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Original Article

Intraosseous versus intravenous fluid resuscitation in gastrointestinal tumor-related acute hemorrhage: impact on 30-day mortality and lactate clearance

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Abstract: This retrospective study evaluated the impact of intraosseous infusion (IO) versus traditional intravenous infusion (IV) on 30-day mortality and clinical outcomes in 518 patients with acute gastrointestinal bleeding (AGIB) secondary to gastrointestinal tumors from January 2022 to July 2024. Patients were divided into IO (n=217) and IV (n=301) groups based on initial resuscitation strategy. Compared to IV group, the IO group demonstrated higher first-attempt catheterization success rate, shorter vascular access time, and faster blood pressure recovery (all P<0.001), alongside higher 6-hour lactate (LA) clearance (34% vs. 22%, P<0.001) and lower 30-day mortality (11.98% vs. 18.6%, P=0.016). Multivariate analysis identified IO infusion as protective factor for lactate metabolism (HR=0.289, 95% CI: 0.092-0.864), while advanced age (HR=1.125), diabetes (HR=3.23), and low LA clearance (HR=0.016) were independent risk factor for mortality. Causal mediation analysis revealed that 6-hour LA clearance mediated 68% of the IO-associated mortality reduction (P<0.001), whereas diabetes history was not a significant mediator (P=0.156). Complication rates were comparable between groups (P>0.05). These findings indicate that IO infusion improves survival in AGIB due to gastrointestinal tumors by rapidly restoring hemodynamics and enhancing lactate metabolism. The mortality benefit is primarily driven by accelerated LA clearance rather than comorbidities like diabetes. Given its safety profile comparable to IV, IO infusion should be prioritized in critical care settings.

Keywords: Gastrointestinal tumor, acute massive hemorrhage, intraosseous infusion, intravenous infusion, 30-day mortality, lactate clearance, prognostic factors

Introduction

Gastrointestinal (GI) tumors rank among the most prevalent malignancies globally, with rising incidence rates, particularly in regions where gastric and esophageal cancers are common [1]. Global cancer burden data indicate that gastric and esophageal cancers remain major contributors to cancer-related mortality [2]. Despite advances in early detection and treatment, patients with advanced GI tumors often experience severe complications, such as acute gastrointestinal bleeding (AGIB), which significantly threatens survival and quality of life [3].

AGIB is a common and potentially fatal complication in patients with GI malignancies. In advanced stages of gastric, esophageal, or other GI cancers, tumor invasion into blood vessels or ulcer formation can lead to massive hemorrhage [4], resulting in hypovolemia, hypotension, electrolyte disturbances, shock, and multi-organ failure [5]. Prompt fluid resuscitation and blood transfusion are therefore vital, as delays may lead to a 30-day mortality rate ranging from 30% to 40% [6]. Thus, early and effective management is essential for improving clinical outcomes.

Intravenous (IV) infusion is the standard method for fluid resuscitation. However, it presents

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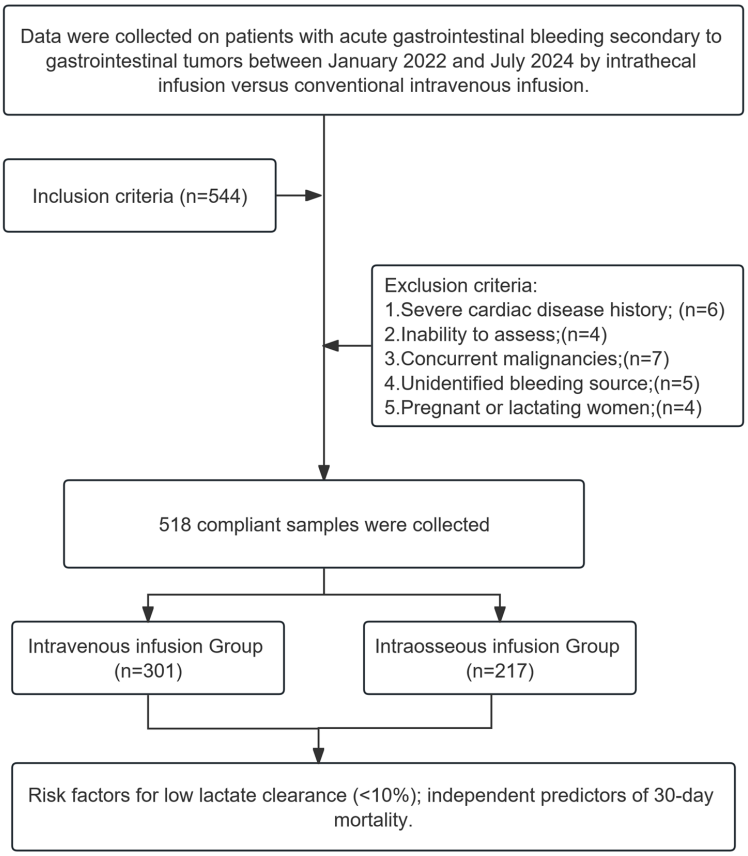

Figure 1. Sample collection flow chart.

challenges in AGIB patients [7]. Peripheral vasoconstriction, hypoperfusion, and hypotension often impair IV catheterization success, and infusion rates may be inadequate for rapid volume replacement [8]. Intraosseous (IO) infusion has emerged as a promising alternative, providing rapid and reliable vascular access via the bone marrow cavity and enabling efficient fluid delivery in emergency and critical care settings [9].

IV access is particularly difficult in patients with hemorrhagic shock or profound hypotension due to collapsed peripheral veins [10]. Delays in achieving vascular access and initiating resuscitation can worsen patient outcomes and elevate mortality risk. In contrast, IO infusion overcomes peripheral vascular limitations by enabling rapid fluid administration through bone marrow access [11]. It has been increasingly adopted in emergency medicine and critical care, particularly for scenarios such as cardiac arrest and acute hemorrhage [12]. However, limited evidence exists on its effectiveness in GI tumor-related AGIB, and its impact on 30-day mortality remains underexplored.

This study retrospectively compared the clinical efficacy of IO versus IV infusion in patients with GI tumors complicated by AGIB, with a primary focus on 30-day mortality. By assessing outcomes such as resuscitation efficiency, lactate clearance, and survival, we seek to determine whether IO infusion offers a more superior alternative in this high-risk population.

Methods and materials

Sample size calculation

Based on the study by Gong et al. [13], which reported a 30-day mortality rate of 17.8% in cancer-related non-variceal upper gastrointestinal bleeding treated with transarterial embolization, the sample size was calculated using the formula: $N = Z^2 \times [P \times (1 - P)]/E^2$, where E=0.05, Z=1.96, and P=0.178. The estimated minimum sample size was 225 patients, with the final sample size adjusted based on clinical availability.

Patient selection

This retrospective study included 518 patients with gastrointestinal (GI) tumors complicated by active gastrointestinal bleeding (AGIB), admitted between January 2022 and July 2024. The study was approved by the ethics committee of The People's Hospital of Rugao (**Figure 1**).

Inclusion and exclusion criteria

Inclusion criteria: (1) Confirmed diagnosis of a GI tumor (e.g., esophageal, gastric, colorectal, or other GI tract tumors) with concurrent AGIB; (2) Age ≥18 years; (3) Definitive AGIB diagnosis confirmed by clinical symptoms, endoscopy, and/or imaging; (4) Treatment initiated within

72 hours of bleeding onset; (5) Complete clinical records.

Exclusion criteria: (1) History of severe cardiac disease (e.g., advanced heart failure or myocardial infarction); (2) Inability to assess conditions (e.g., unconsciousness or poor cooperation); (3) Concurrent malignancies affecting outcome interpretation; (4) Unidentified bleeding source despite endoscopy or imaging; (5) Pregnant or lactating women due to potential treatment risks.

Definition of AGIB

AGIB was defined as an acute blood loss of ≥500 mL with significant physiological impact. Common clinical presentations included hematemesis (vomiting of bright red or coffee-ground-like blood), melena (black, tarry stools), or hematochezia (passage of fresh blood per rectum). Melena typically indicates upper GI bleeding, while hematochezia suggests lower GI sources [14].

