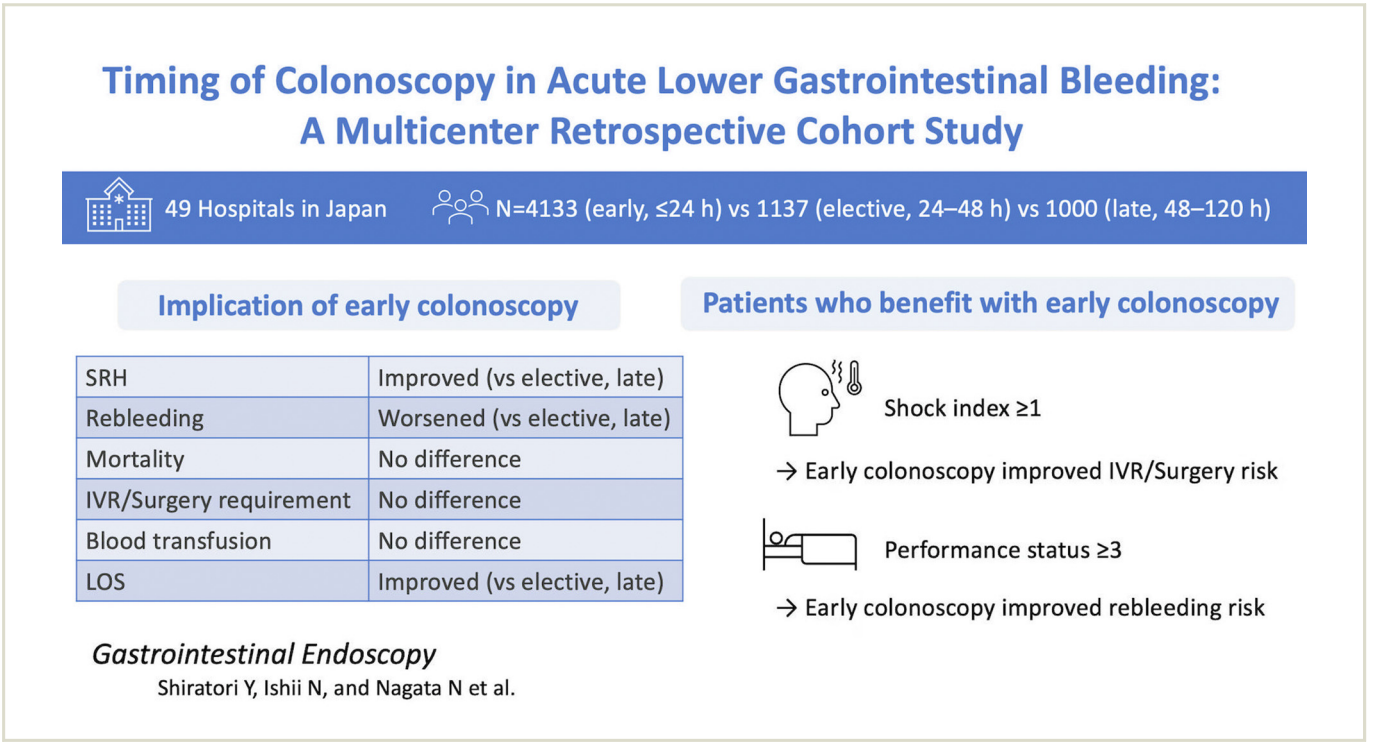
Timing of colonoscopy in acute lower GI bleeding: a multicenter retrospective cohort study

Yasutoshi Shiratori, MD, MPH, PhD,[1] Naoki Ishii, MD, MPH, PhD,[2] Tomonori Aoki, MD, PhD,[3] Katsumasa Kobayashi, MD,[4] Atsushi Yamauchi, MD,[5] Atsuo Yamada, MD, PhD,[3] Jun Omori, MD,[6] Taiki Aoyama, MD, PhD,[7] Naoyuki Tominaga, MD,[8] Yoshinori Sato, MD, PhD,[9] Takaaki Kishino, MD,[10] Tsunaki Sawada, MD,[11] Masaki Murata, MD, PhD,[12] Akinari Takao, MD, PhD,[13] Kazuhiro Mizukami, MD, PhD,[14] Ken Kinjo, MD, PhD,[15] Shunji Fujimori, MD, PhD,[16] Takahiro Uotani, MD, PhD,[17] Minoru Fujita, MD, PhD,[18] Hiroki Sato, MD, PhD,[19] Sho Suzuki, MD,[20] Toshiaki Narasaka, MD, PhD,[21,22] Junnosuke Hayasaka, MD, PhD,[23] Tomohiro Funabiki, MD, PhD,[24,25] Yuzuru Kinjo, MD, PhD,[26] Akira Mizuki, MD, PhD,[27] Shu Kiyotoki, MD, PhD,[28] Tatsuya Mikami, MD, PhD,[29] Ryosuke Gushima, MD, PhD,[30] Hiroyuki Fujii, MD,[31] Yuta Fuyuno, MD, PhD,[32] Naohiko Gunji, MD, PhD,[33] Yosuke Toya, MD, PhD,[34] Kazuyuki Narimatsu, MD, PhD,[35] Noriaki Manabe, MD, PhD,[36] Koji Nagaike, MD,[37] Tetsu Kinjo, MD, PhD,[38] Yorinobu Sumida, MD, PhD,[39] Sadahiro Funakoshi, MD, PhD,[40] Kiyonori Kobayashi, MD, PhD,[41] Tamotsu Matsuhashi, MD, PhD,[42] Yuga Komaki, MD, PhD,[43] Kuniko Miki, BA,[44] Kazuhiro Watanabe, MD, PhD,[45] Kazuki Yamamoto, MD,[1] Takaaki Yoshimoto, MD,[1] Ayaka Takasu, MD,[1] Takashi Ikeya, PhD,[1] Fumio Omata, MD, MPH, PhD,[1] Katsuyuki Fukuda, MD, PhD,[1] Mitsuru Kaise, MD, PhD,[6] Naoyoshi Nagata, MD, PhD[44,45]

Tokyo, Osaka, Hiroshima, Saga, Kanagawa, Nara, Aichi, Kyoto, Oita, Fukuoka, Chiba, Shizuoka, Okayama, Niigata, Miyazaki, Ibaraki, Okinawa, Yamaguchi, Aomori, Kumamoto, Fukushima, Iwate, Saitama, Akita, Kagoshima, Japan

GRAPHICAL ABSTRACT



Background and Aims: We aimed to determine the optimal timing of colonoscopy and factors that benefit patients who undergo early colonoscopy for acute lower GI bleeding.

Methods: We identified 10,342 patients with acute hematochezia (CODE BLUE-J study) admitted to 49 hospitals in Japan. Of these, 6270 patients who underwent a colonoscopy within 120 hours were included in this study. The inverse probability of treatment weighting method was used to adjust for baseline characteristics among early

(≤24 hours, n = 4133), elective (24-48 hours, n = 1137), and late (48-120 hours, n = 1000) colonoscopy. The average treatment effect was evaluated for outcomes. The primary outcome was 30-day rebleeding rate.

Results: The early group had a significantly higher rate of stigmata of recent hemorrhage (SRH) identification and a shorter length of stay than the elective and late groups. However, the 30-day rebleeding rate was significantly higher in the early group than in the elective and late groups. Interventional radiology (IVR) or surgery requirement and 30-day mortality did not significantly differ among groups. The interaction with heterogeneity of effects was observed between early and late colonoscopy and shock index (shock index <1, odds ratio [OR], 2.097; shock index ≥1, OR, 1.095; *P* for interaction = .038) and performance status (0-2, OR, 2.481; ≥3, OR, .458; *P* for interaction = .022) for 30-day rebleeding. Early colonoscopy had a significantly lower IVR or surgery requirement in the shock index ≥1 cohort (OR, .267; 95% confidence interval, .099-.721) compared with late colonoscopy.

Conclusions: Early colonoscopy increased the rate of SRH identification and shortened the length of stay but involved an increased risk of rebleeding and did not improve mortality and IVR or surgery requirement. Early colonoscopy particularly benefited patients with a shock index ≥1 or performance status ≥3 at presentation. (Gastrointest Endosc 2023;97:89-99.)

(footnotes appear on last page of article)

Colonoscopy plays both diagnostic and therapeutic roles in patients with acute lower GI bleeding (ALGIB). Although guidelines for the treatment of ALGIB have been published in the United States,[1,2] Europe,[3,4] and Asia,[5] consensus on the ideal time to perform colonoscopy is lacking. The American College of Gastroenterology,[1] the American Society for Gastrointestinal Endoscopy guidelines,[2] and the Japan Gastroenterological Association[5] recommend performing colonoscopy within 24 hours of presentation. Contrarily, the British Society of Gastroenterology[3] and the European Society of Gastrointestinal Endoscopy[4] do not recommend early colonoscopy for patients with ALGIB as part of the usual clinical practice.

Several randomized controlled trials (RCTs) revealed that early (≤24 hours) colonoscopy neither improves stigmata of recent hemorrhage (SRH) identification nor reduces rebleeding or mortality.[6-8] Systematic reviews of studies on ALGIB have concluded that although early colonoscopy is associated with higher rates of endoscopic intervention, there is no improvement in rebleeding or mortality.[9-11] One such review reported a difference in the effectiveness of early colonoscopy reported by RCTs and observational studies.[10] One possible reason for the discrepancy could be that background characteristics were balanced in the design phase and selection bias by indication was eliminated in RCTs. In contrast, this may be related to the restriction of patients enrolled in RCTs (eg, exclusion because of age, comorbidities, and severity of clinical status), which has contributed to the lower proportion of hemodynamically unstable patients in RCTs compared with that in observational studies. Considering the limited number of ALGIB patients recruited and the low incidences of rebleeding and mortality, it was considered difficult to observe significant differences for clinical outcomes in RCTs.[10] Although observational studies using insurance databases have included a large number of patients, detailed patient-level data were lacking, and it was not ideal in assessing emergency interventions such as colonoscopy and interventional radiology (IVR).[10] Additionally, no comparative studies have been performed on the nonearly (>24 hours) colonoscopy group. In an RCT from Japan,[7] most of the elective group underwent colonoscopy within 24 to 48 hours. Outcomes may differ if the timing of colonoscopy is classified into 24 to 48 hours and 48 to 120 hours, and it may be valuable to determine whether to perform colonoscopy on weekends or holidays.

