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Onset Time and Characteristics of Postprocedural Bleeding after Endoscopic Resection of Colorectal Lesions: A Multicenter Retrospective Study

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Keywords
Postprocedural bleeding · Endoscopic resection · Colorectal lesion · Colorectal adenoma · Endoscopic mucosal resection

Abstract
Introduction: Postprocedural bleeding is a major adverse event after endoscopic resection of colorectal lesions, but the optimal surveillance time after endoscopy is unclear. In this study, we determined onset time and characteristics of postprocedural bleeding events. ***Methods:*** We retrospectively screened patients who underwent endoscopic resection of colorectal lesions at three German hospitals between 2010 and 2019 for postprocedural bleeding events using billing codes. Only patients who required re-endoscopy were included for analysis. For identified patients, we collected demographic data, clinical courses, characteristics of colorectal lesions, and procedure-related variables. Factors associated with late-onset bleeding were determined by univariate and multivariate logistic regression analysis. ***Results:*** From a total of 6,820 patients with eligible billing codes, we identified 113 cases with postprocedural bleeding after endoscopic mucosal (61.9%) or snare resection (38.1%) that required re-endoscopy. The median size of the culprit lesion was 20 mm (interquartile range 14–30 mm). The median onset time of postprocedural bleeding was day 3 (interquartile range: 1–6.5 days), with 48.7% of events occurring within 48 h. Multivariate logistic regression analysis demonstrates that a continued intake of antiplatelet drugs (OR: 3.98, 95% CI: 0.89–10.12, $p = 0.025$) and a flat morphology of the colorectal lesion (OR: 2.98, 95% CI: 1.08–8.01, $p = 0.031$) were associated with an increased risk for late postprocedural bleeding (>48 h), whereas intraprocedural bleeding was associated with a decreased risk (OR: 0.12, 95% CI: 0.04–0.50, $p = 0.001$). ***Conclusion:*** Significant postprocedural bleeding can occur up to 18 days after endoscopic resection of colorectal lesions, but was

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predominantly observed within 48 h. Continued intake of antiplatelet drugs and a flat polyp morphology are associated with risk for late postprocedural bleeding.

Introduction

Colorectal cancer (CRC) is one of the most frequent cancer entities worldwide and a leading cause of cancer-related death [1]. Screening colonoscopy can reduce CRC-associated mortality [2, 3] and has been implemented in many national cancer prevention programs. Colonoscopy with endoscopic adenoma removal is generally considered a safe method, with adverse events such as bleedings and perforations occurring in 0.42% of screening colonoscopies [4]. However, the frequency of adverse events is higher for endoscopic resection of large non-pedunculated colorectal adenomas [5]. Here, the most frequent adverse event is postprocedural bleeding, with a reported frequency of 0.9–6.8% [4, 6–10]. Although few cases of bleeding-associated mortality are reported [5, 11], major postprocedural bleeding can result in requirement for blood transfusion, endoscopic intervention, radiological embolization, and partial colectomy [11]. A number of studies identified risk factors for postprocedural bleeding and found associations with patients' age [7, 12], use of antithrombotic agents [7, 13–15], and history of hypertension [16, 17]. Furthermore, lesion-related factors such as polyp size [12, 18–20], location within the colon [12, 18, 21], and pedunculated shape [22] were identified as risk factors [8]. Finally, associations were also described for procedure-related factors. For instance, mucosal defects after endoscopic resection that are not closed by clips [12] and intraprocedural bleeding [7, 23, 24] were associated with increased risk for postprocedural bleeding.

So far, the optimal duration of surveillance after endoscopic resection of colorectal lesions is unclear. Postprocedural bleeding can occur between several hours and 29 days after colorectal endoscopic resection, with an average onset time of 1.7–4.1 days [7, 17, 22, 24–26]. Most postprocedural bleeding events are observed in an early phase (<48 h) [9, 27, 28], while the occurrence of late postprocedural bleeding (occurring >48 h) is less predictable [21]. Since there is a considerable economic pressure to discharge patients early after endoscopic procedures, the identification of risk factors for severe late postprocedural bleeding after endoscopic resection of colorectal lesions can help to optimize the surveillance of patients.