Fluid resuscitation protocols

IV group: Central venous access was established via the external jugular or subclavian vein (1 cm below the midclavicular point). Following local anesthesia with 2% lidocaine (2 mL), a puncture needle was inserted, and successful venous entry was confirmed by blood return. A guidewire was introduced, the skin was dilated, and a catheter was placed and connected to the infusion device.

IO group: Patients were positioned supine, and the puncture site was selected 1-3 cm below the tibial tuberosity on the medial flat surface. After standard disinfection, an IO needle was inserted into the bone marrow at a 90° angle using a power driver. Entry was confirmed by loss of resistance and bone marrow aspiration. A pre-flushed connector was attached, followed by a 10 mL saline bolus and connection to the infusion device. After 24 hours, IO access was transitioned to conventional IV infusion per standard clinical protocol [11].

Data collection

Baseline variables included demographics (age, gender, BMI), tumor type, TNM stage, estimated 24-hour blood loss, time from bleeding onset to admission, hemorrhagic shock status, and comorbidities (diabetes, hypertension, prior radiotherapy/chemotherapy). Treatment details encompassed fluid resuscitation method (IV vs. IO), hemostatic intervention (endoscopy vs. embolization), first-attempt catheterization success rate, time to vascular access, time to blood pressure recovery, infusion rate, and urine output. Laboratory data involved pre- and 6-hour post-infusion levels of lactate (LA) and albumin (ALB); lactate clearance rate = [(pre-infusion LA - 6-hour post-infusion LA)/pre-infusion LA] × 100%. Outcomes included 30-day all-cause mortality, complication rates (local swelling, catheter dislodgement, infection, fluid extravasation), and resuscitation success rate.

All data were extracted from the hospital information system (HIS), including admission notes, progress records, laboratory results, nursing records, and discharge summaries.

Laboratory testing

Lactate (LA) and albumin (ALB) levels were measured using the Beckman Coulter AU5800 automatic biochemical analyzer (Beckman Coulter, USA). Peripheral venous blood (5 mL) was collected before and 6 hours after infusion into heparinized tubes and then centrifuged at 3000 rpm for 10 minutes (radius 15 cm) to isolate plasma. LA was assayed using the lactate oxidase colorimetric method (kit OSR6120, λ=540 nm), and ALB was measured using the bromocresol green method (kit OSR6102, λ= 628 nm). Lactate clearance was calculated as described above and reported in mmol/L for LA and g/L for ALB.

Outcome definitions

Hemorrhagic death: Caused by AGIB-related events (e.g., hypovolemic shock, multi-organ failure, refractory bleeding).

Non-hemorrhagic death: Attributed to tumor progression, septic shock, or cardiopulmonary failure.

Cause of death was determined based on electronic health record (EHR) documentation and death certificates.

Outcome measures

Primary outcomes: Risk factors for low lactate clearance (<10%); independent predictors of 30-day mortality.

Secondary outcomes: First-attempt catheterization success rate and overall resuscitation success; time to establish infusion access, blood pressure recovery, infusion rate, and urine output; changes in LA and ALB levels before and 6 hours after infusion; 6-hour LA clearance; complications (e.g., swelling, catheter dislodgement, infection, extravasation).

Statistical analysis

Data were analyzed using SPSS version 27.0 and R version 4.3.3. Categorical variables were reported as frequencies and percentages and compared using the chi-square test or Correction should test, as appropriate. Continuous variables were assessed for normality with the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean ± standard deviation and analyzed using independent-samples or paired-samples t-tests. Non-normally distributed data were reported as medians with interquartile ranges and compared using the Mann-Whitney U test or Wilcoxon signed-rank test.

Logistic regression was used to identify independent risk factors for low lactate clearance (<10%). Cox proportional hazards regression models were applied to analyze factors associated with 30-day mortality, with hazard ratios (HRs) and 95% confidence intervals (CIs) calculated. Receiver operating characteristic (ROC) curves and area under the curve (AUC) values were generated using the *pROC* package, with differences compared via DeLong's test. Kaplan-Meier survival curves and forest plots were constructed using the survival package, with group comparisons assessed by the log-rank test.

Competing risk analysis was conducted using the Fine-Gray model with the *cmprsk* package to account for non-hemorrhagic death as a competing event. Mediation analysis was performed using the mediation package in R to explore mechanisms between independent variables and outcomes through potential mediators, with standardized path coefficients assessing mediation effect magnitude.

All models were tested for appropriate assumptions, and confidence intervals were computed. All hypothesis tests were two-sided, with a P value <0.05 considered statistically significant.

Results

Comparison of baseline characteristics between the IV and IO groups

Baseline characteristics were well-balanced between patients with GI tumor-related massive hemorrhage receiving IO and IV treatments. No significant differences were observed between the IO and IV groups in age (P=0.411), gender (P=0.560), body mass index (P=0.238), cancer type (P=0.753), TNM stage (P=0.580), 24-hour blood loss (P=0.374), transfusion therapy within 24 hours (P=0.261), time from bleeding onset to admission (P=0.358), occurrence of hemorrhagic shock (P=0.560), history of chemotherapy/radiotherapy (P=0.456), diabetes (P=0.153), or hypertension (P=0.497), indicating strong comparability between groups (**Table 1**).

Comparison of first-attempt cannulation and resuscitation success rates between the IV and IO groups

The IO group exhibited a significantly higher first-attempt cannulation success rate compared to the IV group (P<0.001, **Figure 2A**), demonstrating greater efficiency in emergency vascular access. However, no significant difference was found in resuscitation success rates between the two groups (P=0.194, **Figure 2B**).

Comparison of fluid-related indicators between the IV and IO groups

The IO group required significantly less time to establish an infusion channel (P<0.001, **Figure 3A**) and achieved faster blood pressure recovery after fluid resuscitation (P<0.001, **Figure 3B**) compared to the IV group. No significant differences were observed in infusion rate (P=0.823, **Figure 3C**) or urine output (P=0.466, **Figure 3D**) between the groups.

Table 1. Comparison of baseline characteristics between IO group and IV group

Variable	Total	IV Group (n=301)	IO Group (n=217)	Statistic	*P*-Value
Age (years)	65.12±7.84	65.36±7.73	64.79±7.99	0.822	0.411
Gender					
Male	384 (74.13%)	226 (75.08%)	158 (72.81%)	0.339	0.560
Female	134 (25.87%)	75 (24.92%)	59 (27.19%)		
BMI (kg/m^2)	24.00±2.99	24.13±3.00	23.81±2.97	1.180	0.238
Cancer Type					
Gastric Cancer	305 (58.88%)	181 (60.13%)	124 (57.14%)	0.567	0.753
Esophageal Cancer	185 (35.71%)	105 (34.88%)	80 (36.87%)		
Other	28 (5.41%)	15 (4.98%)	13 (5.99%)		
TNM Stage					
Stage II	56 (10.81%)	30 (9.97%)	26 (11.98%)	1.091	0.580
Stage III	134 (25.87%)	75 (24.92%)	59 (27.19%)		
Stage IV	328 (63.32%)	196 (65.12%)	132 (60.83%)		
24 h Blood Loss					
≥1000 mL	105 (20.27%)	57 (18.94%)	48 (22.12%)	0.790	0.374
<1000 mL	413 (79.73%)	244 (81.06%)	169 (77.88%)		
24 h Blood Transfusion					
Yes	281 (54.25%)	157 (52.16%)	124 (57.14%)	1.262	0.261
No	237 (45.75%)	144 (47.84%)	93 (42.86%)		
Time from Bleeding to Admission					
≥12 h	315 (60.81%)	178 (59.14%)	137 (63.13%)	0.846	0.358
<12 h	203 (39.19%)	123 (40.86%)	80 (36.87%)		
Hemorrhagic Shock					
Yes	134 (25.87%)	75 (24.92%)	59 (27.19%)	0.339	0.560
No	384 (74.13%)	226 (75.08%)	158 (72.81%)		
Received Radiation/Chemotherapy					
Yes	346 (66.80%)	205 (68.11%)	141 (64.98%)	0.557	0.456
No	172 (33.20%)	96 (31.89%)	76 (35.02%)		
Diabetes History					
Yes	104 (20.08%)	54 (17.94%)	50 (23.04%)	2.045	0.153
No	414 (79.92%)	247 (82.06%)	167 (76.96%)		
Hypertension History					
Yes	187 (36.10%)	105 (34.88%)	82 (37.79%)	0.461	0.497
No	331 (63.90%)	196 (65.12%)	135 (62.21%)		
Hemostasis Method					
Interventional Embolization	333 (64.29%)	137 (63.13%)	196 (65.12%)	0.216	0.642
Endoscopic Hemostasis	185 (35.71%)	80 (36.87%)	105 (34.88%)		

Note: BMI: Body Mass Index.

