Received: 14 April 2020 | First decision: 29 April 2020 | Accepted: 5 June 2020

DOI: 10.1111/apt.15925

AP&T Alimentary Pharmacology & Therapeutics WILEY

Systematic review with meta-analysis: limited benefits from early colonoscopy in acute lower gastrointestinal bleeding

Omar Kherad[1] | Sophie Restellini[2,3] | Majid Almadi[3,4] | Lisa L. Strate[5] | Charles Ménard[6] | Myriam Martel[3] | Ira Roshan Afshar[3] | Mohamad Seyed Sadr[3] | Alan N. Barkun[3]

[1]Division of Internal Medicine, Hôpital de la Tour and University of Geneva, Geneva, Switzerland

[2]Division of Gastro-enterology and Hepatology, Geneva University Hospitals and University of Geneva, Geneva, Switzerland

[3]Division of Gastroenterology, McGill University Health Centre, McGill University, Montréal, QC, Canada

[4]Division of Gastroenterology, King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia

[5]Division of Gastroenterology, University of Washington School of Medicine, Seattle, WA, USA

[6]Medicine, University of Sherbrooke, Sherbrooke, QC, Canada

Correspondence
Dr. Alan N. Barkun, McGill University and the McGill University Health Centre, 1650 Cedar Avenue, D7.346, Montréal, QC H3G1A4, Canada.
Email: alan.barkun@muhc.mcgill.ca

Funding information
This manuscript was in part supported through a grant from the Saudi Gastroenterology Association, which had no involvement in any aspect of the manuscript development or preparation.

Summary

Background: The optimal timing of colonoscopy in acute lower gastrointestinal bleeding (LGIB) remains controversial.

Aim: To characterise the utility of early colonoscopy (within 24 hours) in managing acute LGIB.

Methods: A systematic literature search to October 2019 identified fully published articles and abstracts of randomised controlled trials (RCTs) and observational studies with control groups assessing early colonoscopy in acute LGIB. The primary outcome was rebleeding. Secondary outcomes included mortality, surgery, length of stay (LOS), definite cause of bleeding and adverse events. Odds ratios (ORs) and mean differences (MD) were calculated.

Results: Of 1116 citations, 4 RCTs (466 patients) and 13 observational studies with elective colonoscopy (>24 hours) as control group (1 061 281 patients) were included. No differences in rebleeding were noted between early and elective colonoscopy groups among RCTs alone (OR = 1.70; 0.79; 3.64), or observational studies alone (OR = 1.20; 0.69; 2.09). No other significant between-group differences in outcomes were found when restricting the analysis to RCTs. Among observational studies only, early colonoscopy was associated with lower rates of all-cause mortality (OR = 0.86; 0.75; 0.98), surgery (OR = 0.52; 0.42; 0.64), blood transfusion (OR = 0.81; 0.75; 0.87), units of blood transfusion (MD = −4.30; −6.24; −2.36) and shorter LOS (MD = −1.70; −1.70; −1.70 days).

Conclusion: In contradistinction to observational studies, data from RCTs do not support a role for early colonoscopy in the routine management of acute LGIB with regards to the most important clinical outcomes. Further research is needed to better identify patients with high-risk LGIB who may benefit from early colonoscopy.

Omar Kherad and Sophie Restellini equally contributed as first author.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. The Handling Editor for this article was Dr Colin Howden, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Acute lower gastrointestinal bleeding (LGIB)—defined as bleeding occurring from the colon, rectum or anus, and usually defined as distal to the ligament of Treitz, presenting either as haematochezia (bright red blood, clots or burgundy stools) or melena, has an annual incidence of hospitalisation of approximately 33 to 87/100 000 population.[1–3] The clinical presentation can range from self-limiting bleeding to life-threatening haemorrhage, and the initial management of LGIB includes haemodynamic resuscitation with or without red blood cell transfusion. While most LGIB will cease spontaneously, patients with ongoing bleeding and perhaps major stigmata of haemorrhage may require urgent diagnosis and intervention to achieve definitive haemostasis. Refractory cases may need to undergo percutaneous embolisation and infrequently surgery.[4]

Colonoscopy remains an important modality for establishing and at times sometimes treating the origin of the bleed, with one of the most common causes being a diverticular origin that is present in approximately 30% of cases.[3]

Differences wherever fundamental exist between the role of colonoscopy and gastroscopy in managing GIB. Indeed, in LGIB, colonoscopy is mainly a diagnostic tool as demonstrated by the very low number of therapeutic interventions. Alternative investigation strategies like CT angiography can be equally or more helpful. Treatment for severe LGIB is mainly angiography or surgery and not colonoscopy. There are no high-quality studies showing which therapies applied via colonoscopy can help in contrast to a mountain of evidence for gastroscopy interventions in upper GI bleeding (UGIB) where gastroscopy is a therapeutic intervention.[3,4]

However, the optimal timing of colonoscopy in LGIB remains controversial. Indeed, there persist large gaps in the evidence to guide clinicians as to whether early colonoscopy performed within 12-24 hours of admission provides any clinical benefits in comparison to a more elective timing of colonoscopy (>24 hours).[5,6] Clinical benefits of interest include mortality,[7–9] rebleeding, the yield of diagnostic interventions and efficacy of therapeutic procedures, a decreased need for blood transfusion, and length of stay (LOS).[10–13]

Guidelines by the American Society for Gastrointestinal Endoscopy (ASGE),[14] and the American College of Gastroenterology (ACG)[4] both recommend early colonoscopy (<24 hours) in high-risk patients, but the evidence supporting this statement is of "low" quality. These recommendations are based on the belief that an early colonoscopy approach identifies more patients with a definitive cause of bleeding,[4] which has been confirmed in recently published meta-analyses limited by statistical heterogeneity amidst a paucity of controlled studies.[15–17] In contradistinction to the American guidelines, as there exists no clear evidence of benefits from RCTs in terms of rebleeding or mortality from early colonoscopy (<24hours), the British society of Gastroenterology (BSG) has recommended inpatient colonoscopy to be performed only on the next available list for patients presenting with acute LGIB requiring inpatient investigation and who do not require more urgent percutaneous embolisation.[18] In keeping with these latter guidelines, two recent meta-analyses[19,20] that includes two recently completed RCTs[21,22] suggest that early colonoscopy should not be performed. However, half of all available RCTs were published over a decade ago[7,10] while, in contradistinction to the RCT results, many recent observational studies continue to suggest many clinical benefits attributable to early colonoscopy.[9,23,24] Amidst these disparate data sources and guideline recommendations, it is not surprising that clinicians remain unclear as to how to proceed in an evidence-based manner when treating patients with this common condition.

We thus proceeded to update a systematic review and meta-analysis[16] weighing carefully both randomised trials- and observational studies-derived evidence in order to better determine whether the current totality of published data support or do not support performance of colonoscopy within 24 hours of admission with an aim of improving clinical outcomes, including mortality and rebleeding.

2 | METHODS

2.1 | Search strategy

A comprehensive literature search was performed to identify the benefits of early colonoscopy compared to other approaches, including elective colonoscopy, from 1978 to October 2019 using OVID MEDLINE, EMBASE, Cochrane Library and ISI Web of Knowledge databases, with validated search terms specified for acute LGIB and endoscopy (Appendix 1A). Abstracts presented at major gastroenterology conferences (ACG, CDDW, DDW, UEGW) in the past 5 years were also hand-searched. Additional relevant studies were identified from cross-referencing and hand-searches of references of the retrieved articles. All human adult studies published in English were considered.

2.2 | Study selection and patient population

We selected all randomised trials. We also included all observational comparative studies that included early colonoscopy in at least one group of patients presenting with symptoms suggestive of acute LGIB. Because of marked heterogeneity in the literature, we decided a priori to accept any definition of acute LGIB (detailed in Table 1). Early colonoscopy was defined as performed within 24 hours of presentation for RCTs and observational studies.[13] We excluded studies assessing paediatric patients, and those in which patients had undergone an initial colonoscopy performed only after 24 hours, or diagnostic testing other than colonoscopy (such as radionuclide red blood cell scan or computerised tomography [CT] angiography) unless these represented a control group.

