RESEARCH ARTICLE

Preoperative Level of Insulin-Like Growth Factor Binding Protein 2 Predicts The Suboptimal Outcome After Primary Debulking Surgery in Patients with Advance Ovarian Cancer

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Abstract

BACKGROUND: The need for clinically useful biomarkers which can predict the surgical outcome after primary debulking surgery (PDS) in patients with advance ovarian cancer (AOC) is really important. Insulin-like growth factor-binding protein 2 (IGFBP2) is the main binding protein expressed by ovarian cancer cells, which plays a prominent role in promoting proliferation, driving invasion, and suppressing apoptosis. This study was conducted to assess the performance of IGFBP2 in predicting the surgical outcome after PDS in patients with AOC.

METHODS: Twenty-four subjects with AOC (Stage IIIc/ IV) who underwent PDS were recruited consecutively. Clinicopathologic data were obtained from subjects' medical records. Blood samples were withdrawn form each subject and preoperative level of IGFBP2 were measured using enzyme-linked immunosorbent assay (ELISA). Multivariate analysis was employed to test the performance of multiple predictors of surgical outcome.

RESULTS: Eighteen patients (75%) had suboptimal outcome after PDS. Mean IGFBP2 level was significantly higher in the suboptimal group (1157.5±359.9 ng/mL *vs.* 679.1±504.5 ng/mL, p=0.018). In bivariate model, higher preoperative level of IGFBP2 predict the suboptimal outcome with good accuracy (AUC: 0.796, sensitivity: 83.3%, specificity: 83.3%, p=0.033, optimal threshold level 870 ng/mL). Higher IGFBP2 level was associated with higher risk of suboptimal outcome, although IGFBP2 was not an independent risk factor (adjusted OR: 5.0, 95% CI: 0.43-57.9, p=0.198).

CONCLUSION: IGFBP2 is a novel and promising biomarker for surgical outcome prediction following PDS in AOC patients. Since it is predictive for suboptimal outcome, patients with higher preoperative level of IGFBP2 needs more thorough preoperative evaluation as well as meticulous surgical technique to optimize the surgical outcome.

KEYWORDS: IGFBP2, advance ovarian cancer, PDS, surgical outcome, predictor

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Introduction

Ovarian cancer (OC) still poses a major health problem among women worldwide. More than 300,000 new cases diagnosed and more than 200,00 new deaths were attributed to ovarian cancer worldwide in the year of 2020.(1) The majority of OC are diagnosed in advance stage owing to the lack of effective screening strategy and the silent nature of disease progression in the early stage.(2) However, the survival from OC is inversely related to the stage at diagnosis. The 5-year survival rate for advance OC (AOC) are 26% for stage III and 14% for stage IV, as compared to 87% for stage I and 62% for stage II.(3) One of the

major determinants of survival in AOC is the amount of residual disease (RD) after primary debulking surgery (PDS). AOC patients who achieve complete or optimal cytoreduction (no macroscopic RD or RD ≤1 cm) have better survival than those with suboptimal outcome (RD >1 cm) after PDS.(4) Thus, removing all visible tumour and achieving no macroscopic residual disease is the ultimate goal of PDS. However, some patients are not amenable to complete cytoreduction due to extensive involvement of intraperitoneal organs. For those with stage IV AOC, involvement of liver parenchyme and lung metastases can preclude optimal cytoreduction.(5)

The ability to accurately predict surgical outcome is of the utmost importance before deciding the modality of treatment for patients with AOC. For those who are not a fit candidate for PDS, alternative strategy such as treatment with neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) may become a more rational approach. Several factors determine the surgical outcome such as patient's characteristics, the surgical skill of the operating gyneco-oncologist, as well as the center experience and facilities.(6) The use of molecular biomarkers for surgical outcome prediction is an interesting field of research. Several studies have reported the use of gene expression profile (7), serum or plasma level of cancer related proteins (8,9), and inflammatory markers (10) to predict the surgical outcome following PDS. Our previous study has demonstrated that the preoperative level of insulin-like growth factor binding protein 2 (IGFBP2) can accurately differentiate OC from benign ovarian masses, especially at the advance stage.(11) The clinical utility of IGFBP2 as a predictor of surgical outcome in AOC patients following PDS has never been demonstrated before. Ovarian cancer mainly express IGFBP2, which exhibit biologic activities involved in the regulation of proliferation, invasion, and inhibition of apoptosis.(12,13)

