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Original Article

The efficacy of sodium bicarbonated Ringer's solution versus lactated Ringer's solution in elderly patients undergoing gastrointestinal surgery: a prospective randomized controlled trial

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Abstract: Objective: To investigate the effect of sodium bicarbonated Ringer's solution (BRS) on lactate metabolism, acid-base balance, and clinical outcomes in elderly patients undergoing gastrointestinal surgery. Methods: A total of 60 elderly patients undergoing gastrointestinal surgery were enrolled in this prospective, randomized controlled study. The participants were randomly assigned to the BRS group (n = 30) or sodium lactated Ringer's solution (LRS) group (n = 30) where they received goal-directed fluid therapy with BRS or LRS, respectively. The primary outcome was the incidence of postoperative hyperlactatemia, whereas the secondary outcomes included pH, bicarbonate, base excess (BE), liver function, and postoperative complications within 30 days. Linear regression was conducted to screen the factors affecting lactate concentration. Results: After fluid therapy, the probability of hyperlactatemia was lower in the BRS group than in the LRS group (3.3% vs. 40.0%, $P < 0.001$). No significant difference in bicarbonate, pH, and BE was observed between the groups ($P > 0.05$). Furthermore, the incidence of major complications and the length of hospital stay were not significantly different ($P > 0.05$). However, the BRS group had a lower risk of minor complications than the LRS group (50.0% vs. 76.7%, $P = 0.032$), particularly in terms of impaired liver function (16.7% vs. 43.3%, $P = 0.024$). Diabetes, hypotension, and volume of LRS infused were highly correlated with lactate concentration. Conclusion: BRS is more beneficial to the reduction of the incidence of postoperative hyperlactatemia and the risk of minor postoperative complications in elderly patients undergoing gastrointestinal surgery. Therefore, BRS may be a better option for perioperative fluid therapy in elderly patients undergoing gastrointestinal surgery.

Keywords: Sodium bicarbonated Ringer's solution, elderly, lactate, goal-directed fluid therapy, gastrointestinal surgery

Introduction

With population aging, the number of surgeries performed in elderly patients is expected to significantly increase, with gastrointestinal cancers being the leading causes of morbidity and mortality in this population [1]. Patients undergoing gastrointestinal surgery are prone to tissue and organ hypoperfusion due to rigorous bowel preparation, anesthesia-induced vasodilation, capillary leak caused by surgery-induced inflammation, and intraoperative fluid loss, traditionally [2]. Furthermore, elderly individuals have declined organ function reserve and weakened cell metabolic capacity, are susceptible to water changes and electrolyte fluctuations [3-5], and are at risk for metabolic acidosis and hyperlactatemia. Previous studies have found that the incidence rate of postoperative hyperlactatemia in patients undergoing major abdominal surgery is 22.7%-61.9% [6-9]. Tissue hypoperfusion and lactic acid accumulation can lead to complications such as hypotension, inflammation, acid-base imbalance, and organ function impairment. Therefore, effective fluid therapy and lactate concentration control are essential for elderly patients.

At present, goal-directed fluid therapy (GDFT) has been clinically recognized as the best approach for fluid management in high-risk surgical patients, and crystalloid is the fluid solution used in patients [10-12]. However, the optimal strategy of crystalloid solution use has long been controversial [13]. Sodium lactated Ringer's solution (LRS) is one of the most commonly used solutions in surgical procedures [12], and it has been shown to aggravate inherent lactic acidosis and increase aerobic demand [14, 15]. Sodium bicarbonated Ringer's solution (BRS) is a newly emerging crystalloid solution that has been recently used. The composition of BRS is closer to that of human plasma, and bicarbonate is metabolized more quickly, requiring less oxygen demand and extra hepatic metabolism. Recent studies have demonstrated that BRS is more effective in stabilizing the internal environment, reducing lactic acid concentration, correcting acidosis, and reducing the incidence of complications in shock patients [16-18].

However, systematic studies on the use of BRS in elderly patients undergoing gastrointestinal surgery are lacking. Therefore, we conducted a randomized controlled trial to compare the effects between BRS and LRS based on GDFT in elderly patients undergoing gastrointestinal surgery.

Materials and methods

Study design and participants

This randomized controlled trial was approved by the Clinical Medical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University, China (PJ2020-15-21), and registered at the Chinese Clinical Trial Registry (ChiCTR2000039406). It was also conducted at the same institution from January to November 2021. The study was conducted in accordance with the CONSORT guidance and the Declaration of Helsinki.

The inclusion criteria were patients aged 60-85 years, classified as American Society of Anesthesiologists (ASA) II-III, with confirmed diagnosis of gastrointestinal cancer, in accordance with the indications of elective open gastrointestinal surgery, with surgery duration of 2-4 h, and who signed informed consent after being informed of the study.

The exclusion criteria were significant arrhythmia or aortic insufficiency; severe cardiac insufficiency; serious dysfunction of the liver (Child-Pugh grade C), kidney (renal failure), lung, and other organs; preoperative mental illness; hypermagnesemia or hypothyroidism; and emergency surgery. Patients with incomplete data were also excluded.

Randomization and blinding

All the included patients were divided into two groups, BRS and LRS, at a ratio of 1:1 via computer-generated randomization. Anesthesiologists were not blinded to the arm assignment, but all investigators and patients were unaware of the treatment allocation during the study; statistical analysis was also blinded. Intraoperative and postoperative data were collected by medical students not involved in the trial.

Perioperative management

All the patients were fasted for at least 8 h prior to surgery with intestinal preparation. Standard monitoring for this procedure included pulse oximetry (SpO_2), electrocardiogram, invasive blood pressure, and processed electroencephalography (BIS, Aspect Medical Systems, Inc., USA). Subsequently, all patients received complete intravenous anesthesia. Anesthesia was induced using etomidate (0.2-0.3 mg/kg), sufentanil (0.2-0.5 μg/kg), and cisatracurium (0.15-0.3 mg/kg), followed by propofol to maintain BIS at 40-60 combined with remifentanil (2-6 ng/mL) during the whole surgery. Mechanical ventilation parameters were set to maintain the pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) near 35 mmHg, and tidal volume was set to 8-10 $mL{\cdot}kg^{-1}$. Nasopharyngeal temperature was monitored, and normal body temperature (core temperature > 36°C) was maintained by forced air heating. Stroke volume variation (SVV) was continuously monitored using FloTrac/Vigileo.