We hypothesized that we could elucidate the optimal timing of colonoscopy for ALGIB and specify the patients who benefited from early colonoscopy after presentation by using a large database of detailed patient data.[12] In this multicenter cohort study, we evaluated the effects of colonoscopy timing on the clinical outcomes of patients with ALGIB. Further, we investigated the interaction between colonoscopy timing and baseline characteristics for the primary outcome and aimed to identify which patients with ALGIB benefited from early colonoscopy.

METHODS

Patients and study design

This multicenter, retrospective, cohort study was conducted in Japan using real-world data collected by gastroenterologists who were directly involved in the treatment of hematochezia between January 2010 and December 2019. The CODE-BLUE-J study has been described previously (Supplementary Table 1, available online at www.giejournal.org).[12] We identified 10,342 patients hospitalized for acute hematochezia and excluded those who did

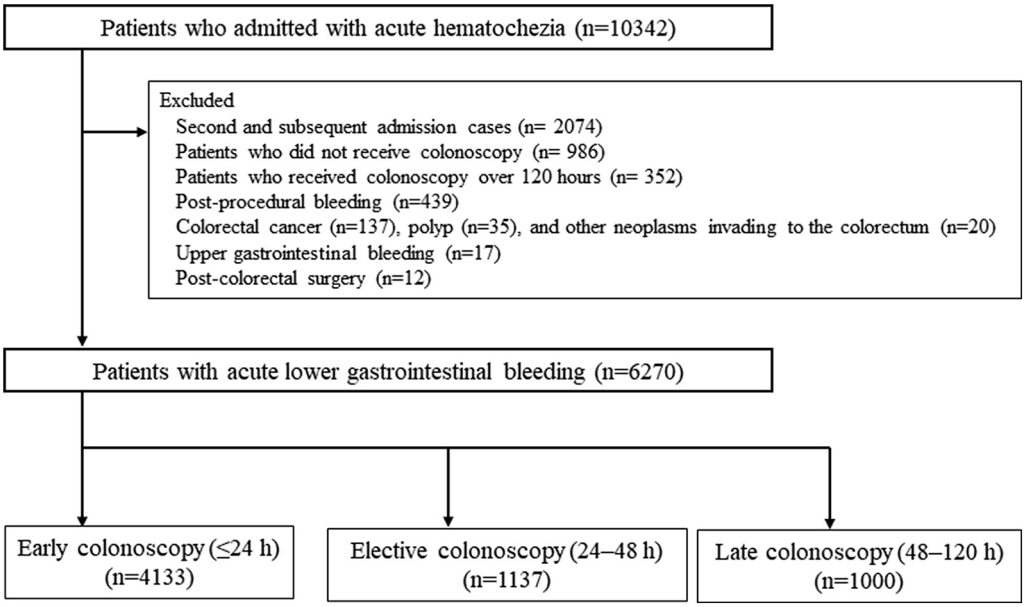


Figure 1. Study flowchart.

not undergo colonoscopy (4 patients died within 24 hours after admission, before they underwent colonoscopy, because of multiple organ failure caused by liver cirrhosis, hepatoma, or sepsis), underwent colonoscopy >120 hours after presentation, experienced postprocedural bleeding, or were diagnosed with upper GI bleeding and colorectal tumors. A few studies have noted that tumor bleeding is associated with substantially higher mortality[13,14]; hence, we excluded patients with tumor bleeding in the present study. Additionally, because we intended to compare the outcomes using the propensity score, we excluded patients with second or subsequent episodes of acute hematochezia. Ultimately, a cohort of 6270 patients with ALGIB was included and divided into the early (≤24 hours), elective (24-48 hours), and late (48-120 hours) colonoscopy groups (Fig. 1). Considering the insufficient evidence of colonoscopy after 24 hours and the management of patients with ALGIB on weekends or holidays, we set the elective and late groups.

Certain terms have been defined for this study. SRH was defined as the presence of active bleeding or detection of a nonbleeding visible vessel or an adherent clot on colonoscopy.[15] Rebleeding was defined as a significant quantity of fresh blood loss or passage of wine-colored stools after colonoscopy, associated with any of the following: systolic blood pressure <100 mm Hg, pulse rate ≥100 beats/min, or >2 g/dL decrease in hemoglobin levels.[7] Furthermore, the requirement for IVR or surgery after colonoscopy during admission was evaluated. Blood transfusion was measured by the amount of packed red blood cells (PRBCs) received during admission, and the length of stay was measured in days.

The study protocol was approved by the Institutional Ethics Committee of Tokyo Medical University (T2019-0244). A single institutional review board review was applied to this study, and approval from the ethical committees and institutional review boards of all 49 participating hospitals was obtained through the opt-out method (Supplementary Table 1). The requirement for acquiring informed consent from patients was waived because of the retrospective nature of this study.

Outcomes

The primary outcome was 30-day rebleeding rate. Secondary outcomes were the rate of SRH identification, the requirement for corrective IVR or surgery, 30-day mortality, amount of PRBCs, and length of stay. In the subgroup analyses, we aimed to clarify the characteristics of patients who benefited from early colonoscopy for 30-day rebleeding. The requirements of IVR or surgery, mortality, blood transfusion, and length of stay were considered to be located downstream of rebleeding.[10]

Statistical analyses

The characteristics of 6270 patients with ALGIB are shown in Supplementary Table 2 (available online at www.giejournal.org). Three data sets were derived from the 6270 cases: early versus elective, elective versus late, and early versus late.

Missing data were observed in this study; a missing-data analysis was performed using Little's test of missing completely at random test in each data set.[16] The probability that the data were missing completely at random was <.0001 in the 3 data sets. Because complete-case

analysis is valid only under missing completely at random,[16,17] multiple imputation was performed in each data set by chained equations,[18] fully conditional specification, or sequential generalized regression. No missing data were noted in colonoscopy timing and clinical outcomes including 30-day rebleeding, the requirement of IVR or surgery, and mortality. The outcome of 30-day rebleeding and patient characteristics were included in the imputation models, and 20 imputed sheets were created for each set.

A propensity score was constructed in each sheet of imputed data using age ≥75 years; sex[19]; body mass index ≥25 kg/m^2; current habits of smoking and drinking; performance status (PS); histories of ALGIB[19] and colorectal surgery, hypertension, diabetes mellitus, dyslipidemia, and cerebral and cardiovascular diseases; malignancy; Charlson comorbidity index score ≥3[20]; use of antiplatelets,[21,22] anticoagulants, and nonsteroidal anti-inflammatory drugs[19]; shock index ≥1[19]; syncope[21,22]; abdominal pain[21]; diarrhea[20]; hemoglobin level; albumin level[19,20]; creatinine level; C-reactive protein level; prothrombin time-international normalized ratio; platelet count; and bleeding causes for colonoscopy timing. The inverse probability of treatment weighting (IPTW) method was used to adjust for the baseline characteristics among groups, and the average treatment effect of colonoscopy timing was evaluated for outcomes on the multiply imputed data in each comparison group. The average treatment effect is an average effect on all subjects in the population. The average treatment effect of colonoscopy timing is considered the effect of the experimental arm of colonoscopy timing on all subjects in the population if patients were forced to receive the experimental arm of colonoscopy timing. A robust sandwich variance estimator was used to correctly estimate the variance and confidence interval (CI) for the pseudo-population.

Sensitivity analyses were performed by IPTW for the complete-case data (n = 4148) and multivariate logistic and linear regression for the multiply imputed data (n = 6270). SRH identification, 30-day rebleeding, corrective IVR or surgery requirement, 30-day mortality, amount of PRBCs, and length of stay were compared depending on the timing of colonoscopy.

The interaction between the timing of colonoscopy (early vs elective vs late) and baseline characteristics was investigated for 30-day rebleeding using multivariate logistic regression on multiply imputed data. If an interaction was observed, 3 data sets (early vs elective, elective vs late, and early vs late) were divided depending on the characteristics on which the interaction was observed. Multiple imputation was performed by chained equations in each divided data set. A propensity score was constructed in each sheet of the multiply imputed data, and the average treatment effect of colonoscopy timing was investigated for outcomes using the IPTW method.

A 2-tailed $P < .05$ was considered statistically significant. Multiple subgroup analyses can lead to false-positive results.[23] A P value was not demonstrated, and the magnitude and direction of treatment differences and a corresponding 95% CI were described in the subgroup analyses. Statistical analyses were performed using the Stata software, version 16 (Stata Corp LP, College Station, Tex, USA).

RESULTS

Patient characteristics

Detailed characteristics of patient with acute hematochezia were published previously in the CODE BLUE-J study report.[12] We studied 6270 patients with hematochezia who met the inclusion criteria. The characteristics of the study population are shown in Supplementary Table 2. More than 10% of the information on current smoking, current drinking, and prothrombin time-international normalized ratio was missing. However, the data of colonoscopy timing were all included in the present study. The predominant causes of ALGIB were colonic diverticular bleeding, ischemic colitis, rectal ulcer, inflammatory bowel disease, hemorrhoids, and small-bowel bleeding.

