Clinical Outcomes and Predicted Model of Surgical Patients With Enhanced Recovery After Surgery (ERAS): A Multicenter Prospective Clinical Study

Li Ren
First Affiliated Hospital of Chongqing Medical University
Feng Lv
First Affiliated Hospital of Chongqing Medical University
Su Min (459910606@qq.com)
First Affiliated Hospital of Chongqing Medical University
Juying Jin
First Affiliated Hospital of Chongqing Medical University
Wenjian Wang
First Affiliated Hospital of Chongqing Medical University
Peipei Qin
First Affiliated Hospital of Chongqing Medical University

Research Article

Keywords: surgery, prediction, enhanced recovery after surgery

Posted Date: February 4th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-153824/v1

Abstract

Enhanced recovery after surgery (ERAS) has been accepted widely in the whole world. However, clinical effects of ERAS in China have not been systematically reported, and it is still unclear whether there is key component with the present ERAS program to secure enhanced recovery. Patients who were undergoing operations with ERAS program were included. All the perioperative information were collected via a website and a nomogram to predict postoperative complication was conducted. 950 subjects from 59 hospitals were included in this study. Illness of cardiovascular (22.6%) and endocrine system (11.1%) were the top two coexisted diseases preoperatively. The recovery time of ability of drinking water after surgery was 6 (4-8) h, and almost half of patients could do active exercises in bed within 6 h postoperatively. The overall incidence of complications within 1 month postoperatively was 11.1%. Preoperative creatinine and bilirubin, intraoperative maximum systolic blood pressure and NRS scores at rest at postoperative 3 days were independent risk factors for complications within 1 month postoperatively. However, minimally invasive surgery was associated with a decrease probability of the complications. This study firstly indicates preoperative hepatorenal function, intraoperative systolic blood pressure, minimally invasive surgery and postoperative pain control can independently influence the prognosis of surgical patients.

Introduction

Enhanced recovery after surgery (ERAS) is a multimodal perioperative care pathway to reduce the physiological and psychological stress of surgical patients and achieve early recovery after surgery[1]. The concept rested on several elements: a multidisciplinary team, evidence-based perioperative management to prevent and resolve complications[2]. The advantages of ERAS has been strongly proved by many studies[3-7]. It was reported that ERAS could reduce the need for hospital stay by about 30% and major complications by as much as 40% after major abdominal surgery[8]. Nowadays, ERAS is becoming standard care for many surgical patients in the whole world.

About 16-25 evidenced-based interventions of ERAS were summarized and guided by ERAS Society for different types of surgery (http://erassociety.org). More and more studies found and highlighted the importance of compliance of ERAS program: the better compliance, the better outcomes[9,10]. However, it was difficult to adhere strongly to all ERAS items in most medical centers, in fact, the elements were implemented in part[11]. And it is still debatable that all the item of ERAS program are important equally and whether there are obligatory elements for the recovery of patients[12]. In addition, with the ERAS program, the effects of other perioperative factors on the prognosis is still unclear.

ERAS was carried out for more than 10 years in China and increasing achievement were reported in the recent 5 years[13]. However, to the best of our knowledge, the clinical outcomes of ERAS in China have not been examined, and the comprehensive understanding the effect of all the perioperative elements on the recovery of patients has not been established. And understanding the corrections of different elements and outcomes of surgical patients may help us to optimize the ERAS program further. Therefore, we conducted this multicenter clinical trial to investigate the current status and clinical outcomes of ERAS and its' contributed element in Chinese population.

Results

Demographics of the study population

Among a total of 1013 screened patients, 63 were excluded for not meeting the criteria or refusing to participate. Finally, 950 subjects from 59 hospitals in the region of Chongqing, Sichuan, Hubei and Ningxia Province were enrolled (All the participating hospital were shown in the file of supplementary information). The median of age was 52 years old with BMI being 23.5 kg/m^2. 363 male and 587 female were included. And most of them were complained with cardiovascular diseases (215 cases, 22.6%) and endocrine diseases (106 cases, 11.1%) for past illness. In addition, 190 patients had the history of drinking or/and smoking. A total of 731 subjects were assessed with lower-risk for surgery (ASA classification I and II). For the report of blood examination, the median of red blood cells, hemoglobin, albumin, creatinine, bilirubin was $4.24*10^{12}$/L, 127 g/L, 42.04 g/L, 60.6 μmol/L, 10.9 μmol/L, relatively. All the data of the characteristic of the patients were shown in table 1.

Characteristic of surgery/anesthesia and intraoperative vital sign of the patients

Orthopedic surgeries (287 cases, 30.2%), hepatobiliary surgeries (198 cases, 20.8%) and gynecology and obstetrics (192 cases, 20.2%) surgeries were the three most frequent operation categories. According to the severity of surgery injure, most surgeries were major, including joint replacement surgery, hepatic, gynecological, gastrointestinal and lung tumor surgery, etc. Most surgery was elective, the proportion of emergency surgery was only 5.6%. 76.2% of patients received minimally invasive surgery, and 59.6% of surgeries were conducted with general anesthesia. A great amount of surgeries were completed within 125 min. Correspondingly, most patients were under anesthesia condition within 180 min. Results suggested that the vital signs (heart rate, breathe, blood pressure, temperature) of patient were relative stable during the operation although a certain fluctuation in heart rate and blood pressure was shown. The volume of fluid therapy was also reported and the input were 1100 (800-1600) ml, crystalloid was the main component. The volume of output were 350 (85-600) ml (Table 2).

Compliance and clinical outcomes with ERAS program

ERAS program was consisted of 16 items in our study. The highest compliance was counseling and education, the lowest compliance was belonged to the item of carbohydrate intake. And there were 3 items which the compliance was over 90%. However, the compliance of 4 items, including carbohydrate intake, prevention of DVT, prevention of PONV and multimodal analgesia, were less than 70% (Figure 1).

The time of anal exhaust and defecation were 12 (6-26)h and 30 (18-50)h postoperatively. Moreover, about 50% patients could drink water within 6h postoperatively, and a quarter of patients even could drink water within 4h postoperatively. A half of patients could returned to liquid diet within 11h postoperatively and gradually converted to normal diet within 30h postoperatively. Otherwise, 25% of patients could not fully recovered to normal diet at postoperative 48h. The time of active exercises in bed for patients postoperatively was 6(2-10)h. About 75% patients had the ability to stand without assist within 48h postoperatively. The time of walking with assist was 24 (13-55)h postoperatively while the time of walking without assist was 33 (20-72)h postoperatively (Table 3).