The LRS group received LRS (H20065323, specification 500 mL; Sichuan Pacific Pharmaceutical, China), whereas the BRS group received BRS (H20190021, specification 500 ml; Jiangsu Hengrui Pharmaceutical, China), depending on the randomization. Throughout the surgery, the patients received 2 $mL{\cdot}kg^{-1}{\cdot}h^{-1}$ as baseline rate infusion. The ideal body weight for fluid administration according to Robinson's formula [14] was as follows: male: 52 kg + 1.9 kg per 2.5 cm above 150 cm, female: 49 kg +

1.7 kg per 2.5 cm above 150 cm. In both groups, crystalloid solution (single bolus: 100 mL) was administered when SVV > 12%, but in case hypotension (mean arterial pressure falling below 65 mmHg within 5 min) occurred when SVV < 12%, ephedrine or phenylephrine was administered intermittently, or even noradrenaline continuously. The use of hydroxyethyl starch or gelatins was not allowed. The perioperative patient blood management followed the guidelines of the China, transfusion of whole blood and blood components WS/T 623-2018. Red blood cells were transfused to maintain hemoglobin ≥ 70 g/L when the hemoglobin level dropped below 70 g/L. Albumin was infused when the albumin level was lower than 30 g/L. To eliminate any possible effects of the surgical technique, the procedures and perioperative management were performed by the same surgical group. All patients received 1.5 $mL \cdot kg^{-1} \cdot h^{-1}$, 5% dextrose-NaCl as postoperative maintenance fluid. If additional volume was required, LRS or normal saline was given as preferred by the doctor.

Outcome measures

The primary outcome was the incidence of postoperative hyperlactatemia. Hyperlactatemia is generally defined as arterial blood lactate concentration > 2.0 mmol/L [19]. Moderate hyperlactatemia is defined as lactate concentration between 2 and 5 mmol/L, whereas lactate concentration > 5 mmol/L is referred to as severe hyperlactatemia.

The secondary outcomes included changes in pH, bicarbonate, base excess (BE), liver function, and postoperative complications within 30 days (the definition of the complications is presented in **Appendix 1**), and the risk factors for lactate accumulation were analyzed.

Data collection

Arterial blood gas analysis was conducted using GEM Premier 3500 (Instrumentation Laboratory Co., USA) at T_0 (before fluid therapy), T_1 (1 h after the start of surgery), and T_2 (end of the surgery). Lactate concentration, pH, BE, and bicarbonate acid were measured. Venous blood (3-5 mL) was collected pre- and postoperatively to test albumin, total bilirubin (TBIL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) using the Au2700 automatic biochemical analyzer (Olympus Corporation). At follow-up, the patients' clinical symptoms, examination reports, and medical files within 30 days were collected, and then data was compiled with the surgeons report to diagnose the postoperative complications.

Statistical analysis

Sample size was calculated using PASS 11.0 (NCS-PASS 11), the incidence of postoperative hyperlactatemia was 35% in the LRS group based on our pre-experimental results, and we estimated that a sample size of 54 patients (27 in each group) would reduce 80% power to 5% in the BRS group after randomization with a two-sided α level of 0.05. Considering the 15% dropout rate, a total of 64 patients (32 in each group) should be enrolled in this study.

The SPSS software version 25.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. The normality of continuous data was determined using the Shapiro-Wilk test. Quantitative data were expressed as mean ± standard deviation or median (quartile distance, IQR) depending on their distribution. Normally distributed data were evaluated using independent t-test, whereas other quantitative data were analyzed using the Mann-Whitney U test. Pearson's χ^2 test or Fisher's exact test was used to compare the categorical variables between the two groups. Univariate and multivariable linear regression analyses were conducted to study the relationship between lactate concentration and some independent variables. For all analyses, $P < 0.05$ indicated a statistically significant difference. GraphPad Prism 8.0 (GraphPad Software, La Jolla, California, USA) was used to construct the figures.

Results

Baseline characteristics

A total of 64 patients were initially recruited for the study, and four were lost to follow-up. Thus, only 60 patients were included in the final analysis (**Figure 1**). The baseline clinical data of the two groups are summarized in **Table 1**. No significant differences were observed between the two groups in terms of sex, age, body mass index (BMI), ASA, type of surgery, and other baseline data (all $P > 0.05$).