Thus, this study was conducted to assess the performance of IGFBP2 in predicting the surgical outcome of AOC patients undergoing PDS. To our knowledge, this is the first study that confirms the clinical use of preoperative level of IGFBP2 in predicting the surgical outcome after PDS in patients with AOC.

Methods

This cohort prospective study was approved by the Institutional Review Board of Faculty of Medicine, Universitas Udayana/Prof. dr. I Gusti Ngoerah Gede Ngoerah General Hospital, Denpasar, Bali, Indonesia (Ethical Clearance No. 222/UN14.2.2.VII/ LP/2019).

Subjects Selection

Women aged older than 18 years with primary resectable AOC Stage IIIc/IV who underwent PDS at the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology Faculty of Medicine, Universitas Udayana/Prof. dr. I Gusti Ngoerah Gede Ngoerah General Hospital during the period of May to December 2019 were consecutively recruited into the study population. PDS consisted of total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic or para-aorta lymph node dissection, omentectomy, appendectomy, and resection of all other visible tumour mass within the pelvis and abdominal peritoneal cavity. Patients with apparent unresectable stage IVB disease from clinical examination and imaging: *i.e.*, the presence of multifocal parenchymal liver metastases, pulmonary metastases including diffuse pleural involvement, brain metastases, or bulky thoracic adenopathy (not including cardiophrenic lymphadenopathy) were excluded from the study. AOC patients with obesity and diabetes mellitus were also excluded.(14) Before the commencement of the study, a written informed consent was obtained from all subjects or their legal surrogate.

Sensitivity value was the primary interest for prediction performance in this study. Pre-determined values of 90% for sensitivity (Se), while prevalence of suboptimal outcome (Prev) of 70% were used.(15) In order for the maximum marginal error of estimate (d) does not exceed from 15% with 95% confidence level (α=0.05, $Z\alpha/2$=1.96), the total required sample size was obtained from the calculation of: $n= Z\alpha/22 \times Se(1-Se)/d2 \times Prev$.(16) Following the formula, the minimum required total number of sample was 22.

Medical Records Data Collection

Data regarding the clinicopathologic characteristics (including age, FIGO stage, histologic type, tumour diameter, bilaterality, the presence of ascites, and omental carcinomatosis) were obtained from the subjects' medical records. Investigator who performed data extraction from the medical records were blinded to the subjects' identity and each subject was assigned to a specific code for identification to maintain the anonymity of the data. The 2014 International Federation of Gynecologists and Obstetricians criteria was used to determine the stage (17), and the WHO classification was used to categorize the histologic subtype.(18)

CT-scan and X-ray

Imaging (abdomino-pelvic ultrasound and CT, chest X-ray or CT, or head CT according to the clinical suspicion of metastasis) were used to help determining clinical stage preoperatively and in combination with clinical examination. The findings were later confirmed intraoperatively. Stage IIIc was defined as the presence of macroscopic, extrapelvic, peritoneal metastasis >2 cm ± positive retroperitoneal lymph nodes. Stage IIIc includes extension to capsule of liver/spleen. Stage IV was defined as distant metastasis such as pleural effusion with positive cytology. Abdomino-pelvic ultrasonography or CT was also used to determine the tumour diameter, bilaterality, ascites and omental carcinomatosis, in combination with findings from physical examination and the intraoperative evaluation. Ascites was defined as the presence of intraperitoneal fluid with 500 mL volume or more. Surgical outcomes after PDS was assessed by the gynecologic oncologists who performed the procedure and defined using the criteria from Gynecologic Oncology Group and categorized as optimal if there was no macroscopic residual mass or RD ≤1 cm and suboptimal if there was RD >1 cm.(19)

