Effect of intraoperative amino acid infusion on postoperative acute kidney injury after open abdominal aortic aneurysm repair: a retrospective cohort study

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Abstract

Background: The incidence of acute kidney injury (AKI) after open abdominal aortic aneurysm (AAA) repair is reportedly higher than the incidence after general surgery. Amino acid infusion has been shown to increase renal blood flow, thus protecting the kidneys. Therefore, we hypothesized that intraoperative amino acid infusion, which was used to maintain body temperature, is associated with a lower incidence of postoperative AKI. The aim of this study was to validate this hypothesis.

Methods: In this retrospective, observational, single-center cohort study, we included patients who underwent open AAA repair between January 2007 and April 2019. Perioperative data were abstracted from medical records. The primary outcome was AKI diagnosed according to Kidney Disease: Improving Global Outcomes criteria. Secondary outcomes were creatinine-AKI diagnosed based on serum creatinine alone and postoperative serum creatinine trajectory. A Fine and Gray proportional hazards regression analysis was conducted to examine the relationship between amino acid infusion and AKI. Similarly, multivariable logistic regression was performed for creatinine-AKI. Postoperative serum creatinine trajectory was assessed using a multivariable non-linear regression model with the Huber-White method.

Results: Of 696 patients, 310 patients received an amino acid infusion. Most patients received an amino acid infusion of 20 g. The amino acid group had a lower prevalence of AKI (24.7% vs. 25.3%; adjusted Hazard Ratio (HR)=0.86; 95% CI, 0.67–1.11; P=0.24) and creatinine-AKI (23.5% vs. 19.2%; adjusted odds ratio (OR)=0.84; 95% CI, 0.50–1.43; P=0.52) than the control group, but the differences were not statistically significant. Postoperative serum creatinine levels were significantly lower in the amino acid infusion group on postoperative days 5 and 6.

Conclusions: Intraoperative amino acid infusion has a tendency to reduce the incidence of postoperative AKI among patients undergoing open AAA repair. However, we could not show a statistically significant difference.

Trial registration: UMIN000038527, 09/11/2019

Background

Acute kidney injury (AKI) is one of the most common complications after open repair of both suprarenal and infrarenal abdominal aortic aneurysms (AAAs). The incidence of AKI was 20–37.3% [1–6], which is higher than the incidence of AKI after general surgery (1.0%) [7]. There are not enough reliable methods to prevent postoperative AKI, despite the fact that it is associated with approximately 10 times higher odds of mortality [8].

High protein intake or amino acid infusion therapy results in afferent arteriolar vasodilatation and a decrease in renal vascular resistance, with a consequent increase in renal blood flow. In response, the glomerular filtration rate (GFR) increases by up to 35% over resting baseline GFR [9–12]. Therefore, perioperative protein intake might prevent postoperative AKI. A randomized controlled trial suggested that patients who underwent amino acid infusion during cardiac surgery had 45% less occurrence of AKI [13]. However, there is minimal evidence that amino acid infusion can prevent renal dysfunction following open AAA repair. Therefore, we hypothesized that intraoperative amino acid infusion, which was used to maintain body temperature, is associated with a lower incidence of postoperative AKI. To test this hypothesis, we conducted a retrospective observational cohort study.

Methods

Study design and participants

This retrospective, observational, single-center cohort study enrolled patients who underwent open surgical AAA repair from January 2007 to April 2019 at our institution. The exclusion criteria were preoperative estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73 m^2. For each patient, only the first surgical AAA repair was included in the analysis.

Surgical indications and procedure

Surgical indications were based on the 2011 Japanese Circulation Society Guidelines for Diagnosis and Treatment of Aortic Aneurysm and Aortic Dissection [14], as follows: a maximal transverse diameter ≥ 55 mm in males and ≥ 50 mm in females, an increase in the transverse diameter ≥ 5 mm/6 months, or an infected aneurysm.

