Research Square

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Fluids beyond Volumes: A Retrospective Study on Compositional Descriptors of Intraoperative Fluid Therapy in Pediatric Liver Transplantation

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Abstract

Background

Intraoperative fluid therapy is commonly evaluated according to administered volumes or restrictive versus liberal strategies. These approaches may incompletely characterize the compositional aspects of fluid administration. We explored whether ratio-based descriptors of intraoperative fluid composition showed association with perioperative outcomes in pediatric liver transplantation.

Methods

This retrospective study included all pediatric patients under 40 kg of body weight who underwent liver transplantation between 2018 and 2025 at our institute. Children under one year of age were analyzed as subgroup. To characterize intraoperative fluid administration, we explored three compositional metrics: albumin per kilogram of body weight (AlbBW), albumin contribution to total administered fluids (Alb%), and the colloid-to-crystalloid ratio (CCR). Outcomes included recovery time (RT) and need of intraoperative vasoactive support or transfusion. Associations were assessed using multivariable regression models, and significant associations were explored according to linear, quadratic, and restricted cubic splines.

Results

The study included 142 children (median age 15 months [8–54], body weight 9 kg [7–16]), including 66 infants < 12 months. Median PELD was 12 (1–24). Preoperative albumin was 2.9 g/dl (2.5–3.3). Median albumin administered intraoperatively was 1.48 g/kg (1.02–2.11); intraoperative total fluid balance was − 119 ml (-443–114). Median Alb% was 1.97% (1.12–2.75), and median CCR was 0.13 (0.05–0.22). Thirty-one (31) patients (22%) required vasoactives during the intervention, while 83 (59%) received PRBC transfusion. Median RT was 19 days. In multivariable analysis, Alb% was independently associated with shorter RT (β − 1.02; 95% CI − 1.76 to − 0.27; p = 0.007). Linearity checks confirmed a predominantly linear inverse relationship, with a mild attenuation of effect at Alb% values > 3.5%. In infants, higher Alb% was also associated with lower odds of intraoperative PRBC transfusion (OR 0.56; 95% CI 0.33–0.95; p = 0.033). Instead, total intraoperative fluid balance showed no association with RT.

Conclusions

Ratio-based descriptors of intraoperative fluid composition provided complementary information beyond total fluid balance, and demonstrated measurable associations with perioperative outcomes, supporting further investigation into compositional approaches to intraoperative fluid therapy.

Background

In pediatric liver transplantation (PLT) intraoperative fluid management is paramount. Albumin is commonly administered to limit large crystalloid volumes because of its colloid properties and its potential role in maintaining intravascular volume (1–3). However, evidence supporting its clinical use remains inconsistent, and the clinical implications of albumin administration during major surgery, including liver transplantation, are still incompletely understood (4–8).

Most studies evaluating perioperative fluid therapy in PLT have primarily focused on total fluid volume or on broad categorical comparisons such as crystalloids versus colloids or restrictive versus liberal strategies (9). However, these approaches may only partially describe the qualitative composition of intraoperative fluid administration. In some pediatric critical care settings, ratio-based metrics have been proposed as pragmatic descriptors of resuscitation patterns rather than strict dosing targets (10, 11). Building on this concept, we explored whether compositional metrics describing the relative contribution of albumin-containing and crystalloid-based fluids might provide complementary information beyond total fluid balance alone.

The aim of this study was to explore whether ratio-based metrics describing intraoperative fluid composition are associated with perioperative outcomes in PLT.

Methods

This retrospective cohort study included all the consecutive PLT recipients (0–17 years) between January 2018 and December 2025 at our institute. A 40-kg cut-off of body weight was selected to focus on patients with smaller circulating blood volumes, in whom differences in fluid composition may have a greater impact. A subgroup analysis was conducted in recipients younger than 12 months.

Data Acquisition

Data collection was based on electronic medical records. Pre-transplant variables were selected based on their potential impact on intraoperative fluid requirements and hemodynamic stability (age, weight, baseline serum albumin, and PELD score). Surgical variables included donor type and duration of surgery.

To calculate the total fluid balance (TFB), infused crystalloids, albumin, blood products, and other intravenous fluids recorded were collected, as well as the hourly intraoperative urine output (UO), estimated fluid loss (EFL) and estimated blood loss (EBL). Insensible losses were assumed to be 10 $mL \cdot kg^{-1} \cdot h^{-1}$ over the time spent with open abdomen and applied uniformly to minimize systematic bias across patients. This approach was adopted in light of the lack of standardized recommendations in the literature, contributing to substantial interoperator variability in clinical calculations[12]. The amount of ascites aspirated following incision was directly measured. EFL was calculated using the formula: *EFL = (10 ml* weight (Kg) * duration of surgery(h)) + aspirated ascites content (ml)*. EBL was computed as the

quantity of blood loss on the surgery field estimated by the anesthesiologist. Perioperative variables and clinical outcomes also included intraoperative use of vasopressors and blood-products, extubation timing, anesthesia adverse events, and recovery time (RT), defined as the number of days from transplantation to hospital discharge.

Outcomes and Exposure

The objective of this study was to evaluate the association between intraoperative fluid metrics and recovery time (RT), computed in days from surgery to hospital discharge. Secondary outcomes included intraoperative use of vasopressors and PRBC transfusion.

To characterize intraoperative fluid administration beyond absolute volumes, we explored three complementary ratio-based descriptors of fluid composition. These metrics were intended as pragmatic compositional indices rather than physiologically validated measures of intravascular oncotic effect.

AlbBW was intended to reflect the absolute albumin-related oncotic load administered per kilogram of body weight. Alb% was designed to describe the relative contribution of albumin-containing fluids within the overall fluid strategy. Finally, CCR was used as a global descriptor of the balance between colloid-containing and crystalloid-based fluid administration.

$$AlbBW = \frac{(Albumininfusion\,(ml) \times\ concentration) + (Plasma\,(ml) \times\ 0.035)}{Bodyweight\,(kg)}$$

$$Alb\,\% = \left(\frac{(Albumininfusion\,(ml) \times\ concentration) + (Plasma\,(ml) \times\ 0.035)}{Crystalloids + Intravenousdrugs + Albumininfusion\,(ml)} \right) \times\ 100$$

$$CCR = \frac{Albumininfusion + Plasma + Gelatin\,(ml)}{Crystalloids + Intravenousdrugs\,(ml)}$$

These variables were analyzed as continuous exploratory exposure variables.

Because plasma contains albumin and contributes to oncotic load, its administered volume was incorporated into AlbBW, Alb%, and CCR calculations (12).

Statistical Analysis

Continuous variables are summarized as median and interquartile range (IQR); categorical variables are reported as absolute counts and percentages.

Linear regression was used to assess association with RT, and multivariable models were adjusted for clinically relevant covariates selected a priori. QQ-plots and residuals-versus-fitted plots showed no substantial departures from model assumptions across all three models. Associations between continuous exposures and binary outcomes were analyzed using binomial logistic regression models.

