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Original Contribution

# Risk factors of upper gastrointestinal hemorrhage with acute coronary syndrome

Nana Wang, MD [a], Tiegang Li, MD [b,*,1], Qiang Du, MD [a,*,1]

[a] Endocrinology Department, Shengjing Hospital of China Medical University, Shenyang 110004, China
[b] Emergency Department, Shengjing Hospital of China Medical University, Shenyang 110004, China

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ABSTRACT

*Background:* Research showed that the mortality of upper gastrointestinal hemorrhage (UGH) complicated with acute coronary syndrome (ACS) was higher than single UGH in elderly patients. This study aimed to determine the risk factors that associated with an increased risk of ACS occurrence after UGH.
*Methods:* A population-based nested case-control study was conducted analyzing the hospital information system database of Shengjing Hospital of China Medical University from September 1, 2009 to December 31, 2014. We included 3217 elderly patients who experienced a UGH, among which 152 cases were identified and matched 604 selected controls. Multivariate conditional logistic regression models were used to characterize risk factors associated with ACS occurrence and death after UGH.
*Results:* Diabetes (odds ratio (OR) = 1.84, 95% confidence interval (CI) 1.13–2.71, P = 0.039), smoking (OR = 1.87, 95% CI 1.19–2.73, P = 0.028), vasopressin or terlipressin use (OR = 1.51, 95% CI 1.02–2.14, P = 0.043), liver cirrhosis (OR = 2.43, 95% CI 1.45–4.38, P = 0.013), hemoglobin level (OR = 2.36, 95% CI 1.65–3.79, P = 0.014) and history of ACS (OR = 1.98, 95% CI 1.13–3.49, P = 0.017) increased risk of ACS incidence in elderly patients with UGH. Moreover, diabetes (OR = 2.14, 95% CI 1.15–4.21, P = 0.041), smoking (OR = 2.93, 95% CI 1.17–5.31, P = 0.043) and hemoglobin levels (OR = 1.95, 95% CI 1.24–3.16, P = 0.038) were independent variables for the mortality underwent UGH with ACS in elderly patients.
*Conclusions:* History of diabetes, vasopressin or terlipressin use, smoking, liver cirrhosis, hemoglobin level and history of ACS are risk factors to develop ACS in elderly patients with UGH. Importantly, diabetes, smoking and lower hemoglobin level are key variables for mortality.



## 1. Introduction

Acute upper gastrointestinal hemorrhage (UGH) is a very common diagnosis in emergency department. The incidence is reported to be 500/100,000 per year in those aged over 75 years, compared with that of around 48–160/100,000 per year in the general population in western countries, and lead to 300,000 admission every year [1-7], costing nearly five billion dollars annually to the health system in USA [8]. In most cases, it is caused by nonvariceal factors, and the mortality is up to 3–14% [9]. Some patients with UGH may suffer from dyspnea and chest pain, which indicate that they may develop acute coronary syndrome (ACS). It is reported that cardiovascular disease or its complications is often the cause of death among elderly patients with UGH. The mortality of UGH with ACS is up to 62% [10], much higher than the 20% mortality of patients with UGH alone [11]. But, the occurrence of ACS after UGH is frequently ignored, because the signs and symptoms may be covered up by severe UGH [1]. Until now, the risk factors, incidence, and outcomes associated with ACS in UGH patients have not been clear yet. Given this, increased awareness of potential risk factors for ACS after UGH is imperative to reduce mortality.

So, in this study, we carried out study on ACS in elderly patients with UGH presenting to the Emergency Department in Shengjing Hospital of China Medical University from September 2009 to December 2014. We hypothesized that ACS may develop in patients with UGH, and we examined the clinical variables associated with concurrent ACS and UGH. We aimed to identify risk factors for the development of ACS in elderly patients with UGH.

*Abbreviations:* UGH, upper gastrointestinal hemorrhage; ACS, acute coronary syndrome; OR, odds ratio; CI, confidence interval; HIS, hospital information system; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; UA, unstable angina; NSAID, nonsteroidal anti-inflammatory drug.

* Corresponding authors.
*E-mail addresses:* litg@sj-hospital.org, (T. Li), duq1@sj-hospital.org (Q. Du).

[1] The authors contributed equally to the work.

