Associations between intraoperative nociceptive and early postoperative C-reactive protein levels in patients undergoing non-cardiac surgery under general anesthesia

Shiroh Nakamoto
Hyogo College of Medicine
Hiroki Ogata
Hyogo College of Medicine
Ayano Saeki
Hyogo College of Medicine
Ryusuke Ueki
Hyogo College of Medicine
Nobutaka Kariya
Hyogo College of Medicine
Tsuneo Tatara
Hyogo College of Medicine
Munetaka Hirose (mhirose@hyo-med.ac.jp)
Hyogo College of Medicine https://orcid.org/0000-0003-1291-2827

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Abstract

Background: Early detection of postoperative increase in C-reactive protein (CRP) predicts complications after surgery. The preoperative and intraoperative factors associated with postoperative CRP changes are potentially significant in the prophylactic management of postoperative complications. Although ongoing nociception during surgery under general anesthesia is one of potential candidates for these factors, it has not been evaluated with the unavailability of valid nociception measures in clinical practice. Then we adopted averaged values of nociceptive response (NR) throughout surgery as intraoperative nociceptive levels, being examined the association between perioperative factors, early changes in postoperative CRP levels, and postoperative complications

Material and Methods: Data from 174 adult patients undergoing elective non-cardiac surgery under general anesthesia on perioperative variables, including age, sex, BMI, American Society of Anesthesiologists-physical status (ASA-PS), duration of surgery, mean NR during surgery as intraoperative nociceptive level, CRP levels before and after surgery on postoperative day (POD) 1, and postoperative complications using the extended Clavien-Dindo classification were retrospectively obtained in a training cohort. Multivariate regression analysis was performed to determine the independent factor of CRP levels on POD1and to develop a prediction model. In two validation cohorts, both 75 patients undergoing mastectomy (validation cohort A) and 139 patients undergoing laparoscopic or open abdominal surgery (validation cohort B) were separately selected, and retrospectively utilized to evaluate the value of the prediction model.

Results: CRP levels on POD1 in the training cohort significantly increased in the order of Clavien-Dindo grades. Multivariate regression analysis selected mean NR, BMI, and duration of surgery to set up the prediction model of CRP level on POD1, which showed significant correlation with the measured CRP in both two validation cohorts. To confirm associations between mean NR, postoperative CRP, and major complications (Clavien-Dindo grade ≥ IIIa), we performed a propensity score matching in the validation cohort B, using age, BMI, ASA-PS, and duration of operations, finding that both mean NR and CRP levels on POD1 were significantly higher in patients with major complications than those without major complications.

Conclusion: Increases in the intraoperative nociceptive level likely associated with early increases in CRP level after surgery.

Keywords: C-reactive protein, Postoperative complications, Nociception.

Background

Early diagnosis and treatment of postoperative complications is crucial for suppression of the associated morbidity and mortality. C-reactive protein (CRP) is an acute phase reactant, which increases postoperatively in response to inflammation or intraoperative tissue damage. Recently, CRP is increasingly being studied as an early marker of postoperative complications, with early detection of an

increase in CRP levels on postoperative days (POD) 1-5 reportedly being predictive of the occurrence of complications after surgery [1-7]. The preoperative and intraoperative factors associated with postoperative CRP changes are potentially significant in the prophylactic management of postoperative complications. Although intraoperative factors, including heart rate, body temperature, lactate level, base excess, and transfusion, were reported to associate with postoperative CRP elevation after cardiac surgery [8], no intraoperative parameters have been evaluated well for the association with postoperative CRP levels after non-cardiac surgery.

Nociceptive stimulation during surgery increases intraoperative inflammation and tissue damage. It activates the autonomic nervous system and the hypothalamic-pituitary-adrenal axis, inducing potentially harmful outcomes such as cardiac dysfunction, vascular instability, or coagulopathy [9]. Therefore, we hypothesized that ongoing nociception during surgery under general anesthesia would be one of the candidates for intraoperative factors associating with postoperative CRP elevation.

Intraoperative nociceptive level, however, has not been evaluated for those factors with a result of the unavailability of valid nociception measures during surgery under general anesthesia [10]. Several nociceptive indices using variables derived from autonomic responses indicate the degree of nociceptive stimulation under general anesthesia. The analgesia nociception index (ANI) is calculated from heart rate variability [11], and the surgical pleth index (SPI) is calculated using photoplethysmographic pulse wave amplitude and heart beat interval [12]. Recently, we developed the nociceptive response (NR) for the evaluation of nociceptive levels under general anesthesia, which is calculated using the variables of heart rate, systolic blood pressure, and perfusion index [13]. Given that nociceptive indices likely correspond to the intensity of inflammation or tissue damage during surgery under general anesthesia [13], we considered that an averaged value of the NR throughout surgery under general anesthesia represent the intraoperative nociceptive level in each surgery.

To reveal the relationship between intraoperative nociceptive levels under general anesthesia with early postoperative C-reactive protein levels, we developed and validated a prediction model for CRP levels on POD1 in training and validation cohorts, and investigated the association between perioperative risk factors, CRP levels on POD1, and postoperative complications after non-cardiac surgery under general anesthesia.

Methods

This retrospective cohort study was approved by the Ethics Committee of Hyogo College of Medicine (#2566). We obtained clinical data of patients who underwent surgery at Surgical Center of Hyogo College of Medicine Hospital. As American Society of Anesthesiologists-physical status (ASA-PS) and preoperative CRP levels were reported to associate strongly with postoperative complications [14-17], we determined eligibility criteria for the present study as the following: age over 20 years, ASA-PS I–II, and preoperative CRP level <0.3 $mg \cdot dL^{-1}$. In a training cohort to develop the prediction model, patients who underwent elective mastectomy, spine surgery, laparoscopic surgery, open abdominal surgery, or thoracic

surgery, were selected from November 2017 to December 2017, as CRP levels on POD1 were routinely measured after those surgeries. In two validation cohorts to verify the value of the prediction model, patients who underwent elective mastectomy (validation cohort A), and also patients who underwent elective laparoscopic or open abdominal surgery (validation cohort B), were selected from May 2018 to August 2018.

Perioperative management

All patients did not receive premedication. General anesthesia was induced with propofol, fentanyl and rocuronium, followed by insertion of a tracheal tube, and was maintained with sevoflurane / desflurane, fentanyl, rocuronium and a continuous infusion of remifentanil. The doses of remifentanil and fentanyl were adjusted to maintain mean blood pressure within a range of ± 20% of the pre-anesthesia level. Additional regional anesthesia was determined by anesthesiologists in charge. Bispectral index was maintained between 40 and 60 by adjusting the concentration of sevoflurane / desflurane. Rocuronium bromide was used for muscle relaxation during surgery, as needed. After surgery, continuous administration intravenous fentanyl, 25 – 50 $\mu g.hr^{-1}$, was routinely performed until POD 1-2 for postoperative analgesia. Intravenous flurbiprofen axetil or acetaminophen was used for rescue analgesia after surgery.