In generally, postoperative pain was controlled well although a significant minority of patients experienced moderate-severe pain in hospital. The NRS scores were 2 (1-3) at POD1, 1 (0-2) at POD2 and 1 (0-1) at POD3 at rest. While for pain in motion, the NRS scores were 3 (2-4) at POD1, 2 (1-3) at POD2 and 2 (1-3) at POD3, respectively. And no patients were reported more than 3 points at 1 month postoperatively (Figure 2).

106 cases of postoperative complication were reported within 1 month postoperatively in this study, and the incidence of complication was 11.1%. The complications included death (1 case, 0.1%), stroke (1 case, 0.1%), organ failure (1 case, 0.1%), ileus (3 cases, 0.4%), postoperative hemorrhage (2 cases, 0.2%), surgical site infection (8 cases, 0.8%), urinary infection (2 cases, 0.2%), pulmonary infection (8 cases, 0.8%), deep venous thrombosis (1 case, 0.1%), perioperative neurocognitive disorders (1 case, 0.1%), mechanical ventilation last for 48h (2 cases, 0.2%), re-admission within 30 days (6 cases, 0.6%), postoperative nausea and vomiting (23 cases, 2.4%), severe sedation with analgesia (2 cases, 0.2%), respiratory depression with analgesia (2 cases, 0.2%), uncontrolled postoperative pain (40 cases, 4.6%), others (3 cases, 0.3%). The median of hospital stay postoperatively was 6 days, about 75% patients could discharge within postoperative 10 days. And the median of hospitalization expenses were 13000 CNY, and the satisfaction scores was 9 (Table 3).

Clinical risk factors of complications within 1 months postoperatively

The risk factors were summarized with univariate and multivariate logistical regression analysis in table 4. Univariate analysis revealed that 20 potential perioperative factors (age, preoperative hemoglobin, hematocrit, red blood cell, creatinine, total protein, albumin, bilirubin, and fibrinogen, mode of anesthesia, duration of anesthesia, intraoperative maximum of heart rate, pulse and systolic blood pressure, NRS at rest and in motion at 3 days postoperatively, time of activity in bed, minimally invasive surgery, no drainage placed as usual and early exercise) were associated with postoperative complications. And the final multivariate logistical regression showed 5 significant independent predictors: preoperative creatinine (OR 1.012, 95%CI 1.002-1.021) and bilirubin (OR 1.017, 95%CI 1.001-1.033), intraoperative maximum systolic blood pressure (OR 1.015, 95%CI 1.001-1.029), NRS scores at rest at postoperative 3 days (OR 1.43, 95%CI 1.111-1.84), minimally invasive surgery (OR 0.539, 95%CI 0.292-0.995). Results of the Hosmer-Lemeshow test suggested a good fit of the model ($\chi2=11.869$, df=8, $P=0.157$).

Prediction model for complications within 1 months postoperatively

To identify the high-risk patients of complications after surgery, a predictive nomogram model based on the results of multivariate logistical regression analysis was conducted to present the probability of complications within 1 months postoperatively. “Points” were calculated with the corresponding independent predictors. “Total points” were summed with each single points, and we draw a vertical line and projected it from the “Total points” scale to the “Probability” scale to predict the probability of complications within 1 months postoperatively. Results of ROC curve suggested a good discrimination with AUC 0.702 (95%CI 0.624-0.779). At the optimal cutoff value of 0.241, the sensitivity and specificity were 57.7% and 73.2%, respectively. The model showed a relatively good calibration because the actual line was not significantly deviated from the ideal line (Figure 3).

Discussion

In this multicenter, prospective study, we found that the most common preoperative comorbidity was cardiovascular disease among the patients. With ERAS program, almost half of patients could drink water and active exercises in bed within 6h postoperatively with a good control of postoperative pain. For the compliance of ERAS program, there were 3 items (counseling and education, preoperative fast and hypothermia prevention) which the compliance was over 90%, however, 4 of 16 items (carbohydrate intake, prevention of DVT, prevention of PONV and multimodal analgesia) were less than 70%. The overall incidence of complications within 1 month postoperatively among the patients with ERAS program was 11.1%, and preoperative creatinine and bilirubin, intraoperative maximum systolic blood pressure and NRS scores at rest at postoperative 3 days were independent risk factors for the complications, conversely, minimally invasive surgery was associated with a decrease probability of complications within 1 month postoperatively.

It is well known that preoperative general condition and comorbidities of the patient were related to the safety of surgery and postoperative prognosis[15,16]. In this study, we found that 22.6% of patients were coexistent with cardiovascular diseases (CVDs). CVDs remained a major cause of health loss in the whole world[17]. And according to the latest report from national center for cardiovascular disease, there were an estimated of 290 million CADs patients in China[18]. Perioperative management of cardiac patients undergoing noncardiac surgery was still a challenge to the anesthesiologists and surgeons although a series of guidelines have been published[19-21]. In our study, a certain fluctuation in heart rate and blood pressure was found in a small group of patients. Furthermore, intraoperative maximum systolic blood pressure was found to be an independent risk factor for complications, which was in line with the results of previous study[22]. However, recent studies reported that intraoperative hypotension, but not hypertension, was associated with shortened survival[23,24]. Several factors might explain this difference: (1) the definition of intraoperative hemodynamic aberration or intraoperative hypertension/hypertension was, for awhile, loosely defined. (2) specific blood pressure target management from group data cannot be extrapolated to be optimal for all patients[25]. (3) In addition to the cutoff value of intraoperative hypertension/hypotension, other factors[26-28] (including duration of hemodynamic aberration, improper treatment during hemodynamic aberration) could also impacted the outcomes. It was widely accepted that a smooth intraoperative course with minimal blood pressure aberrations was related to better prognosis although a certain variation of blood pressure seemed to be inevitable virtually[29]. To the best of our knowledge, the effects of variation of intraoperative blood pressure on the outcomes of the surgical patients were still controversial. And further researches are needed to identify whether and to what extent hemodynamic aberration impacts the prognosis of surgical patients with ERAS program.

