

# Blood potassium level associated with recovery of post-operative gastrointestinal motility during continuous renal replacement therapy in critically ill patient undergoing open abdominal surgery

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# Abstract

**Background:** The purpose of the present study was to explore the potential therapeutic goal of blood potassium level beneficial to the post-operative recovery of gastrointestinal motility during continuous renal replacement therapy (CRRT) in critically ill patient undergoing open abdominal surgery. **Methods:** 538 critically ill patients after open abdominal surgery and receiving CRRT were retrospectively recruited as the study cohort. Demographic and clinical data including plasma potassium levels were recorded along with evaluation of post-operative gastrointestinal motility. The median of first gastrointestinal motility recovery time was 4 days of the present study cohort, and we used gastrointestinal motility recovery during 4-day period and un-recovery at 4 days after the completion of surgery as the primary endpoints. **Results:** The received operating characteristic (ROC) curve analysis demonstrated that the post-operative blood potassium level during CRRT was significantly associated with the recovery of gastrointestinal motility (AUC = 0.72,  $p < 0.001$ ), and plasma potassium concentration at the cut-off point of the ROC curve was 4.00 mmol/L. Kaplan–Meier analysis indicated that compared with the patients with insufficient blood potassium level (plasma potassium concentration  $< 4.00$  mmol/L), those with sufficient level (plasma potassium concentration  $\geq 4.00$  mmol/L) had higher rate of 4-day post-operative recovery of gastrointestinal motility ( $p < 0.001$ ). Logistic regression analysis indicated that the post-operative blood potassium level was independently associated with the recovery of gastrointestinal motility, patients with a sufficient blood potassium level conferred an increase in the rate of 4-day post-operative recovery of gastrointestinal motility (OR= 4.36, 95% CI 2.92-6.52,  $p < 0.001$ ). **Conclusions:** Our data indicated that keeping the blood potassium concentration at a relative high level of the regular blood potassium range during CRRT, would be beneficial to post-operative recovery of gastrointestinal motility, and eventually implied the potential therapeutic goal of blood potassium level for the recovery of post-operative gastrointestinal motility during CRRT in critically ill patient undergoing open abdominal surgery.

## Background

Patients undergoing abdominal surgery will develop the episode of impaired gastrointestinal motility, even postoperative ileus [1, 2]. Prolonged gastrointestinal paralysis after surgery may result in a longer hospital stay and increased medical costs [3]. Electrolyte homeostasis, in particular, the blood potassium level, is very important to post-operative recovery of gastrointestinal function [4]. Lot of studies suggested that hypokalemia was an independent risk factor for post-operative complications, including delayed recovery of gastrointestinal motility, while sufficient potassium supplementation might accelerate the recovery of gastrointestinal function [5, 6].

Numerous factors would cause potassium disturbance after abdominal surgery, especially in the critically ill patients receiving intensive care therapy, including insufficient potassium intake, excessive potassium discharge, hypercatabolism, concomitant acute kidney injury, therapy related factors, and so on [7-9]. Continuous renal replacement therapy (CRRT) is one of the most important methods to maintain the electrolyte homeostasis of critically ill patient with or without kidney injury [10, 11]. One of the fundamental goals of the CRRT is to maintain blood potassium levels within a regular range. It is

relatively easy to avoid hyperkalemia or hypokalemia, diagnosed with the classic standard, in the clinical setting when patients received CRRT [12]. However, on the point of optimized treatment, to maintain the blood potassium in the rational level, helping for the post-operative recovery of gastrointestinal motility, is the updated concern for clinicians. Unfortunately, very rare data have been reported to imply this crucial clinical problem and the rational goal of blood potassium level during CRRT is still unclear so far.

In the present study, we retrospectively investigated a critically ill patient cohort after abdominal surgery who received CRRT to explore the potential therapeutic goal of blood potassium level, which is beneficial to the post-operative recovery of gastrointestinal motility.

## Methods

### Patient selection

Between 1 January 2008 and 30 December 2017, about 14,400 critically ill patients brought to the intensive care unit (ICU), emergency ICU or surgical ICU at the First Affiliated Hospital, College of Medicine, Zhejiang University, were retrospectively reviewed. From among those patients, 538 individuals after open abdominal surgery and receiving CRRT served as the patient cohort for the present study.