Data collection

Information on serum concentrations of CRP before surgery and POD1, and complications occurring during hospitalization within 30 days after surgery were obtained from our institutional medical records. The normal range for CRP at our institution is below 0.3 $mg{\cdot}dL^{-1}$. Postoperative complications were graded according to the extended Clavien-Dindo classification [18]. Major complication was defined as the extended Clavien-Dindo grade IIIa or greater.

Intraoperative nociceptive level

Figure 1 shows a typical anesthetic record, representing NR, SBP, HR, and PI during general anesthesia. The NR value typically decreases from 0.9 to 0.6-0.7 after induction of anesthesia, and then increases after tracheal intubation. At the time of skin incision, it increases again, then keeping around 0.7-0.9 during surgery. The NR value was calculated using the following hemodynamic equation: NR = -1 + 2 / (1 + exp (-0.01HR – 0.02SBP + 0.17PI)) [13]. NR value represents no nociceptive stimulus under 0.70, minor noxious stimulus like very small incision between 0.70 and 0.75, moderate noxious stimulus like laparoscopic surgery between 0.75 and 0.85, severe noxious stimulus like open abdominal surgery between 0.85and 0.90, and extreme noxious stimulus over 0.90. After we installed the equation of NR on our institutional anesthesia information managing system (ORSYS, PHILIPS, Amsterdam, Netherlands), the averaged value of NR data from the start to end of surgery (mean NR), which was considered the intraoperative nociceptive level, was obtained using the data-search software (Vi-Pros, Dowell, Sapporo, Japan) (Figure 1).

Statistics

All statistical testing was two-sided with a significance level of 5% and was performed using JMS Pro version 13.1.0 (SAS Institute Inc. Cary, NC, United States). To investigate the association between CRP levels on POD1 and preoperative/intraoperative variables (age, sex, BMI, ASA-PS, duration of operation, mean NR, and preoperative CRP level), we performed multiple linear regression analyses in the training cohort, and then developed the prediction model for CRP level on POD1. The prediction model was applied on two validation cohorts to evaluate its value using linear regression analysis between measured and predicted CRP levels. After 3 variables of BMI, duration of surgery, and mean NR were selected to construct the prediction model, we performed propensity score matching of patients who did and did not suffered major complications after surgery in the validation cohort B to confirm the associations between intraoperative nociceptive levels, postoperative CRP levels, and postoperative complications (Complication and Control groups, respectively). Propensity score was calculated by logistic regression analysis using age, BMI, ASA-PS, and duration of surgery as independent variables. Patients with major complications (Complication group) whose propensity scores deviated by more than 0.02 from those without major complications (Control group) were considered unmatched. The unpaired t-test, the chi-square test, the one-way ANOVA followed by Tukey's test, or the Kruskal-Wallis test and the Mann-Whitney U-test, were used to compare appropriate variables. The prediction of major complications using this model was evaluated in the validation cohort B using a receiver-operating characteristic (ROC) curve analysis.

Results

Postoperative CRP levels and Clavien-Dindo classification

A total of 174 patients in the training cohort were assessed for eligibility (Table 1). The number of operations selected were 58 for mastectomy, 34 for spine surgery, 40 for laparoscopic surgery, 24 for open abdominal surgery, and 18 for thoracic surgery. Laparoscopic surgery included colectomy, gastrectomy, hysterectomy, cholecystectomy, and hepatic resection. Open abdominal surgery included colectomy, gastrectomy, hysterectomy, and hepatic resection. Prevalence of complications graded by the extended Clavien-Dindo classification were 57.2% in grade I, 30.1% in grade II, and 4.0% in grade IIIa. No patients showed grade over IIIb. There were no postoperative complications in 8.7% of patients. Postoperative CRP levels significantly increased in the order of Clavien-Dindo grades (Figure 2). CRP levels on POD1 at Clavien-Dindo Grade II and IIIa were both significantly higher than those without postoperative complications.

Development of prediction model

We performed multivariate linear regression analysis to explore predictive factors for the increase in postoperative CRP levels, which showed that CRP levels on POD1 were significantly associated with the duration of surgery, mean NR value during surgery, and BMI (Table 2). The prediction model was

developed as follows: predicted CRP level on POD1 = -7.473 + 7.261 x Mean NR + 0.087 x BMI ($kg \cdot m^2$) + 0.007 x Duration of surgery (min).

Validation of prediction model

To validate the prediction model, we selected two cohorts of patients undergoing mastectomy, of which intraoperative nociceptive levels were expected to be low, and patients undergoing elective laparoscopic or open abdominal surgery, of which intraoperative nociceptive levels were expected to be high. In a total of 80 patients undergoing mastectomy, 75 patients in the validation cohort A were assessed for eligibility (Table 1). In a total of 399 patients undergoing elective laparoscopic or open abdominal surgery, 139 patients in the validation cohorts B were assessed for eligibility (Table 1, Figure 3). The number of operations selected were 87 for laparoscopic surgery and 52 for open abdominal surgery. Age, mean NR, and CRP level on POD1 in the validation cohort A were significantly lower than those in the training cohort (Table 1). Duration of surgery, mean NR, and CRP level on POD1 in the validation cohort B were significantly higher than those in the training cohort and the validation cohort A. The incidence of major complications in the validation cohort B was also significantly higher than that in the validation cohort A (Table 1). Predicted CRP levels on POD1 showed a significant correlation with measured CRP levels on POD1 in both validation cohorts (Figure 4).

Propensity score analysis

The complication group (n = 11) in the validation cohort B, where patients suffered major complications (Clavien-Dindo grade ≥IIIa), showed longer duration of surgery and higher levels of perioperative CRP than the control group (n = 128) before propensity score matching (Table 3). After propensity score matching, 11 patients in each group were selected (Figure 3). Although there were no significant differences in BMI and duration of surgery between two groups, mean NR and CRP levels on POD1 showed significantly higher in the complication group than those in the control group. There was no significant difference in the number of rescue analgesia of acetaminophen and /or flurbiprofen axetil, used on POD1, between the control and complication groups (Table 4).

Prediction of major complications

Figure 5 shows ROC curves for prediction of major complications with measured and predicted CRP levels on POD1. The area under the curve (AUC) obtained in the ROC curve was 0.75 for the measured CRP level (P=0.005) and 0.69 for the predicted CRP level (P=0.049).

Discussion

In the present study involving ASA-PS I–II adult patients with preoperative CRP levels <0.3 mg/dL undergoing non-cardiac surgery, the prediction model using mean NR, duration of surgery, and BMI was evaluated to be eligible for the prediction of CRP levels on POD1 in patients undergoing mastectomy and also in patients undergoing laparoscopic or open abdominal surgery. Higher mean intraoperative NR

value, longer surgical duration, and higher BMI significantly correlated with the higher CRP value on POD1 in both cohorts. High levels of mean NR during surgery correlated to high levels of CRP after surgery and high incidence of major complications.

Although either longer duration of surgery or obesity has been reported to be a risk factor for postoperative complications [18-21], intraoperative nociceptive level has not been evaluated. The degree of inflammation or tissue damage caused by surgical trauma affects both the intraoperative nociceptive level [13] and postoperative CRP level [9]. Given that minimizing surgical trauma by performing laparoscopy instead of open surgery reportedly reduces early postoperative CRP levels [22-24], it seems plausible that the mean NR value for possible estimation of the intraoperative nociceptive level was selected as one of intraoperative factors for the prediction of early postoperative CRP level in the present study.

