Outcomes in high and low volume hospitals in patients with acute hematochezia in a cohort study

Naoki Ishii1,2, Naoyoshi Nagata2,3, Katsumasa Kobayashi4, Atsushi Yamauchi5, Atsu Yamada6, Jun Omori7, Takashi Ikeya8, Taiki Aoyama9, Naoyuki Tominaga10, Yoshinori Sato11, Takaaki Kishino12, Tsunaki Sawada13, Masaki Murata14, Akinari Takaao15, Kazuhiro Mizukami16, Ken Kinjo17, Shunji Fujimori18, Takahiro Uotani19, Minoru Fujita20, Hirotoshi Sato21, Sho Suzuki22, Toshiaki Narasaka23,24, Junnosuke Hayasaka25, Tomohiro Funabiki26,27, Yuzuru Kinjo28, Akira Mizuki29, Shu Kiyotoki30, Tatsuya Mikami31, Ryosuke Gushima32, Hiroyuki Fujii33, Yuta Fuyuno34, Naohiko Gunji35, Yosuke Toya36, Kazuyuki Narimatsu37, Noriaki Manabe38, Koji Nagaie39, Tetsu Kinjo40, Yorinobu Sumida41, Sadahiro Funakoshi42, Kana Kawagishi43, Ken Kinjo44, Sho Suzuki45, Toshiaki Narasaka46, Junnosuke Hayasaka47, Yosuke Toya48, Kazuhiro Watanabe49, Fumio Omata5, Yasutoshi Shiratori5, Noriatsu Imamura5, Takahiko Yano6 & Mitsuru Kaise7

1Division of Gastroenterology, Tokyo Shinagawa Hospital, 6-3-22 Higashi-Ooi, Shinagawa-ku, Tokyo 140-8522, Japan. 2Department of Gastroenterological Endoscopy, Tokyo Medical University, Tokyo, Japan. 3Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Tokyo, Japan. 4Department of Gastroenterology, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan. 5Department of Gastroenterology and Hepatology, Kitano Hospital, Tazuke Kofuku Medical Research Institute, Osaka, Japan. 6Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan. 7Department of Gastroenterology, Nippon Medical School, Graduate School of Medicine, Tokyo, Japan. 8Department of Gastroenterology, St. Luke's International University, Tokyo, Japan. 9Department of Gastroenterology, Hiroshima City Asa Citizens Hospital, Hiroshima, Japan. 10Department of Gastroenterology, Kagoshima University School of Medicine, Kagoshima, Japan. 11Division of Gastroenterology and Hepatology, Graduate School of Medicine, Nishinippon Medical School, Kitakyushu, Japan. 12Division of Gastroenterology and Hepatology, Department of Internal Medicine, St Marianna University School of Medicine, Tokyo, Japan. 13Department of Gastroenterology, Saga Medical Center, Saga, Japan. 14Division of Gastroenterology and Hepatology, Department of Internal Medicine, St Marianna University School of Medicine, Kanagawa, Japan. 15Department of Gastroenterology and Hepatology, National Hospital Organization Tokyo Medical Center, Tokyo, Japan. 16Department of Endoscopy, Nagoya University Hospital, Aichi, Japan. 17Department of Gastroenterology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan. 18Department of Gastroenterology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan. 19Department of Gastroenterology, Oita University, Oita, Japan. 20Department of Gastroenterology, Fukushima University Chikushi Hospital, Fukushima, Japan. 21Department of Gastroenterology, Chiba Hokusoh Hospital, Nippon Medical School, Chiba, Japan. 22Department of Gastroenterology, Japanese Red Cross Shizuoka Hospital, Shizuoka, Japan. 23Division of Endoscopy and Ultrasonography, Department of Clinical Pathology and Laboratory Medicine, Kawasaki Medical School General Medical Center, Okayama, Japan. 24Division of Gastroenterology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan. 25Department of Gastroenterology and Hepatology, Center for Digestive Disease and Division of Endoscopy, University of Miyazaki Hospital, Miyazaki, Japan. 26Department of Gastroenterology, University of Tsukuba, Ibaraki, Japan. 27Division of Endoscopic Center, University of Tsukuba, Ibaraki, Japan. 28Department of Emergency Medicine, Fujita Health University Hospital, Aichi, Japan. 29Emergency and Critical Care Center, Saiseikai Yokohamashi Toku Hospital, Kanagawa, Japan. 30Department of Gastroenterology, National Hospital Organization Fukuokahigashi Medical Center, Fukuoka, Japan. 31Division of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan. 32Department of Gastroenterology, Fukushima Medical University, Fukushima, Japan. 33Division of Gastroenterology, Department of Internal Medicine, Iwate Medical University, Iwate, Japan. 34Department of Internal Medicine,
Outcomes of acute lower gastrointestinal bleeding have not been compared according to hospital capacity. We aimed to perform a propensity score-matched cohort study with path and mediation analyses for acute hematochezia patients. Hospitals were divided into high- versus low-volume hospitals for emergency medical services. Rebleeding and death within 30 days were compared. Computed tomography, early colonoscopy (colonoscopy performed within 24 h), and endoscopic therapies were included as mediators. A total of 2644 matched pairs were yielded. The rebleeding rate within 30 days was not significant between high- and low-volume hospitals (16% vs. 17%, \( P = 0.44 \)). The mortality rate within 30 days was significantly higher in the high-volume cohort than in the low-volume cohort (1.7% vs. 0.8%, \( P = 0.003 \)). Treatment at high-volume hospitals was not a significant factor for rebleeding (odds ratio [OR] = 0.91; 95% confidence interval [CI], 0.79–1.06; \( P = 0.23 \)), but was significant for death within 30 days (OR = 2.03; 95% CI, 1.17–3.52; \( P = 0.012 \)) on multivariate logistic regression after adjusting for patients’ characteristics. Mediation effects were not observed, except for rebleeding within 30 days in high-volume hospitals through early colonoscopy. However, the direct effect of high-volume hospitals on rebleeding was not significant. High-volume hospitals did not improve the outcomes of acute hematochezia patients.

