<u>original research</u>

Delta-SVV as a Predictor for Circulating Blood Volume Evaluation during Intraoperative Period: A Prospective Cohort Study

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ABSTRACT

Background • Precise fluid therapy is extremely important during surgeries, as enough circulating blood volume ensures tissue perfusion and cell oxygenation. Yet, extra fluid volume could cause other adverse events, such as heart failure, intestinal swelling, etc. Thus, precise evaluation of the circulating blood volume is essential for maintaining sufficient circulating blood volume and avoiding excessive fluid infusion.

Objective •This study aimed to evaluate the relationship between SVV and circulating blood volume during intraoperative fluid therapy.

Methods • SVV was measured by FloTrac/Vigileo in the study. A prospective cohort study was conducted. 103 patients aged from 20 to 60 years old with an ASA Grade I-II and a diagnosis of meningioma less than 3 centimeters planning for selective neurosurgery were randomly divided into the Crystalloid Group and the Colloid Group. After induction, each Patient received 15 ml/kg of Plasma-Lyte-A or 6% hydroxyethyl starch in 30 min followed by continuous infusion at the speed of 0.1 ml/kg during the

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INTRODUCTION

Precise fluid therapy is extremely important during surgeries, especially among elderly patients, as insufficient fluid can cause ischemia of tissues and organs, resulting in myocardial injury, renal failure, etc. In contrast, excessive fluid may cause perioperative heart failure, affecting patients' next 60 min. Hb concentration, Hct, Delta-BV/kg, and Delta-SVV were recorded every 5 minutes.

Results • The delta-SVV and Delta-bv/kg were significantly higher in the Crystalloid Group than that of the Colloid Group. There was a strong linear correlation between Delta-SVV and Delta-bv/kg in both Crystalloid Group (Delta-bv / kg = 1.108 Delta-SVV + 0.0712, P < .001) and Colloid Group (Delta-bv / kg = 1.047 Delta-SVV + 0.4153, P < .001). An equation between Delta-bv/kg and Delta-SVV was established (Delta-bv / kg = 1.099 Delta-SVV + 0.1139, P < .001).

Conclusion • In conclusion, SVV measured by FloTrac / Vigileo could guile fluid therapy precisely by predicting the blood volume of patients during the intraoperative period, as it has a strong linear correlation with the blood volume of patients who underwent general anesthesia, meaning anesthesiologist could calculate the exact fluid volume for patients' infusion. Further studies with large cohorts and centers would be needed to validate its efficiency. (*Altern Ther Health Med.* [E-pub ahead of print.])

prognosis.¹ The goal of intraoperative fluid therapy is to keep effective circulating blood volume and hemodynamic stability, ensure tissue perfusion and cell oxygenation, and maintain a stable internal environment.² Yet; precise fluid therapy requires more as the extra fluid volume could cause other adverse events, such as heart failure, intestinal swelling, etc. Thus, precise evaluation of the circulating blood volume is essential because physicians could rely on this to decide the exact fluid volume patients receive to both maintain sufficient circulating blood volume and avoid excessive fluid infusion.

However, as the classic Frank-Starling curve, infusion of a certain amount of fluid to patients with normal cardiac function could increase cardiac output as they are in the steep part of the curve under the same preload state, while further infusion to patients with weakened myocardial contractility would not bring benefits but easily cause edema and hypoxia as they are already in the flat part of the curve,³ we still could not calculate the exact volume of circulating blood volume and fluid therapy as each Patient has different cardiac function, fluid status, reaction to fluid infusion, etc. As a result, dynamic and accurate monitoring of circulatory volume is a prerequisite to ensure volume therapy. With this monitoring, clinicians could individualize fluid infusion volume for patients according to their specific physical status.

Among various measurements to dynamically monitor patients' blood volume, like central venous pressure (CVP), Cardio Output (CO), pulse pressure variability (PPV), etc., Stroke volume variation (SVV), monitored with PiCCO (pulse indicator continuous cardiac output) or the FloTrac/ Vigileo system, is the most promising one as meta-analysis has shown that SVV is of diagnostic value in predicting fluid responsiveness in various settings with a sensitivity of 0.81 and specificity of 0.80.4 There are also studies focusing on the relationship between SVV and blood volume of patients. Tadokoro el found that SVV obtained from the FloTrac/ Vigileo(TM) monitoring system revealed a strong correlation with blood volume during acute normovolemic hemodilution without surgical stimulation.5 SVV is an important monitoring indicator as physicians could rely on it to determine whether patients need more fluid or not.6 It is generally believed that SVV $\geq 13\%$ means patients under general anesthesia need more fluid.⁶ However, the quantitative relationship between SVV changes and real circulating blood volume in patients under general anesthesia has not been fully elucidated, meaning an SVV $\geq 13\%$ can not indicate how many milliliters of liquid are needed for the patient. Yet, it is important to accurately predict the blood volume during an operation because the instant circulating blood volume of the Patient could guide infusion volume directly.

