

# Effect of Goal-directed Fluid Therapy on the Shedding of the Glycocalyx Layer in Retroperitoneal Tumour Resection

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## ABSTRACT

**Objective:** To evaluate the effects of different stroke volume variation (SVV) targets on endothelial glycocalyx (EG) shedding.

**Study Design:** Randomised controlled trial.

**Place and Duration of Study:** Department of Anaesthesiology, Peking University International Hospital, Beijing, China, from February to June 2018.

**Methodology:** Patients undergoing elective retroperitoneal tumour resection were assigned to one of two groups. SVV 9% group ( $n=40$ ), who received a more traditional (liberal) fluid therapy with  $SVV \leq 9\%$ ; and the SVV 14% group ( $n=40$ ), received restrictive fluid therapy with  $SVV \leq 14\%$ . Patients' serum concentrations of syndecan-1 (SDC-1), interleukin-6 (IL-6) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) were measured at the time that patients entered the operating theatre; at 1- and 4-hours following initiation of the surgery; and at 24- and 72-hours post-surgery. Postoperative complications, and one-year survival rates were also noted.

**Results:** Perioperative serum SDC-1, IL-6 and TNF- $\alpha$  concentrations were significantly elevated in both groups, which were more pronounced in SVV 9% ( $p = 0.028$ ,  $<0.001$ , and  $<0.001$  respectively). A positive correlation was observed between SDC-1 and TNF- $\alpha$ , IL-6, and infusion volume, respectively. Postoperative complications, including fever and blood transfusion, were more aggravated in SVV 9% than those in SVV 14% (80% vs. 59%, and 45% vs. 23.1%, both  $p < 0.05$ ). However, no significant difference in the one-year survival rate was observed.

**Conclusion:** Using SVV 14% as a target for guiding fluid therapy in elective retroperitoneal tumour resection was associated with reduced perioperative glycocalyx shedding, ameliorated inflammatory response, and reduced postoperative complications.

**Key Words:** Randomised controlled trial, Retroperitoneal neoplasms, Glycocalyx, Tumour necrosis factor-alpha, Interleukin-6, Fluid therapy, Stroke volume.

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## INTRODUCTION

The endothelial glycocalyx (EG) is a negatively-charged, carbohydrate-mesh covering the luminal side of blood vessels.<sup>1,2</sup> It is crucial in maintaining vascular wall homeostasis and physiological functions of the microcirculation, including vascular permeability, immunity, blood coagulation, and interaction with serum proteins.<sup>2,3</sup> Unfortunately, the EG is particularly vulnerable to damage in response to sepsis, ischemia-reperfusion, trauma, and surgeries.<sup>2,4-6</sup> Retroperitoneal tumour (RPT) is a general term for latent retroperitoneal tumours.

Resection of such tumours characterised by considerable trauma, extended operation procedural times, and significant changes in effective circulating blood volume, often involves profound ED shedding. Thus, prevention of glycocalyx damage may be a promising therapeutic target in patients receiving retroperitoneal tumour resection.

Fluid infusion strategy profoundly impacts on the glycocalyx shedding.<sup>1,2</sup> Hypervolemia is strongly correlated with enhanced glycocalyx degradation. Goal-directed fluid therapy (GDFT) is now recognised as an effective perioperative fluid management.<sup>7,8</sup> Stroke volume variation (SVV), an indicator of GDFT, may serve as a promising predictor of intraoperative fluid responsiveness during resection of retroperitoneal tumour.<sup>8,9</sup> Using SVV as a monitoring index, it may more precisely determine the actual effective blood volume of patients during the surgery. SVV  $< 9\%$  fluid challenge cannot improve the cardiac output (CO), while SVV  $> 14\%$  fluid challenge can improve the CO.<sup>10</sup> However, its range within the bracket of 9% to 14% is the grey zone of GDFT. To the best of authors' knowledge, there are

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no reports on the effects of different SVV targets on EG shedding during resection of retroperitoneal tumour. It was hypothesised that a more restrictive fluid therapy with SVV 14% may lead to reduced perioperative glycocalyx shedding, ameliorated inflammatory response, and improved postoperative complications.

In this study, the objective was to evaluate the effects of different SVV targets on perioperative EG shedding during retroperitoneal tumour resection.