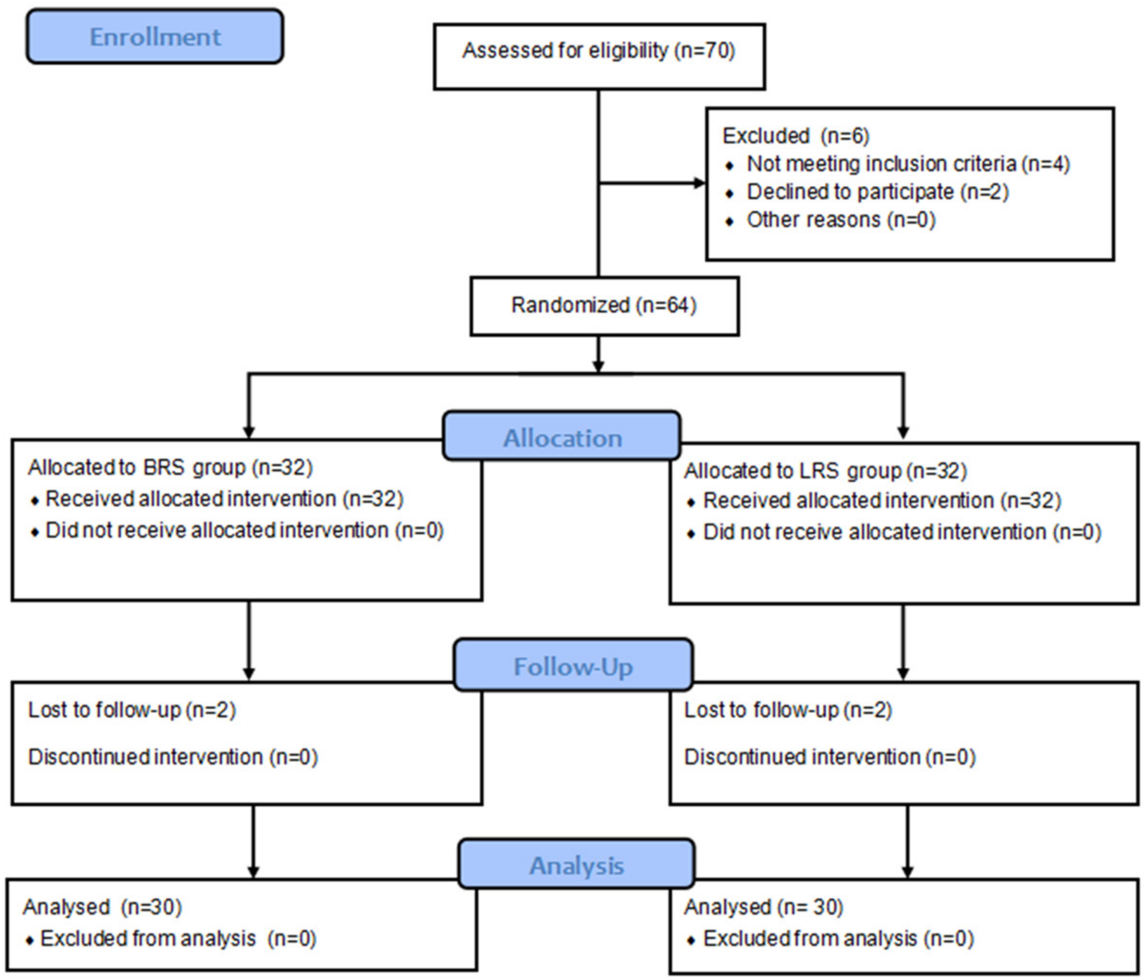

Figure 1. Flowchart Diagram. BRS: sodium bicarbonated Ringer's solution; LRS: sodium lactated Ringer's solution.

Perioperative parameters

As presented in **Table 2**, the duration of surgery and anesthesia was comparable between the two groups. Similarly, fluid replacement, blood loss, urine volume, hypotension, utilization rate of vasoactive drugs, blood component transfusion, and hemodynamics were not different between the groups (all $P > 0.05$).

Incidence of postoperative hyperlactatemia

No statistical difference in lactate concentration was observed between the two groups before fluid therapy (**Figure 2**). After infusion, lactate concentration increased in the LRS group but decreased in the BRS group, and postoperative hyperlactatemia occurred in 3.3% (1/30) of the patients in the BRS group versus 40.0% (12/30) of the patients in the LRS group ($P < 0.001$, **Table 3**). In addition, hyperlactatemia was moderate in both groups.

Perioperative pH, bicarbonate and BE levels

Bicarbonate, pH, and BE had no statistical significance at any time points and were within the normal range (all $P > 0.05$, **Figure 2**).

Liver function indices before and after surgery

Before surgery, no significant difference was observed in the liver function indices between the groups (all $P > 0.05$). After surgery, the ALT was significantly lower in the BRS than in the LRS group ($P < 0.05$, **Figure 3**), whereas no significant difference was observed in albumin, TBIL, and AST (all $P > 0.05$).

Table 1. Baseline characteristics of the patients

Characteristics	BRS (n = 30)	LRS (n = 30)	χ^2/t	*P*
Age (years)	70.3 ± 6.5	71.0 ± 6.2	0.406	0.686
Sex, male (n, %)	22 (73.3)	21 (70)	0.082	0.774
Weight (kg)	59.4 ± 7.3	58.2 ± 10.2	-0.553	0.582
Height (cm)	164.7 ± 6.2	163.9 ± 7.6	-0.482	0.632
BMI (kg/m^2)	22.0 (19.6, 23.5)	21.6 (18.7, 24.4)	-0.473	0.636
Ideal body weight (kg)	62.3 ± 5.6	61.0 ± 7.2	-0.804	0.425
ASA physical status (n, %)			1.111	0.292
II	10 (33.3)	14 (46.7)		
III	20 (66.7)	16 (53.3)		
CCI	6 (5, 7)	6 (5, 7)	0.654	0.694
Hypertension (n, %)	10 (33.3)	12 (40)	0.287	0.592
Diabetes (n, %)	6 (20)	5 (16.7)	0.111	0.739
Type of surgery (n, %)			0.000	1.000
Gastrectomy	21 (70)	21 (70)		
Colon surgery	3 (10)	3 (10)		
Rectal surgery	6 (20)	6 (20)		

Note: Values are expressed as mean ± SD, median (IQR), or number (%). BRS: sodium bicarbonated Ringer's solution; LRS: sodium lactated Ringer's solution; BMI: body mass index; ASA: American Society of Anesthesiologists; CCI: Charlson Co-morbidity index.

Incidence of postoperative complications within 30 days

In terms of major postoperative complications and length of hospital stay, no significant difference was observed between the two groups ($P > 0.05$, **Table 4**). Four (13.3%) and nine (30%) patients developed major complications in the BRS and LRS groups, respectively ($P = 0.117$). Contrarily, the overall incidence of minor complications was significantly lower in the BRS than in the LRS group (50.0% vs. 76.7%, $P = 0.032$), particularly to reduce the incidence of impaired liver function (16.7% vs. 43.3%, $P = 0.024$, **Table 4**).

Linear regression of lactate concentration

Table 5 presents the coefficients and *p*-values from the simple linear regression models and adjusted multivariable linear regression model of lactate concentration. Diabetes, hypotension, volume of LRS infused, and volume of BRS infused were significant ($P < 0.05$) in the simple linear predictions of lactate concentration. Furthermore, diabetes, hypotension, and volume of LRS infused were highly correlated with lactate concentration in the adjusted multivariable model, and the model described 68.0% of the variation in lactate concentration.

