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Upper gastrointestinal bleeding as a warning sign of gastrointestinal cancer

Haozhe Cui [a,c,1], Qinglun Gao [d,1], Zhiming Zhao [b,*], Xiangming Ma [c,**]

[a] School of Medicine, Nankai University, Tianjin, China
[b] The Faculty of Hepatopancreatobiliary Surgery, The First Medical Center, Chinese People's Liberation Army General Hospital, Beijing, China
[c] Department of Hepatobiliary Surgery, Kailuan General Hospital, Tangshan, China
[d] Department of Hepatobiliary Surgery, Shandong Provincial Third Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China

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ABSTRACT

Background: Upper gastrointestinal bleeding (UGIB) is a prevalent etiology for hospital admissions on a global scale. However, the significance of UGIB as a warning sign of gastrointestinal (GI) cancer is frequently disregarded due to its uncommon and atypical symptoms.
Methods: In the Kailuan study, participants diagnosed with UGIB were assigned as the case group and were randomly matched in a 1:4 ratio with a control group of comparable age and sex from 2006 to 2018 in Tangshan. The statistical analysis included a total of 1250 UGIB patients and 5000 individuals without UGIB. The impact of UGIB on cancer incidence was evaluated using a Cox proportional hazards model, enabling the investigation of both site-specific and time-dependent effects of UGIB on cancer incidence.
Results: The mean age of the patients was 60.91 ± 13.08 years. Over an average follow-up period of 8.92 years, there were 102 cases of cancer in the UGIB group and 210 cases in the non-UGIB group. The results of the Cox model analysis indicated that the strength of association between UGIB and cancer depends on specific cancer site. Excluding patients with follow-up periods of less than 1, 3, and 5 years weakened the associations between UGIB and GI cancer in sensitivity analysis.
Conclusion: UGIB may serve as a sign of occult cancer, necessitating thorough evaluation of middle-aged and elderly patients presenting with this warning symptom to detect the possibility of missing a cancer diagnosis.

1. Introduction

Acute upper gastrointestinal bleeding (UGIB) is a frequently encountered gastrointestinal condition necessitating hospitalization, with documented annual incidences ranging from 48 to 172 per 100,000 individuals (Longstreth, 1995; van Leerdam, 2008). More than 300,000 people in the USA are admitted to hospital every year (Dorn et al., 2010). In the general population, the most common cause of UGIB is peptic ulcer disease caused by nonsteroidal anti-inflammatory drug use and Helicobacter pylori infection. Esophagogastric variceal bleeding is the second most common cause of UGIB, followed by esophagitis which accounts for 10 % of UGIB. Gastrointestinal (GI) cancer can also lead to UGIB, although these are a relatively uncommon cause of an acute bleed in the general population (Kamboj et al., 2019). UGIB from upper GI cancer has been reported to be responsible for 1–5 % of all acute bleeding (Kim and Choi, 2015; Sheibani et al., 2013). Despite its role as an indicative symptom of gastrointestinal (GI) cancer, UGIB often goes unnoticed (Rasmussen et al., 2015).

Previous studies have reported that a correlation between bleeding events in individuals undergoing antithrombotic or anticoagulant treatments for heart-related conditions and an increased risk of cancer. Eikelboom et al. found that UGIB in patients with arteriosclerotic heart disease who are receiving anti-thrombotic drugs had an increased risk of recently-detected cancer (Eikelboom et al., 2019). Rasmussen et al. also found that patients with lower gastrointestinal bleeding had a significantly increased risk of colorectal cancer among people with atrial fibrillation who were treated with anti-coagulants (Rasmussen et al., 2020).The potential association between UGIB and cancer as a risk factor is subject to debate. One possible explanation for this relationship is that UGIB serves as a warning sign for occult cancer. The occult cancer

* Corresponding author at: The Faculty of Hepatopancreatobiliary Surgery, The First Medical Center, Chinese People's Liberation Army General Hospital, Beijing 100853, China.
** Corresponding author at: Department of Hepatobiliary surgery, Kailuan General Hospital, Tangshan 063000, China.
E-mail addresses: zhaozhiming153@126.com (Z. Zhao), brighter_ma@163.com (X. Ma).
[1] These authors share the first authorship on this work.