For AAA, open repair was generally performed at our institution; however, the vascular team considered endovascular aneurysm repair (EVAR) if the AAA satisfied any of the following conditions: anatomical characteristics that made EVAR favorable [14], age > 75 years, history of open abdominal surgery, and history of smoking. In Japan, EVAR has been covered by health insurance since 2007.

Anesthetic management

In all patients, general anesthesia was performed with concomitant electrocardiography, pulse oximetry, non-invasive blood pressure measurement, and capnometry. An arterial cannula was inserted in the radial artery and a central venous catheter was inserted into the jugular vein. Arterial pressure and central venous pressure were continuously monitored. Anesthesia was managed by the attending anesthesiologist. Epidural anesthesia was also performed unless patients had a low platelet count or coagulopathy, or were undergoing antiplatelet or anticoagulation therapy. Patients were transferred to the surgical intensive care unit (ICU) after open AAA repair.

The attending anesthesiologist decided whether to administer an amino acid preparation, and if so, the dose. The amino acid preparation consisted of a standard mixture of amino acids (AMIPAREN Injection; Otsuka Pharmaceutical). Its composition is listed in Table 1.

Diagnostic criteria for AKI

AKI was defined by the Kidney Disease: Improving Global Outcomes criteria, as follows: an increase in serum creatinine of ≥ 0.3 mg/dl within 48 hours; an increase in serum creatinine to ≥ 1.5 times baseline within the previous 7 days; or urine volume < 0.5 ml/kg/h for 6 hours [15]. Baseline creatinine was defined as the most recent creatinine value before surgery.

Since urine output was no longer measured hourly after discharge from the ICU, we defined creatinine-AKI as an alternative to AKI diagnosed based only on creatinine. The criteria for creatinine were the same as above.

Data acquisition

We retrospectively collected the following data from medical records: age, sex, height, weight, American Society of Anesthesiologist physical status, location of the cross-clamp, anesthesia time, operative time, date of surgery, intraoperative blood loss, intraoperative urine output, intraoperative fluid volume, intraoperative transfusion volume, and intraoperative volume of amino acids administered, and serum creatinine (before surgery and on postoperative days (PODs) 0–7).

Statistical analysis

Continuous variables were summarized as medians and interquartile ranges. Categorical variables and ordinal variables were summarized as numbers and percentages (%).

We estimated the cumulative probability of incident postoperative AKI, which was the primary outcome of this study, using the product-limit estimator. Furthermore, we assessed the effect of amino acid infusion on postoperative AKI using Fine and Gray proportional hazards regression. In the regression model, we treated discharge from ICU as the competing risk event for AKI [16]. To avoid overfitting, we selected the following potential confounders *a priori* based on clinical priority for adjustment in the regression model: age, sex, body mass index, preoperative serum creatinine, location of the cross-clamp, and year of surgery. Non-linear associations between continuous variables and the outcome were considered using restricted cubic spline functions. We also assessed the impact of the treatment on creatinine-AKI using multivariable logistic regression. In addition to the covariates described above, American Society of Anesthesiologists physical status, anesthesia time, intraoperative fluid volume, and intraoperative transfusion volume were included because the number of subjects with the event was sufficient to avoid overfitting. In the regression models described above, all missing values were imputed using the multiple imputation method.

In addition, we used multivariable linear regression to examine the effect of amino acid infusion on the postoperative trajectory of serum creatinine. Since the outcome variable was measured at multiple time points repeatedly, we used a robust estimation method with a Huber-White variance–covariance matrix to account for the correlation between repeated measurements within each patient. Adjustments for covariates were conducted similar to adjustments for creatinine-AKI with multivariable logistic regression. For missing value imputation with the repeatedly measured outcome, serum creatinine values were imputed with the last observation carried forward method. Covariates were imputed via the single imputation method. All statistical analyses were performed using two-sided tests at the 5% significance level using R software version 4.1.0 (www.r-project.org).