Discussion

Timely fluid therapy can ensure blood perfusion of tissues and organs, particularly for elderly patients, physiologic aging changes make the incidence of occult hypovolemia as high as 60%, but also prone to fluid overload [20]. Compared with open and restricted fluid therapy, GDFT can more accurately control the infusion volume and improve prognosis [21, 22]. However, the effect of fluid therapy needs to be improved further by using better fluid.

In this study, we compared the efficacy of LRS and BRS in elderly patients undergoing gastrointestinal surgery and found that BRS reduced arterial blood lactate concentration and the incidence of postoperative hyperlactatemia. In fact, there are no new clinically relevant indicators in the internal environment for elderly patients, and previous studies consider BE 24 h [23] after inclusion or blood gas (lactate concentration, serum electrolytes, and pH from blood gas) [24] as the primary outcome. BE is generally used as an indirect estimate of tissue acidosis and a surrogate marker for lactate elevation in patients with tissue perfusion injury, such as sepsis [25]. However, based on GDFT in combination with vasoactive drugs for hemodynamic management in our study, the results indicated less probability of tissue hypo-

Table 2. Perioperative profiles of the patients

Variables	BRS (n = 30)	LRS (n = 30)	χ^2/t	*P*
Surgery duration (min)	130.5 (120, 160)	128.5 (120, 170)	-0.127	0.899
Anesthesia duration (min)	157.5 (140, 180)	150 (138, 185)	-0.422	0.673
Cumulative fluid volume (ml)	1850 (1675, 2125)	1750 (1600, 1925)	-1.433	0.152
Fluid per minute of anesthesia (ml·kg^{-1}·h^{-1})	11.21 (10.44, 13.81)	11.84 (9.42, 13.44)	-0.414	0.679
Blood loss (ml)	400 (200, 625)	400 (200, 600)	-0.106	0.916
Urine volume (ml)	225 (200, 425)	200 (138, 300)	-1.518	0.129
Hypotension (n, %)	10 (33.3)	12 (40)	0.287	0.592
Duration of hypotension (min)				
MAP < 65 mmHg	0 (0, 5)	5 (0, 15)	1.002	0.149
MAP < 60 mmHg	0 (0, 0)	0 (0, 1)	0.332	0.511
MAP < 50 mmHg	0 (0, 0)	0 (0, 0)	0.134	0.317
Patients requiring vasopressors (n, %)				
Ephedrine	8 (26.7)	7 (23.3)	0.089	0.766
Phenylephrine	4 (13.3)	8 (26.7)	0.938	0.333
Noradrenaline	0 (0)	1 (3.3)	0.000	1.000
Blood component transfusion				
red blood cells (units)	0 (0, 0)	0 (0, 0)	-0.732	0.464
albumin (g)	0 (0, 5)	0 (0, 20)	-0.755	0.450
MAP (mmHg)				
Preoperative	96.3 ± 9.7	101.0 ± 15.1	1.432	0.157
Postoperative	97.2 ± 16.2	96.2 ± 18.9	-0.227	0.821
Heart rate (beats/min)				
Preoperative	73 ± 12	73 ± 14	0.150	0.881
Postoperative	68 ± 13	71 ± 16	0.664	0.509
SVV (%)				
Preoperative	12.61 ± 3.10	14.03 ± 2.96	1.812	0.075
Postoperative	7.49 ± 2.74	6.92 ± 2.28	-1.019	0.317
Postoperative maintenance fluid (ml)				
LRS	0 (0, 0)	0 (0, 0)	0.853	0.393
normal saline	0 (0, 100)	0 (0, 0)	0.605	0.545

Note: Values are expressed as mean ± SD, median (IQR), or number (%). BRS: sodium bicarbonated Ringer's solution; LRS: sodium lactated Ringer's solution; MAP: mean arterial pressure; SVV: stroke volume variation.

perfusion. Meanwhile, hyperlactatemia may occur with or without concurrent metabolic acidosis because buffering mechanisms may compensate when hyperlactatemia occurs without worsening tissue perfusion [26]. This suggests that BE has limited significance in the diagnosis for exogenous lactate infusion; thus, we finally considered lactate concentration as the primary outcome. As regards lactate, as a precursor of bicarbonate, 70% is metabolized through the liver in about 60 min and 25%-30% through the kidney [27]. Although Zitek et al. [28] have illustrated that administration of 30-mL/kg LRS does not increase serum lactate in healthy individuals, our results indicated that the application of LRS during surgery is likely to promote lactate accumulation in elderly patients as it exceeds the liver function reserve [29, 30]. Lactate accumulation can increase the metabolic burden of liver, negatively affect the acid-base balance, and weaken the buffering effect of LRS and is closely related to postoperative complications and mortality after abdominal surgery [7, 31, 32].

Then we further investigated the liver function indices. The ALT level was significantly lower in the BRS than in the LRS group after fluid therapy. AST is present primarily in the liver and other organs, including cardiac and skeletal