IGFBP2 Level Measurement

To determine the preoperative serum level of IGFBP2, 3-5 mL of subject's venous blood was drawn and collected with EDTA-containing tube a day prior to the surgery. The blood was centrifuged immediately at 400 g for 5 minutes to collect the plasma. Quantikine ELISA Human IGFBP2 Immunoassay (Cat. #DGB200; R&D Systems, Shanghai, PRC) was the assay kit used to determine the level of IGFBP2. The procedure for IGFBP2 quantification follows the manufacturer's instruction.(20)

Cancer Antigen 125 (CA125) Level Measurement

To determine the preoperative serum level of CA125, 3-5 mL of patient's venous blood was drawn and collected with EDTA-containing tube a day prior to the surgery. The blood was centrifuged immediately at 400 g for 5 minutes to collect the plasma. Elecsys CA125 Roche Cobas (Cat #07030207; Roche Diagnostics GmbH, Sandhofer Strasse, Mannheim, Germany) was the assay kit used to determine the level of CA125. The procedure for CA125 quantification follows the manufacturer's instruction.(21)

Statistical Analysis

Numerical data were tested using independent T-test or Mann-Whitney U test while categorical data were tested using Chi square or Fisher exact test. Correlations between normally distributed numeric variables were assessed with the Pearson r correlation. The receiver operating characteristic (ROC) curve was used to determine the cut-off value of IGFBP2 in predicting the surgical outcome. For CA125 level, a threshold level of 500 U/mL was used.(22) Multivariate analysis using binary logistic regression was employed to test the performance of multiple predictors in predicting the surgical outcome. All tests were two-sided, and $p<0.05$ was considered statistically significant. Data were analyzed using SPSS version 28.0. (IBM Corporation, Armonk, NY, USA).

Results

Baseline Characteristics of Subjects

Twenty four patients with AOC were enrolled into this study and 18 (75%) of them achieved suboptimal surgical outcome following PDS. The baseline characteristics of the subjects were summarized in Table 1. Age, FIGO stage, tumour diameter, bilaterality, and the presence of ascites did not differ significantly between the two groups ($p>0.05$). Among those with suboptimal outcome, 6 (33.3%) had extensive omental carcinomatosis involving small bowel and mesenteric root, 8 (44.4%) had extensive carcinomatosis involving pelvic sidewalls, and 4 (22.2%) had spreading to the peritoneal surface of diaphragm (Figure 1). High grade serous and clear cell were the most frequent histologic type (5/18 or 27.8% each), followed by mucinous (3/18, 16.7%) and low grade serous (3/18, 16.7%), endometrioid (1/18, 5.6%) and mixed epithelial (1/18, 5.6%). However, data about the grade of differentiation was unavailable.

Mean IGFBP2 level was significantly higher in the suboptimal group, as compared to the optimal group (mean±SD: 1157.5±359.9 ng/mL *vs.* 679.1±504.5 ng/mL, $p=0.018$). IGFBP2 level did not differ between high-grade *vs.* non high-grade serous OC (mean±SD: 1302.4±250.9 ng/mL *vs.* 968.3±460.2 ng/mL, $p=0.136$) and did not correlate with tumour size (r=0.331, $p=0.115$). Median CA125 level did not differ significantly between the suboptimal and optimal groups (median (IQR): 577.9 (1282.8) U/mL *vs.* 308.8 (1003.4) U/mL, $p=0.581$) (Figure 2).

Performance of Preoperative IGFBP2 Level for Surgical Outcome Prediction

The area under the curve (AUC) of IGFBP2 level for surgical outcome prediction was 0.796 (95% CI: 0.548-1.000, $p=0.033$) (Figure 3). With the threshold level of 870 ng/mL, the sensitivity and specificity of preoperative

Table 1. Baseline characteristics of the study population.