## METHODOLOGY

This is a single-centre, prospective, and randomised controlled clinical study, registered in the China Clinical Research Registry (Registration No. ChiCTR-IIR-17014180). Ethical approval for this study was provided by the Ethical Committee of Peking University International Hospital, Beijing, China (Approval No. 2016-029). The study was conducted at Peking University International Hospital, Beijing, China, from February to June 2018. All subjects were given an informed consent form before participating, which was signed after the subjects were notified of the research study and its intent.

Eligibility criteria were: Diagnosis of retroperitoneal tumours by abdominal CT before surgery, age of 18-65 years, an ASA grade of I-II.<sup>11</sup> Exclusion criteria were the following: Evidence of pre-existing cardiopulmonary disease, liver and/or kidney dysfunction, systemic infection, abnormal coagulation, hypoproteinaemia, and anaemia seen in any of the prospective study subjects, Surgery that was not completed for various reasons, an operation time that was less than four hours, and patients that simply refused to cooperate midway through the study, resulting in the aggregation of an incomplete data set.

To estimate the sample size, a pilot study was conducted to measure serum concentrations of SDC-1 at four hours following skin incision in 20 patients that received RPT resection (10 in the SVV 9% group and 10 in the SVV 14% group). The mean value and standard deviation of both groups were  $24.87 \pm 8.94$  and  $15.28 \pm 6.01$ , respectively. With an alpha value of  $\alpha=0.05$ , two-tailed analysis and the beta value set at  $\beta=0.20$ , the authors calculated the required sample size to be about 76 cases from this power analysis. Additionally, considering a loss rate of five percent, we enrolled 80 patients, scheduled for retroperitoneal tumour resection.

Computer randomisation of study identification (ID) numbers for both groups was followed by the placement of printed ID number slips into numerically ordered envelopes matching the computer randomisation file. According to the envelope method, the enrolled patients were randomly divided into the SVV 14% group ( $n=40$ ) and the SVV 9% group ( $n=40$ ). After the subject signed the informed consent form, the investigator opened the next sealed, opaque envelope in the numerical sequence to assign the patient to their group. Using the single-blinded principle, subjects were unaware of the grouping.

All patients were anaesthetised according to the standard protocol in this hospital. During the operation, lactated Ringer's solution (LR); (Otsuka Pharmaceutical Co., Ltd, China) was continuously infused at a rate of 2-3 ml/Kg/h to maintain intraoperative basic fluid intake (physiological requirement plus evaporation), and the corresponding dose of LR was supplemented according to the urine output volume every 30 minutes. Fluid challenge was performed while monitoring with the aid of the FloTrac/Vigileo system (Edwards Life sciences LLC, US). In the SVV 14% group, the SVV target value was set to 14 percent. If  $SVV > 14\%$ , LR was rapidly administered at a volume of 200 ml, and reappraise it five minutes later. If SVV was still  $\geq 14\%$ , LR was rapidly administered again at a volume of 200 ml. If not, the rapid rehydration was suspended. In the same way, the SVV target value was set to 9 percent in the SVV 9% group. If  $SVV \geq 9\%$ , LR was rapidly administered at a volume of 200 ml, followed by re-evaluation five minutes later. If SVV remained  $\geq 9$  percent, LR was rapidly administered again at a volume of 200 ml. If not, the rapid rehydration was suspended. Meanwhile, cardiac index (CI) and mean arterial pressure (MAP) were also monitored. If  $CI < 2.5$  L/min/m, dopamine was administered at a dose of 5 ug/Kg/min until  $CI \geq 2.5$  L/min/m was achieved. In case of  $CI \geq 2.5$  L/min/m and  $MAP < 65$  mmHg, norepinephrine was administered at a dose of 0.5 ug/Kg/min to achieve a  $MAP \geq 65$  mmHg. Consideration should also be given in the context of blood transfusions (*i.e.*, a red cell suspension and plasma ratio of 1:1) when the bleeding volume exceeded 1/4 of the blood volume or the haematocrit (HCT)  $< 25\%$ .