Outcomes compared among the 3 groups on weighting multiply imputed data

Of 6270 patients, 4133 (66%), 1137 (18%), and 1000 (16%) patients were categorized into the early (≤24 hours), elective (24-48 hours), and late (48-96 hours) groups, respectively (Table 1). The baseline characteristics were not balanced in observed and multiply imputed data. Therefore, weighting multiply imputed data was conducted, and most absolute standardized differences became <.1. Outcomes among the groups using observed data (Supplementary Table 3, available online at www.giejournal.org) and the IPTW method are demonstrated (Table 2). The rate of SRH identification was significantly higher in the early group: early versus elective (ref) (odds ratio [OR], 1.785; 95% CI, 1.521-2.094), elective versus late (ref) (OR, 1.505; 95% CI, 1.188-1.906), and early versus late (ref) (OR, 2.562; 95% CI, 2.089-3.143). More endoscopic therapies were performed in the early group (Supplementary Table 4, available online at www.giejournal.org). However, the results of 30-day rebleeding were diametrically opposite (Table 2). Early colonoscopy was associated with higher 30-day rebleeding: early versus elective (ref) (OR, 1.347; 95% CI, 1.119-1.622), elective versus late (ref) (OR, 1.712; 95% CI, 1.287-2.277), and early versus late (ref) (OR, 2.259; 95% CI, 1.752-2.914). No significant differences were noted in the requirement for IVR or surgery, mortality, and transfused PRBCs among the groups. Length of stay was significantly shorter in the early group than in the elective and late groups.

Our analyses did not use the Oakland score as a covariate because we created a propensity score using the covariates used to estimate the Oakland score.[3] For reference,

TABLE 1. Patient characteristics of observed, multiply imputed, and weighting multiply imputed data between colonoscopy timing (n = 6270)

	Observed data (n = 6270)						Multiply imputed data (n = 6270)			Weighting multiply imputed data (n = 6270)		
				Absolute standardized difference			Absolute standardized difference			Absolute standardized difference		
Demographic characteristics	**Early (n = 4133)**	**Elective (n = 1137)**	**Late (n = 1000)**	**Early vs elective**	**Elective vs late**	**Early vs late**	**Early vs elective**	**Elective vs late**	**Early vs late**	**Early vs elective**	**Elective vs late**	**Early vs late**
Age ≥75 y	1899 (45.9)	562 (49.4)	465 (46.5)	.034	.019	.015	.155	.145	.010	.083	.089	.014
Sex, male	2653 (64.2)	726 (63.9)	540 (54.0)	.015	.217	.232	.002	.166	.164	.025	.021	.020
Body mass index ≥25 kg/m^2	1013 (26.3)	264 (24.7)	212 (22.6)	.015	.100	.115	.091	.070	.002	.038	.124	.093
Current smoker	660 (18.2)	191 (18.8)	182 (20.7)	.022	.024	.046	.014	.083	.055	.018	.046	.010
Current alcohol user	1669 (47.3)	469 (47.8)	387 (46.0)	.012	.041	.030	.022	.022	.043	.002	.038	.038
Performance status ≥3	258 (6.3)	57 (5.1)	54 (5.4)	.077	.054	.023	.005	.049	.054	.053	.059	.010
History of lower GI bleeding	921 (22.3)	229 (20.1)	207 (20.7)	.084	.037	.047	.011	.036	.026	.064	.063	.031
History of colorectal surgery	292 (7.1)	79 (7.0)	65 (6.5)	.004	.026	.022	.019	.002	.022	.016	.006	.051
Hypertension	2341 (56.6)	638 (56.1)	526 (52.6)	.025	.082	.107	.010	.045	.035	.027	.020	.092
Diabetes mellitus	741 (17.9)	227 (20.0)	191 (19.1)	.048	.028	.021	.052	.008	.044	.022	.005	.015
Dyslipidemia	1062 (25.7)	316 (27.8)	268 (26.8)	.044	.072	.028	.037	.090	.128	.024	.114	.122
Cerebral and cardiovascular disease	588 (14.2)	194 (17.1)	149 (14.9)	.053	.057	.004	.126	.064	.062	.054	.007	.078
Malignancy*	506 (12.2)	149 (13.1)	130 (13.0)	.020	.020	0	.025	.037	.063	.005	.036	.044
Charlson comorbidity index ≥3	1006 (24.3)	300 (26.4)	248 (24.8)	.008	.001	.008	.156	.115	.041	.126	.092	.042
Medications												
Antiplatelet	1231 (29.8)	327 (28.8)	281 (28.1)	.071	.007	.078	.075	.031	.044	.086	.001	.132
Anticoagulant	564 (13.6)	156 (13.7)	100 (10.0)	.039	.066	.104	.084	.229	.146	.086	.129	.033
Nonsteroidal anti-inflammatory drugs	403 (9.8)	102 (9.0)	99 (9.9)	.036	.017	.054	.011	.133	.122	.010	.101	.149
Initial measurements												
Shock index ≥1	362 (9.0)	72 (6.4)	83 (8.4)	.136	.133	.003	0	.058	.073	.081	.115	.054
Syncope	357 (8.7)	81 (7.1)	47 (4.7)	.100	.056	.156	.029	.201	.173	.082	.105	.013
Abdominal pain	423 (10.3)	161 (14.2)	254 (25.4)	.129	.290	.418	.097	.276	.370	.025	.003	.031
Diarrhea	303 (7.4)	115 (10.1)	160 (16.0)	.101	.163	.262	.089	.206	.289	.017	.024	.022
Hemoglobin ≤11 g/dL	1919 (46.4)	556 (48.9)	453 (45.3)	.046	.032	.014	.063	.166	.102	.029	.083	.103
Albumin ≤3.0 g/dL	468 (11.8)	114 (10.4)	122 (12.6)	.028	.067	.039	.066	.040	.025	.005	.015	.049

(*continued on the next page*)

TABLE 1. Continued

Demographic characteristics	Observed data (n = 6270)			Absolute standardized difference			Multiply imputed data (n = 6270) Absolute standardized difference			Weighting multiply imputed data (n = 6270) Absolute standardized difference		
	Early (n = 4133)	Elective (n = 1137)	Late (n = 1000)	Early vs elective	Elective vs late	Early vs late	Early vs elective	Elective vs late	Early vs late	Early vs elective	Elective vs late	Early vs late
Creatinine ≤1.5 mg/dL	503 (12.2)	136 (12.0)	130 (13.1)	.047	.118	.071	.074	.167	.096	.076	.181	.123
C-reactive protein ≥5 mg/dL	155 (3.8)	60 (5.3)	64 (6.5)	.079	.037	.116	.059	.072	.131	.003	.036	.016
Prothrombin time-international normalized ratio ≥1.5	343 (9.5)	88 (8.7)	72 (7.9)	.076	.036	.040	.098	.171	.072	.123	.135	.014
Platelets ≤15 $10^4/\mu L$	608 (14.7)	170 (15.0)	147 (14.7)	.003	.011	.008	.030	.049	.021	.052	.018	.006
Bleeding causes												
Colonic diverticular bleeding †	3154 (76.3)	756 (66.5)	588 (58.8)	.218	.202	.424	.231	.067	.299	.008	.083	.067
Ischemic colitis	152 (3.7)	78 (6.9)	135 (13.5)	.175	.222	.387	.079	.218	.294	.055	.014	.043
Enterocolitis†	155 (3.8)	64 (5.6)	91 (9.1)	.092	.130	.219	.083	.140	.221	.009	.005	.008
Rectal ulcer	163 (3.9)	36 (3.2)	30 (3.0)	.039	.004	.035	.038	.036	.074	.013	.021	.034
Anal bleeding†	106 (2.6)	36 (3.2)	29 (2.9)	.059	.018	.041	0	.009	.009	.028	.002	.027
Small-bowel bleeding†	111 (2.7)	33 (2.9)	27 (2.7)	.006	.003	.002	.051	.043	.008	.037	.037	.005
Vascular ectasia	65 (1.6)	25 (2.2)	15 (1.5)	.036	.066	.031	.065	.023	.043	.028	.030	.062
Radiation colitis	39 (.9)	9 (.8)	4 (.4)	.012	.079	.067	.072	.010	.062	.066	.061	.007
Varices	12 (.3)	1 (.1)	3 (.3)	.043	.058	.016	.064		.064	.053		.064
Dieulafoy's ulcer	5 (.1)	3 (.3)	1 (.1)	.006	.005	.001	.088	.106	.037	.041	.073	.039
Other diseases†	171 (4.1)	96 (8.4)	77 (7.7)	.138	.032	.170	.256	.157	.103	.062	.145	.043

Values are n (%). The covariates used for the construction of the propensity score were well balanced in the weighting multiply imputed data.
*Malignancy included solid tumors and malignant lymphomas.
†Colonic diverticular bleeding included definitive and presumptive. Enterocolitis included infectious colitis, inflammatory bowel disease, drug-induced colitis, nonspecific ulcer, and nonspecific colitis. Anal bleeding included hemorrhoids and anal lesions such as anal laceration. Small-bowel bleeding included definitive small-bowel bleeding, presumptive small-bowel bleeding, and Meckel's diverticulum. Other diseases included miscellaneous and unknown lesions.

we also included the Oakland score in our analyses, but the results were similar.

Sensitivity analyses

We evaluated the robustness of our results by using the IPTW method of complete-case data and multivariate regression (Table 3). Baseline characteristics of weighting complete data are demonstrated in Supplementary Table 5 (available online at www.giejournal.org). The baseline characteristics were well balanced among the 3 groups in the weighting complete data. The higher rates of SRH identification and 30-day rebleeding were observed in the early group, similar to the results on weighting multiply imputed data. There were no significant differences in the requirement for IVR or surgery and transfused PRBCs among the groups. Mortality was significantly higher in the early group than in the late group (OR, 4.584; 95% CI, 1.027-20.466). Length of stay was significantly shorter in the early group than in the late group (Table 3).

Multivariate logistic regression using the multiply imputed data revealed that the rates of SRH identification and 30-day rebleeding were significantly higher in the early group (Table 3). No significant differences were observed in the requirement for IVR or surgery and mortality among the groups. Length of stay was shorter in the early group than in the elective and late groups.