Results

We used a surgical database to collect data from 709 patients who underwent 715 elective open surgical repairs. Six procedures were excluded because they were repeat procedures. In addition, 13 patients were excluded because of their preoperative eGFR (Fig. 1). Of 696 patients who met the inclusion criteria, 310 (44.5%) underwent amino acid infusion. Most patients who received infused amino acids received a dose of 20 g. The baseline characteristics of the study participants are listed in Table 2.

Data on urine output were collected in 346 patients. AKI occurred in 86 (24.9%) of 346 patients. ICU discharge by POD 7 occurred in 258 (74.6%) patients (Table 3). Creatinine-AKI occurred in 147 (21.1%) of 696 patients (Table 4).

Figure 2 shows the cumulative incidence of ICU discharge and AKI in both groups. The amino acid group had a lower prevalence of AKI (adjusted hazard ratio (HR) = 0.86; 95% confidence interval (CI), 0.67–1.11; $P = 0.24$) and creatinine-AKI (adjusted odds ratio (OR) = 0.84; 95% CI, 0.50–1.43; $P = 0.52$) than the control group, but these differences were not statistically significant (Table 5).

Figure 3 shows the trajectory of serum creatinine levels in both groups. Postoperative serum creatinine levels were significantly lower in the amino acid infusion group on PODs 5 and 6.

Discussion

This study examined the effect of intraoperative amino acid infusion on the occurrence of postoperative AKI and creatinine-AKI. The occurrence of postoperative AKI with open AAA repair was 24.9% in this study. This result was compatible with previous reports [1–6]. We could not show a significant association between amino acid infusion and the occurrence of postoperative AKI. However, the HR for postoperative AKI was 0.86 and the direction of the effect was consistent with previous studies. In addition, postoperative serum creatinine levels were significantly lower in the amino acid infusion group on PODs 5 and 6.

One reason that amino acid infusion had a small effect on the occurrence of AKI might be the low dose of amino acids administered. The median dose of amino acids in our study was 20 g. This amount is much smaller than in a previous study in which 100 g of amino acids were administered daily [13]. Another study showed that there was a dose–response relationship between physiological increments in plasma amino acid concentrations and the stimulation of GFR and renal blood flow[17]. A threefold increase in plasma amino acid concentrations resulted in maximum increases in GFR and renal blood flow of 22% and 27%, respectively.

The effect of amino acid infusion on renal function has been reported previously. For instance, amino acid intake has been shown to decrease renal vascular resistance and increase renal blood flow [9–12]. Endothelium-derived nitric oxide has been thought to play an important role [18]. The vascular endothelium and renal tubule cells produce nitric oxide, which serves as an endogenous vasodilator that regulates renal blood flow and function. Since renal blood flow is reduced by inhibition of nitric oxide synthesis secondary to renal ischemia–reperfusion injury [19], aortic declamping might be a cause of AKI after AAA repair. The aforementioned studies suggest that intraoperative amino acid infusion can mitigate the increase in renal vascular resistance caused by aortic cross-clamping.

The role of individual amino acids in renal vasodilation is controversial. Chen et al. argued that arginine, a nitric oxide precursor, is the most important for renal vasodilation[18]. Castellino et al. reported that metabolism of glucogenic amino acids in the kidney increased both GFR and renal blood flow [20]. The proportion of these individual amino acids in our preparation was similar to those in the preparations used in other studies [13, 21]. On the other hand, Jeppsson et al. suggested that aspartate, glutamate, glycine, and histidine could play important roles in renal vasodilation [22]; their study included higher amounts of these amino acids than in this study. The optimal proportion of amino acids should maximize the degree of renal vasodilation achieved.

This study had several limitations. We could not adjust for several factors that might be associated with postoperative outcomes such as postoperative fluid balance, intraoperative cardiovascular variables, and preoperative comorbidity. Some data were unavailable because of automated extraction from medical records.

