Preoperative albumin-to-fibrinogen ratio predicts severe postoperative complications in elderly gastric cancer subjects after radical laparoscopic gastrectomy

Xuexue You¹, Qun Zhou¹, Jie Song¹, Linguang Gan², Junping Chen² and Huachun Shen²*

Abstract

Background: A high prevalence of postoperative complications is closely associated with a worse short- and long-term outcome. This current study aimed to investigate potential risk factors including albumin-to-fibrinogen ratio (AFR) for severe postoperative complications (SPCs) in surgical gastric cancer (GC) patients.

Methods: Elderly patients (≥65 years) with primary GC who underwent elective radical laparoscopic gastrectomy under general anesthesia were included. According to the Clavien–Dindo classification system, the severity of complications was assessed from Grade I to V and SPCs were defined as C-D Grade ≥ IIIa. The clinicopathological features, operative-associated characteristics, postoperative recovery and laboratory tests were compared between patients with or without SPCs. Receiver operating characteristic (ROC) curve analysis using Youden’s Index was established for determining the predictive value and cut-off threshold of AFR for SPCs. Binary univariate and multivariate logistic regression models were used to assess factors influencing SPCs.

Results: A total of 365 elderly GC patients were finally included in the analysis, of which 52 (52/365, 14.2%) patients had developed SPCs within postoperative 30 days. Preoperative AFR level predicted SPCs in surgical GC patients with an AUC of 0.841, a sensitivity of 76.36% and a specificity of 80.77%, respectively (P < 0.001). The multivariate analysis revealed that a lower AFR level (OR: 1.94, 95% CI: 1.09–3.36, P = 0.017) and an older age (OR: 1.81, 95% CI: 1.06–3.04, P = 0.023) were two independent predictive factors for SPCs in surgical GC patients.

Conclusions: Preoperative AFR level is a useful predictor for SPCs in elderly GC subjects after radical laparoscopic gastrectomy.

Keywords: Gastric cancer, Severe postoperative complications, Predictor, Albumin, Fibrinogen

Background

Gastric cancer (GC) is the fourth most common malignant neoplasm with an increasing incidence and it ranks second in cancer mortality worldwide [1]. Due to the high prevalence, recurrence rate and mortality rate, GC has become a significant global health problem [2]. As for resectable GC, surgical resection with systematic lymphadenectomy remains the standard treatment [3]. Advances in surgical techniques, instruments, and experiences have led to a corresponding decrease of postoperative complications, as well as improved outcomes [4]. However, a high prevalence of postoperative complications, with ranges from 14.3 to 34.0%, is closely associated with an increased economic burden, a prolonged hospital stay, a worse short- and long-term outcome [5]. Therefore, to improve the overall prognoses of GC patients, robust biomarkers for predicting severe postoperative complications (SPCs) after radical
gastrectomy could help with the risk identification, follow-up facilitation and more aggressive postoperative care. Despite the significant improved perioperative managements, multidisciplinary therapeutic strategies and surgical techniques, a high prevalence of SPCs still remains to some extent [6].

Albumin (Alb), as a negative acute phase protein and a nutritional biomarker, usually decreases after surgery due to the surgery stress and increased capillary leakage [7]. Preoperative serum Alb is reported to be a predictive factor for postoperative recovery [8] and long-term survival [9] in GC patients. Another study has revealed that postoperative decrease of serum Alb expression can serve as a predictor for short-term complications in GC patients [10]. Preoperative low serum Alb expression was reported to be a potential risk factor for SPCs in elderly GC subjects [11]. Fibrinogen (Fib) is an essential protein for coagulation cascade as well as an acute-phase reaction protein in response to systemic inflammation [12]. Kanda et al. have indicated that Fib level is associated with tumor stage, metastasis, and outcomes in solid tumors, including GC [13]. Moreover, low preoperative Fib level is suggested as a potential risk factor for neurological complications after cardiac surgeries [14]. However, whether Alb or Fib can serve as a predictor for SPCs in GC patients still remains controversial. Alb-to-Fib ratio (AFR), a combination of Alb and Fib, has been reported to be a prognostic factor for non-small-cell lung cancer patients [15, 16]. This study focused on the potential prognostic role of AFR for SPCs in GC patients.