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## 2. Methods

### 2.1. Data source

We conducted a population-based retrospective nested case-control study to assess the association between risk factors and ACS occurrence in patients with UGH. The UGH patients were identified from the hospital information system (HIS) database of Shengjing Hospital of China Medical University. Shengjing Hospital is the largest hospital located in northeast in China, Liaoning Province. The HIS system is the electronic medical recording system used in both the inpatient and outpatient settings at Shengjing Hospital. The HIS system provided detail of each patient, including date of admission and discharge, general information, present history, past history, personal history, medical procedure during the hospital stay, medical procedure, examination results, primary and secondary diagnoses, etc.

### 2.2. Study population and design

We identified patients presenting to the Emergency Department from September 1, 2009 to December 31, 2014, with a primary diagnosis of UGH (ICD-10 code of K92.208, gastrointestinal hemorrhage; K92.206, gastric hemorrhage; K92.204, upper gastrointestinal hemorrhage; K92.101, melena; K92.001, hematemesis). A patient developed ACS after diagnosis of UGH was defined as case, no ACS was selected as control. By using an incidence density sampling approach, each case was matched by age (±5 years), sex and entry date (±30 days) with up to 4 randomly selected controls.

We assessed the mortality of patients at one month post-admission. They have detailed records about death causes in our HIS system. If the patients had been discharged from our hospital, we assessed their outcomes by telephone call performed by an Emergency Physician. We identified the causes from patients' death proof, in which death cause is recorded by doctors. If the patient died at home, with no death proof, the cause is identified as unknown.

The protocol used in this study was approved by the ethics committee of Shengjing Hospital of the China Medical University, and all subjects gave their written informed consent to participate.

### 2.3. Inclusion and exclusion criteria

Upper gastrointestinal bleeding was defined as symptoms of tarry stools, melena, coffee-ground vomitus, hematemesis, or anemia suspected to be related to UGI bleeding. Endoscopy within 24 h of presentation following successful resuscitation is carried out for most patients with UGH. Patients with variceal bleeding or high risk stigmata were examined by endoscopy in 12 h.

ACS was defined as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA). We defined elderly patients as ≥65 years of age.

Exclusion criteria were hematological diseases with coagulation disorders, history of myocardial bridge, serious infection, severe neurological disease, trauma, pregnancy, and recent myocardial infarction (within 6 weeks of emergency department admission). For patients who died shortly after admission before evaluations for ACS was excluded.

### 2.4. Risk factors

Electrocardiography (ECG) and cardiac enzymes, including creatine kinase (CK), CK-MB, and TnI, were checked after admission. Liver cirrhosis was previously diagnosed in hospital when a typical change in abdomen by ultrasound or CT or MRI, in addition to a hepatitis history or evidence of hepatic decompensation. We evaluated the five traditional cardiac risk factors (diabetes, hypertension, age, hypercholesterolemia and smoking), vasopressin or terlipressin use, alcohol use, drugs used and cause of bleeding, as well as other risk factors (age, male gender, obesity). By early observation, patients seldom had ACS if hemoglobin >90 g/L, so in this study, we selected patients presented with initial hemoglobin≤90 g/L. We classified anemia by hemoglobin level into three levels: ≤30 g/L as very severe anemia, ≤60 g/L as severe anemia, ≤90 g/L as moderate anemia. Previous UGH and myocardial infarction history, underlying malignancy and drug use including aspirin, coumadin, nonsteroidal anti-inflammatory drug (NSAID) and steroid, and history of tobacco and alcohol use were recorded in our system.

### 2.5. Statistical methods

All statistical analyses were performed using SAS 9.2 software. Data was expressed as mean ± SD or median (25th–75th percentiles) or as proportion. The association of variables with ACS was expressed as odds ratio (OR) with 95% confidence interval (CI), quantified by using a conditional logistic analysis. The sample size was calculated according to method of 1:4 matching case-control studies, with OR = 2, exposure rate in control group = 0.2, rate of error type I = 0.05 and rate of error type II = 0.10. Variables with $P < 0.1$ in univariate analysis were entered into multiple logistic regression analysis using a backward algorithm. $P < 0.05$ was considered statistically significance in the multivariate conditional logistic regression.

## 3. Results

A total of 3217 patients who presented with UGH from September 1, 2009 to December 31, 2014 were identified. 203 patients were excluded according to exclusion criteria, leaving 3014 patients as samples. Among them, 152 were diagnosed as elderly patients with ACS as experiment group. 604 without ACS were selected randomly as controls.

