

Original Article



Factors predicting postoperative morbidity after cytoreductive surgery for ovarian cancer: a systematic review and meta-analysis

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ABSTRACT

Objective: Advances in ovarian cancer cytoreductive surgery have enabled more extensive procedures to achieve maximal cytoreduction but with a consequent increase in postoperative morbidity and mortality. The aim of this study was to evaluate factors for postoperative morbidity after extensive cytoreductive surgery for primary epithelial ovarian cancer (EOC), particularly those which may be modifiable.

Methods: Electronic databases were searched. Meta-analysis was conducted using random-effects models.

Results: Fifteen relevant studies, involving 15,325 ovarian cancer patients, were included in this review. Severe 30-day postoperative complications occurred in 2,357 (15.4%) patients. The postoperative mortality rate was 1.92%. Meta-analysis demonstrated that patient with following risk factors; age ($p < 0.001$), Eastern Cooperative Oncology Group score > 0 ($p = 0.001$), albumin level < 3.5 g/dL ($p < 0.001$), presence of ascites on CT scan ($p = 0.013$), stage IV disease ($p < 0.001$) and extensive surgical procedure ($p < 0.001$) has a significantly increase risk of developing postoperative complications. Surgical procedures including peritonectomy ($p = 0.012$), splenectomy ($p < 0.001$) and colon surgery ($p < 0.001$) were significant predictors for postoperative complications. Moreover, we found that patients who received neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) had a lower risk of developing severe complications compared to those who underwent primary debulking surgery (PDS) ($p < 0.001$).

Conclusion: Our study demonstrated that patient performance status and hypoalbuminemia were the only significant adjustable preoperative risk factors associated with postoperative complications. Patients who underwent NACT-IDS had a lower risk of developing severe complications compared to PDS.

Trial Registration

International Prospective Register of Systematic Reviews (PROSPERO) Identifier: [CRD42021282770](https://doi.org/10.1111/CRD4.2021282770)

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: K.M., N.G.M., V.H.J.; Data curation: K.M., N.G.M., U.S., N.C.D., V.H.J.; Formal analysis: K.M., N.G.M., U.S., K.S.J., V.H.J.; Investigation: K.M., N.G.M., U.S., K.S.J., N.C.D., V.H.J.; Methodology: K.M., N.G.M., U.S., K.S.J., V.H.J.; Project administration: V.H.J.; Resources: K.M., U.S., K.S.J., N.C.D.; Software: U.S., K.S.J., N.C.D.; Supervision: N.G.M., V.H.J.; Validation: K.M., N.G.M., U.S., K.S.J., N.C.D., V.H.J.; Visualization: K.M., N.G.M., U.S., K.S.J., N.C.D., V.H.J.; Writing - original draft: K.M.; Writing - review & editing: K.M., N.G.M., U.S., K.S.J., N.C.D., V.H.J.

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Keywords: Morbidity; Mortality; Complication; Ovarian Cancer; Cytoreductive Surgery; Albumin

Synopsis

We conducted a meta-analysis to demonstrate factors associated with postoperative complications in cytoreductive surgery for epithelial ovarian cancer. Our findings highlight the importance of patients' performance and albumin status as the adjustable preoperative factors. These findings could be useful in developing future perioperative protocol to reduce postoperative morbidity.

INTRODUCTION

Globally, ovarian cancer is diagnosed in more than 300,000 women yearly [1]. Unfortunately, approximately 70% of cases are diagnosed in advanced stage. In 2020, ovarian cancer was the second leading cause of death among women with gynecological malignancies [1]. The cornerstone of treatment for advanced stage epithelial ovarian cancer (EOC) includes debulking surgery in combination with platinum-based chemotherapy. The amount of residual disease following cytoreductive surgery is an independent prognostic factor for survival [2]. In order to achieved the maximum degree of cytoreduction, ultra-radical or extensive procedures are often performed. These include peritonectomies, diaphragmatic peritonectomies, resection of subcapsular liver metastases, splenectomy, bowel resection or resection of extra-abdominal metastatic sites. While these extensive procedures can optimize cytoreduction and thus survival, there is an associated cost of increased postoperative morbidity and mortality [3,4].

Recently, few studies focus on factors associated with postoperative morbidity and mortality. The morbidity and mortality rate are inconsistently due to the differences in classifications [3]. Moreover, studies that reported nomogram for predicting postoperative morbidity and mortality were commonly included intra- and postoperative parameters which are limited to identify high risk patient at preoperative state [5-9].

Our study aimed to analyze factors associated with post-operative morbidity in patients who underwent cytoreductive surgery, either primary or interval, for EOC. An understanding of these factors would aid in the pre-operative identification of patients at higher risk of complications or death. It is also possible that adjustable risk factors could be potentially modified preoperatively by the medical professionals, to improve future postoperative outcomes.