Preoperative increase in CRP levels is known to predict postoperative complications [25-27]. As high preoperative CRP levels may induce an increase in postoperative CRP levels, we selected patients with ASA-PS I/II whose preoperative CRP levels were within the normal range to eliminate the confounding effect of preoperative CRP elevation in the present study. Prevalence of major complications, which is defined as Clavien-Dindo grade ≥IIIa, reportedly ranged from 8.1 to 39.3% after laparoscopic or open abdominal surgery [15, 18, 28]. In the present study, however, the prevalence was 7.9% after laparoscopic or open abdominal surgery. This lower level of prevalence of major complications, compared to the previous reports, might be caused by our selection criteria of patients without serious preoperative conditions or comorbidities. This and the previous discussion suggest that the effects of serious preoperative conditions or comorbidities, if any, might exceed the effects of intraoperative nociceptive level, duration of surgery, and BMI on early CRP levels after surgery.

Perioperative managements reducing early postoperative CRP levels could prevent postoperative complications. Previously, reduction of surgical invasion [29-31], administration of non-steroidal anti-inflammatory drug [32], steroid [33], or β-blocker [34], and Enhanced Recovery After Surgery (ERAS) protocol [31, 35], were reported to reduce postoperative CRP levels. Although the effects of anesthetic managements on postoperative CRP levels are controversial so far [36, 37], combination with these perioperative managements are required for anesthetic management to reduce postoperative CRP levels for prevention of major complications after surgery. Further study is needed to examine the effects of NR-guided anesthetic management, where the NR value is used as an index of nociception during surgery, on CRP levels after surgery.

A limitation of this study is a retrospective study. Higher surgical invasion increases intraoperative nociceptive levels causing postoperative complications, likely augmenting acute postoperative pain [9]. Postoperative analgesia in patients without major complications after laparoscopic or open abdominal surgery, however, was similar in patients with major complications, whose mean NR and postoperative CRP were higher than those without major complications in the present study. Several factors reportedly affect acute postoperative pain, including psychiatric comorbidities, opioid use, preoperative pain,

surgical procedures, and pain management [38]. As our study was retrospectively performed, there are potential reasons for no significant difference in postoperative analgesia, such as small number of patients, case mix of anesthetic managements and surgical procedures, no assessments of pain intensity, and no psychological assessments. Further investigation is needed to examine the association between intraoperative nociceptive levels and postoperative pain in a prospective study.

Another limitation of this study is that the present results cannot be applied to surgery under regional anesthesia in the conscious state. Although the NR value varied between 0.6 and 0.9 during surgery under general anesthesia in the unconscious state, only a few of the values ranged around 0.9, which is the level corresponding to the levels in the awake state without nociceptive stimulation, as well as during surgery in the conscious state under regional anesthesia (data not shown). Similar results have also been reported with other nociceptive indices using variables derived from autonomic responses to nociceptive stimuli, such as SPI and ANI values in the conscious state [39-43]. Recently, Lichtner et al. examined the transmission of somatosensory stimuli from the spinal cord to the brain with and without propofol anesthesia in humans, showing that although the somatosensory processing induced by moderate noxious stimulation was suppressed depending on the propofol concentration, intense noxious stimuli induced somatosensory cortical processing even under deep propofol anesthesia [44]. They also found that somatosensory signal transmission depends on the intensity of noxious stimuli under the same propofol concentration [44]. Therefore, increases in the depth of general anesthesia likely suppress somatosensory processing in the brain in a dose-dependent manner. Conversely, somatosensory processing under general anesthesia likely occurs in an intensity-dependent manner. Considering the fact that transmission of somatosensory stimuli in the central nervous system would depend on the balance between depth of anesthesia and intensity of noxious stimuli, somatosensory processing in the conscious state would always reach the parts of the brain with higher-order functions regardless of the intensity of noxious stimuli, the processing reaching close to these parts of the brain after intense noxious stimulation under general anesthesia. Taken together, nociceptive indices using autonomic responses (e.g., SPI, ANI, NR) represent the competence of somatosensory processing in the central nervous system. Therefore, the association of intraoperative nociceptive levels with postoperative CRP levels cannot be applied to surgery under regional anesthesia in the awake state. Further investigation is needed to validate this hypothesis.

Conclusions

The nociceptive level during surgery under general anesthesia, the duration of surgery, and BMI likely correlate with early CRP changes after surgery in patients without serious preoperative conditions or comorbidities. This association can be applied to both surgeries with low and high nociceptive levels.

Abbreviations

ANI: analgesia nociception index, ASA-PS: American Society of Anesthesiologists physical status, BMI: body mass index, CRP: C-reactive protein, NR: nociceptive response, POD: postoperative day, SPI: surgical

pleth index.

Declarations

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References

1. Straatman J, Harmsen AM, Cuesta MA, Berkhof J, Jansma EP, van der Peet DL. Predictive value of C-reactive protein for major complications after major abdominal surgery: a systematic review and pooled-analysis. PLoS One. 2015 ;10: e0132995. doi: 10.1371/journal.pone.0132995.

2. Kano K, Aoyama T, Nakajima T, Maezawa Y, Hayashi T, Yamada T, Sato T, Oshima T, Rino Y, Masuda M, Cho H, Yoshikawa T, Ogata T. Prediction of postoperative inflammatory complications after esophageal cancer surgery based on early changes in the C-reactive protein level in patients who received perioperative steroid therapy and enhanced recovery after surgery care: a retrospective analysis. BMC Cancer. 2017 ;17: 812. doi: 10.1186/s12885-017-3831-2.

3. Vasunilashorn SM, Dillon ST, Inouye SK, Ngo LH, Fong TG, Jones RN, Travison TG, Schmitt EM, Alsop DC, Freedman SD, Arnold SE, Metzger ED, Libermann TA, Marcantonio ER. High C-Reactive protein predicts delirium incidence, duration, and feature severity after major noncardiac surgery. J Am Geriatr Soc. 2017; 65: e109-16. doi: 10.1111/jgs.14913.

4. Cabellos Olivares M, Labalde Martínez M, Torralba M, Rodríguez Fraile JR, Atance Martínez JC. C-reactive protein as a marker of the surgical stress reduction within an ERAS protocol (Enhanced Recovery After Surgery) in colorectal surgery: A prospective cohort study. J Surg Oncol. 2018; 117: 717-24. doi: 10.1002/jso.24909.

5. Kröll D, Nakhostin D, Stirnimann G, Erdem S, Haltmeier T, Nett PC, Borbély YM. C-Reactive protein on postoperative day 1: a predictor of early intra-abdominal infections after bariatric surgery. Obes Surg. 2018; doi: 10.1007/s11695-018-3240-x

6. Schutz R, Boukebous B, Boutroux P, Guillon P. C-reactive protein levels for early detection of early postoperative complications after proximal femoral fracture surgery. Eur J Orthop Surg Traumatol. 2018; 28: 907-13. doi: 10.1007/s00590-017-2080-z.

