doi: 10.3978/j.issn.2095-6959.2021.07.039
**View this article at:** https://dx.doi.org/10.3978/j.issn.2095-6959.2021.07.039

# 影响上消化道出血的相关危险因素

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[摘 要] 上消化道出血为内科常见急危重症之一，其因较高的发病率和病死率而在全球范围内受到广泛关注。本文对上消化道出血的相关危险因素进行总结，发现年龄、性别、幽门螺杆菌感染、慢性肾功能不全、心功能不全应用左室辅助装置、长期单独或联合应用非甾体类抗炎药(non-steroid anti-inflammatory drugs，NSAIDs)、选择性5-羟色胺再摄取抑制剂(selective serotonin reuptake inhibitors，SSRIs)等药物、气象因素和吸烟饮酒等不良生活习惯为发病的危险因素。*VKORC*基因多态性等其他可能的危险因素还需进一步研究。明确上消化道出血的危险因素，可优化相关高危人群的管理及治疗策略，有效预防上消化道出血的发生，对提高患者生活质量、节约卫生经费具有重要意义。

[关键词] 上消化道出血；危险因素；非甾体类抗炎药

# Related risk factors for upper gastrointestinal bleeding

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**Abstract** Upper gastrointestinal bleeding (UGIB) is one of the most common acute and critical diseases in internal medicine. With a considerable morbidity and mortality, it has become a global concern. This article summarized the related risk factors for UGIB. We found that age, gender, *Helicobacter pylori* (*H. pylori*) infection, chronic renal insufficiency, cardiac insufficiency with continuous-flow left ventricular assist devices, long-term use of non-steroid anti-inflammatory drugs (NSAIDs) and selective serotonin reuptake inhibitors (SSRIs) alone or in combination, meteorological factors, and unhealthy lifestyle such as smoking and alcohol consumption were risk factors of UGIB. Other possible factors like *VKORC* polymorphism need further studying. Clarifying risk factors of UGIB will definitely aid in optimizing its monitoring, improving therapeutic strategies, and effectively preventing recurrence, which eventually improves life quality and lowers financial burden.

**Keywords** upper gastrointestinal bleeding; risk factors; non-steroid anti-inflammatory drugs

**收稿日期 (Date of reception)**：2020–04–30

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**基金项目 (Foundation item)**：首都卫生发展科研专项项目 ( 首发 2020-2-2034). This work was supported by Capital's Funds for Health Improvement and Research, China (2020-2-2034).

上消化道出血(upper gastrointestinal bleeding，UGIB)是指屈氏韧带以上的消化道病变引起的出血，常见病因包括消化性溃疡、食管胃底静脉曲张、Mallory-Weiss综合征和恶性肿瘤等。美国一项研究[1]显示：每年约有70万人因消化性溃疡出血就诊，总花费达14亿美元，带来了巨大的经济负担。UGIB发病率达82/10万~96/10万，病死率达5%~10%[2-3]。UGIB作为内科常见急危重症之一，在全球范围内受到广泛关注[4]。

明确UGIB的危险因素，优化疾病的管理及治疗策略，有效预防UGIB的发生，对提高患者的生活质量、减少社会经济负担均有重要意义。本文将从患者一般情况、伴随疾病、用药情况以及其他因素等方面，对UGIB的相关危险因素进行综述。

## 1 患者一般情况

年龄、性别为UGIB的危险因素。Luo等[5]用Cox回归模型分析台湾11 105例UGIB患者，发现年龄、性别为UGIB独立危险因素(年龄：HR=1.05，95%CI：1.04~1.06；男性：HR=1.43，95%CI：1.23~1.67)；国内其他地区的研究[6-8]也发现相同的结论。德国一项纳入了45 458名急诊患者的研究[3]显示：年龄、性别为UGIB的危险因素(年龄：OR=1.012，95%CI：1.008~1.017；男性：OR=0.739，95%CI：0.624~0.876)；其他多个国家和地区的研究[3,9-10]结果均显示：UGIB在高龄、男性患者中发病率更高。