Subgroup analyses based on shock index and PS

The interaction between the timing of colonoscopy (early vs elective vs late) and baseline patient characteristics was investigated for 30-day rebleeding. Interactions were observed between early and late colonoscopy and shock indices of <1 and ≥1 (P for interaction = .038)

TABLE 2. Outcomes between colonoscopy timing using inverse probability of treatment weighting on the multiply imputed data

	Identification of stigmata of recent hemorrhage		30-day rebleeding		Interventional radiology or surgery		30-day mortality		Blood transfusion (packs)		Length of stay (days)	
	OR, 95% CI	*P* value	OR, 95% CI	*P* value	OR, 95% CI	*P* value	OR, 95% CI	*P* value	Coefficient, 95% CI	*P* value	Coefficient, 95% CI	*P* value
Elective	Reference		Reference		Reference		Reference		Reference		Reference	
Early	1.785, 1.521-2.094	<.001	1.347, 1.119-1.622	.002	1.021, .676-1.541	.921	1.052, .438-2.527	.909	−.302, −.659 to .055	.097	−.820, −1.504 to −.136	.019
Late	Reference		Reference		Reference		Reference		Reference		Reference	
Elective	1.505, 1.188-1.906	.001	1.712, 1.287-2.277	<.001	.979, .579-1.655	.938	1.362, .425-4.366	.603	.433, −.003 to .868	.051	−.649, −1.752 to .454	.249
Late	Reference		Reference		Reference		Reference		Reference		Reference	
Early	2.562, 2.089-3.143	<.001	2.259, 1.752-2.914	<.001	.958, .619-1.483	.846	1.631, .580-4.586	.353	.056, −.275 to .387	.740	−1.296, −.041 to −.552	.001

P < .05 was considered to indicate statistical significance.
CI, Confidence interval; *OR*, odds ratio.

TABLE 3. Outcomes between colonoscopy timing using inverse probability of treatment weighting on the complete data and multivariate logistic regression on the multiply imputed data

	Identification of stigmata of recent hemorrhage		30-day rebleeding		Interventional radiology or surgery		30-day mortality		Blood transfusion (packs)		Length of stay (days)	
	OR, 95% CI	*P* value	OR, 95% CI	*P* value	OR, 95% CI	*P* value	OR, 95% CI	*P* value	Coefficient, 95% CI	*P* value	Coefficient, 95% CI	*P* value
inverse probability of treatment weighting on complete data												
Elective	Reference		Reference		Reference		Reference		Reference		Reference	
Early	1.914, 1.566-2.337	<.001	1.340, 1.070-1.677	.011	1.127, .683-1.860	.638	1.252, .408-3.842	.694	−.246, −.733 to .240	.321	−.844, −1.765 to .077	.073
Late	Reference		Reference		Reference		Reference		Reference		Reference	
Elective	1.285, .963-1.713	.088	1.652, 1.174-2.324	.004	1.006, .541-1.868	.986	2.297, .412-12.825	.343	.563, −.070 to 1.196	.081	−.215, −1.689 to 1.260	.776
Late	Reference		Reference		Reference		Reference		Reference		Reference	
Early	2.361, 1.848-3.015	<.001	2.047, 1.506-2.783	<.001	.960, .575-1.603	.876	4.584, 1.027-20.466	.046	.132, −.265 to .529	.515	−1.044, −1.200 to −.088	.032
Multivariate logistic and linear regression on multiply imputed data												
Late	Reference		Reference		Reference		Reference		Reference		Reference	
Elective	1.595, 1.252-2.031	<.001	1.755, 1.320-2.333	<.001	.966, .569-1.639	.897	1.336, .378-4.721	.653	.405, .046 -.765	.027	−.640, −1.450 to .170	.121
Early	2.934, 2.396-3.593	<.001	2.409, 1.889-3.072	<.001	.968, .628-1.493	.883	1.148, .392-3.360	.801	.041, −.256 to .338	.787	−1.578, −2.248 to −.908	<.001
Elective	Reference		Reference		Reference		Reference		Reference		Reference	
Early	1.840, 1.562-2.166	<.001	1.372, 1.140-1.652	.001	1.003, .666-1.510	.990	.860, .331-2.232	.756	−.364, −.642 to −.087	.010	−.937, −1.563 to −.312	.003

P < .05 was considered to indicate statistical significance.
CI, Confidence interval; *OR*, odds ratio.

TABLE 4. Subgroup analyses depending on shock index and performance status on the weighting multiply imputed data

	Shock index <1	Shock index ≥1	Performance status 0-2	Performance status ≥3
	OR, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI
Early vs elective (reference)				
30 day-rebleeding	1.317, 1.084-1.599	1.784, .824-3.863	1.384, 1.143-1.676	1.116, .465-2.677
IVR or surgery	1.015, .657-1.568	.659, .172-2.527	1.030, .673-1.577	1.000, .208-4.801
30 day-mortality	.850, .328-2.204	6.475, .768-54.591	1.981, .547-7.176	.433, .123-1.517
	Coefficient, 95% CI	Coefficient, 95% CI	Coefficient, 95% CI	Coefficient, 95% CI
Blood transfusion	−.324, −.690 to .042	.344, −1.374 to 2.061	−.301, −.675 to .073	−.219, −1.532 to 1.094
Length of stay	−.831, −1.527 to −.135	−.934, −4.460 to 2.592	−.787, −1.451 to −.123	−.356, −4.677 to 3.965
Elective vs late (reference)				
	OR, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI
30-day rebleeding	1.853, 1.358-2.528	.553, .221-1.385	1.783, 1.322-2.406	1.116, .366-3.402
IVR or surgery	1.262, .695-2.292	2.135, .331-13.756	1.039, .600-1.800	.688, .105-4.499
30-day mortality	1.166, .350-3.883	1	.881, .194-4.005	4.493, .412-48.993
	Coefficient, 95% CI	Coefficient, 95% CI	Coefficient, 95% CI	Coefficient, 95% CI
Blood transfusion	.473, .021-.926	2.031, −2.184 to 6.245	.487, .031-.943	.579, −1.077 to 2.236
Length of stay	.032, −.937 to 1.000	−2.769, −14.701 to 9.164	−.532, −1.657 to .593	−1.609, −7.308 to 4.091
Early vs late (reference)				
	OR, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI
30-day rebleeding	2.097, 1.553-2.832	1.095, .541-2.218	2.481, 1.898-3.244	.458, .164-1.278
IVR or surgery	1.337, .778-2.297	.267, .099-.721	1.026, .648-1.625	.341, .056-2.091
30-day mortality	1.121, .418-3.008	1	1.667, .526-5.278	1.098, .132-9.119
	Coefficient, 95% CI	Coefficient, 95% CI	Coefficient, 95% CI	Coefficient, 95% CI
Blood transfusion	.108, −.228 to .444	−1.044, −2.935 to .847	.093, −.225 to .411	−1.002, −4.519 to 2.515
Length of stay	−.887, −1.527 to −.247	-4.402, −9.321 to .518	−1.244, −1.963 to −.524	−1.866, −6.817 to 3.087

CI, Confidence interval; *IVR*, interventional radiology; *OR*, odds ratio.

and PS 0 to 2 and PS ≥3 (P for interaction = .022) regarding 30-day rebleeding (Table 4). Although there was a higher OR of early and late colonoscopy to 30-day rebleeding for both a shock indices of <1 and ≥1 (OR, 2.097; 95% CI, 1.553-2.832 and OR, 1.095; 95% CI, .541-2.218, respectively), the direction of OR of early and late colonoscopy to 30-day rebleeding was opposite in the PS 0 to 2 and PS ≥3 cohorts (OR, 2.481; 95% CI, 1.898-3.244 and OR, .458; 95% CI, .164-1.278, respectively). In addition, the early group had a significantly decreased IVR or surgery requirement in the shock index ≥1 cohort compared with the late group (OR, .267; 95% CI, .099-.721).

DISCUSSION

This large retrospective study was conducted to determine the optimal timing of colonoscopy for patients with ALGIB. Although early colonoscopy was associated with higher SRH identification allowing more frequent endoscopic hemostasis and a shorter length of stay, the 30-day rebleeding rate was significantly higher than elective and late colonoscopy. Conversely, the rates of 30-day rebleeding and IVR or surgery requirement were lower in early colonoscopy for patients with shock index ≥1 or PS ≥3 than in late colonoscopy.

Previous RCTs showed that early (≤24 hours) colonoscopy for ALGIB did not improve SRH identification[7] and did not reduce rebleeding or mortality.[6,7] Moreover, a single-center RCT revealed that urgent (≤12 hours) compared with nonurgent (>36 hours) colonoscopy for ALGIB did not improve further bleeding.[8] However, this RCT was discontinued during patient enrollment because of the difficulty in reaching the prespecified sample size, which was a significant limitation of the study. The findings were associated with a potential risk of Type II error and lack of generalizability. Contrarily, 5 retrospective studies[24-28] and 3 systematic reviews[9-11] suggested that early (≤24 hours) colonoscopy may increase the yield of endoscopic intervention, decrease the length of stay, and reduce the requirement for blood transfusion. However, none has demonstrated benefits in reducing rebleeding rates or mortality, a finding corroborated by our study. This differences between RCTs and observational studies may be associated with the restriction of patients enrolled in RCTs (eg, exclusion because of high age, comorbidities, and unstable status) and selection bias by indication.