The study enrollment period was approximately 12 years, although many patients were from a single institution. Since surgical procedures have changed over the course of 12 years, such as the transition from open surgery to endovascular surgery, the characteristics of patients who undergo open surgery might also have changed. To address this issue, our statistical analysis included adjustments for the year of surgery.

There might have been bias in the association between intraoperative amino acid infusion and postoperative serum creatinine concentrations because the attending anesthesiologist decided whether to administer the amino acid preparation. There was no institutional protocol regarding its use. However, the possibility of confounding should be minimal because we used a multivariable linear regression model to adjust for the effects of multiple risk factors that could affect postoperative serum creatinine levels. Lastly, we did not examine adverse events caused by amino acid infusion.

In conclusion, we observed a significant reduction in postoperative serum creatinine concentrations in patients who received an intraoperative amino acid infusion. Amino acids might reduce the incidence of postoperative AKI.

Declarations

Ethics approval and consent to participate

This study adheres to the Declaration of Helsinki. This manuscript adheres to the applicable Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. This study was approved by our institutional ethics committee (National Cerebral and Cardiovascular Center Institutional Review Board, registration number: R19068). Our institutional ethics committee granted a waiver of written informed consent because of the retrospective nature of this study. All protected health information was removed after data abstraction.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the 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

MK, DK, AS, and KM analyzed and interpreted the patient data. MK was a major contributor to manuscript drafting. HS and HM provided information on surgical procedures and assisted in data extraction. KY and YO developed the research plan. All authors read and approved the final manuscript.

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Tables

Table 1. Content of the Mixed Amino Acid Solution (g/200ml)

L-Leucine	2.8
L-Isoleucine	1.6
L-Valine	1.6
L-Lysine acetate	2.96
L-Lysine	2.1
L-Threonine	1.14
L-Tryptophan	0.4
L-Methionine	0.78
L-Cysteine	0.2
L-Phenylalanine	1.4
L-Tyrosine	0.1
L-Arginine	2.1
L-Histidine	1
L-Alanine	1.6
L-Proline	1
L-Serine	0.6
Glycine	1.18
L-Aspartate	0.2
L-Glutamate	0.2

Table 3. Primary outcome

		Amino acids infusion					
	level	No	Yes	p	SMD	Overall	Missing (%)
N		87	259			346	
Event % (freq)	AKI	25.3 (22)	24.7 (64)	0.711	0.125	24.9 (86)	0.0
	ICU discharge	74.7 (65)	74.5 (193)			74.6 (258)	
	No event	0.0 (0)	0.8 (2)			0.6 (2)	

p, Chi-square test; SMD, Standardized Mean Difference; AKI, Acute Kidney Injury; ICU, Intensive Care Unit.

Table 4. Secondary outcome

	level	Amino acids infusion No	Amino acids infusion Yes	p	SMD	Overall	Missing (%)
N		386	310			696	
Creatine-AKI % (freq)	No	80.8 (312)	76.5 (237)	0.160	0.107	78.9 (549)	0.0
	Yes	19.2 (74)	23.5 (73)			21.1 (147)	

p, Chi-square test; SMD, Standardized Mean Difference; Creatine-AKI, Acute Kidney Injury diagnosed by serum creatinine alone.

Table 5. Effects of amino acids on postoperative AKI and Creatinine-AKI

Outcome	Estimator	Effect	95% Confidence Interval Lower	95% Confidence Interval Upper	P
AKI	Hazard Ratio (Yes/No)	0.86	0.67	1.11	0.24
Creatine-AKI	Odds Ratio (Yes/No)	0.84	0.50	1.43	0.52

CI, Confidence Interval; AKI, Acute Kidney Injury; Creatinine-AKI, Acute Kidney Injury diagnosed by serum creatinine alone.

Table 2

Table 2 is available in the Supplementary Files section.