**Methods**

**Patients**

This retrospective study was approved by the Medical Institutional Ethics Committee of Jiangxi province and our hospital. Elderly patients with primary GC who underwent elective radical laparoscopic gastrectomy under general anesthesia at the Department of anesthesiology, Jiangxi maternal and child health hospital from March 2014 to March 2018 were included. All the participants provided written informed consent. Inclusion criteria were described as follows: 1) elderly patients aged between 65 and 80 years; 2) diagnosed with primary GC which was supported by operative and pathological results; 3) undergoing systemic evaluation before the surgery including computed tomography (CT) image and 4) undergoing elective radical laparoscopic gastrectomy for the first time. The exclusion criteria were described as follows: 1) with tumor distant metastasis; 2) undergoing emergency operations due to complications (bowel obstruction, perforation, etc.) before the surgery; 3) with preoperative neoadjuvant treatment (radiotherapy or chemotherapy); 4) combined with other malignancies; 5) undergoing laparotomy or laparoscopic conversion to laparotomy; 6) with incomplete data. A total of 402 patients were initially enrolled and 37 patients were excluded according to the exclusion criteria (4 with tumor distant metastasis, 5 underwent emergency operations, 3 combined with other malignancies, 10 underwent laparotomy or laparoscopic conversion to laparotomy, 15 with data missed).

**Study design**

The operative procedures for GC (the extent of gastrectomy and lymph node dissection) in this study was according to the Japanese Gastric Cancer Treatment Guidelines 2010 (ver. 3) [17]. All the enrolled patients were operated by the same experienced surgeons with the same perioperative managements. The pathological diagnosis was performed following the guidelines of the American Joint Committee on Cancer (AJCC) TNM Staging System for GC [18].

**Data collection**

The following data were extracted and recorded from our database: 1) clinicopathological features, including age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) grade, comorbidities, smoking and drinking habits, abdominal surgery history, tumor location, histologic type, pathological type, tumor size and TNM stage; 2) operative-associated characteristics including extent of resection, operation time, estimated blood loss, intraoperative fluid utilization and perioperative blood transfusion; 3) postoperative recovery including time to first flatus, ambulation, first liquid intake and first soft intake; 4) laboratory tests.

**Assessment and definition of postoperative complications**

The primary end point of this study was set as the occurrence of postoperative complications within postoperative 30 days [19]. According to the Clavien–Dindo classification system, the severity of complications was assessed from Grade I to V and SPCs were defined as C-D Grade ≥ IIIa [20]. If the patient had multiple complications, the grading was performed based on the most serious complication. Each patient was assessed for C-D grading by two independent experienced surgeons and divergences were solved by discussion. Enrolled patients were subdivided into SPCs group and non-SPCs group according to the presence of SPCs within postoperative 30 days.

**Laboratory tests**

Fasting blood samples from each participant were obtained on 1 day before the operation. Blood cell analyses including hemoglobin (Hb), white blood cell (WBC), platelet (Plt) and hematocrit (Hct), biochemistry analyses including creatinine and urea were determined in the laboratory of our hospital. The serum expressions of inflammatory cytokines including tumor necrosis factor-α (TNF-α), C-reactive protein (CRP) and interleukin-6 (IL-
Statistical analysis

Statistical analysis was performed using SPSS 22.0 (SPSS Inc., IA, USA) and GraphPad Prism 5.0 (GraphPad Inc., CA, USA). All variables are expressed as means ± standard deviation (SD) or numbers with percentage (n, %). Continuous variables were compared using Mann–Whitney U test or Student t test, whereas categorical variables using Chi-square test or Fisher exact test as appropriate. Receiver operating characteristic (ROC) curve analysis using Youden’s Index was established for determining the predictive value and cut-off threshold of AFR for SPCs. Binary univariate and multivariate logistic regression models were used to assess factors influencing SPCs. Following univariate analysis, potential risk factors (P < 0.1) were selected for multivariate analysis using the multivariate logistic regression model with binary stepwise regression method. A two-sided P value of < 0.05 was considered statistically significant.