Comparison of lactate (LA) and albumin (ALB) levels between the two groups before and after infusion

Before fluid infusion, LA and ALB levels showed no significant differences between the IO and IV groups (P>0.05). Post-infusion, both groups exhibited significant reductions in LA levels (P<0.001) and increases in ALB levels (P<0.001). The IO group demonstrated significantly greater reductions in LA and increases in ALB compared to the IV group (P<0.001, **Figure 4**).

Comparison of lactate clearance rate between the two groups

The IO group achieved a significantly higher 6-hour lactate clearance rate than the IV group (P<0.001, **Figure 5**).

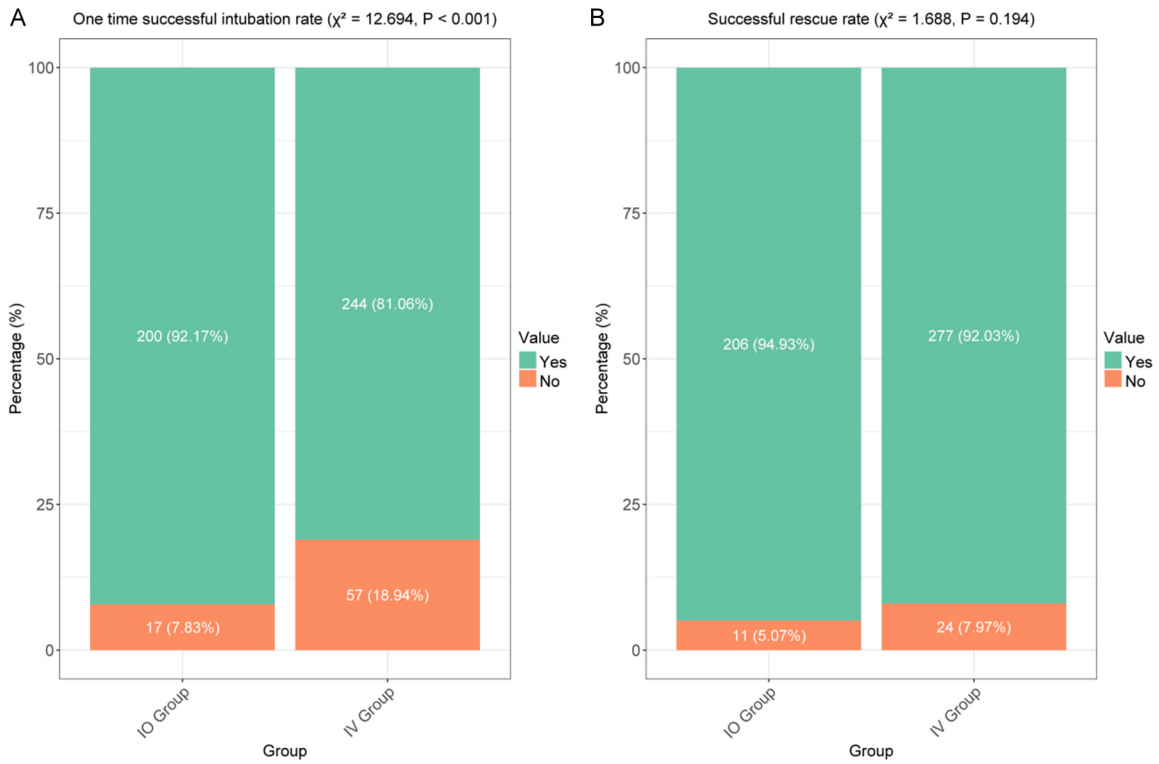

Figure 2. Comparison of first-attempt cannulation success rate and resuscitation success rate between IO group and IV group. A. First-attempt cannulation success rate; B. Resuscitation success rate. Note: IO: Intraosseous infusion, IV: Intravenous infusion.

Comparison of incidence of complications between the two groups

No significant differences in complication rates were observed between the IV and IO groups. Local swelling occurred in 24 cases in the IV group and 15 in the IO group (P=0.651). Catheter dislodgement was reported in 12 cases in the IV group and 9 in the IO group (P=0.927). Infections occurred in 5 cases in the IV group and 4 in the IO group (P=0.854). Fluid extravasation was noted in 12 cases in the IV group and 7 in the IO group (P=0.649) (**Table 2**).

Comparison of baseline characteristics between patients stratified by lactate clearance rate

Older age (P<0.001), 24-hour blood loss ≥1000 mL (P=0.004), time from bleeding onset to admission ≥12 hours (P=0.021), and hemorrhagic shock (P=0.030) were significantly associated with a lactate clearance rate <10%. The proportion of patients with a lactate clearance rate ≥10% was significantly higher in the IV group than in the IO group (P=0.003). Additionally, patients requiring ≥12 hours for blood pressure recovery after fluid resuscitation had a significantly higher proportion with a lactate clearance rate <10% (P=0.024). No significant associations were found with gender, BMI, cancer type, TNM stage, diabetes history, hypertension history, chemotherapy/radiotherapy history, first-attempt cannulation success rate, resuscitation success rate, infusion rate, urine output, or ALB levels before and after infusion (P>0.05) (**Table 3**).

Univariate and multivariate analysis of risk factors for lactate clearance

In univariate analysis, older age (OR=1.122, 95% CI: 1.081-1.168, P<0.001), blood loss ≥1000 mL (OR=0.438, 95% CI: 0.251-0.783, P=0.004), longer time from bleeding onset to admission (OR=0.508, 95% CI: 0.276-0.895, P=0.023), hemorrhagic shock (OR=0.548, 95% CI: 0.319-0.958, P=0.031), IO fluid resuscitation strategy (OR=0.409, 95% CI: 0.220-0.726,