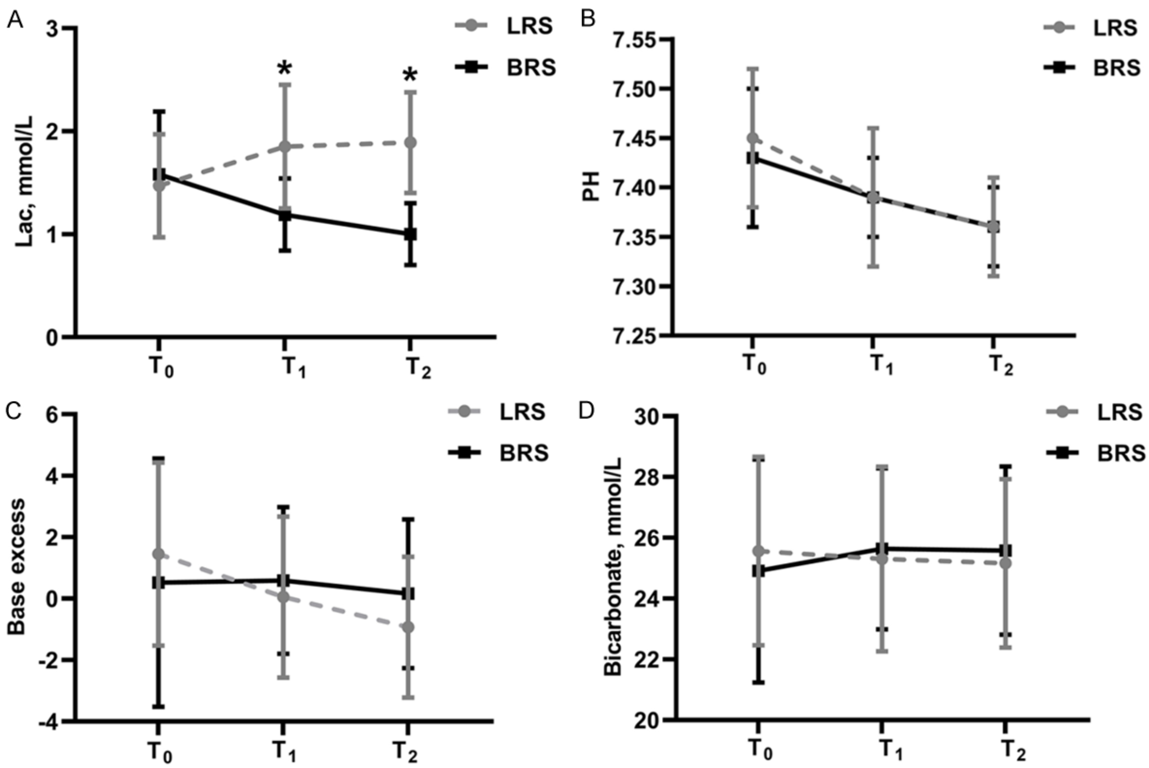

Figure 2. Comparison of lactate (A), pH (B), base excess (C) and bicarbonate (D) at different time points between the two groups. After infusion, lactate concentration in the LRS group increased while decreased in the BRS group, and there were significant differences between the two groups at 1 hour after the start of surgery and at the end of the surgery (*$P < 0.05$). PH, bicarbonate and base excess had no statistical significance at any time points. LRS: sodium lactated Ringer's solution; BRS: sodium bicarbonated Ringer's solution; Lac: lactate; T_0: before fluid therapy; T_1: 1 hour after the start of surgery; T_2: at the end of the surgery.

Table 3. Comparison of postoperative hyperlactatemia between the two groups [n, (%)]

	Severe hyperlactatemia	Moderate hyperlactatemia	No hyperlactatemia	Total hyperlactatemia
BRS (n = 30)	0 (0)	1 (3.3)	29 (96.7)	1 (3.3)
LRS (n = 30)	0 (0)	12 (40)	18 (60)	12 (40)
χ^2				11.882
P				< 0.001

Note: Values are expressed as number (%). BRS: sodium bicarbonated Ringer's solution; LRS: sodium lactated Ringer's solution.

muscles, kidney, and brain, and is thus a more specific marker of hepatocellular cell injury [33]. Indeed, although mostly temporarily elevated, increased enzymatic levels are also associated with metabolic disorders as well as increased hepatic and cardiovascular adverse outcomes [34, 35].

In addition, the results indicated that pH, bicarbonate, and BE were comparable between the two groups. BRS can maintain acid-base balance well without causing complications, such as metabolic alkalosis and CO_2 accumulation. This finding is inconsistent with those of other studies that found BRS to increase BE, bicarbonate, and pH [36]. This may be because bicarbonate is directly dissociated from sodium bicarbonate and can be rapidly excreted through respiration without accumulation over time, particularly in the intervention to control $P_{ET}CO_2$ at a low level.

Although no significant difference was observed in the major complications between the two