Figures

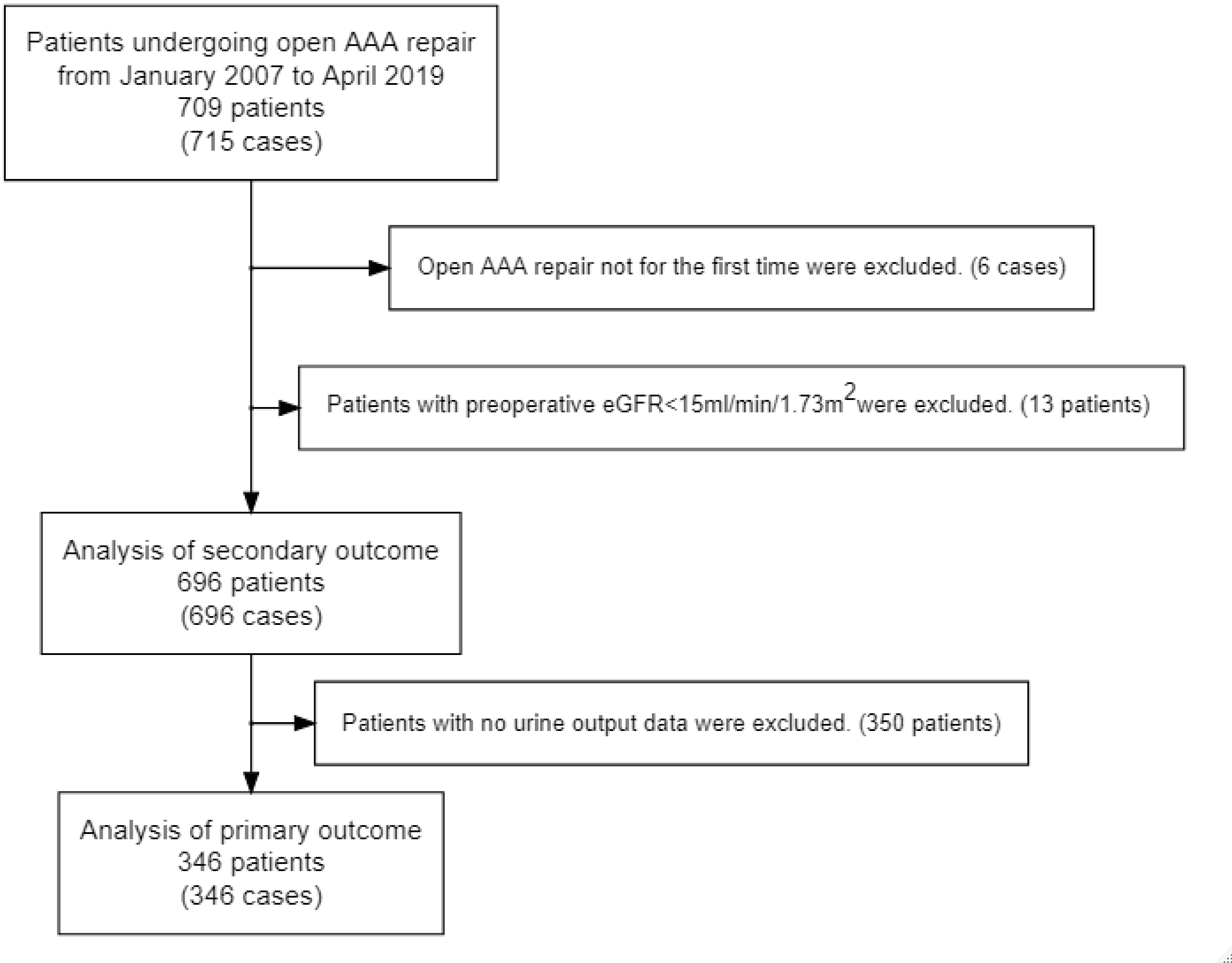

Figure 1

Recruitment flow diagram

AAA, Abdominal Aortic Aneurysm; eGFR, estimated Glomerular Filtration Rate.