In this retrospective study, we determined onset time and characteristics of significant postprocedural bleeding events after endoscopic resection of colorectal lesions that required re-endoscopy. We investigated factors that are associated with late-onset postprocedural bleeding, including patient-, lesion-, and procedure-related characteristics.

Materials and Methods

Data Collection

This multicenter retrospective study was performed at three tertiary medical centers in Germany: Mannheim University Hospital of Heidelberg University, Carl Thiem Hospital Cottbus, and Wolfsburg Hospital. Patients who underwent endoscopic resection of colorectal lesions between January 2010 and April 2019 were identified using Operation and Procedure Classification System (OPS) codes extracted from the electronic databases of the respective hospitals. The OPS is a modification of the International Classification of Procedures in Medicine and the official coding system for medical procedures in German hospitals. Patients with the OPS codes 5–452 (local excision and destruction of diseased tissue in the large intestine) or 5–482 (perianal local excision and destruction of diseased tissue in the rectum) were selected for further evaluation. Patients with bleeding complications were then identified by combining the international classification of disease codes T81.0 (hemorrhage and hematoma complicating a procedure, not elsewhere classified) and K92.2 (gastrointestinal hemorrhage, unspecified). For the Wolfsburg Hospital, an internal documentation of all endoscopic adenoma resections with associated adverse events was available and included in the analysis. Significant postprocedural bleeding was defined as any lower gastrointestinal bleeding that occurred after an endoscopic procedure and required medical attention including re-endoscopy. Identified cases were reviewed in detail and the following were excluded: patients who received forceps biopsy only, patients with additional interventions in the colon (e.g. dilatation), patients with bleeding events related to parallel endoscopic interventions in the upper GI tract or who received colorectal adenoma removal in outpatient facilities, and patients who did not receive re-endoscopy after postprocedural bleeding. Patients who received endoscopic submucosal dissection were also excluded, as well as cases with insufficient documentation of the resection technique.

Clinical information on patients with bleeding events was obtained by a detailed review of medical records. The following information was collected: patient age, sex, time of clinically documented bleeding event (hematochezia, melena, or reduction of hemoglobin levels), intake of anticoagulants or antiplatelet drugs, postprocedural interventions (re-endoscopy, blood transfusion, admission to intensive care unit, surgery), and history of selected comorbidities (arterial hypertension, past history of gastrointestinal bleeding, type II diabetes, chronic kidney disease, hereditary coagulopathy). Endoscopic reports of identified patients were reviewed for the following parameters: size, location, and morphology of the lesion with postprocedural bleeding sign (culprit lesion). If not described in the endoscopy report, polyp size was determined post hoc by comparison with snare or forceps.

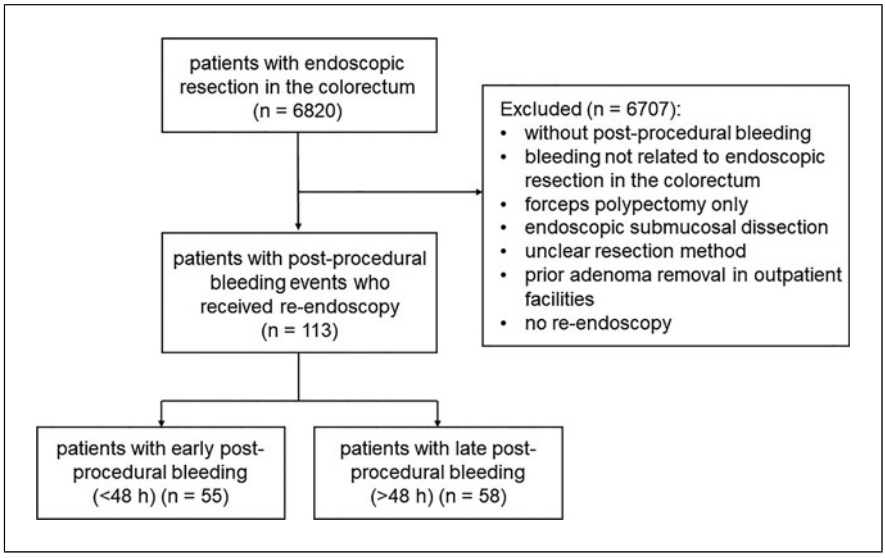

Fig. 1. Flowchart of patient selection.