In this study, the results suggested a moderate compliance to ERAS program, but 4 items (carbohydrate intake, prevention of DVT, prevention of PONV and multimodal analgesia) showed poor compliance. The item of lowest compliance was carbohydrate intake. Preoperative carbohydrate loading has been theorized to reduce insulin resistance and enhance patient comfort[30]. However, in addition to overcoming the inertia to change the outdated fasting guideline, several concerns were still unsolved and might affected widely used in clinical. Effects of preoperative carbohydrate loading on the clinical outcomes and prognosis were unidentified[31,32], Smith and the colleagues reviewed all the clinical studies and no positive result was found about the relationship between preoperative carbohydrate and postoperative complication[33]. In addition, the safety of carbohydrate use in patients with diabetes remained uncertain[34-36]. Furthermore, our previous study found that the composition proportion of carbohydrate could influence tumor growth and malignance in mice[37]. Thus, the impact of carbohydrate on the specific populations, such cancer groups, should be taken into consideration. Nowadays, the ERAS program was recommended in general populations for different types of surgery, and present ERAS procedure should be further optimized in special populations based on high-quality researches.

Growing evidence has been proved that compliance of ERAS program was associated with clinical outcomes of patients[38,39]. Actually, full implementataion of ERAS program seems impossible for most surgical patients because of the complex procedure and labor intensive[40] . Although many authors stressed the important of compliance, little was known about the impact of number of used components. For those reasons, a simplified ERAS program named RAPID (remove, ambulate, postoperative analgesia, introducing diet) was suggested by Lloyd et al, and patients with RAPID protocol also showed shorter hospital stay[41]. In our study, we found that several factors, including minimally invasive surgery, one of the elements in our ERAS program, appeared to be more influential than others. This results are agreed with the study by Demartines who observed that minimally invasive surgery was the single most important component of the ERAS pathway[42]. Pro. Kehlet also concluded five key elements for ERAS in open colonic surgery[43]. At present, accumulative studies revealed that full implementation of ERAS program significantly improved the prognosis of the patients[44,45]. As far as we know, from the aspect of flexibility and utility of clinical practice, implement the well-established core component in the present ERAS program should be more valuable[46]. In addition to minimally invasive surgery, preoperative creatinine and bilirubin, intraoperative maximum systolic blood pressure and NRS scores at rest at postoperative 3 days were also included in the predictive model for complications. The component of this model confirmed the core concept of ERAS which revealed that the better perioperative management, the better clinical outcomes for patients. More narrowly, it is necessary to optimize the function of liver and kidney preoperatively, keep a stable hemodynamics with minimally invasive approach intraoperatively, control the postoperative pain well to reduce the postoperative complications.

However, several limitations exist in this study. First, all participating hospitals are located in the central-western region of China, it may not represent other areas in China. Second, the sample size was relatively small. Finally, the follow-up is completed at 1 months postoperatively, and the long-term outcomes was not explored in this study.

In conclusion, this study revealed that preoperative cardiovascular diseases was the most common comorbidity for the patients with ERAS in western region of China. Most patients got rapid and effective recovery after surgery with our ERAS program. And the overall incidence of complications within 1 month postoperatively was 11.1%. Preoperative creatinine and bilirubin, intraoperative maximum systolic blood pressure, NRS scores at rest at postoperative 3 days and minimally invasive surgery were independent predictors for the complications.

Methods

This is a multicenter, observational study, which was conducted between February 2019 and June 2020. This protocol was approved by the ethics committees of the First Affiliated Hospital of Chongqing Medical University (No. 2019-020), the leading unite of this study. The protocol was also accepted by the ethics committees of other 58 participated unites. This study was registered at Chinese Clinical Trial Registry on 14/1/2019, number: ChiCTR2000037513. All methods were performed in accordance with the Declaration of Helsinki and relevant guidelines.

Subjects

All the participants were informed about the study and consent was obtained. Surgical patients who were undergoing operations with ERAS program were recruited. Participants were excluded if they had serious mental illness, speech impediment, participate rejection. Participating hospitals were amenable to recruit one patients per month at least.

ERAS program

According to the regional medical practice and guidelines of ERAS, 16 items were summarized and applied in this study: 1) Perioperative counseling and patient education; 2) Oral intake of 400ml carbohydrate drink started 3 h before surgery and consumed 2 h prior to surgery; 3) Intake of clear fluid up to 2h and solids up to 8h before anesthesia. 4) Prevention of deep venous thrombosis with active or passive physical exercise, and usage of low molecular weigh heparin in necessity; 5) antibiotic prophylaxis 30min before incision; 6) optimized anesthesia management, especially for administration of lung protective ventilation strategy, depth of anesthesia monitor, neuromuscular monitor, hemodynamics monitor and combined different methods of anesthesia. 7) minimally invasive surgery or laparoscopic surgery; 8) conduct of intraoperative goal-directed fluid therapy; 9) prevention of hypothermia (body temperature less than 36℃); 10) multimodal prevention of postoperative nausea and vomiting (combined with usage of dexamethasone, 5-HT_3 receptor antagonist, metoclopramide and haloperidol); 11) no surgical drains placement as far as possible; 12) multimodal management of postoperative pain (combined with usage of nonsteroidal anti-inflammatory drugs, peripheral never block analgesia, patients controlled analgesia, incision infiltration analgesia, opioids in necessity); 13) Removal of surgical drains within 3 days postoperatively; 14) Early oral feeding (drinking water within 6 hours or/and liquid diet feeding within 24h postoperatively); 15) Early and scheduled mobilization (active exercise in bed within 6 hours and/or out-of-bed activity with assist within 24h postoperatively); 16) Perioperative nutrition support.

Data collection and export

All the required data were collected from the electronic medical record by an anesthesiologist in each participating hospital and then were uploaded via website (https://218.207.2.100:10601/), which was established with the help of Department of Information Technology of the First Affiliated Hospital of Chongqing Medical University. Each participating hospital reported data via the unique account belonged to their hospital, and each hospital except for the leading hospital of this study can only view and download its own dataset in this website. Electronic medical record, which was used for checking whether there was any mistake of the dataset, was also required to uploaded. When eligible patient was admitted to hospital, he/she was announced with the purpose and process of this study, the basic information of the patient should be uploaded to the online database after the consent was obtained from the patient. Data of surgery and anesthesia was required to uploaded within 24h postoperatively, and the follow-up data should be recorded within 24h after the visit. All the important perioperative information were collected, including characteristic of the patients (age, BMI, nationality, history of smoking, alcohol intake and illness, blood biochemical examination), the information of surgery and anesthesia (types of surgery and anesthesia, ASA and NYHA classification, duration of anesthesia and surgery, intraoperative vital signs and volume of input-output), compliance of ERAS program, complications within 30 days postoperatively, pain scores at rest and in motion within 30 days postoperatively, gastrointestinal function recovery and ambulation time, as well as hospital stay, fees and satisfaction. All the data in the database were exported in the form of Excel by a network engineer.