Results

Patient characteristics

According to the inclusion and exclusion criteria, 365 patients were enrolled in the analysis. The mean age of this study population was 73.1 years and the majority (275/365, 75.3%) were male patients. Among these 365 available participants, 52 were categorized into SPCs group with a prevalence of 14.2% (52/365) and the remaining 313 were categorized into non-SPCs group. The actual number and frequency of each complication in SPCs group are shown in Table 1. Of these postoperative events, pulmonary complications (n = 9, 2.5%), intra-abdominal infection (n = 8, 2.2%), bowel obstruction (n = 6, 1.6%), wound infection (n = 5, 1.4%) and anastomotic leakage (n = 4, 1.1%) are the most frequent. The demographic and clinical characteristics of enrolled GC patients associated with SPCs are shown in Table 2. As a result, those patients with an older age and a higher ASA grade were more likely to suffer SPCs (P < 0.05). The presence of preoperative comorbidities (hypertension and diabetes) was closely associated with an increased risk of SPCs (P = 0.013 and 0.019, respectively). The SPCs group experienced significantly longer operation time (P = 0.023), higher estimated blood loss (P = 0.012) and intraoperative fluid utilization (P = 0.007). No statistical differences were observed between SPCs and non-SPCs groups in gender, BMI, hyperlipidaemia, smoking and drinking habits, abdominal surgery history, tumor location, histologic type, pathological type, tumor size, TNM stage, extent of resection, perioperative blood transfusion, time to first flatus, ambulation, first liquid intake and first soft intake (P > 0.05).

Laboratory tests and SPCs

Table 3 shows the results of preoperative laboratory tests in surgical patients with or without SPCs. Patients who suffered SPCs had higher preoperative expressions of CRP (P = 0.012) and TNF-α (P = 0.016) than those who did not. Moreover, those patients with a lower preoperative AFR level were more likely to develop SPCs (P < 0.001). There were no significant differences in blood cell analyses, IL-6, Alb, Fib, creatinine and urea between the two groups (P > 0.05).

AFR and SPCs

ROC curve analysis was performed to evaluate the predictive value of AFR for SPCs in GC patients. As illustrated in Fig. 1, preoperative AFR level predicted SPCs in surgical GC patients with an AUC of 0.841, a sensitivity of 76.36% and a specificity of 80.77%, respectively (P < 0.001). Furthermore, an AFR value of 8.49 was set as the optimal cut-off threshold for SPCs based on the Youden’s Index. Enrolled patients were then subdivided by AFR based on the cut-off value, high-AFR group (AFR>8.49) and low-AFR group (AFR ≤ 8.49).