In case multiple colonic lesions were removed and postprocedural bleeding could not be assigned to a specific lesion, we selected the largest as the culprit lesion. Information on the use of clips (either for hemostasis or for prophylactic defect closure) or argon plasma coagulation (APC) during primary resection, resection techniques (snare polypectomy or endoscopic mucosal resection [EMR], use of hot or cold snare), intraprocedural bleeding, and signs of active or nonactive bleeding during re-endoscopy was collected.

Statistical Analysis

Characteristics of patients were described using descriptive statistics. Categorical values were reported as numbers with percentages, and continuous variables (age, number of resections, lesion size) were reported as median with interquartile range (IQR: 25–75th percentiles). Univariate and multivariate logistic regression models were used to identify factors associated with late postprocedural bleeding and estimated by odds ratio (OR) with 95% confidence intervals (95% CI). For multivariate logistic regression analysis, multiple imputation of missing values was performed [29]. Variance inflation factors were calculated to assess collinearity. p values below 0.05 were considered statistically significant. All analyses were performed with the software R 4.2 [30].

Results

Patient Selection, Baseline Characteristics, and Outcome

A total of 6,820 patients who underwent endoscopic resection of colorectal lesions were identified by combined OPS and international classification of disease codes. Of these patients, 4,216 (61.8%) were male and 2,604 (38.2%) female, with a median age of 68 years (IQR: 59–76). After application of the exclusion criteria described in the methods section, we identified 113 patients (1.7%) with significant postprocedural bleeding complications following endoscopic resection in the colon who received re-endoscopy (Fig. 1). All baseline characteristics of identified patients are shown in Table 1. Seventy-four patients (65.5%) were male and 39 (34.5%) were female with a median age of 69 years (IQR: 60–75 years). Continued intake of antiplatelet drugs during the endoscopic procedure was reported in 21 patients (19.8%), with 19 cases of acetylsalicylic acid and 2 cases of clopidogrel intake, including 1 case of dual acetylsalicylic acid and clopidogrel therapy. Paused intake of anticoagulants (vitamin K antagonists and direct oral anticoagulants) was described in 26 patients (23.4%). A history of hypertension was reported in 63 patients (55.8%). A total of 281 colorectal lesions were removed in the identified patient cohort. The median number of resected lesions per patient was 2 (IQR: 1–3). The median size of the culprit lesion was 20 mm (IQR 14–30 mm). Fifty-one (45.1%) lesions were located in the left colon and 62 (54.9%) in the right colon. Most lesions were removed by EMR (61.9%), and fewer by snare polypectomy (38.1%). Resection was performed with hot snare in 33 and cold snare in 55 cases (missing data in 25 cases). Intraprocedural bleeding was documented in 31 cases (27.4%). APC was applied in 22 (19.5%) and clips were used in 38 cases (33.6%). In 22 of those cases, clips were applied for hemostasis and in 16 for prophylactic defect closure.

All patients with documented postprocedural bleeding received re-endoscopy. Active bleeding was observed in 44 patients (38.9%), while no signs of active bleeding or signs of self-limited bleeding were found in the others

Table 1. Baseline characteristics of patients with early (<48 h) and late (>48 h) postprocedural bleeding (*N* = 113)