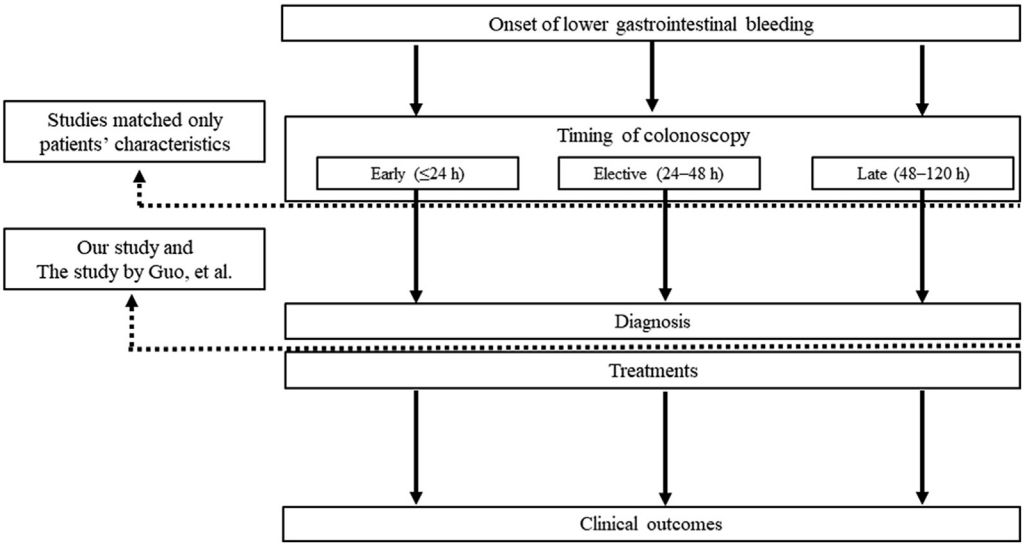


Figure 2. Schema of colonoscopy timing for acute lower GI bleeding. Considering the onset of GI bleeding, causes of bleeding precede the allocation of endoscopy timing and are not changed by colonoscopy timing. The causes of bleeding were considered the confounders between colonoscopy timing and clinical outcomes from the viewpoint of causal inference. The causes of bleeding and confounders were not omitted in the analysis of the association between colonoscopy timing and clinical outcomes in the cohort study that matched patient characteristics.

Our study potentially helps estimate the optimal timing of colonoscopy by comparing outcomes among early, elective, and late colonoscopy groups. In addition to our large database with detailed patient data, no studies have been done on colonoscopy conducted after 24 hours of presentation. The early group experienced a higher rate of SRH identification, whereas a higher 30-day rebleeding rate was observed. This may be explained by the fact that bleeding stops spontaneously in most ALGIB patients,[29] and ALGIB patients may be triaged as those requiring interventions through subsequent colonoscopy. Although the requirements for IVR or surgery and mortality were not different based on the colonoscopy timing, early colonoscopy was significantly associated with a shorter length of stay in the present study. Because this design was a multicenter observational study and an indication for extending the length of stay was not prespecified, the length of stay may be dependent on the timing of colonoscopy and the preference of each gastroenterologist. Outcomes such as 30-day rebleeding, IVR or surgery requirement, and mortality did not differ between elective and late colonoscopy. These results may be valuable, especially in the areas in which there is no timely availability of staff and other support services after work hours on weekends and holidays.

We observed interactions between early and late colonoscopy and patient characteristics (PS and shock index) for 30-day rebleeding, and a subgroup analyses based on PS 0 to 2 and PS ≥3 and shock indices of <1 or ≥1 were performed. The direction and the magnitude of ORs for 30-day rebleeding were different between patients with PS 0 to 2 and PS ≥3. Therefore, PS was determined to be a modifier of the qualitative effect of colonoscopy timing on 30-day rebleeding. Although the magnitude of ORs for rebleeding was different between patients with shock indices of <1 and ≥1, the direction of ORs was the same. The shock index was the quantitative effect modifier between early and late colonoscopy on 30-day rebleeding. However, the direction and magnitude of ORs were different between shock indices of <1 and ≥1 for IVR or surgery requirement. Early colonoscopy significantly decreased the risk of requiring IVR or surgery in patients with shock index ≥1 compared with late colonoscopy.

To find the reason for the interaction, we compared the causes of bleeding by subgroups on shock index and PS. The results of the comparison of bleeding causes regarding shock index and PS subgroups are demonstrated in Supplementary Table 6 (available online at www.giejournal.org). The proportion of rectal ulcer was significantly higher in the PS ≥3 subgroup than in the PS 0 to 2 subgroup. Significant differences were observed in colonic diverticular bleeding, ischemic colitis, rectal ulcer, small-bowel bleeding, colorectal varices, and Dieulafoy's ulcer between shock indices of <1 and ≥1. The different causes of bleeding may contribute to the effectiveness of colonoscopy timing through baseline characteristics of shock index and PS. Because the guideline of the British Society of Gastroenterology recommends the use of a shock index as a risk stratification tool for patients with ALGIB, and IVR and endoscopic therapy were considered the treatment options depending on the results of enhanced CT in patients with shock index ≥1,[3] our results support the management algorithm of this guideline.

The difference in analyses between our study and other studies may be explained by adjusting the bleeding causes. We used the IPTW method as previously conducted by Guo et al,[30] who performed an observational study of endoscopy timing for upper GI bleeding. Considering the

onset of GI bleeding, the causes of bleeding may precede the allocation of endoscopy timing. Bleeding causes were included for the construction of the propensity score to eliminate the confounding effect of bleeding causes in our study (Fig. 2). In the previous observational study, the proportion of bleeding causes was significantly different among the timing of endoscopy.[10] Certainly, in our study, when baseline characteristics except for causes of bleeding were balanced on our weighted data (Supplementary Table 7, available online at www.giejournal.org), the absolute standardized differences were >.2 regarding the cause of bleeding (Supplementary Table 8, available online at www.giejournal.org). When observational studies of endoscopy timing for GI bleeding are being planned as quasi-RCTs, it may be better to manage the causes of bleeding as covariates to be balanced.[28]

The notable strength of this study was the large population that was analyzed for the influence of pertinent confounding factors on colonoscopy timing such as clinical status, blood investigation findings, comorbidities, and concomitant medications.[12] Essentially, the proportion of hemodynamically unstable patients is higher in observational studies, including the present study, than in RCTs (6.0%-47.2%[24,26] vs .02%-5.1%[6,7]). Furthermore, we investigated the characteristics of patients who benefit from early colonoscopy.

The limitations of this study are its retrospective and observational design. However, we applied robust inclusion and exclusion criteria to eliminate selection bias as much as possible and maintained internal validity. Conversely, the generalizability of results from RCTs may sometimes be reduced because of the differences in patient characteristics between RCTs and observational studies. Second, unmeasured confounders may still exist in the IPTW method. Finally, our study only included patients who received colonoscopy. Patients who received colonoscopy had relatively greater ALGIB severity, and this may be a limitation of generalizability. Nonetheless, by using interaction analysis, we were able to identify the patient characteristics that were considered as indications for early colonoscopy.

In summary, we have demonstrated that early colonoscopy improved SRH identification and shortened the length of stay. However, early colonoscopy was associated with a higher 30-day rebleeding rate and did not improve IVR or surgery requirement or mortality. Early colonoscopy was beneficial for those with a shock index $\geq$1 or PS $\geq$3. Therefore, most ALGIB patients do not need to receive colonoscopy immediately but rather vitals and PS can be an indication of the requirement for early colonoscopy. Further RCTs are warranted to clarify these findings.

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Abbreviations: ALGIB, acute lower GI bleeding; CI, confidence interval; IPTW, inverse probability of treatment weighting; IVR, interventional radiology; OR, odds ratio; PRBC, packed red blood cell; PS, performance status; RCT, randomized controlled trial; SRH, stigmata of recent hemorrhage.

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Current affiliations: Department of Gastroenterology, St Luke's International University, Tokyo, Japan (1), Department of Gastroenterology, Tokyo Shinagawa Hospital, Tokyo, Japan (2), Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan (3), Department of Gastroenterology, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan (4), Department of Gastroenterology and Hepatology, Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Japan (5), Department of Gastroenterology, Nippon Medical School, Graduate School of Medicine, Tokyo, Japan (6), Department of Gastroenterology, Hiroshima City Asa Citizens Hospital, Hiroshima, Japan (7), Department of Gastroenterology, Saga Medical Center Koseikan, Saga, Japan (8), Division of Gastroenterology and Hepatology, Department of Internal Medicine, St Marianna University School of Medicine, Kanagawa, Japan (9), Department of Gastroenterology and Hepatology, Center for Digestive and Liver Diseases, Nara City Hospital, Nara, Japan (10), Department of Endoscopy, Nagoya University Hospital, Aichi, Japan (11), Department of Gastroenterology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan (12), Department of Gastroenterology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan (13), Department of Gastroenterology, Oita University, Oita, Japan (14), Department of Gastroenterology, Fukuoka University Chikushi Hospital, Fukuoka, Japan (15), Department of Gastroenterology, Chiba Hokusoh Hospital, Nippon Medical School, Chiba, Japan (16), Department of Gastroenterology, Japanese Red Cross Shizuoka Hospital, Shizuoka, Japan (17), Division of Endoscopy and Ultrasonography, Department of Clinical Pathology and Laboratory Medicine, Kawasaki Medical School General Medical Center, Okayama, Japan (18), Division of Gastroenterology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan (19), Department of Gastroenterology and Hepatology, Center for Digestive Disease and Division of Endoscopy, University of Miyazaki Hospital, Miyazaki, Japan (20), Department of Gastroenterology, University of Tsukuba, Ibaraki, Japan (21), Division of Endoscopic Center, University of Tsukuba Hospital, Ibaraki, Japan (22), Department of Gastroenterology, Toranomon Hospital, Tokyo, Japan (23), Department of Emergency Medicine, Fujita Health University Hospital, Aichi, Japan (24), Emergency and Critical Care Center, Saiseikai Yokohamashi Tobu Hospital, Kanagawa, Japan (25), Department of Gastroenterology, Naha City Hospital, Okinawa, Japan (26), Department of Internal Medicine, Tokyo Saiseikai Central Hospital, Tokyo, Japan (27), Department of Gastroenterology, Shuto General Hospital, Yamaguchi, Japan (28), Division of Endoscopy, Hirosaki University Hospital, Aomori, Japan (29), Department of Gastroenterology and Hepatology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan (30), Department of Gastroenterology and Hepatology, National Hospital Organization Fukuokahigashi Medical Center, Fukuoka, Japan (31), Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan (32), Department of Gastroenterology, Fukushima Medical University, Fukushima, Japan (33), Division of Gastroenterology, Department of Internal Medicine, Iwate Medical University, Iwate, Japan (34), Department of Internal Medicine, National Defense Medical College, Saitama, Japan (35), Division of Endoscopy and Ultrasonography, Department of Clinical Pathology and Laboratory Medicine, Kawasaki Medical School, Okayama, Japan (36), Department of Gastroenterology and Hepatology, Suita Municipal Hospital, Osaka, Japan (37), Department of Endoscopy, University of the Ryukyus Hospital, Okinawa, Japan (38), Department of Gastroenterology, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan (39), Department of Gastroenterological Endoscopy, Fukuoka University Hospital, Fukuoka, Japan (40), Department of Gastroenterology, Kitasato University, School of Medicine, Kanagawa, Japan (41), Department of Gastroenterology and Neurology, Akita University Graduate School of Medicine, Akita, Japan (42), Digestive and Lifestyle Diseases, and Hygiene and Health Promotion Medicine, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan (43), Department of Gastroenterological Endoscopy, Tokyo Medical University, Tokyo, Japan (44), Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Tokyo, Japan (45).