Abbreviations

ALGIB         Acute lower gastrointestinal bleeding
CDB          Colonic diverticular bleeding
CCI          Charlson comorbidity index
CODE BLUE J-Study  Colonic Diverticular Bleeding Leaders Update Evidence from the Multicenter Japanese Study
COVID-19     Coronavirus disease 2019
CRP          C-reactive protein
CT           Computer tomography
EBL          Endoscopic band ligation
EDSL         Endoscopic detachable snare ligation
IQR          Interquartile range
IVR          Interventional radiology
LOS          Length of hospital stay
NSAIDs       Non-steroidal anti-inflammatory drugs
PT-INR       Prothrombin time-international normalized ratio
PR           Pulse rate
PRBC         Packed red blood cell
PS           Performance status
RCT          Randomized controlled trial
SRH          Stigmata of recent hemorrhage
SBP          Systolic blood pressure
SD           Standard deviation
UGIB         Upper gastrointestinal bleeding

Medical centers are classified as high or low-volume centers in terms of the treatment strategies followed and clinical outcomes achieved for different diseases\(^1\)–\(^3\). The outcomes following the management of acute pancreatitis and upper gastrointestinal bleeding, as well as the outcomes of high-risk surgeries, were noted to be superior in high-volume centers\(^1\)–\(^3\). However, the differences between these settings in terms of clinical outcomes for the management of patients with acute hematochezia—specifically acute lower gastrointestinal bleeding (ALGIB)—have not been sufficiently investigated.

The incidence of ALGIB, including colonic diverticular bleeding, has been increasing in recent years\(^4\). The global coronavirus disease (COVID-19) pandemic has strained health systems worldwide and created a need to use evidence-based strategies to effectively prioritize the use of limited medical resources shared between patients with COVID-19 and other urgent conditions, including ALGIB\(^5\). Role allotments, especially for emergency diseases, are required according to hospital characteristics. If outcomes of ALGIB are better in high-volume hospitals than in low-volume hospitals, ALGIB cases should be primarily managed at high-volume hospitals with sufficient medical resources. On the other hand, because the clinical course of most ALGIB cases, including colonic diverticular hemorrhage, are generically mild with spontaneous resolution of bleeding episodes in 70–80% of cases\(^6\), there may be a possibility of equal outcomes irrespective of hospital capacity.
Recently, path analysis and a generalized structural equation model (GSEM) have been used not only in causal pathways but also for the evaluation of complex network and mediation analysis. As acute hematochezia has many possible causes and the diagnosis of ALGIB requires computed tomography (CT) and colonoscopy, management strategies remain complicated despite the currently available guidelines. The introduction of path and mediation analyses may be required for the evaluation of these diagnostic and treatment modalities for patients with ALGIB.

This propensity score-matched cohort study aimed to compare outcomes and management strategies for patients with acute hematochezia treated at the high-volume and low-volume hospitals for emergency medical services and perform path and mediation analyses that influence clinical outcomes using GSEM.