All the clinical characteristics were compared in Table 1. Patients in the cases group had higher BMI (odds ratio = 1.23, 95% confidence interval 1.06–1.81, P = 0.043), higher incidence of diabetes (OR = 2.68, 95% CI 1.72–4.16, P < 0.001), hypertension (OR = 1.38, 95% CI 0.95–2.01, P = 0.093), hypercholesterolemia (OR = 1.67, 95% CI 0.94–2.98, P = 0.083), smoking (OR = 1.90, 95% CI 1.26–2.86, P = 0.002), vasopressin or terlipressin use (OR = 1.99, 95% CI 1.22–3.27, P = 0.006), alcohol (OR = 1.59, 95% CI 1.10–2.29, P = 0.014), higher incidence of liver cirrhosis (OR = 5.39, 95% CI 3.50–8.30, P < 0.001), lower blood hemoglobin level after bleeding (OR = 1.72, 95% CI 1.32–2.25, P < 0.001) and history of ACS (OR = 1.91, 95% CI 1.08–3.39, P = 0.027). Given these findings, we selected BMI, hemorrhage volume, incidence of diabetes, hypertension, hypercholesterolemia, vasopressin or terlipressin use, alcohol, liver cirrhosis, blood hemoglobin level, and history of ACS as variables for multivariate conditional logistic regression in the subsequent evaluation.

In the multivariate conditional logistic regression analysis, incidence of diabetes (OR = 1.84, 95% CI 1.13–2.71, P = 0.039), smoking (OR = 1.87, 95% CI 1.19–2.73, P = 0.028),vasopressin or terlipressin use (OR = 1.51, 95% CI 1.02–2.14, P = 0.043), liver cirrhosis (OR = 2.43, 95% CI 1.45–4.38, P = 0.013), hemoglobin level (OR = 2.36, 95% CI 1.65–3.79, P = 0.014) and history of ACS (OR = 1.98, 95% CI 1.13–3.49, P = 0.017) remained significant associated with a higher odds of developing ACS, while BMI (OR = 1.12, 95% CI 0.84–1.43, P = 0.072), alcohol (OR = 1.52, 95% CI 0.73–1.94, P = 0.079), hypertension (OR = 1.16, 95% CI 0.87–1.84, P = 0.134) and hypercholesterolemia (OR = 1.43, 95% CI 0.83–2.15, P = 0.091) were not found to be significant risk factors (Fig. 1).

In the subsequent step, we analyzed the association of variables with mortality of UGH complicated by ACS in elderly patients. We assessed hospital outcomes of admitted patients at one month post-admission. If the patients had been discharged from the hospital, we assessed their outcomes by telephone call performed by an Emergency Physician. Causes of death were identified in 24 patients including cardiovascular death (45.8%, n = 11), GI bleeding (25%, n = 6), sepsis (16.7%, n =

**Table 1**
Clinical characteristics of UGH in elderly patients.

| Variables | Cases (n = 152) | Controls (n = 604) | OR (95% CI) | P[a] |
|---|---|---|---|---|
| Age (yrs) | 72.34 ± 11.19 | 71.73 ± 9.88 | 1.06 (0.65–1.34) | 0.84 |
| Male sex % (n) | 59.8 (91) | 57.5 (347) | 1.11 (0.77–1.59) | 0.59 |
| BMI | 25.2 ± 2.6 | 24.5 ± 1.9 | 1.23 (1.06–1.81) | 0.043 |
| Diabetes % (n) | 25.7 (39) | 11.4 (69) | 2.68 (1.72–4.16) | <0.001 |
| Hypertension % (n) | 36.2 (55) | 29.1 (176) | 1.38 (0.95–2.01) | 0.093 |
| Hypercholesterolemia % (n) | 11.8 (18) | 7.5 (45) | 1.67 (0.94–2.98) | 0.083 |
| Smoking % (n) | 28.3 (43) | 17.2 (104) | 1.90 (1.26–2.86) | 0.002 |
| Vasopressin or terlipressin use % (n) | 17.8 (27) | 9.8 (59) | 1.99 (1.22–3.27) | 0.006 |
| Alcohol % (n) | 40.8 (62) | 30.3 (183) | 1.59 (1.10–2.29) | 0.014 |
| Liver cirrhosis % (n) | 35.5 (54) | 9.3 (56) | 5.39 (3.50–8.30) | <0.001 |
| Hemoglobin (g/L) | | | 1.72 (1.32–2.25) | <0.001 |
| ≤30% (n) | 61.8 (94) | 42.1 (254) | | |
| ≤60% (n) | 27.0 (41) | 39.2 (237) | | |
| ≤90% (n) | 11.2 (17) | 18.7 (113) | | |
| History of ACS % (n) | 12.5 (19) | 7.0 (42) | 1.91 (1.08–3.39) | 0.027 |
| History of drugs usage | | | | |
| Anti-coagulation drug[b] % (n) | 8.6 (13) | 8.9 (54) | 0.95 (0.51–1.80) | 0.88 |
| Antiplatelets drug[c] % (n) | 51.3 (78) | 52.3 (316) | 0.96 (0.67–1.37) | 0.83 |
| NSAIDs[d] % (n) | 42.8 (65) | 35.6 (215) | 1.35 (0.94–1.94) | 0.103 |
| Steroid % (n) | 5.3 (8) | 3.1 (19) | 1.71 (0.73–3.99) | 0.214 |
| Proton pump inhibitor % (n) | 75 (114) | 76.7 (463) | 0.91 (0.61–1.38) | 0.67 |
| Cause of bleeding | | | 0.88 (0.73–1.05) | 0.149 |
| Peptic ulcer[e] % (n) | 45.4 (69) | 51.5 (311) | | |
| Varices % (n) | 30.9 (47) | 25.3 (153) | | |
| Cancer % (n) | 11.2 (17) | 16.7 (101) | | |
| Others[f] % (n) | 12.5 (19) | 6.5 (39) | | |