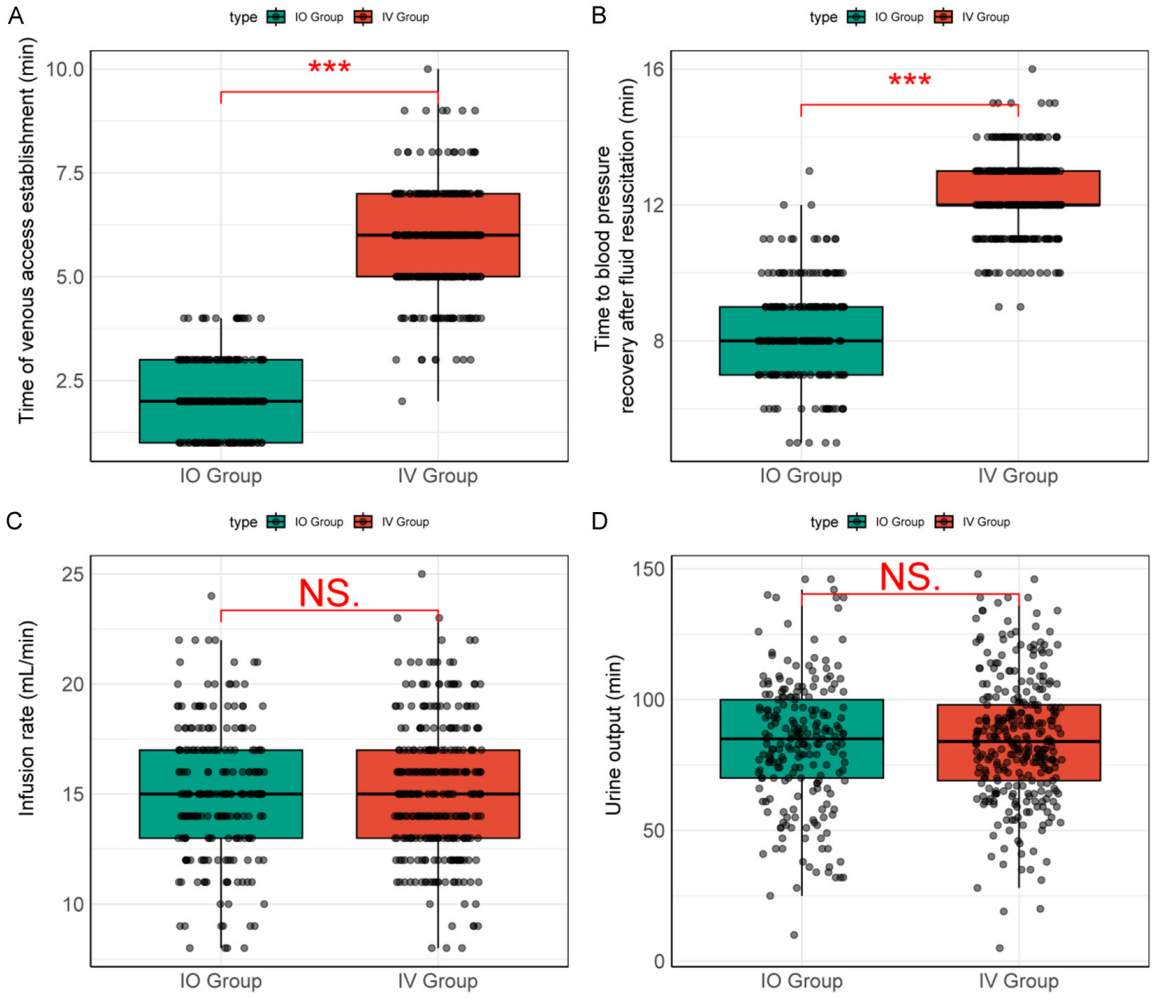

Figure 3. Comparison of fluid-related indicators between IO group and IV group. A. Time required for establishing an infusion pathway; B. Time required for blood pressure recovery after fluid resuscitation; C. Infusion rate; D. Urine output. Note: IO: Intraosseous infusion, IV: Intravenous infusion; "ns" indicates no significant difference, "***" indicates P<0.001.

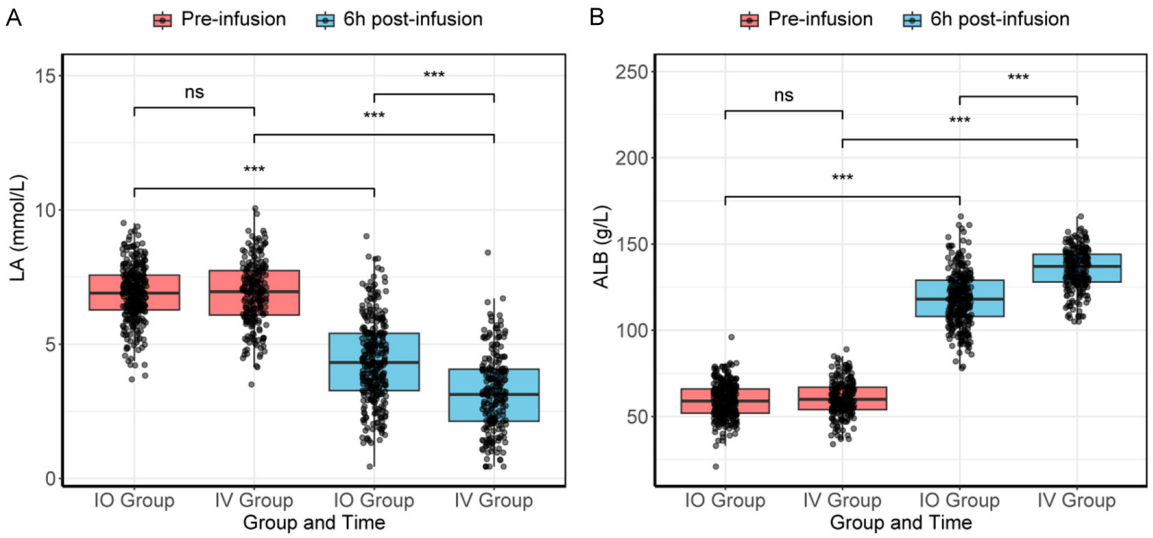

Figure 4. Comparison of changes in LA and ALB levels between IO and IV groups before and after infusion. A. Change in LA levels before and 6 hours after infusion; B. Change in ALB levels before and 6 hours after infusion. Note: LA: Lactate, ALB: Albumin, IO: Intraosseous infusion, IV: Intravenous infusion; "ns" indicates no significant difference, "***" indicates P<0.001.

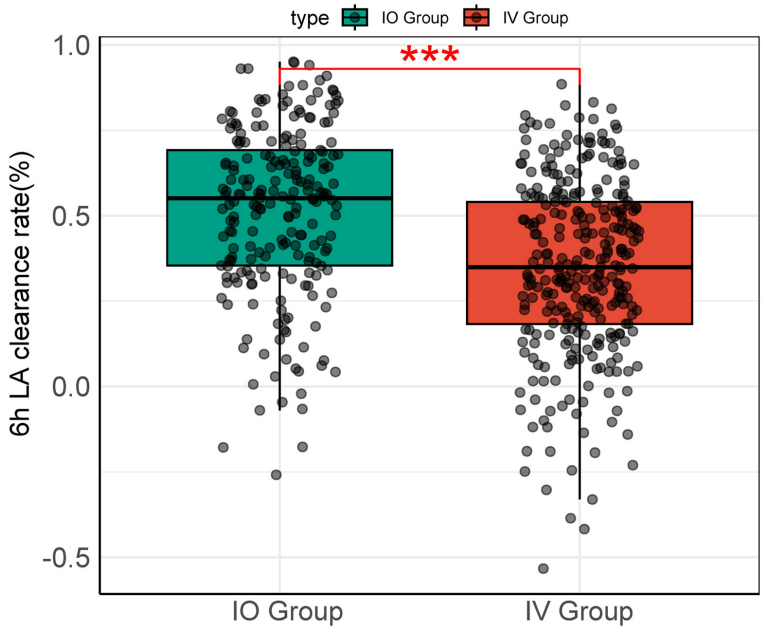

Figure 5. Comparison of 6-hour LA clearance rate between IO and IV groups. Note: LA: Lactate, IO: Intraosseous infusion, IV: Intravenous infusion; "***" indicates P<0.001.

Table 2. Comparison of complication incidence between IV group and IO group

Group	Local Swelling	Catheter Dislodgement	Infection	Fluid Extravasation
IV Group (n=301)	24	12	5	12
IO Group (n=217)	15	9	4	7
Chi-square Value	0.204	0.008	0.034	0.207
P Value	0.651	0.927	0.854	0.649

Note: IV: Intravenous, IO: Intraosseous.

P=0.003), and longer time for blood pressure recovery (OR=1.148, 95% CI: 1.021-1.298, P=0.024) were associated with a lactate clearance rate <10%. Multivariate analysis identified age (OR=1.125, 95% CI: 1.081-1.175, P<0.001) and IO fluid resuscitation strategy (OR=0.289, 95% CI: 0.092-0.864, P=0.029) as independent risk factors for a lactate clearance rate <10%. Hemorrhagic shock showed a trend toward significance (OR=0.586, 95% CI: 0.324-1.076, P=0.080), while time for blood pressure recovery was not significant (OR=0.953, 95% CI: 0.754-1.201, P=0.682) (**Figure 6**).