RCTs and observational studies were analysed both separately and pooled together as the advantages of including observational studies with RCTs in a meta-analysis could outweigh the disadvantages of

TABLE 1 Included studies

Study Country Type of study Quality score	Patient population	Definition of LGIB	Early colonoscopy	Control	Definition of rebleeding and time to rebleeding
Randomised controlled trials					
Green et al, 2005 (USA)	Acute LGIB	Haematochezia	<8 h of hospitalisation for the diagnosis of haematochezia Mean delay before endoscopy: 7.2 h (4.2-7.6 h)	Standard of care[a] Mean delay before endoscopy: 38.1 h (27.2-74 h)	Haematochezia developing after index colonoscopy or angiography was defined as that occurring after clinical cessation of the index bleeding event. Reported early rebleeding (prior to hospital discharge) or late rebleeding (after hospital discharge).
Laine et al, 2010 (USA)	Acute LGIB	Haematochezia (red or maroon rectal output) without haematemesis, melena, or bloody nasogastric aspirate, and had one of the following high-risk features: heart rate >100 beats/ min, systolic blood pressure <100 mm Hg, orthostatic changes in systolic blood pressure >20 mm Hg or in heart rate >20 beats/ min, blood transfusion, or drop in haemoglobin ≥1.5 g/dL within a 6-h period.	<12 h after presentation Mean delay before endoscopy: 11 h (6-5 h)	Elective colonoscopy (36-60 h after presentation) Mean delay before endoscopy 47 h (36-88 h)	Haematochezia persisting for >24 h, recurrent haematochezia after initial resolution of haematochezia (eg brown stool followed by recurrent haematochezia), heart rate >100 beats/ min or systolic blood pressure <100 mm Hg after haemodynamic stability for ≥1 h, or haemoglobin drop >2 g/ dL after stable haemoglobin values
Van Rongen et al, 2018 (The Netherlands)	Acute LGIB	Bloody bowel movement within 24 h of presentation and an upper gastrointestinal bleeding source was either not suspected or excluded by upper endoscopy	≤24 h of presentation Median delay before endoscopy: 0.9 d (IQR, 0.8-1.1 d)	Standard colonoscopy (24-72 hours) Median delay before endoscopy: 2.1 d (IQR, 1.8-2.9 d)	Rectal bleeding within 30 d after colonoscopy
Niikura et al, 2019 (Japan) –	Severe acute LGIB	Moderate-to-severe haematochezia or melena	≤24 h of admission Mean delay before endoscopy: 13.9 h	Elective colonoscopy (24-96 h) Mean delay before endoscopy: 41.4 h	Significant fresh blood loss after an initial colonoscopy with any of the following: (a) haemorrhagic shock, including cold sweats, nausea, syncope, or systolic blood pressure ≤90 mm Hg; (b) need for transfusion, according to the guidelines of the Ministry of Health, Labour and Welfare; (c) further colonoscopy identifying blood pooling or (d) SRH in the lower gastrointestinal tract; (e) contrast-enhanced CT identifying extravasation in the colorectal region. Rebleeding within 30 d
Prospective studies					
Albeldawi et al, 2014 (USA) NOS Score: 8	Acute LGIB	No definition	≤24 h of admission	Elective endoscopy (>24 h)	Bleeding occurring after colonoscopy and clinical cessation of index bleeding event during the hospitalisation

(Continues)

TABLE 1 (Continued)

Study Country Type of study Quality score	Patient population	Definition of LGIB	Early colonoscopy	Control	Definition of rebleeding and time to rebleeding
Retrospective studies					
Strate et al, 2003 (USA) NOS Score: 8	Acute LGIB (excluded small bowel source)	Identified 69 International Classification of Diseases, 9th Edition, codes representing LIB, as well as a wide range of diagnoses associated with LIB (eg "diverticulosis of colon") Exclusion criteria included: evidence of upper GI bleeding or a small bowel source of bleeding, bleeding more than 3 d before presentation (2), low-grade bleeding (occult blood positive stools or scant blood visible on toilet tissues only), patients transferred from inpatient units at other acute care hospitals, and patients already hospitalised for other indications.	<12 h from admission and 12-24 h from admission	Colonoscopy (24-48 h) and colonoscopy (>48 h)	Blood per rectum after 24 h of stability accompanied by a drop in Hct of at least 20%, and/or a requirement of additional blood transfusions.
Navaneethan et al, 2014 (USA) NOS Score: 8	LGIB	Patients with ICD-9-CM codes indicative of nonspecific aetiology of lower intestinal bleeding required a concomitant code of either haemorrhage of the GI tract site unspecified (578.9) along with possible source of lower intestinal bleeding including malignant neoplasm of the colon, rectum, rectosigmoid junction, or anus; benign neoplasm of colon or rectum; inflammatory bowel disease; infectious enterocolitis; non-infectious colitis including radiation enteritis; ulceration of the intestine/colon; vascular injury of the intestine; angiodysplasia of the intestine without mention of haemorrhage; GI vessel anomaly; solitary rectal ulcer syndrome; and anal fissure	≤24 h of admission	Delayed colonoscopy (>24 h)	Not reported
Niikura et al, 2015 (Japan) NOS Score: 9	Acute, continuous or severe haematochezia	Acute, continuous, or severe haematochezia and underwent colonoscopy	≤24 h	24-48 h and >48 h	Significant amount of fresh bloody or wine-coloured stool (>200 mL) without lower abdominal pain after discharge and was evaluated by colonoscopy with or without multidetector CT wherever possible.

(Continues)

TABLE 1 (Continued)

Study Country Type of study Quality score	Patient population	Definition of LGIB	Early colonoscopy	Control	Definition of rebleeding and time to rebleeding
Nagata et al, 2016 (Japan) NOS Score: 9	Acute LGIB	Acute overt LGIB	≤24 h of admission	Elective endoscopy (>24 h after hospital admission)	Significant amounts of fresh bloody or wine-coloured stools after index colonoscopy with unstable vital signs, systolic blood pressure ≥90 mm Hg or pulse ≥110 beats/min, and/or the need for blood transfusion Rebleeding within 30 d
Hassan et al, 2016 (USA) Abstract NOS Score: 5	Diverticular haemorrhage	No definition	≤24 h of admission	Elective endoscopy (>24 h)	Not specified
Winn et al, 2016 (USA) Abstract NOS Score: 5	LGIB	No definition	≤24 h	Elective endoscopy (>24 h)	Not specified
El Douaihy et al, 2017 (USA) Abstract NOS score: 5	Acute LGIB	No definition	≤24 h of admission	Elective endoscopy (>24 hours)	Not specified
Devani et al, 2018 (USA) Abstract NOS Score: 5	Acute LGIB	ICD-9-CM codes to extract LGIB discharges as a primary diagnosis or with LGIB as a secondary diagnosis with a concomitant primary diagnosis of unspecified LGIB	≤24 h of admission	Elective endoscopy (>24 h)	Not specified
Kim et al, 2018 (Korea) NOS Score: 5	Lower GI Bleeding in an ICU setting[a]	Overt bleeding, such as haematemesis, bloody nasogastric drainage, melena or haematochezia. Patients who underwent colonoscopies were included	≤24 h of detection of bleeding	Elective endoscopy (>24 h)	Haematemesis or haematochezia, bloody nasogastric drainage, instability of vital signs and a greater than 2 g/dL reduction in haemoglobin level within 24 h after successful primary haemostasis
Saraireh et al, 2019 (USA) NOS Score: 8	Diverticular haemorrhage	Diagnosis of DB (diverticulosis with haemorrhage, ICD-9 code: 56212; and diverticulitis with haemorrhage, ICD 9 code: 56213).	≤24 h of admission	Elective endoscopy (>24 h)	Not specified
Nigam et al, 2019 (USA) NOS Score: 9	Diverticular bleeding	Diverticular bleeding as defined by an ICD-9 code 562.12	≤24 h of admission	Elective endoscopy (>24 h)	Rebleeding was defined as a claim for readmission to any hospital within 30 d because of recurrent GIB defined by a primary ICD-9 discharge diagnosis of GIB. An expanded definition for rebleeding (including upper and lower GIB) was used to capture all bleeding events requiring hospitalisation (including recurrent diverticular bleeding, ICD-9 code 562.12) after index hospitalisation.