MATERIALS AND METHODS

1. Data sources and searches

This review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [10] and the Prisma-S extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews [11]. The systematic

review was prospectively registered on International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42021282770). The search was initially developed in Embase.com, then extended to other databases. The search was carried out on 1 August 2021 Embase.com, Medline ALL via Ovid, Web of Science Core Collection and the Cochrane Central Register of Controlled Trials via Wiley. An additional search was performed in Google Scholar, and the 200 most relevant references were downloaded using Publish or Perish software [12]. We also searched Cochrane Central which indexes the contents of ClinicalTrials.gov and World Health Organization's International Clinical Trials Registry Platform. The search terms used in these databases is shown in **Table S1**. No authors or subject experts were contacted.

2. Study selection

Studies published in English-language with adequate information according to study inclusion criteria and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [13], were included in our review. Key inclusion criteria were reported risk factors for 30-day morbidity in patients who underwent primary debulking surgery (PDS) or interval debulking surgery (IDS) for ovarian cancer, tubal cancer and primary peritoneal cancer. Studies which failed to report individual factors were excluded. Two authors (K.M. and N.G.M.) independently screened the titles and abstracts of the retrieved electronic citations. Full texts of the relevant articles were retrieved and reviewed by both authors. Any disagreements between K.M. and N.G.M. were resolved through discussion and arbitration by a third author (V.H.J.). The reference lists of retrieved articles were also searched for possibly missed, but relevant studies.

3. Data extraction and quality assessment

The main outcome in the present review were factors associated with postoperative morbidity for primary EOC patients who underwent cytoreductive surgery. Postoperative morbidity was defined as any adverse event within 30 days after surgery. The severity was divided as mild or severe complications, according to the Clavien-Dindo Classification [14], based on information reported in the original article. Mild complications requiring no treatment, or supportive medical treatment only for resolution, were considered minor complications, i.e., grade 1–2 according to the Clavien-Dindo classification. Complications that required interventional procedures for resolution such as CT or ultrasound-guided percutaneous drainage, returning to the operating room or intensive care support and/or patient's death within 30 days of surgery were considered as major complication, i.e., Clavien-Dindo grade 3–5 events [14], Memorial Sloan-Kettering Cancer Center (MSKCC) surgical secondary events grading system grade 3–5 events [15] and Accordion classification grade 3–4 events [16].

The following study characteristics were extracted: name of first author, year of publication, country, study center, sample size, study design, complication classification. Patient-related characteristics were extracted as following: age, body mass index, cancer antigen 125, preoperative albumin level, Eastern Cooperative Oncology Group (ECOG) performance status, stage of disease according to International Federation of Gynecology and Obstetrics (FIGO) staging system, histology, American Society of Anesthesiologists (ASA) classification, neoadjuvant chemotherapy (NACT) status, surgical procedure, morbidity and mortality rate. Surgical complexity was extracted as standard procedure or extensive procedure. Hysterectomy, bilateral salpingo-oophorectomy, bilateral paraaortic and pelvic lymph node dissection, omentectomy, appendectomy and peritoneal tumor resection were considered as standard surgeries. Extended surgery was considered when additional surgery included one

of the following procedures: bowel resection, splenectomy, pelvic peritonectomy, diaphragm peritonectomy or extra abdominal tumor debulking was performed. The Newcastle-Ottawa Quality Assessment Scale [17] was used to evaluate the quality and the risk of bias in the observational studies included in our meta-analysis.

4. Data synthesis and analysis

Results were synthesized quantitatively by performing random-effects meta-analyses to compute weighted mean difference (WMD) for continuous variables and pooled odds ratios (ORs) for binary variables, along with their 95% confidence intervals (CIs). The mean and standard deviation (SD) were calculated based on the method described by Wan et al. [18] if not provided in the study. Existence of heterogeneity among study effect sizes was examined using the I^2 index and the Q-test p-value. An I^2 index >75% indicated medium to high heterogeneity. Categorical variables are presented as number (%) and continuous variables as mean \pm SD. Statistical significance was defined as a p-value <0.05. Publication bias was formally assessed using the Egger test. The analyses were performed using Stata 17 (StataCorp LLC, College Station, TX, USA).

5. Ethical considerations

This meta-analysis and systematic review did not directly obtain data from human or animal subject. All of the included studies' information were extracted from published scientific journals.