During neurosurgery, precise control of patient fluids is necessary. Excessive fluid can lead to elevated intracranial pressure, affecting surgical field of view, which may causing difficulty in surgery, even failure. In contrast, insufficient fluid can result in inadequate perfusion of patient tissues and organs, leading to more serious complications and affecting prognosis. SVV is currently used to evaluate the circulating blood volume of patients as it is non-invasive, real-time monitoring and accurate compared with other methods such as CVP, PPV, etc. It generally considered to be greater than 13%, and patients require fluid replacement. However, anesthesiologists cannot accurately calculate the amount of fluid required by patients, which may result in an excess of fluid during the process of fluid supplementation. Thus, finding a way for anesthesiologists to accurately calculate the volume of fluid patients needed is essential. Exploring the relationship between SVV and circulating blood volume can enable anesthesiologists to accurately calculate the amount of fluid required by patients through SVV, avoiding insufficient or excessive fluid, which may reduced complications and enhance recovery for patients receiving neurosugery. Thus, we intended to investigate the relationship between SVV and blood volume (by monitoring SVV using FloTrac/Vigileo system) in patients under general anesthesia to evaluate the value of SVV in predicting circulating blood volume when

patients were under general anesthesia during craniotomy, which could further explore the accuracy and reliability of SVV in guiding perioperative volume therapy. The result of the study may change the current fluid management in neurosurgery as anesthesiologists could use delta-SVV to calculate the exact infusion volume for patients.

METHODS

The study was a prospective cohort study conducted at Shanghai Cancer Center, Fudan University, and Huashan Hospital, Fudan University. The study protocol was approved by the ethics committee of both Shanghai Cancer Center, Fudan University, and Huashan Hospital, Fudan University (KY2015-228) under the declaration of Helsinki and registered at http://www.chictr.org.cn/index.aspx (registration number ChiCTR2100054461). After written informed consent was obtained, a total of 103 patients scheduled for elective neurosurgery were enrolled from October 2015 to March 2018, a period of 2.5 years.

Patients

Patients for both groups were eligible for inclusion if: 1) Patients were aged from 20 to 60 years old. No gender preference; 2) Patient's ASA Grade (American Society of Anesthesiologists physical status): I-II; 3) BMI < 30 kg·m⁻².4) Patient was diagnosed with meningioma and planned to undergo craniotomy for tumor resection, with a tumor diameter of less than 3 centimeters because other major complication (such as massive hemorrhage) may happened during the perioperative period in a patient with a tumor bigger than larger than 3 centimeters.

Patients with the following conditions were excluded: 1) BMI > 30 kg·m⁻²; 2) patients without sinus rhythm; 3) History of severe cardiovascular, cerebrovascular, brain, liver, kidney, and hematopoietic system diseases or other serious primary diseases; 4) airway pressure > 40 mmHg after intubation; 5) Recent participation in other clinical trials.

Study Protocol

The patients were divided into two groups, crystalloid group and colloid group, according to whether the patient received crystalloid or colloid after induction. A crystalloid is a solution composed of electrolytes and sterile water. Balanced electrolyte crystal solution is usually chosen for routine perioperative fluid replacement to maintain normal intraoperative blood volume. Colloids are derivatives of human plasma or semi-synthetic products. Colloids can expand microvascular capacity and minimize capillary leakage, thereby minimizing edema formation and total fluid replacement. It is believed that colloids could maintain the blood volume longer than crystalloid.⁷ As Plasma-Lyte-A and 6% Hydroxyethyl starch are widely used for infusion intraoperatively, we chose these 2 fluid for this study.