Statistical Analysis

All data were expressed as median (interquartile range) for continuous variables and total number (percent frequency) for categorical variables. Risk factors for major complications were identified with odds ratio (OR) and 95% confidence interval (CI) using a univariate logistical regression analysis, the variables with P values ≤ 0.1 were included in multivariable model to determine the independent factors by using the method of backward stepwise (conditional). The nomogram performance was assessed by discrimination and calibration[14]. The discrimination was evaluated by receiver operation characteristic (ROC) curve. A value of area under curve (AUC) closer to 1 suggested a good performance of the model, an AUC ≥0.7 was generally considered to be relatively good discrimination. The calibration was assessed by a visual calibration plot comparing the predicted and actual probability of major complications. A ideal line was drawn with 45 degree-angle, and the model revealed perfect calibration if actual line was identical to the ideal line. In addition, the nomogram was subjected to 1000 bootstrap resamples to evaluate the predictive accuracies. All the statistical analysis were conducted by SPSS (version 21.0 IBM Corp, Armonk, NY, USA) and R (reversion 4.0.2, http://www.R-project.org). *P* value less than 0.05 was considered statistically significant.

Declarations

Author contributions

LR contributed to design of the work, acquisition, analysis and interpretation of data

FL contributed to analysis of data

SM contributed to design of the work and interpretation of data

JYJ contributed to analysis of data

WJW contributed to analysis of data

PPQ contributed to acquisition of data

Conflict of interest

The authors declare no competing interests.

Funding

This work was supported by Chongqing technology innovation and application project (No. cstc2018jscx-msybX0139)

References

1. Kehlet, H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth* **78**, 606-617 (1997).
2. Ljungqvist, O., Scott, M. & Fearon, K. C. Enhanced Recovery After Surgery: A Review. *JAMA Surg* **152**, 292-298 (2017).
3. Dietz, N. *et al.* Enhanced Recovery After Surgery (ERAS) for Spine Surgery: A Systematic Review. *World Neurosurg* **130**, 415-426 (2019).
4. Coyle, M. J., Main, B., Hughes, C., Craven, R., Alexander, R., Porter, G. & Thomas, S. Enhanced recovery after surgery (ERAS) for head and neck oncology patients. *Clin Otolaryngol* **41**, 118-126 (2016).

5. Boitano, T. *et al.* Impact of enhanced recovery after surgery (ERAS) protocol on gastrointestinal function in gynecologic oncology patients undergoing laparotomy. *Gynecol Oncol* **151**, 282-286 (2018).
6. Kowalsky, S. J. *et al.* A Combination of Robotic Approach and ERAS Pathway Optimizes Outcomes and Cost for Pancreatoduodenectomy. *Ann Surg* **269**, 1138-1145 (2019).
7. Frees, S. K. *et al.* A prospective randomized pilot study evaluating an ERAS protocol versus a standard protocol for patients treated with radical cystectomy and urinary diversion for bladder cancer. *World J Urol* **36**, 215-220 (2018).
8. Greco, M., Capretti, G., Beretta, L., Gemma, M., Pecorelli, N. & Braga, M. Enhanced recovery program in colorectal surgery: a meta-analysis of randomized controlled trials. *World J Surg* **38**, 1531-1541 (2014).
9. Gustafsson, U. O., Hausel, J., Thorell, A., Ljungqvist, O., Soop, M., Nygren, J. & Enhanced Recovery After Surgery Study Group. Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. *Arch Surg* **146**, 571-577 (2011).
10. ERAS Compliance Group. The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry. *Ann Surg* **261**, 1153-1159 (2015).
11. Pędziwiatr, M., Mavrikis, J., Witowski, J., Adamos, A., Major, P., Nowakowski, M. & Budzyński, A. Current status of enhanced recovery after surgery (ERAS) protocol in gastrointestinal surgery. *Med Oncol* **35**, 95 (2018).
12. Carmichael, J. C. *et al.* Clinical Practice Guidelines for Enhanced Recovery After Colon and Rectal Surgery From the American Society of Colon and Rectal Surgeons and Society of American Gastrointestinal and Endoscopic Surgeons. *Dis Colon Rectum* **60**, 761-784 (2017).
13. Jiang, Z. & Li, J. [Current Status of Enhanced Recovery After Surgery in China]. *Zhonghua Wei Chang Wai Ke Za Zhi* **19**, 246-249 (2016).
14. Iasonos, A., Schrag, D., Raj, G. V. & Panageas, K. S. How to build and interpret a nomogram for cancer prognosis. *J Clin Oncol* **26**, 1364-1370 (2008).
15. Louwman, W. J., Janssen-Heijnen, M. L., Houterman, S., Voogd, A. C., van der Sangen, M. J., Nieuwenhuijzen, G. A. & Coebergh, J. W. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. *Eur J Cancer* **41**, 779-785 (2005).
16. Hwang, K., Lee, J. P., Yoo, S. Y. & Kim, H. Relationships of comorbidities and old age with postoperative complications of head and neck free flaps: A review. *J Plast Reconstr Aesthet Surg* **69**, 1627-1635 (2016).
17. Roth, G. A. *et al.* Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J Am Coll Cardiol* **70**, 1-25 (2017).
18. Ma, L. Y. *et al.* China cardiovascular diseases report 2018: an updated summary. *J Geriatr Cardiol* **17**, 1-8 (2020).

19. Fleisher, L. A. *et al.* 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* **64**, e77-137 (2014).
20. Wijeysundera, D. N. *et al.* Perioperative beta blockade in noncardiac surgery: a systematic review for the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* **130**, 2246-2264 (2014).
21. Levine, G. N. *et al.* 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation* **134**, e123-155 (2016).
22. Reich, D. L., Bennett-Guerrero, E., Bodian, C. A., Hossain, S., Winfree, W. & Krol, M. Intraoperative tachycardia and hypertension are independently associated with adverse outcome in noncardiac surgery of long duration. *Anesth Analg* **95**, 273-277, table of contents (2002).
23. Huang, W. W., Zhu, W. Z., Mu, D. L., Ji, X. Q., Li, X. Y., Ma, D. & Wang, D. X. Intraoperative hypotension is associated with shortened overall survival after lung cancer surgery. *BMC Anesthesiol* **20**, 160 (2020).
24. Monk, T. G. *et al.* Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. *Anesthesiology* **123**, 307-319 (2015).
25. Brady, K. & Hogue, C. W. Intraoperative hypotension and patient outcome: does "one size fit all?". *Anesthesiology* **119**, 495-497 (2013).
26. Wilkman, E., Kaukonen, K. M., Pettilä, V., Kuitunen, A. & Varpula, M. Association between inotrope treatment and 90-day mortality in patients with septic shock. *Acta Anaesthesiol Scand* **57**, 431-442 (2013).
27. Inoue, T., Manley, G. T., Patel, N. & Whetstone, W. D. Medical and surgical management after spinal cord injury: vasopressor usage, early surgerys, and complications. *J Neurotrauma* **31**, 284-291 (2014).
28. Walsh, M. *et al.* Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* **119**, 507-515 (2013).