The primary outcome measure was patients' serum concentrations of syndecan-1 (SDC-1); (Perlong Medical Equipment Co., Ltd), which was detected by standard enzyme-linked immunosorbent assay (ELISA); (Perlong Medical Equipment Co., Ltd,) at the following time points: the time that patients entered the operating theatre (T0); at 1 (T1) and 4 (T2) hours following initiation of the surgery; and at 24 (T3) and 72 (T4) hours post-surgery. Secondary outcome measures included: Perioperative changes in serum levels of IL-6 and TNF- $\alpha$ , extubation time, duration of hospital stay, postoperative complications and one-year survival rate, hemodynamic parameters (*i.e.*, MAP, HR, central venous pressure (CVP), SVV and CI) that were measured every 30 minutes from the time point of skin incision to surgery within 4 hours, the intraoperative fluid volume, urine volume, blood loss, blood transfusion volume, norepinephrine dosage. Postoperative complications, according to the Dindo-Clavien grading system<sup>12</sup> were all recorded. Patients were followed up for their survival for one year via telephone follow-up every month.

Data were analysed using the SPSS version 23.0 software programme (IBM). Measured data that followed a normal distribution were expressed as  $\bar{x} \pm SD$ , and independent sample Student's *t*-test was used for inter-group comparison. Data collected at each time-point were analysed by repeated measures analysis of variance (ANOVA). The data that did not follow a normal distribution were expressed as the median (and inter-quartile range (IQR), and the Mann-Whitney *U*-test was

used for inter-group comparisons. Count data were expressed as frequencies or percentages for categorical variables, and Chi-square or Fisher's Exact test was used for inter-group comparison. Pearson correlation analysis was applied in this study and multiple linear regression analysis was used to get its relationship with multiple variables. The Kaplan-Meier method estimated the probability of survival; and log rank test was used for survival analysis. An alpha value of  $p \leq 0.05$  indicated that the differences between sets of data were statistically significant.

In addition, the authors took T0 as the starting point and T3 as the end-point, and subsequently calculated the concentrations of SDC-1, IL-6, and TNF- $\alpha$ , urine volume, blood loss, infusion volume, erythrocyte transfusion, plasma transfusion, and norepinephrine dosage infusion volume that were generated during this period, and expressed those values as C-SDC-1, C-IL-6, C-TNF- $\alpha$ , etc. The authors analysed the correlations between C-IL-6, C-TNF- $\alpha$ , age, gender, height, weight, body mass index (BMI), C-urine volume, C-blood loss, C-infusion volume, C-erythrocyte transfusion, C-plasma transfusion, C-norepinephrine dosage and C-SDC-1 respectively. First, the authors plotted a scatter plot and performed linear correlation analysis on linearly related variables. Then, multiple linear regression analysis was used to explore linear dependency of the influencing factors on the shedding products of the glycocalyx. All variables had a tolerance of  $>0.1$  and a variance inflation factor (VIF)  $<10$ .

## RESULTS

A total of 80 patients, who were undergone retroperitoneal tumour resection, were enrolled. One patient in the SVV 14% group refused to participate in the experiment before anaesthesia induction, and was subsequently excluded from the analysis. As a result, there were 40 patients in the SVV 9% group and 39 in the SVV 14% group (Figure 1). No unintended effects or harms happened during this study.

There were no significant differences observed in terms of age, body mass index (BMI), gender composition, ASA grade, co-morbidities (*i.e.*, hypertension, diabetes) and surgical duration (all  $p > 0.05$ ; Table I).

HR, MAP, CVP and CI in both groups changed over time ( $p < 0.001$ ), and compared with the SVV 9% group. It was found that CVP decreased in the SVV 14% group ( $p < 0.05$ ). No difference in HR, MAP and CI was observed between groups ( $p > 0.05$ ; Figure 2).

There were no significant differences observed in the context of erythrocyte transfusion, plasma transfusion, blood loss, urine volume between the two groups ( $p > 0.05$ ). When compared with the SVV 9% group, the infusion volume in the SVV 14% group decreased ( $p < 0.05$ ). The difference observed in the amount of norepinephrine was particularly significant between the two groups, with  $161.43 \pm 217.40 \mu\text{g}$  in the SVV 9% group and  $910.74 \pm 489.15 \mu\text{g}$  in the SVV 14% group respectively ( $p < 0.001$ ; Table II).