(Continues)

TABLE 1 (Continued)

Study Country Type of study Quality score	Patient population	Definition of LGIB	Early colonoscopy	Control	Definition of rebleeding and time to rebleeding
Ferman et al, 2019 (Australia) NOS Score: 7	Acute gastrointestinal bleeding[a]	Haematemesis, melena and or haematochezia Patients who underwent colonoscopies were included	≤12 h of admission	Elective endoscopy (>12 h)	Not specified

Abbreviations: CT, computerised tomography; ICD-9, International Classification of Diseases, 9th revision; LGIB, lower gastrointestinal bleeding; n/a, not applicable; NOS Score, Newcastle-Ottawa scale score; RCT, randomised controlled trial.

[a]Study included results for upper gastrointestinal bleeding as well.

such an approach.[25] Summary results are presented in our main manuscript for RCTs only and observational studies only. Results of the meta-analysis of combined RCTs and observational studies are included in Table S1. As these did not form the primary focus of this report that attempts to contrast differences between RCT and observational data.

Results for observational studies that included control approaches other than an elective colonoscopy are not included in the current manuscript; those results are rather presented in Table S2A,B.

2.3 | Outcome measures

The primary outcome of the study was the overall rebleeding rate (definitions in Table 1). Secondary outcomes included rates of surgery, mortality (overall mortality and related to LGIB), total duration of hospital LOS, identification of a definite cause of LGIB, identification of a definite or a probable cause of LGIB, and adverse events (both overall and related to the index procedure). Additional secondary outcomes included: stigmata of recent haemorrhage, length of intensive care unit (ICU) stay, blood transfusions rate, total units of blood received, endoscopic therapy, and the need for angiography.

2.4 | Validity assessment and data abstraction

Two reviewers evaluated the eligibility of all identified citations independently with a third resolving disagreements. Study quality was assessed using the Cochrane Risk of bias tool for randomised trials,[26] and the Ottawa-Newcastle criteria for observational studies.[27] The GRADE rating of evidence was used to characterise the body of literature for each outcome.[28]

2.5 | Sensitivity and subgroup analyses

Pre-planned subgroup and sensitivity analyses were carried out for the primary outcome. They included, assessing only fully published articles, performing a fixed effect model (when appropriate), assessing early colonoscopy ≤12 hours only as intervention/experimental arm, excluding large cohorts, correcting for double-zero events (when appropriate), and only including studies with a clearly stated definition of acute LGIB or rebleeding.

2.6 | Statistical analysis and possible sources of statistical heterogeneity

Descriptive results were reported as proportions and 95% confidence intervals (CI), and summary statistics expressed as means and standard deviations (SD) for continuous variables and proportions for categorical variables. Effect size was calculated with mean differences (MDs) for continuous variables, medians were used if means were not available and SD were calculated or imputed when possible.[29] Odds ratios (ORs) were calculated for categorical variables. The DerSimonian and Laird method[30] for random effect models was applied to all outcomes to determine corresponding overall effect sizes and their confidence intervals. The sensitivity analyses were performed using the Mantel-Haenszel method with fixed effects models when no statistical heterogeneity was noted. MDs were handled as continuous variables using the inverse variance approach. The presence of heterogeneity across studies was defined using a chi-square test of homogeneity with a 0.10 significance level.[31] The Higgins I^2 statistic[32] was calculated to quantify the proportion of variation in treatment effects attributable to between-study heterogeneity. Values of <40% are considered not important heterogeneity, 30%-60% moderate, 50%-90% substantial, 75%-100% considerable, respectively while taking into account into account the magnitude and direction of effects.[33] For all comparisons, publication bias was evaluated using funnel plots if at least 10 citations were identified. In order to ensure that zero event trials did not significantly affect the pooled estimate and between-study heterogeneity, sensitivity analyses were performed using a continuity correction that was added to each trial with zero events using the reciprocal of the opposite treatment arm size.[34,35] All statistical analyses were done using Revman 5.3 and Meta package in R version 2.13.0, (R Foundation for Statistical Computing, 2008).

3 | RESULTS

3.1 | Study selection and interventions

3.1.1 | Study selection

We initially identified 1116 citations. After review, a total of 1092 studies were excluded. The corresponding PRISMA diagram is shown in Figure 1. We finally selected a total of 17 citations. Four RCTs[7,10,21,22] (n = 266) compared early colonoscopy done within 8[10] to 12[7] hours of presentation or within 24 hours[21,22] to standard of care or elective colonoscopy. Among observational studies (n = 1 061 281), early colonoscopy (≤24hours) was compared to elective or delayed colonoscopy (>24 hours) in 13 studies (1 prospective[36] and 12 retrospective[8,9,13,23,24,37–43]).

Definitions of acute LGIB and rebleeding are detailed in Table 1. This table also lists corresponding patient and design characteristics for each study. Most studies used clinical symptoms as evidence of rebleeding, with endoscopic confirmation.

3.2 | Study quality assessment and risk of publication bias

The quality scores attributed to each study are displayed in Table 1, except for the Cochrane Bias Risk Assessment tool summaries for the four RCTs that are included in Appendix 1B. All RCTs exhibited a high risk of bias due to lack of blinding of study personnel. A high risk of bias was also attributed to the RCT by Laine et al[10] since the trial was terminated before reaching the calculated sample size. The Newcastle-Ottawa ranged from 5 to 9 stars; (the highest quality studies are given 9 stars) for the observational studies (Table 1).

Statistical heterogeneity was observed for the following outcomes: overall rebleeding, definite cause of acute LGIB, stigmata of recent haemorrhage, blood transfusion rate and endoscopic therapy (Table 2). Less than 10 citations prevented the generation of a funnel plot. The GRADE score of evidence for the different outcomes was low for the RCTs (Appendix 1C).

The presentation of the results for each of the studies outcomes has been chosen to facilitate interpretation of the analyses as we in turn present first RCT data only and then summary results from the observational studies only.

3.3 | Patient and study characteristics

Overall, 466 patients were included from four RCTs (230 patients in the early colonoscopy and 236 in the control group, mean age ranged from 52 to 72 years, 38.2% female), while 13 observational studies reported on 1 061 281 patients with four of these totalling more than 10 000 patients each (931 366 in the abstract from Devani et al,[23] 88 600 from Saraireh et al,[24] 22 720 in Navaneethan et al,[41] and 16 640 from Nigam et al[9]). 628 046 patients underwent early colonoscopy whereas 433 235 had an elective colonoscopy. Overall, for the observational studies, the mean age of patients ranged from 59 to 76 years. A total of 51.6% of patients were female. Details of included RCT and observational studies are shown in Table 1. In all studies, it was specified that the colonoscopies were performed by an expert, defined as a physician trained in gastroenterology, internal medicine or general surgery.

Endoscopic findings are reported in Table 3. Three studies[9,24,39] included only patients with diverticular bleeding as a definite or probable cause of bleeding. Excluding those three studies, the most common causes of probable or definite bleeding remained diverticular bleeding (38.8%), colitis (15.0%), ulcer (7.2%), cancer (5.3%), angiodysplasia (5.3%), polyps (3.3%) and post-polypectomy bleeding (2.4%).

3.4 | Primary outcomes

Among the four RCTs,[7,10,21,22] (n = 466) rebleeding rates did not demonstrate any significant between-group differences (OR = 1.70: 95% CI: 0.79; 3.64). (Table 1 and Figure 2A). Similarly, there was no significant difference in rebleeding rates when comparing early to elective colonoscopy for the seven observational studies (n = 17 988) (OR = 1.20; 95% CI: 0.69; 2.09) who reported this outcome. Subgroup and sensitivity analyses are detailed in Appendix 1D and demonstrated no change in the results when assessing only fully published articles, performing a fixed effect model (when appropriate), assessing early colonoscopy ≤12 hours only as intervention/experimental arm, excluding large cohorts, or when only including studies with a clearly stated definition of acute LGIB or rebleeding. There were not double-zero events needing a coefficient of correction.