Results

**Patient characteristics.** The area under the receiver operating curve of propensity scores for high-volume settings was 0.57 (95% confidence interval [CI], 0.56–0.59). Propensity scores were constructed in 6822 complete-data cases and a total of 2644 matched pairs were yielded (Fig. 1). The characteristics of unmatched and matched patients in the high- and low-volume hospitals are shown in Table 1. The absolute value of standardized differences determined after balance checking was less than 0.1 for all variables.

**Diagnosis of ALGIB.** The performances of CT and colonoscopy are shown in Table 2. CT and enhanced CT were performed more frequently in high-volume hospitals than in low-volume hospitals (80% vs. 67%, P < 0.0001 and 76% vs. 67%, P < 0.0001, respectively). However, the proportions of colonoscopy and early colonoscopy performed were significantly lower in the high-volume hospitals than in low-volume hospitals (85% vs. 95%, P < 0.0001 and 55% vs. 72%, P < 0.0001, respectively). CT was more frequently used as the first-line diagnostic modality in high-volume hospitals than in low-volume hospitals (77% vs. 61%, P < 0.0001).

The sources of bleeding are listed in Table 3. Although diverticular bleeding was the most common cause of acute hematochezia in both groups, the proportion of definitive diverticular bleeding was significantly lower in the high-volume hospitals than in low-volume hospitals (19% vs. 26%, P < 0.0001). The proportion of patients with upper gastrointestinal bleeding was significantly higher in the high-volume hospitals than in low-volume hospitals (3.4% vs. 0.3%, P < 0.0001).

**Treatments and outcomes.** Treatments and outcomes in the high- and low-volume hospitals are shown in Table 2. Endoscopic therapy was performed less frequently in high-volume hospitals than in low-volume hospitals (24% vs. 30%, P < 0.0001). The rebleeding rate within 30 days was not significantly different between the two cohorts (16% vs. 17%, P = 0.44). The number of deaths within 30 days was significantly higher in the high-volume cohort than in the low-volume cohort (45 [1.7%] vs. 21 [0.8%], P = 0.003). A significant difference...
was observed regarding transfusion of packed red blood cells between the high- and low-volume hospitals (0 [interquartile range (IQR), 0–4] vs. 0 [IQR, 0–2], \(P < 0.0001\). No significant difference was found in the length of stay between the two groups (7 [IQR, 5–12] vs. 7 [IQR, 5–11], \(P = 0.25\)).

Being treated at a high-volume hospital was not a significant factor for rebleeding within 30 days, but was a significant factor for death within 30 days according to the multivariate logistic regression data after adjusting for patients’ characteristics in the matched cohort, respectively (odds ratio [OR], 0.91, 95% CI, 0.79–1.06, \(P = 0.25\); OR, 0.70; 95% CI, 0.55–0.89; \(P = 0.0001\)) (Table 4). Being treated at a high-volume hospital was a significant factor in increasing the amount of packed red blood cells transfused and the length of stay on the multivariate linear regression after controlling for patients’ characteristics (Table 4). Statistical difference was also observed in the unmatched cohort.

**Path and mediation analyses using a GSEM.** The results of path analyses between hospital characteristics and rebleeding and death within 30 days with or without mediators using a GSEM are demonstrated in Table 5 and Supplementary Note. CT was used as a first-line diagnostic modality, early colonoscopy, and endoscopic therapies were included as the mediators. Considering coefficient differences between the results with and without the use of mediators, absolute coefficient differences were larger on death within 30 days.

The results of mediation analyses in each mediator are demonstrated in Table 6. Indirect effects were not statistically significant in all analyses, except for early colonoscopy on the association between high-volume hospitals and rebleeding within 30 days (coefficient, \(-0.083, 95\%\) CI, \(-0.144–0.053; P < 0.0001\). However, the direct effect, the subtraction of the indirect effect from the total effect, was not statistically significant on the association.

**Discussion**

To the best of our knowledge, this study is the first to compare the management and clinical outcomes of patients with acute hematochezia according to hospital characteristics and perform path and mediation analyses. Unlike in the study for upper gastrointestinal bleeding\(^1\), high-volume hospitals for emergency medical services did not improve rebleeding and death within 30 days compared to low-volume hospitals in the present study, although adjunctive outcomes such as performance of CT and colonoscopy, and the bleeding causes were significantly different between the two groups. Patients with acute hematochezia could have equal treatment outcomes regardless of the hospital capacity if CT and emergency endoscopy were available 24/7.