7. Straatman J, Cuesta MA, Tuynman JB, Veenhof AAFA, Bemelman WA, van der Peet DL. C-reactive protein in predicting major postoperative complications are there differences in open and minimally invasive colorectal surgery? Substudy from a randomized clinical trial. Surg Endosc. 2018; 32 :2877-85. doi: 10.1007/s00464-017-5996-9.

8. Min JJ, Nam K, Kim TK, Kim HJ, Seo JH, Hwang HY, Kim KB, Murkin JM, Hong DM, Jeon Y. Relationship between early postoperative C-reactive protein elevation and long-term postoperative major adverse cardiovascular and cerebral events in patients undergoing off-pump coronary artery bypass graft surgery: a retrospective study. Br J Anaesth. 2014; 113: 391-401. doi: 10.1093/bja/aeu099.

9. Dobson GP. Addressing the global burden of trauma in major surgery. Front Surg 2015; 2; 43.

10. 10. Lichtner G, Auksztulewicz R, Velten H, Mavrodis D, Scheel M, Blankenburg F, von Dincklage F. Nociceptive activation in spinal cord and brain persists during deep general anesthesia. Br J Anaesth. 2018; 121: 291-302. doi: 10.1016/j.bja.2018.03.031.

11. 11. Logier R, Jeanne M, Tavernier B, De Jonckheere J. Pain/analgesia evaluation using heart rate variability analysis. Conf Proc IEEE Eng Med Biol Soc. 2006; 1: 4303-6. doi: 1109/IEMBS.2006.260494.

12. 12. Huiku M, Uutela K, van Gils M, Korhonen I, Kymäläinen M, Meriläinen P, Paloheimo M, Rantanen M, Takala P, Viertiö-Oja H, Yli-Hankala A. Assessment of surgical stress during general anaesthesia. Br J Anaesth. 2007; 98: 447-55. doi: 1093/bja/aem004.

13. 13. Hirose M, Kobayashi Y, Nakamoto S, Ueki R, Kariya N, Tatara T. Development of a Hemodynamic Model Using Routine Monitoring Parameters for Nociceptive Responses Evaluation During Surgery Under General Anesthesia. Med Sci Monit. 2018; 24: 3324-31. doi: 10.12659/MSM.907484.

14. 14. Perry TE, Muehlschlegel JD, Liu KY, Fox AA, Collard CD, Body SC, Shernan SK; CABG Genomics Investigators. Preoperative C-reactive protein predicts long-term mortality and hospital length of stay after primary, nonemergent coronary artery bypass grafting. Anesthesiology. 2010; 112: 607-13. doi: 10.1097/ALN.0b013e3181cea3b5.

15. 15. Ishino Y, Saigusa S, Ohi M, Yasuda H, Tanaka K, Toiyama Y, Mohri Y, Kusunoki M. Preoperative C-reactive protein and operative blood loss predict poor prognosis in patients with gastric cancer after laparoscopy-assisted gastrectomy. Asian J Endosc Surg. 2014; 7: 287-94. doi: 10.1111/ases.12126.

16. 16. Hackett NJ, De Oliveira GS, Jain UK1, Kim JY. ASA class is a reliable independent predictor of medical complications and mortality following surgery. Int J Surg. 2015; 18: 184-90. doi: 10.1016/j.ijsu.2015.04.079.

17. 17. Zhang R, Kyriss T, Dippon J, Hansen M, Boedeker E, Friedel G. American Society of Anesthesiologists physical status facilitates risk stratification of elderly patients undergoing thoracoscopic lobectomy. Eur J Cardiothorac Surg. 2018; 53: 973-9. doi: 10.1093/ejcts/ezx436.

18. 18. Katayama H, Kurokawa Y, Nakamura K, Ito H, Kanemitsu Y, Masuda N, Tsubosa Y, Satoh T, Yokomizo A, Fukuda H, Sasako M. Extended Clavien-Dindo classification of surgical complications:

Japan Clinical Oncology Group postoperative complications criteria. Surg Today. 2016; 46: 668-85. doi: 10.1007/s00595-015-1236-x.

19. 19. Scilletta R, Pagano D, Spada M, Mongiovì S, Pesce A, Portale TR, Guardabasso V, Puleo S, Gruttadauria S. Comparative analysis of the incidence of surgical site infections in patients with liver resection for colorectal hepatic metastases after neoadjuvant chemotherapy. J Surg Res. 2014; 188: 183-9. doi: 10.1016/j.jss.2013.11.1092.

20. 20. Amisaki M, Saito H, Tokuyasu N, Sakamoto T, Honjo S, Fujiwara Y. Prognostic value of postoperative complication for early recurrence after curative resection of hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int. 2018; 17: 323-9. doi: 10.1016/j.hbpd.2018.03.016.

21. 21. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC.Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg. 2015; 102: 462-79. doi: 10.1002/bjs.9697.

22. 22. Atabekoglu C, Sönmezer M, Güngör M, Aytaç R, Ortaç F, Unlü C. Tissue trauma in abdominal and laparoscopic-assisted vaginal hysterectomy. J Am Assoc Gynecol Laparosc. 2004; 11: 467-72. PMID: 15701187.

23. 23. Demir A, Bige O, Saatli B, Solak A, Saygili U, Onvural A. Prospective comparison of tissue trauma after laparoscopic hysterectomy types with retroperitoneal lateral transsection of uterine vessels using ligasure and abdominal hysterectomy. Arch Gynecol Obstet. 2008; 277: 325-30. doi: 1007/s00404-007-0485-3.

24. 24. Liang F, Xu X, Liang Comparison of Intraoperative Indicators and Postoperative Efficacy in Treatment of Benign Ovarian Tumor: Laparoscopy Versus Open Surgery. Am J Ther. 2017; 24: e681-8. doi: 10.1097/MJT.0000000000000367.

25. 25. Liu SA, Liang MT, Wang CP, Wang CC, Lin WD, Ho HC, Chiu YT. Preoperative blood sugar and C-reactive protein associated with persistent discharge after incision and drainage for patients with deep neck abscesses.Clin Otolaryngol. 2009; 34: 336-42. doi: 10.1111/j.1749-4486.2009.01972.x.

26. 26. Choi ES, Kim HS, Han I. Elevated preoperative systemic inflammatory markers predict poor outcome in localized soft tissue sarcoma. Ann Surg Oncol. 2014; 21: 778-85. doi: 10.1245/s10434-013-3418-3.

27. 27. Mansukhani V, Desai G, Shah R, Jagannath P. The role of preoperative C-reactive protein and procalcitonin as predictors of post-pancreaticoduodenectomy infective complications: A prospective observational study. Indian J Gastroenterol. 2017; 36: 289-95. doi: 10.1007/s12664-017-0770-4.

28. Kim DJ, Lee JH, Kim W. Comparison of the major postoperative complications between laparoscopic distal and total gastrectomies for gastric cancer using Clavien-Dindo classification. Surg Endosc 2015; 29: 3196-204.