3.5 | Secondary outcomes

When limited to RCTs, no significant differences were noted between early and elective colonoscopy for any of the planned secondary outcomes measures (Table 2.). Only the proportion of detection for a "definite cause of bleeding" exhibited a trend for being greater when performing an early colonoscopy[7,10,21,22] (OR = 1.71; 95% CI: 1.00; 2.93).

The following secondary outcome analyses pertain specifically to data extracted only from the included observational studies.

3.5.1 | Mortality

All-cause mortality was significantly lower for early colonoscopy in six observational studies when compared to later colonoscopy

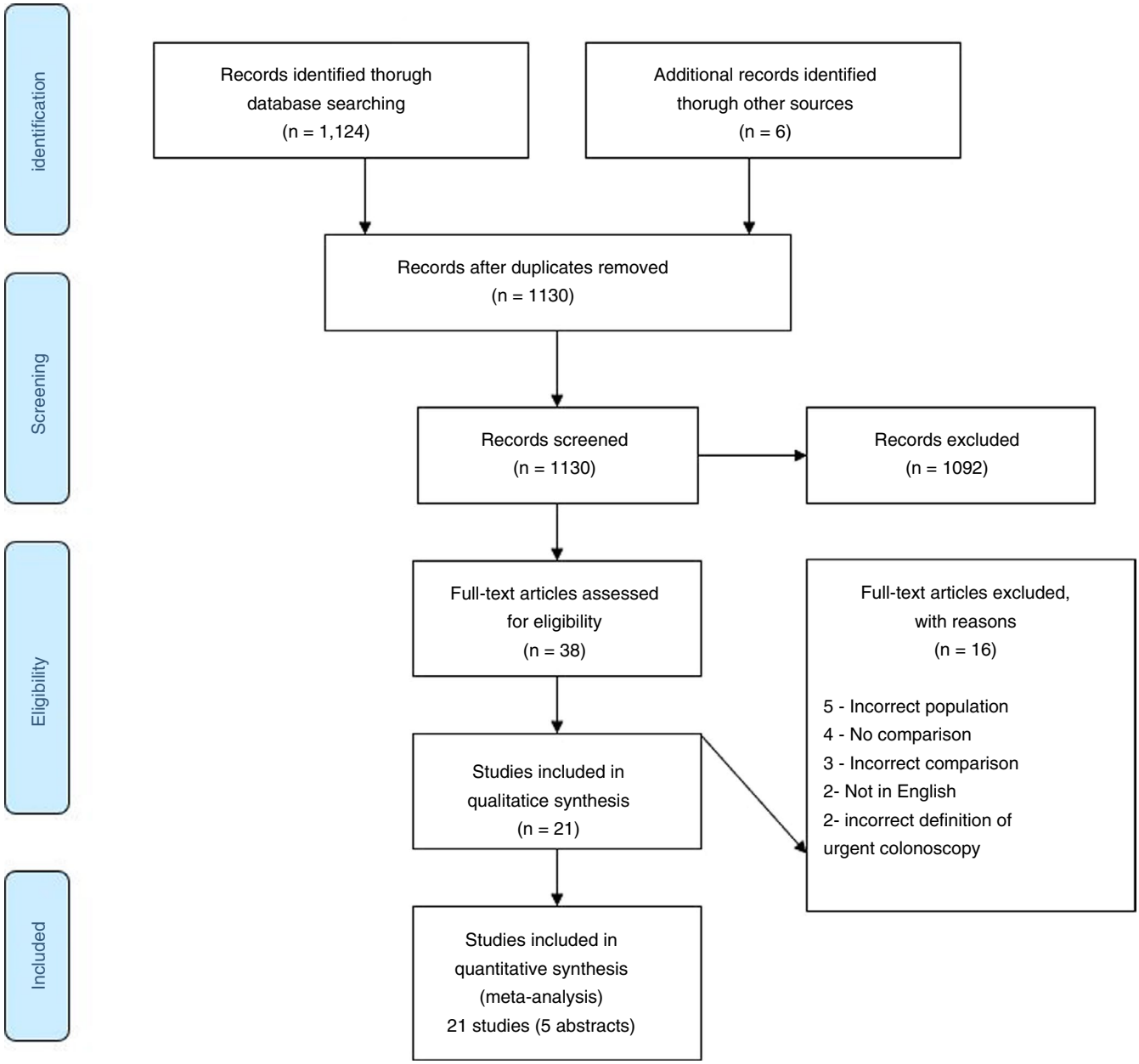


FIGURE 1 PRISMA diagram of trial selection

(n = 112,069)[8,24,36,39–41] (OR = 0.86; 95% CI: 0.75; 0.98), (Table 2 and Figure 2B). When assessing bleeding-related mortality, there were no significant differences (three studies observational studies,[36,39,40] n = 423; OR = 2.47; 95% CI: 0.27; 22.74) (Figure 2C).

3.5.2 | Surgery

In four observational studies[8,9,36,40] (n = 17 092) that assessed surgery, patients undergoing early colonoscopy underwent fewer surgical interventions than any other approach (OR = 0.52; 95% CI: 0.42; 0.64). Nigam et al,[9] was the only study that reported significant lower rates of surgery with early compared to elective colonoscopy (1.6% vs 3.0%, $P < 0.01$). When excluding this large observational study, results were not significantly different between the two groups (OR = 0.74; 95% CI: 0.27; 2.01).

3.5.3 | Length of stay

There was a significantly shorter LOS attributable to early colonoscopy in four observational studies[8,23,39,40] (n = 931 366) (MD = −1.70; 95% CI: −1.70; −1.70). Length of ICU stay was significantly shorter in the early colonoscopy group (MD = −3.14; 95% CI: −6.12; −0.15) in two studies.[36,40] The first reported a length of ICU stay of 33.3 ± 41.3 vs 42.8 ± 45.1 days ($P = 0.37$), favouring early colonoscopy. The second study[36] did not report any significant difference (2.0 days vs 5.0 days, $P = 0.06$) for this outcome.

TABLE 2 Primary and secondary outcomes

	N studies	N patients	OR or MD (95% CI)	*P* value Heterogeneity	I^2
Primary outcomes					
Overall rebleeding rate					
RCT only	4	466	1.70 (0.79; 3.64)	0.14	45%
Observational only	7	17 988	1.20 (0.69; 2.09)	<0.01	70%
Secondary outcomes					
Mortality (related to LGIB)					
RCT only	4	466	0.49 (0.04; 5.58)	[a]	[a]
Observational only	3	423	2.47 (0.27; 22.74)	0.53	0%
Mortality (all causes)					
RCT only	4	466	0.93 (0.04; 19.36)	0.11	62%
Observational only	6	112 069	0.86 (0.75; 0.98)	0.47	0%
LOS					
RCT only	2	234	−0.10 (−1.44; 1.24)	0.51	0%
Observational only	4	931 366	−1.70 (−1.70; −1.70)	0.42	0%
Definite cause of Acute LGIB (including SHR)					
RCT only	4	466	1.71 (1.00; 2.93)	0.33	12%
Observational only	4	935	2.69 (0.74; 9.72)	<0.01	89%
Adverse events (procedure related)					
RCT only	4	466	1.02 (0.20; 5.12)	0.68	0%
Observational only	1	326	0.43 (0.13; 1.43)	—	—
Adverse events (any adverse events)					
RCT only	4	466	1.38 (0.77; 2.50)	0.63	0%
Observational only	1	326	0.43 (0.13; 1.43)	-	-
Surgery					
RCT only	4	466	0.86 (0.30; 2.41)	0.46	0%
Observational only	4	17 092	0.52 (0.42; 0.64)	0.86	0%
Additional secondary outcomes					
Definite or probable cause of Acute LGIB					
RCT only	4	466	2.06 (0.92; 4.60)	0.10	52%
Observational only	3	597	2.69 (0.30; 24.24)	<0.01	90%
SRH only					
RCT only	4	466	1.76 (0.52; 5.95)	0.06	60%
Observational only	3	791	3.09 (0.44; 21.40)	<0.01	93%
Length of ICU stay					
RCT only	0	0	—	—	—
Observational only	2	126	−3.14 (−6.12; −0.15)	0.54	0%
Blood transfusion rate					
RCT only	2	294	1.35 (0.78; 2.34)	0.64	0%
Observational only	7	1 057 016	0.81 (0.75; 0.87)	<0.01	92%
Blood transfusion (total)					
RCT only	2	172	−0.06 (−1.62; 1.50)	<0.01	92%
Observational only	1	69	−4.30 (−6.24; −2.36)	—	—
Endoscopic therapy					

(Continues)

TABLE 2 (Continued)

	N studies	N patients	OR or MD (95% CI)	*P* value Heterogeneity	I^2
RCT only	3	366	1.38 (0.77; 2.46)	0.41	0%
Observational only	6	40 043	1.32 (0.65; 2.72)	<0.01	98%
Angiography					
RCT only	2	204	6.08 (0.69; 53.74)	0.62	0%
Observational only	4	17 092	0.66 (0.30; 1.44)	1.00	0%

Abbreviations: I^2, I-square statistic for heterogeneity; LOS, length of stay; MD, mean difference; OBS, observational study; OR, odds ratio; RCT, randomised controlled trial; SRH, stigmata of recent haemorrhage.