When entering the operating room, every patient received the same anesthesia protocol. Routine monitoring consisted of continuous electrocardiogram, pulse oximetry,

non-invasive blood pressure, andend-tidal carbon dioxide monitoring. A bispectral index monitoring (A-2000; Aspect Medical System, Newton, MA, USA) was applied to the patient's forehead before the induction of anesthesia. The arterial catheter was also inserted into the radial artery of all the patients before induction for continuous invasive arterial blood pressure measurements and connected to Vigileo®. All the patients received normal saline at the speed of 0.1 ml·kg⁻¹·h⁻¹. Induction was performed using fentanil 3-4 μ g/ kg, midazolam 0.04 mg/kg, propofol 3-4 µg/ml (TCI), and Rocuronium 0.6 mg/kg. After tracheal intubation, general anesthesia was maintained by propofol 3-4 µg/ml (TCI) and remifentanil 0.5-6 ng/ml (TCI). Intermittent positive pressure ventilation (IPPV) mode was used. Tidal volume was adjusted to 10 ml·kg⁻¹. The respiratory rate was set 10 bpm. During mechanical ventilation, a patient would be excluded if the airway pressure was more than 40 mmHg. The depth of anesthesia was controlled based on the bispectral index (BIS) values (target value ranges from 40 to 60).

After anesthesia induction, patients in crystalloid received 15 ml/kg of Plasma-Lyte-A in 30 minutes. Then, they received Plasma-Lyte-A at the speed of 0.1 ml·kg ⁻¹·h ⁻¹ for another 60 minutes. Similarly, patients in the colloid group received 15 ml/kg of 6% Hydroxyethyl starch (Hetastarch) in 30 minutes. Then, they received 6% Hydroxyethyl starch at the speed of 0.1ml·kg ⁻¹·h ⁻¹ for another 60 minutes. Hemoglobin, HCT, and SVV were recorded every 5 minutes from the start to 90 minutes (From T₁ to T₁₉, supplement table 1). Demographic, anesthetic, and surgical information of all patients were also documented. In this study, we used Hct to calculate blood volume.

Surgery began after the above procedure. Postoperatively, Patient-controlled intravenous analgesia (PCIA) was administered with a formula of 0.1 mg/kg hydromorphone, 0.25 mg palonosetron, and physiological saline to 200 ml (setting parameters: background dose of 3 ml/h, single press of 1 ml, locking time of 8 Min); When the VAS pain score at rest is \geq 4 points or the VAS pain score at activity is \geq 6 points after surgery, intravenous injection of 5 mg morphine is used for salvage analgesia.

Calculation of SVV and Delta-bv/kg

When collecting SVV, Patient's age, gender, height, and weight were input into Vigileo[®]. After automatic in vivo calibration for about 1 minute, the stroke volume variation (SVV) could be obtained, and the value was updated every 20 s.

The basic blood volume (BVbase) was obtained from height and weight, and the basic HCT was measured. As the surgery did not begin until the infusion procedure was over, the total volume of red blood cells in the blood of each Patient remained unchanged before and after infusion.⁸ So, the blood volume at each time point could be calculated by HCT values recorded at the corresponding time point. Also, the increase of blood volume per kilogram of body weight and the decrease of blood volume per kilogram of body weight (Delta-bv/kg) during infusion therapy could be calculated. The formula was as follows:

- BVbase (ml) = 366.9 × height ³(m) + 32.19 × weight (kg) + 604.1 (male)
- BVbase (ml) = $356.1 \times \text{height}^3$ (m) + $33.08 \times \text{weight}$ (kg) + 183.3 (female)

$$BV_{t}(ml) = BV_{tm} \times Hct_{tm} / Hct$$

 $Delta-bv/kg (ml/kg) = (BV_{base} - BV_{t}) / kg$

Statistical Analysis

Statistic Package for Social Science (SPSS) (ver.21.0, SPSS Inc., Chicago, IL, USA) was used for analysis. Continuous variables were presented as medians \pm SD. Mann–Whitney U-test (Wilcoxon rank-sum test), Student's t-test, Pearson χ^2 test, and Fisher's exact test were used to assess statistical significance as appropriate. The relationship between Delta-SVV and Delta-bv/kg at each time point was analyzed by linear correlation and regression. In this study, *P* < .05 was considered to indicate statistical significance.

RESULTS

A total of 103 patients were enrolled between November 2017 and November 2020. Figure 1 illustrates participant recruitment, reasons for exclusions, and treatment allocations. Of all the patients, 5 were excluded before the trial, and 2 were excluded during the trial. Finally, 51 subjects in the Crystalloid Group and 52 subjects in the Colloid Group were eligible for this trial.