### Patient data

All patients' data were extracted from medical records as well as the linked clinical inspection database and blood purification database of the hospital. We collected the following demographic and clinical information of the patients at the admission to ICU and during CRRT treatment: age, gender, operative characteristics, Acute Physiology Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) score at the admission to ICU, technical parameters and duration of CRRT, ICU stay time, and daily plasma potassium level. Plasma potassium level tests were performed every 4 hours and the mean was adopted to stand for the daily plasma level. Potassium supplementation in the replacement fluid managed to maintain the patients' plasma potassium at the regular range, according to the results of the routine tests. Plasma potassium was tested by ABL800 FLEX analyzer (Radiometer Medical, Copenhagen, Denmark). The Accura Hemofiltration System was used to administer CRRT. Polysulfone or polyamide filters were used for the patients, and the filter was changed when the transmembrane pressure (TMP) of the filter was greater than 250 mmHg. Central venous access was used with catheters of 11.5Fr or 13.5Fr × 16 cm, 11.5Fr or 13.5Fr × 19.5 cm. Replacement fluid was delivered into the extracorporeal circuit at a predilution/postdilution ratio of 2:1. Anticoagulation was performed according to each patient's condition with unfractionated heparin, low-molecular-weight heparin, heparin-free, or citrate anticoagulation.

### Variables

Observation indices of gastrointestinal motility included bowel sound, flatus, or defecation. The first gastrointestinal motility recovery time defined as any of the following episode: (1) the first bowel sound

time, defined as the time from the completion of the surgery to the first bowel sound; (2) the first flatus time, defined as the time from the completion of surgery to the first spontaneous flatus after the surgery; and (3) the first defecation time, defined as the time from the completion of surgery to the first spontaneous defecation after the surgery. In the present study cohort, the first gastrointestinal motility recovery time presented abnormal distribution, and the median of the time was 4 days. Therefore, we used gastrointestinal motility recovery during 4-day period and un-recovery at 4 days after the completion of surgery as the primary endpoints. The results of the plasma potassium concentration before the primary endpoint were recorded to calculate the mean, adopted as the post-operative blood potassium level.

## Statistical analysis

Statistical analysis was performed using SPSS version 23.0 software (SPSS, Inc, Chicago, IL, USA). A *p*-value less than 0.05 was considered statistically significant. A univariate comparison was performed to compare variables between two groups using an unpaired t-test for continuous variables and a  $\chi^2$  test or Fisher's exact test for categorical variables. Binary logistic regression analysis was applied to identify the independent contribution of prognostic factors to the prediction of gastrointestinal motility recovery in 4 days after the completion of surgery. When constructing the multivariate model, univariate factors with *p*-values less than 0.2 were used. The odds ratios with 95% confidence intervals (CIs) were used to estimate the association between the independent variables and the dependent variable.

## Results

The median of the first gastrointestinal motility recovery time was 4 days of the present study cohort. Thus, according to the primary endpoint described in the methods section, all the recruited patients was divided into following two groups: recovery group is defined as the time of gastrointestinal motility recovery  $\leq 4$  days after the completion of surgery, and  $> 4$  days considered as non-recovery group. The baseline demographics and clinical characteristics of the patients were summarized in Table 1. The mean age ( $\pm$ SD) for patients of the study cohort was  $53.50 \pm 15.95$  years, and 364 patients (67.66%) were male. A total of 156 patients (29.00%) underwent gastrointestinal operation. Univariate analysis indicated that recovery patients were significantly different from non-recovery ones with regard to some demographic and clinical characteristics, including less time of the duration of operation, different CRRT modality ( $p=0.079$ , with statistical tendency), and higher plasma potassium concentration (4.14 vs. 3.78 mmol/L,  $p < 0.001$ ). Meanwhile, age, gender, with or without gastrointestinal operation, intra-operative blood loss, mean APACHE II and SOFA score, and dose of CRRT demonstrated no significance between the recovery and non-recovery cohorts.

Thereafter, the received operating characteristic (ROC) curve analysis demonstrated that the post-operative blood potassium level was significantly associated with the recovery of gastrointestinal motility (Area under the curve (AUC) = 0.72,  $p < 0.001$ ), and plasma potassium concentration at the cut-off point of the ROC curve was 4.00 mmol/L (Fig 1). Thus we divided the total recruited patients into following two

groups: potassium insufficient group was defined as the patient's mean post-operative plasma potassium concentration  $< 4.00$  mmol/L before the primary endpoint, and  $\geq 4.00$  mmol/L considered as sufficient group. Kaplan–Meier analysis indicated that the post-operative gastrointestinal motility would recover more quickly in the potassium sufficient patient ( $p < 0.001$ , Fig 2).