[a]Two trials with double-zero events.

TABLE 3 Endoscopic findings and nature of endoscopic therapy

	Early colonoscopies <24 h	Elective colonoscopies	ONLY RCT: early endoscopy arm
Endoscopic findings of probable of definite cause of bleeding[a]			
Diverticula	38.8%	30.3%	53.7%
Ulcer	7.2%	12.4%	1.3%
Angiodysplasia	5.3%	2.3%	6.0%
Cancer	5.3%	6.4%	5.4%
Colitis	15.0%	34.6%	10.1%
Small bowel bleeding	0.5%	0.9%	0.0%
Polyps	3.3%	3.7%	2.0%
Post-polypectomy	2.4%	0.0%	0.0%
Other	19.0%	11.0%	12.8%
Nondiagnostic	8.1%	17.0%	8.7%

Abbreviations: RCT, randomised controlled trial.

[a]Excluding studies of diverticular bleeding alone.

3.5.4 | Source of bleeding

Among four observational studies[8,13,40,42] (n = 935) reporting a definite source of acute LGIB, no between-group difference was noted (OR = 2.69; 95% CI: 0.74; 9.72). When grouping definite or probable causes of bleeding together (three observational studies,[13,36,42] n = 597), early colonoscopy did not yield significantly more culprit lesions when compared to elective colonoscopy (OR = 2.69; 95% CI: 0.30; 24.24). Detection rates of stigmata of recent haemorrhage (3 observational studies,[24,40,42] n = 791) did not differ between groups (OR = 3.09; 95% CI: 0.44; 21.40).

3.5.5 | Adverse events

Procedure-related adverse events included perforations, cardiovascular complications as well as minor events such as fever and hypotension. Haemodynamic instability and death were not considered adverse events related to the colonoscopy since, in all studies, the former was recorded prior to endoscopy only, and death was categorised as all-cause, bleeding- or disease-related rather than procedure related. Using analysable data from one study[8] (n = 326), there were no significant between-group differences (OR = 0.43; 95% CI: 0.13; 1.43) in adverse event rates when early colonoscopy was compared to elective colonoscopy. Results were similar when including preparation-related adverse events.

3.5.6 | Blood transfusion

Blood transfusion rates were significantly lower in the early compared to elective colonoscopy group (seven observational studies,[8,9,23,24,38,39,41] n = 1 057 016) (OR = 0.81; 95% CI: 0.75; 0.87). The number of units of blood transfused was lower in the early colonoscopy group for the sole observation study with analysable data[41] (MD = −4.30, 95% CI −6.24; −2.36).

3.5.7 | Endoscopic therapy and findings

No significant differences were noted with regards to need for endoscopic therapy or use of angiography (Table 2).

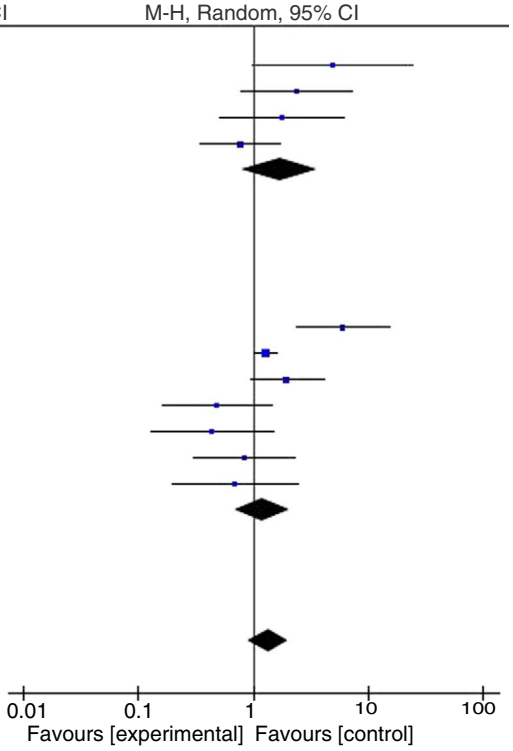
4 | DISCUSSION

The aim of this systematic review was to update existing evidence on the role of early colonoscopy in the management of patients with acute LGIB, integrating the most contemporary data, while contrasting the results from RCTs and observational studies. The timing of this work is especially important in light of the publications of many recent large observational studies,[9,23,24] two new RCTs on the topic,[21,22] and conflicting societal guidelines.[4,14]

Our two meta-analyses that included the 466 patients from 4 RCTs and 1 061 281 patients from 13 observational studies with relevant control groups, respectively, are congruent and demonstrate no differences in rebleeding rates among patients undergoing early colonoscopies compared to elective colonoscopy. This is

(A)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 RCT						
van Rogen 2018	8	63	2	69	5.0%	4.87 [0.99, 23.89]
Niikura et al., 2018	11	81	5	81	8.0%	2.39 [0.79, 7.22]
Laine et al 2010	8	36	5	36	7.1%	1.77 [0.52, 6.05]
Green et al 2005	19	50	22	50	10.9%	0.78 [0.35, 1.73]
Subtotal (95% CI)		230		236	30.9%	1.70 [0.79, 3.64]
Total events	46		34			
Heterogeneity: $Tau^2 = 0.27$; $Chi^2 = 5.45$, df = 3 (P = 0.14); $I^2 = 45\%$						
Test for overall effect: Z = 1.36 (P = 0.17)						
1.2.2 Elective colonoscopy						
Winn et al., 2016	8	29	22	370	9.6%	6.03 [2.40, 15.14]
Nigam et al., 2019	173	8320	135	8320	17.1%	1.29 [1.03, 4.11]
Nagata et al., 2016	22	163	12	163	11.5%	1.96 [0.94, 4.11]
Kim et al., 2018	7	36	11	33	8.1%	0.48 [0.16, 1.45]
Hassan et al., 2016	3	65	23	232	7.0%	0.44 [0.13, 1.51]
El Douaihy et al., 2017	6	67	14	133	8.8%	0.84 [0.31, 2.28]
Albeldawi et al., 2014	5	24	9	33	6.9%	0.70 [0.20, 2.44]
Subtotal (95% CI)		8704		9284	69.1%	1.20 [0.69, 2.09]
Total events	224		226			
Heterogeneity: $Tau^2 = 0.34$; $Chi^2 = 19.71$, df = 6 (P = 0.003); $I^2 = 70\%$						
Test for overall effect: Z = 0.65 (P = 0.51)						
Total (95% CI)		8934		9520	100.0%	1.35 [0.89, 2.05]
Total events	270		260			
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 25.27$, df = 10 (P = 0.005); $I^2 = 60\%$						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: $Chi^2 = 0.51$; df = 1 (P = 0.47); $I^2 = 0\%$						