AlbBW and Alb% were adjusted for baseline serum albumin levels. RT was analyzed using generalized linear models with inverse Gaussian distribution and identity link. To assess the assumption of linearity between Alb% and RT, we explored potential non-linear relationships using both quadratic terms and restricted cubic spline (RCS) functions with four knots. Model fit was compared using Akaike Information Criterion (AIC) and likelihood ratio tests. Graphical diagnostics, including QQ-plots and deviance residuals, were also visually inspected to assess model adequacy. Pediatric End-Stage Liver Disease (PELD) score, total duration of surgery, intraoperative transfusion, vasoactive support, and delayed extubation were included as categorical factors. For the relationship with RT in the subgroup of infants < 12 months, weight-for-age z-score (WAZ) was also added to adjust multivariable linear regression. Binary outcomes — intraoperative PRBC transfusion and intraoperative vasoactive support — were analyzed using binary logistic regression.

Effect estimates were reported as regression coefficients (β) for linear models and odds ratios (ORs) with 95% IC for logistic regression models.

Given the mathematical overlap between AlbBW, Alb%, and CCR, which share albumin and plasma volume as common components, the three metrics were never entered simultaneously into the same model. Each metric was analyzed in a separate model to avoid collinearity and preserve interpretability of the individual estimates.

All statistical analyses were done using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Over the 8 years of the study, and following the inclusion criteria, 142 children (81 [57%] female) were enrolled (median age 15 months [8–54], weight 9 kg [7–16]. Sixty-six (66) recipients were less than 12 months old and were considered in the infant subgroup: median age 8 months [7–10], weight 7 kg [6–8]). The leading indication for PLT was cholestatic liver disease (n = 107, 75.4%), primarily biliary atresia (n = 87, 61.3%), followed by congenital cholestasis and progressive familial intrahepatic cholestasis (PFIC). Metabolic disorders accounted for 8 transplants (5.6%). Oncologic indications included hepatoblastoma (n = 5, 3.5%) and Langerhans cell histiocytosis (n = 1, 0.7%). Other indications comprised Alagille syndrome (n = 7, 4.9%); portal vein anomalies (n = 6, 4.2%), including portal cavernoma or thrombosis and Abernethy syndrome; acute hepatitis (n = 2, 1.4%); graft failure (n = 3); autoimmune acute hepatitis (n = 1); hemosiderosis (n = 1); and parenteral nutrition–associated liver failure (n = 1). In the majority of cases, the grafts were procured *ex vivo*, with a total of 106 living donor liver transplants (LDLT) (75%) and 26 cadaveric liver transplants (CLT). Preoperative and intraoperative data for the overall cohort and the infant subgroup are summarized in Table 1.

Table 1
Baseline Characteristics

Age at transplantation, months	**Overall cohort**	**< 12 months**
	N = 142	**N = 66**
	15 (8–54)	**8 (7–10)**
Sex assigned at birth, female	**81** (57%)	**40** (61%)
Weight, kg	**9.0** (7.0–15.6)	**7.0** (6.1–7.6)
Weight for age z-score (WAZ)	**-1.10** (-2.00 – -0.10)	**-1.3** (-2.1 – -0.2)
Serum albumin before transplantation, g/dl	**2.9** (2.5–3.3)	**2.6** (2.3–2.9)
PELD score	**12** (1–24)	**23** (15–29)
Glomerular filtration rate (GFR), ml/min	**190** (139–237)	**162** (133–203)
Graft procurement, LDLT	**106** (75%)	**59** (89%)
Total duration of surgery, minutes	**455** (410–510)	**465** (420–540)

Results are presented as median and percentiles (25–75) or number and percentages.

Intraoperative fluid administration

Crystalloid administration was comparable between groups, though infants received slightly higher median volumes (9.0 vs. 8.0 mL/kg/h). Overall, 28 patients (19.7%) did not receive albumin, 21 (14.8%) received 5% albumin, while 20% albumin was administered in 93 patients (65.5%). Albumin-related compositional metrics were largely similar between the overall cohort and the infant subgroup. As shown in Fig. 1, Alb% in the majority of cases was in the range between 1 and 2. Only two patients received gelatin during surgery.

Nineteen patients (14%) received FFP, mostly in association with PRBC. Median intraoperative PRBC transfusion was 6.1 mL/kg (IQR 0.0–16.4) in the overall cohort, and substantially higher among infants 16.4 mL/kg (IQR 10.0–21.0). Intraoperative fluid data and perioperative outcomes are summarized in Table 2.

Table 2
Intraoperative Fluid Administration and Management

Crystalloids administered, mL/kg/h	**Overall cohort**	**< 12 months**
	8.0 (6.0–11.0)	**9.0 (6.3–12.0)**
Patients transfused with PRBC, n (%)	**83** (58%)	59 (89%)
PRBC transfusion during surgery, ml/kg	**14.6** (8.6–17)	**16.9** (12.5–22.5)
Patients transfused with FFP, n (%)	**19** (13.4)	**13 (19.7%)**
FFP transfusion during surgery, ml/kg	**150** (50–250)	**0.0** (0.0–0.0)
Total intraoperative fluid balance, ml	**-119** (-443–114)	**-42** (-237–127)
Intraoperative urine output, ml/kg/h	**2.2** (1.6–3.2)	**2.11** (1.38–3.16)
AlbBW	**1.5** (1–2.1)	**1.21** (0.39–2.61)
Alb%	**2** (1.1–2.7)	**1.59** (0.54–3.21)
CCR	**0.1** (0.1–0.2)	**0.14** (0.08–0.22)
Vasoactive support during surgery	**32** (23%)	**19** (29%)
Immediate extubation	**128** (90%)	**56** (85%)
Recovery time, days	**19** (14–26)	**19** (16–23)

Results are presented as median and percentiles (25–75) or number and percentages.

The amount of Alb% was higher in patients who did not receive PRBC transfusion as shown in Fig. 2, and this finding is more evident in the subgroup of recipients with less than 12 months.

Fluid administration metrics and outcomes

In a generalized linear model with inverse Gaussian distribution and identity link, higher albumin percentage was significantly associated with shorter recovery time, with each unit increase in Alb% associated with a reduction of approximately 1.4 days in recovery time (β = −1.377; 95% CI − 2.31 to − 0.45; p = 0.0037). The association between Alb% and recovery time was consistent with a linear relationship. The addition of a quadratic term did not improve model fit, and was not statistically significant. Similarly, restricted cubic spline analysis using four knots did not show evidence of non-linearity (likelihood ratio test p = 0.24). Despite this, in the range between 1.5 and 3.5 of Alb%, there was higher variance, and two non-linear spline terms were borderline non-significant (p ~ 0.10) (Fig. 3).

In multivariable analyses with several clinically relevant variables as adjustments (baseline albumin, PELD, surgery duration, intraoperative transfusion of PRBC, and use of vasopressor, immediate extubation), this association was still confirmed and significant; therefore, at a lower magnitude, higher

intraoperative albumin percentage was independently associated with shorter recovery time in the overall cohort (β − 1.02, 95% CI − 1.76 to − 0.27; p = 0.007). No significant association was observed for colloid-to-crystalloid ratio or total albumin administered per kilogram (Fig. 4). Intraoperative vasoactive drug administration was not significantly associated with any fluid exposure metric. Higher albumin exposure was nevertheless associated with lower odds of intraoperative PRBC transfusion, particularly in the subgroup aged < 12 months (Fig. 5).