ROC curve analysis of risk predictive ability

A risk model was constructed: (Logit(p) = -4.416 + 0.118 × age + 0.765 × 24-hour blood loss ≥1000 mL + 0.816 × time from bleeding onset to admission + 1.241 × fluid resuscitation strategy). ROC curve analysis revealed that the risk model had the highest discriminatory ability for predicting a lactate clearance rate <10% (AUC=0.777), surpassing each variable alone [age (AUC=0.705), 24-hour blood loss (AUC=0.578), time from bleeding onset to admission (AUC=0.575), and fluid resuscitation strategy (AUC=0.599)]. Comparisons showed significant differences between the risk model and individual variables (P<0.05), indicating superior predictive performance of the risk model, followed by fluid resuscitation strategy (**Figure 7A**, **7B**).

Cox regression analysis of prognostic factors for 30-day all-cause mortality

Cox regression analysis identified age, diabetes history, and lactate clearance rate as independent prognostic factors for 30-day all-cause mortality. Each 1-year increase in age was associated with an increased mortality risk (univariate HR=0.384, 95% CI: 0.237-0.623, P<0.001; multivariate HR=0.572, 95% CI: 0.345-0.949, P=0.031). Diabetes history was linked to higher mortality risk (univariate HR=2.446, 95% CI: 1.179-5.074, P=0.016; multivariate HR=3.23, 95% CI: 1.507-6.926, P=0.003). Each unit increase in lactate clearance rate was associated with a reduced mortality risk (univariate HR=0.017, 95% CI: 0.009-0.031, P<0.001; multivariate

Table 3. Analysis of risk factors affecting LA clearance rate in patients

Variable	Total	<10% (n=65)	≥10% (n=453)	Statistic	*P*-Value
Age (years)	65.00 [60.00, 70.00]	65.00 [59.00, 70.00]	69.00 [64.00, 78.00]	5.345	<0.001
Gender					
Male	384 (74.13%)	337 (74.39%)	47 (72.31%)	0.129	0.720
Female	134 (25.87%)	116 (25.61%)	18 (27.69%)		
BMI (kg/m^2)	24.20 [21.98, 25.99]	24.21 [21.75, 26.00]	24.12 [22.82, 25.85]	0.543	0.587
Cancer Type					
Gastric Cancer	305 (58.88%)	262 (57.84%)	43 (66.15%)	1.922	0.382
Esophageal Cancer	185 (35.71%)	165 (36.42%)	20 (30.77%)		
Other	28 (5.41%)	26 (5.74%)	2 (3.08%)		
TNM Stage					
Stage II	56 (10.81%)	48 (10.60%)	8 (12.31%)	0.787	0.675
Stage III	134 (25.87%)	120 (26.49%)	14 (21.54%)		
Stage IV	328 (63.32%)	285 (62.91%)	43 (66.15%)		
24 h Blood Loss					
≥1000 mL	105 (20.27%)	83 (18.32%)	22 (33.85%)	8.476	0.004
<1000 mL	413 (79.73%)	370 (81.68%)	43 (66.15%)		
24 h Blood Transfusion					
Yes	281 (54.25%)	244 (53.86%)	37 (56.92%)	0.214	0.643
No	237 (45.75%)	209 (46.14%)	28 (43.08%)		
Time from Bleeding to Admission					
≥12 h	315 (60.81%)	267 (58.94%)	48 (73.85%)	5.300	0.021
<12 h	203 (39.19%)	186 (41.06%)	17 (26.15%)		
Hemorrhagic Shock					
Yes	134 (25.87%)	110 (24.28%)	24 (36.92%)	4.736	0.030
No	384 (74.13%)	343 (75.72%)	41 (63.08%)		
Received Radiation/Chemotherapy					
Yes	346 (66.80%)	301 (66.45%)	45 (69.23%)	0.199	0.656
No	172 (33.20%)	152 (33.55%)	20 (30.77%)		
Diabetes History					
Yes	104 (20.08%)	94 (20.75%)	10 (15.38%)	1.020	0.313
No	414 (79.92%)	359 (79.25%)	55 (84.62%)		
Hypertension History					
Yes	187 (36.10%)	163 (35.98%)	24 (36.92%)	0.022	0.883
No	331 (63.90%)	290 (64.02%)	41 (63.08%)		

Hemostasis Method					
Interventional Embolization	333 (64.29%)	45 (69.23%)	288 (63.58%)	0.792	0.374
Endoscopic Hemostasis	185 (35.71%)	20 (30.77%)	165 (36.42%)		
Fluid Resuscitation Plan					
IV	301 (58.11%)	252 (55.63%)	49 (75.38%)	9.114	0.003
IO	217 (41.89%)	201 (44.37%)	16 (24.62%)		
First Cannulation Success Rate					
Success	444 (85.71%)	389 (85.87%)	55 (84.62%)	0.073	0.787
Failure	74 (14.29%)	64 (14.13%)	10 (15.38%)		
Resuscitation Success Rate					
Success	483 (93.24%)	424 (93.60%)	59 (90.77%)	0.722	0.395
Failure	35 (6.76%)	29 (6.40%)	6 (9.23%)		
Time of Venous Access Establishment (min)	4.50 [2.00, 6.00]	4.00 [2.00, 6.00]	5.00 [4.00, 6.00]	1.327	0.185
Time to Blood Pressure Recovery After Fluid Resuscitation (min)	11.00 [9.00, 12.00]	11.00 [9.00, 12.00]	12.00 [10.00, 13.00]	2.254	0.024
Infusion Rate (mL/min)	15.00 [13.00, 17.00]	15.00 [13.00, 17.00]	15.00 [13.00, 17.00]	0.798	0.425
Urine Output (mL)	84.04±24.19	84.14±24.39	83.40±22.96	0.229	0.819
Pre-fluid ALB (g/L)	59.91±10.16	59.99±10.21	59.37±9.83	0.461	0.645
6 h Post-fluid ALB (g/L)	126.00 [114.00, 138.00]	127.00 [114.00, 139.00]	121.00 [110.00, 133.00]	1.651	0.099

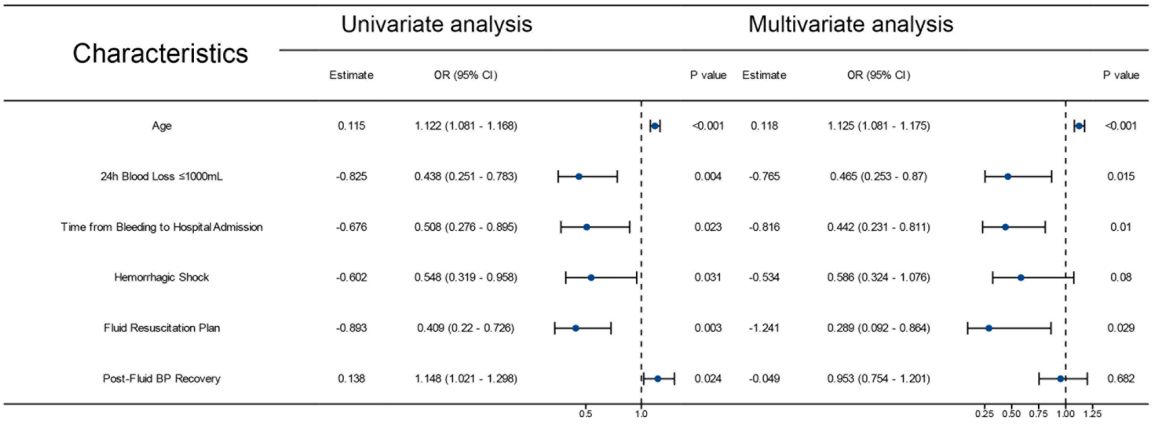

Figure 6. Univariate and multivariate analysis of risk factors affecting lactate clearance rate.