(B)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.5.1 RCT						
Green et al 2005	1	50	4	50	0.6%	0.23 [0.03, 2.18]
Laine et al 2010	2	36	0	36	0.3%	5.29 [0.25, 114.16]
Niikura et al., 2018	0	81	0	81		Not estimable
van Rogen 2018	0	63	0	69		Not estimable
Subtotal (95% CI)		230		236	0.9%	0.93 [0.04, 19.36]
Total events	3		4			
Heterogeneity: $Tau^2 = 3.01$; $Chi^2 = 2.61$, df = 1 (P = 0.11); $I^2 = 62\%$						
Test for overall effect: Z = 0.05 (P = 0.96)						
1.5.2 Elective colonoscopy						
Albeldawi et al., 2014	0	24	0	33		Not estimable
Hassan et al., 2016	0	65	2	232	0.3%	0.70 [0.03, 14.84]
Kim et al., 2018	23	36	17	33	3.3%	1.67 [0.64, 4.36]
Nagata et al., 2016	2	163	0	163	0.3%	5.06 [0.24, 106.26]
Navaneethan et al. 2014	27	9156	54	13564	13.4%	0.74 [0.47, 1.18]
Saraireh et al., 2019	340	45020	385	43580	81.7%	0.85 [0.74, 0.99]
Subtotal (95% CI)		54464		57605	99.1%	0.86 [0.75, 0.98]
Total events	392		458			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.54$, df = 4 (P = 0.47); $I^2 = 0\%$						
Test for overall effect: Z = 2.19 (P = 0.03)						
Total (95% CI)		54694		57841	100.0%	0.86 [0.72, 1.02]
Total events	395		462			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.19$, df = 6 (P = 0.40); $I^2 = 3\%$						
Test for overall effect: Z = 1.70 (P = 0.09)						
Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.96), $I^2 = 3\%$						

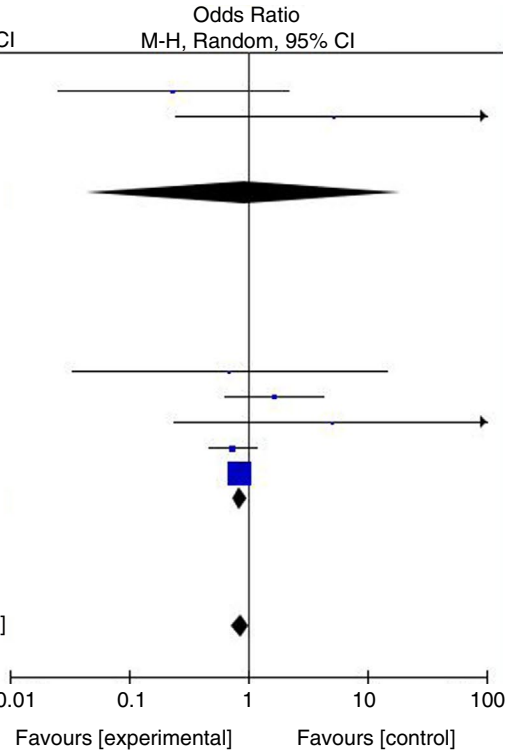


FIGURE 2 Comparisons between early (<24h) vs elective colonoscopy. (A) Rebleeding. (B) Mortality all cause. (C) Mortality related to bleeding

traditionally the most objective contemporary outcome that reflects the downstream benefits of endoscopic intervention, as adopted in the upper GI bleeding literature.[10]

These findings mirror several meta-analyses that failed to show a clinical benefit of early colonoscopy in rebleeding[16,19] including a recent study by Tsay et al,[19] another one by Anvari et al[20] and editorial

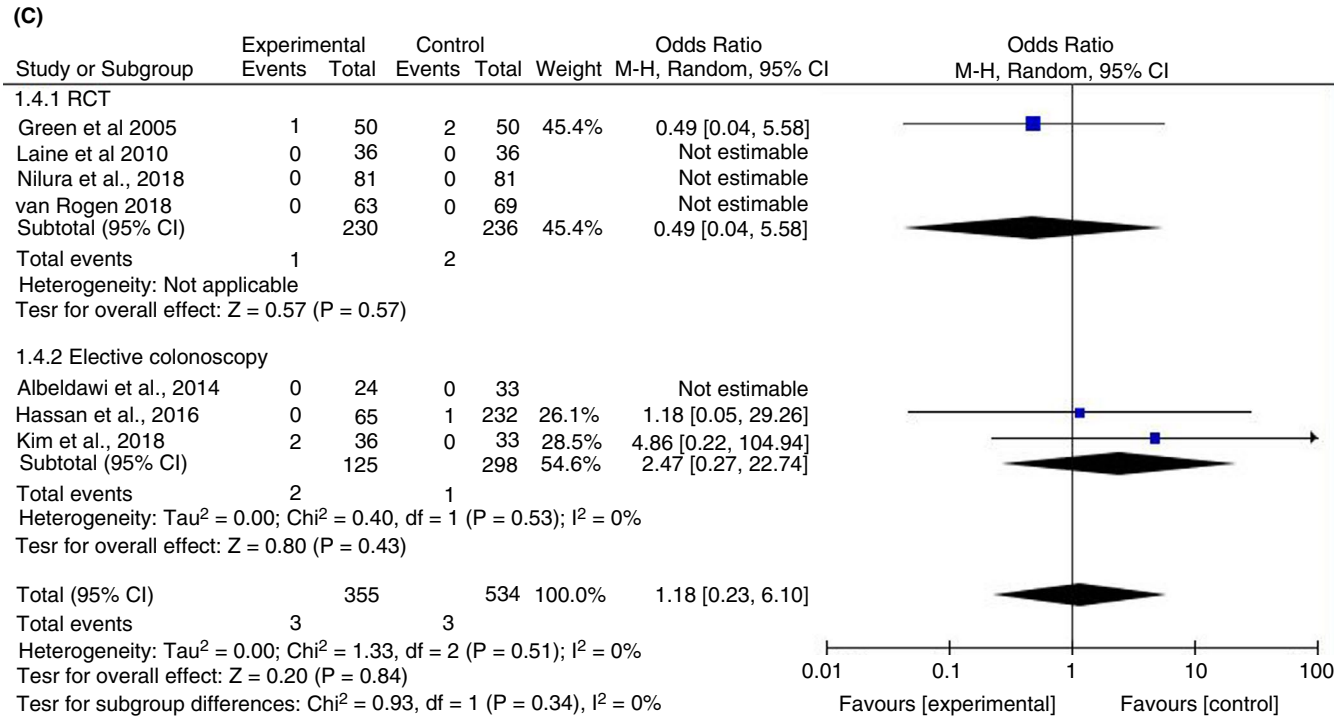


FIGURE 2 (Continued)

by Laine.[44] Interestingly, in a propensity-matched analysis using a US nationwide insurance claims database, Nigam et al[9] concluded that early colonoscopy may even be associated with increased risk of rebleeding events and hospital readmissions. Similar findings were reported in one of the recently published RCTs conducted in the Netherlands in which 63 patients were randomised to colonoscopy within 24 hours and 69 to a later colonoscopy.[22] Indeed, there too and for unclear reasons not pertaining to lead-time bias since the definition of rebleeding was the same in both groups, rebleeding rates and hospital readmissions were significantly more frequent in the under 24-hour group (13% vs 3% [$P = 0.04$] and 11% vs 2% [$P = 0.02$] respectively). Interestingly, in our current meta-analysis of only the four existing RCTs, a pre-planned sensitivity analysis of removing the study by Green et al[10] resulted in a significant increased risk of rebleeding for patients undergoing early colonoscopy (OR = 2.50; 95% CI: 1.20; 5.18, with $I^2 = 0$ suggesting no heterogeneity).

Even if such a potential negative outcome remains unexplained, the consistent negative impact noted across many high-quality studies that includes an increased readmission rate in one RCT[19] should in light of limited proof of clinical benefit lead to caution when opting for early colonoscopy as a default approach.