Table 1 illustrates the epidemiological information of all the patients recruited. There was no significant difference between the two groups in demographic information, including gender, age, BMI, etc (Table 1). In both groups, preoperative hemoglobin was similar: 33 ± 2.18 in the crystalloid group and 31 ± 2.48 in the colloid group (P = .069). Also, there was no significant difference in hematocrit (HCT) between the two groups (P = .428).

Table 2 illustrates the heart rate and mean blood pressure of all the patients recruited. There was no significant difference in heart rate between the two groups. The mean arterial pressure presented no significant difference between the two groups from T1 to T7 (first 30 min of the study), while the

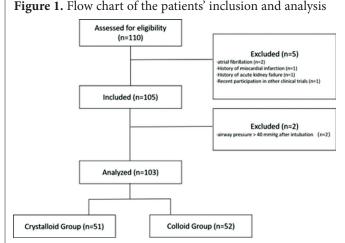


 Table 1. Demographic Data in crystalloid group and colloid group

	Crystalloid group	Colloid group	
	(n=51)	(n=52)	P value
Gender (F/M)	20/31	28/24	.168
Age (yr)	43±10	42±12	.186
BMI (kg/m ²)	21.7±2.5	22.7±3.3	.087
Pathologic Diagnosis			
Glioma	14	10	.359
Meningioma	37	42	.359
Preoperative baseline MMSE scores (0-30)	28.51±1.00	28.25±1.66	.339
Cardiac Function(NYHA I/II)	39/12	42/10	.637
ASA physical status (I/II)	40/11	45/7	.310
Comorbidities			
Hypertension	7	4	.358
Diabetes	4	3	.710
Hematocrit (HCT, %)	33±2.95	34±2.55	.069
hemoglobin (g/L)	128±7.18	127±5.48	.428

Note: Data were expressed as means ± SD or number.

Abbreviations: BMI, body mass index. MMSE, Mini-mental State Examination. NYHA, New York Heart Association.

 Table 2. Hemodynamic parameters in crystalloid group and colloid group

	HR			MAP		
	Crystalloid	Colloid		Crystalloid	Colloid	
	group (n=51)	group (n=52)	P value	group (n=51)	group (n=52)	P value
T1	70.3±9.3	71.3±8.9	.58	80.6±11.6	79.2±12.2	.55
T2	72.8±8.8	72.4±10.9	.84	79.7±12.1	78.7±11.3	.67
T3	76.1±10.1	73.1±9.4	.12	78.6±10.1	78.3±8.9	.87
T4	75.9±9.8	73.8±10.1	.29	77.7±8.5	77.5±9.3	.91
T5	76.5±8.7	74.3±9.5	.22	76.3±9.5	77.2±11.9	.67
T6	76.8±10.3	76.3±10.7	.81	73.8±8.8	76.1±10.1	.22
T7	81.4±11.1	78.4±12.3	.20	71.8±11.2	77.5±11.4	a
T8	81.7±10.8	79.6±11.3	.34	72.1±11.7	77.7±10.9	a
T9	83.1±10.2	80.3±9.9	.16	71.4±10.5	77.5±11.1	a
T10	83.7±11.3	80.3±11.7	.14	70.9±7.9	75.6±9.5	a
T11	83.5±10.6	82.1±10.5	.50	69.3±7.7	75.4±8.7	a
T12	85.1±11.1	81.5±11.3	.11	67.7±7.8	74.6±8.3	a
T13	84.7±10.9	80.9±12.1	.10	66.8±7.7	73.7±8.1	a
T14	85.6±13.1	81.4±12.8	.10	65.6±7.4	72.5±7.6	a
T15	85.3±11.4	82.5±11.8	.22	65.6±7.1	70.9±8.8	a
T16	84.8±11.9	81.5±12.5	.17	63.4±7.1	69.8±7.5	a
T17	86.3±11.4	82.3±12.3	.10	61.9±6.9	68.9±7.1	a
T18	86.7±10.3	82.7±11.7	.07	61.5±5.8	69.1±6.7	a
T19	87.9±11.5	83.6±13.2	.08	60.1±5.3	68.4±5.7	a

 $^{a}P < .05$

Note: Data were expressed as means ± SD.