TFB was not associated with recovery time (RT) either in the overall cohort (95% CI − 0.056–0.256) or in the infant subgroup (95% CI − 0.099–0.396).

Discussion

In this single-center cohort of PLT recipients, we describe the intraoperative fluid administration through exploratory ratio-based descriptors. The relative contribution of albumin-containing fluids (Alb%) showed association with perioperative outcomes, whereas both albumin dosing (AlbBW) and total fluid balance failed to show associations, supporting the hypothesis that a compositional fluid consideration might be useful in improving outcomes after PLT.

Most perioperative fluid studies have evaluated administered volume or broad categorical strategies, such as restrictive versus liberal fluid management. However, these approaches may incompletely describe the compositional characteristics of intraoperative fluid administration. In this context, ratio-based metrics may represent pragmatic descriptors of how albumin-containing and crystalloid-based fluids are proportionally combined within a perioperative fluid strategy.

In pediatric anesthesia and critical care, fluid management is a mainstay of the treatment oriented toward early recovery and improvement of short-term outcomes (13). Previous studies have shown that substantially larger crystalloid volumes may be required to achieve similar hemodynamic targets compared with colloids, while recent pediatric critical care data have suggested that both cumulative fluid administration and colloid-to-crystalloid ratios may correlate with short-term clinical outcomes (11, 14). These observations support the concept that quantitative and compositional aspects of fluid therapy are closely interrelated.

Previous studies in PLT comparing restrictive versus liberal intraoperative fluid management strategies have associated higher intraoperative fluid administration with prolonged mechanical ventilation, longer ICU and hospital stay, and overall poorer postoperative recovery, supporting the rationale for restrictive fluid management in this population (9). In our study, TFB did not evidence any significant association with RT in either the overall cohort or the infant subgroup. A recent multicenter study suggested that, though intraoperative fluid volume may correlate with postoperative recovery parameters, it should not be interpreted as a dominant determinant, as additional modifiable perioperative factors should be considered (15). Similarly, the compositional characteristics of fluid administration are unlikely to independently explain postoperative recovery trajectories, but may represent one component within the broader perioperative context influencing recovery, and considering these more articulated metrics could

potentially increase the situational awareness in perioperative fluid administration. Importantly, the association between albumin percentage and recovery time was found to be linear across the observed range of values, with no evidence of threshold effects or non-linear patterns.

However, Alb% should be interpreted as a marker of fluid composition strategy rather than as a causal determinant of recovery. The clinical relevance of the observed associations should be interpreted cautiously. Effect sizes were small, and the low proportion of explained variance suggests that intraoperative fluid composition accounts for only a limited component of postoperative recovery variability. This is not unexpected in PLT, where recovery trajectories are influenced by multiple perioperative, surgical, organizational, and patient-related factors that indicate the recovery as a system-determined outcome. Despite that, in such an intricate picture as PLT the relevance of different metrics might raise the plausible hypothesis of usefulness that should be explored more in deep prospectively.

This study has several limitations, including its single-center retrospective design, which limits generalizability and precludes causal inference. The relatively small sample size may have reduced statistical power for some outcomes, while clinician-driven intraoperative fluid and transfusion management may have introduced variability and residual confounding. In particular, recovery time should be interpreted cautiously, as it is influenced by multiple postoperative and organizational factors beyond intraoperative care. Moreover the topic of fluids is here examined as volume infused and compositional infusions, while the electrolytes and acid base were not considered because during the operative phase they could be much more a confounding than explanatory factor.

Conclusion

In this exploratory cohort of PLT recipients, a ratio-based descriptor of intraoperative fluid composition showed associations with perioperative outcomes, while total fluid balance did not. These findings could be integrated into the broader concept of perioperative fluid stewardship that should ideally start early in the perioperative pathway and not be limited to postoperative care, as intraoperative administration contributes to cumulative, system-level fluid exposure (16). In this perspective, fluid administration represents a system-level intervention in which both volume and composition may influence downstream recovery trajectories. Further prospective investigations of compositional approaches to perioperative fluid characterization are warranted to substantiate this hypothesis.

Abbreviations

PLT: pediatric liver transplantation; LDLT: living donor liver transplantation; PELD: pediatric end-stage liver disease; PRBC: packed red blood cells; IE: immediate extubation; TFB: total fluid balance; EFL: estimated fluid loss; RT: recovery time

Declarations

Ethics approval and consent to participate

The study was approved by the ISMETT's Ethics Committee (Comitato Etico Locale IRRB/39/24). The requirement for informed consent for the participation in the study was waived by the Ethics Committee because of the inclusion of the study into the national research program "Ricerca Corrente" by the Italian Ministry of Health.

All procedures and research conduction were performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed 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

VS: conception and design of the study, data acquisition, data analysis, manuscript drafting. **FT:** data analysis. **GM:** supervision, data interpretation, manuscript editing and critical revision. **DK, GF:** data acquisition and management. **AA, GB:** manuscript editing, institutional oversight and support in the research activity.

All authors read and approved the final manuscript.

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Origin of liver graft and ethical statement

Liver grafts were obtained from deceased or living donors through legally approved transplantation programs. According to the national registration living donors undergo to a legal procedure to give the informed consent for donation. For deceased donors the absence of opposition to donation from the legally authorized representative was obtained by the team managing the donation. No organs or tissues were obtained from prisoners or other vulnerable populations, and all organ donations complied with national and institutional ethical requirements. The origin of both graft were explicitated in the protocol

submitted to and approved by the ISMETT's Ethics Committee (Comitato Etico Locale IRRB/39/24). The requirement for informed consent for the participation in the study was waived by the Ethics Committee because of the inclusion of the study into the national research program "Ricerca Corrente" by the Italian Ministry of Health.