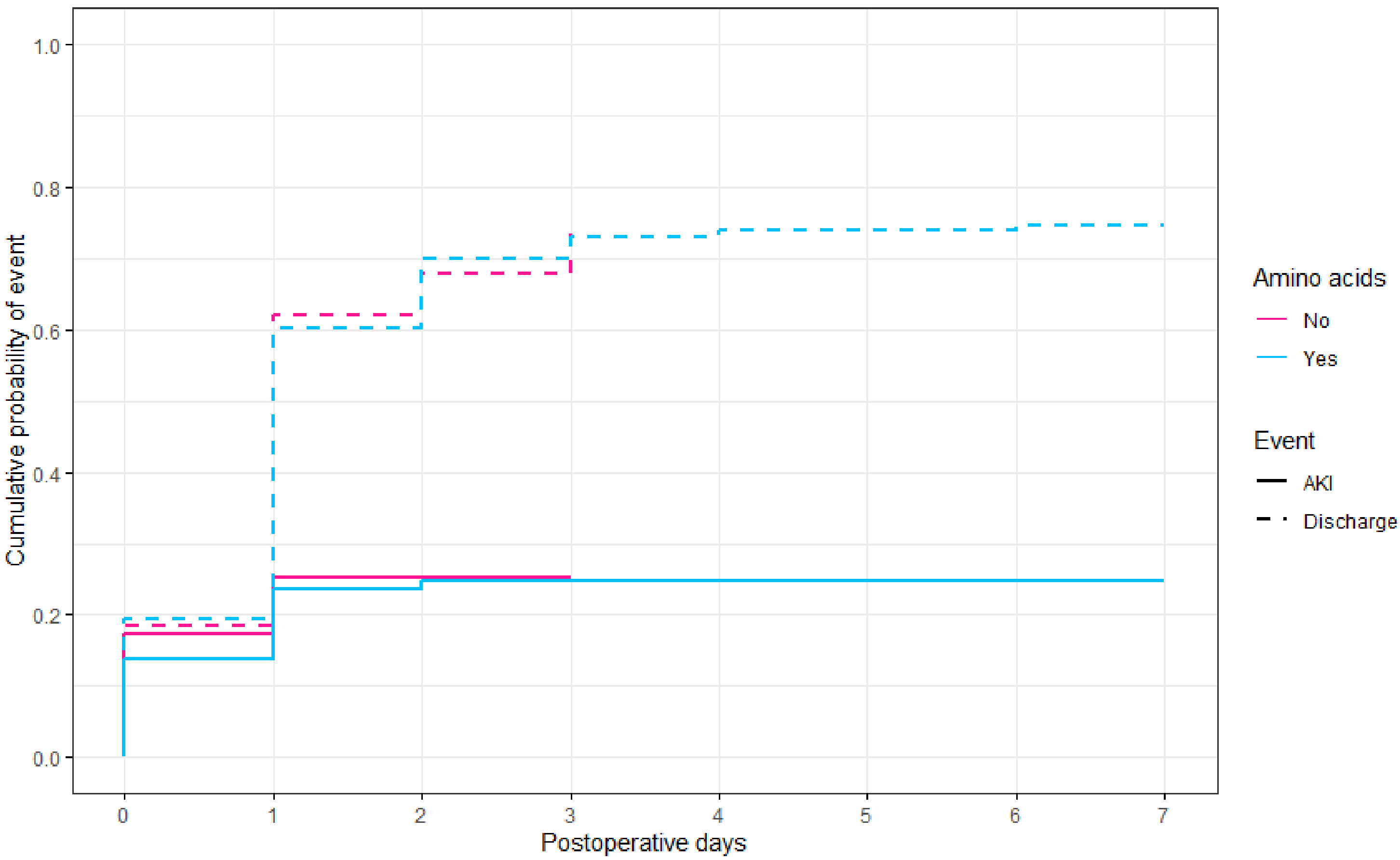

Figure 2

Cumulative incidence of ICU discharge and AKI

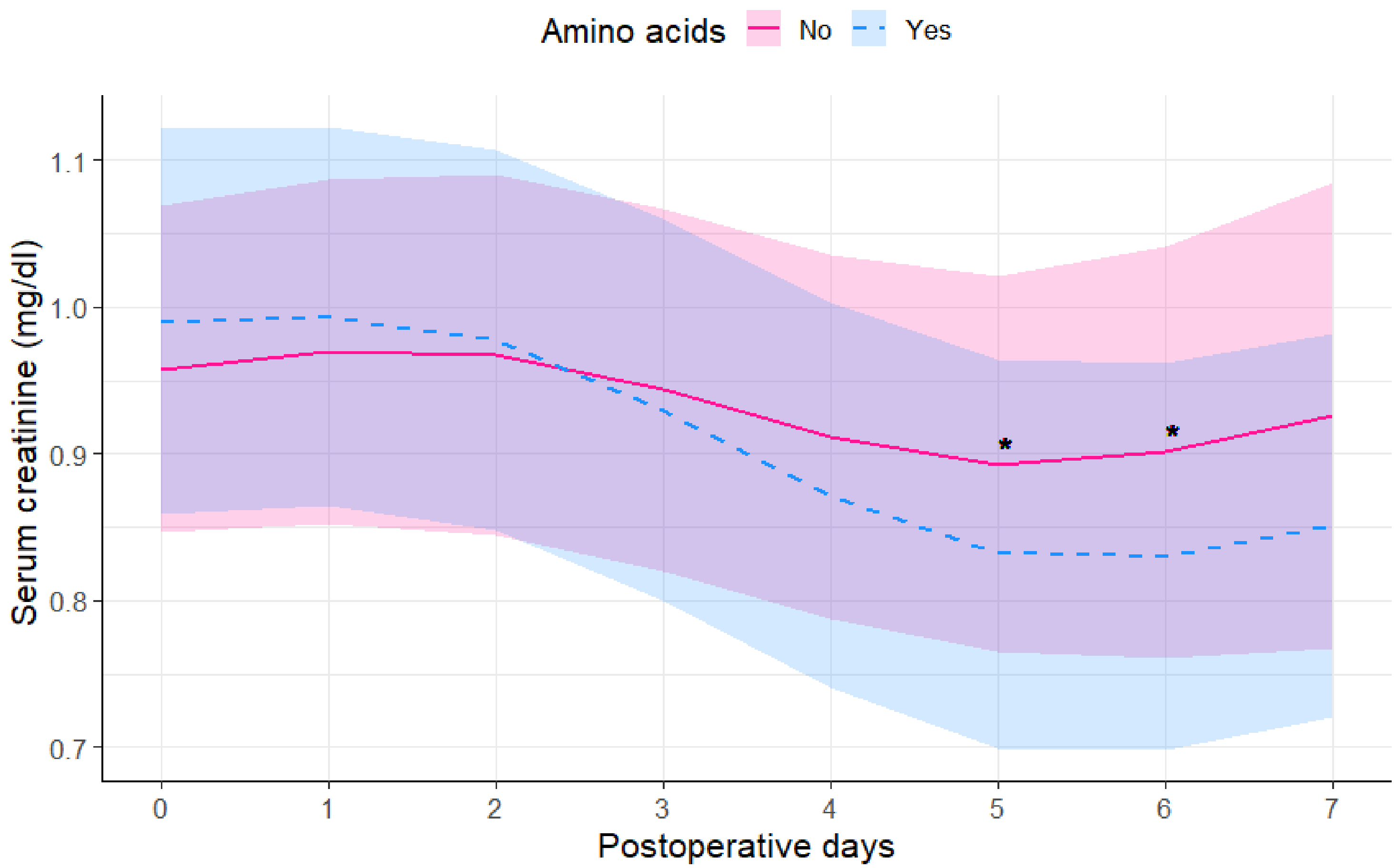

Figure 3

Effect of amino acid on postoperative serum creatinine

Supplementary Files

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- Table2.csv