RESULTS

1. Study characteristics

Fig. S1 shows the flow diagram of study selection. A total 1,953 citations were initially retrieved using our searching criteria. After duplicate citations and irrelevant studies were excluded, 66 articles underwent full-text review. Finally, 15 articles comprising 15,325 ovarian cancer patients were included in the final meta-analysis. Details of each study are summarized in **Table S2**. The studies were published between 2005 to 2021. Most of the studies were retrospective cohort studies. One study was prospective cohort [19]. Ten of 15 studies [6,7,9,15,16,19-23] were single center cohorts, 2 studies [5,24] were multicenter cohorts and 3 studies [8,25,26] were population-based. The classification of postoperative morbidity and mortality varied among studies. Five of 15 studies did not mention the complication instrument used to determine severity [6,7,20,24,26]. Five studies reported 30-day complications based on the Clavien-Dindo classification [9,19,21,23,25]. Two studies reported adverse events according to the American college of surgeon's national surgical quality improvement program [8,22], 2 studies used MSKCC surgical secondary events grading system [5,15] and one study used the Accordion classification [16]. Severe postoperative complications at 30 days occurred in 2,357 (15.38%) patients and postoperative mortality rate was 1.92%. The Newcastle-Ottawa Quality Assessment Scale of the included studies are shown in the **Table S3**. All studies were considered high quality studies.

2. Meta-analysis

The pooled baseline characteristics of patient and number of studies were presented in **Table 1**. The mean age of patients with and without postoperative complications were 63.96 ± 13.23 and 60.81 ± 13.14 years, respectively. Patients with postoperative complications were significantly older than those without complications (WMD of 4.078 year [95% CI=2.58–5.58; p-value <0.001; $I^2=34.40\%$]).

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Table 1. Pooled baseline characteristics of patients included in the systematic review

Variable	Patients with complication	Patients without complication	No. of studies	No. of patients
Total	2,492 (16.26)	12,833 (83.74)	15	15,325
Clinical characteristic				
Age	63.96±13.22	60.81±13.15	7	6,175
Age ≥60 yr	139 (56.05)	256 (40.82)	4	875
BMI	27.64±4.31	25.69±5.09	3	470
ECOG performance score >0	95 (58.64)	117 (43.01)	3	434
ASA classification score >1	64 (76.19)	161 (81.73)	3	321
Comorbidity	256 (67.02)	936 (63.85)	7	1,848
Presence of ascites	169 (71.00)	308 (51.10)	4	841
FIGO stage IV	728 (42.13)	1,732 (32.48)	6	7,061
NACT-IDS	42 (40.38)	373 (52.46)	2	815
Procedure				
Diaphragmatic peritonectomy	65 (31.40)	162 (16.96)	6	1,202
Peritonectomy	21 (33.33)	22 (28.21)	2	141
Splenectomy	43 (31.62)	78 (9.71)	4	939
Liver surgery	34 (40.48)	26 (3.72)	3	783
Colon surgery	81 (56.25)	209 (23.83)	4	1,061
Extensive surgery*	896 (49.83)	1,689 (32.80)	8	6,988
Blood transfusion	43 (54.43)	42 (29.17)	2	223
Post-operative outcome				
No gross residual tumor	29 (25.89)	72 (30.13)	2	351
Serous carcinoma	206 (72.54)	841 (68.09)	4	1,519
High-graded histology	136 (80.4)	78 (71.84)	2	652

Values are presented as number (%) or mean ± standard deviation.

ASA, American Society of Anesthesiologists; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; NACT-IDS, neoadjuvant chemotherapy followed by interval debulking surgery.

*Additional surgery included one of the following procedures: bowel resection, splenectomy, pelvic peritonectomy, diaphragm peritonectomy or extra abdominal tumor debulking.

Preoperative patient characteristics associated with postoperative complications are presented in **Table 2**. Three out of 15 studies reported ECOG performance status, ASA classification and presence of ascites from preoperative imaging. Four studies categorized patient's age as age <60 years and age ≥60 years. Seven studies reported patient's comorbidity status. Patients with the following preoperative status were at higher risk for having postoperative complications: age ≥60 years (OR=1.93; 95% CI=1.35–2.76; p-value<0.001; I²=15.10%), ECOG score >0 (OR=1.95; 95% CI=1.29–2.94; p-value=0.001; I²=0%), presence of comorbidity (OR=2.06; 95% CI=1.09–3.90; p-value=0.026, I²=78.8%) and presence of ascites on preoperative images (OR=2.746; 95% CI=1.48–5.11; p-value=0.001; I²=62%).