Predictor	Total (n=24)	Suboptimal (n=18)	Optimal (n=6)	*p* -value
Age (years), mean±SD	44.7±13.8	46.3±14.0	40.2±13.4	0.361
FIGO stage, n (%)				
IIIc	19 (79.2)	13 (72.2)	6 (100)	0.28
IVa	5 (20.8)	5 (27.8)	0	
Tumour diameter (cm), mean±SD	23.3±7.5	23.4±7.8	21.7±6.8	0.543
Bilaterality, n (%)				
Yes	10 (41.7)	6 (33.3)	0	0.277
No	14 (58.3)	12 (66.7)	6 (100)	
Ascites, n (%)				
Yes	19 (79.2)	14 (77.8)	5 (83.3)	1.000
No	5 (20.8)	4 (22.2)	1 (16.7)	
Omental carcinomatosis, n (%)				
Yes	16 (66.7)	15 (83.3)	1 (16.7)	0.007*
No	8 (33.3)	3 (16.7)	5 (83.3)	
Histologic type, n (%)				
Epithelial	18 (75)	12 (66.7)	6 (100)	0.277
Non-epithelial	6 (25)	6 (33.3)	0	
IGFBP2 level, n (%)				
Higher	16 (66.7)	15 (83.3)	1 (16.7)	0.007*
Lower	8 (33.3)	3 (16.7)	5 (83.3)	
CA125 level, n (%)				
Higher	11 (45.8)	10 (55.6)	1 (16.7)	0.166
Lower	13 (54.2)	8 (44.4)	5 (83.3)	

Threshold level of IGBP2 and CA125 were 870 ng/mL and 500 U/mL, respectively. All categorical variables were analysed using Fisher exact test. All numerical variables were normally distributed, presented in mean±standard deviation (SD), and analysed using independent student T-test. *Significant predictors that were included in the multivariate analysis ($p<0.05$). The *p*-values were set for suboptimal *vs.* optimal outcome.

IGFBP2 level in predicting the suboptimal outcome was both 83.3%. The AUC for CA125 was 0.583 (95% CI: 0.331-0.835, $p=0.549$).

Performance of Clinicopathologic Predictors for Surgical Outcome Prediction

In bivariate analysis (Table 1), IGFBP2 level (crude OR: 25.0, 95% CI: 2.1-298.3, $p=0.007$) and omental carcinomatosis (crude OR: 25.0, 95% CI: 2.1-298.3, $p=0.007$) both predict the surgical outcome. However, when multivariable analysis was performed (Table 2), IGFBP2 level did not independently predict the surgical outcome (adjusted OR: 5.0, 95% CI: 0.43-57.952, $p=0.198$). Thus, IGFBP2 was not an independent predictor of surgical outcome following PDS.

Discussion

We propose the use of threshold value at 870 ng/mL to predicts the suboptimal surgical outcome following PDS, with sensitivity and specificity were both 83%. Previously, IGFBP2 has been demonstrated as a novel biomarker for the diagnosis of OC.(11, 23) A threshold level of 804 ng/mL gave 83.3% sensitivity, 96.7% specificity, 95.2% positive predictive value, and 87.9 negative predictive value in diagnosing advance OC.(11) In this study, we observed that AOC patients with suboptimal outcome following PDS had significantly higher level of preoperative IGFBP2. This finding was in accordance to the result of another study. (24) They also demonstrated that IGFBP2 level returned to