UGH, upper gastrointestinal hemorrhage; ACS, acute coronary syndrome; NSAID, nonsteroidal anti-inflammatory drug.
[a] Significance was obtained by conditional logistic regression.
[b] Warfarin and apixaban, use were categorized as use of anti-coagulations.
[c] Aspirin and clopidogrel use were categorized as use of antiplatelets.
[d] Acetaminophen, ibuprofen, celecoxib, etc., use were categorized as use of NSAIDs.
[e] Including esophageal, gastric, and duodenal ulcers.
[f] Including esophagitis, acute gastric mucosal lesion, and gastric erosion.

4), and others (12.5%, n = 3). Cause of cardiovascular death included myocardial infarction, malignant arrhythmia and heart failure, and miscellaneous. Of the three patients who died from other causes, one patient died from hepatic encephalopathy, and two died from unknown causes. After adjusting for the confounding variables of age, other predictors of in-hospital mortality was shown in Table 2. Deceased patients with UGH and ACS had higher incidence of diabetes (OR = 2.73, 95% CI 1.09–6.81, P = 0.032) and liver cirrhosis (OR = 2.95, 95% CI 0.98–4.87, P = 0.064), smoking (OR = 3.24, 95% CI 1.25–8.41, P = 0.016), lower hemoglobin levels (OR = 2.16, 95% CI 0.94–4.95, P = 0.068), and history of ACS (OR = 2.95, 95% CI 0.99–8.75, P = 0.051). Thus, in the subsequent step, we selected diabetes, liver cirrhosis, hemoglobin levels and history of ACS as variables for multivariate conditional logistic regression.

In the subsequent multivariate conditional logistic regression analysis, diabetes (OR = 2.14, 95% CI 1.15–4.21, P = 0.041), smoking (OR = 2.93, 95% CI 1.17–5.31, P = 0.043) and lower hemoglobin levels (OR = 1.95, 95% CI 1.24–3.16, P = 0.038) were identified as independent variables for the mortality in elderly patients with UGH complicated by ACS, while liver cirrhosis (OR = 2.02, 95% CI 0.83–5.19, P = 0.076), and history of ACS (OR = 2.53, 95% CI 0.81–5.34, P = 0.059) were not statistically significant (Fig. 2).

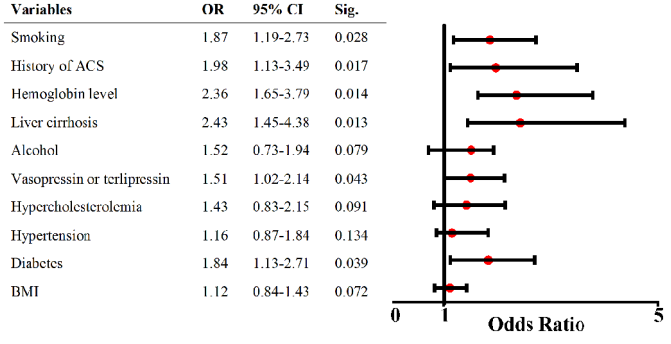


**Fig. 1.** Risk factors for ACS in elderly UGH patients. Multivariate conditional logistic regression analysis demonstrated diabetes, vasopressin or terlipressin use, smoking, liver cirrhosis, hemoglobin level and history of ACS as independent variables for ACS in elderly UGH patients. OR, odds ratio; CI, confidence interval.

