y, Peng L, Guo W, Zhang Y, Lu C and Xue Q. Safety of tirofiban in the perioperative application of percutaneous coronary intervention in elderly patients with acute coronary syndrome. Chinese Journal of Multiple Organ Diseases in the Elderly 2014; 732-737.

[14] Liu H, Chen X, Zheng R, Li W, Qian H and Zhang H. Effect of nursing follow-up on prognosis of patients with acute coronary syndrome at high risk of gastrointestinal bleeding. Chinese Journal of Modern Nursing 2014; 000: 434-437.

[15] Li J, Sun H, Tao Y, Wang G, Huang J, Li L and Su H. The effect of Qilin Xintongshu on patients with non ST elevation acute coronary syndrome complicated with gastrointestinal hemorrhage. Chinese Journal of Integrated Chinese and Western Medicine 2014; 265.

[16] Wang N, Li T and Du Q. Risk factors of upper gastrointestinal hemorrhage with acute coronary syndrome. Am J Emerg Med 2019; 37: 615-619.

[17] Lu J, Xuan S, Downing NS, Wu C, Li L, Krumholz HM and Jiang L. Protocol for the China PEACE (patient-centered evaluative assessment of cardiac events) million persons project pilot. BMJ Open 2016; 6: e010200.

[18] Yang QY, Ouyang J and Yang JD. Sepsis as an important risk factor for gastrointestinal bleeding in acute coronary syndrome patients: two case reports. Medicine (Baltimore) 2018; 97: e12273.

[19] Han YL. Advances of antiplatelet therapy in acute coronary syndrome patients accompanied with high risk factors of bleeding and ischemic events. Clinical Journal of Medical Officers 2018.

[20] El Hajj MS, Jaam MJ and Awaisu A. Effect of pharmacist care on medication adherence and cardiovascular outcomes among patients post-acute coronary syndrome: a systematic review. Res Social Adm Pharm 2018; 14: 507-520.

[21] Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, Richardt G, Liebetrau C, Witzenbichler B, Antoniucci D, Akin I, Bott-Flügel L, Fischer M, Landmesser U, Katus HA, Sibbing D, Seyfarth M, Janisch M, Boncompagni D, Hilz R, Rottbauer W, Okrojek R, Möllmann H, Hochholzer W, Migliorini A, Cassese S, Mollo P, Xhepa E, Kufner S, Strehle A, Leggewie S, Allali A, Ndrepepa G, Schühlen H, Angiolillo DJ, Hamm CW, Hapfelmeier A, Tölg R, Trenk D, Schunkert H, Laugwitz KL and Kastrati A. Ticagrelor or Prasugrel in patients with acute coronary syndromes. N Engl J Med 2019; 381: 1524-1534.

[22] Liu JJ, Liu WH and He ML. Risk factors of stress-induced upper gastrointestinal hemorrhage in acute cerebral infarction. Chin J Nervous Mental Dis 2019; 045: 135-138.

[23] Rumalla K and Mittal MK. Gastrointestinal bleeding in acute ischemic stroke: a population-based analysis of hospitalizations in the United States. J Stroke Cerebrovasc Dis 2016; 25: 1728-1735.

[24] Cook D and Guyatt G. Prophylaxis against upper gastrointestinal bleeding in hospitalized patients. N Engl J Med 2018; 378: 2506-2516.

[25] Kelly CR, Kirtane AJ, Stant J, Stone GW, Minutello RM, Wong SC, Manuzon H, Gerow-Smith R, Kelley N and Rabbani LE. An updated protocol for evaluating chest pain and managing acute coronary syndromes. Crit Pathw Cardiol 2017; 16: 7-14.

[26] Patel NJ, Pau D, Nalluri N, Bhatt P, Thakkar B, Kanotra R, Agnihotri K, Ainani N, Patel N, Patel N, Shah S, Kadavath S, Arora S, Sheikh A, Badheka AO, Lafferty J, Alfonso C and Cohen M. Temporal trends, predictors, and outcomes of in-hospital gastrointestinal bleeding associated with percutaneous coronary intervention. Am J Cardiol 2016; 118: 1150-1157.

[27] Wang C, Wang S, Wang J, Wang S, Zheng Z, Liu J and Chen Y. Predictive risk factors for massive gastrointestinal hemorrhage in patients with coronary artery disease after elective percutaneous coronary intervention. Chinese Journal of Multiple Organ Diseases in the Elderly 2016; 015: 739-743.

[28] Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD and Zeiher AM. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018; 379: 2097-2107.