Although CT is more commonly performed in high-volume hospitals, the use of colonoscopy is the reverse of CT. Upper gastrointestinal bleeding should be suspected in cases of gastrointestinal bleeding with unstable vitals, even for patients presenting with acute hematochezia. CT was recommended as a first-line diagnostic modality.
for these patients\textsuperscript{10-14}. Our finding that CT was performed more frequently in high-volume hospitals might explain the high proportion of patients with unstable vital signs, such as patients with upper gastrointestinal bleeding who presented with acute hematochezia. The proportions of early colonoscopy and endoscopic therapies were lower in high-volume hospitals than in low-volume hospitals in the present study. The systematic review and meta-analysis demonstrated that early colonoscopy was associated with the performance of endoscopic therapies\textsuperscript{15}. In the mediation analyses shown in Table 6, the indirect effect of early colonoscopy was significant, showing an inverse effect on rebleeding within 30 days in high-volume hospitals. The lower performance of early colonoscopy, a negative coefficient in this path, and the association of early colonoscopy with rebleeding within 30 days, a positive coefficient, contributed to this result (Table 2 and Supplementary Note) because the indirect effects were calculated by multiplication of each coefficient on a path. However, further studies are required to clarify the influence of early colonoscopy by comparing early vs. non-early colonoscopy groups.

The most common cause of acute hematochezia was diverticular bleeding (Table 3). However, the proportion of definitive diverticular bleeding was significantly lower in high-volume hospitals. The performance of CT as the first-line diagnostic modality and early colonoscopy seemed to be conflicting in the diagnosis proportion of definitive diverticular bleeding because the more introduction of CT or early colonoscopy could have the possibility of increasing the definitive diagnosis\textsuperscript{16,17}. The role of CT as the first-line diagnostic should be elucidated after time.

The higher performance of hemostatic modalities used was quite different (Table 2). The difference in the diagnosis of acute hematochezia might have influenced the selection of treatment modalities. A few recent studies have reported the therapeutic utility of ligation therapy for colonic diverticular bleeding\textsuperscript{18,19}. Moreover, the role of CT as the first-line diagnostic modality and early colonoscopy seemed to be conflicting in the diagnosis proportion of definitive diverticular bleeding because the more introduction of CT or early colonoscopy could have the possibility of increasing the definitive diagnosis\textsuperscript{16,17}. The role of CT as the first-line diagnostic should be elucidated after time.

Table 2. Management and outcomes in patients with acute hematochezia in the unmatched and the matched cohorts: high-volume versus low-volume hospitals. A two-tailed $P$-value < 0.05 was considered to indicate statistical significance. CT computed tomography, EBL endoscopic band ligation, EDSL Endoscopic detachable snare ligation, IVR interventional radiology, PRBCs packed red blood cells, IQR interquartile range.
### Table 3. Diagnosis in patients with acute hematochezia in the unmatched and the matched cohorts: high-volume versus low-volume hospitals. A two-tailed $P$-value $< 0.05$ was considered to indicate statistical significance. DB diverticular bleeding, IBD inflammatory bowel disease, GI gastrointestinal.