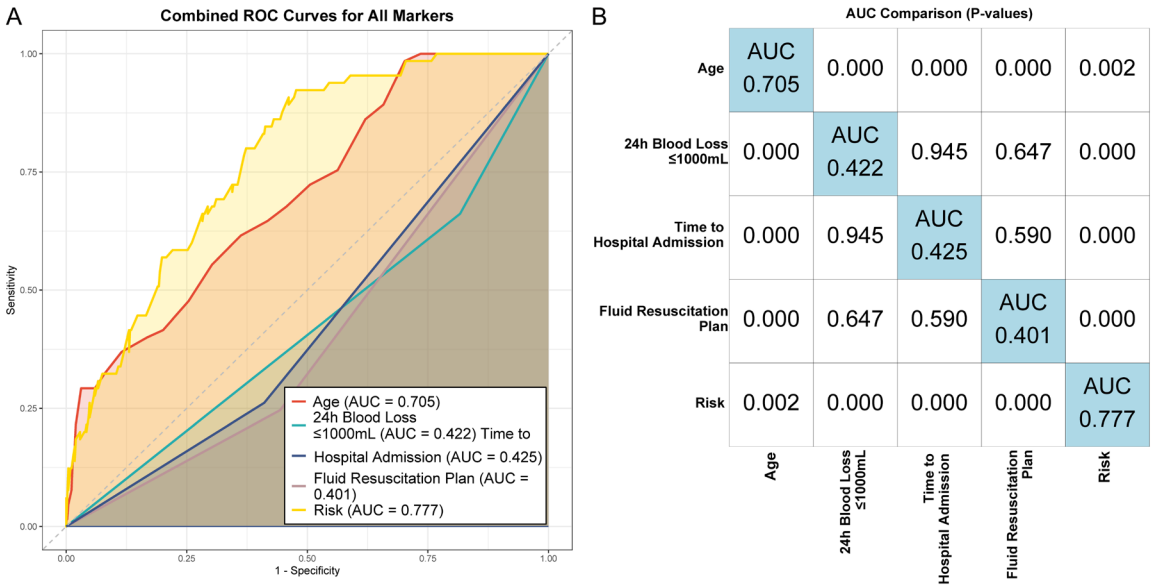

Figure 7. ROC curve analysis of different markers. A. ROC curves for various markers and their combined prediction; B. Comparison of the AUC values among various markers and their combination. Note: POC: Receiver operating characteristic, AUC: Area under the curve.

HR=0.016, 95% CI: 0.009-0.031, P<0.001). While 24-hour blood loss was significant in univariate analysis (HR=0.544, 95% CI: 0.34-0.87, P=0.011), it was not significant in multivariate analysis (HR=0.831, 95% CI: 0.517-1.336, P=0.446) (**Table 4**; **Figure 8**).

Competing risk model for 30-day mortality risk

In the competing risk model, a 6-hour lactate clearance rate <0.16 was significantly associated with 30-day mortality risk in both univariate (HR=0.1, 95% CI: 0.047-0.235, P<0.001) and multivariate analyses (HR=0.11, 95% CI: 0.051-0.254, P<0.001). Other factors, including 24-hour blood loss, diabetes history, hemorrhagic shock, fluid resuscitation strategy, age, BMI, and 6-hour serum albumin levels, were not significant in multivariate analysis. Fluid resuscitation strategy (IO group) and gender also showed no significant impact on 30-day mortality risk (**Table 5**).

Mediating effects of diabetes history and 6-hour lactate clearance on fluid therapy and mortality

Causal mediation analysis evaluated the direct and indirect effects of fluid therapy on mortality, with diabetes history and 6-hour lactate

Table 4. Cox regression analysis of independent prognostic factors for 30-day all-cause mortality

Variable	Univariate analysis			Multivariate analysis		
	Beta	HR (95% CI)	*P* Value	Beta	HR (95% CI)	*P* Value
Age	-0.956	0.384 (0.237-0.623)	<0.001	-0.559	0.572 (0.345-0.949)	0.031
BMI	0.599	1.82 (0.737-4.498)	0.194			
Gender						
Male						
Female	0.284	1.328 (0.834-2.115)	0.232			
Cancer Type						
Gastric Cancer						
Esophageal Cancer	0.088	1.092 (0.694-1.719)	0.703			
Other	-0.111	0.895 (0.323-2.485)	0.832			
TNM Stage						
II						
III	0.013	1.014 (0.444-2.315)	0.975			
IV	0.195	1.215 (0.579-2.551)	0.606			
24 h Blood Loss						
≥1000 mL						
<1000 mL	-0.610	0.544 (0.34-0.87)	0.011	-0.185	0.831 (0.517-1.336)	0.446
24 h Blood Transfusion Treatment						
Yes						
No	-0.192	0.826 (0.532-1.281)	0.393			
Time from Bleeding to Admission						
≥12 h						
<12 h	-0.419	0.658 (0.411-1.052)	0.081			
Hemorrhagic Shock						
Yes						
No	-0.021	0.979 (0.560-1.713)	0.941			
Received Radiation/Chemotherapy						
Yes						
No	0.086	1.089 (0.693-1.713)	0.711			
Diabetes History						
Yes						
No	0.895	2.446 (1.179-5.074)	0.016	1.173	3.23 (1.507-6.926)	0.003
Hypertension History						
Yes						
No	0.153	1.166 (0.735-1.847)	0.515			
Fluid Therapy Plan						
IV						
IO	-0.519	0.595 (0.374-0.947)	0.029	0.175	1.192 (0.734-1.935)	0.479
Hemostasis method						
Interventional embolization						
Endoscopic hemostasis	-0.463	0.630 (0.386-1.026)	0.063			
First Intubation Success Rate						
Success						
Failure	0.138	1.148 (0.635-2.077)	0.648			
Resuscitation Success Rate						
Success						
Failure	-0.090	0.914 (0.37-2.258)	0.845			
Time of Venous Access Establishment						
≥3						
<3	-0.455	0.634 (0.376-1.07)	0.088			

Post-Fluid BP Recovery						
≥10						
<10	-0.292	0.747 (0.464-1.202)	0.229			
Infusion Rate						
≥13						
<13	-0.432	0.649 (0.344-1.225)	0.182			
Urine Output						
≥105						
<105	0.291	1.337 (0.725-2.467)	0.352			
Pre-Fluid ALB						
≥49						
<49	0.128	1.137 (0.602-2.146)	0.692			
6 h Post-Fluid ALB						
≥122						
<122	0.385	1.469 (0.953-2.265)	0.082			
6 h LA clearance rate						
≥0.16						
<0.16	-4.101	0.017 (0.009-0.031)	<0.001	-4.119	0.016 (0.009-0.031)	<0.001

Note: BMI: Body Mass Index, TNM: Tumor, Node, Metastasis, BP: Blood Pressure, ALB: Albumin, IV: Intravenous, IO: Intraosseous, IA: lactate.