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Figures

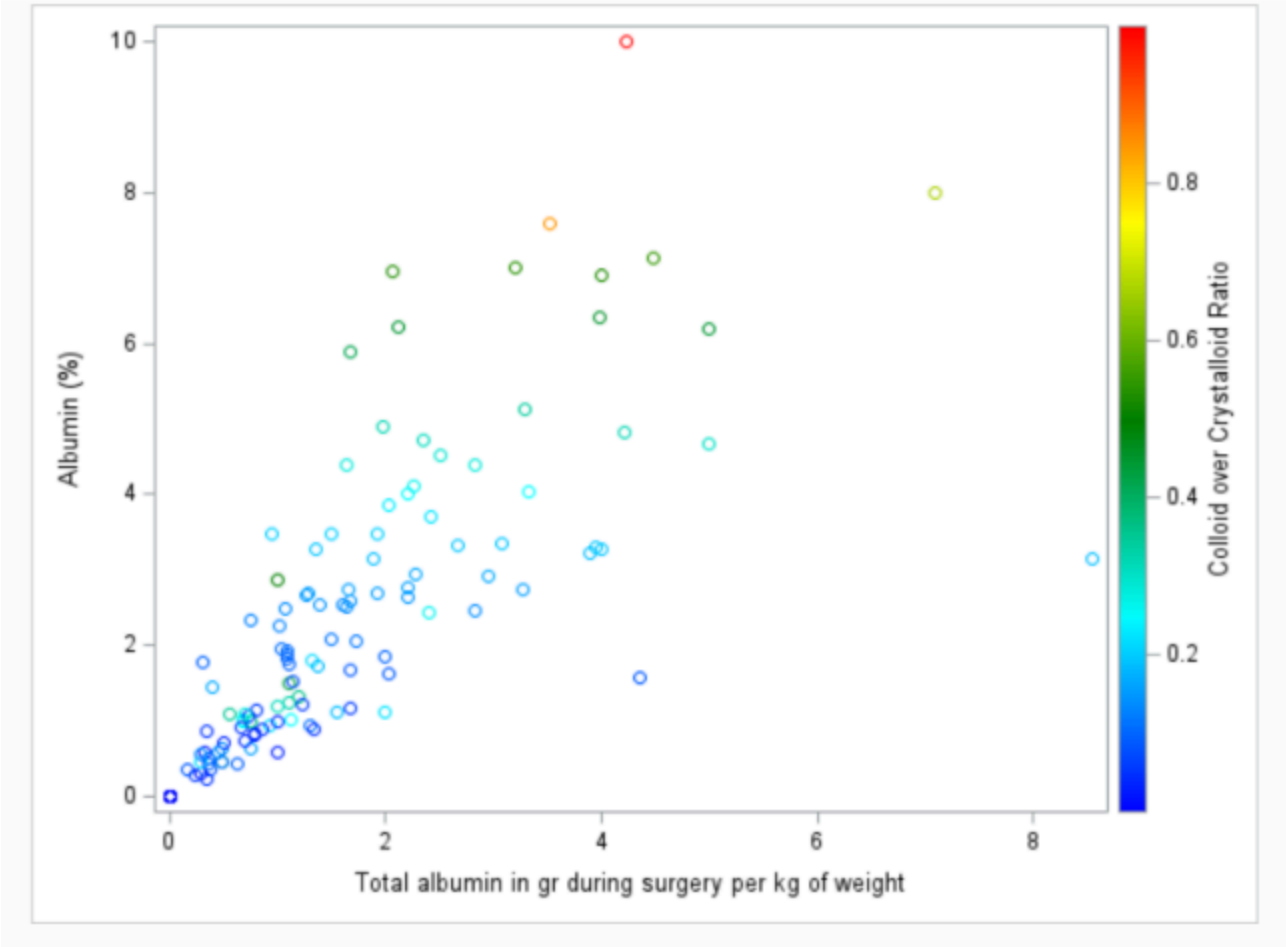


Figure 1

Relationship between albumin dose (AlbBW), albumin concentration (Alb%), and colloid-to-crystalloid ratio (CCR). *Scatter plot showing albumin concentration (Alb%, y-axis) versus total intraoperative albumin administered per kilogram of body weight (AlbBW, g·kg⁻¹; x-axis). Each point represents an individual patient and is color-coded according to the colloid-to-crystalloid ratio (CCR), as indicated by the color scale.*