Abbreviations: HR, heart rate (b·min–1); MAP, mean arterial pressure (mmHg); T1: start of the study; T2: 5 min after the start; T3: 10 min after the start; T4: 15min after the start; T5: 20 min after the start; T6: 25 min after the start; T7: 30 min after the start; T8: 35 min after the start; T9: 40 min after the start; T10: 45 min after the start; T11: 50 min after the start; T12: 55 min after the start; T13: 60 min after the start; T14: 65 min after the start; T15: 70 min after the start; T16: 75 min after the start; T17: 80 min after the start; T18: 85 min after the start; T19: 90 min after the start.

mean arterial pressure decreased significantly in the crystalloid group from T8 to T19 (last 60 min of the study). This indicated that colloids might present a better effect of expanding blood volume than crystalloids during surgeries.

Linear regression was used to investigate the correlation between Delta-SVV and Delta-bv/kg in the Crystalloid Group and Colloid Group separately. The results confirmed a linear correlation between Delta-SVV and Delta-bv/kg in both groups. In the Crystalloid Group, the linear regression equation was Delta-bv/kg = 1.108 Delta-SVV + 0.0712, P <.001 (Figure 2). Also, the linear regression equation in the colloid group was Delta-bv/kg = 1.047 Delta-SVV + 0.4153, **Figure 2.** The linear correlation between Delta SVV and Delta-bv/kg in Crystalloid Group. X-axis presents Delta-SVV at each time point; Y-axis presents corresponding Delta-bv/kg at each time point.

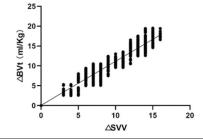


Figure 3. The linear correlation between Delta-SVV and Delta-bv/kg in Colloid Group; X-axis presents Delta SVV at each time point; Y-axis presents corresponding Delta-bv/kg at each time point.

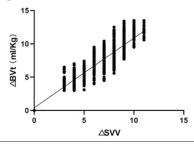
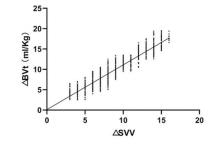


Figure 4. The linear correlation between Delta-SVV and Delta-bv/kg; X-axis presents Delta-SVV at each time point; Y-axis presents corresponding Delta-bv/kg at each time point.



P < .001 (Figure 3). Further, There was no statistical difference between the linear regression equations of the Crystalloid Group and Colloid Group (Slope in the crystalloid group, 95% CI 1.071 to 1.129; Slope in the colloid group, 95% CI 1.009 to 1.087. Y-intercept in the crystalloid group, 95% CI -0.1431 to 0.2854; Y-intercept in the crystalloid group, 95% CI 0.1498 to 0.6808. X-intercept in the crystalloid group, 95% CI -0.2621 to 0.1269; X-intercept in the colloid group, 95% CI -0.6735 to -0.1384), indicating that Delta-SVV could evaluate the circulating blood volume of patients regardless the type of the infusing fluid.

Then, linear regression was applied using 80% of the data from both groups to generate a clinical model to evaluate circulating blood volume via Delta-SVV precisely. The linear regression equation was Delta-bv/kg = 1.099 Delta-SVV + 0.1139, P < .001 (Figure 4), suggesting the equation could calculate circulating blood volume accurately.

DISCUSSION

In the perioperative period, it is important to maintain the appropriate volume state to ensure the perfusion and oxygenation of important organs for patients. Many factors can cause fluid imbalance and microcirculation disorders in surgical patients during the perioperative period, such as prolonged fasting, blood loss, surgical field evaporation, circulatory redistribution caused by surgical stimulation and trauma stress, urine excretion, postoperative nausea, and vomiting, etc. Sufficient fluid for patients under surgery could improve low blood volume and maintain tissue perfusion and oxygen supply, preventing postoperative multi-organ dysfunction.⁹ However, extra fluid would cause increased postoperative circulatory and respiratory complications, affecting wound healing and increasing the risk of perioperative mortality.¹⁰

However, due to various reasons, including bleeding, excretion, redistribution, transfusion, etc, the volume of circulating blood fluctuates frequently. So, it is difficult for anesthesiologists or physicians to determine or modify fluid infusion plans during the perioperative period.¹¹ Clinical parameters include blood pressure, heart rate, blood gas analysis, CVP, PAWP, etc. However, these parameters could be misleading due to factors such as anesthetic drug usage, surgical stimulation, changes in cardiac compliance, fluctuation of intrathoracic pressure, etc. Recently, more and more functional hemodynamic indexes have been used to evaluate the volume state in patients so that clinicians can accurately predict the response of fluid therapy.¹²

SVV, which refers to the variation of stroke volume (SV) in a respiratory cycle, is one of these functional hemodynamic monitoring indexes. It could directly monitor the variability of cardiac output and exclude the influence of arterial compliance. Therefore, SVV could well predict fluid responsiveness.¹³ Previous studies mainly focused on the comparison of SVV and other functional hemodynamic indexes in predicting fluid responsiveness and confirming their predictive ability. For example, Zhang el found that SVV was more useful than CVP in the assessment of responsiveness to volume infusion.¹⁴ Previous studies have confirmed that SVV can achieve consistent results with PAWP and can effectively predict the response to liquid therapy.^{15,16} However, the operation of SVV is simpler and safer, while measuring PAWP requires the placement of a Swan-Ganz catheter, which itself carries certain risks.