Risk factors for SPCs

All potential risk factors (P < 0.05 in Tables 2 and 3, n = 10 in this study, see Table 4) were enrolled in the univariate and multivariate logistic regression analyses. In the univariate analysis, five risk factors with P values < 0.1 (age, diabetes, operation time, CRP and AFR) were selected for multivariate analysis. The multivariate analysis revealed that a lower AFR level (OR: 1.94, 95% CI: 1.09–3.36, P = 0.017) and an older age (OR: 1.81, 95% CI: 1.07–3.06, P = 0.023) were associated with an increased risk of SPCs (P < 0.05).
| Parameters                      | SPCs No (n = 313) | Yes (n = 52) | P-value |
|--------------------------------|-------------------|--------------|---------|
| Age (year)                     | 72.3 ± 5.7        | 77.6 ± 6.3   | < 0.001*|
| Gender, n (%)                  | 238               | 37           | 0.449   |
| Male                           | 75                | 15           | 0.331   |
| Female                         | 26                | 7            | 0.072   |
| BMI (kg/m²)                    | 21.2 ± 2.1        | 20.9 ± 1.9   |         |
| Hypertension                   | 38                | 13           | 0.013*  |
| Diabetes                       | 27                | 10           | 0.019*  |
| Hyperlipidaemia                | 22                | 7            | 0.122   |
| Heavy drinkers, n (%)          | 26                | 7            | 0.230   |
| Current smokers, n (%)         | 33                | 10           |         |
| ASA grade, n (%)               | 247               | 33           | 0.015*  |
| I/II                           | 66                | 19           |         |
| Abdominal surgery history, n (%) | 26               | 7            |         |
| Tumor location, n (%)          | 32                | 6            | 0.449   |
| Cardia                         | 201               | 28           |         |
| Pylorus                        | 67                | 14           |         |
| Corpus                         | 13                | 4            |         |
| Histologic type                | 221               | 30           | 0.177   |
| Differentiated                 | 33                | 8            |         |
| Signet-ring cell carcinoma     | 59                | 14           |         |
| Pathological type              | 273               | 42           | 0.210   |
| Ulcerative                     | 40                | 10           |         |
| Non-ulcerative                 | 4.3 ± 1.9         | 4.5 ± 2.1    | 0.489   |
| Tumor size (cm)                | 185               | 32           |         |
| Extent of resection            | 128               | 20           | 0.741   |
| Distal gastrectomy             | 130               | 21           |         |
| Total gastrectomy              | 183               | 31           |         |
| T stage                        | 1.7               | 3            | 0.876   |
| T1/T2/T3                      | 130               | 32           |         |
| T4/T5/T6                      | 183               | 31           |         |
| N stage                        | 201               | 35           | 0.952   |
| NO                             | 101               | 17           |         |
| N1/N2/N3                      | 212               | 35           |         |
| TNM stage                      | 147               | 28           | 0.654   |
| I                              | 77                | 11           |         |
| II                             | 89                | 13           |         |
| III                            | 245.7 ± 38.2      |              |         |
| Operation time (min)           | 234.6 ± 31.3      |              | 0.023*  |
| Estimated blood loss (mL)      | 187.9 ± 78.8      | 217.2 ± 70.6 | 0.012*  |
It is well known that diabetes closely correlates with postoperative complications. Patients who had comorbidities of diabetes before surgery were associated with a high risk of major postoperative complications after reconstructive microsurgery for head and neck cancer [23]. Furthermore, Saji et al. indicated a comprehensive risk scoring system, which included diabetes mellitus as a component, capable of predicting SPCs in patients with medically operable lung cancer [24]. A previous study by Sung et al. reported that a long operation time (>3 h) was an independent risk factor for severe and overall postoperative complications, as well as poor surgical outcomes [11]. As reported by recent studies, CRP is suggested to be a valid predictor of postoperative complications after various operations, such as minimally invasive colorectal resection [25], minimally invasive esophagectomy [26] and major noncardiac surgery [27]. A randomized controlled trial has also proved the significantly predictive value of CRP for surgical site infection [28]. Our univariate analyses showed that five variables (age, diabetes, operation time, CRP and AFR) might be potential risk factors for SPCs. However, the results from our multivariate analyses only supported age and AFR as two independent risk factors for SPCs. The different sample sizes, operation types, perioperative managements may explain the different conclusions.

Accumulating evidence has demonstrated that aging is an independent risk factor for postoperative complications following various operation types, including pancreatic resection [29], laparoscopic gastrectomy [30], and robotic-assisted pulmonary lobectomies [31]. As expected, our results also supported an older age as an independent risk factor for SPCs. Several studies have indicated that older age is associated with high postoperative morbidity and mortality rates due to increased preoperative comorbidities [32]. We consider that the age-associated gradual loss of reserve capacity (e.g. circulatory, immune system changes) [33] and more preexisting diseases [34] may be possible mechanisms for its predictive value for SPCs in this study. However, there is still no consensus with

| Table 2 | Demographic and clinical characteristics of GC patients with SPCs or not (Continued) |
|---------|---------------------------------------------------------------|
| Parameters | SPCs | P-value |
| Intraoperative fluid utilization (mL) | 1910.3 ± 245.3 | 2014.3 ± 306.4 | 0.007* |
| Perioperative blood transfusion, n (%) | 105 | 16 | 0.694 |
| Time to first flatus (d) | 2.9 ± 0.7 | 3.0 ± 0.9 | 0.362 |
| Time to ambulation (d) | 2.1 ± 0.7 | 2.2 ± 0.6 | 0.332 |
| Time to first liquid intake (d) | 3.9 ± 1.1 | 4.0 ± 1.3 | 0.555 |
| Time to first soft intake (d) | 5.4 ± 1.3 | 5.3 ± 1.5 | 0.616 |

P-values were calculated by Chi-square test, Fisher exact test, Mann-Whitney U or t test