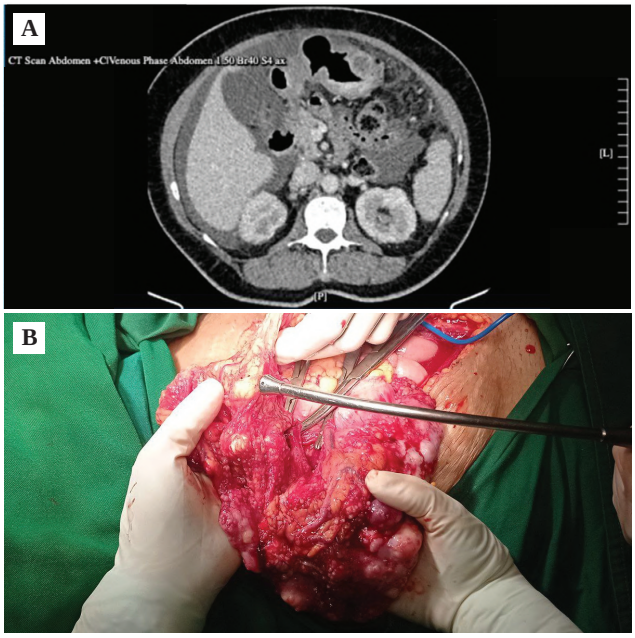

Figure 1. Presence of omental carcinomatosis. A: An abdomino-pelvic CT-scan showing irregular peritoneal and omental thickening with contrast enhancement suggesting an omental carcinomatosis occupying the pelvic and abdominal cavity; B: Intraoperative evaluation confirmed the presence of omental carcinomatosis.

normal after complete cytoreduction but rose significantly during relapse. Higher preoperative level of IGFBP2 also has been shown to predict shorter progression free interval and overall survival of OC patients.(24) IGFBP2 has been shown to contributes to worse overall survival in various cancer such as glioblastoma, colorectal cancer, and lung cancer.(25) In regard to the role of IGFBP2 expression in driving tumorigenesis, a recent study demonstrated that IGFBP2 promoter was found to undergo hypomethylation and be increased at the protein level in serous tubal intraepithelial carcinoma (STIC), the precursor lesion to OC.(26) IGFBP2 is involved in the initiation of signalling pathways that regulate cancer cell proliferation, invasion, and inhibition of apoptosis, such as integrin β1/ERK, integrin/ILK/NF-κB, EGFR/STATA3, and PI3K/Akt pathways.(25)

In this study, the rate of suboptimal outcome was quite high (75%). Other studies reported that the rate of suboptimal outcome after PDS range from 60% to 72%.(4,27) The majority of patients who achieved suboptimal outcome in our study had extensive carcinomatosis involving the pelvic sidewalls. Other reasons for suboptimal cytoreduction were the presence of extensive omental carcinomatosis involving the mesenteric root and small bowels and extension to the peritoneal surface of the diaphragm. The presence of ascites, diaphragmatic or omental carcinomatosis, and suprarenal