由此可见高龄、男性为UGIB的危险因素，可能原因为平均寿命的延长、老年人胃肠黏膜屏障功能的减弱、长期应用抗血小板和/或抗凝药物等因素所致[11]；而吸烟、饮酒在男性人群中更为多见，可能通过促进胃肠道的运动、分泌及黏膜血流量，增加其UGIB的发生风险[12]。

## 2 伴随疾病

### 2.1 幽门螺杆菌感染

消化性溃疡为非静脉曲张性上消化道出血最常见的病因[13]，约70%的胃溃疡及95%以上的十二指肠溃疡均感染幽门螺杆菌(*Helicobacter pylori*，*Hp*)，*Hp*感染者溃疡发生率可达13%，显著高于未感染者[14]。Papatheodoridis等[15]对21项研究进行荟萃分析，发现*Hp*感染为消化性溃疡出血的独立危险因素，台湾地区的两项队列研究[5-6]也得到相同的结论。而清除*Hp*可降低UGIB的发生率[16]。

### 2.2 慢性肾脏病

慢性肾脏病(chronic kidney disease，CKD)可增加UGIB的发生风险。Lin等[6]通过Cox回归模型对12 145例病例进行研究，发现：CKD为UGIB的独立危险因素(HR=1.60，95%CI: 1.28~1.92)；Luo等[5]也得到相同的结论(HR=1.58，95%CI：1.18~2.13)。同时，UGIB增加了CKD患者的病死率[17]。CKD患者UGIB风险增加的原因尚不明确，可能与终末期肾脏病透析过程中应用抗凝剂、血小板功能不良[18-19]、血液透析过程中血压波动大及黏膜营养不良有关[20]。近年来，越来越多的研究关注到CKD患者胃肠道血管发育异常[21-23]，其机制尚不明确，可能与多种化学介质，如血管内皮生长因子、肿瘤坏死因子α、血管生成素2等诱导不成熟、不稳定的新生血管形成有关[22]。相关生物标志物可能是评估病变严重程度、预测出血发生和治疗反应的有效工具，值得进一步研究。

### 2.3 心血管系统疾病

心血管系统疾病与UGIB的发生有关[9]。Nikolsky等[24]进行的多中心研究发现13 819例急性冠脉综合征患者中，178例(1.3%)在30 d内发生消化道出血；多变量分析发现：消化道出血与30 d全因病死率显著相关(HR=4.87，$P$<0.05)。对于心功能不全的患者，连续流动左室辅助装置(continuous-flow left ventricular assist devices，CF-LVADs)是治疗手段之一，应用CF-LVADs的患者消化道出血发病率为20.5%~61%[25-27]。动静脉畸形(arteriovenous malformations，AVMs)是UGIB最常见的病因[28]，它可能与抗栓治疗、继发于动脉搏动减少的血管生成增强和血管生成素2的合成有关[29-30]。对于AVMs所致的UGIB，内镜治疗是暂时的治疗措施，并不能防止新发病变的出现和再出血的发生[28]。在心血管系统疾病治疗过程中，常应用抗凝或抗血小板药物，可能增加UGIB发生风险，一旦出血发生将带来治疗上的矛盾，增加病死率[31]，因此应以预防出血为重点。

*Hp*感染是人们已熟知的UGIB危险因素，而CKD及心血管系统疾病对UGIB的影响值得进一步关注。

## 3 药物

### 3.1 非甾体类抗炎药

阿司匹林广泛应用于心脑血管疾病的治疗[32]；其他非甾体类抗炎药(non-steroid anti-

inflammatory drugs，NSAIDs)，广泛应用于痛风、类风湿性关节炎等疾病中，发挥镇痛消炎作用。NSAIDs在治疗原有疾病的同时，增加了消化道损伤的风险[33-34]。新西兰一项病例对照研究[35]对5 194 256名患者进行分析，发现NSAIDs为UGIB的独立危险因素(AOR=4.16，95%CI：3.90~4.43)；我国研究亦有相同发现[5,7]。为了减少胃肠道损伤，保留NSAIDs类药物的解热、镇痛和抗炎作用，选择性环氧化酶2(COX-2)抑制剂问世。Masclee等[36]通过分析114 835例UGIB病例发现：应用COX-2抑制剂者UGIB发生风险低于应用非选择性NSAIDs者(IRR：2.9 vs 4.3)。台湾地区一病例对照研究[6]经Cox回归分析发现：昔布类药物可以增加UGIB的发病风险(HR=1.37，95%CI：1.19~1.55)。故NSAIDs可增加UGIB发生风险，应用选择性COX-2抑制剂者UGIB发病率低于应用非选择性NSAIDs者，但仍高于未用NSAIDs者。