Table 3 | Laboratory tests and SPCs in GC patients |
|-----------------|---------------------------------|-------|
| Preoperative laboratory tests | SPCs | P-value |
| Hb (g/L) | 117.5 ± 7.5 | 116.4 ± 8.4 | 0.337 |
| Plt (×10^9/L) | 207.6 ± 41.2 | 214.3 ± 49.7 | 0.293 |
| WBC (×10^9/L) | 7.1 ± 2.2 | 6.9 ± 1.9 | 0.537 |
| Hct | 0.43 ± 0.07 | 0.42 ± 0.06 | 0.332 |
| CRP (mg/L) | 6.3 ± 3.1 | 7.5 ± 3.5 | 0.012* |
| IL-6 (pg/mL) | 15.7 ± 7.1 | 16.3 ± 6.6 | 0.569 |
| TNF-α (nmol/L) | 76 ± 1.9 | 83 ± 2.1 | 0.016* |
| Creatinine (mmol/L) | 83.1 ± 17.3 | 82.6 ± 18.4 | 0.848 |
| Urea (mmol/L) | 64 ± 1.8 | 62 ± 1.7 | 0.455 |
| Albumin (g/L) | 39.2 ± 5.5 | 37.9 ± 6.2 | 0.122 |
| Fibrinogen (mg/dL) | 3.6 ± 1.3 | 3.9 ± 1.5 | 0.134 |
| AFR | 99 ± 2.2 | 74 ± 2.1 | <0.001* |

P-values were calculated by Mann-Whitney U or t test

**Discussion**

In this present study, we observed that preoperative AFR level and age were two independent predictive factors for SPCs in GC patients undergoing elective radical laparoscopic gastrectomy. Our study reported a prevalence of SPCs of 14.2% in surgical GC patients, which was a little higher than 10.2% by Zhang et al. [21] and 8.1% by Kang et al. [11]. Another study by Fukuda et al. has reported a prevalence of 13.2% [22], which is quite in accordance with our results. In our consideration, the different sample sizes, age ranges, inclusion and exclusion criteria, SPCs evaluation deviations and some missed data might be possible explanations for the different results.
respective to the cut-offs of ages among the published studies [29].

Alb is a sensitive biomarker for nutritional status evaluation and an acute-phase protein in response to systemic inflammation [35]. Alb expressions are recommended to be a reliable prognostic factor in patients with cancers [36]. Fib, which is synthesized by liver, is a crucial component of blood coagulation system via promoting platelet aggregation. Moreover, Fib is reported to be an important biomarker reflecting systemic inflammation [37] and it serves as a candidate prognostic biomarker in patients with non-small cell lung cancer (NSCLC) [38]. AFR, a ratio of Alb-to-Fib, combines these two biomarkers and amplifies the sensitivity for evaluating inflammation and nutrition status. The combination of Alb and Fib is superior to the single Alb and Fib and it has been widely

![ROC curve analysis of AFR for SPCs](image)

**Fig. 1** Predictive value of AFR for SPCs in GC patients by ROC curve analysis. The results indicated preoperative AFR as a potential predictive factor for SPCs in GC patients with an AUC of 0.841, 95%CI of 0.783–0.900, a cut-off value of 8.49, a sensitivity of 76.36% and a specificity of 80.77%, respectively (P < 0.001); AFR, albumin-to-fibrinogen ratio; SPCs, severe postoperative complications; GC, gastric cancer; ROC, receiver operating characteristic; AUC, the area under the curve; CI, confidence interval

![Table 4](image)

**Table 4** Risk factors for SPCs by univariate and multivariate logistic regression analyses

| Variables                               | Univariate       | Multivariate    |
|-----------------------------------------|------------------|-----------------|
|                                         | OR (95%CI)       | P value         | OR (95%CI)       | P value         |
| Age (≥74 vs < 74)                        | 2.22 (1.37–3.58) | 0.005*          | 1.81 (1.06–3.04) | 0.023*          |
| Hypertension (yes vs no)                | 1.41 (0.83–2.39) | 0.21            |                 |                 |
| Diabetes (yes vs no)                    | 1.72 (1.04–2.88) | 0.031*          | 1.29 (0.78–2.19) | 0.41            |
| ASA grade (I/II vs III/IV)              | 0.96 (0.59–1.51) | 0.81            |                 |                 |
| Operation time (high vs low)            | 1.71 (1.03–2.85) | 0.029*          | 1.54 (0.85–2.63) | 0.14            |
| Estimated blood loss (high vs low)      | 0.94 (0.51–1.79) | 0.85            |                 |                 |
| Intraoperative fluid utilization (high vs low) | 0.92 (0.53–1.58) | 0.79            |                 |                 |
| Preoperative CRP (high vs low)          | 1.83 (1.11–3.08) | 0.024*          | 1.37 (0.79–2.33) | 0.25            |
| Preoperative TNF-α (high vs low)        | 1.15 (0.73–1.77) | 0.42            |                 |                 |
| AFR (≤8.49 vs >8.49)                    | 2.54 (1.52–4.22) | 0.001*          | 1.94 (1.09–3.36) | 0.017*          |