29. Reich, D. L. & Fischer, G. W. Perioperative interventions to modify risk of morbidity and mortality. *Semin Cardiothorac Vasc Anesth* **11**, 224-230 (2007).
30. Pogatschnik, C. & Steiger, E. Review of Preoperative Carbohydrate Loading. *Nutr Clin Pract* **30**, 660-664 (2015).
31. Pachella, L. A., Mehran, R. J., Curtin, K. & Schneider, S. M. Preoperative Carbohydrate Loading in Patients Undergoing Thoracic Surgery: A Quality-Improvement Project. *J Perianesth Nurs* **34**, 1250-1256 (2019).
32. Makuuchi, R. *et al.* Enhanced recovery after surgery for gastric cancer and an assessment of preoperative carbohydrate loading. *Eur J Surg Oncol* **43**, 210-217 (2017).
33. Smith, M. D., McCall, J., Plank, L., Herbison, G. P., Soop, M. & Nygren, J. Preoperative carbohydrate treatment for enhancing recovery after elective surgery. *Cochrane Database Syst Rev* CD009161 (2014).
34. Talutis, S. D., Lee, S. Y., Cheng, D., Rosenkranz, P., Alexanian, S. M. & McAneny, D. The impact of preoperative carbohydrate loading on patients with type II diabetes in an enhanced recovery after surgery protocol. *Am J Surg* (2020).
35. Ackerman, R. S. *et al.* How Sweet Is This? A Review and Evaluation of Preoperative Carbohydrate Loading in the Enhanced Recovery After Surgery Model. *Nutr Clin Pract* **35**, 246-253 (2020).
36. Rushakoff, R. J., Wick, E. C. & McDonnell, M. E. Enhanced Recovery in Patients With Diabetes: Is it Time for a Moratorium on Use of Preoperative Carbohydrate Beverages. *Ann Surg* **269**, 411-412 (2019).
37. Yu, C., Lv, B., Min, S., Ren, L. & Yu, J. Combined usage of monosaccharides with polysaccharides may decelerate tumor growth and malignance versus solely using a certain kind of saccharide. *Biochem Biophys Res Commun* **525**, 800-805 (2020).
38. Gustafsson, U. O., Oppelstrup, H., Thorell, A., Nygren, J. & Ljungqvist, O. Adherence to the ERAS protocol is Associated with 5-Year Survival After Colorectal Cancer Surgery: A Retrospective Cohort Study. *World J Surg* **40**, 1741-1747 (2016).
39. Gianotti, L. *et al.* Association Between Compliance to an Enhanced Recovery Protocol and Outcome After Elective Surgery for Gastric Cancer. Results from a Western Population-Based Prospective Multicenter Study. *World J Surg* **43**, 2490-2498 (2019).
40. Polle, S. W., Wind, J., Fuhring, J. W., Hofland, J., Gouma, D. J. & Bemelman, W. A. Implementation of a fast-track perioperative care program: what are the difficulties. *Dig Surg* **24**, 441-449 (2007).
41. Lloyd, G. M., Kirby, R., Hemingway, D. M., Keane, F. B., Miller, A. S. & Neary, P. The RAPID protocol enhances patient recovery after both laparoscopic and open colorectal resections. *Surg Endosc* **24**, 1434-1439 (2010).
42. Jurt, J., Slieker, J., Frauche, P., Addor, V., Solà, J., Demartines, N. & Hübner, M. Enhanced Recovery After Surgery: Can We Rely on the Key Factors or Do We Need the Bel Ensemble. *World J Surg* **41**, 2464-2470 (2017).
43. Kehlet, H. Fast-track colorectal surgery. *Lancet* **371**, 791-793 (2008).

44. Pisarska, M. *et al.* Do we really need the full compliance with ERAS protocol in laparoscopic colorectal surgery? A prospective cohort study. *Int J Surg* **36**, 377-382 (2016).

45. Pache, B., Jurt, J., Grass, F., Hübner, M., Demartines, N., Mathevet, P. & Achtari, C. Compliance with enhanced recovery after surgery program in gynecology: are all items of equal importance. *Int J Gynecol Cancer* (2019).

46. Kehlet, H. ERAS Implementation-Time To Move Forward. *Ann Surg* **267**, 998-999 (2018).

Tables

Table 1 Baseline characteristics of subjects

Variables	Value
Age (years, median, IQR)	52 (39-68)
BMI (kg/m^2, median, IQR)	23.5 (21.1-25.7)
Nationality n(%)	
Han	908 (95.5%)
Minority	42 (4.5%)
Sex n(%)	
Male	363 (38.2%)
Female	587 (61.8%)
ASA n(%)	
I	119 (12.5%)
II	612 (64.4%)
III	190 (20.0%)
IV	29 (3.1%)
NYHA n(%)	
I	474 (49.8%)
II	467 (49.1%)
III	9 (0.9%)
History n(%)	
Smoking	79 (8.3%)
Drinking	31 (3.2%)
Smoking& Drinking	80 (8.4%)
Cardiovascular disease	215(22.6%)
Respiratory disease	90 (9.4%)
Endocrine disease	106 (11.1%)
Neurological disease	51 (5.3%)
Digestive disease	30 (3.1%)
Urological disease	34 (3.5%)
Otolaryngological disease	5 (0.7%)

Blood examination (median, IQR)	
Red blood cell (10^{12}/L)	4.24 (3.82-4.73)
White blood cell (10^{9}/L)	6.79 (5.35-8.6)
Platelet (10^{9}/L)	205 (167-254)
Hemoglobin (g/L)	127 (115-139.5)
Hematocrit (%)	38.3 (34.3-41.9)
Total protein (g/L)	69 (63.8-73.75)
Albumin (g/L)	42.04 (37.4-45.3)
Globulin (g/L)	26.9 (24-30.1)
Bilirubin (μmol/L)	10.9 (7.77-15.62)
AST (U/L)	20 (16-25.7)
ALT (U/L)	17 (11-26)
BUN (mmol/L)	4.71 (3.76-5.9)
Creatinine (μmol/L)	60.6 (49.8-74.7)
APTT (s)	27.95 (25.1-31.47)
PT (s)	11.3 (10.5-12.3)
TT (s)	16.7 (15.3-17.9)
Fibrinogen (g/L)	3.2 (2.56-4)
INR	0.95 (0.89-1.01)

AST: glutamic oxalacetic transaminase; ALT: glutamic pyruvate transaminase; BUN: urea nitrogen; APTT: activated partial thromboplastin time; PT: prothrombin time; TT: thrombin time; INR: international normalized ratio.