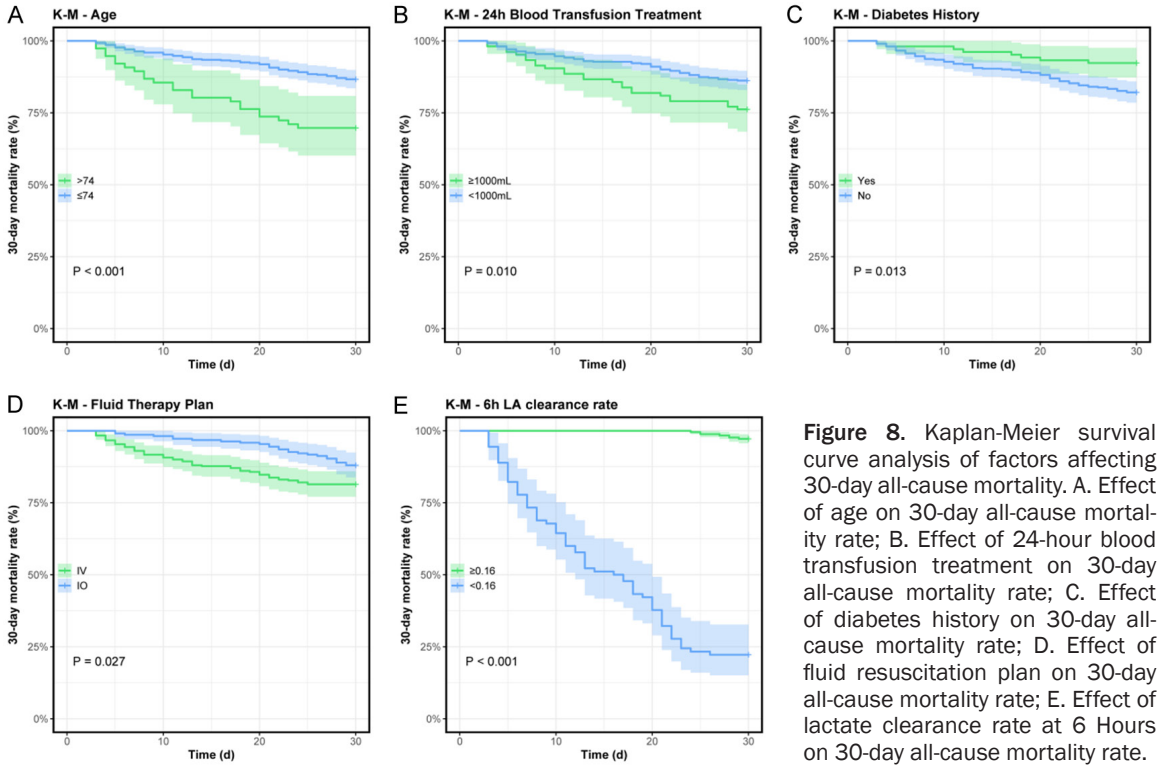

Figure 8. Kaplan-Meier survival curve analysis of factors affecting 30-day all-cause mortality. A. Effect of age on 30-day all-cause mortality rate; B. Effect of 24-hour blood transfusion treatment on 30-day all-cause mortality rate; C. Effect of diabetes history on 30-day all-cause mortality rate; D. Effect of fluid resuscitation plan on 30-day all-cause mortality rate; E. Effect of lactate clearance rate at 6 Hours on 30-day all-cause mortality rate.

clearance rate as potential mediators. The direct effect of diabetes history on mortality was significant (P=0.043), but its indirect effect was not (P=0.156). The 6-hour lactate clearance rate significantly mediated the effect of fluid therapy on mortality (indirect effect, P<0.001), indicating that fluid therapy influences mortality primarily through lactate clearance. The direct effect of the 6-hour lactate clearance rate approached significance (P= 0.069) (**Figure 9**).

Discussion

Gastrointestinal (GI) tumors, particularly gastric and esophageal cancers, are major contrib-

Table 5. Application of competitive risk model in the assessment of 30-day mortality risk in patients with gastrointestinal bleeding

Variable	Univariate analysis			Multivariate analysis		
	Cof	HR (95% CI)	*P* Value	Cof	HR (95% CI)	*P* Value
Gender						
Male						
Female	0.307	1.360 (0.588-3.14)	0.470			
Cancer Type						
Gastric Cancer						
Esophageal Cancer	-0.274	0.760 (0.311-1.858)	0.550			
Other	0.784	2.190 (0.651-7.373)	0.210			
TNM Stage						
II						
III	-0.885	0.410 (0.12-1.414)	0.160			
IV	-0.680	0.510 (0.186-1.379)	0.180			
24 h Blood Loss						
≥1000 mL						
<1000 mL	-0.628	0.530 (0.231-1.231)	0.140			
24 h Blood Transfusion Treatment						
Yes						
No	-0.592	0.550 (0.239-1.282)	0.170			
Time from Bleeding to Admission						
≥12 h						
<12 h	-0.324	0.720 (0.313-1.671)	0.450			
Hemorrhagic Shock						
Yes						
No	-0.493	0.610 (0.27-1.38)	0.240			
Received Radiation/Chemotherapy						
Yes						
No	-0.057	0.940 (0.409-2.183)	0.890			
Diabetes History						
Yes						
No	0.620	1.860 (0.556-6.211)	0.310			
Hypertension History						
Yes						
No	0.002	1.000 (0.443-2.264)	1.000			
Hemostasis method						
Interventional embolization						
Endoscopic hemostasis	-0.177	0.840 (0.363-1.933)	0.680			
Fluid Therapy Plan						
IV						
IO	-0.452	0.64 (0.277-1.463)	0.290			
First Intubation Success Rate						
Success						
Failure	-0.662	0.52 (0.122-2.185)	0.370			
Resuscitation Success Rate						
Success						
Failure	0.201	1.22 (0.285-5.247)	0.790			
Age (year)						
≥74						
<74	-0.111	0.9 (0.307-2.611)	0.840			

BMI						
≥27.93						
<27.93	1.020	2.77 (0.374-20.523)	0.320			
Time of Venous Access Establishment						
≥3						
<3	-0.091	0.91 (0.384-2.167)	0.840			
Post-Fluid BP Recovery						
≥10						
<10	-0.118	0.89 (0.387-2.043)	0.780			
Infusion Rate						
≥13						
<13	-0.543	0.58 (0.174-1.946)	0.380			
Urine Output						
≥105						
<105	0.514	1.67 (0.504-5.544)	0.400			
Pre-Fluid ALB						
≥49						
<49	0.003	1 (0.301-3.342)	1.000			
6 h Post-Fluid ALB						
≥122						
<122	0.827	2.29 (1.031-5.065)	0.042	0.541	1.72 (0.767-3.846)	0.190
6 h LA clearance rate						
≥0.16						
<0.16	-2.254	0.1 (0.047-0.235)	<0.001	-2.172	0.11 (0.051-0.254)	<0.001

Note: BMI: Body Mass Index, TNM: Tumor, Node, Metastasis, ALB: Albumin, IV: Intravenous, IO: Intraosseous, BP: Blood Pressure, lA: lactate.

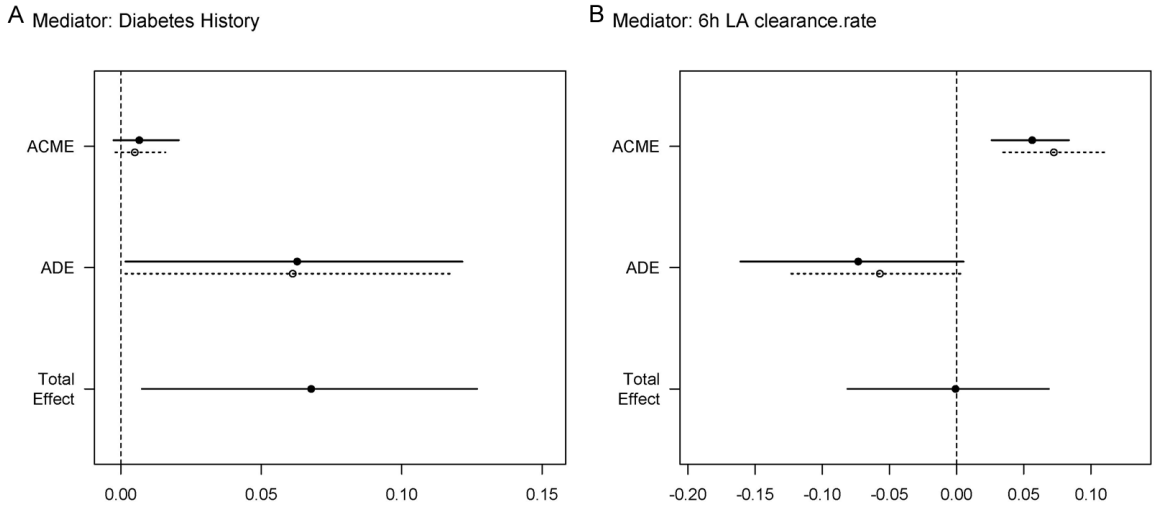

Figure 9. Causal mediation analysis of fluid therapy's effect on mortality through diabetes history and 6-hour lactic acid clearance rate. A. Mediating effect of diabetes history on the effect of fluid therapy on mortality; B. Mediating effect of 6-hour lactate clearance on the effect of fluid therapy on mortality. Note: ME: mediating effect, DE: direct effect.

utors to global cancer-related mortality [15]. In advanced stages, patients often develop AGIB, a life-threatening complication driven by tumor invasion of blood vessels or ulcer formation. This can lead to massive hemorrhage, hemorrhagic shock, hypotension, organ failure, and death [16]. Intravenous (IV) fluid resuscitation is the standard approach for AGIB management, but challenges arise in cases of difficult vascular access or hemorrhagic shock, where

slow IV infusion rates impede rapid volume restoration [17]. In recent years, IO fluid resuscitation has emerged as a promising alternative, enabling rapid establishment of a reliable infusion pathway and delivering fluids efficiently, offering significant advantages for critically ill patients, such as those with AGIB [18].