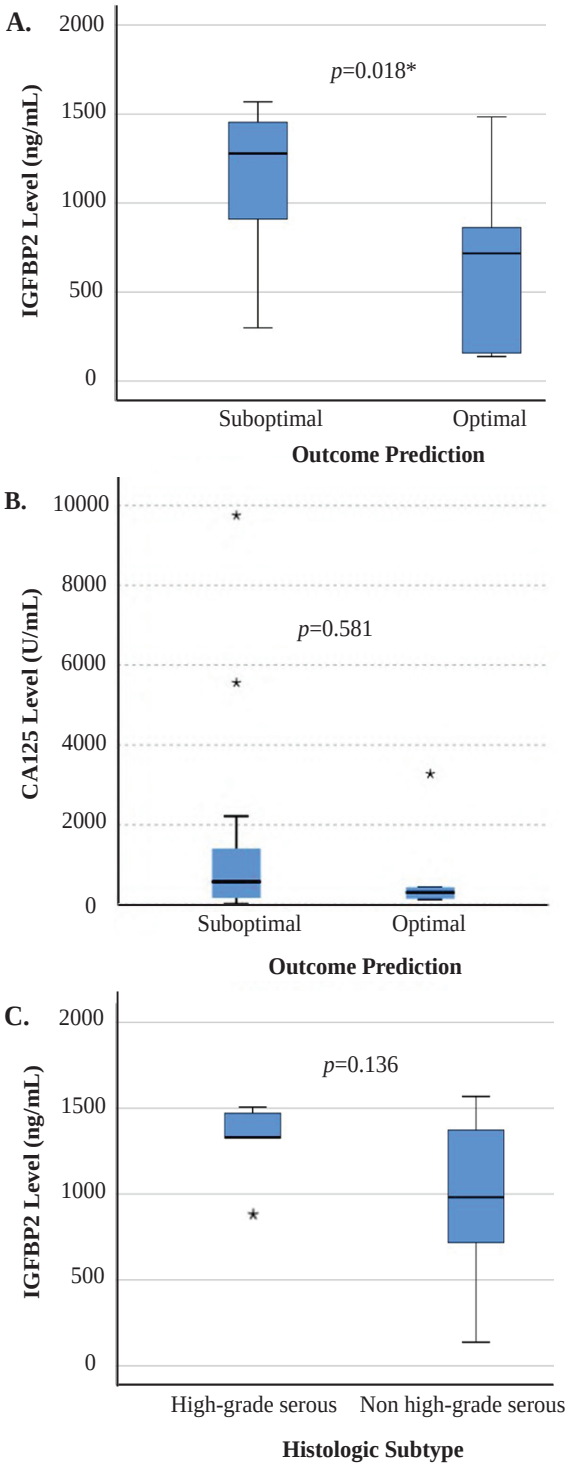

Figure 2. Preoperative IGFBP2 and CA125 levels based on surgical outcome and histologic subtype. A: preoperative level of IGFBP2 based on surgical outcome; B: preoperative level of CA125 based on surgical outcome; C: preoperative level of IGFBP2 based on histologic subtype. A and C are normally distributed, presented in mean±SD, and tested using independent T-student. Horizontal line above and below the graph represent standard deviation and bold line within the graph represent mean value. B is non-normally distributed, presented in median (IQR), and tested using Mann-Whitney test. Horizontal line above and below the graph represent range (max-min), the bold line within the graph represent median value. *Significant if $p<0.05$.

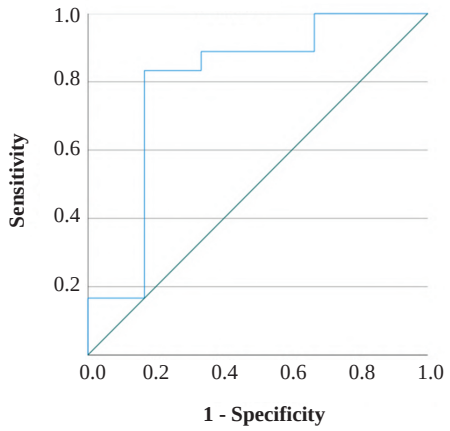

Figure 3. The ROC curve of preoperative IGFBP2 level for surgical outcome prediction. The threshold value for the best sensitivity and specificity in predicting surgical outcome was 870 ng/mL. The area under curve (AUC) was 0.796 (95% CI: 0.548-1.000, *p*=0.033)

retroperitoneal lymph nodes enlargement were associated with suboptimal outcome.(28,29)