| Diagnosis                        | High-volume hospitals | Low-volume hospitals | $P$-value | High-volume hospitals | Low-volume hospitals | $P$-value |
|----------------------------------|-----------------------|----------------------|-----------|-----------------------|----------------------|-----------|
| Unmatched cohort (n = 8268)      |                       |                      |           |                       |                      |           |
| High-volume hospitals            | 4653                  | 3615                 |           | 2644                  | 2644                 |           |
| Definitive DB, n (%)             | 821 (18)              | 920 (25)             | < 0.0001  | 510 (19)              | 697 (26)             | < 0.0001  |
| Presumptive, n (%)               | 1632 (35)             | 1474 (41)            | < 0.0001  | 1035 (39)             | 1105 (42)            | 0.05      |
| Ischemic colitis, n (%)          | 615 (13)              | 251 (6.9)            | < 0.0001  | 279 (11)              | 160 (6.1)            | < 0.0001  |
| Colorectal cancer, n (%)         | 109 (2.3)             | 54 (1.5)             | 0.06      | 57 (2.2)              | 49 (1.9)             | 0.43      |
| Metastatic cancer, n (%)         | 11 (0.2)              | 5 (0.1)              | 0.31      | 7 (0.3)               | 5 (0.2)              | 0.56      |
| Other cancer, n (%)              | 8 (0.2)               | 0 (0)                | 0.013     | 5 (0.2)               | 0 (0)                | 0.025     |
| Poly, n (%)                      | 18 (0.4)              | 18 (0.5)             | 0.45      | 10 (0.4)              | 16 (0.6)             | 0.24      |
| Infectious colitis, n (%)        | 106 (2.3)             | 23 (0.6)             | < 0.0001  | 37 (1.4)              | 11 (0.4)             | < 0.0001  |
| IBD, n (%)                       | 101 (2.2)             | 86 (2.4)             | 0.53      | 29 (1.1)              | 57 (2.2)             | 0.002     |
| Post-endoscopic therapy, n (%)   | 232 (5.0)             | 214 (5.9)            | 0.062     | 91 (3.4)              | 113 (4.3)            | 0.12      |
| Post-colectomy, n (%)            | 6 (0.13)              | 8 (0.22)             | 0.31      | 4 (0.15)              | 6 (0.23)             | 0.53      |
| Drug-induced ulcer, n (%)        | 4 (0.09)              | 5 (0.14)             | 0.47      | 2 (0.08)              | 5 (0.2)              | 0.27      |
| Non-specific ulcer, n (%)        | 34 (0.7)              | 16 (0.3)             | 0.094     | 24 (0.9)              | 13 (0.5)             | 0.07      |
| Non-specific colitis, n (%)      | 31 (0.7)              | 8 (0.2)              | 0.003     | 18 (0.7)              | 7 (0.3)              | 0.027     |
| Dieulafoy's ulcer, n (%)         | 6 (0.1)               | 5 (0.1)              | 0.91      | 3 (0.11)              | 5 (0.2)              | 0.48      |
| Diverticulitis, n (%)            | 6 (0.13)              | 1 (0.03)             | 0.12      | 1 (0.04)              | 1 (0.04)             | 1         |
| Varices, n (%)                   | 11 (0.2)              | 7 (0.2)              | 0.68      | 9 (0.3)               | 6 (0.2)              | 0.44      |
| Radiation proctocolitis, n (%)   | 27 (0.6)              | 27 (0.8)             | 0.35      | 16 (0.6)              | 17 (0.6)             | 0.86      |
| Rectal ulcer, n (%)              | 135 (2.9)             | 109 (3.0)            | 0.76      | 87 (3.3)              | 86 (3.3)             | 0.94      |
| Vascular ectasia, n (%)          | 52 (1.1)              | 64 (1.8)             | 0.012     | 32 (1.2)              | 53 (2.0)             | 0.022     |
| Hemorrhoids, n (%)               | 101 (2.2)             | 72 (2.0)             | 0.57      | 51 (1.9)              | 52 (1.8)             | 0.92      |
| Anal diseases, n (%)             | 4 (0.09)              | 6 (0.17)             | 0.3       | 3 (0.11)              | 4 (0.15)             | 0.71      |
| Upper GI bleeding, n (%)         | 140 (3.0)             | 8 (0.2)              | < 0.0001  | 87 (3.4)              | 7 (0.3)              | < 0.0001  |
| Small intestinal bleeding, n (%) | 113 (2.4)             | 83 (2.3)             | 0.69      | 65 (2.5)              | 60 (2.3)             | 0.65      |
| Others, n (%)                    | 23 (0.5)              | 9 (0.3)              | 0.075     | 14 (0.5)              | 6 (0.2)              | 0.73      |
| Not identified, n (%)            | 307 (6.6)             | 142 (3.9)            | < 0.0001  | 168 (6.4)             | 103 (3.9)            | < 0.0001  |

### Table 4. Association with rebleeding and death within 30 days, the amount of PRBCs, and length of hospital stay in the unmatched and the matched cohorts. Adjusted for patients' characteristics used for the construction of propensity scores. A two-tailed $P$-value $< 0.05$ was considered to indicate statistical significance. $OR$ odds ratio, $CI$ confidence interval, $PRBCs$ packed red blood cells.

|                                      | Unmatched cohort (n = 6822) | Matched cohort (n = 5288) |
|--------------------------------------|-----------------------------|---------------------------|
| Rebleeding within 30 days            |                             |                           |
| High-volume                          |                             |                           |
| OR, 95% CP                           | 0.89, 0.78–1.02             | 0.91, 0.79–1.06           | 0.23 |
| $P$-value                             | 0.091                       |                           |
| Death within 30 days                  |                             |                           |
| High-volume                           |                             |                           |
| OR, 95% CP                           | 1.96, 1.18–3.25             | 2.03, 1.17–3.52           | 0.012 |
| $P$-value                             | 0.010                       |                           |
| Transfused PRBCs, packs               |                             |                           |
| High-volume                           |                             |                           |
| β coefficient, 95% CI                | 0.48, 0.28–0.68             | 0.54, 0.31–0.78           | < 0.0001 |
| $P$-value                             | < 0.0001                    |                           |
| Length of hospital stay, days         |                             |                           |
| High-volume                           |                             |                           |
| β coefficient, 95% CI                | 1.08, 0.54–1.63             | 0.99, 0.41–1.57           | 0.001 |
| $P$-value                             | < 0.0001                    |                           |
perform path and mediation analyses. Several guidelines for the management of ALGIB have been published10–14.