Table 2 Information of surgery and anesthesia

Variable	Value
Type of Surgery n(%)	
Orthopedic surgery	287 (30.2%)
Joint replacement surgery	192 (20.2%)
Major spinal surgery	67 (7.0%)
Limb fracture surgery	28 (3.0%)
Hepatobiliary surgery	198 (20.8%)
Laparoscopic cholecystectomy	84 (8.8%)
Hepatic tumor surgery	114 (12.0%)
Gynecology and obstetrics surgery	192 (20.2%)
Gynecological tumor surgery	122 (12.8%)
Cesarean section	70 (7.4%)
Gastrointestinal surgery	141 (14.8%)
Gastrointestinal tumor surgery	131 (13.7%)
Acute abdominal surgery	10 (1%)
Thoracic surgery	27 (2.9%)
Lung tumor surgery	26 (2.8%)
Esophageal tumor surgery	1 (0.1%)
Otolaryngological surgery	19 (2%)
Nasal endoscopic surgery	14 (1.4%)
Ear surgery	5 (0.6%)
Oral and maxillofacial surgery	9(0.9%)
Facial fracture surgery	9(0.9%)
Thyroid and breast surgery	27 (2.9%)
Thyroid tumor surgery	93(1.4%)
Breast tumor surgery	14 (1.5%)
Neurosurgery	9(0.9%)
Intracranial tumor surgery	9 (0.9%)
Urological surgery	41 (4.3%)

Urological tumor surgery		15(1.6%)
Urological calculus		26 (2.7%)
Invasiveness of surgery n(%)		
Endoscopic surgery		724 (76.2%)
Open surgery		226 (23.8%)
Urgency of surgery n(%)		
elective surgery		897 (94.4%)
Emergency surgery		53 (5.6%)
Mode of Anesthesia n(%)		
General anesthesia		566 (59.6%)
Intraspinal anesthesia		234 (24.6%)
Nerve block		20 (2.1%)
Combined anesthesia[1]		130 (13.7%)
Duration of surgery (min, median, IQR) [2]		90 (57.2-125)
Duration of anesthesia (min, median, IQR) [3]		120 (85-180)
Intraoperative Fluid (ml, median, IQR)		
Input		1100 (800-1600)
Crystalloid		1000 (600-1200)
Colloid		0 (0-500)
Blood products		0 (0-0)
Output		350 (85-600)
Bleeding		100 (10-300)
Urine		200 (100-400)
Intraoperative vital signs (median, IQR)		
HR (beat/min)	Minimum	62 (56-70)
	Average	75(68-81)
	Maximum	89 (80-98)
Breath (time/min)	Minimum	12 (12-15)
	Average	16 (13-18)

	Maximum	20 (16-20)
Systolic blood pressure (mmHg)	Minimum	100 (91-110)
	Average	116 (110-125)
	Maximum	138 (126-152)
Diastolic blood pressure (mmHg)	Minimum	59(52-65)
	Average	70 (65-75)
	Maximum	85 (78-90)
MAP (mmHg)	Minimum	71(63-80)
	Average	85 (77-90)
	Maximum	100 (92-110)
Temperature (°C)	Minimum	36.3 (36.1-36.5)
	Average	36.5 (36.4-36.6)
	Maximum	36.7 (36.5-36.9)

[1] combined with more than two methods of anesthesia

[2] time from incision to closure

[3] time from induction to discontinuation of anesthetics

Table 3 Clinical outcomes of the patients with ERAS protocol

Variables	Value
Recovery time of gastrointestinal function and diet (h , median, IQR)	
Anal exhaust	12 (6-26)
Defecation	30 (18-50)
Drink water	6(4-8)
Liquid diet	11 (6-24)
Semi-liquid diet	20 (12-32)
Normal diet	30 (20-48)
Recovery time of activity (h, median, IQR)	
Active exercises in bed	6 (2-10)
Stand with assist	20(10-48)
Stand without assist	24 (14-48)
Walk with assist	24(13-55)
Walk without assist	33(20-72)
Length of stay (d, median, IQR)	8 (6-15)
Hospital stay postoperatively (d, median, IQR)	6(4-10)
Hospitalization expenses (CNY, median, IQR)	13000(8579-34630)
Satisfaction (median, IQR)	9(8-10)
Complications within 1 month postoperatively n(%)	106 (11.1%)
Death	1 (0.1%)
Cardiac arrest	0
Myocardial infarction	0
Pulmonary embolism	0
Stroke	1 (0.1%)
Organ failure (heart, liver, kidney, lung, brain)	1 (0.1%)
Coma	0
Re-operation	0

Ileus	3 (0.4%)
Postoperative hemorrhage	2 (0.2%)
Pneumothorax	0
Surgical site infection	8 (0.8%)
Urinary infection	2 (0.2%)
Pulmonary infection	8 (0.8%)
Sepsis	0
Deep venous thrombosis	1 (0.1%)
Perioperative neurocognitive disorders	1 (0.1%)
Mechanical ventilation last for 48h	2 (0.2%)
Re-admission within 30 days	6 (0.6%)
Postoperative nausea and vomiting	23 (2.4%)
Severe sedation with analgesia	2 (0.2%)
Respiratory depression with analgesia	2 (0.2%)
Uncontrolled postoperative pain	40 (4.6%)
Others	3 (0.3%)

Table 4 Univariate and multivariate regression analysis for complications within 1 month postoperatively