Besides the use of imaging modalities, several studies have proposed the use of serum biomarkers for surgical outcome prediction following PDS in AOC patients as they are non-invasive and can reflect the disease progression. human epididymis protein 4 (HE-4) was found useful in predicting optimal cytoreduction after PDS with a sensitivity of 86.1% and a specificity of 89.5%.(30) One study reported that CA125 and HE-4 combination can be useful for diagnosing suboptimal cytoreduction after PDS with the diagnostic accuracy, negative predictive values (NPV), positive predictive values (PPV) and specificity were 71, 100, 68, and 100%, respectively.(9) Another study reported that HE-4 was superior to CA125 in predicting surgical outcome following PDS (AUC: 0.758 *vs.* 0.633).(31) In our study, CA125 failed to predict the suboptimal outcome (AUC: 0.583, *p*=0.549). This finding is in accordance to the finding by another study that reported an AUC of 0.576 and *p*=0.617.(32) However, one meta-analysis reported a strong association between preoperative level of CA125 and the risk of suboptimal outcome.(33) Our study demonstrated a good performance of IGFBP2 with AUC of 0.796 (*p*=0.033). However, after adjusting with another predictor, *i.e.*, omental carcinomatosis, we did not demonstrate that IGFBP2 independently predict the suboptimal outcome following PDS. Multivariable model of prediction combining serum biomarker with patient-specific clinical predictors may enhance the prediction accuracy and thus, optimizing the safety and outcome of PDS. One study demonstrated that demonstrate a logistic model incorporating age, histologic type, and preoperative CA125 and HE-4 level to predict optimal cytoreduction with AUC of 0.71.(9) Another study demonstrates the multivariate model of Cancer Ovarii Non-invasive Assessment of Treatment Strategy (CONATS) index, can predict suboptimal outcome with AUC of 0.80.(34) One study demonstrated a triage algorithm incorporating clinical (age, albumin level, CA125 level, American Society of Anesthesiologist score) and radiologic data from contrast-enhanced abdominal and pelvic CT scan. (35) The implementation of that multimodal algorithm led to excellent surgical results, i.e. the rate of suboptimal cytoreduction was only 6%. One study developed a simple triage system to allocate the patients into PDS or NACT-IDS that involves preoperative albumin level, age, ECOG performance status, and the likelihood of complex surgery.(36) Comparable outcomes for PDS and IDS were demonstrated after implementing that triage system. By implementing the multivariable prediction model, AOC patients who are not a fit candidate to PDS may be switched to NACT followed by IDS to optimize the outcome although in a recent meta-analysis, there is little or no difference in primary survival outcomes between PDS and NACT.(37) NACT is associated with reduction in the risk of serious perioperative adverse events and postoperative mortality. Following NACT-IDS, one report shows that perioperative complications and mortality are significantly reduced by 70-80%.(38)

Our study has several limitations. We were only able to identified two predictors to include them in the multivariable analysis, *i.e.*, the presence of omental carcinomatosis and preoperative serum IGFBP2 level, despite our efforts to include other relevant clinical parameters. On the other hand, this study is a single-institutional study with no external validation group. However, this study belongs to one of new application of specific biomarkers as predictor of

Table 2. Multivariate analysis for surgical outcome prediction.

Predictor	B	S.E.	Wald	Df	Sig.	Exp(B)	95% CI
Omental carcinomatosis	1.609	1.25	1.657	1	0.198	5	0.431-57.952
IGFBP2 level	1.609	1.25	1.657	1	0.198	5	0.431-57.952

clinical outcome in OC after surgery, leading to future better management of ovarian cancer. Future study investigating the multivariable prediction model involving IGFBP2 and clinical or imaging data is urgently needed. Furthermore, patients with higher preoperative level of IGFBP2 needs more thorough preoperative evaluation such as better imaging and multidisciplinary collaborative approach as well as meticulous surgical technique to optimize the surgical outcome.

Conclusion

IGFBP2 is a novel and promising biomarker for surgical outcome prediction following PDS in AOC patients. Since it is predictive for suboptimal outcome, patients with higher preoperative level of IGFBP2 needs more thorough preoperative evaluation as well as meticulous surgical technique to optimize the surgical outcome.

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Authors Contribution

PKAP, INGB, KYS, IGSW, and INBM were involved in the conception and study design. PKAP was involved in the acquisition of data, as well as drafted the manuscript and conducted the statistical anlysis. PKAP and INGB analyzed and interpreted the data. INGB, KYS, IGSW, INBM, and KS gave administrative, technical, or material support for the study. KS supervised the study. All authors critical revisions and already approved the final draft of the manuscript.

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