We performed path and mediation analyses using propensity score-matched data and included candidate mediators in a colonoscopy-based management strategy (Supplementary Note). The coefficient difference between the results with or without the use of mediators composed of CT, early colonoscopy, and endoscopic therapies had a larger effect for high-volume hospitals on death within 30 days (Table 5). The indirect effect of early colonoscopy contributed to rebleeding within 30 days in high-volume hospitals possibly due to the lower performance of early colonoscopy as described before. However, the direct effect of high-volume hospitals on rebleeding was not significant as the total effect. Although the selected diagnostic and treatment modalities contributed to death within 30 days considering the coefficients differences in the path analysis (Table 5), the indirect effects on death within 30 days, one of the most important outcomes, were not significant through these mediators (Table 6). The diagnostic and treatment modalities may not substantially influence the associations between hospital characteristics and outcomes in the colonoscopy-based management of patients with acute hematochezia. These findings are intriguing and warrant further investigation.

The present study had some limitations. First, as a retrospective cohort study, the possibility of selection bias could not be eliminated. Moreover, although the accuracy of the collected data was verified multiple times, the risk of misclassification cannot be ruled out. Second, although measured confounders could be balanced using propensity score matching, unmeasured confounders could not be balanced in the present study. In addition, other variables might be required to be included for elucidating the association between hospital types and outcomes. Third, we performed path and mediation analyses on a colonoscopy-based strategy. However, there are different paths, such as interventional radiology for the management of patients with acute hematochezia10–14, additional path and mediation analyses were required to evaluate the mediation effects between hospital characteristics and outcomes.

This study has several strengths. First, there was a higher proportion of definitive diagnosis of acute hematochezia, which was made based on colonoscopy and/or CT (unknown bleeding etiology 5.2% in the CODE BLUEJ-Study vs. 22.8% in the United Kingdom Study), and important outcomes were evaluated using a database with a robust proportion of definitive diagnoses10,21. Second, this study is the first to report a comparison of management and clinical outcomes for patients with acute hematochezia according to hospital characteristics and perform path and mediation analyses. Several guidelines for the management of ALGIB have been published10–14.

### Table 5. Association of hospital characteristics with rebleeding and death within 30 days by using generalized structural equation model (GSEM).

| Mediator, CT first | Coefficient, 95% CI | P-value | Mediator, early colonoscopy | Coefficient, 95% CI | P-value |
|-------------------|--------------------|---------|-----------------------------|--------------------|---------|
| Total effect      | −0.057, −0.201–0.088 | 0.443   | Total effect                | 0.771, 0.266–1.277 | 0.003   |
| Indirect effect   | −0.002, −0.028–0.024 | 0.872   | Indirect effect             | 0.020, −0.086–0.125 | 0.715   |
| Direct effect     | −0.054, −0.203–0.094 | 0.472   | Direct effect               | 0.752, 0.232–1.272 | 0.005   |

| Mediator, endoscopic therapies | Coefficient, 95% CI | P-value | Mediator, endoscopic therapies | Coefficient, 95% CI | P-value |
|-------------------------------|--------------------|---------|-------------------------------|--------------------|---------|
| Total effect                  | −0.057, −0.204–0.091 | 0.451   | Total effect                  | 0.771, 0.162–1.381 | 0.013   |
| Indirect effect               | −0.004, −0.013–0.006 | 0.430   | Indirect effect               | 0.014, −0.016–0.045 | 0.357   |
| Direct effect                 | −0.053, −0.201–0.096 | 0.486   | Direct effect                 | 0.757, 0.141–1.373 | 0.016   |

### Table 6. Mediation analysis between hospital characteristics and rebleeding and death within 30 days in the matched cohort. Computed tomography used as a first-line diagnostic modality, early colonoscopy, and endoscopic therapies were included in the mediation analysis as the mediators. A two-tailed P-value < 0.05 was considered to indicate statistical significance. CT: computed tomography. CI: confidence interval.
However, there is little information on the association between hospital characteristics and clinical outcomes, types of hospitals that should receive patients with acute hematochezia, and mediation effects on important outcomes. Therefore, the results of this study could be helpful to guide patients with acute hematochezia and emergency transport services to an appropriate center and construct management strategies for patients with acute hematochezia.