	Early onset	Late onset	Overall
Number of patients	55 (48.7)	58 (51.3%)	113
Characteristics			
Gender			
Male, *n* (%)	34 (61.8)	40 (69.0)	74 (65.5)
Female, *n* (%)	21 (38.2)	18 (31.0)	39 (34.5)
Median age, years (range)	69.0 (55.5–74.5)	70.5 (61.0–75.0)	69.0 (60.0–75.0)
Comorbidities/medication, *n* (%)			
Arterial hypertension	25 (46.3)	38 (67.9)	63 (57.3)
Continued use of antiplatelet drugs	5 (9.6)	16 (29.6)	21 (19.8)
Use of anticoagulation drugs	10 (18.2)	16 (28.6)	26 (23.4)
Characteristics of postprocedural bleeding, *n* (%)			
Active bleeding	29 (52.7)	15 (25.9)	44 (38.9)
Nonactive bleeding	26 (47.3)	43 (74.1)	69 (61.1)
Lesion-related factors			
Median number of removed lesions	2 (1, 3)	2 (1, 3)	2 (1, 3)
Median size of culprit lesion, mm (range)	20.0 (15.0–30.0)	20.0 (13.3–25.0)	20.0 (14.0–30.0)
Endoscopic morphology of lesion, *n* (%)			
Pedunculated	26 (51.0)	20 (38.5)	46 (44.7)
Flat	25 (49.0)	32 (61.5)	57 (55.3)
Anatomical localization of culprit lesion, *n* (%)			
Left colon	24 (43.6)	27 (46.6)	51 (45.1)
Right colon	31 (56.4)	31 (53.4)	62 (54.9)
Procedure-related factors			
Resection techniques, *n* (%)			
EMR	36 (65.5)	34 (58.6)	70 (61.9)
Snare polypectomy	19 (34.5)	24 (41.4)	43 (38.1)
Hot snare polypectomy	18 (42.9)	15 (32.6)	33 (37.5)
Cold snare polypectomy	24 (57.1)	31 (67.4)	55 (62.5)
Use of APC	10 (18.2)	12 (20.7)	22 (19.5)
Use of clips	20 (36.4)	18 (31.0)	38 (33.6)
for hemostasis	14 (70.0)	8 (44.4)	22 (57.9)
for prophylactic defect closure	6 (30.0)	10 (55.6)	16 (42.1)
Intraprocedural bleeding	21 (38.2)	10 (17.2)	31 (27.4)

Values are presented as numbers (% of total) or median [IQR]. APC, argon plasma coagulation; EMR, endoscopic mucosal resection.

(61.1%). Among all patients with postprocedural bleeding, no lethal complications were observed. Four patients (3.5%) suffered from hemorrhagic shock, and one of them (0.9%) underwent surgery after failure of endoscopic hemostasis. Blood transfusions were required in 13 patients (11.5%).

Onset of Postprocedural Bleeding Events

First, we determined the onset time of the documented postprocedural bleeding. Postprocedural bleeding occurred from within 24 h up to 18 days after resection. The main peak of postprocedural bleeding was observed at day 1 (within 24 h after endoscopic resection), while the median onset time was at day 3 (IQR: 1–6.5 days) (Fig. 2). Next, we classified bleeding events into early (<48 h) and late bleeding (>48 h) as previously done by other studies [9, 31, 32]. Among the 113 patients with postprocedural bleeding, early bleeding occurred in 55 (48.7%) and late bleeding in 58 patients (51.3%).

Factors Associated with the Late Postprocedural Bleeding after Endoscopic Resection

To identify factors that influence the timing of postprocedural bleeding, we performed group comparisons between patients with early (<48 h) and late postprocedural bleeding (>48 h) (Table 2). Patient- (gender, age, comorbidities, use of antiplatelet agents, and use of anticoagulants), lesion- (size, number,

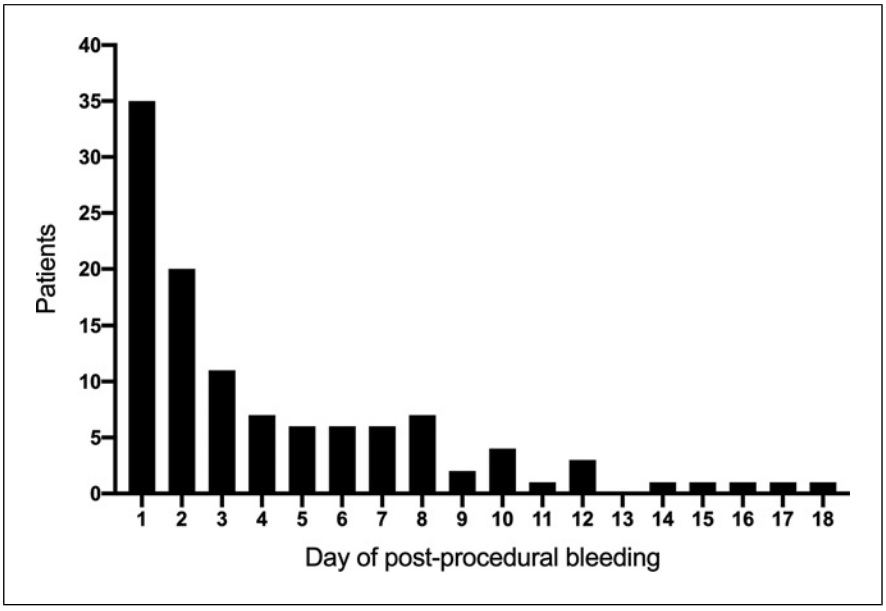

Fig. 2. Time of onset of postprocedural bleeding. Day 1 was defined as <24 h after endoscopic resection. The median time of postprocedural bleeding was day 3 (IQR 1–6.5 days).