Similarly, compared to CVP, SVV can more accurately predict a patient's fluid therapy response.^{17,18} Therefore, SVV is considered a good indicator for predicting patient fluid response. However, the relationship between the value of SVV and the value of circulating blood volume has not been confirmed.

In the 1990s, Stahle et al. proposed the first-order and second-order kinetic models of fluid dynamics. They applied the analysis method similar to pharmacokinetics to the dynamic effect of fluid infusion on plasma volume expansion (PVE) and the distribution and metabolism of fluid in the body, which provided a new research basis for the theory of fluid dynamics.⁸ The idea was mean that the larger the

plasma dilution, the more the blood volume of the circulatory system, and vice versa. In our research, we also used this method to evaluate the circulating blood volume of patients receiving fluid infusion.

Our results showed that there was a good linear correlation between the change of SVV (Delta-SVV) and the change in blood volume per unit weight (Delta-bv/kg). Also, we developed a linear regression equation to evaluate Delta-bv/kg via Delta SVV (Delta-bv/kg = 1.099 Delta-SVV + 0.1139, P < .001), which could calculate the fluid volume the Patient needed instantly and guide intraoperative fluid therapy.

In our study, SVV was monitored by Vigileo^{*}, which has several advantages. First, it was easy to operate.¹⁹ The monitor FloTrac sensor system was connected to the peripheral artery, like the radial artery. Other monitoring systems, such as PiCCO^{*}, require connection to the femoral or brachial artery. Moreover, SVV could be automatically and continuously displayed on the monitor and updated every 20s. Furthermore, SVV monitored by Vigileo^{*} has a good correlation with the traditional pulmonary artery catheter (PAC) thermodilution method in measuring cardiac output and has fewer complications.²⁰ Kubitz el al. confirmed that the SVV obtained by pulse profile analysis is consistent with the "gold standard"— SVV obtained by aortic blood flow probe.²¹

Yet the application of SVV also has some limitations. First, the patient needs to have a sinus heart rate. If the Patient has arrhythmia, the stroke volume might have a large difference in each heartbeat. Thus, it is impossible to accurately evaluate the changing trend caused by the change of the respiratory cycle. Second, the FloTrac / Vigileo* SVV monitoring system could only reflect the blood volume changes of patients with tidal volume in a certain range. Suchiro K et al. showed that SVV had acceptable sensitivity and specificity in predicting blood volume when the tidal volume was more than 8 ml/kg.²² Thirdly, for patients with spontaneous breathing, because the change of intrapleural pressure during spontaneous breathing is very small, the change of hemodynamic parameters such as SVV is also very small.²³

In the study, Delta-SVV was found to have a linear relationship with circulating blood volume. Therefore, we believed Delta-SVV could indirectly reflect the volume state. Meanwhile, our study does have limitations. First, the prediction model was not validated by prospective data and more complicated situations (such as bleeding), which would be included in our further studies. Second, there was still an error between the calculated value and the real value. This might be solved by including more parameters that are correlated with circulating blood volume, like blood pressure, CVP, etc. Future study of this kind is in preparation.

CONCLUSION

In conclusion, SVV measured by FloTrac / Vigileo could guile fluid therapy precisely by predicting the blood volume of patients during the intraoperative period as it has a strong linear correlation with the blood volume of patients who underwent general anesthesia.

DECLARATION

The authors have no conflicts of interest or financial ties to disclose.

FUNDING

No funding.

AUTHOR CONTRIBUTIONS

Bei Wang: Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft; Yiqi Wu: Conceptualization; Methodology; Project administration; Writing – original draft. Jianghui Xu: Conceptualization; Methodology; Project administration; Writing – review & editing.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was approved by the ethics committee of both Shanghai Cancer Center, Fudan University, and Huashan Hospital, Fudan University (KY2015-228) under the declaration of Helsinki.

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