Mediation effects were not observed, except for rebleeding within 30 days in high-volume hospitals through early colonoscopy. High-volume hospitals for emergency medical services did not improve the outcomes of patients with acute hematochezia. This suggests that patients with ALGIB have equal treatment outcomes regardless of the hospital capacity to manage the condition.

Methods
Patients and database development. We performed a retrospective cohort study using a propensity score drawing from a national large-scale database of ALGIB in Japan, the Colonic Diverticular Bleeding Leaders Update Evidence from the Multicenter Japanese Study (CODE BLUE J-Study)20. Forty-nine hospitals in Japan collaborated to build a database of patients aged > 20 years hospitalized with acute hematochezia—regardless of presentation with diarrhea, abdominal pain, or fever—between January 2010 and December 2019. The characteristics of the 49 hospitals are listed in Supplementary Table 1. Patient characteristics were collected from medical charts and endoscopy databases at each hospital. The characteristics included age, sex, height, body weight, Eastern Cooperative Oncology Group Performance Status (PS)22, vital signs (systolic blood pressure and heart rate), laboratory data, comorbidities, use of non-steroidal anti-inflammatory drugs (NSAIDs), results and timing of enhanced or plain CT, colonoscopy, endoscopic therapies, and clinical outcomes including rebleeding, thromboembolic events, and deaths. Collected data were checked by the research center. Three to four confirmation processes to ensure accurate data collection and correct fit for the required structures were required and performed between the research center and each hospital to minimize misclassifications and develop a robust database from the medical charts and endoscopy database in each hospital. Active ascertainment of patients’ data by use of telephone or mailing was not performed. The details of the CODE BLUE J-Study are described in a previous report20.

Hospital characteristics and outcome measures. All 49 hospitals were equipped to perform CT and emergency endoscopy which were available 24/7. The diagnosis of patients with acute hematochezia, mainly ALGIB, was based on the colonoscopy and/or CT findings, mainly referring to previous reports16,17. Diverticular bleeding was divided into definitive diverticular bleeding with stigmata of recent hemorrhage (SRH; active bleeding, non-bleeding visible vessel, or adherent clot) and presumptive diverticular bleeding without SRH and with no other bleeding sources by colonoscopy23. On enhanced CT, diverticula with or without extravasation were considered definitive or presumptive bleeding sources, respectively. If bleeding sources were not identified by colonoscopy and/or CT, then capsule endoscopy, balloon endoscopy, or esophagogastroduodenoscopy were performed, as appropriate, to reevaluate the bleeding sources. The origin of acute hematochezia was categorized as “unknown” for patients in whom bleeding sources could not be definitively diagnosed.

The primary outcomes were rebleeding and mortality within 30 days. Massive rectal bleeding after interventions, such as colonoscopy, interventional arterial embolization, and surgery, and decreased hemoglobin levels, were considered as rebleeding. The amount of transfused packed red blood cells and length of stay were secondary outcomes. Bleeding causes, management strategies such as performance of CT, enhanced CT, colonoscopy, and early colonoscopy (performed within 24 h after admission), and treatment methods were also collected and assessed as adjunctive outcomes.

Study setting. This study set is demonstrated in Fig. 1. As death within 30 days was one of the important outcomes, the second and subsequent admission events were excluded to reduce selection bias, and the first admission cases were included in the study. A total of 8268 cases were divided into high- and low-volume groups.

We obtained information about the number of emergency medical services from the gastroenterologists participating in the present study. The cut-off value was the 70 percentiles of 49 hospitals. High-volume emergency medical service was defined as > 5000 services provided in the 2019 calendar year (15 hospitals). Low-volume medical service was defined as > 5000 services provided in the same time interval (34 hospitals).

Statistical analysis. A logistic regression model was used to calculate the case propensity score based on age (years), sex, history of colonic diverticular bleeding and colectomy, presence of diabetes mellitus, hypertension, and dyslipidemia; Charlson Comorbidity Index (equal to or more than 2)24; use of NSAIDs, anticoagulants, and antiplatelets; equal to or more than performance status 3; vital signs (systolic blood pressure ≤ 100 mmHg, heart rate ≥ 100/min) at the initial visit; and laboratory data at admission (hemoglobin, platelet, serum albumin, and prothrombin time-international normalized ratio)25. One-to-one matching was performed between the two groups using the nearest neighbor method with a caliper width of 0.2 of the standard deviation of the logit of the propensity score.