Table 2. Uni- and multivariate logistic regression analysis of factors associated with late postprocedural bleeding (n = 113)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Patient-related factors				
Gender				
Male (vs. female)	1.37 (0.63–3.01)	0.425	1.22 (0.48–3.20)	0.674
Age, years	1.02 (0.99–1.05)	0.251	0.99 (0.96–1.04)	0.744
Comorbidities/medication				
Arterial hypertension	2.45 (1.14–5.39)	0.024	2.41 (0.82–5.93)	0.079
Continued use of antiplatelet drugs	3.96 (1.41–13.00)	0.013	3.98 (0.89–10.12)	0.025
Use of anticoagulation drugs	1.80 (0.74–4.54)	0.199	2.20 (0.59–7.53)	0.221
Lesion-related factors				
Median number of removed lesion	0.95 (0.80–1.14)	0.604	0.92 (0.71–1.15)	0.491
Median size of culprit lesion, mm	0.99 (0.96–1.01)	0.335	1.00 (0.96–1.04)	0.928
Endoscopic morphology of lesion				
Flat (vs. pedunculated)	1.66 (0.76–3.68)	0.203	2.98 (1.08–8.01)	0.031
Anatomical localization				
Left colon (vs. right colon)	1.12 (0.54–2.37)	0.756	1.54 (0.58–3.66)	0.356
Procedure-related factors				
Resection techniques				
Snare polypectomy (vs. EMR)	1.34 (0.62–2.89)	0.455	1.10 (0.44–2.85)	0.846
Cold snare polypectomy (vs. hot)	1.55 (0.65–3.73)	0.322	2.37 (0.72–6.07)	0.111
Use of APC	1.17 (0.46–3.04)	0.737	1.33 (0.40–5.45)	0.666
Use of clips	0.79 (0.36–1.72)	0.549	2.03 (0.66–7.05)	0.237
Intraprocedural bleeding	0.34 (0.14–0.79)	0.015	0.12 (0.04–0.50)	0.001

Values are presented as odds ratio with 95% confidence interval. APC, argon plasma coagulation; EMR, endoscopic mucosal resection.

location, endoscopic appearance), and endoscopic procedure-related factors (resection techniques, use of clips or APC, hot or cold snare polypectomy) were selected as potential variables. Comorbidities such as diabetes, chronic kidney disease, or hereditary coagulopathies were excluded due to low case numbers in our cohort. Regarding the use of antiplatelet agents, we compared patients with continued intake of antiplatelet drugs during the endoscopic procedure to those who did not use antiplatelet drugs or had paused them at least 6 days before the intervention. Patients with paused anticoagulation drugs during the endoscopic procedure were compared to patients who did not require them.

To identify factors associated with late postprocedural bleeding, we performed univariate and multivariate analysis using logistic regression models. In the univariate analysis, a history of arterial hypertension (OR: 2.45, 95% CI: 1.14–5.39, $p = 0.024$) and a continued intake of antiplatelet medication (OR: 3.96, 95% CI: 1.41–13.00, $p = 0.013$) were significantly associated with a higher risk for late postprocedural bleeding, while documented intraprocedural bleeding was associated with a lower risk (OR: 0.34, 95% CI: 0.14–0.79, $p = 0.015$) (see Table 2). Lesion-related factors, such as size, anatomic location, and number of resected lesions, as well as procedure-related factors including resection techniques, the use of APC, or clips, were not associated with late-onset postprocedural bleeding. In the multivariate analysis, a significant association was confirmed for the continued use of antiplatelet agents (OR: 3.98, 95% CI: 0.89–10.12, $p = 0.025$) and intraprocedural bleeding (OR: 0.12, 95% CI: 0.04–0.50, $p = 0.001$), while no association was observed for arterial hypertension. In addition, a flat morphology of the culprit lesion was identified as a risk factor for late postprocedural bleeding (OR: 2.98, 95% CI: 1.08–8.01, $p = 0.031$) (see Table 2).