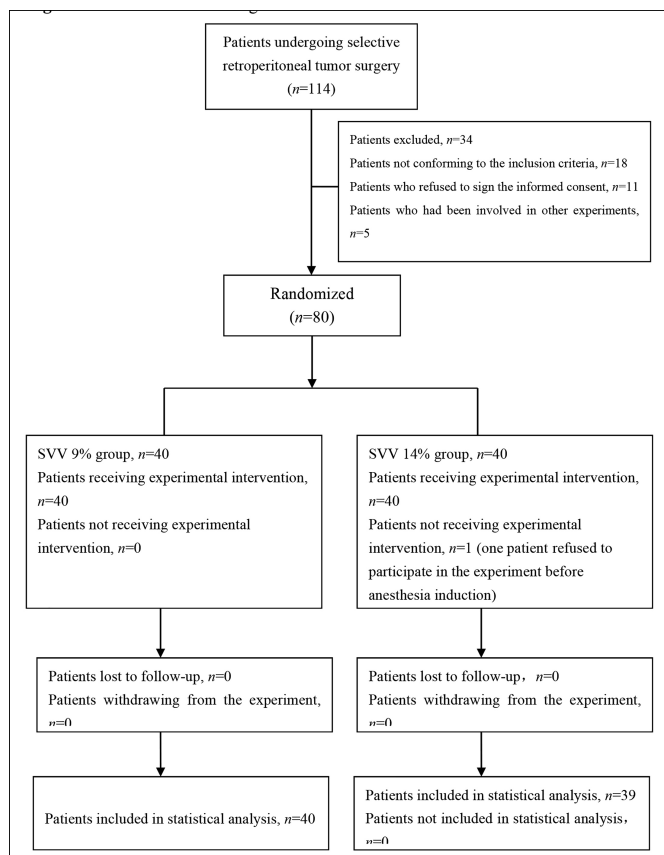


Figure 1: CONSORT flow diagram.

Table I: General data of patients and surgery.

	SVV 9% group (n=40)	SVV 14% group (n=39)	P
<i>Patient characteristics</i>			
Age (years) (Mean $\pm$ SD)	49.08 $\pm$ 13.16	47.23 $\pm$ 12.55	0.526
BMI ( $\text{kg}/\text{m}^2$ ) (Mean $\pm$ SD)	22.05 $\pm$ 2.94	23.32 $\pm$ 3.10	0.067
Males / Females [n (%)]	22(55) / 18(45)	19(48.7) / 20(51.3)	0.576
ASA I / II [n (%)]	5(12.5) / 35(87.5)	8(20.5) / 31(79.5)	0.337
<i>Co-morbidities [n (%)]</i>			
Hypertension	31(77.5)	29(74.4)	0.744
Diabetes	28(70)	29(74.4)	0.666
<i>Other (Mean <math>\pm</math> SD)</i>			
Operation time (min)	324.73 $\pm$ 77.72	349.21 $\pm$ 90.00	0.199

The concentrations of SDC-1, IL-6 and TNF- $\alpha$  have changed greatly over time ( $p < 0.001$ ) and peaked at T2, while subsequently gradually decreasing post-surgery. Notably, the concentrations at T4 remained higher than those observed at baseline levels. Compared with the SVV 9% group, serum concentrations of SDC-1, IL-6 and TNF- $\alpha$  in SVV 14% group were decreased ( $p = 0.028$ ,  $<0.001$ ,  $<0.001$ , respectively). There was a time-group interaction effect between the time and group factors for IL-6 ( $p < 0.001$ ; Figure 3).

C-SDC-1 was positively correlated with C-IL-6, C-TNF- $\alpha$  and infusion volume ( $r = 0.693$ ,  $0.821$ ,  $0.820$ , respectively; all  $p < 0.001$ ). In particular, a marked correlation was observed between C-SDC-1 and C-TNF- $\alpha$ . Finally, the equation was derived as  $\text{C-SDC-1} = -3.722 + 0.216 (\text{C-TNF-}\alpha) + 0.031 (\text{C-IL-6}) + 0.002 (\text{C-infusion volume})$ .