Continuous and categorical variables of patient characteristics were compared using the student’s t-test and a chi-square test, respectively. The amount of transfused packed red blood cells and length of stay was compared using the Mann–Whitney U test. Multivariate logistic regression was used to examine the effects of hospital characteristics on rebleeding and deaths within 30 days while controlling for patient demographics. Because the amount of packed red blood cells and that of the length of stay were compared as continuous variables between high- and low-volume hospitals, these outcomes were evaluated using multivariate linear regressions while controlling for patient demographics. Multivariate logistic and linear regression were required in the matched cohort.
for the double robustness of evaluating the effect of hospital volume in addition to the propensity score-matched analyses. In addition, because there can be the risk of losing a substantial number of patients in the propensity score-matched analyses, multivariate regression was also used in the unmatched cohort.

At first, endoscopy was considered a mainstay for the management of ALGIB10–14. Path analysis was performed mainly based on colonoscopy-based strategy by GSEM, and mediation effect was analyzed between hospital characteristics and rebleeding and death within 30 days. As CT, the timing of colonoscopy, and endoscopic therapies were considered candidate mediators which may influence outcomes15–17,23, these factors were included in the path. A Stata command, Idecmp, was used for the mediation analysis26. A two-tailed P-value < 0.05 was considered to indicate statistical significance. All analyses were performed using STATA version 16 (Stata Corp, College Station, TX, USA; https://www.stata.com).

This study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The need to obtain patient informed consent was waived by the central institution (Tokyo Medical University) because of the retrospective nature of the study. The central institution (Tokyo Medical University) has a licensing committee/Institutional review board to approve the study on human participants. The study protocol was approved by the Institutional Ethics Committee of Tokyo Medical University (T2019-0244). A single IRB review was applied to this study and approved in all hospitals (Supplementary Table 1).

Data availability
If requested, access to the data of this study can be reviewed through the principal investigator of this study and the corresponding author, although this data is not available to the public due to privacy and ethical restrictions.

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Author contributions
All the authors have contributed significantly to and agree on the content of the manuscript. Each author's contribution to the manuscript is as follows: conception and design, N.I., N.N., and M.K.; analysis and interpretation of the data, N.I., N.N., K.K., A.Y., A.Y., J.O., T.I., T.A., N.T., Y.S., T.K., T.S., M.M., A.T., K.M., K.K., S.F., T.U., M.F., H.S., S.S., T.N., J.H., T.F., Y.K., A.M., S.K., T.M., R.G., H.F., Y.F., N.G., Y.T., K.N., N.M., K.N., T.K., Y.S., S.F., K.K., T.M., Y.K., K.M., K.W., Y.S., N.I., T.Y.; drafting of the article, N.I.; critical revision of the article for important intellectual content, N.N., N.T., F.O., and M.K.; final approval of the article, N.I., N.N., K.K., A.Y., A.Y., J.O., T.I., T.A., N.T., Y.S., T.K., T.S., M.M., A.T., K.M., K.Kinjo, S.F., T.U., M.F., H.S., S.S., T.N., J.H., T.F., Y.K., A.M., S.K., T.M., R.G., H.F., Y.F., N.G., Y.T., K.N., N.M., N.K., T.K., Y.S., S.F., K.K., T.M., Y.K., K.M., K.W., Y.S., N.I., T.Y., and M.K.; N.I., N.N., K.K., A.Y., A.Y., J.O., T.I., T.A., N.T., Y.S., T.K., T.S., M.M., A.T., K.M., K.Kinjo, S.F., T.U., M.F., H.S., S.S., T.N., J.H., T.F., Y.K., A.M., S.K., T.M., R.G., H.F., Y.F., N.G., Y.T., K.N., N.M., N.K., T.K., Y.S., S.F., K.K., T.M., Y.K., K.M., K.W., Y.S., N.I., T.Y., and M.K.; N.I., N.N., K.K., A.Y., A.Y., J.O., T.I., T.A., N.T., Y.S., T.K., T.S., M.M., A.T., K.M., K.Kinjo, S.F., T.U., M.F., H.S., S.S., T.N., J.H., T.F., Y.K., A.M., S.K., T.M., R.G., H.F., Y.F., N.G., Y.T., K.N., N.M., N.K., T.K., Y.S., S.F., K.K., T.M., Y.K., K.M., K.W., Y.S., N.I., T.Y., and M.K. approved the submitted version and agreed both to be personally accountable for the author's contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

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Competing interests
The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to N.I.

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