## 4. Discussion

ACS is a serious complication of UGH. It is reported that the morbidity of severe UGH with ACS is 5–10% in intensive care units [12], and it is 0.94% in patients with UGH outside intensive care units [13]. The mechanism of ACS in UGH patient is thought to be related to hypovolemia, vasoconstriction and low myocardial perfusion, particularly in patients with underlying coronary disease, diabetes mellitus, smoking history, inadequate fluid supply and gastrointestinal bleeding [14]. The symptoms and signs of ACS can be disguised by those of UGH such as hypotension, abdominal pain, nausea, vomiting, and sudden dysphoria, particularly in elderly patients. Elderly patients often exhibit subtle symptoms of ACS, which can increase the incidence of misdiagnosis.

Our observational nested case-control study indicated that patients with cirrhosis were at high risk to develop myocardial injury during acute UGH. We analyzed the use of vasopressin and terlipressin, which is common in treatment of variceal bleeding. This study suggested that vasopressin and terlipressin may cause coronary vasoconstriction as a side effect. The results concur with the findings of previous studies [12, 15]. This finding emphasizes the importance of close attention to possible ACS while treating UGH in elderly patients with cirrhosis.

In this study, we analyzed the presence of traditional cardiac risk factors as an independent variable in the development of ACS in UGH patients. These traditional risk factors include diabetes, hypertension, elderly age, hypercholesterolemia, and tobacco use. We found that UGH patients with diabetes and smoking had a higher incidence of

**Table 2**
Variables of mortality underwent UGH with ACS in elderly patients.

| Variables | Death (n = 24) | Non-death (n = 128) | OR (95% CI) | P[a] |
|---|---|---|---|---|
| Age (yrs) | 81.4 ± 12.3 | 74.8 ± 9.4 | – | – |
| Male sex n (%) | 62.5 (15) | 59.4 (76) | 1.14 (0.46–2.80) | 0.775 |
| BMI | 25.4 ± 2.3 | 25.5 ± 1.7 | 1.57 (0.85–2.16) | 0.24 |
| Diabetes % (n) | 41.7 (10) | 22.66 (29) | 2.73 (1.09–6.81) | 0.032 |
| Hypertension % (n) | 58.3 (14) | 47.7 (61) | 1.54 (0.64–3.72) | 0.34 |
| Hypercholesterolemia % (n) | 16.7 (4) | 10.9 (14) | 1.63 (0.49–5.45) | 0.43 |
| Smoking % (n) | 37.5 (9) | 15.6 (20) | 3.24 (1.25–8.41) | 0.016 |
| Vasopressin or terlipressin use % (n) | 20.8 (5) | 17.2 (22) | 1.27 (0.43–3.76) | 0.67 |
| Alcohol n (%) | 54.2 (13) | 38.3 (49) | 1.91 (0.79–4.59) | 0.15 |
| Liver cirrhosis n (%) | 45.8 (11) | 30.5 (38) | 2.95 (0.98–4.87) | 0.064 |
| Hemoglobin (g/L) | | | 2.16 (0.94–4.95) | 0.068 |
| ≤30 | 75.0 (18) | 59.4 (76) | | |
| ≤60 | 25.0 (6) | 27.3 (35) | | |
| ≤90 | 0 (0) | 13.3 (17) | | |
| History of ACS % (n) | 25 (6) | 10.15 (13) | 2.95 (0.99–8.75) | 0.051 |
| History of drugs usage | | | | |
| Anti-coagulation drug[a] n (%) | 12.5 (3) | 7.8 (10) | 1.69 (0.43–6.64) | 0.46 |
| Antiplatelets drug[b] n (%) | 58.3 (14) | 50.0 (64) | 1.40 (0.58–3.38) | 0.46 |
| NSAIDs[c] n (%) | 50.0 (12) | 41.4 (53) | 1.42 (0.59–3.39) | 0.44 |
| Steroid n (%) | 8.3 (2) | 4.7 (6) | 1.85 (0.35–9.76) | 0.47 |
| Cause of bleeding | | | 0.95 (0.62–1.44) | 0.79 |
| Peptic ulcer[d] | 33.3 (8) | 47.7 (61) | | |
| Varies | 45.8 (11) | 28.1 (36) | | |
| Cancer | 12.5 (3) | 10.9 (14) | | |
| Others[e] | 8.3 (2) | 13.3 (17) | | |

UGH, upper gastrointestinal hemorrhage; ACS, acute coronary syndrome; NSAID, nonsteroidal anti-inflammatory drug.
[a] Warfarin and apixaban, use were categorized as use of anti-coagulations.
[b] Aspirin and clopidogrel use were categorized as use of antiplatelets.
[c] Acetaminophen, ibuprofen, celecoxib, etc., use were categorized as use of NSAIDs.
[d] Including esophageal, gastric, and duodenal ulcers.
[e] Including esophagitis, acute gastric mucosal lesion, and gastric erosion.