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may detect through UGIB. Using a large prospective cohort study, we aim to elucidate the significance of UGIB as an alarming symptom of occult cancer.

2. Materials and methods

2.1. Study participants

Our study was performed on a large-scale community-based prospective cohort study, namely Kailuan Study. Details of the study design and procedure have been described elsewhere (Cui et al., 2022). Briefly; a total of 179,328 participants from January 2006 to December 2018 were recruited, underwent clinical and laboratory examinations, as well as questionnaire interview (including income, educational level, drinking and so on). In addition to routine follow-up examinations, data for the annual occurrence of UGIB and cancer are collected using medical insurance information system. We selected patients with UGIB during the follow-up period as the case group, referring to the method of Sattar et al., and those without UGIB as the control group, using the method of random matching (Sattar et al., 2019).

Participants were included if they had UGIB and who received treatment in hospital during the follow-up period. Participants were excluded if they had history of cancer and death during hospitalization owing to UGIB. The control population criteria were the following: same sex, age ±1 year, and no history of cancer. We used 1:4 random matching during the same physical examination. Patients were divided into a case group (UGIB group) and control group (non-UGIB group), and these groups constituted the final observation participants.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the Kailuan General Hospital Ethics Committee. All the participants agreed to take part in the study and provided written informed consent.

2.2. Data collection and covariates

Epidemiological data, namely age, sex, lifestyle (smoking, drinking, physical exercise), administration of antiplatelet drugs, diabetes, and hypertension were collected using questionnaires. The contents of the questionnaires were according to our previous study (Cui et al., 2022). Serum biochemical indices, namely total cholesterol(TC), triglycerides (TG), fasting blood glucose(FBG), hypersensitive C-reactive protein(Hs-CRP), glutamic-pyruvic transaminase(ALT), and uric acid(UA), were measured using an automatic biochemical analyzer (Hitachi 747; Hitachi, Tokyo, Japan), and all tests were performed by professionals in the Central Laboratory of Kailuan general hospital. Smoking and drinking status were classified as current or never/former smoker or drinker. Former drinker is defined as stopped drinking for more than a year. Not drinking any alcoholic beverages in the past 12 months were categorized as 0 g/wk. Active physical exercise was defined as ">4 times per week and 20 min at time". Body weight, height and WC were reported by trained nurses according to the standard methods. We collected the history of ulcer from health insurance information. Age, sex, BMI, TC, FBG, UA, Hs-CRP, ALT, smoking, drinking, physical exercise, hypertension, anti-platelet medication use and history of ulcer served as covariates in the adjusted analyses.

2.3. Definition of UGIB

UGIB, including bleeding caused by lesions in the esophagus, stomach, duodenum, and patients with manifestations of overt UGIB, which include hematemesis (vomiting of red blood or coffee-grounds material), melena (black, tarry stool), or hematochezia (passage of red or maroon material per rectum) was defined according to the The American Gastroenterologist Association (Mullady et al., 2020). Data collection was undertaken from January 2006 to December 2018. The database of UGIB diagnoses was linked to the Municipal Social Insurance Institution and Hospital Discharge Register and was updated once a year during the follow-up period. An expert panel was set up to review and confirm annual medical records from local hospitals to identify patients who were suspected of UGIB. The cause and location of UGIB was not distinguished in this study. The code for UGIB in the International Classification of Diseases (ICD-10) was K92.2.

2.4. Assessment of cancer

Follow-up ended at the first record of cancer event, all-cause death or at the end of follow-up on 31 December 2021, whichever came first. The follow-up began from the date of diagnosis of UGIB, and the non-UGIB group began follow-up on the same day. Data for the occurrence of cancer were retrieved from the data provided by the medical insurance system. Trained investigators went to the hospital where new cases were diagnosed and treated to extract medical history data to verify the diagnosis every year. Cancer was defined according to the ICD-10 and were divided into GI cancer and non-GI cancer. The former comprised esophageal cancer (ICD-10, C15), gastric cancer (C16), small intestinal cancer (C17), cancer of other sites and systems were defined as non-GI cancer.

2.5. Statistical analysis

Continuous variables were compared using analysis of variance or the Kruskal-Wallis test according to distribution, and categorical variables were compared with the chi-square test.