29. Karayiannakis AJ, Makri GG, Mantzioka A, Karousos D, Karatzas G. Systemic stress response after laparoscopic or open cholecystectomy: a randomized trial. Br J Surg 1997; 84: 467-71.

30. Demir A, Bige O, Saatli B, Solak A, Saygili U, Onvural A. Prospective comparison of tissue trauma after laparoscopic hysterectomy types with retroperitoneal lateral transsection of uterine vessels using ligasure and abdominal hysterectomy. Arch Gynecol Obstet 2008; 277: 325-30.

31. Cabellos Olivares M, Labalde Martínez M, Torralba M, Rodríguez Fraile JR, Atance Martínez JC. C-reactive protein as a marker of the surgical stress reduction within an ERAS protocol (Enhanced Recovery After Surgery) in colorectal surgery: A prospective cohort study. J Surg Oncol 2018; 117: 717-24.

32. Esme H, Kesli R, Apiliogullari B, Duran FM, Yoldas B. Effects of flurbiprofen on CRP, TNF-α, IL-6, and postoperative pain of thoracotomy. Int J Med Sci 2011; 8: 216-21.

33. Maruta K, Aoki A, Omoto T, Iizuka H, Kawaura H. The Effect of Steroid Therapy on Postoperative Inflammatory Response after Endovascular Abdominal Aortic Aneurysm Repair. Ann Vasc Dis 2016; 9: 168-72.

34. Kim Y, Hwang W, Cho ML, Her YM, Ahn S, Lee J. The effects of intraoperative esmolol administration on perioperative inflammatory responses in patients undergoing laparoscopic gastrectomy: a dose-response study. Surg Innov 2015; 22: 177-82.

35. Mari G, Costanzi A, Crippa J, Falbo R, Miranda A, Rossi M, Berardi V, Maggioni D. Surgical Stress Reduction in Elderly Patients Undergoing Elective Colorectal Laparoscopic Surgery within an ERAS Protocol. Chirurgia (Bucur) 2016; 111: 476-80.

36. Fant F, Tina E, Sandblom D, Andersson SO, Magnuson A, Hultgren-Hörnkvist E, Axelsson K, Gupta A. Thoracic epidural analgesia inhibits the neuro-hormonal but not the acute inflammatory stress response after radical retropubic prostatectomy. Br J Anaesth 2013; 110: 747-57.

37. Kuchálik J, Magnuson A, Tina E, Gupta A. Does local infiltration analgesia reduce peri-operative inflammation following total hip arthroplasty? A randomized, double-blind study. BMC Anesthesiol 2017; 17: 63.

38. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, Carter T, Cassidy CL, Chittenden EH, Degenhardt E, Griffith S, Manworren R, McCarberg B, Montgomery R, Murphy J, Perkal MF, Suresh S, Sluka K, Strassels S, Thirlby R, Viscusi E, Walco GA, Warner L, Weisman SJ, Wu CL. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 2016; 17: 131-57.

39. 39. Ryu KH, Song K, Lim TY, Choi WJ, Kim YH, Kim HS. Does Equi-Minimum Alveolar Concentration Value Ensure Equivalent Analgesic or Hypnotic Potency?: A Comparison between Desflurane and Sevoflurane. 2018; 128: 1092-8. doi: 10.1097/ALN.0000000000002158.

40. 40. Ilies C, Gruenewald M, Ludwigs J, Thee C, Höcker J, Hanss R, Steinfath M, Bein B. Evaluation of the surgical stress index during spinal and general anesthesia. Br J Anaesth. 2010; 105: 533-7. doi: 10.1093/bja/aeq203.

41. 41. Boselli E, Musellec H, Martin L, Bernard F, Fusco N, Guillou N, Hugot P, Paqueron X, Yven T, Virot C. Effects of hypnosis on the relative parasympathetic tone assessed by ANI (Analgesia/Nociception Index) in healthy volunteers: a prospective observational study. J Clin Monit Comput. 2018; 32: 487-92. doi: 10.1007/s10877-017-0056-5.

42. 42. Jess G, Pogatzki-Zahn EM, Zahn PK, Meyer-Frieβem CH. Monitoring heart rate variability to assess experimentally induced pain using the analgesia nociception index. Eur J Anaesthesiol. 2016; 33: 118-25. doi: 10.1097/EJA.0000000000000304.

43. 43. Issa R, Julien M, Décary E, Verdonck O, Fortier LP, Drolet P, Richebé P. Evaluation of the analgesia nociception index (ANI) in healthy awake volunteers. Can J Anaesth. 2017; 64: 828-35. doi: 10.1007/s12630-017-0887-z.

44. 44. Lichtner G, Auksztulewicz R, Kirilina E, Velten H, Mavrodis D, Scheel M, Blankenburg F, von Dincklage F. Effects of propofol anesthesia on the processing of noxious stimuli in the spinal cord and the brain. Neuroimage. 2018; 172: 642-53. doi: 10.1016/j.neuroimage.2018.02.003.

Tables

Table 1. Comparison of patient demographics between training and validation cohorts

Variables	Training cohort (n = 174)	Validation cohort A (n = 75)	Validation cohort B (n = 139)
Age (years)	61 ± 14	56 ± 13*	61 ± 15
Sex (M/F)	68/106	2/73**	69/66$^{\#\#}$
BMI	22.5 ± 3.2	21.9 ± 3.4	22.5 ± 3.6
ASA-PS I/II	27/147	23/52**	17/118$^{\#\#}$
Duration of surgery (min)	192 ± 114	160 ± 96	256 ± 143$^{**\#\#}$
Mean NR	0.801 ± 0.057	0.760 ± 0.066**	0.816 ± 0.051$^{*\#\#}$
Preoperative CRP level (mg•dL^{-1})	0.07 ± 0.08	0.06 ± 0.11	0.07 ± 0.06
CRP level on POD1 (mg•dL^{-1})	1.64 ± 2.20	0.62 ± 0.81**	2.77 ± 2.94$^{**\#\#}$
Major complications (n(%))	7(4.0)	0(0.0)	11(7.9) $^{\#}$

Data are presented as mean ± SD. ASA-PS: American Society of Anesthesiologists physical status, BMI: body mass index, CRP: C-reactive protein, NR: nociceptive response, POD: postoperative day. $^{*}P<0.05$ and $^{**}P<0.01$ vs. Training cohort, $^{\#}P<0.05$ and $^{\#\#}P<0.01$ vs. Validation cohort A are significant.

Table 2. Multivariate linear regression analysis of the association between CRP levels on POD1 and perioperative variables in training cohort

Variables	β	*P*
Age (years)	-0.073	0.338
Sex (M/F)	-0.056	0.436
BMI	0.129	0.069*
ASA-PS (I/II)	0.035	0.621
Duration of surgery (min)	0.346	0.001*
Mean NR	0.205	0.009*

Data are presented as standardized beta coefficient (β). CRP: C-reactive protein, NR: nociceptive response, POD: postoperative day. $^{*}P<0.10$ on multivariate analysis.