ACS. Moreover, diabetes and smoking are also independent variables for mortality. Thus, elderly patients with diabetes and smoking have higher risk of ACS after UGH, and the mortality is much higher than those without these underlying risk factors.

In our study, we identified hemoglobin level as a risk factor for development of ACS in UGH patients. In our subsequent analysis, we also confirmed it as an individual predictor of mortality in elderly UGH patients with ACS. Thus, hemoglobin level is an important index to monitor ACS of UGH patients. The importance of closely monitoring hemoglobin is in accordance with the present treatment recommendations [16]. In these recommendations, blood transfusion is advised when the hemoglobin level is <70 g/L in UGH patients. Transfusion can rectify anemia and supplement blood volume, improve coronary vasoconstriction, and improve systemic and local oxygen exchange. It is also reported that blood transfusion can decrease the incidence of ACS in elderly patients with coronary disease, diabetes mellitus and tobacco use [14].

The treatment of UGH with ACS is complex, particularly regarding the use of medications that affected clotting. The usage of hemostatic drugs for UGH can increase the morbidity of ACS, while anticoagulants and antiplatelet agents used in treating ACS can worsen gastrointestinal bleeding. In our study, we observed that pharmacologic hemostasis increased the incidence of ACS in UGH patients. Despite this, usage of hemostasis, anti-coagulations and antiplatelets drugs did not increase the mortality. So, how to utilization of medications that affected clotting is an important problem in treatment. At present, it is recommended that aspirin should be taken as soon as UGH is controlled when cardiovascular risks are greater than gastrointestinal ones [17]. It is generally advised that aspirin or clopidogrel should be stopped for 24 h after gastrointestinal bleeding. After assessing the gastrointestinal and bleeding conditions, clopidogrel can be restarted in 1–2 days, and aspirin in 1–2 weeks [18, 19]. Until now, there is no clear-cut recommendations on hemostasis in patients with UGH complicated by ACS.

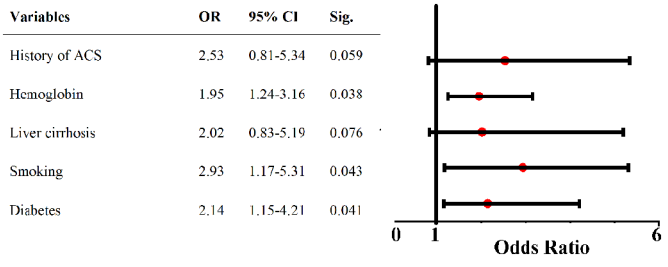


**Fig. 2.** Risk factors for mortality in elderly patients with UGH complicated by ACS. By multivariate conditional logistic regression analysis, diabetes, smoking and hemoglobin level are independent variables for mortality of UGH with ACS. OR, odds ratio; CI, confidence interval.

There are some limitations in our investigation. We only included 152 cases and 604 controls from one single hospital. A large scale, multicenter investigation is needed in the future. But, low development degree of shared electric hospital information in China limits the gain of data. We need a nationally shared database, locally at least, to collect more data. Meanwhile, our investigation supplied important information to alert ACS in possible elderly UGH patients, especially with diabetes, smoking and lower hemoglobin level. Further investigations on interventions to prevent the development of ACS after UGH are needed.

## 5. Conclusions

In conclusion, the mortality of UGH with ACS is much higher than in UGH or ACS alone. Our study showed that elderly patient with diabetes, more vasopressin or terlipressin use, smoking, liver cirrhosis, low hemoglobin level and history of ACS are at increased risk of developing ACS during an episode of UGH. Moreover, diabetes, smoking and hemoglobin level are key predictors of mortality in these patients. These findings suggest that it is imperative to carefully monitor electrocardiographic findings and cardiac enzymes in elderly UGH patients to recognize ACS, particularly in those with underlying risk factors, and thus reduce mortality.

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