The cumulative incidence of cancers in the UGIB group and the non-UGIB group was calculated by the Kaplan-Meier method and compared by the log-rank test. We used a Cox proportional hazards model to analyze the hazard ratios (HR) and 95 % confidence intervals (95 % CI) for UGIB for cancers. To analyze whether UGIB is site-specific to the risk of cancer, we also used Cox regression model analysis after dividing cancer into GI cancer and non-GI cancer. To explore whether the effect of UGIB on cancer is time-dependent, we repeated the Cox regression model analysis after excluding patients with follow-up times of <1 year, <3 years, and <5 years.

3. Results

According to the inclusion criteria, 1343 patients with UGIB were included. Of these patients, we excluded 93 patients with a history of cancer and death during hospitalization, 1250 patients with UGIB were enrolled in the statistical analysis. According to the matching criteria, 5000 cases were randomly included into the non-UGIB group. A total of 6250 patients were included in the final statistic analysis, with an average age of 60.91 ± 13.08 years, 5707 patients were men (91.28 %).

Comparisons of the patients' general characteristics in the UGIB group compared with the non-UGIB group revealed that BMI, TC, and the proportions of patients with a history of smoking, drinking, taking antiplatelet drugs, and history of ulcer were higher in the UGIB group, and the proportion with hypertension was lower (Table 1).

During an average follow-up period of 8.52 years, 312 cancers occurred in 6250 patients, namely 102 patients in the UGIB group and 210 patients in the non-UGIB group, with cumulative incidences of 10.71 % and 4.02 %, respectively ($P < 0.001$). There were 61 cases of cancers in GI tract, namely 31 cases in the UGIB group and 30 cases in the non-UGIB group, with cumulative incidences of 2.88 % and 0.76 %, respectively ($P < 0.001$), and 251 cases of non-GI cancer, namely 71 cases in the UGIB group and 180 cases in the non-UGIB group, with cumulative incidences of 7.93 % and 4.97 %, respectively ($P < 0.01$).

In the UGIB group, there were 35 cases of cancer in the first year, 19 cases from year 2 to year 3, and 21 cases from year 4 to year 5, accounting for 34.31 %, 18.63 %, and 20.59 % of the patients, respectively, with a total of 102 cases (73.53 %). The incidence of cancer in the UGIB group showed a decreasing trend over time. There were 8 cases of

Table 1
Baseline Characteristics in the UGIB and Non-UGIB Groups, Kailuan Study 2006–2018.

	UGIB	Non-UGIB	*P*
	(n = 1250)	(n = 5000)	
Age[years]	60.94 ± 13.10	60.90 ± 13.08	0.92*
Male[n,%]	1142(91.29)	4565(91.29)	–
BMI[kg/m^2]	25.36 ± 4.10	24.92 ± 3.24	<0.001*
TC[mmol/L]	4.84 ± 1.23	4.93 ± 1.43	0.03*
FBG[mmol/L]	5.86 ± 2.01	5.82 ± 1.99	0.52*
UA[mmol/L]	308.90 ± 97.62	311.78 ± 86.96	0.31*
ALT[U/L]	18.00 (13.00–27.00)	18.00 (13.00–25.00)	0.07*
Hs-CRP[mg/L]	1.10(0.47–2.88)	1.10(0.45–2.62)	0.23*
Smoke[n,%]	307(24.54)	1035(20.70)	<0.001#
Drink[n,%]	188(15.03)	611(12.22)	<0.001#
Exercise[n,%]	240(19.18)	1008(20.16)	0.44#
Hypertension[n,%]	585(46.84)	2518(50.35)	0.02#
Anti-platelet medication use [n,%]	178(14.23)	553(11.06)	<0.001#
History of ulcer [n,%]	257(20.54)	10(0.2)	<0.001#

Note: UGIB upper gastrointestinal bleeding; non-UGIB non-upper gastrointestinal bleeding; BMI body mass index; TC total cholesterol; FBG fasting blood glucose; UA uric acid; ALT alanine aminotransferase; Hs-CRP high-sensitivity C-reactive protein. Significant difference (* using T test, # using Chi-square test).

cancer in the first year, 58 cases from year 2 to year 3, and 40 cases from year 4 to year 5, accounting for 3.81 %, 27.62 %, and 19.05 %, respectively, with a total of 210 cases (50.48 %) in non-UGIB group. The incidence trend changed significantly over time (Fig. 1).