Reprint requests: Naoki Ishii, MD, PhD, MPH, Department of Gastroenterology, Tokyo Shinagawa Hospital, 6-3-22 Higashi-Ooi, Shinagawa-ku, Tokyo 140-8522, Japan. E-mail: naoishi0328@gmail.com; or Naoyoshi Nagata, MD, PhD, Department of Gastroenterological Endoscopy, Tokyo Medical University, Tokyo, Japan. E-mail: nnagata_ncgm@yahoo.co.jp.

SUPPLEMENTARY TABLE 1. Affiliations of and ethics committee approval numbers from 49 participating hospitals

	Institution	Prefecture	Department	Ethics committee approval no.	Period of data collection	No. of cases
1	Tokyo Medical University	Tokyo	Department of Gastroenterological Endoscopy	T20190244	2013.01.02 to 2019.11.13	134
2	National Center for Global Health and Medicine	Tokyo	Department of Gastroenterology and Hepatology	3539	2010.01.19 to 2019.06.18	1375
3	Tokyo Shinagawa Hospital	Tokyo	Department of Gastroenterology	20-A-04	2014.07.28 to 2019.12.30	250
4	Nippon Medical School, Graduate School of Medicine	Tokyo	Department of Gastroenterology	B-2020-147	2014.10.31 to 2019.12.23	538
5	Chiba Hokusoh Hospital, Nippon Medical School	Chiba	Department of Gastroenterology	802	2011.08.28 to 2019.12.23	188
6	Saga Medical Center Koseikan	Saga	Department of Gastroenterology	20-01-01-03	2013.01.02 to 2019.12.30	394
7	St Luke's International University	Tokyo	Department of Gastroenterology	20-R012	2014.01.03 to 2019.12.29	536
8	Kawasaki Medical School	Okayama	Division of Endoscopy and Ultrasonography, and Department of Clinical Pathology and Laboratory Medicine	3890	2014.03.27 to 2018.2.18	156
9	Kawasaki Medical School General Medical Center	Okayama	Division of Endoscopy and Ultrasonography, and Department of Clinical Pathology and Laboratory Medicine	3890	2012.02.07 to 2017.12.27	88
10	University of Tsukuba	Ibaraki	Department of Gastroenterology, and Division of Endoscopic Center	R02-030	2013.01.02 to 2019.12.30	134
11	Tokyo Metropolitan Bokutoh Hospital	Tokyo	Department of Gastroenterology	02-024	2013.04.02 to 2019.12.31	808
12	Saiseikai Yokohamashi Tobu Hospital	Kanagawa	Emergency and Critical Care Center	20200030	2011.01.22 to 2019.12.17	131
13	The University of Tokyo	Tokyo	Department of Gastroenterology	2020067NI	2010.01.04 to 2018.08.10	542
14	Toranomon Hospital	Tokyo	Department of Gastroenterology	2021	2011.04.02 to 2019.12.04	134
15	Nagoya University Hospital	Aichi	Department of Endoscopy	2020-0152	2016.01.02 to 2019.12.27	206
16	Hiroshima City Asa Citizens Hospital	Hiroshima	Department of Gastroenterology	2002/1/24	2010.01.02 to 2019.12.27	517
17	National Hospital Organization Fukuokahigashi Medical Center	Fukuoka	Department of Gastroenterology and Hepatology	2020-臨-2	2017.04.02 to 20.9.12.3	107
18	Nara City Hospital	Nara	Department of Gastroenterology and Hepatology, and Center for Digestive and Liver Diseases	NCH倫20-8	2013.05.02 to 2019.12.25	264

(*continued on the next page*)

SUPPLEMENTARY TABLE 1. Continued

	Institution	Prefecture	Department	Ethics committee approval no.	Period of data collection	No. of cases
19	Graduate School of Medical and Dental Sciences, Niigata University	Niigata	Division of Gastroenterology	2020-0052	2010.8.28 to 2019.12.18	142
20	St Marianna University School of Medicine	Kanagawa	Division of Gastroenterology and Hepatology, Department of Internal Medicine	4802	2013.08.12 to 2019.12.13	343
21	Oita University	Oita	Department of Gastroenterology	1845	2010.03.06 to 2019.12.03	199
22	Tokyo Saiseikai Central Hospital	Tokyo	Department of Internal Medicine	2020-015-01	2017.01.09 to 2019.12.29	120
23	Fukuoka University Hospital	Fukuoka	Department of Gastroenterological Endoscopy	U20-05-016	2016.03.30 to 2019.12.12	80
24	Fukuoka University Chikushi Hospital	Fukuoka	Department of Gastroenterology	C20-052	2010.01.05 to 2017.03.04	199
25	Kitano Hospital, Tazuke Kofukai Medical Research Institute	Osaka	Department of Gastroenterology and Hepatology	P200500400	2010.1.24 to 2019.12.21	586
26	Graduate School of Medical Sciences, Kyushu University	Fukuoka	Department of Medicine and Clinical Science	2020-289	2010.05.30 to 2019.12.25	101
27	University of Miyazaki Hospital	Miyazaki	Department of Gastroenterology and Hepatology, and Center for Digestive Disease and Division of Endoscopy	0-0734	2010.07.16 to 2019.10.20	142
28	University of the Ryukyus Hospital	Okinawa	Department of Endoscopy	1656	2016.01.04 to 2019.12.08	86
29	Naha City Hospital	Okinawa	Department of Gastroenterology	2004a4	2018.11.02 to 2019.12.26	121
30	Kagoshima University Graduate School of Medical and Dental Sciences	Kagoshima	Digestive and Lifestyle Diseases	200041疫	2019.02.26 to 2019.10.07	7
31	Kagoshima City Hospital	Kagoshima	Department of Gastroenterology	2020-25	2019.01.27 to 2019.12.27	45
32	Kagoshima Kouseiren Hospital	Kagoshima	Department of Gastroenterology	215	2019.01.03 to 2019.12.25	28
33	Kagoshima Medical Center	Kagoshima	Department of Gastroenterology	2020-22	2019.01.01 to 2019.12.25	40
34	Izumi General Medical Center	Kagoshima	Department of Gastroenterology	60	2019.01.08 to 2019.12.26	34
35	Kirishima City Medical Association Medical Center	Kagoshima	Department of Gastroenterology	202005	2019.01.16 to 2019.10.12	19
36	Kagoshima Prefectural Oshima Hospital	Kagoshima	Department of Gastroenterology	97	2018.12.25 to 2019.12.27	23

(*continued on the next page*)

SUPPLEMENTARY TABLE 1. Continued

	Institution	Prefecture	Department	Ethics committee approval no.	Period of data collection	No. of cases
37	National Hospital Organization Kyoto Medical Center	Kyoto	Department of Gastroenterology	20-020	2011.05.31 to 2019.12.20	205
38	Fukushima Medical University	Fukushima	Department of Gastroenterology	一般2020-112	2013.12.07 to 2019.12.26	100
39	Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital	Tokyo	Department of Gastroenterology	2503	2010.06.15 to 2019.12.16	205
40	Kitasato University, School of Medicine	Kanagawa	Department of Gastroenterology	C20-174	2010.10.07 to 2019.12.26	76
41	Suita Municipal Hospital	Osaka	Department of Gastroenterology and Hepatology	2020-研2	2011.03.04 to 2019.12.30	88
42	Akita University Graduate School of Medicine	Akita	Department of Gastroenterology and Neurology	2491	2010.09.22 to 2019.05.11	69
43	Japanese Red Cross Shizuoka Hospital	Shizuoka	Department of Gastroenterology	Jun-20	2010.01.08 to 2019.12.30	173
44	Hirosaki University Hospital	Aomori	Division of Endoscopy	2020-32	2010.04.16 to 2019.12.28	112
45	Graduate School of Medical Sciences, Kumamoto University	Kumamoto	Department of Gastroenterology and Hepatology	2040	2010.01.03 to 2019.12.22	111
46	National Hospital Organization Kyushu Medical Center	Fukuoka	Department of Gastroenterology	20C065	2010.4.12 to 2019.12.23	82
47	Iwate Medical University	Iwate	Department of Internal Medicine	MH2020-050	2015.01.07 to 2019.7.19	98
48	Shuto General Hospital	Yamaguchi	Department of Gastroenterology	H31-24	2014.07.25 to 2019.08.19	114
49	National Defense Medical College	Saitama	Department of Internal Medicine	4217	2010.04.12 to 2019.12.07	92