Discussion

Postprocedural bleeding is one of the most common and serious adverse events after endoscopic resection of colorectal lesions [31]. Systematic assessment of the onset time of postprocedural bleeding is critical to optimize the clinical monitoring period of patient who undergo endoscopic resection in the colon. In our retrospective study, we found that the median onset of postprocedural bleeding was on day 3, with 48.7% of bleeding events occurring <48 h after resection of colorectal lesions. This is in line with previous studies, which reported that postprocedural bleedings occurred predominantly within the first 48 h [9, 27, 28]. Similar to our study, Elliott et al. [11] observed a median onset time of 3 days after piecemeal EMR in 330 patients with large non-pedunculated colorectal adenomas. In contrast, Okugawa et al. [33] showed that postprocedural bleeding occurred at a median of 1 day in a cohort of 1,002 patients with colorectal polyps. A summary of studies investigating the onset of postprocedural bleeding after endoscopic resection in the colon can be found in Table 3.

In our study, we observed that among patients with significant postprocedural bleeding who required re-endoscopy, those who continued intake of antiplatelet drugs during endoscopy had a higher risk of late bleeding events. Several studies showed that continuing antiplatelet therapy with acetylsalicylic acid was not or only associated with a minor risk of postprocedural bleeding after colorectal polypectomy [11, 14, 15, 35–37]. Hence, in current guidelines of the American Society for Gastrointestinal Endoscopy and European Society of Gastrointestinal Endoscopy, a continued use of acetylsalicylic acid was recommended for most endoscopic procedures [38, 39]. However, for patients undergoing EMR of large, non-pedunculated colonic lesions (>2 cm), several studies found that the continued use of antiplatelet agents increased the risk of postprocedural bleeding [12, 13, 39, 40]. Other studies also indicate that the risk of bleeding after polypectomy depends on the specific type of antiplatelet drugs and is increased by dual antiplatelet therapy [15, 36]. However, how intake of antiplatelet drugs affects the onset of postprocedural bleeding is poorly investigated. In this context, our study suggests that the continued intake of antiplatelet drugs is associated with late postprocedural bleeding, which was observed by another recent study [41]. In our cohort, acetylsalicylic acid was predominantly used as antiplatelet agent; therefore, we are unable to assess the impact of other antiplatelet drugs on the onset of postprocedural bleeding.

We also observed that patients with flat colorectal lesions have a higher risk of late onset postprocedural bleeding compared to patients with pedunculated lesions. Previous studies that investigated associations between polyp morphology and risk for postprocedural bleeding showed inconclusive results. While some studies observed an increased risk for flat or sessile polyps [42, 43], others made the same observations for pedunculated lesions [44]. Additionally, some studies found no significant correlation of bleeding risk with polyp morphology [16, 21]. However, none of these studies focused on the onset of postprocedural bleeding. Given the controversial state of evidence, further studies are needed to validate our observation.

Table 3. Selected studies on the onset time of postprocedural bleeding after endoscopic removal of colorectal lesions

Country	Cohort (bleeding/total)	Onset time	Lesion type	Resection techniques	Ref.
UK	22/330	Median time: day 3 (range days 1–8)	Large non-pedunculated adenomas (≥2 cm)	Piecemeal EMR	[11]
Netherlands	28/412	Within 48 h: 67.9%; >48 h: 32.1%	Large non-pedunculated adenomas (≥2 cm)	EMR	[9]
Spain	46/1,247	Within 48 h: 37%; between days 3–7: 50%; >7 d: 13%	Large non-pedunculated lesions (≥2 cm)	EMR	[12]
Australia	21/288	Within 24 h: 65%; 24 h–48 h: 23%; after 48 h: 12%	Large laterally spreading colonic tumors	EMR	[27]
Japan	17/403	Median time: 2 days (range 1–14 days)	Colorectal tumors ≥2 cm	EMR	[34]
Australia	73/1,172	Within 24 h: 43.8%; 24 h–48 h: 24.7%; 48 h to 7 days: 20.5%; from 7 to 14 days: 11.0%	Large sessile colonic polyps	EMR	[28]
USA	41/4,592	Mean time: 6 days (range 1–14 days)	Colorectal polyps	NA	[10]
China	35/2,267	Median time: 3 days (range 1–7 days)	Colorectal polyps	EMR or HSP	[35]
Japan	20/1,002	Median time: 1 day (IQR: 1–3 days)	Colorectal polyps	HSP/EMR/CSP/CFP	[36]
Korea	133/8,175	Mean time: 1.7 days (range 1–15 days)	Colorectal polyps	Forceps biopsy and EMR	[7]
Korea	42/3,253	Mean time: 4.1 days (range 1–12 days)	Colorectal polyps	Snare resection/ EMR/ESD	[22]
Netherlands	117/NA	Within 24 h: 23%; 24 h–72 h: 31%; after 72 h: 46%	Colorectal polyps	Diverse endoscopic procedures	[21]