Not surprisingly, considering their low incidences and the paucity of patients included in comparative trials, no significant differences were noted in all-cause or bleeding-related mortality in RCTs[7,10,21,22] (OR = 0.93; 95% CI, 0.04; 19.36 and OR = 0.49; 95% CI: 0.04; 5.58 respectively) (Figure 2B,C). Conversely, all-cause mortality was significantly lower when comparing early to elective colonoscopy in six observational studies (n = 122 535)[8,24,36,39–41] (OR = 0.86; 95% CI: 0.75; 0.98). Nevertheless, when looking at the biggest cohorts in a post hoc analysis, there were no differences in in-hospital or all-cause mortality. Indeed, no difference was noted in Navaneethan et al[41] (n = 22 720) with regards to in-hospital deaths for early (≤24 hours) vs elective (>24 hours) colonoscopy (0.3% vs 0.4%, $P = 0.24$). In the other large cohort from Saraireh et al,[24] there were no between-group differences (0.75% vs 0.88%, $P = 0.34$) in all-cause mortality. Any inference based on bleeding-related mortality is limited due to the subjectivity of this allocation; furthermore, it probably only represents a small fraction of all-cause mortality in this patient population with multiple co-morbidities as is the case in UGIB.[45]

Previously, meta-analyses based mainly on observational studies[12,15,16] have noted that early colonoscopy may result in more frequent detection of definite lesions responsible for the episode of LGIB. In our meta-analysis, this association was borderline significant when considering solely the four RCTs (OR = 1.71; 95% CI: 1.00; 2.93) and was not found to be significant when assessing only the four observational studies reporting this outcome (OR = 2.69; 95% CI 0.74; 9.72).

Interestingly, in the meta-analysis that combines RCT and observational studies (reported in Appendix), the odds of detecting a definite source of rebleeding was greater in the early colonoscopy group (OR = 2.30, 95% CI: 1.11; 4.73). This finding is likely due to the increased statistical power brought about by pooling RCTs and observational studies.

The finding that increased earlier detection as a whole does not result in better clinical outcomes in RCTs patients is somewhat surprising, and that the absence of subsequent increased rates in performed endoscopic therapy (no difference between groups

(OR = 1.38; 95% CI: 0.77; 2.46) (Table 2), is just as perplexing. Possible reasons for these findings include inconsistent or subjective definitions of what is a culprit lesion, the effect of pooling patients with different bleeding aetiologies (some of which may not be amenable to endoscopic haemostasis), a limitation of current endoscopic therapies dedicated to the treatment of lower GI bleeding in contradistinction to upper gastrointestinal bleeding lesions, or a poor characterisation of what is in fact a definite cause of bleeding. There are no widely recognised recommendations on how to treat LGIB at endoscopy in contrast to guidance for variceal- and ulcer-based UGIB.

Additional contributing factors may be a clinical heterogeneity in included study designs, the presence of older studies with limited options for haemostasis or adopted management schemes, variability in endoscopic expertise impacting both diagnosis and therapy, and the self-resolving natural history of LGIB[3] with underpowering of the statistical comparisons (particularly for the RCT data in which confounding would be minimised). Regardless, the absence of downstream clinical benefits decreases any clinical importance of any differences in definitive lesions detection.

Our results based on observational studies confirm a shorter LOS in the early colonoscopy group in six studies (all control groups combined, n = 931 366) (MD = −1.70; 95% CI: −1.70; −1.70). In contradistinction, no difference was noted when grouping data from the two RCTs that reported on this outcome. Overall, LOS in ICU based on two observational studies was also shorter in the early colonoscopy group (MD = −3.14; 95% CI: −6.12; −0.15). However, one study did not find a difference,[40] while the mean duration of LOS in the ICU in the second study was surprisingly long (up to 42.8 days (±45.1 days),[40] bringing into question the clinical validity of this conclusion. The need for surgical interventions and blood transfusion rates were lower with early colonoscopy (OR = 0.52; 95% CI: 0.42; 0.64 and OR = 0.81; 95% CI: 0.75; 0.87), respectively, but again only among observational studies and not RCTs. The clinical bias involved in this decision in clinical management may explain such discrepancy.

In summary, when analysing RCTs only, no clinical benefits are noted except for the detection of bleeding lesions that is borderline significant but does not result in downstream improvements in clinical outcomes. In contrast, when assessing observational data, all-cause mortality, surgery, LOS, LOS in ICU and blood transfusions are all improved with early colonoscopy, with arguably only length of stay truly appearing to be robust after a priori defined sensitivity and a posteriori exploratory analyses. A schematic representation of the discrepancy between each group of study methodologies is shown in Figure 2A-C. It is likely that the discrepancy in findings between RCTs and observational data in large part relates to the introduction of bias in the latter as has been noted in many therapeutic areas.[46] Drawing firm conclusions from observational studies where association does not infer causation can lead to questionable conclusions as imbalances between the study arms in terms of prognostically important variables must be adjusted for to reduce selection bias. Additionally insurance database studies are large but lack clear patient-level data and are not ideal in assessing emergency interventions.

This realisation coupled to the unexplained finding of possible increased rebleeding in the early colonoscopy group among RCTs should convince clinicians to be cautious when advocating for such an approach that includes early colonoscopy. Additional large RCTs reflecting contemporary management would be needed to clarify the issue further. Assuming the RCTs to date have been misleading and the observational results are in fact closer to the truth in suggesting any benefit, we performed a posteriori trial sequential analysis that indicates that for the rebleeding outcome, an additional 1120 patients would be required in the amalgamated RCT trial data to confidently prove a risk reduction in the control event rate of 15%, assuming an alpha error of 0.05, and statistical power of 0.80.

Our study is subject to certain limitations. The main limitation is the clinical heterogeneity of existing literature with disparate and poor study methodologies, principally in the observational studies. Because of marked heterogeneity in the literature, we accepted a broad definition of acute LGIB. The definitions and timing of rebleeding also varied widely, further limiting the validity of available summary data, even across RCTs.[7,10,21,22]

It is possible that a subset of patients at particularly high risk may benefit from early colonoscopy and thus perhaps the decision to pursue such management should be made on a case-by-case basis and not as a "one size fits all" recommendation. The current amalgamation of data, lack of patient-level data, and absence of a single common widely accepted risk stratification scheme in LGIB precluded any such pertinent subgroup analysis. More recently a new predictive score (Oakland score) recommended in the BSG guidelines has been suggested[15] that appears promising especially in predicting low-risk patient, yet requires additional prospective validation.

5 | CONCLUSION

The most recent high-certainty data do not support the routine adoption of early colonoscopy to reduce the risks of rebleeding or mortality in contradistinction to results from observational studies. Further research is needed to better identify patients with high-risk LGIB who may benefit from early colonoscopy.

ACKNOWLEDGEMENT

Declaration of personal interest: None.

AUTHORSHIP

Guarantor of the article: A Barkun.

Authors contribution: O. Kherad, S. Restellini, M. Almadi, L. Strate, M Martel, C Menard, I Roshan Afshar, M Seyed Sadr and A N. Barkun were involved in study concept and design, acquisition of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. O. Kherad, S. Restellini, M. Almadi, L. Strate, M Martel, C Menard and A N. Barkun were involved in

analysis and interpretation of data. M. Almadi, M Martel and A N. Barkun were involved in statistical analysis. All authors approved the final version of the manuscript.

ORCID

Omar Kherad https://orcid.org/0000-0002-6003-0776
Alan N. Barkun https://orcid.org/0000-0002-1798-5526