Insufficient or sufficient blood potassium level and other univariate factors with  $p$ -values less than 0.2 showed in Table 1 including duration of operation, SOFA score, modality of CRRT, were recruited in the binary logistic regression model and indicated that the post-operative blood potassium level was independently associated with the recovery of gastrointestinal motility. Compared with the patients with insufficient blood potassium level (plasma potassium concentration  $< 4.00$  mmol/L), those with a sufficient blood potassium level (plasma potassium concentration  $\geq 4.00$  mmol/L), conferred an increase in the rate of 4-day post-operative recovery of gastrointestinal motility (OR= 4.36, 95% CI = 2.92 to 6.52,  $p < 0.001$ , Table 2).

The baseline demographics and clinical characteristics of potassium insufficient or sufficient group were summarized in Table 3. Some technical parameters of CRRT were compared between two groups besides the rate of post-operative gastrointestinal motility recovery. Compared with the potassium insufficient patients, the potassium sufficient individuals were more frequently receiving CRRT with the modality including hemodialysis method. There was no significant difference on the dose of CRRT between the sufficient and insufficient groups.

## Discussion

Electrolyte homeostasis is crucial for the regular gastrointestinal function, in particular, the blood potassium level. Maintenance the blood potassium concentration at a sufficient level is the cornerstone to a stable transmembrane potential to permit regular muscle function, including the gastrointestinal motility [13]. In the general population, the regular range for serum potassium levels is typically reported between 3.5 and 5.3 mmol/L, whereas the optimal range of potassium concentration in patients is different. For instance, lots of studies indicated that a relative higher blood potassium level of the regular blood potassium range was associated low incidence of all-cause mortality in hemodialysis patients [14–16]. Adequate potassium supplementation might accelerate the recovery of gastrointestinal motility after abdominal surgery [6]. The data of the present study also demonstrated that a relative higher blood potassium level in the normal range was beneficial to the post-operative recovery of gastrointestinal motility, maintenance the plasma potassium concentration  $\geq 4.0$  mmol/L associated with a significant increase in the rate of 4-day post-operative recovery of gastrointestinal motility.

In the critically ill setting, multiple factors might mediate the disturbance of the blood potassium level, inducing delayed post-operative recovery of gastrointestinal motility. It is a challenge to maintain the electronic concentration at rational level. CRRT is one of the widely used therapeutic strategies to manage the fluid, electron and acid-base balance in the critically ill patient. So far, the indication for the initiation of CRRT is far beyond the typical clinical conditions, including fluid overload, hyperkalemia, severe

acidosis, and so on [17]. To maintain the internal environment homeostasis is the fundamental therapeutic goal of medical treatment and CRRT may be adopted in many cases even without acute kidney injury [10]. In fact, a portion of the total patients of the present study received CRRT according to the extended application indication. Based on the technical feature of CRRT, hyperkalemia is relatively easy to manage in clinical practice. No patient developed hyperkalemia episode during CRRT in the present study cohort. Alternatively, insufficient blood potassium level, even hypokalemia, is more frequently in critically ill patients, especially caused by CRRT itself. It was reported in the ATN Study that the incidence of hypokalemia was 4.5% in the low-intensity group and 7.5% in the high-intensity group [18]. In the RENAL Trial, the incidence of hypokalemia in the low- and high-intensity groups was 24.4% and 23.4%, respectively [19]. Since the updated of technologies of CRRT, in particular, one of the most important methods that we currently have at our clinical management is the ability to modify potassium concentration of dialysate or replacement fluid [12]. Theoretically, clinicians can prescribe the regiment for any therapeutic goal of the blood potassium level. Therefore, the information of the rational goal, as least in part, becomes a fundamental element of the whole strategy of CRRT. Unfortunately, the data of the rational blood potassium level in critically ill patient during CRRT is very rare. Our data provided the evidence for the potential therapeutic goal of blood potassium concentration in the scenario as described above.