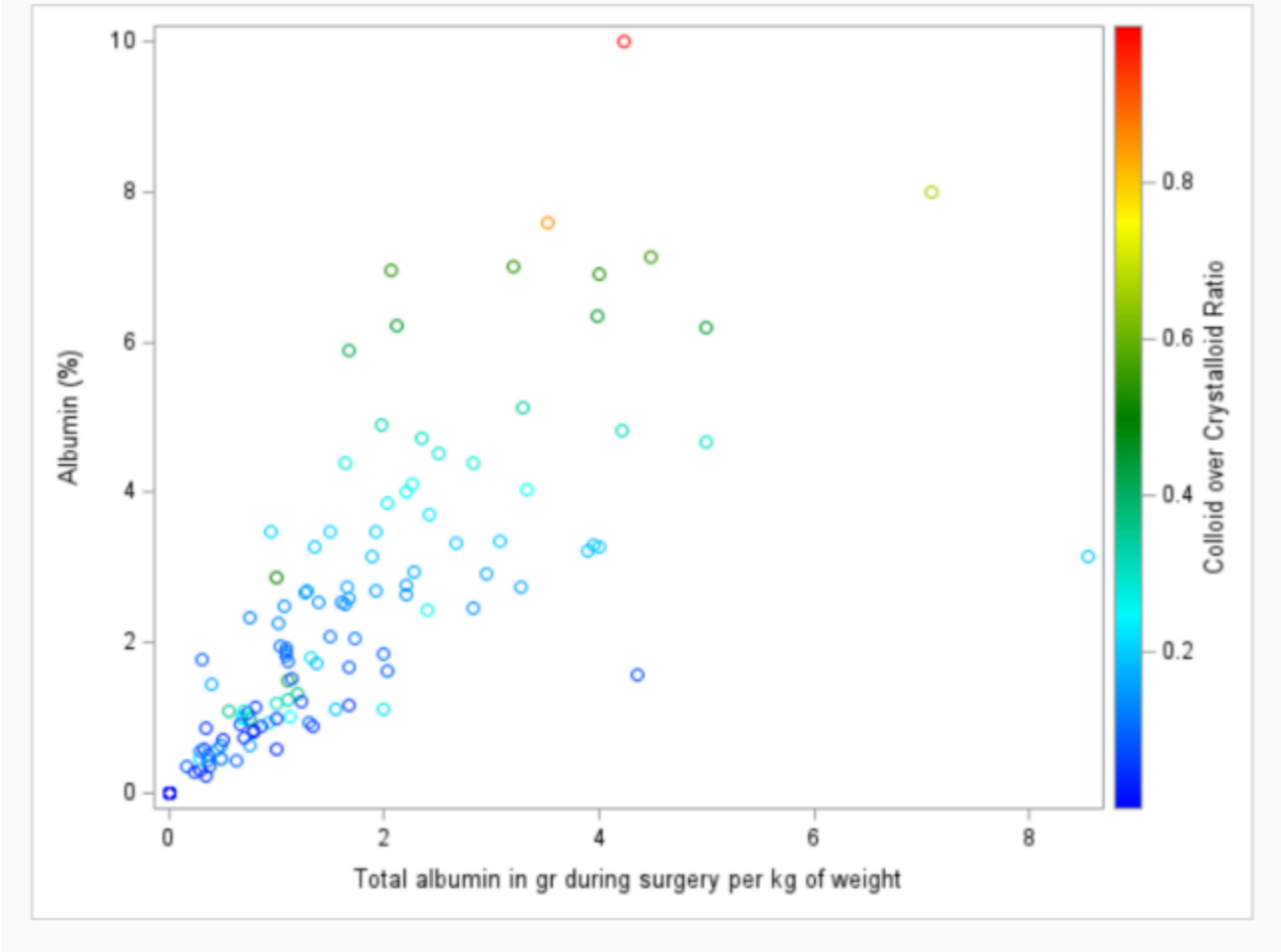


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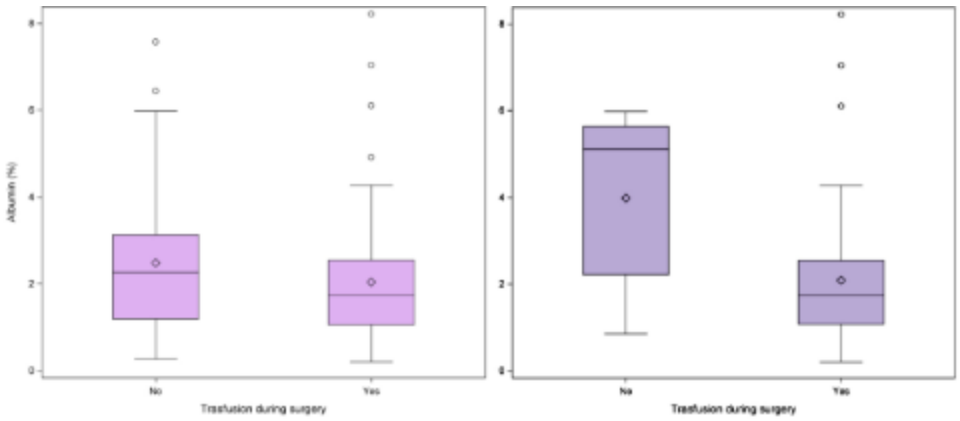


Figure 2

Intraoperative albumin percentage in the total fluid mixture among patients who did and did not receive packed red blood cell transfusion. *Boxplots show distributions for the overall cohort (left) and for children aged <12 months (right), including median, interquartile range, whiskers, mean values, and outliers. In the overall cohort, albumin percentage was similar between transfused and non-transfused patients. In contrast, in the <12-month subgroup, transfused patients exhibited a visibly lower albumin percentage, consistent with the age-specific association observed in multivariable analyses.*

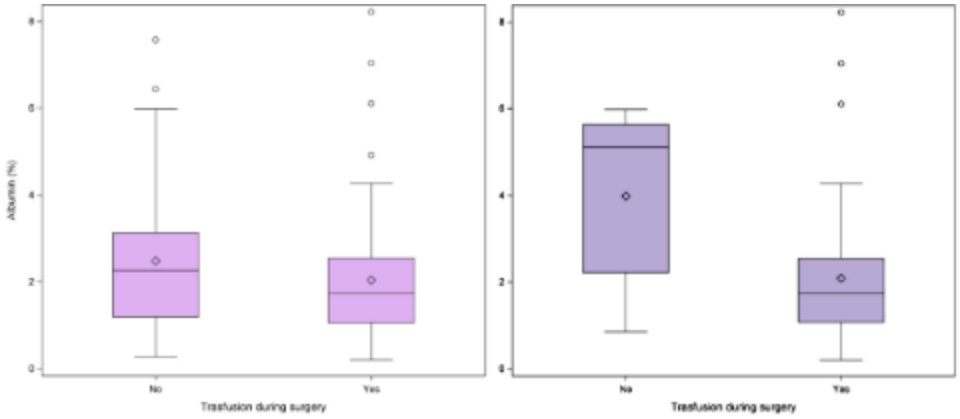


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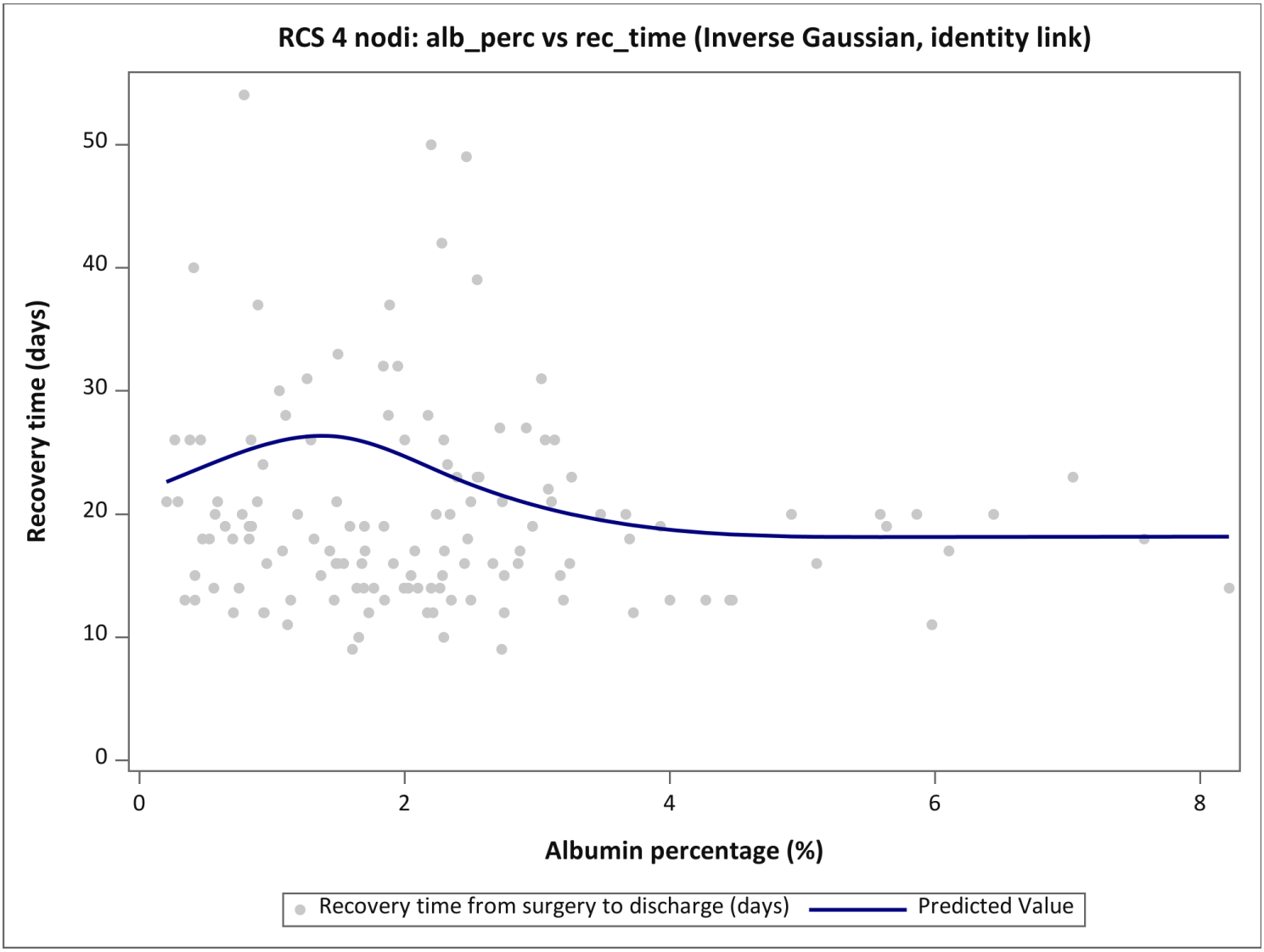