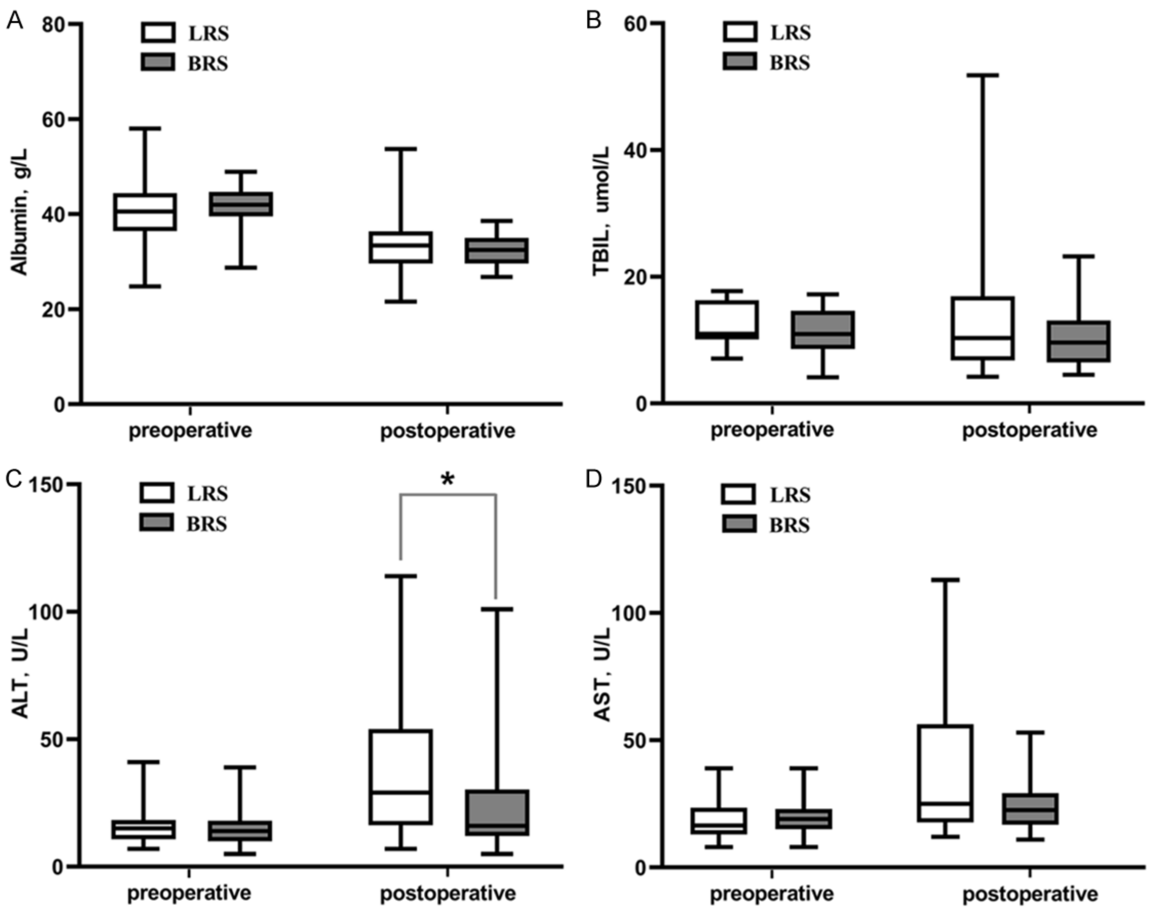

Figure 3. Liver function indices preoperative and postoperative. A: Albumin; B: TBIL; C: ALT; D: AST. No significant difference was observed in albumin, TBIL and AST, while ALT values were significant lower in BRS group than LRS group after surgery (**P* < 0.05). TBIL: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LRS: sodium lactated Ringer's solution; BRS: sodium bicarbonated Ringer's solution.

groups, the overall incidence of minor complications was significantly lower in the BRS than in the LRS group. This may be because LRS can cause granulocyte respiratory burst, release inflammatory mediators, and increase tissue edema [37]. Previous studies have also found that BRS can improve lactate metabolism and coagulation function as well as inhibit the expression of inflammatory factors, thereby reducing the risk of complications [18, 36, 38, 39]. An observational study involving 874 patients undergoing major abdominal surgery demonstrated that elderly patients were at an increased risk of minor complications and that the rate of major complications was similar to those in younger patients [40]. Therefore, reducing the rate of minor complications through BRS infusion is meaningful for the prognosis of elderly patients undergoing gastrointestinal surgery.

Finally, investigating the factors influencing the arterial lactate concentration, the adjusted multivariable regression model indicated that the LRS infusion volume, hypotension, and hyperglycemia were statistically significant. Previous studies have suggested that LRS infusion causes lactate accumulation in patients with poor liver function; however, there is no clear study on the relationship between infusion volume and lactate concentration. Our study found a strong correlation between infusion volume and lactate concentration in elderly patients undergoing gastrointestinal surgery. Meanwhile, we found that the estimated lactate levels in patients with hyperglycemia were 0.285 mmol/L higher than those in healthy patients. Patients with diabetes have elevated glycated hemoglobin levels, decreased hemoglobin oxygen-carrying capacity, disturbed glucose metabolism, and increased glycolysis,

Table 4. Postoperative recovery profile

Variables	BRS (n = 30)	LRS (n = 30)	χ^2/t	*P*
Major complications (n, %)	4 (13.3)	9 (30.0)	2.455	0.117
Anastomotic leakage	1 (3.3)	4 (13.3)	0.873	0.350
Peritonitis	0 (0)	1 (3.3)	0.000	1.000
Re-operation	0 (0)	1 (3.3)	0.000	1.000
Pneumonia	2 (6.7)	4 (13.3)	0.185	0.667
Deep venous thrombosis	1 (3.3)	0 (0)	0.000	1.000
Arrhythmia	0 (0)	1 (3.3)	0.000	1.000
Stroke	1 (3.3)	1 (3.3)	0.000	1.000
Mortality	0 (0)	0 (0)	-	NA
Minor complications (n, %)	15 (50.0)	23 (76.7)	4.593	0.032
Urinary and other infection	2 (6.7)	0 (0)	0.517	0.472
Wound bleeding	3 (3.3)	11 (36.7)	4.565	0.033
PONV	9 (30.0)	11 (36.7)	0.300	0.584
Cough and expectoration	8 (26.7)	14 (46.7)	2.584	0.108
Impaired liver function	5 (16.7)	13 (43.3)	5.079	0.024
Pruritus	1 (3.3)	2 (6.7)	0.000	1.000
Length of hospital stay (days)	9 (8, 11)	11 (8, 14)	-1.379	0.058

Note: Values are expressed as median (IQR) or number (%). BRS: sodium bicarbonated Ringer's solution; LRS: sodium lactated Ringer's solution; PONV: postoperative nausea and vomiting.

Table 5. Variables and their coefficients and *p*-values for simple and adjusted multivariable linear regression models of lactate concentration

Variables	Simple Coefficient	*P*	Adjusted Multivariable Coefficient	*P*
Age (years)	0.013	0.305		
Sex, male	0.087	0.616		
BMI (kg/m^2)	0.007	0.749		
CCI	0.083	0.272		
Diabetes	0.490	0.013	0.343	< 0.001
Hypertension	0.168	0.409		
Type of surgery	-0.112	0.250		
Hypotension	0.331	0.031	0.222	0.007
LRS (ml·kg^{-1}·h^{-1})	0.069	< 0.001	0.491	0.018
BRS (ml·kg^{-1}·h^{-1})	-0.064	< 0.001	-0.246	0.230
Surgery duration (min)	0.001	0.780		

Note: The multivariable model explained 68.0% of the variation in lactate. BMI: body mass index; CCI: Charlson Co-morbidity index; LRS: sodium lactated Ringer's solution; BRS: sodium bicarbonated Ringer's solution.

leading to increased lactate production [41]. Hypotension during anesthetic surgery causes hypoxia and hypoperfusion, which increase lactic acid production; our results indicate that hypotension is a risk factor for increased postoperative lactate after gastrointestinal surgery [42]. According to our results, monitoring of lactate concentration and rational control of blood pressure should be strengthened in patients with diabetes and patients with decreased liver function reserve during fluid therapy.