Evaluation of gastrointestinal motility is important but difficult in clinical practice. Several parameters usually used to evaluate the gastrointestinal motility, including bowel sounds, flatus, defecation and tolerate solid food [20]. In clinical trials, the time to return of bowel sounds, first flatus and defecation are often used as primary and/or secondary outcome measures [21]. In the present study, the recovery of gastrointestinal motility defined as any of the following three situations: return of bowel sound, spontaneous flatus, or spontaneous defecation. It is important to underline that these parameters are difficult to assess accurately in practice. Theoretically, passing stool or flatus may rather reflect rectal emptying than the recovery of effective gastrointestinal motility [20]. Furthermore, complicated situation of critically ill patient may restrict the collection or record of the information, for instance, mechanical ventilation, sedation, conscious disturbance, parenteral nutrition, and so on. Therefore, the parameters for the evaluation of gastrointestinal motility adopted in the present study still might cause bias. Another important issue needed to be emphasized that the AUC of the ROC curve analysis in the present study was small (0.72). So it should be very cautions to draw the conclusion based on the special plasma potassium concentration with 4.00 mmol/L (presented as the cut-off point of ROC curve analysis). Nevertheless, our data might in part imply the objective of the present study, and explored the trend relation that keeping the blood potassium concentration at a relative high level of the regular blood potassium range during CRRT, would be beneficial to post-operative recovery of gastrointestinal motility

Electrolyte operation via CRRT in clinical practice depends on the selection of technical parameters, especially the modality and therapeutic dose [8, 9, 17]. Our data also indicated that the modality adopted with hemodialysis method was more frequently to maintain the blood potassium level at the sufficient concentration. Yet we did not find the therapeutic dose effect on the maintaining of blood potassium level. The present data implied that plus hemodilysis method to the CRRT modality might be beneficial

to maintain the patient's blood potassium level at a special therapeutic goal, due to the innate technical character of hemodialysis method [22], in particular, at the clinical setting with mass fluid replacement.

## Limitations

The current study had several limitations. The retrospective study design decreased the power of the conclusions. We defined gastrointestinal motility recovery during 4-day period and un-recovery at 4 days after the completion of surgery as the primary endpoints, according with the median of the first gastrointestinal motility recovery time of the study cohort. It should be cautious to use the median as the surrogate of regular post-operative gastrointestinal motility recovery time. As described above, the definition we adopted for the evaluation of gastrointestinal motility might cause bias. In addition, various clinical settings may affect post-operative recovery of gastrointestinal function in critically ill patient, so we could never exclude the potential that factors other than blood potassium level during CRRT would impact the study outcome. A rational prospective randomized controlled trial should be designed to resolve this bias.

## Conclusions

We retrospectively investigated a critically ill patient cohort after open abdominal surgery receiving CRRT and found that blood potassium level during CRRT was significantly associated with the post-operative recovery of gastrointestinal motility. Keeping patient's blood potassium concentration at relative high level of the regular blood potassium range (plasma potassium concentration  $\geq 4.00$  mmol/L) was beneficial to the post-operative recovery of gastrointestinal function. Compared with the patients with insufficient blood potassium level (plasma potassium concentration  $< 4.00$  mmol/L), those with sufficient level (plasma potassium concentration  $\geq 4.00$  mmol/L) had an increase in the rate of 4-day post-operative recovery of gastrointestinal motility (OR= 4.36, 95% CI = 2.92 to 6.52,  $p < 0.001$ ). Our data indicated that keeping the blood potassium concentration at a relative high level of the regular blood potassium range during CRRT, would be beneficial to post-operative recovery of gastrointestinal motility, and eventually implied the potential therapeutic goal of blood potassium level for the recovery of post-operative gastrointestinal motility during CRRT in critically ill patient undergoing open abdominal surgery.

## Declarations

### Ethics approval and consent to participate

This study was approved by the Institutional Ethics Committee of Zhejiang University, and informed consent was obtained from the patients and/or their guardians.

### Consent for publication

Not applicable

## Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

YY conceived the study, participated in its design and coordination and drafted the manuscript. XEY and JJY participated in patient recruitment and contributed to drafting the manuscript. YC and XBL collected patient data. BBW and FFW performed all statistical analysis. PZ and JY revised the manuscript for important intellectual content. JHC revised the manuscript for the final version. All authors read and approved the final manuscript.