质子泵抑制剂(proton pump inhibitor，PPI)可用于UGIB的治疗及预防，但有研究[37]提出：PPI为心肌梗死的独立危险因素。现有研究尚不能说明PPI增加患者心血管事件和总病死率，在评估患者心血管风险及消化道风险，权衡利弊后，仍可考虑应用PPI减少消化道损伤。

### 3.2 选择性5-羟色胺再摄取抑制剂

选择性5-羟色胺再摄取抑制剂(selective serotonin reuptake inhibitors，SSRIs)是目前临床常见的抗抑郁药物。Jiang等[38]对以往的22项相关研究进行综述，发现：应用SSRIs的患者UGIB发病率较未应用者高1.55倍(OR=1.55；95%CI：1.35~1.78)。Anglin等[39]分析了15项病例对照研究和4项队列研究，发现：应用SSRIs者较对照组UGIB发病风险显著增加，且当SSRIs与NSAIDs联用时UGIB风险更高(OR=4.25，95%CI: 2.82~6.42)。对于SSRIs引起UGIB风险增加的机制目前尚不明确，有观点认为5-羟色胺可以诱导血小板的聚集，应用SSRIs时可能导致血小板聚集和止血功能受损，使得UGIB发生风险增加[40]。

此外，研究[41-42]提出应用糖皮质激素，特别是NSAIDs与糖皮质激素连用，可增加UGIB的发生风险。氯吡格雷、新型口服抗凝药等也可增加UGIB的出血风险，但与阿司匹林通过局部及全身作用引起胃肠黏膜损伤不同，这些药物通常是通过抑制新生血管形成等方式，阻碍已受损的消化道黏膜愈合来参与UGIB的发生[43]。

## 4 气象因素

UGIB的发病与季节及气象因素的关系研究众多，但说法不一。北京地区研究发现UGIB的发病存在显著季节差异($\chi^2$=102.715，$P$<0.05)[44]；德国研究[3]发现冬季因UGIB就诊于急诊的人数最多，其余多项研究[45-48]均发现UGIB在寒冷天气高发。但是希腊的研究[49]显示：十二指肠溃疡出血的发病率冬季最低，在春秋季呈上升趋势。西班牙[50]及秘鲁[51]的研究显示UGIB的发生在四季无显著差异。不同地区气候特点不同，UGIB发病规律不同。

UGIB的发病与气象因素的关系：北京地区研究[52]显示：气温、气压对UGIB的发生有独立影响(气温$r$=−0.3785，气压$r$=−0.3002，$P$<0.05)。吉林省的研究[53]发现UGIB的发生与月平均气温、气压显著相关(气温$r$=−0.533，气压$r$=0.738，$P$<0.05)。台湾地区的研究[45]发现：气温降低可使食管胃底静脉曲张出血的发生风险增加。德国研究[54]发现：静脉曲张出血的发生与日最低气温相关(IRR：0.961，$P$<0.05)，溃疡出血与气压变化相关(IRR：1.031/hPa，$P$<0.05)。西班牙的研究[50]显示：UGIB的发生于气象因素无关。综上，在温带及部分亚热带，大陆性气候为主的地区UGIB的发生与气温、气压有关。在热带及部分亚热带，海洋气候及地中海气候为主地区，UGIB的发生与气象因素无关。不同地区气象因素变化特点不同，UGIB的发生受到气象因素变化的影响。