In the Cox regression model analysis, after adjust for potential confounding factors, the risk of cancer in patients with UGIB was 2.29 (95 % CI: 1.77–2.97) compared with patients without UGIB. The risk of GI cancer was 4.65 (95 % CI 2.69–8.04), and that of non-GI cancer was 1.89 (95 % CI 1.40–2.56). Given recent reports on sex discrepancies in cancer, we equally investigated possible sex effects in UGIB with risk of cancer (P for interaction < 0.001). We obtained similar results in male, but no statistically significant difference was noted in female (Table 2, Table 3).

In the sensitivity analysis, we repeated the Cox regression model analysis after excluding patients with follow-up periods of ≤1 year (n = 219), ≤3 years (n = 472), and ≤5 years (n = 1530). The results showed that the risk of cancer in patients with UGIB with prolonged follow-up was 1.53 (95 % CI: 1.13–2.08), 1.54 (95 % CI: 1.07–2.23), and 1.23 (95 % CI: 0.77–1.97), respectively, compared with non-UGIB group. The risk of non-GI cancer for each follow-up period was 1.48 (95 % CI: 1.06–2.07), 1.50 (95 % CI: 1.02–2.21), and 1.21 (95 % CI 0.73–1.99), respectively. The risk of GI cancer was not statistically different during the follow-up periods (Table 4).

4. Discussion

In this study, we conducted a prospective cohort investigation and further developed a case-control design within a longitudinal cohort study. We gathered data on patients with UGIB as well as a control group, and our findings indicate that UGIB can serve as an indicator for occult cancer within the GI tract. It is crucial to emphasize the significance of advising middle aged and elderly patients with UGIB to remain vigilant and promptly seek medical attentions.

In this study, we found that the incidence of cancer in patients with UGIB increased in the short term compared with non-UGIB group, and this trend declined over time until the difference disappeared. The incidence of cancer was the highest in the short term (during the first year) after the bleeding episode, accounting for 34.31 % of the total incidence, and then decreased annually; after 5 years of follow-up, the proportion of patients with cancer was only 26.47 %. Patients without UGIB had no significant change in the incidence of cancer over time. Although no study supports our conclusion, the RE-LY study had similar finding and indicated that patients with cancer in the digestive system after lower gastrointestinal bleeding were diagnosed mainly during the first year of follow-up, and that the incidence was significantly higher than that during the 5-year and >5-year follow-up periods (Viborg et al., 2016).

UGIB may not be a risk factor for GI cancer but rather a warning sign of occult GI cancer. Even though our results indicated that compared with the non-UGIB group, patients with UGIB had a 4.65-fold increased risk of GI cancer, this result should be interpreted with caution. Similarly, Eikelboom et al. obtained similar results after an average follow-up of 2 years in 27,395 ASCVD patients receiving antithrombotic drugs in the COMPASS study; the risk of digestive system cancer increased by 20.6-fold in patients with digestive bleeding (Rasmussen et al., 2015). Rasmussen et al. found a 24.2-fold increased in the risk of colorectal cancer in patients with atrial fibrillation receiving anticoagulant therapy (Eikelboom et al., 2019). One plausible interpretation of those results is that the use of antithrombotic or anticoagulant drugs induces shedding by occult cancer in vivo, subsequently leading to bleeding in the GI tract (Clemens et al., 2014). In a prior investigation involving 354 individuals diagnosed with GI cancer, it was discovered