Variable	Univariate analysis			Multivariate analysis		
	OR	95%CI	*P*	OR	95%CI	*P*
Age	1.012	0.999-1.025	0.073			
Hemoglobin	0.984	0.972-0.996	0.008			
Hematocrit	0.947	0.906-0.989	0.014			
Red blood cell	0.605	0.407-0.897	0.013			
Creatinine	1.01	1.002-1.018	0.014	1.012	1.002-1.021	0.016
Total protein	0.971	0.943-1	0.049			
Albumin	0.953	0.912-0.997	0.035			
Bilirubin	1.015	1.002-1.028	0.025	1.017	1.001-1.033	0.039
Fibrinogen	1.132	1.022-1.254	0.017			
Mode of anesthesia			0.066			
General anesthesia	1(Ref)					
Intraspinal anesthesia	0.598	0.296-1.211	0.153			
Nerve block	1.132	0.536-2.391	0.744			
Combined anesthesia	1.925	0.462-8.015	0.368			
Duration of anesthesia	1.002	1-1.005	0.045			
MaxHR[1]	1.02	1.003-1.036	0.018			
MaxP[2]	1.019	1.003-1.036	0.02			
MaxSBP[3]	1.02	1.008-1.032	0.001	1.015	1.001-1.029	0.04
NRS at rest at POD3	1.46	1.159-1.839	0.001	1.43	1.111-1.84	0.005
NRS in motion at POD3	1.303	1.078-1.574	0.006			
Time of activity in bed	1.01	0.999-1.005	0.083			
Minimally invasive surgery	0.47	0.281-0.788	0.004	0.539	0.292-0.995	0.048
No drainage placed as usual	0.599	0.358-1.004	0.052			
Early exercise	0.553	0.319-0.958	0.035			

[1] intraoperative maximum heart ratio

[2] intraoperative maximum pulse

[3] intraoperative maximum systolic blood pressure

Figures

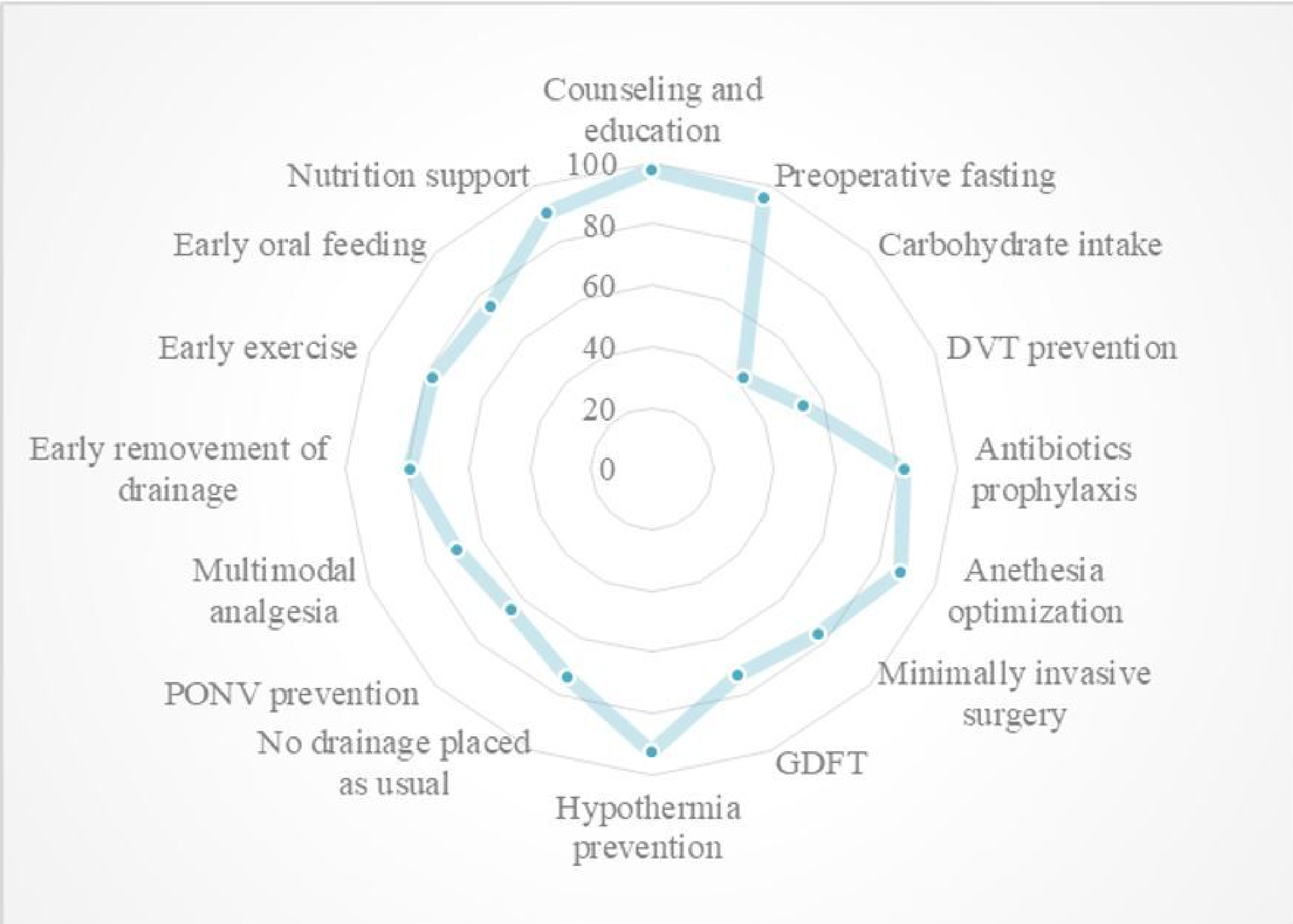

Figure 1.

Figure 1

Compliance of ERAS program.