气象因素影响UGIB的机制暂不明确。考虑与气象因素变化引起体内神经内分泌变化有关。寒冷季节胃溃疡的患者胃黏膜厚度变薄、热休克蛋白70表达下降、胃酸增加[3,55]。由此推断，不同气候条件下，消化性溃疡患者黏膜屏障功能存在差异。食管胃底静脉曲张出血与门静脉压力及门脉血流量相关，寒冷环境可以升高血压、增加心输出量，增加门脉压力；还可以使血流重新分布，体表血流量减少而内脏血流量增加[45,56]。中医理论也对气象因素变化与UGIB的关系做出了解释。《内经》指出：低温与“六淫”中“寒邪”相关，寒主收引，其性凝滞。寒邪来临，血行迟缓瘀滞，致瘀而出血。

以往研究主要关注UGIB与单个气象因素变化的关系，或选用线性回归对多个气象因素进行分析，实际气候环境是多个气象因素共同构成的复杂环境，UGIB与气象因素之间的关系可能为更复杂的非线性关系，而忽略各气象因素间的相互作用可致研究结果偏离实际情况。另外，以往研究均着眼于出血当天气象因素情况，缺少对出血前

连续时间段内气象因素变化趋势的分析，若能明确变化趋势可对UGIB的预防起到更有效的指导作用。今后还可以开展多地理多中心的研究，更全面的认识UGIB与气象因素的关系。

## 5 不良生活习惯

Groza等[12]经logistic回归分析发现吸烟(OR=2.498，95%CI：1.358~4.597；$P$<0.05)，饮酒(OR=3.283，95%CI：1.796~6.000；$P$<0.05)为非静脉曲张性上消化道出血的危险因素。Nagata等[57]发现饮酒为消化性溃疡出血的危险因素(AOR=2.2；$P$<0.05)。酒精可降低胃排空能力，刺激胃酸分泌，吸烟可引起胃十二指肠黏膜血管收缩，降低其防御能力[12]，从而增加UGIB发生风险。

## 6 其他危险因素

VKORC1-1639 G>A AA基因型可能是UGIB的危险因素(OR=1.364，95%CI：0.998~1.863)，应用NSAIDs的该基因型患者较非基因变异者UGIB发病风险更高(OR 7.6 vs 3.6，$P$<0.05)，其机制尚不明确，可能为VKORC纯合子基因型导致维生素K依赖性蛋白质羧基化不足，凝血酶原不能有效参与凝血级联反应[12]。但该研究样本量较小，可进一步扩大样本量进行研究。

此外，不同病因所致的UGIB存在其特有的危险因素。复合溃疡、溃疡面积较大、活动期溃疡[7]、既往消化性溃疡病史[57]是消化性溃疡出血的危险因素。而对于食管胃底静脉曲张出血，血小板计数减少、门静脉内径增加、红色征[58-59]和腹水[8]为其危险因素。白细胞计数高、血清ALT升高、血清总胆红素升高[60]及菌血症[61]是病死率增加的独立预测因素。

## 7 结语

UGIB因其较高的发生率和其所带来的经济负担而在全球范围内受到广泛关注。高龄男性、合并幽门螺旋杆菌感染、慢性肾功能不全、心血管疾病，长期单独或联合应用NSAIDs和SSRIs等药物是UGIB的危险因素。此外，气象因素、吸烟、饮酒也影响着UGIB的发生。*VKORC*基因变异是可能的危险因素，有待进一步研究。了解UGIB的危险因素，有助于改进这一急危重症的预防和管理策略，有利于提高患者生存质量，节约卫生经费，故应引起消化内科医生的重视。

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**本文引用：** 袁玥, 郝建宇, 刘心娟. 影响上消化道出血的相关危险因素[J]. 临床与病理杂志, 2021, 41(7): 1709-1714. doi: 10.3978/j.issn.2095-6959.2021.07.039
***Cite this article as:*** YUAN Yue, HAO Jianyu, LIU Xinjuan. Related risk factors for upper gastrointestinal bleeding[J]. Journal of Clinical and Pathological Research, 2021, 41(7): 1709-1714. doi: 10.3978/j.issn.2095-6959.2021.07.039