Articles were identified in the following databases: PubMed (1966 to Nov 2022), EMBASE (1947 to Nov 2022), Ovid (1950 to Nov 2022), and Web of Science (1900 to Nov 2022). Literature search was performed by using "endoscopic resection," "EMR," "snare polypectomy," "bleeding," "colorectal lesions," and "onset time" as key words. The search strategy was modified according to the database. The reference lists of targeted articles were reviewed and manually searched to obtain additional related studies. APC, argon plasma coagulation; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; FTR, full-thickness resection; HSP, hot snare polypectomy; CSP, cold snare polypectomy; CFP, cold forceps polypectomy; NA, not applicable.

The retrospective approach of our study has several limitations. First, due to the lack of a structured follow-up, subjective assessment of onset time of bleeding events might cause selection bias. Furthermore, the frequency of bleeding is most likely underestimated by our study, as we only included significant bleeding events that required patients to receive re-endoscopy, neglecting those with minor, self-limiting bleeding. Potential heterogeneity of resection procedures and expertise between different endoscopy units may also introduce bias regarding procure-related risks. Additionally, in a few cases of patients with resection of multiple adenomas, the culprit lesion responsible for the postoperative bleeding could not be clearly determined; therefore, lesion-related risk factors such as the location and size of culprit lesion must be interpreted with care. Lastly, it should be noted that our study did not focus on identifying risk factors of postprocedural bleeding as such. Addressing this question would require comparison with a cohort of patients who underwent the same endoscopic procedures, but did not experience bleeding complications. Instead, our study focused on the onset time of postprocedural bleeding in a large cohort of patients experiencing significant bleeding complications. To our knowledge, this has not been the focus of many studies so far. Due to this specific focus, we did not discover any significant association for several factors that were previously identified to reduce the risk of postprocedural bleeding, such as use of cold snare polypectomy [41, 45] or prophylactic clipping [46]. Similarly, factors that increase the risk for postprocedural bleeding such as large polyp size [47] and right-sided location [21] were not found to be associated with late-onset bleeding in our study.

In conclusion, postprocedural bleeding can occur up to 18 days after endoscopic resection of colorectal lesions, but was predominantly observed within 48 h. These results indicate that a short clinical monitoring period, either in-hospital or by out-patient care, is sufficient in most cases. The continued use of antiplatelet drugs and a flat shape of the lesion were associated with late postprocedural bleeding. Therefore, our data suggest that patients with these characteristics might benefit from extended clinical surveillance.

Statement of Ethics

Data collection for this study was approved by the Local Ethics Committee of Heidelberg University (identifier: 2018-891R-MA). For the retrospective approach, no written informed consent from patients was required as decided by the Ethics Committee II of Heidelberg University. Research for this study was conducted in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors declare no conflict of interests for this article.

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Author Contributions

Q.X. and M.E. were involved in acquisition, analysis, and interpretation of the data, and drafted and revised the manuscript. A.M., H.E., A.B., and N.H. assisted with obtaining clinical data. G.K., M.E., and S.B. revised the manuscript for intellectual content and assisted with acquisition of clinical data. T.H. performed statistical analysis. S.B. and T.Z. supervised the study and revised the manuscript. All authors reviewed and approved the submitted manuscript.

Data Availability Statement

All data generated and analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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