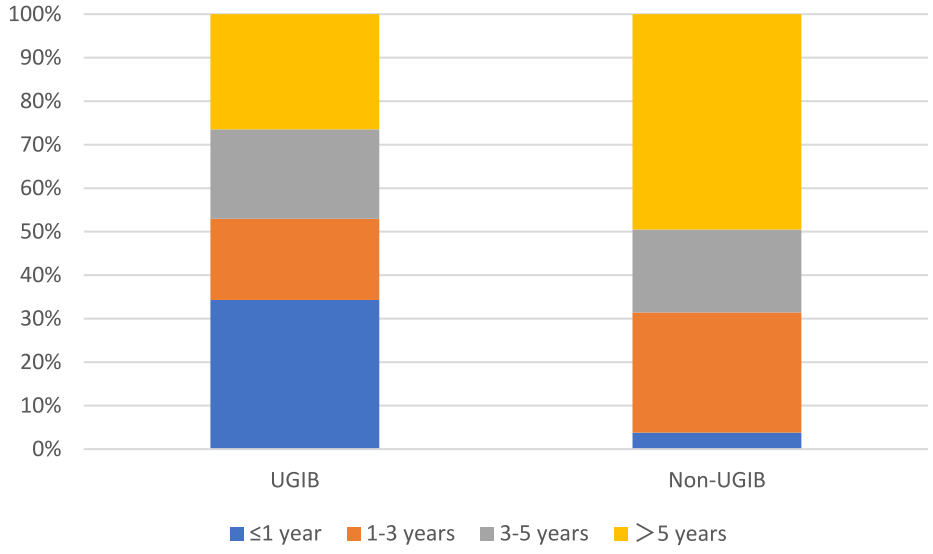

Fig. 1. The proportions and numbers of cancers diagnosed in patients with UGIB and non-UGIB by year, Kailuan Study 2006–2018.

Table 2
Adjusted hazards ratios (95 % CI) for cancer in UGIB patients, Kailuan study 2006–2018.

	Total				Male				Female			
	N	Case	Age-and sex-adjusted	Multivariable adjusted*	N	Case	Age-and sex-adjusted	Multivariable adjusted*	N	Case	Age-and sex-adjusted	Multivariable adjusted*
Non-UGIB	5020	210	Ref.	Ref.	4565	186	Ref.	Ref.	436	24	Ref.	Ref.
UGIB*	1250	102	2.40 (1.89–3.04)	2.29(1.77–2.97)	1142	95	2.53 (1.98–3.25)	2.40(1.83–3.15)	109	7	1.36 (0.59–3.16)	1.73(0.80–4.29)

Note: UGIB upper gastrointestinal bleeding; non-UGIB non-upper gastrointestinal bleeding.
*The model was adjusted for age, sex, BMI, TC, FBG, UA, Hs-CRP, ALT, smoking, drinking, physical exercise, hypertension, anti-platelet medication use and history of ulcer.

Table 3
Adjusted Hazards Ratios (95 % CI) for GI Cancer in UGIB Patients, Kailuan Study 2006–2018.

	Total				Male				Female			
	Non-UGIB		UGIB*		Non-UGIB		UGIB*		Non-UGIB		UGIB*	
	Case	HR(95 %CI)	Case	HR(95 %CI)	Case	HR(95 %CI)	Case	HR(95 %CI)	Case	HR(95 %CI)	Case	HR(95 %CI)
GI cancer	30	Ref.	31	4.65(2.69–8.04)	29	Ref.	31	4.85(2.80–8.42)	1	Ref.	0	–
Non-GI cancer	180	Ref.	71	1.89(1.40–2.56)	157	Ref.	64	1.94(1.41–2.67)	23	Ref.	7	1.77(0.71–4.40)

Note: UGIB upper gastrointestinal bleeding; non-UGIB non-upper gastrointestinal bleeding; GI gastrointestinal; Non-GI non gastrointestinal.
*The model was adjusted for age, sex, BMI, TC, FBG, UA, Hs-CRP, ALT, smoking, drinking, physical exercise, hypertension, anti-platelet medication use and history of ulcer.

Table 4
Adjusted hazards ratios (95 % CI) for total and individual cancer in UGIB patients (excluding outcomes within 1, 3, or 5 years of Follow-Up), Kailuan study 2006–2018.

	Excluded ≤ 1 year		Excluded ≤ 3 years		Excluded ≤ 5 years	
	Non-UGIB	UGIB*	Non-UGIB	UGIB*	Non-UGIB	UGIB*
Total	Ref.	1.53(1.13–2.08)	Ref.	1.54(1.07–2.23)	Ref.	1.23(0.77–1.97)
GI cancer	Ref.	1.82(0.83–4.01)	Ref.	1.18(0.41–3.39)	Ref.	0.73(0.17–3.06)
Non-GI cancer	Ref.	1.48(1.06–2.07)	Ref.	1.50(1.02–2.21)	Ref.	1.21(0.73–1.99)

Note: UGIB upper gastrointestinal bleeding; non-UGIB non-upper gastrointestinal bleeding; GI gastrointestinal; Non-GI non gastrointestinal.
*The model was adjusted for age, sex, BMI, TC, FBG, UA, Hs-CRP, ALT, smoking, drinking, physical exercise, hypertension, anti-platelet medication use and history of ulcer.

that 71 of them exhibited an endoscopically identified bleeding site. Furthermore, a significant majority of 77 % of these patients experienced bleeding symptoms as their initial manifestation (Schatz and Rockey, 2017). We therefore speculate that UGIB as a warning sign helped facilitate patients of GI cancer identification.