This retrospective study compared the efficacy of IO versus IV fluid resuscitation, focusing on 30-day mortality. The IO group demonstrated superior fluid resuscitation efficiency, with significantly higher first-attempt cannulation success rates, shorter times to establish infusion channels, and faster blood pressure recovery compared to the IV group. These findings align with prior research reporting an 88% cannulation success rate for IO in trauma patients [18] and an increasing use of IO as the initial vascular access method in shock patients [19]. IO's independence from peripheral vascular conditions makes it particularly effective in cases of hemorrhagic shock or collapsed veins [20]. The anatomical advantage of intraosseous access facilitates rapid and reliable fluid delivery, swiftly improving hemodynamics [21], thereby enhancing treatment efficiency in AGIB patients. However, while fluid resuscitation efficiency differed significantly, its ultimate impact on mortality must be considered alongside hemostatic interventions. For instance, transcatheter arterial embolization (TAE), a common hemostatic approach for cancer-related upper GI bleeding, achieves a 99.1% technical success rate but has a 43.9% clinical failure rate due to rebleeding, contributing to a 17.8% 30-day mortality rate, with rebleeding directly causing 13.1% of deaths [13]. This underscores the critical role of synergistic "resuscitation-hemostasis" strategies. The lower mortality rate in the IO group (11.98% vs. 18.6% in the IV group) may reflect IO's ability to provide a critical time window for subsequent hemostatic interventions. Delays in IV fluid delivery may postpone hemostasis, exacerbating outcomes. This hypothesis is supported by studies on septic shock, where early restrictive fluid resuscitation reduces complications such as acute respiratory distress syndrome (ARDS), enhances LA clearance, and shortens ICU stays, highlighting the importance of balancing fluid resuscitation efficiency with metabolic regulation [22].

The 30-day all-cause mortality rate was significantly lower in the IO group, likely due to rapid hemodynamic restoration, which reduced the risk of organ failure. Multivariate analysis identified IO fluid resuscitation as a significant predictor of higher LA clearance (HR=0.289), a critical marker of tissue perfusion and metabolic recovery. Effective LA clearance relies on adequate liver and kidney perfusion, which IO facilitates by delivering fluids directly into the bone marrow cavity, increasing cardiac output by 20%-30% [21]. In contrast, IV resuscitation may result in inadequate visceral perfusion due to peripheral vascular leakage, delaying LA clearance [19]. This mechanism partly explains the 3.5-fold increased mortality risk in patients with low LA clearance in this study.

Sepsis studies provide further evidence: LA clearance ≤40.3% [23] or lactate kinetic models (e.g., MELD-ΔLA score) [24] are strong predictor of 28-day mortality, while 20% albumin resuscitation in cirrhotic patients accelerates LA clearance and improves hemodynamics [25], underscoring liver metabolic capacity as a limiting factor. Additionally, baseline hemoglobin ≤60 g/L independently predicts mortality in TAE studies [13]. Low hemoglobin combined with low LA clearance creates a vicious cycle of oxygen delivery-metabolism imbalance, where insufficient hemoglobin limits oxygen transport, and lactate accumulation suppresses red blood cell production, forming a positive feedback loop.

Diabetes history was identified as an independent mortality risk factor, likely due to microvascular damage and mitochondrial dysfunction in diabetic patients. Hyperglycemia inhibits pyruvate dehydrogenase, impairing lactate conversion to the tricarboxylic acid cycle, thus delaying LA metabolism despite adequate resuscitation [26, 27]. This effect is mirrored in septic patients, where the association between LA clearance and 28-day mortality is stronger with concurrent hyperbilirubinemia (TBIL≥2 mg/dL) [28], suggesting a synergistic lethal impact of liver dysfunction and metabolic disorders.

This study confirms IO's advantages in GI tumor-related massive hemorrhage, improving fluid resuscitation efficiency, enhancing LA metabolism, and reducing mortality risk. IO

serves as an effective alternative for patients with challenging venous access, such as those with peripheral vascular collapse or drug-induced vasoconstriction [20]. Its ability to rapidly establish access is critical in hemorrhagic shock [21], and its clinical adoption is increasing [19]. IO's dual benefits-rapid restoration of effective circulating volume and preferential enhancement of visceral perfusion (e.g., liver and kidneys)-promote LA clearance and mitigate organ failure risk. However, reliance solely on fluid resuscitation has limitations, as evidenced by the 13.1% rebleeding-related mortality in TAE studies [13]. Future research should explore optimal timing for integrating IO with hemostatic therapies (e.g., endoscopy or embolization). For example, IO could stabilize hemodynamics during early resuscitation, creating a "golden time window" for TAE or surgical hemostasis. This strategy's feasibility is supported by critical care studies: point-of-care echocardiography-guided septic shock management shortens LA clearance time by optimizing vasopressor use [29], and in polytrauma patients, a lactate/albumin ratio (LAR) ≥1.50 better predicts 28-day mortality than LA alone [30], suggesting that combined metabolic and inflammatory markers could enhance risk stratification. Additionally, the unique metabolic profiles of diabetic patients necessitate tailored approaches, such as combining IO resuscitation with enhanced glycemic control and antioxidant therapies (e.g., vitamin C) to improve LA metabolism and prognosis. Future studies could adapt sepsis prediction models (e.g., integrating IL-6, PCT, and LA clearance) [31] to develop AGIB-specific risk assessment tools for precision resuscitation and stratified interventions.

Mediation analysis provided critical insights into the mechanisms linking fluid resuscitation to mortality. The 6-hour LA clearance rate was a significant mediator of the relationship between fluid therapy and mortality, with IO resuscitation significantly enhancing LA clearance, a key indicator of tissue perfusion and metabolic recovery. The indirect effect of fluid therapy on mortality via LA clearance was highly significant, underscoring IO's role in rapidly restoring hemodynamics, improving metabolic function, and reducing organ failure risk. In contrast, diabetes history was not a significant mediator, despite being a known mortality risk factor. This may reflect diabetes' complex pathophysiology, including microvascular damage and mitochondrial dysfunction, which may impede metabolic recovery despite effective resuscitation. These findings highlight that while comorbidities like diabetes contribute to mortality risk, the primary mechanism by which fluid therapy improves survival is through efficient LA clearance and metabolic recovery, particularly with IO resuscitation. This emphasizes the need to understand how fluid resuscitation strategies influence key metabolic processes to optimize patient outcomes.

Despite robust evidence supporting IO use in GI tumor-related AGIB, this study has limitations. As a retrospective analysis, it is susceptible to selection bias, particularly in treatment allocation, and physician judgment may introduce confounding factors. Additionally, data from a single center may limit generalizability due to regional differences, necessitating validation through multicenter, large-scale studies. Patient heterogeneity, including variations in GI tumor types and clinical conditions, may also influence IO efficacy, warranting subgroup analyses in future research. Prospective, multicenter studies are needed to confirm IO's efficacy across diverse populations and assess its impact on long-term survival, quality of life, and complications. Given the focus on LA clearance, future investigations should explore the role of LA clearance and other biomarkers in AGIB patients to develop personalized fluid resuscitation strategies. Furthermore, evaluating the combined effects of IO with other emergency interventions (e.g., endoscopy, embolization) could inform comprehensive treatment protocols for clinical practice.

Conclusion

This study demonstrates that intraosseous fluid resuscitation offers significant advantages in patients with gastrointestinal tumor-related massive hemorrhage. IO significantly enhances fluid resuscitation efficiency, improves lactate metabolism, and reduces 30-day mortality risk while maintaining a safety profile comparable to IV resuscitation.

Disclosure of conflict of interest

None.

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