Table 3. Variables before propensity score matching in validation cohort B

	Control group (n = 128)	Complication group (n = 11)	*P* value
Age (yrs)	61 ± 14	66 ± 16	0.252
Gender (Female / Male)	63/65	5/6	0.792
BMI ($kg \cdot m^{-2}$)	22.5 ± 3.5	22.6 ± 4.8	0.908
ASA-PS I/II	18/110	0/11	0.195
Duration of surgery (min)	249 ± 143	350 ± 121	0.028*
Mean NR	0.815 ± 0.050	0.841 ± 0.035	0.355
Preoperative CRP level ($mg \cdot dL^{-1}$)	0.07 ± 0.13	0.14 ± 0.13	0.046*
CRP level on POD1 ($mg \cdot dL^{-1}$)	2.48 ± 2.55	6.40 ± 4.83	0.001**

ASA-PS: American Society of Anesthesiologists – Physical status, BMI: body mass index, CRP: C-reactive protein, NR: Nociceptive Response, POD: postoperative day. $^{*}P<0.05$ and $^{**}P<0.01$ are significant.

Table 4. Variables after propensity score matching in validation cohort B

	Control group (n = 11)	Complication group (n = 11)	*P* value
Age (yrs)	65 ± 17	66 ± 16	0.862
Gender (Female / Male)	2/9	5/6	0.170
BMI ($kg•m^{-2}$)	23.6 ± 2.7	22.6 ± 4.8	0.632
ASA-PS I/II	0/11	0/11	1.000
Duration of Operation (min)	375 ± 181	350 ± 121	0.712
Mean NR	0.806 ± 0.033	0.841 ± 0.035	0.026*
Preoperative CRP level ($mg•dL^{-1}$)	0.08 ± 0.13	0.14 ± 0.13	0.073
CRP level on POD1 ($mg•dL^{-1}$)	2.01 ± 1.25	6.40 ± 4.83	0.009**
Acetaminophen and/or flurbiprofen axetil as needed on POD1 (yes/no)	6/5	7/4	0.665

ASA-PS: American Society of Anesthesiologists – Physical status, BMI: body mass index, CRP: C-reactive protein, NR: Nociceptive Response, POD: postoperative day. $^{*}P<0.05$ and $^{**}P<0.01$ are significant.

Figures

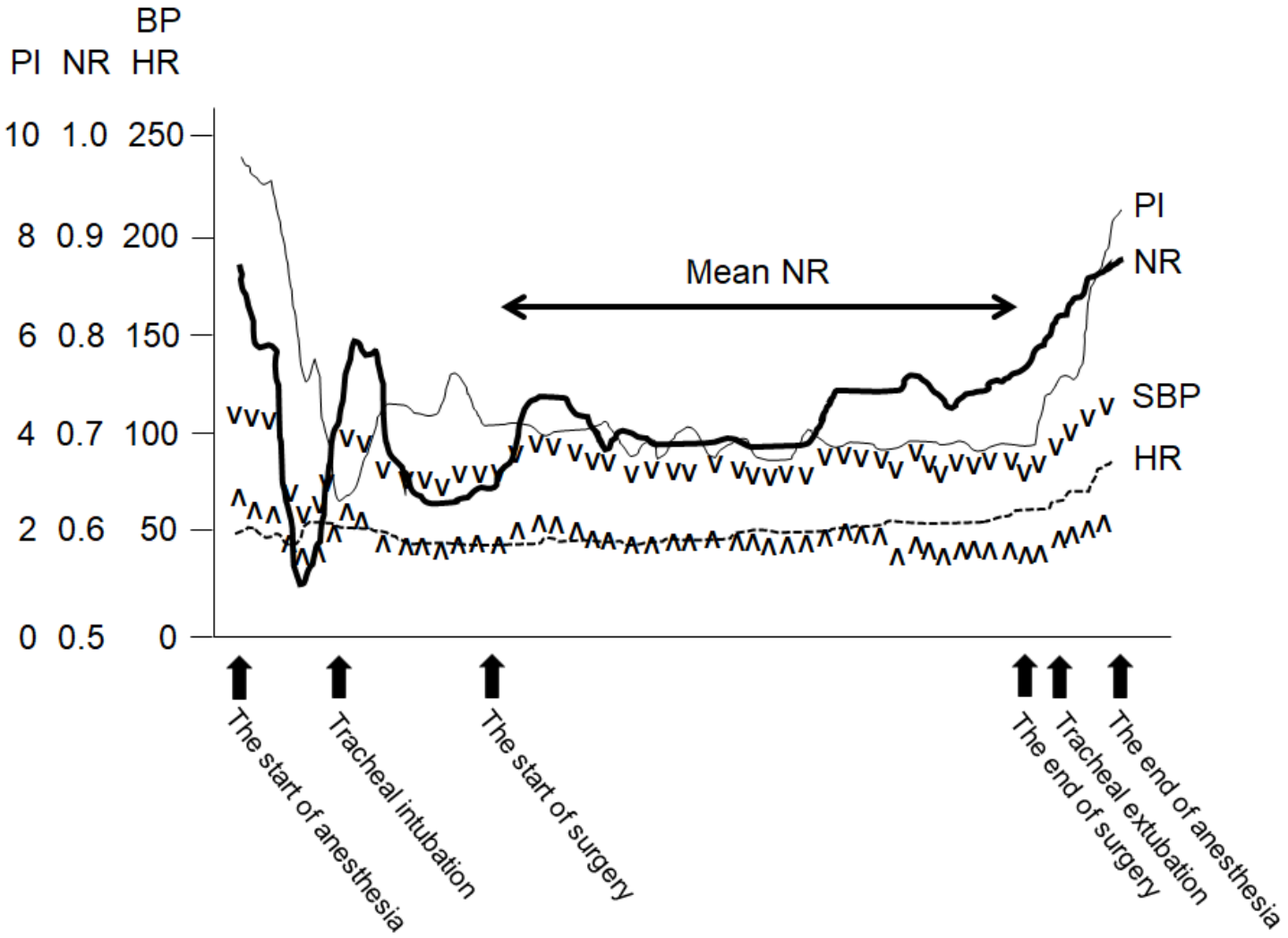

Figure 1

Representative anesthesia record. A bold line shows NR, a thin line shows PI, and a dotted line shows HR. BP: blood pressure, HR: heart rate, NR: nociceptive response, PI: perfusion index, SBP: systolic blood pressure. Mean NR is calculated by the averaged values of NR from the start to end of surgery.