Our study found that although patients with UGIB had an increased risk of GI cancer, this association was time-dependent. The increased risk occurred mainly within 1 year after the onset of UGIB. After excluding cases with follow-up periods of <1 year, <3 years, and <5 years, the risk of GI cancer in patients with UGIB was 1.82 (95 % CI: 0.83–4.01), 1.18 (95 % CI: 0.41–3.39), and 0.73 (0.17–3.06), respectively, compared with the non-UGIB group. The risk showed a decreasing trend over time, and the association between UGIB and GI cancer was time-dependent. This result also indirectly supportsour above-mentioned views. Therefore, even if cancer is not detected during hospitalization, the symptom of UGIB should not be ignored. A comprehensive and detailed physical examination should be conducted regularly after bleeding to exclude the possibility of occult cancer or precancerous lesions, as early as possible.

UGIB is a relatively uncommon symptom and can be easily missed. A physician-confirmed UGIB diagnosis was obtained for 1343/179328 (0.75 %) in Kailuan study. In Danish 33,040 persons > 45 years were included in a cross-sectional study, UGIB occured in 1.4 % in general population, while less than their quarter sought assistance with a general practitioner (Rasmussen et al., 2018). The failure to identify suspicious symptoms, such as persistent cough, rectal bleeding, or breast changes, is frequently cited by cancer patients as a contributing factor to delayed help-seeking (Quaife et al., 2014). Given that the majority of cancers do not exhibit symptoms until advanced stages, diagnoses resulting from symptomatic presentation often lead to poorer prognoses (Schatz and Rockey, 2017; Hofvind et al., 2008). Consequently, the timely recognizing a warning sign and pursuit of medical care is crucial in mitigating cancer-related morbidity and mortality.

The present study has multiple strengths. First, we selected all participants from the Kailuan study who had good compliance and a low rate of loss to follow-up, and randomly matched these participants with age- and sex-matched controls. Second, the data for UGIB and cancer collected through hospitalization information were more accurate than those collected through self-reports. Finally, sufficient numbers of patients with new case of cancer were detected during the average follow-up period of 5.97 years. However, this study also has shortcomings. First, we did not collect data indicating the stage and grade when cancer was diagnosed, and second, the definition of UGIB failed to distinguish the volume and precise location of the bleeding. Furthermore, because the selected patients with UGIB all received in-hospital treatment, some patients with bleeding symptoms who did not receive treatment may have been missed. In addition, due to vast majority of the patients were male, the above conclusions still need to be further verified in female. Finally, the percentage of patients receiving antiplatelet agents in this study may be slightly lower than the actual use rate because the data were collected using questionnaires.

5. Conclusion

Using the data provided by the Kailuan study, we found that UGIB can serve as an warning sigh for occult GI cancer. This also suggests that patients should be thoroughly and carefully evaluated for the presence of occult cancer as soon as possible after an episode of UGIB. Early detection and treatment may help improve the prognosis.

CRediT authorship contribution statement

Haozhe Cui: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Qinglun Gao:** Formal analysis. **Zhiming Zhao:** Writing – review & editing, Conceptualization. **Xiangming Ma:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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

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Author contributions

Haozhe Cui wrote the main manuscript text and conceived and designed the study. Qinglun Gao analyzed the data and carried out literature search. Xiangming Ma and Zhiming Zhao performed the manuscript review. All authors have read and approved the content of the manuscript.

Lay summary

In this large, population-based, cohort study we found that upper gastrointestinal bleeding (UGIB) serves as a warning symptom for the presence of cancer within the gastrointestinal (GI), but not non-GI cancer. Engaging in proactive investigation of the potential underlying cause contributing to UGIB among the middle-aged and elderly demographic is expected to facilitate the timely identification and intervention of GI cancer.

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