Figure 3

Association between albumin concentration (Alb%) and recovery time modeled using restricted cubic splines. *The curve suggests a predominantly linear inverse relationship, with no statistically significant deviation from linearity. 0–1.5: region of high uncertainty due to scant data, where the curve appears relatively flat or slightly increasing and should be interpreted with caution. 1.5–3.5: mild decline, representing the range with the greatest observed variation. 3.5–4: plateau, with no further meaningful reduction in recovery time observed at higher albumin values.*

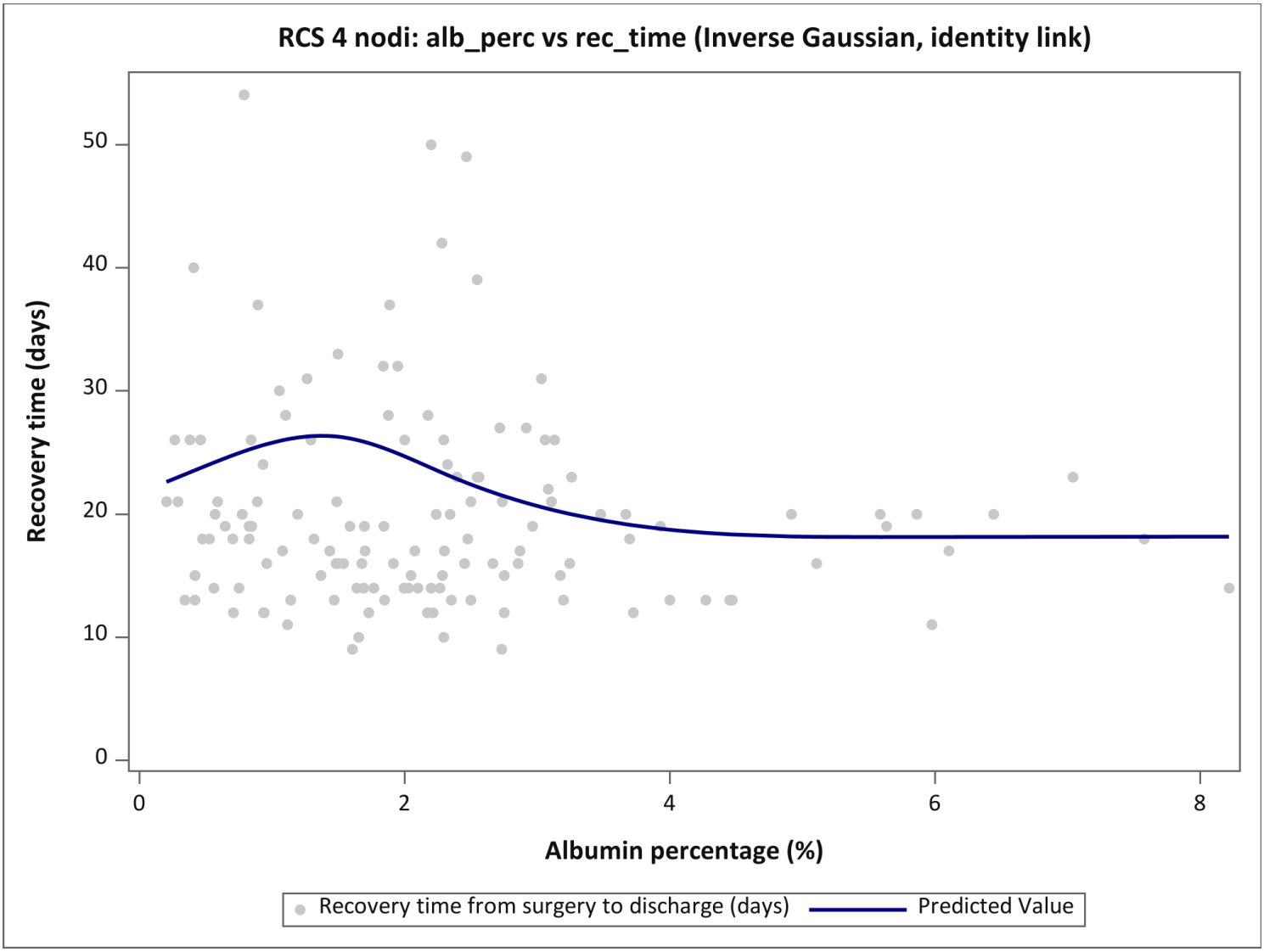


Figure 3

Association between albumin concentration (Alb%) and recovery time modeled using restricted cubic splines. *The curve suggests a predominantly linear inverse relationship, with no statistically significant deviation from linearity. 0–1.5: region of high uncertainty due to scant data, where the curve appears relatively flat or slightly increasing and should be interpreted with caution. 1.5–3.5: mild decline, representing the range with the greatest observed variation. 3.5–4: plateau, with no further meaningful reduction in recovery time observed at higher albumin values.*