This study has some limitations that need to be acknowledged. First, we only recruited elderly patients who underwent open gastrointestinal surgery. Whether the current findings could be generalized to other patients need to be determined. Second, this is a single-center study; although the sample size was sufficient for the primary outcome, further multicenter, large-sample randomized controlled trials are warranted to determine variations in adverse outcomes (i.e., complications, mortality). We will study the related inflammatory factors and coagulation function to further explain the mechanism of the effect on complications.

In conclusion, sodium bicarbonated Ringer's solution is more effective than sodium lactated Ringer's solution in reducing the incidence of postoperative hyperlactatemia and postoperative minor complications, particularly impaired liver function. Hence, BRS may be a better choice of fluid for elderly patients undergoing gastrointestinal surgery.

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Disclosure of conflict of interest

None.

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References

[1] Polanczyk CA, Marcantonio E, Goldman L, Rohde LE, Orav J, Mangione CM and Lee TH. Impact of age on perioperative complications and length of stay in patients undergoing noncardiac surgery. Ann Intern Med 2001; 134: 637-43.

[2] Bamboat ZM and Bordeianou L. Perioperative fluid management. Clin Colon Rectal Surg 2009; 22: 28-33.

[3] Stahl EC, Haschak MJ, Popovic B and Brown BN. Macrophages in the aging liver and age-related liver disease. Front Immunol 2018; 9: 2795.

[4] Sun Z, Chai J, Zhou Q and Xu J. Establishment of gender- and age-specific reference intervals for serum liver function tests among the elderly population in northeast China: a retrospective study. Biochem Med (Zagreb) 2022; 32: 020707.

[5] Seifter JL. Integration of acid-base and electrolyte disorders. N Engl J Med 2014; 371: 1821-31.

[6] Xiaojuan Y, Xiaojia W, Xiaohong W and Xiaojun Y. Analysis of risk factor of hyperlactacidemia after gastrointestinal surgery: a clinical data analysis of 216 patients. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2015; 27: 875-9.

[7] Creagh-Brown BC, De Silva AP, Ferrando-Vivas P and Harrison DA. Relationship between peak lactate and patient outcome following high-risk gastrointestinal surgery: influence of the nature of their surgery: elective versus emergency. Crit Care Med 2016; 44: 918-25.

[8] Romano D, Deiner S, Cherukuri A, Boateng B, Shrivastava R, Mocco J, Hadjipanayis C, Yong R, Kellner C, Yaeger K, Lin HM and Brallier J. Clinical impact of intraoperative hyperlactatemia during craniotomy. PLoS One 2019; 14: e0224016.

[9] Yu B, Park CM, Gil E, Yoo K, Choi KJ, Yoon SJ and Han IW. Clinical impact of lactate on postoperative pancreatic fistula after pancreaticoduodenectomy: a single-center retrospective study of 1,043 patients. Pancreatology 2023; 23: 245-50.

[10] Tang A and Zhou S. Analysis on the application value of goal-directed fluid therapy in patients undergoing laparoscopy-assisted radical gastrectomy with fast-track anesthesia. Am J Transl Res 2021; 13: 5174-82.

[11] Diaper J, Schiffer E, Barcelos GK, Luise S, Schorer R, Ellenberger C and Licker M. Goal-directed hemodynamic therapy versus restrictive normovolemic therapy in major open abdominal surgery: a randomized controlled trial. Surgery 2021; 169: 1164-74.

[12] Myburgh JA and Mythen MG. Resuscitation fluids. N Engl J Med 2013; 369: 1243-51.

[13] Ellekjaer KL, Perner A, Jensen MM and Moller MH. Lactate versus acetate buffered intravenous crystalloid solutions: a scoping review. Br J Anaesth 2020; 125: 693-703.

[14] Pfortmueller CA, Funk GC, Reiterer C, Schrott A, Zotti O, Kabon B, Fleischmann E and Lindner G. Normal saline versus a balanced crystalloid for goal-directed perioperative fluid therapy in major abdominal surgery: a double-blind randomised controlled study. Br J Anaesth 2018; 120: 274-83.

[15] Guidet B, Soni N, Della Rocca G, Kozek S, Vallet B, Annane D and James M. A balanced view of balanced solutions. Crit Care 2010; 14: 325.

[16] Satoh K, Ohtawa M, Katoh M, Okamura E, Satoh T, Matsuura A, Oi Y and Ogawa R. Pharmacological study of BRS, a new bicarbonated Ringer's solution, in haemorrhagic shock dogs. Eur J Anaesthesiol 2005; 22: 703-11.

[17] Wang L, Lou J, Cao J, Wang T, Liu J and Mi W. Bicarbonate Ringer's solution for early resuscitation in hemorrhagic shock rabbits. Ann Transl Med 2021; 9: 462.

[18] Yu LQ, Meng CC, Jin XS and Cai J. Clinical study of sodium bicarbonated Ringer's solution on fluid resuscitation of patients with hemorrhagic shock. Eur Rev Med Pharmacol Sci 2022; 26: 1535-42.

[19] Madias NE. Lactic acidosis. Kidney Int 1986; 29: 752-74.

[20] Irwin MG, Chung CKE, Ip KY and Wiles MD. Influence of propofol-based total intravenous anaesthesia on peri-operative outcome measures: a narrative review. Anaesthesia 2020; 75 Suppl 1: e90-e100.

[21] Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, Grocott MP, Ahern A, Griggs K, Scott R, Hinds C and Rowan K; OPTIMISE Study Group. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. JAMA 2014; 311: 2181-90.

[22] Lee KY, Yoo YC, Cho JS, Lee W, Kim JY and Kim MH. The effect of intraoperative fluid management according to stroke volume variation on postoperative bowel function recovery in colorectal cancer surgery. J Clin Med 2021; 10: 1857.