SUPPLEMENTARY TABLE 2. Characteristics of patients with acute lower GI bleeding (n = 6270)

	Study population	Missing data
Demographic characteristics		
Mean age, y (SD)	70.7 (14.3)	0
Age ≥75 y	2926 (46.7)	0
Sex, male	3919 (62.5)	0
Mean body mass index, kg/m^2 (SD)	22.8 (3.9)	413
Body mass index ≥25 kg/m^2	1489 (25.4)	413
Current smoker	1033 (18.7)	757
Current alcohol user	2525 (47.2)	922
Performance status ≥3	369 (6.0)	78
History of lower GI bleeding	1357 (21.6)	0
History of colorectal surgery	436 (7.0)	2
Hypertension	3505 (55.9)	0
Diabetes mellitus	1159 (18.5)	0
Dyslipidemia	1646 (26.3)	1
Cerebral and cardiovascular disease	931 (14.9)	1
Malignancy*	785 (12.5)	0
Charlson comorbidity index ≥3	1554 (24.8)	0
Medications		
Antiplatelet	1839 (29.3)	0
Low-dose aspirin	1317 (21.0)	0
Thienopyridine	647 (10.3)	0
Cilosotazol	143 (2.3)	0
Other antiplatelet	193 (3.1)	0
Anticoagulant	820 (13.1)	0
Warfarin	459 (7.3)	0
Direct oral anticoagulants	361 (5.8)	0
Nonsteroidal anti-inflammatory drugs	604 (9.6)	0
Initial measurements		
Shock index ≥1	517 (8.4)	125
Systolic blood pressure ≤100 mm Hg	867 (14.1)	105
Heart rate ≥100 beats/min	1246 (20.3)	122
Syncope	485 (7.7)	9
Abdominal pain	838 (13.4)	11
Diarrhea	578 (9.3)	23
Mean hemoglobin, g/dL (SD)	11.0 (2.6)	2
Hemoglobin ≤11 g/dL	2928 (46.7)	2
Mean albumin, g/dL (SD)	3.63 (.59)	253
Albumin ≤3.0 g/dL	704 (11.7)	253
Mean creatinine, mg/dL (SD)	1.17 (1.31)	27
Creatinine ≤1.5 mg/dL	769 (12.3)	27
Mean C-reactive protein, mg/dL (SD)	.90 (2.44)	130
C-reactive protein ≥5 mg/dL	279 (4.5)	130
Mean prothrombin time-international normalized ratio (SD)	1.14 (.59)	723
Prothrombin time-international normalized ratio ≥1.5	503 (9.1)	723
Mean platelets, $10^4/\mu L$ (SD)	21.7 (8.3)	1

(*continued on the next page*)

SUPPLEMENTARY TABLE 2. Continued

	Study population	Missing data
Platelets ≤15 $10^4/\mu L$	925 (14.8)	1
Mean time of colonoscopy, h (SD)	24.2 (27.0)	0
Diagnoses		
Colonic diverticular bleeding	4498 (71.7)	0
Definitive Colonic diverticular bleeding	1726 (27.5)	0
Presumptive colonic diverticular bleeding	2771 (44.2)	0
Colonic diverticulitis	1 (.0)	0
Ischemic colitis	365 (5.8)	0
Enterocolitis	310 (4.9)	0
Infectious colitis	75 (1.2)	0
Inflammatory bowel disease	150 (2.4)	0
Drug-induced colitis	9 (.1)	0
Nonspecific ulcer	46 (.7)	0
Nonspecific colitis	30 (.5)	0
Rectal ulcer	229 (3.7)	0
Anal bleeding	171 (2.7)	0
Hemorrhoids	161 (2.6)	0
Anal lesions	10 (.2)	0
Small-bowel bleeding	171 (2.7)	0
Definitive small-bowel bleeding	71 (1.1)	0
Presumptive small-bowel bleeding	89 (1.4)	0
Meckel's diverticulum	11 (.2)	0
Vascular ectasia	105 (1.7)	0
Radiation colitis	52 (.8)	0
Varices	16 (.3)	0
Dieulafoy's ulcer	9 (.1)	0
Other diseases	344 (5.5)	0
Miscellaneous†	26 (.4)	0
Unknown	318 (5.1)	0
Outcomes		
Stigmata of recent hemorrhage identification	1813 (28.9)	0
Endoscopic therapy	1738 (27.7)	0
Clipping	1029 (16.4)	0
Ligation	548 (8.7)	0
Coagulation	158 (2.5)	0
30-day rebleeding	1103 (17.6)	0
Interventional radiology or surgery	178 (2.8)	0
30-day mortality	37 (.6)	0
Mean blood transfusion, packs (SD)	1.99 (4.52)	0
Mean length of stay, days (SD)	9.72 (10.26)	0

Values are n (%) unless otherwise defined. Colonic diverticular bleeding is the most common cause (71.7%). More than 10% of the information of current smoking, current drinking, and prothrombin time-international normalized ratio was missed.

SD, Standard deviation.

*Malignancy included solid tumors and malignant lymphomas.

†Miscellaneous (n = 26) included mucosal bleeding (n = 7), colorectal laceration (n = 4), mucosal prolapse syndrome (n = 4), pseudoaneurysm (n = 2), hematoma (n = 2), fistula or penetration into the colorectum (n = 2), mucosal lymphoid hyperplasia (n = 1), Kaposi's sarcoma (n = 1), stoma-related bleeding (n = 1), graft-versus-host disease (n = 1), and Cronkite-Canada syndrome (n = 1).

SUPPLEMENTARY TABLE 3. Outcomes between colonoscopy timing on the observed data (n = 6270)

	Early (n = 4133)	Elective (n = 1137)	Late (n = 1000)	*P* value
Stigmata of recent hemorrhage identification	1442 (34.9)	240 (21.1)	131 (13.1)	<.001
Endoscopic therapy	1352 (32.7)	249 (21.9)	137 (13.7)	<.001
Clipping	809 (19.6)	146 (12.8)	74 (7.4)	<.001
Ligation	426 (10.3)	74 (6.5)	48 (4.8)	<.001
Coagulation	112 (2.7)	30 (2.6)	16 (1.6)	.13
30-day rebleeding	856 (20.7)	165 (14.5)	82 (8.2)	<.001
Interventional radiology or surgery	119 (2.9)	31 (2.7)	28 (2.8)	.96
30-day mortality	25 (.6)	7 (.6)	5 (.5)	.92
Mean blood transfusion, packs (SD)	1.97 (4.21)	2.25 (5.72)	1.76 (4.22)	.043
Mean length of stay, days (SD)	9.19 (8.84)	10.24 (11.62)	11.33 (13.40)	<.001

Values are n (%) unless otherwise defined. $P < .05$ was considered to indicate statistical significance.
SD, Standard deviation.

SUPPLEMENTARY TABLE 4. Endoscopic therapies between colonoscopy timing using inverse probability of treatment weighting on the multiply imputed data

	Endoscopic therapies		Clipping		Ligation		Coagulation	
	OR, 95% CI	*P* value	OR, 95% CI	*P* value	OR, 95% CI	*P* value	OR, 95% CI	*P* value
Elective	Reference		Reference		Reference		Reference	
Early	1.524, 1.301-1.785	<.001	1.478, 1.218-1.794	<.001	1.448, 1.116-1.879	.005	.997, .655-1.516	.987
Late	Reference		Reference		Reference		Reference	
Elective	1.488, 1.179-1.877	.001	1.575, 1.168-2.123	.003	1.228, .840-1.793	.289	1.302, .698-2.428	.407
Late	Reference		Reference		Reference		Reference	
Early	2.227, 1.822-2.722	<.001	2.317, 1.791-2.998	<.001	1.674, 1.216-2.303	.002	1.294, .732-2.290	.375

$P < .05$ was considered to indicate statistical significance.
CI, Confidence interval; *OR*, odds ratio.

SUPPLEMENTARY TABLE 5. Patient characteristics of weighting complete data between colonoscopy timing (n = 4148)