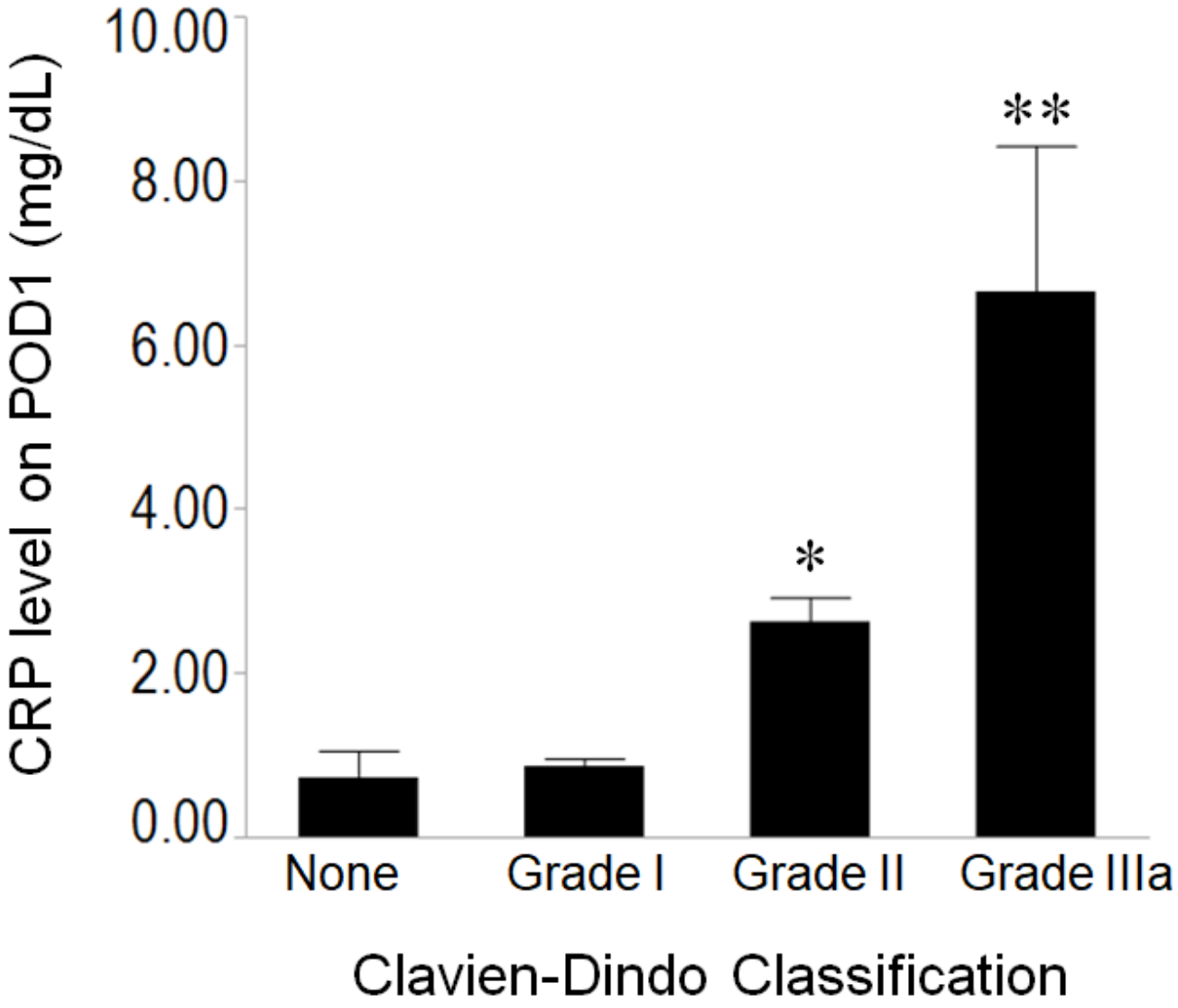

Figure 2

CRP levels on POD1 and Clavien-Dindo classification in the training cohort. CRP: C-reactive protein, POD: postoperative day. *P<0.05 and **P<0.01 are significant.

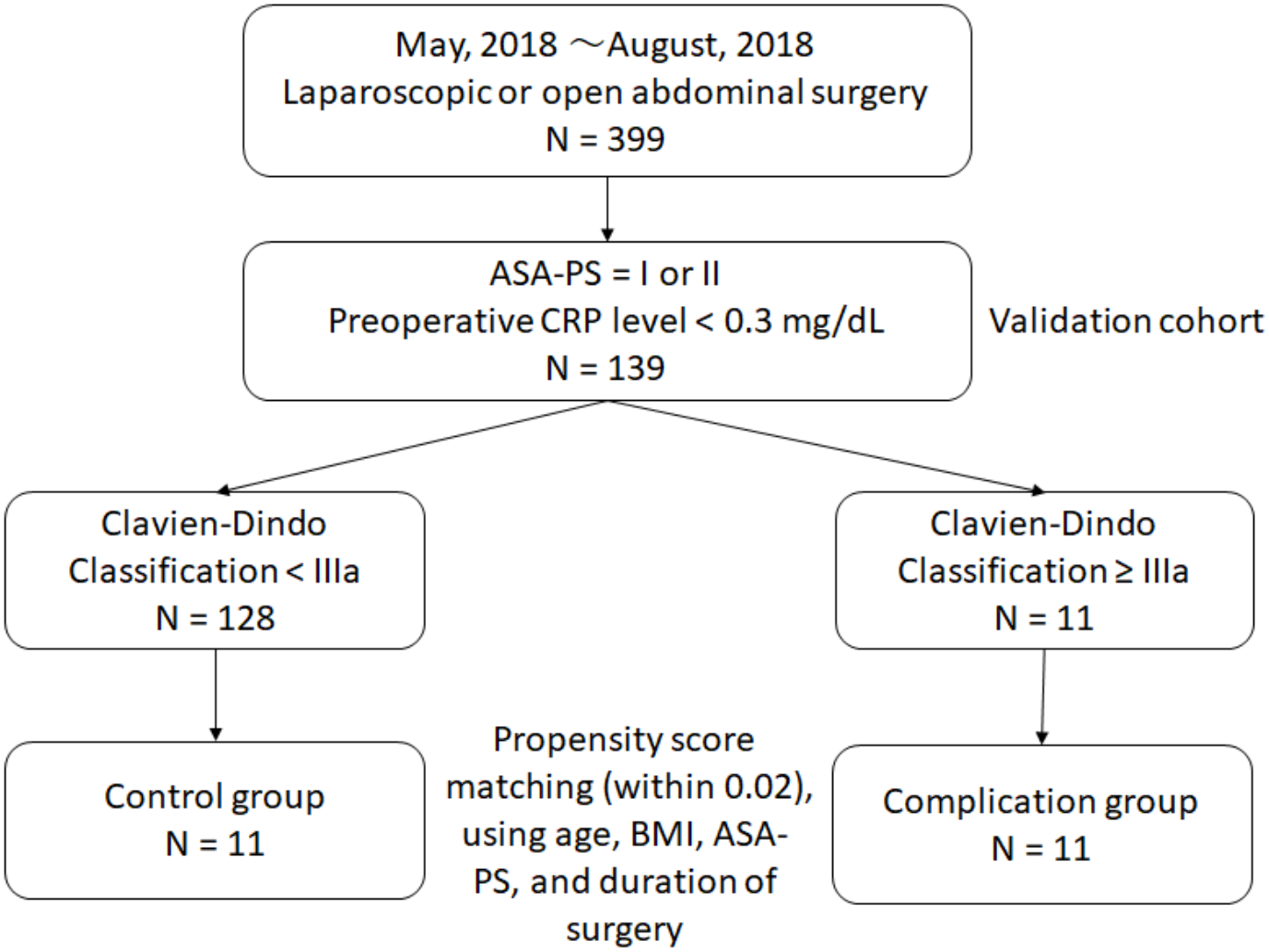

Figure 3

Diagram showing the process for analysis using propensity score matching. ASA-PS: American Society of Anesthesiologists – Physical status, BMI: body mass index, CRP: C-reactive protein.