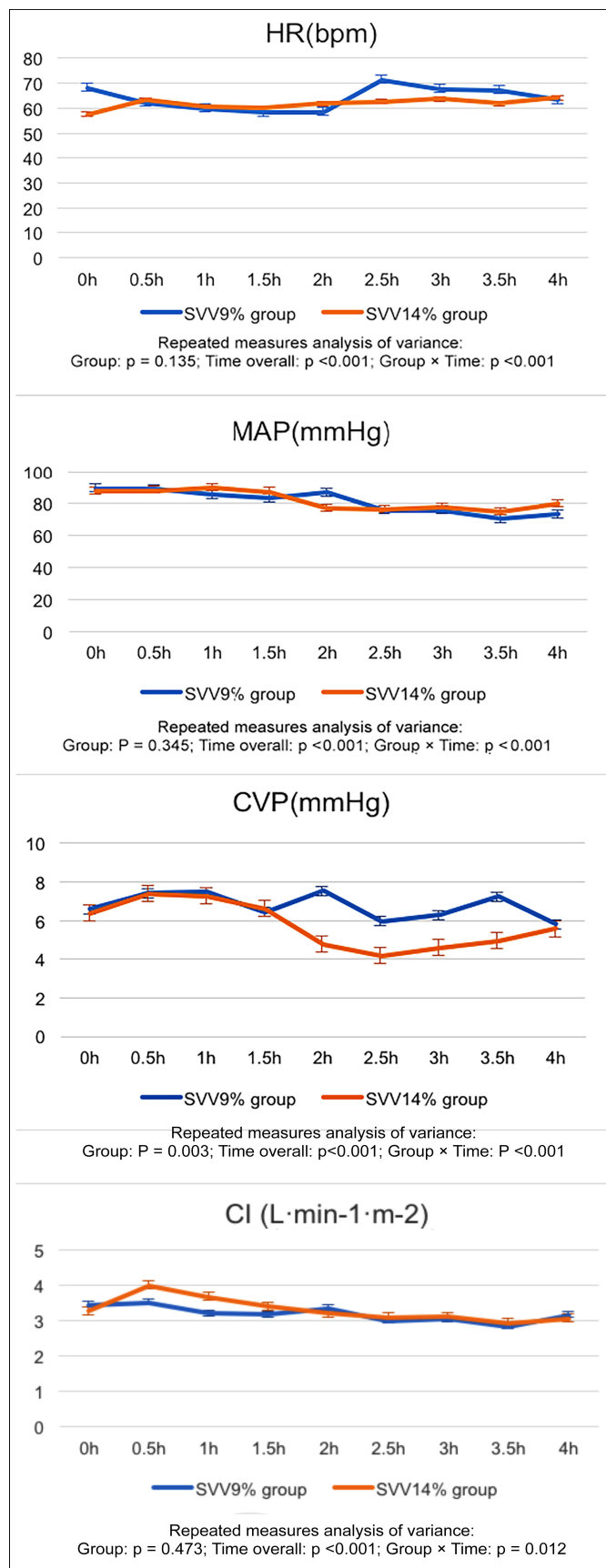


Figure 2: Intraoperative hemodynamics changes.

Table II: Intraoperative fluid infusion and the dosage of vasoactive drugs.

	SVV 9% group (n=40)	SVV 14% group (n=39)	P
<b>Fluid input</b>			
Infusion (ml) (Mean ± SD)	4191.00 ± 1424.57	3283.46 ± 1144.66	0.003*
Erythrocyte (U) [Median (IQR 25 to 75)]	4 (0-4)	4 (2-6)	0.800
Plasma (ml) [Median (IQR 25 to 75)]	0 (0-400)	0 (0-400)	0.863
<b>Fluid output</b>			
Blood Loss (ml) (Mean ± SD)	1196.5 ± 796.52	1400 ± 913.06	0.294
Urine (ml) (Mean ± SD)	847.50 ± 427.72	767.95 ± 287.80	0.334
<b>Medication (Mean ± SD)</b>			
NE <sup>a</sup> (μg)	161.43 ± 217.40	910.74 ± 689.15	<0.001*