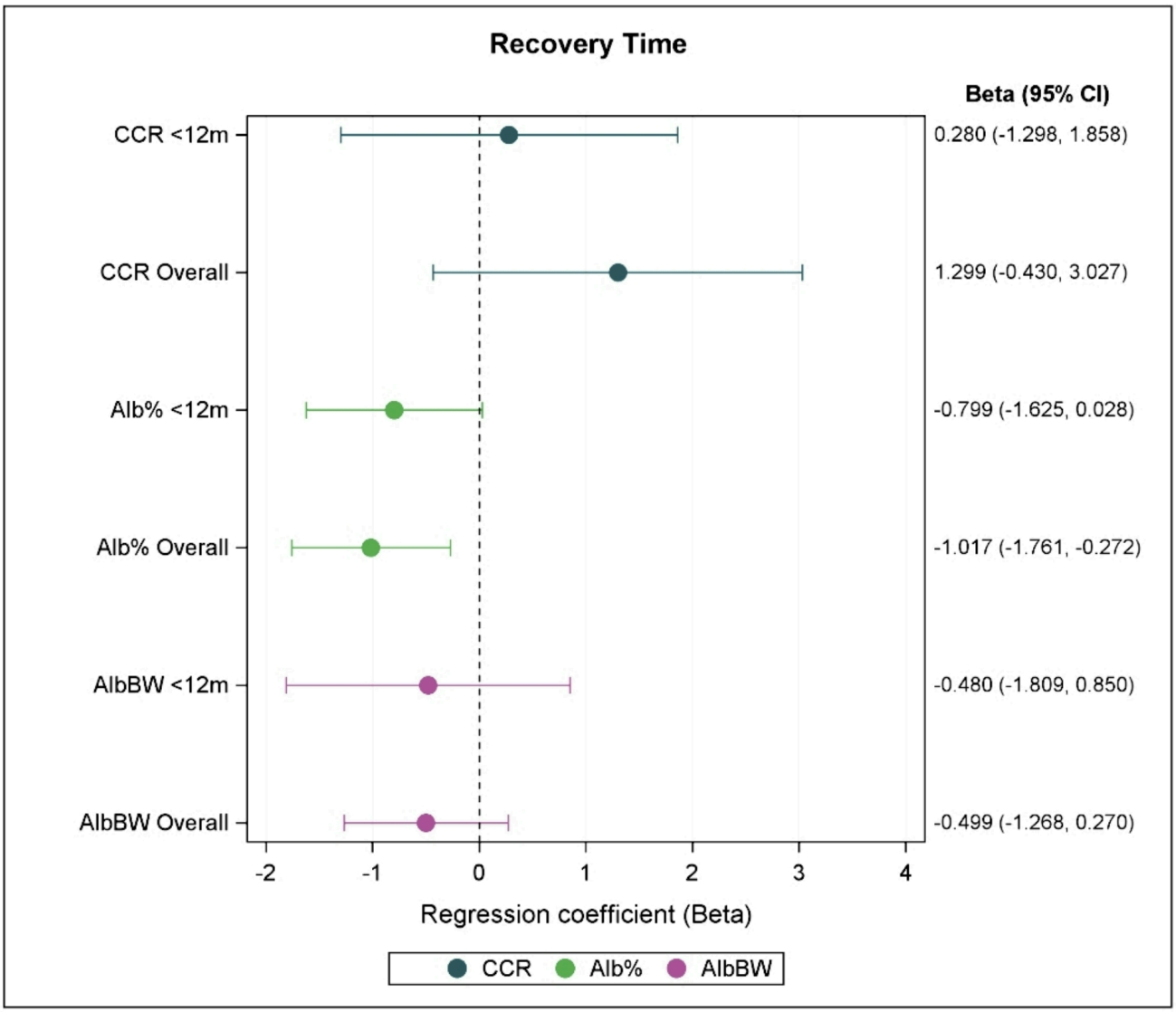


Figure 4

Associations between albumin dose (AlbBW), albumin concentration (Alb%), colloid-to-crystalloid ratio (CCR), and recovery time. *Forest plot displaying regression coefficients (β) and 95% confidence intervals (CI). Positive coefficients indicate longer recovery times, while negative coefficients suggest shorter recovery times relative to the reference.*