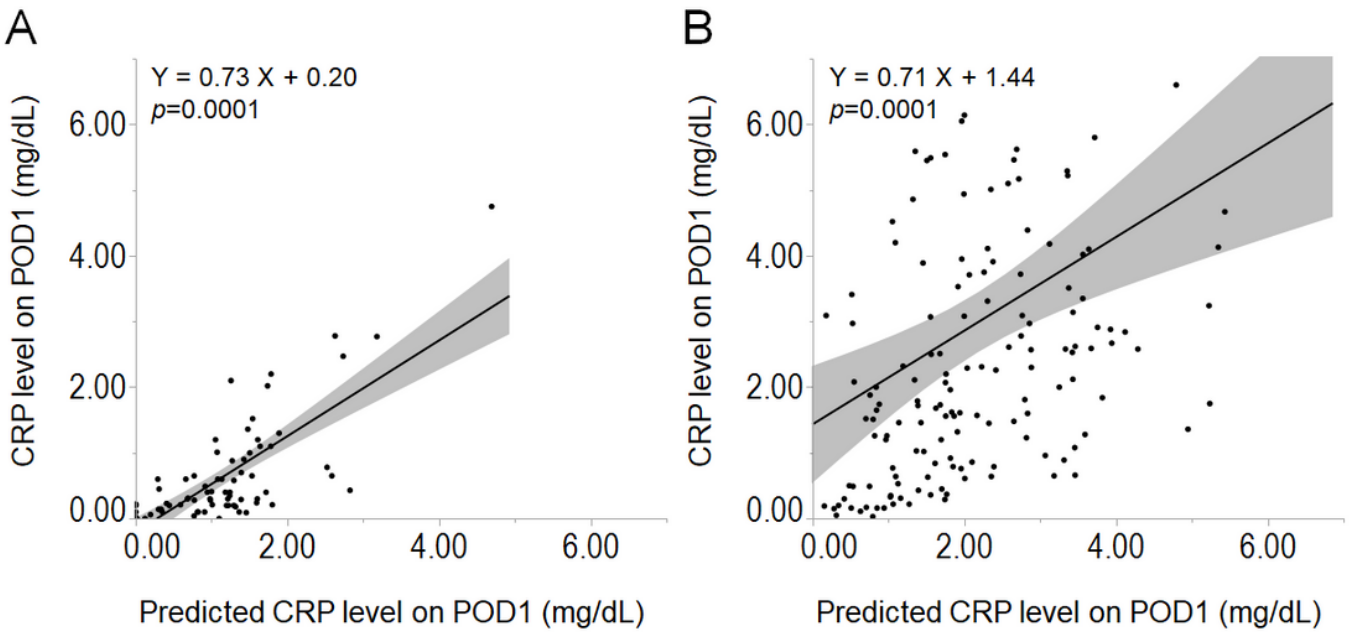

Figure 4

Relationship between predicted and measured CRP levels on POD1 in Validation cohort A after mastectomy (A), and in Validation cohort B after laparoscopic or open abdominal surgery (B). Scatter-points represent actual data, and the regression line (solid) and the 95% confidence interval (shaded area) are also shown. CRP: C-reactive protein, POD: postoperative day.

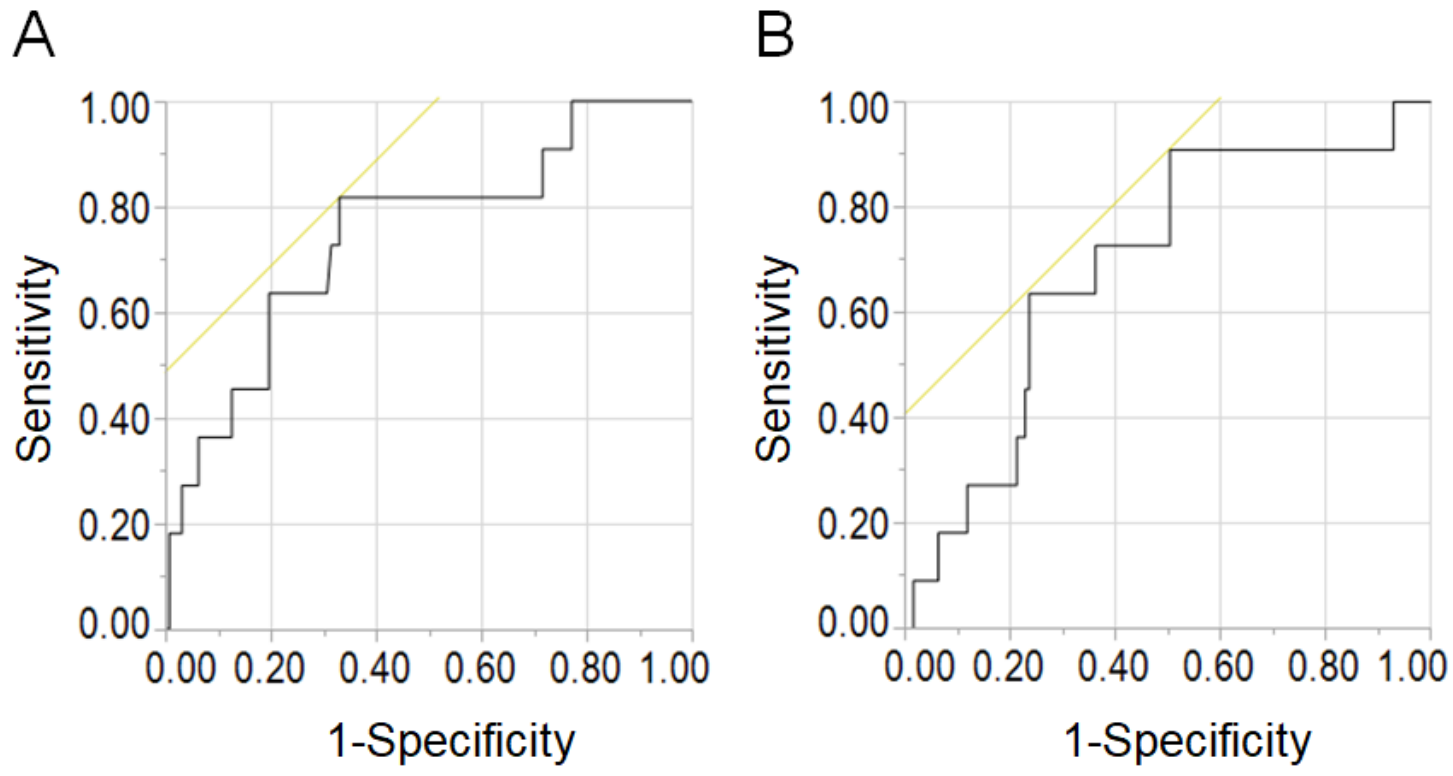

Figure 5

Receiver operating characteristic curves for prediction of major complications with measured and predicted C-reactive protein levels on postoperative day 1.