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## **Table 1. Baseline Demographic And Clinical Characteristics Of The Patients**

Characteristics	Patients (n=538)	Recovery (n=336)	Non-recovery (n=202)	<i>p</i>
Male sex (%)	364 (67.66)	224 (66.67)	140 (69.31)	0.526
Mean age (yr)	53.50±15.95	53.61±16.17	53.31±15.61	0.831
<b>Operative characteristics</b>				
Gastrointestinal operation (%)	156 (29.00)	101 (30.06)	55 (27.23)	0.483
Non-gastrointestinal operation (%)	382 (71.00)	235 (69.94)	147 (72.77)	0.483
Duration of operation (mean, min)	229.68±140.79	219.63±139.38	246.41±141.87	0.033
Intraoperative blood loss (median, ml)	400 (100-1025)	300 (100-1000)	500 (100-1200)	0.750
APACHE II score (mean)	16.80±7.78	16.83±7.39	16.77±8.48	0.939
SOFA score (mean)	8.64±3.99	8.43±3.92	8.99±4.10	0.116
CRRT modality				0.079
CVVH (%)	464 (86.25)	283 (84.23)	181 (89.60)	
CVVHD/CVVHDF (%)	74 (13.75)	53 (15.77)	21 (10.40)	
Prescribed dose of CRRT (mean in first 72 hours, ml/kg/h)	39.25±10.62	38.86±10.64	39.92±10.56	0.261
Delivered dose of CRRT (mean in first 72 hours, ml/kg/h)	29.65±13.30	29.62±14.04	29.70±11.98	0.952
Plasma potassium level (mmol/L)	4.00±0.47	4.14±0.48	3.78±0.34	<0.001

a Recovery is defined as the time of gastrointestinal motility recovery  $\leq$  4.0 days after the completion of surgery, and  $>$  4 days considered as None-recovery.

CVVH stands for continuous veno-venous hemofiltration, CVVHD stands for continuous veno-venous hemodialysis, and CVVHDF stands for continuous veno-venous hemodiafiltration.

Plasma potassium level was defined as the mean plasma potassium concentration before the primary endpoints.

*p*-value represents recovery cohort vs. non-recovery cohort.

## Table 2. Variables Included In The Multivariable Logistic Regression Analysis And Hazard Ratios

Variable	OR (95% CI)	<i>P</i>
Duration of operation (min)	0.999 (0.998-1.000)	0.098
SOFA score (mean)	0.963 (0.919-1.008)	0.109
CRRT modality	0.870 (0.487-1.554)	0.638
With sufficient plasma potassium level	4.364 (2.921-6.522)	<0.001

b potassium sufficient group was defined as the patient's mean post-operative plasma potassium level  $\geq$  4.00 mmol/L before the primary endpoints defined in the present study

**Table 3. Baseline Demographic And Clinical Characteristics Of The Potassium Insufficient Or Sufficient Group**

Characteristics	Patients (n=538)	potassium insufficient (n=305)	potassium sufficient (n=233)	<i>p</i>
Male sex (%)	364 (67.66)	193 (63.28)	171 (73.39)	0.013
Mean age (yr)	53.50±15.95	54.47±16.06	52.22±15.74	0.104
<b>Operative characteristics</b>				
Gastrointestinal operation (%)	156 (29.00)	88 (28.85)	68 (29.18)	0.933
Non-gastrointestinal operation (%)	382 (71.00)	217 (71.15)	165 (70.82)	0.933
Duration of operation (mean, min)	229.68±140.79	237.19±137.89	219.85±144.20	0.157
Intraoperative blood loss (mean, ml)	400 (100-1025)	500 (100-1000)	300 (100-1150)	0.365
APACHE II score (mean)	16.80±7.78	16.67±8.23	16.97±7.23	0.689
SOFA score (mean)	8.64±4.00	8.63±4.00	8.64±3.99	0.967
<b>CRRT modality</b>				<0.001
CVVH (%)	464 (86.25)	278 (91.15)	186 (79.83)	
CVVHD/CVVHDF (%)	74 (13.75)	27 (8.85)	47 (20.17)	
Prescribed dose of CRRT (mean in first 72 hours, ml/kg/h)	39.25±10.62	38.79±10.76	39.86±10.42	0.242
Delivered dose of CRRT (mean in first 72 hours, ml/kg/h)	29.65±13.30	29.49±14.31	29.87±11.87	0.743
Post-operative gastrointestinal motility recovery in 4.0 days (%)	336 (62.45)	148 (48.52)	188 (80.69)	<0.001

c potassium insufficient group was defined as the patient's mean post-operative plasma potassium level < 4.00 mmol/L before the primary endpoint defined in the present study, and ≥4.00mmol/L considered as sufficient group.