REFERENCES

1. Hreinsson JP, Gumundsson S, Kalaitzakis E, Bjornsson ES. Lower gastrointestinal bleeding: incidence, etiology, and outcomes in a population-based setting. *Eur J Gastroenterol Hepatol*. 2013;25:37-43.
2. Laine L, Yang H, Chang S-C, Datto C. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. *Am J Gastroenterol*. 2012;107(8):1190-1195; quiz 6.
3. Oakland K, Guy R, Uberoi R, et al. Acute lower GI bleeding in the UK: patient characteristics, interventions and outcomes in the first nationwide audit. *Gut*. 2018;67:654-662.
4. Strate LL, Gralnek IM. ACG Clinical Guideline: management of patients with acute lower gastrointestinal bleeding. *Am J Gastroenterol*. 2016;111:755.
5. Jensen DM, Machicado GA, Jutabha R, Kovacs TO. Urgent colonoscopy for the diagnosis and treatment of severe diverticular hemorrhage. *N Engl J Med*. 2000;342:78-82.
6. Kouanda AM, Somsouk M, Sewell JL, Day LW. Urgent colonoscopy in patients with lower GI bleeding: a systematic review and meta-analysis. *Gastrointest Endosc*. 2017;86:107-117.e1.
7. Green BT, Rockey DC, Portwood G, et al. Urgent colonoscopy for evaluation and management of acute lower gastrointestinal hemorrhage: a randomized controlled trial. *Am J Gastroenterol*. 2005;100:2395-2402.
8. Nagata N, Niikura R, Sakurai T, et al. Safety and effectiveness of early colonoscopy in management of acute lower gastrointestinal bleeding on the basis of propensity score matching analysis. *Clin Gastroenterol Hepatol*. 2016;14:558-564.
9. Nigam N, Ham SA, Sengupta N. Early colonoscopy for diverticular bleeding does not reduce risk of postdischarge recurrent bleeding: a propensity score matching analysis. *Clin Gastroenterol Hepatol*. 2019;17:1105-1111.e1.
10. Laine L, Shah A. Randomized trial of urgent vs. elective colonoscopy in patients hospitalized with lower GI bleeding. *Am J Gastroenterol*. 2010;105:2636-2641; quiz 42.
11. Schmulewitz N, Fisher DA, Rockey DC. Early colonoscopy for acute lower GI bleeding predicts shorter hospital stay: a retrospective study of experience in a single center. *Gastrointest Endosc*. 2003;58:841-846.
12. Sengupta N, Tapper EB, Feuerstein JD. Early versus delayed colonoscopy in hospitalized patients with lower gastrointestinal bleeding: a meta-analysis. *J Clin Gastroenterol*. 2017;51:352-359.
13. Strate LL, Syngal S. Timing of colonoscopy: impact on length of hospital stay in patients with acute lower intestinal bleeding. *Am J Gastroenterol*. 2003;98:317-322.
14. Davila RE, Rajan E, Adler D, et al. ASGE guideline: the role of endoscopy in the diagnosis, staging, and management of colorectal cancer. *Gastrointest Endosc*. 2005;61:1-7.
15. Oakland K, Isherwood J, Lahiff C, et al. Diagnostic and therapeutic treatment modalities for acute lower gastrointestinal bleeding: a systematic review. *Endosc Int Open*. 2017;5:E959-E973.
16. Roshan Afshar I, Sadr MS, Strate LL, Martel M, Menard C, Barkun AN. The role of early colonoscopy in patients presenting with acute lower gastrointestinal bleeding: a systematic review and meta-analysis. *Therap Adv Gastroenterol*. 2018;11:1756283X18757184.
17. Seth A, Khan MA, Nollan R, et al. Does urgent colonoscopy improve outcomes in the management of lower gastrointestinal bleeding? *Am J Med Sci*. 2017;353:298-306.
18. Oakland K, Chadwick G, East JE, et al. Diagnosis and management of acute lower gastrointestinal bleeding: guidelines from the British Society of Gastroenterology. *Gut*. 2019;68:776-789.
19. Tsay C, Shung D, Frumento KS, Laine L. Early colonoscopy does not improve outcomes of patients with lower gastrointestinal bleeding: systematic review of randomized trials. *Clin Gastroenterol Hepatol*. 2020;18(8):1696–1703. https://doi.org/10.1016/j.cgh.2019.11.061
20. Anvari S, Lee Y, Yu J, Doumouras AG, Khan KJ, Hong D. Urgent versus standard colonoscopy for management of acute lower gastrointestinal bleeding: a systematic review and meta-analysis of randomized controlled trials. *J Clin Gastroenterol*. 2020;54(6):493–502. https://doi.org/10.1097/MCG.0000000000001329. Publish Ahead of Print
21. Niikura R, Nagata N, Yamada A, et al. Efficacy and safety of early vs elective colonoscopy for acute lower gastrointestinal bleeding. *Gastroenterology*. 2020;158:168-175.e6.
22. van Rongen I, Thomassen BJW, Perk LE. Early versus standard colonoscopy: a randomized controlled trial in patients with acute lower gastrointestinal bleeding: results of the BLEED study. *J Clin Gastroenterol*. 2019;53:591-598.
23. Devani K, Charilaou P, Radadiya D, et al. Trends of early colonoscopy and their outcomes in patients admitted with acute lower gastrointestinal bleeding: Fellows-in-Training Award (GI bleeding category). *Am J Gastroenterol*. 2018;113:S304-S305.
24. Saraireh H, Tayyem O, Siddiqui MT, Hmoud B, Bilal M. Early colonoscopy in patients with acute diverticular bleeding is associated with improvement in healthcare-resource utilization. *Gastroenterol Rep (Oxf)*. 2019;7:115-120.
25. Shrier I, Boivin J-F, Steele RJ, et al. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. *Am J Epidemiol*. 2007;166:1203-1209.
26. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
27. The Newcastle-Ottawa scale (NOS) for assessing the quailty of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed February 1, 2009.
28. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926.
29. HigginsJPT, Li T, Deeks JJ.Chapter 6: Choosing effect measures and computing estimates of effect. *Cochrane Handbook for Systematic Reviews of Interventions*. 2019. https://training.cochrane.org/handbook/current/chapter-06#section-6-5-2-8
30. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
31. Hardy RJ, Thompson SG. Detecting and describing heterogeneity in meta-analysis. *Stat Med*. 1998;17:841-856.
32. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539-1558.
33. Jonathan JD, Julian PTH, Douglas GA; on behalf of the Cochrane Statistical Methods Group. Identifying and measuring heterogeneity. Version 6, *Cochrane Handbook for Systematic Reviews of Interventions*. 2019. https://training.cochrane.org/handbook/current/chapter-10
34. Friedrich JO, Adhikari NK, Beyene J. Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. *BMC Med Res Methodol*. 2007;7:5.

35. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med*. 2004;23:1351-1375.
36. Albeldawi M, Ha D, Mehta P, et al. Utility of urgent colonoscopy in acute lower gastro-intestinal bleeding: a single-center experience. *Gastroenterol Rep (Oxf)*. 2014;2:300-305.
37. El Douaihy Y, Nassani N, Al Moussawi H, et al. Outcomes of early versus late colonoscopy in acute lower gastrointestinal bleeding: a single center experience. *Am J Gastroenterol*. 2017;112:S1474.
38. Ferman M, Sheikh M, Shawki M, Leung E, Al-Ansari M. Early endoscopic intervention in acute gastrointestinal bleeding may reduce the need for blood transfusion. *Australas Med J*. 2019;12:56-62.
39. Hassan M, Meighani A, Rao B, Abboud R, Pompa R. Sa1735 early versus late colonoscopy in patients presenting with diverticular bleeds: a single center experience. *Gastrointest Endosc*. 2016;83:AB280.
40. Kim JH, Kim JH, Chun J, Lee C, Im JP, Kim JS. Early versus late bedside endoscopy for gastrointestinal bleeding in critically ill patients. *Korean J Intern Med*. 2018;33:304-312.
41. Navaneethan U, Njei B, Venkatesh PG, Sanaka MR. Timing of colonoscopy and outcomes in patients with lower GI bleeding: a nationwide population-based study. *Gastrointest Endosc*. 2014;79:297-306.e12.
42. Niikura R, Nagata N, Aoki T, et al. Predictors for identification of stigmata of recent hemorrhage on colonic diverticula in lower gastrointestinal bleeding. *J Clin Gastroenterol*. 2015;49:e24-e30.
43. Winn J, Abdul-Kafi O, Rao S, et al. Optimal timing of endoscopy for lower gastrointestinal bleeding. *Am J Gastroenterol*. 2016;111:S153-S154.
44. Laine L. Colonoscopy for lower gastrointestinal bleeding-time is not of the essence. *Gastroenterology*. 2020;158:38-39.
45. Sung JJ, Tsoi KK, Ma TK, Yung MY, Lau JY, Chiu PW. Causes of mortality in patients with peptic ulcer bleeding: a prospective cohort study of 10,428 cases. *Am J Gastroenterol*. 2010;105:84-89.
46. Poole D, Mayo PH, Moller MH. The wicked path of causal inference in observational studies. *Intensive Care Med*. 2020;46(4):799-801.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Kherad O, Restellini S, Almadi M, et al. Systematic review with meta-analysis: limited benefits from early colonoscopy in acute lower gastrointestinal bleeding. *Aliment Pharmacol Ther*. 2020;52:774–788. https://doi.org/10.1111/apt.15925