<sup>a</sup> NE, norepinephrine, \* P < 0.05

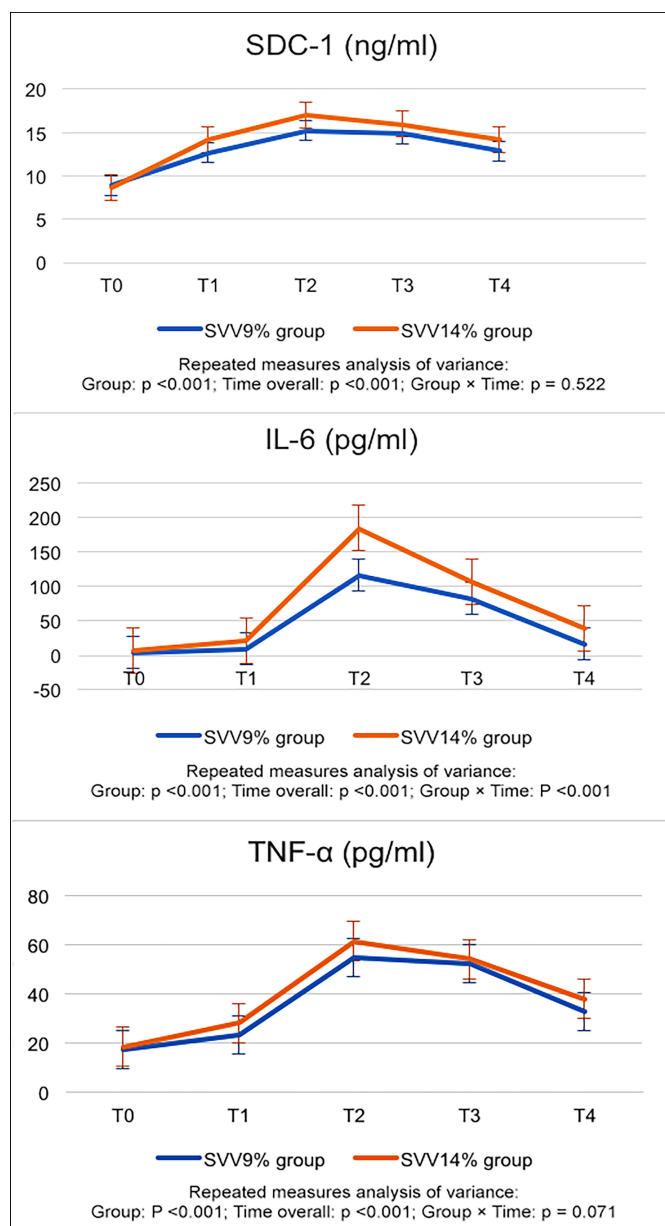


Figure 3. Perioperative changes of SDC-1, IL-6 and TNF-α.

\*Compared with T0, and at an alpha value of p < 0.05 in each group.

△Compared with the SVV 9% group at p < 0.05.



**Table III: Comparison of post-operative conditions between the two groups.**

	SVV 9% group (n=40)	SVV 14% group (n=39)	P
Extubation time (min)	23.83 ± 10.66	19.46 ± 10.82	0.075
Hospital stay (d)	26.38 ± 13.06	24.85 ± 13.22	0.607
Postoperative complications [n (%)]			
Grade I			
Fever (>37.2)	32 (80)	23 (59)	0.042
Use of analgesic	6 (15)	5 (12.8)	0.780
Use of antiemetic	10 (25)	7 (17.9)	0.446
Use of diuretic	4 (10)	0 (0)	0.116
Grade II			
Blood transfusion	18 (45)	9 (23.1)	0.040
Antibiotic promotion	5 (12.5)	7 (17.9)	0.500
Grade III			
Surgical, endoscopic, or radiological intervention	2 (5)	1 (2.6)	>0.999
Grade IV			
Requiring ICU management	1 (2.5)	0 (0)	>0.999
One-year survival rate [n(%)]	38(95)	36(92.3)	0.642

Compared with the SVV 9% group, the incidence of postoperative complications in grade I and grade II in the SVV 14% group decreased ( $p < 0.05$ ). In addition, more patients in the SVV 9% group experienced postoperative fever, applied diuretics, and required blood transfusions. There was no significant difference in the extubation duration, length of hospital stay, and the incidence of serious complications between the two groups (all  $p > 0.05$ ). The log-rank test was used to compare survival rates between the two groups, which showed no statistical difference ( $p > 0.05$ , Table III).