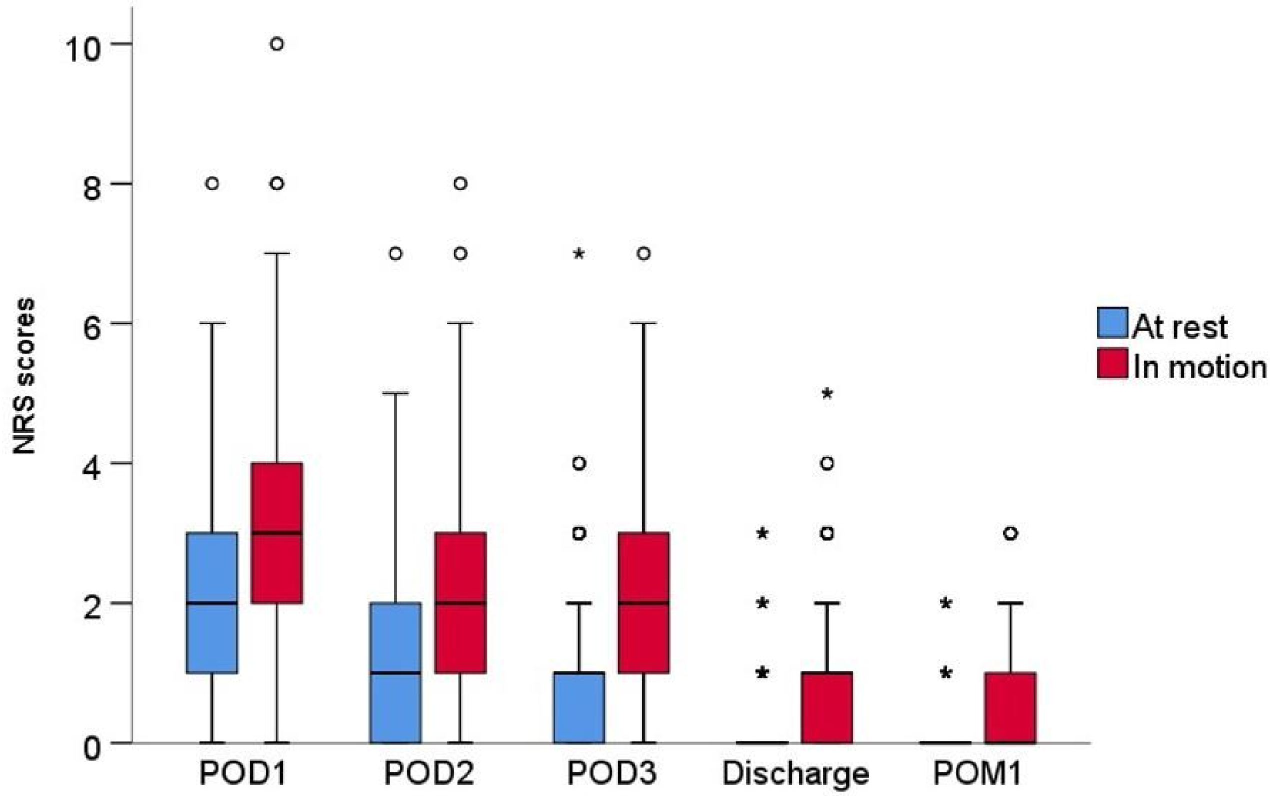

Figure 2

Figure 2

NRS scores at different times postoperatively POD 1, 2, 3: postoperative 1, 2, 3 days; POM1: postoperative 1 month.

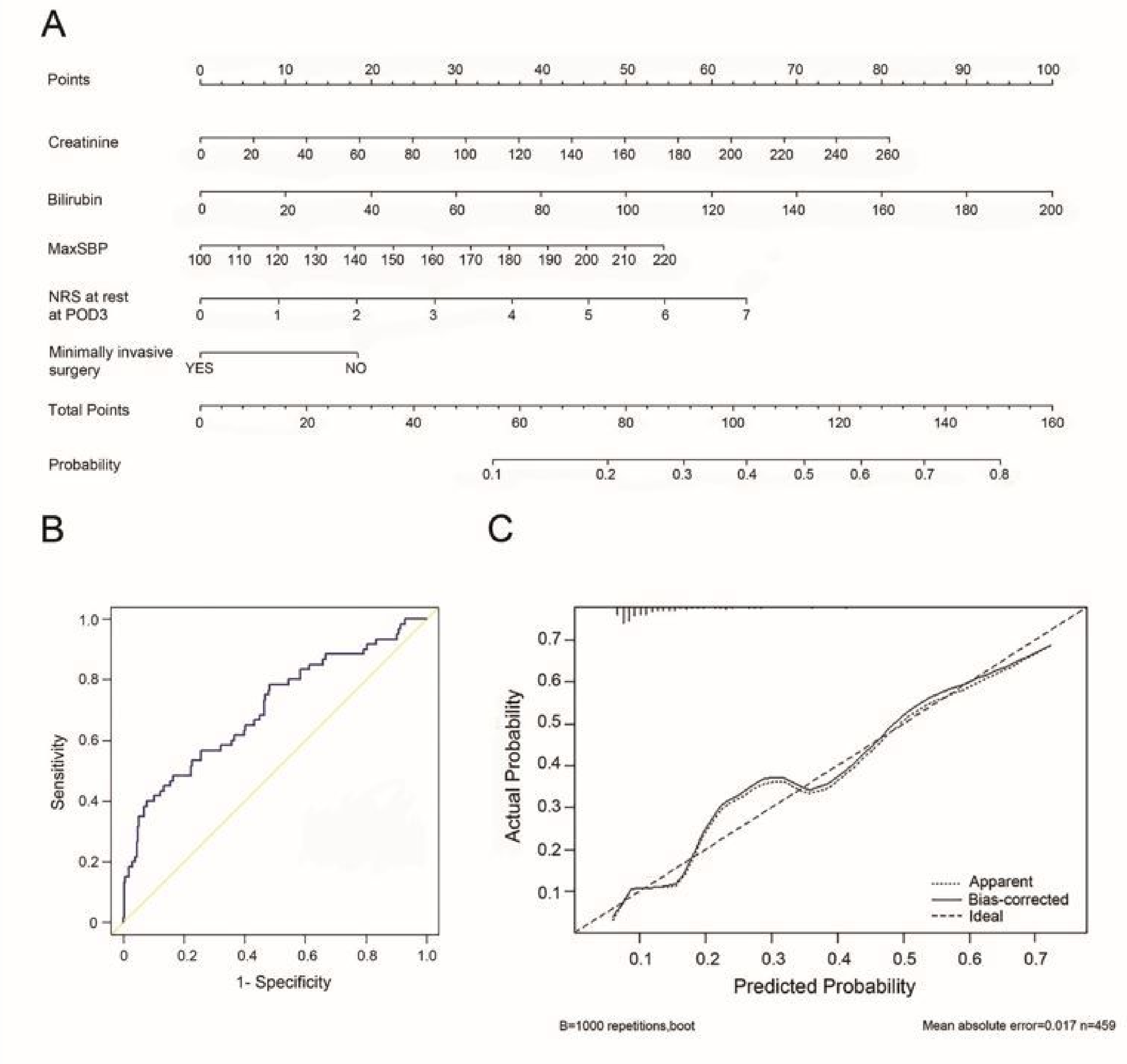

Figure 3

Figure 3

Nomogram predicting probability of complications within 1 month postoperatively in patients with ERAS program. (A) The value of each element was calculated a score on the point axis. Total points were summed with each single points, by projecting the total point to the lower probability axis, we were able to assess the probability of complications. (B) ROC for the nomogram. AUC was generally used for the discrimination evaluation for the nomogram. (C) Calibration curve for the nomogram. The x and y axia represents the predicted and actual probability of complications. Perfect prediction would correspond to the 45° line.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementaryfile.docx