[23] Chaussard M, Depret F, Saint-Aubin O, Benyamina M, Coutrot M, Jully M, Oueslati H, Fratani A, Cupaciu A, Poniard A, Asehnoune K, Dimby SF, Mebazaa A, Houze P and Legrand M. Physiological response to fluid resuscitation with Ringer lactate versus Plasmalyte in criti-

cally ill burn patients. J Appl Physiol (1985) 2020; 128: 709-14.
[24] Liu X, Cao H, Tan X, Shi J, Qiao L, Zhang Q and Shi L. The effect of acetate Ringer's solution versus lactate Ringer's solution on acid base physiology in infants with biliary atresia. BMC Pediatr 2021; 21: 585.
[25] Qi J, Bao L, Yang P and Chen D. Comparison of base excess, lactate and pH predicting 72-h mortality of multiple trauma. BMC Emerg Med 2021; 21: 80.
[26] Li D, Liu S, Zhang J, Cheng W, Mao J and Cui N. Exploring dynamic change in arterial base excess with patient outcome and lactate clearance in the intensive care unit by hierarchical time-series clustering. Front Med (Lausanne) 2022; 9: 1020806.
[27] Pino RM and Singh J. Appropriate clinical use of lactate measurements. Anesthesiology 2021; 134: 637-44.
[28] Zitek T, Skaggs ZD, Rahbar A, Patel J and Khan M. Does intravenous lactated Ringer's solution raise serum lactate? J Emerg Med 2018; 55: 313-318.
[29] Gladden LB. Lactate metabolism: a new paradigm for the third millennium. J Physiol 2004; 558: 5-30.
[30] Rajan S, Srikumar S, Tosh P and Kumar L. Effect of lactate versus acetate-based intravenous fluids on acid-base balance in patients undergoing free flap reconstructive surgeries. J Anaesthesiol Clin Pharmacol 2017; 33: 514-9.
[31] Henry K, Merab K, Leonard M, Ronald KL, Nasser K and Moses G. Elevated serum lactate as a predictor of outcomes in patients following major abdominal surgery at a tertiary hospital in Uganda. BMC Surg 2021; 21: 319.
[32] Ergin B, Kapucu A, Guerci P and Ince C. The role of bicarbonate precursors in balanced fluids during haemorrhagic shock with and without compromised liver function. Br J Anaesth 2016; 117: 521-528.
[33] Kwo PY, Cohen SM and Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. Am J Gastroenterol 2017; 112: 18-35.
[34] Ruhl CE and Everhart JE. Elevated serum alanine aminotransferase and gamma-glutamyltransferase and mortality in the United States population. Gastroenterology 2009; 136: 477-85, e11.
[35] Ioannou GN, Weiss NS, Boyko EJ, Mozaffarian D and Lee SP. Elevated serum alanine aminotransferase activity and calculated risk of coronary heart disease in the United States. Hepatology 2006; 43: 1145-51.
[36] Ma J, Han S, Liu X and Zhou Z. Sodium bicarbonated Ringer's solution effectively improves coagulation function and lactic acid metabolism in patients with severe multiple injuries and traumatic shock. Am J Transl Res 2021; 13: 5043-50.
[37] Khanduja JS, Calvo IA, Joh RI, Hill IT and Motamedi M. Nuclear noncoding RNAs and genome stability. Mol Cell 2016; 63: 7-20.
[38] Smith SA, Livingston MH and Merritt NH. Early coagulopathy and metabolic acidosis predict transfusion of packed red blood cells in pediatric trauma patients. J Pediatr Surg 2016; 51: 848-52.
[39] Chen M, Li W, Li L, Chai Y, Yang Y and Pu X. Ankylosing spondylitis disease activity and serum vitamin D levels: a systematic review and meta-analysis. Medicine (Baltimore) 2022; 101: e31764.
[40] Straatman J, Van der Wielen N, Cuesta MA, de Lange-de Klerk ES and van der Peet DL. Major abdominal surgery in octogenarians: should high age affect surgical decision-making? Am J Surg 2016; 212: 889-95.
[41] He D, Kuang W, Yang X and Xu M. Association of hemoglobin H (HbH) disease with hemoglobin A(1c) and glycated albumin in diabetic and non-diabetic patients. Clin Chem Lab Med 2021; 59: 1127-32.
[42] Evans AS, Levin MA, Lin HM, Lee K, Weiner MM, Anyanwu A, Adams DH and Mittnacht AJC. Prognostic value of hyperlactatemia and lactate clearance after mitral valve surgery. J Cardiothorac Vasc Anesth 2018; 32: 636-43.

Appendix 1. Definitions of complications

Complications	Requirement
Major complications	
Anastomotic leakage	A defect of the intestinal wall at the anastomotic site leading to a communication between the intra- and extra-luminal compartments.
Peritonitis	Infection or inflammation of the peritoneum caused by intestinal perforation, trauma, postoperative infection from drains, or direct spread of infected organ.
Re-operation	Need re-surgery to repair because of postoperative anastomotic fistula and other problems.
Pneumonia	The presence of new and/or progressive pulmonary infiltrates on chest radiograph plus two or more of the following: ● fever of 38.5°C or higher, or postoperative hypothermia less than 36°C; ● leukocytosis of 10,000 white blood cell/mm^3 or greater or leukopenia less than 4,000 white blood cell/mm^3; ● purulent sputum; and/or; ● new onset or worsening cough or dyspnea.
Deep venous thrombosis	Venous reflux disorder caused by abnormal coagulation of blood in deep veins.
Arrhythmia	Electrocardiograph evidence of cardiac rhythm disturbance.
Stroke	Embolic, thrombotic, or hemorrhagic cerebrovascular event with persistent motor, sensory, or cognitive dysfunction confirmed by computerized tomography, magnetic resonance imaging, or autopsy.
Mortality	Patient death after primary surgery.
Minor Complications	
Urinary and other infection	Local inflammatory signs and specific antibiotic treatment.
Wound bleeding	Postoperative wound dehiscence or bleeding requiring drug treatment.
Postoperative nausea and vomiting	Nausea or vomiting within 24 to 48 h of surgery and requiring antiemetic therapy.
Cough and expectoration	Did not meet the diagnostic criteria for pneumonia.
Impaired liver function	Aspartate aminotransferase, alanine aminotransferase greater than 2 times normal value.
Pruritus	Severe itching of the skin.