## DISCUSSION

Shedding of the glycocalyx layer on the luminal surface of vascular endothelial cells, an adverse complication of surgery and perioperative hypervolemia, has been a major concern for anaesthesiologist and surgeons in the past few decades. Optimal fluid management is vital for the maintenance and rescue of endothelial glycocalyx.<sup>1,3,13,14</sup> Reports on the primary monitoring indicators for fluid therapy and titration fluid administration by anaesthesiologists remain less understood. Previous studies reported that excessive fluid infusion exacerbates glycocalyx shedding as evidenced by elevated SDC-1 concentrations.<sup>4,5</sup> Belavic *et al.* showed that 15 ml/Kg/hr fluid infusion intraoperatively and 10 ml/Kg/hr six hours postoperatively led to higher levels of SDC-1 and hyaluronic acid as compared to 1 ml/Kg/hr fluid infusion.<sup>5</sup> Nevertheless, such empirical fluid management may not precisely determine the effective blood volume in real world.<sup>15</sup> The present data demonstrated that perioperative glycocalyx shedding products and inflammatory cytokines, namely TNF- $\alpha$  and IL-6, were significantly increased as compared with that prior to surgery. Intriguingly, the SVV 14% group displayed significantly reduced SDC-1, IL-6 and TNF- $\alpha$  concentrations compared with the SVV 14% group, suggesting preserved glycocalyx layer which correlated with improved operational complications. Thus, SVV may be a promising index to guide fluid therapy and setting a target SVV of 14% could be beneficial for better surgery outcomes.

The timeframe for the glycocalyx layer to repair following surgical damage remains unclear. Potter *et al.* indicated that it may

take 5-7 days before the glycocalyx layer restore to its previous thickness.<sup>16</sup> The present study showed a significant increase in SDC-1 concentrations in a time-dependent manner following surgery. The increased SDC-1 levels were detected at one hour (T1), and plateaued at four hours following skin incision (T2), with a peak concentration of 16.09 ng/ml, which subsequently decreased significantly at 72-hour post-surgery (T4), which was nonetheless still higher than the pre-operative concentrations. A similar trend was found in the concentrations of IL-6 and TNF- $\alpha$ . Thus, an intricate fluid management therapy is warranted throughout the relatively long timeframe to ensure reduced damage and faster recovery.

The endothelial glycocalyx layer serves as a vascular barrier that regulates vascular permeability and molecule transport.<sup>17,18</sup> Inflammatory cytokines, namely TNF- $\alpha$  and IL-6, are also mediators of glycocalyx degradation in animal models and human subjects.<sup>19-21</sup> Indeed, SDC-1 is associated with IL-6 and increased mortality in trauma patients.<sup>21</sup> The present data demonstrate that the concentration pattern of shedding products was comparable with that of inflammatory cytokine, including TNF- $\alpha$  and IL-6 during the perioperative period. Once the glycocalyx layer degraded, the vascular permeability is increased, leading to tissue oedema, augmented leukocyte adhesion, platelet aggregation and dysregulated vasodilation.<sup>22</sup> In the SVV 9% group, the higher concentrations of SDC-1 and both inflammatory cytokines are also correlated with higher incidence of postoperative fever, amount of diuretics administration, and blood transfusions required, when compared with SVV 14% group. However, with regard postoperative 1-year survival rates, there was no difference between both groups, since survival rates of 95 percent were found in the SVV 9% group and 92.3 percent in the SVV 14% group. However, incidence of all complications including wound infection, abdominal complications and post-operative hypotension is reduced.

There are several limitations to this study that must be considered. First of all, this is a single-centre pilot study, thus the sample size should be enlarged in future investigations. Secondly, the follow-up period of the postoperative survival status was only pursued for one year after surgery. Thirdly, in this study, the loss of glycocalyx was determined by measuring the plasma concentration of its exfoliated product. If the structure of the ESL layer can be observed by intravital microscopy (IVM), the results will be more intuitive, as this approach has been used in septic mice.<sup>23</sup>

## CONCLUSION

Results supported the efficacy of restrictive fluid therapy during retroperitoneal tumour resection. More importantly, using an SVV-guided goal-directed fluid therapy would reduce the perioperative glycocalyx shedding and ameliorate operational complications. Therefore, this data indicate that SVV 14% is recommended for preserving the glycocalyx layer in the setting of retroperitoneal tumour resection.

## ETHICAL APPROVAL:

Ethics Committee approval was received for this study from

the Ethical Committee of Peking University International Hospital, Beijing, China (Chairperson Prof Feng Yu) on 7 July 2016 (Approval No. 2016-029).

# PATIENTS' CONSENT:

Informed consents were obtained from all patients prior to their participation in the study.

# CONFLICT OF INTEREST:

The authors declared no conflict of interest.

# AUTHORS' CONTRIBUTION:

XW, YD: Involved in experiment design and performed the majority of experiments, analysed results and drafted the paper.

ZG: Designed the experiment, supervised and funded the study, and analysed the data.

JG: Data analysis and experiment design.

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