Demographic characteristics	Early (n = 2679)	Elective (n = 781)	Late (n = 688)	Absolute standardized difference		
				Early vs elective	Elective vs late	Early vs late
Age ≥75 y	1207 (45.1)	365 (46.7)	315 (45.8)	0	.005	.005
Sex, male	1748 (65.2)	504 (64.5)	371 (53.9)	0	.003	.021
Body mass index ≥25 kg/m^2	704 (26.3)	200 (25.6)	147 (21.4)	.003	.003	.006
Current smoker	481 (18.0)	147 (18.8)	136 (19.8)	.003	.006	.001
Current alcohol user	1274 (47.6)	376 (48.1)	317 (46.1)	.001	.002	.008
Performance status ≥3	142 (5.3)	29 (3.7)	33 (4.8)	.010	.001	.002
History of lower GI bleeding	617 (23.0)	153 (19.6)	145 (21.1)	0	.001	.001
History of colorectal surgery	186 (6.9)	55 (7.0)	44 (6.4)	.003	0	.011
Hypertension	1556 (58.1)	444 (56.9)	363 (52.8)	.001	.007	.014
Diabetes mellitus	504 (18.8)	162 (20.7)	135 (19.6)	.007	.010	.007
Dyslipidemia	746 (27.8)	233 (29.8)	183 (26.6)	.011	.008	.022
Cerebral and cardiovascular disease	401 (15.0)	132 (16.9)	102 (14.8)	.005	.004	.011
Malignancy*	362 (13.5)	111 (14.2)	93 (13.5)	.001	.001	.025
Charlson comorbidity index ≥3	695 (25.9)	200 (25.6)	176 (25.6)	.005	.002	.020
Medications						
Antiplatelet	831 (31.0)	217 (27.8)	189 (27.5)	.003	.001	.020
Anticoagulant	389 (14.5)	103 (13.2)	76 (11.0)	.017	0	.003
Nonsteroidal anti-inflammatory drugs	276 (10.3)	72 (9.2)	60 (8.7)	.019	.001	.003
Initial measurements						
Shock index ≥1	259 (9.7)	47 (6.0)	66 (9.6)	0	.005	.010
Syncope	243 (9.1)	50 (6.4)	35 (5.1)	.010	.004	.008
Abdominal pain	277 (10.3)	114 (14.6)	180 (26.2)	.003	.005	.007
Diarrhea	198 (7.4)	80 (10.2)	108 (15.7)	.014	0	.015
Hemoglobin ≤11 g/dL	1235 (46.1)	378 (48.4)	322 (46.8)	.006	.002	.007
Albumin ≤3.0 g/dL	305 (11.4)	82 (10.5)	87 (12.6)	.007	.001	.016
Creatinine ≤1.5 mg/dL	332 (12.4)	85 (10.9)	102 (14.8)	.003	.001	.003
C-reactive protein ≥5 mg/dL	97 (3.6)	41 (5.2)	42 (6.1)	.008	.005	.003
Prothrombin time-international normalized ratio ≥1.5	244 (9.1)	55 (7.0)	55 (8.0)	.009	0	.010
Platelets ≤15 10^4/μL	397 (14.8)	115 (14.7)	104 (15.1)	.001	.005	.006
Bleeding causes						
Colonic diverticular bleeding†	2080 (77.6)	531 (68.0)	401 (58.3)	.008	.005	.007
Ischemic colitis	88 (3.3)	56 (7.2)	96 (14.0)	0	.003	.001
Enterocolitis†	99 (3.7)	44 (5.6)	62 (9.0)	.003	.004	.007
Rectal ulcer	90 (3.4)	21 (2.7)	19 (2.8)	.008	.004	.005
Anal bleeding†	57 (2.1)	24 (3.1)	19 (2.8)	.005	.005	.001
Small-bowel bleeding†	71 (2.7)	20 (2.6)	18 (2.6)	0	.003	.003
Vascular ectasia	45 (1.7)	17 (2.2)	9 (1.3)	.006	.008	.009
Radiation colitis	21 (.8)	7 (.9)	2 (.3)	.003	.009	.014
Varices	9 (.3)	1 (.1)	3 (.4)	.026	.006	.001
Dieulafoy's ulcer	4 (.1)	1 (.1)	1 (.1)	.005	0	0
Other diseases†	115 (4.3)	59 (7.6)	58 (8.4)	0	.007	0

Values are n (%). The covariates used for the construction of the propensity score were well balanced in the weighting complete data.
*Malignancy included solid tumors and malignant lymphomas.
†Colonic diverticular bleeding included definitive and presumptive. Enterocolitis included infectious colitis, inflammatory bowel disease, drug-induced colitis, nonspecific ulcer, and nonspecific colitis. Anal bleeding included hemorrhoids and anal lesions such as anal laceration. Small-bowel bleeding included definitive small-bowel bleeding, presumptive small-bowel bleeding, and Meckel's diverticulum. Other diseases included miscellaneous and unknown lesions.

SUPPLEMENTARY TABLE 6. Comparison of the causes of bleeding in shock indices of <1 and ≥1 and PS 0-2 and ≥3 subgroups

Bleeding causes	Shock index <1 (n = 5628)	Shock index ≥1 (n = 517)	*P* value	PS 0-2 (n = 5823)	PS ≥3 (n = 369)	*P* value
CDB*	4074 (72.4)	344 (66.5)	.005	4262 (73.2)	179 (48.5)	<.001
Ischemic colitis	337 (6.0)	20 (3.9)	.049	341 (5.9)	21 (5.7)	.90
Enterocolitis*	266 (4.7)	33 (6.4)	.094	294 (5.0)	12 (3.3)	.12
Rectal ulcer	183 (3.3)	43 (8.3)	<.001	126 (2.2)	99 (26.8)	<.001
Anal bleeding*	149 (2.6)	15 (2.9)	.73	155 (2.7)	15 (4.1)	.11
Small-bowel bleeding*	142 (2.5)	21 (4.1)	.037	159 (2.7)	8 (2.2)	.52
Vascular ectasia	91 (1.6)	10 (1.9)	.59	96 (1.6)	7 (1.9)	.72
Radiation colitis	50 (.9)	2 (.4)	.23	52 (.9)	0 (.0)	.068
Varices	12 (.2)	4 (.8)	.017	15 (.3)	1 (.3)	.96
Dieulafoy's ulcer	6 (.1)	3 (.6)	.007	8 (.1)	1 (.3)	.51
Other diseases*	318 (5.7)	22 (4.3)	.18	315 (5.4)	26 (7.0)	.18

Values are n (%). The proportions of CDB and rectal ulcer were significantly higher in the PS ≥3 subgroup. The significant differences were observed in CDB, ischemic colitis, rectal ulcer, small-bowel bleeding, colorectal varices, and Dieulafoy's ulcer between the shock index <1 and shock index ≥1 cohorts. The data of PS and shock index were missed in 78 and 125 patients.

CDB, Colonic diverticular bleeding; *PS*, performance status.

*CDB included definitive and presumptive. Enterocolitis included infectious colitis, inflammatory bowel disease, drug-induced colitis, nonspecific ulcer, and nonspecific colitis. Anal bleeding included hemorrhoids and anal lesions such as anal laceration. Small-bowel bleeding included definitive small-bowel bleeding, presumptive small-bowel bleeding, and Meckel's diverticulum. Other diseases included miscellaneous and unknown lesions.

SUPPLEMENTARY TABLE 7. Balancing check between endoscopy timing in the complete data and weighting complete data

	Complete data (n = 4148)			Weighting complete data (n = 4148)		
	Absolute standardized difference			Absolute standardized difference		
Demographic characteristics	Early vs elective	Elective vs late	Early vs late	Early vs elective	Elective vs late	Early vs late
Age ≥75 y	.034	.019	.015	.008	.004	.017
Sex, male	.015	.217	.232	.007	.004	.022
Body mass index ≥25 kg/m^2	.015	.100	.115	.008	.002	.006
Current smoker	.022	.024	.046	.006	.005	.011
Current alcohol user	.012	.041	.030	.002	.001	.005
Performance status ≥3	.077	.054	.023	.002	.003	.007
History of lower GI bleeding	−.084	.037	.047	.005	.003	.004
History of colorectal surgery	.004	.026	.022	.004	.002	.010
Hypertension	.025	.082	.107	.001	.007	.010
Diabetes mellitus	.048	.028	.021	.007	.008	.002
Dyslipidemia	.044	.072	.028	.012	.005	.031
Cerebral and cardiovascular disease	.053	.057	.004	.004	.006	.005
Malignancy*	.020	.020	.000	.002	.001	.018
Charlson comorbidity index ≥3	.008	.001	.008	.004	.002	.016
Medications						
Antiplatelet	.071	.007	.078	0	.001	.026
Anticoagulant	.039	.066	.104	.013	.003	.001
Nonsteroidal anti-inflammatory drugs	.036	.017	.054	.014	.001	.009
Initial measurements						
Shock index ≥1	.136	.133	.003	.003	.007	.022
Syncope	.100	.056	.156	.009	.001	.002
Abdominal pain	.129	.290	.418	.001	.003	.002
Diarrhea	.101	.163	.262	.005	.001	.014
Hemoglobin ≤11 g/dL	.046	.032	.014	.004	.004	0
Albumin ≤3.0 g/dL	.028	.067	.039	.004	.001	.005
Creatinine ≤1.5 mg/dL	.047	.118	.071	.001	.002	.005
C-reactive protein ≥5 mg/dL	.079	.037	.116	.004	.009	.003
Prothrombin time-international normalized ratio ≥1.5	.076	.036	.040	.007	.002	.008
Platelets ≤15 10^4/μL	.003	.011	.008	.002	.004	.003

The propensity scores were constructed by demographic characteristics, medications, and initial measurements. The causes of bleeding were not used for the propensity score.
*Malignancy included solid tumors and malignant lymphomas.

SUPPLEMENTARY TABLE 8. Balancing check of the causes of bleeding between endoscopy timing in the complete data and weighting complete data

	Complete data (n = 4148)			Weighting complete data (n = 4148)		
	Absolute standardized difference			Absolute standardized difference		
Bleeding causes	**Early vs elective**	**Elective vs late**	**Early vs late**	**Early vs elective**	**Elective vs late**	**Early vs late**
Colonic diverticular bleeding*	.219	.159	.381	.157	.041	.213
Ischemic colitis	.143	.221	.356	.115	.07	.136
Enterocolitis*	.089	.133	.219	.047	.021	.060
Rectal ulcer	.042	.010	.052	.036	.029	.032
Anal bleeding*	.036	.016	.021	.052	.003	.064
Small-bowel bleeding*	.013	.012	.001	.007	.014	.012
Vascular ectasia	.046	.052	.006	.054	.069	.039
Radiation colitis	.016	.051	.067	.003	.072	.054
Varices	.047	.048	.002	.057	.066	.025
Dieulafoy's ulcer	.033	.038	.006	.002	.003	.015
Other diseases*	.178	.027	.151	.120	.027	.198

The proportion of colonic diverticular bleeding was not well balanced before and after the inverse probability of treatment weighting.
*Colonic diverticular bleeding included definitive and presumptive. Enterocolitis included infectious colitis, inflammatory bowel disease, drug-induced colitis, nonspecific ulcer, and nonspecific colitis. Anal bleeding included hemorrhoids and anal lesions such as anal laceration. Small-bowel bleeding included definitive small-bowel bleeding, presumptive small-bowel bleeding, and Meckel's diverticulum. Other diseases included miscellaneous and unknown lesions.