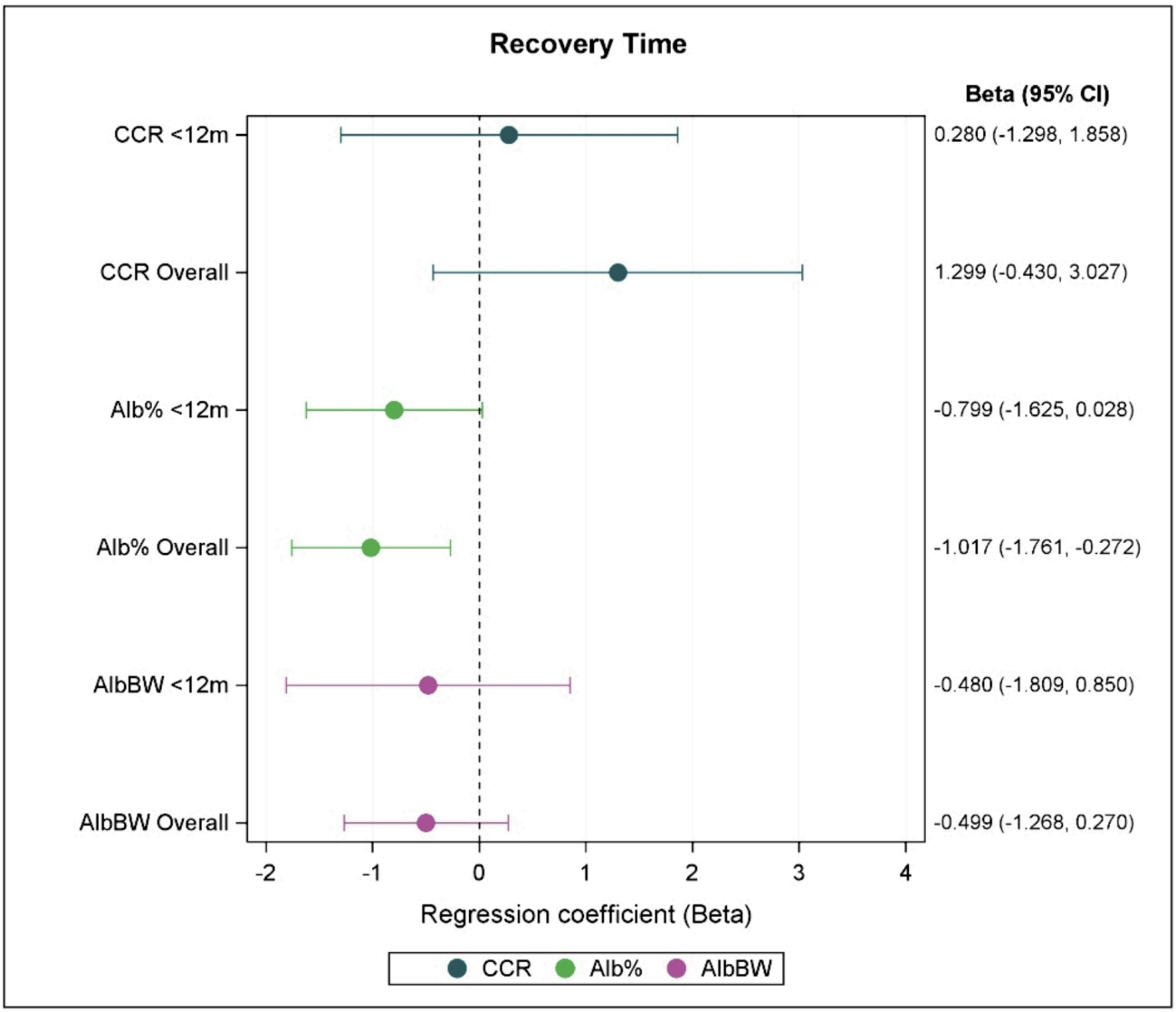


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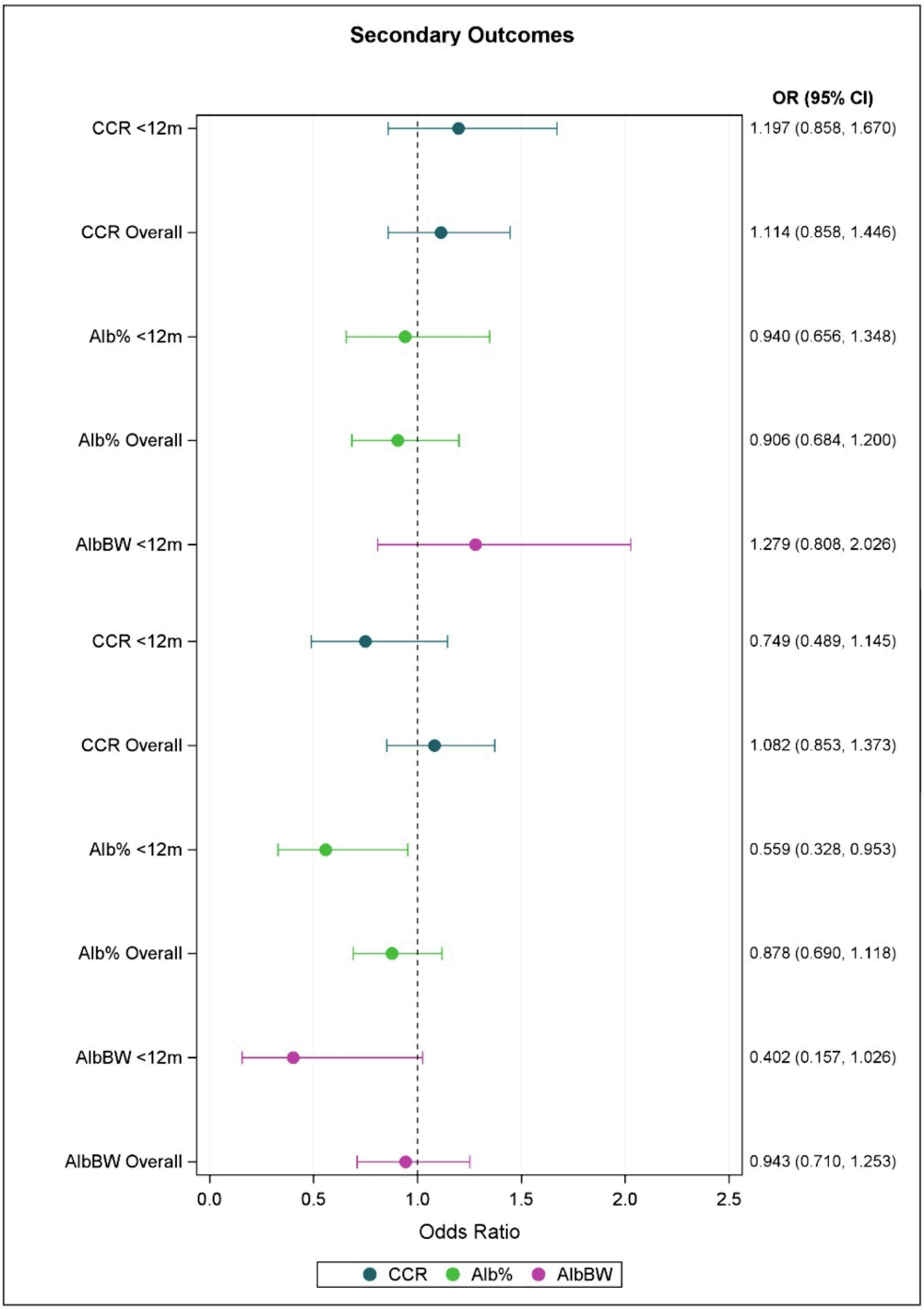


Figure 5

Associations between albumin dose (AlbBW), albumin concentration (Alb%), colloid-to-crystalloid ratio (CCR), and intraoperative vasoactives and PRBC transfusion. *Forest plot illustrating odd ratios (OR) and 95% confidence intervals (CI). OR > 1 indicate increased risk, while OR < 1 suggest lower risk.*

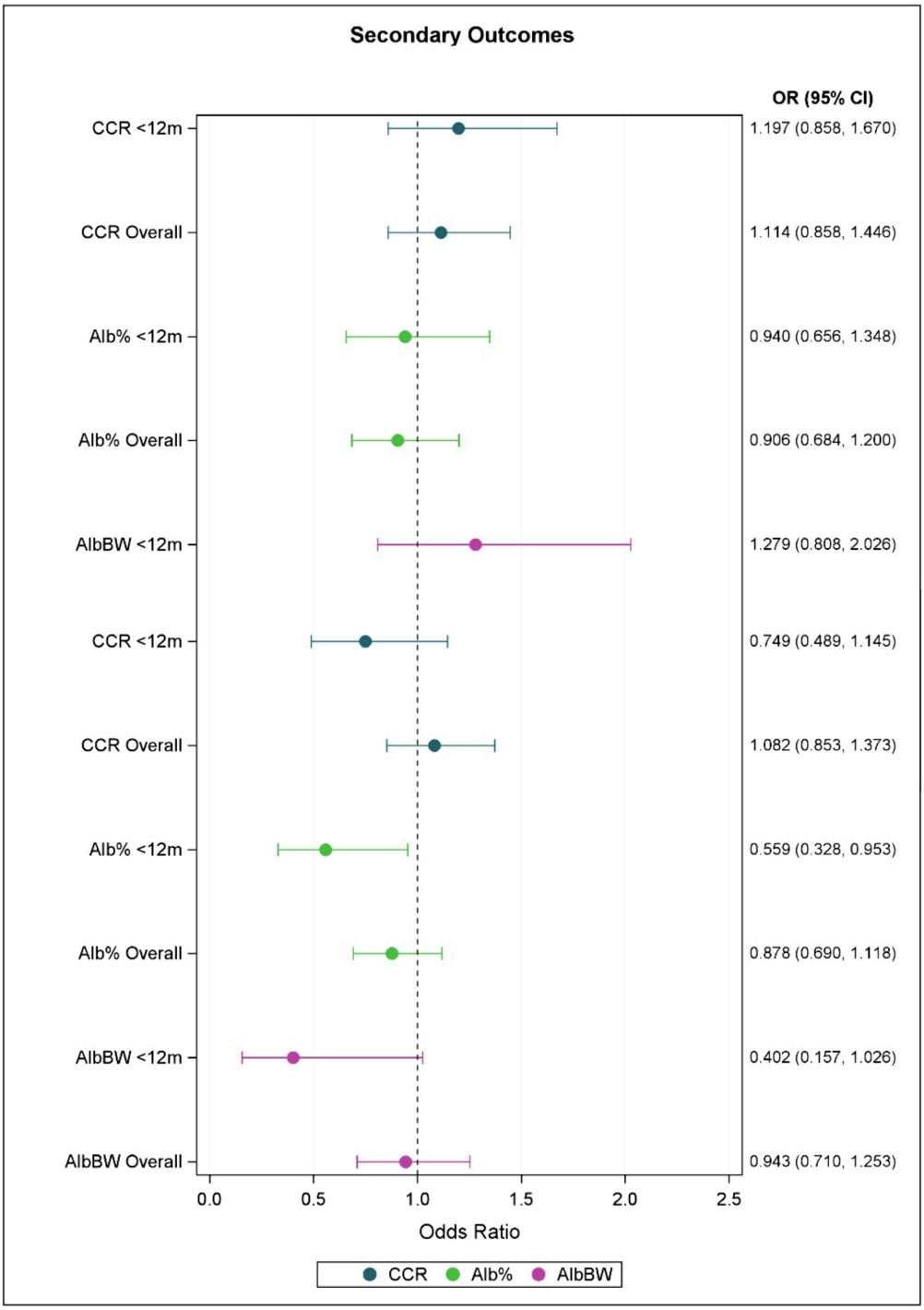


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