CVVH stands for continuous veno-venous hemofiltration, CVVHD stands for continuous veno-venous hemodialysis, and CVVHDF stands for continuous veno-venous hemodiafiltration.

*p*-value represents potassium insufficient cohort vs. potassium sufficient

## Figures

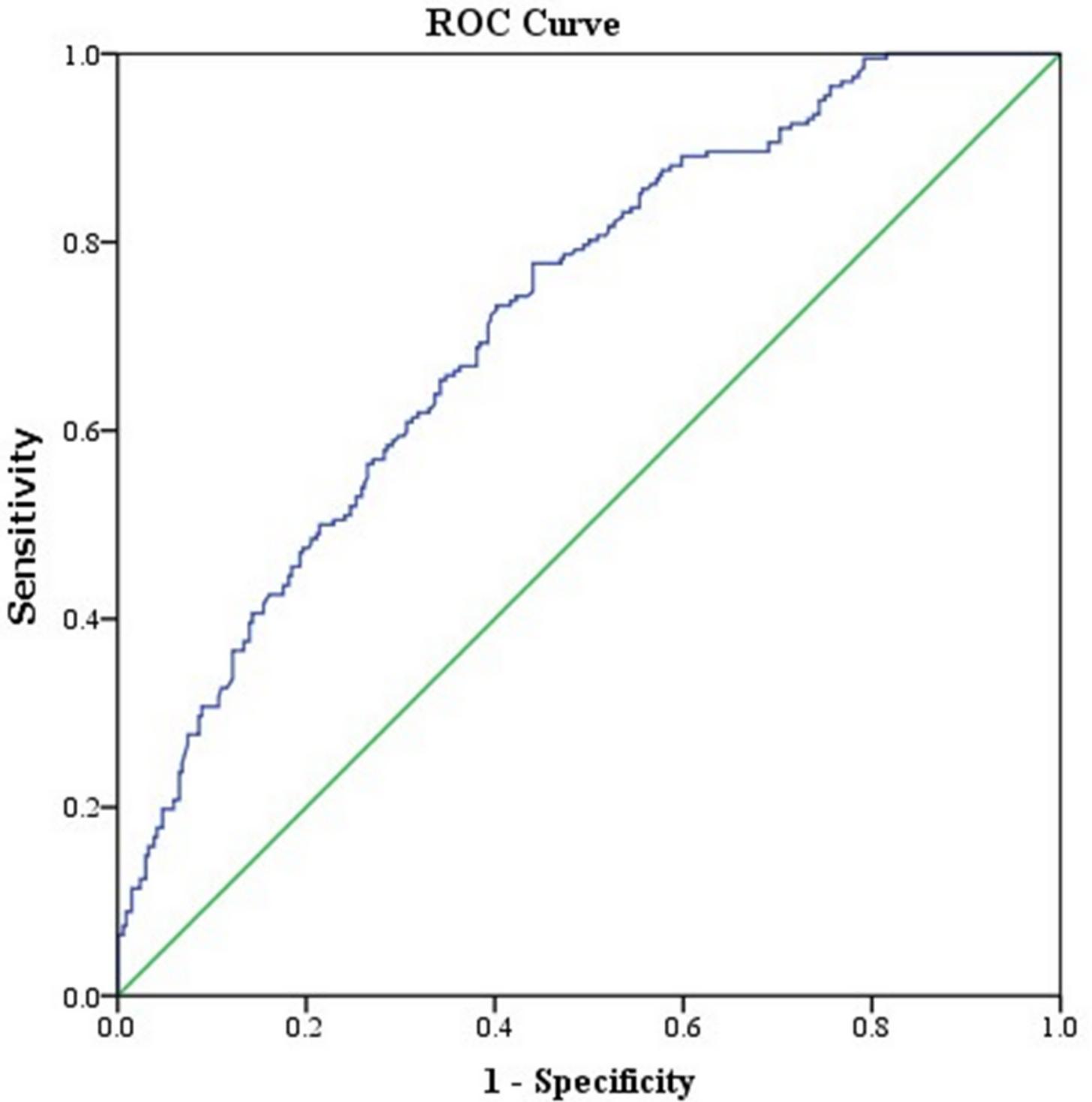


Figure 1

Received operating characteristic (ROC) curve analysis demonstrated that the post-operative blood potassium level was significantly associated with the recovery of gastrointestinal motility (AUC = 0.72,  $p < 0.001$ ), and plasma potassium concentration at the cut-off point of the ROC curve was 4.00 mmol/L.