The high vs low levels were categorized using the median value as the cut-off value

SPCs Severe postoperative complications, ASA American Society of Anesthesiologists, CRP C-reactive protein, TNF-α Tumor necrosis factor-α, AFR Albumin-to-fibrinogen ratio, OR Odds ratio, CI Confidence interval

*P value< 0.05
recommended as a prognostic factor in various models, e.g. acute ST-segment elevation myocardial infarction (STEMI) [39], operable NSCLC [15], and operable soft tissue sarcoma [40]. Preoperative low serum Alb is reported to be an indicator for postoperative complications and mortality in patients undergoing transcatheter aortic valve replacement [41]. Furthermore, early decrease in Alb is a significant predictor for SPCs in colorectal cancer patients undergoing curative laparoscopic surgery [42]. Previous studies have also indicated Fib as an early marker of postoperative complications after laparoscopic sleeve gastrectomy in morbidly obese patients [43] or total joint arthroplasty [44]. This present study was the first to indicate preoperative AFR as an independent risk factor for SPCs in GC patients after radical laparoscopic gastrectomy. The close association between inflammation and SPCs might be a possible mechanism.

This study had some certain limitations. First, this is a single-center study with the retrospective nature, so selection bias is inevitable. An independent prospective cohort is required to validate a definitive conclusion regarding clinical application of AFR and its optimal cut-off for SPCs prediction in surgical GC patients. Second, this study only takes preoperative Alb and Fib into consideration, whether postoperative levels have the predictive value remains unclear. Furthermore, the involved mechanisms for this study remain uncertain. A multicenter study with larger sample size was required to validate the prognostic role of AFR in GC patients. Furthermore, whether the interventions of AFR (e.g. improve the nutritional status, hypoproteinemia, coagulation function) could improve the outcomes in GC patients and decrease SPCs remains unclear.

Conclusions
To the best of our knowledge, this study firstly highlighted that preoperative AFR and age were two independent risk factors for SPCs in elderly surgical GC patients. Of course, our results do not support the delaying of elective surgery according to the preoperative AFR values. Instead, the situations with potential development of SPCs should be considered and intensively cared.

Abbreviations
AFR: Albumin-to-fibrinogen ratio; ASA: American Society of Anesthesiologists; BMI: Body mass index; CI: Confidence interval; CRP: C-reactive protein; GC: Gastric cancer; Hb: Hemoglobin; Hct: Hematocrit; IL-6: Interleukin-6; NSCLC: Non-small cell lung cancer; OR: Odds ratio; Plt: Platelet; SPCs: Severe postoperative complications; STEMI: ST-segment elevation myocardial infarction; TNF-α: Tumor necrosis factor-α; WBC: White blood cell

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Authors’ contributions
H5 was involved in the caring for the patients included in the study, study design and methodology, interpretation and analysis of study results, and the writing of the manuscript. QZ was involved in identification and selection of patients, data acquisition, construction of the database, interpretation and analysis of study results, and administrative support. JS was involved in construction of the database, data acquisition, and administrative support. LG was involved in all statistical analysis, and writing of the manuscript. JC and XY edited the manuscript and supervised the study. All authors read and approved the final manuscript.

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Availability of data and materials
Please contact the author Huachun Shen (shenhuachun_nb@sina.com) upon reasonable requests.

Ethics approval and consent to participate
This study was approved by the Medical Institutional Ethics Committee of Zhejiang province. The patients enrolled all presented written informed consent.

Consent for publication
Not Applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1Department of Anesthesiology, Jiangxi Maternal and Child Health Hospital, Nanchang, China. 2Department of Anesthesiology, HwaMei Hospital, University of Chinese Academy of Sciences, No.41 Xibei Road, Haishu District, Ningbo, Zhejiang Province, China.

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