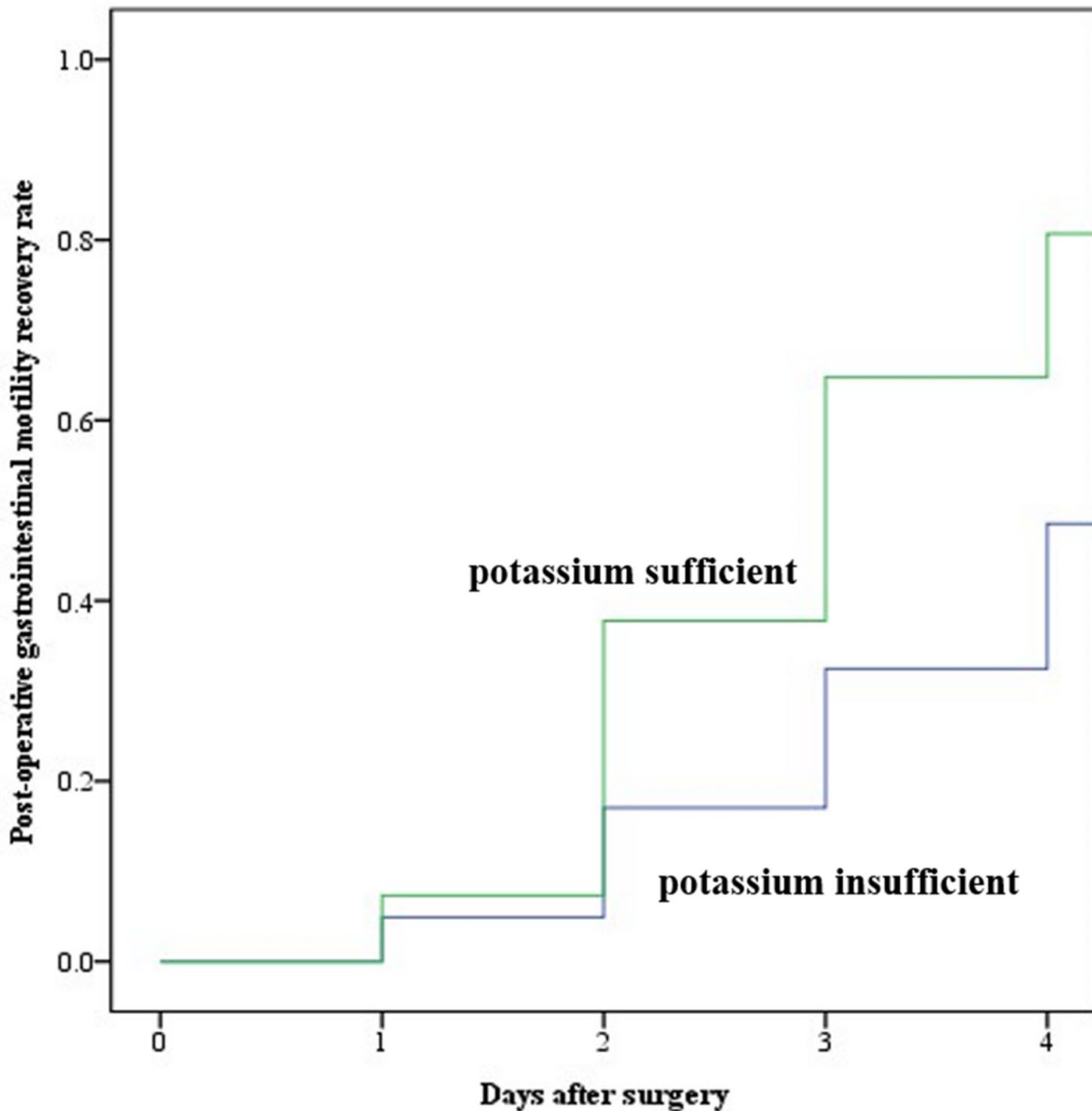


Figure 2

Kaplan–Meier analysis indicated that compared with the patients with insufficient blood potassium level (plasma potassium concentration < 4.00mmol/L), those with sufficient level (plasma potassium concentration  $\geq$ 4.00mmol/L) had higher rate of 4-day post-operative recovery of gastrointestinal motility ( $p < 0.001$ ).