Two studies reported NACT status, patients who received NACT followed by IDS had a lower odds of developing postoperative complications (OR=0.44; 95% CI=0.28–0.70; p-value<0.001; I²=0%) compared to those who underwent PDS. Patients who underwent an extensive surgical procedure had a 2.67-fold higher odds of having complications compared to those having standard procedures (95% CI=1.69–4.22; p-value<0.001; I²=77.37%). For the specific surgical procedure, 6 extensive procedures were reported: pelvic peritonectomy, diaphragmatic peritonectomy, liver surgery, splenectomy and colon surgery. Patients who underwent peritonectomy, splenectomy and colon surgery were at a significantly increased risk of having postoperative complications. While not statistically significant, patients who underwent concomitant liver surgery had an elevated risk of postoperative complications, although the CIs were wide and heterogeneity was high (**Table 2**).

Postoperative outcomes including blood transfusion, residual tumor status, serous histology and high-grade tumor did not increase the risk of postoperative complications.

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Table 2. Meta-analysis of clinical characteristics of patient with postoperative complication compared to patients without postoperative complication

Variable	No. of studies	No. of patients	Pooled OR or WMD (95% CI)	p-value from random effects model	I ² index (%)	Egger's p-value
Total	15	15,325				
Clinical characteristic						
Age	7	6,175	4.08 (2.58–5.58)	<0.001	34.40	0.420
Age ≥60 yr	4	875	1.93 (1.35–2.76)	<0.001	15.10	0.385
BMI	3	470	1.42 (0.81–3.64)	0.212	73.46	0.956
ECOG performance score >0	3	434	1.95 (1.29–2.94)	0.001	0.00	0.485
ASA classification score >1	3	321	0.98 (0.21–4.47)	0.976	72.00	0.702
Comorbidity	7	1,848	2.06 (1.09–3.90)	0.026	78.80	0.342
Presence of ascites	4	841	2.75 (1.48–5.11)	0.001	62.00	0.540
FIGO stage IV	6	7,061	1.56 (1.29–1.89)	<0.001	16.62	0.301
NACT-IDS	2	815	0.44 (0.28–0.70)	<0.001	0.00	-
Procedure						
Diaphragmatic peritonectomy	6	1,202	1.67 (0.93–3.00)	0.083	42.20	0.007
Peritonectomy	2	141	3.55 (1.33–9.49)	0.012	0.00	-
Splenectomy	4	939	4.47 (2.79–7.17)	<0.001	0.00	0.312
Liver surgery	3	783	10.04 (0.95–105.74)	0.055	91.54	0.385
Colon surgery	4	1,061	4.24 (2.87–6.28)	<0.001	0.00	0.879
Extensive surgery*	8	6,988	2.67 (1.69–4.22)	<0.001	77.37	0.793
Blood transfusion	2	223	4.09 (0.73–23.00)	0.110	82.00	-
Post-operative outcome						
No gross residual tumor	2	351	1.09 (0.65–1.85)	0.700	0.00	-
Serous carcinoma	4	1,519	1.26 (0.66–2.39)	0.478	74.54	0.003
High-graded histology	2	652	0.98 (0.28–3.44)	0.978	78.90	-

ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; NACT-IDS, neoadjuvant chemotherapy followed by interval debulking surgery; OR, odds ratio; WMD, weighted mean difference.

*Extensive surgery: additional surgery included one of the following procedures: bowel resection, splenectomy, pelvic peritonectomy, diaphragm peritonectomy or extra abdominal tumor debulking.

3. Pooled adjusted OR for severe postoperative complication from multivariable models in each study

Four of 15 studies presented adjusted (multivariable) models for factors associated with severe morbidity [6,9,16,25]. The pooled OR for age and severe complications from adjusted models was 1.28 per year increase (95% CI=1.09–1.50; p-value=0.003; I²=0%) and is presented in **Fig. 1**. Pooled adjusted OR for presence of ascites was 1.59 (95% CI=1.31–1.94; p-value<0.001; I²=0%). The pooled adjusted OR for preoperative albumin <3.5 g/dL was 1.86 (95% CI=1.40–2.47; p-value<0.001; I²=0%). Pooled adjusted OR for FIGO stage IV was 1.85 (95% CI=1.25–2.73; p-value=0.002; I²=0%) and pooled adjusted OR for extensive surgery was 1.96 (95% CI=1.52–2.52; p-value<0.001; I²=0%).

DISCUSSION

The majority of patients with EOC present with advanced stage [2]. These patients benefit from extensive surgical management preceded and/or followed by adjuvant platinum-based chemotherapy [27]. The impact of residual tumor size on survival has been well recognized especially in the past decades [2]. A meta-analysis demonstrated that each 10% increase in cytoreduction was associated with a 5.5% increase in median survival time [27]. Aggressive surgical procedures for example, upper abdominal procedures including diaphragm peritonectomy, splenectomy, partial liver resection and distal pancreatectomy, increase the rate of optimal cytoreduction and result in superior survival outcomes [21,28]. Since residual disease after surgery is the main prognostic factor, many gynecologic oncologists

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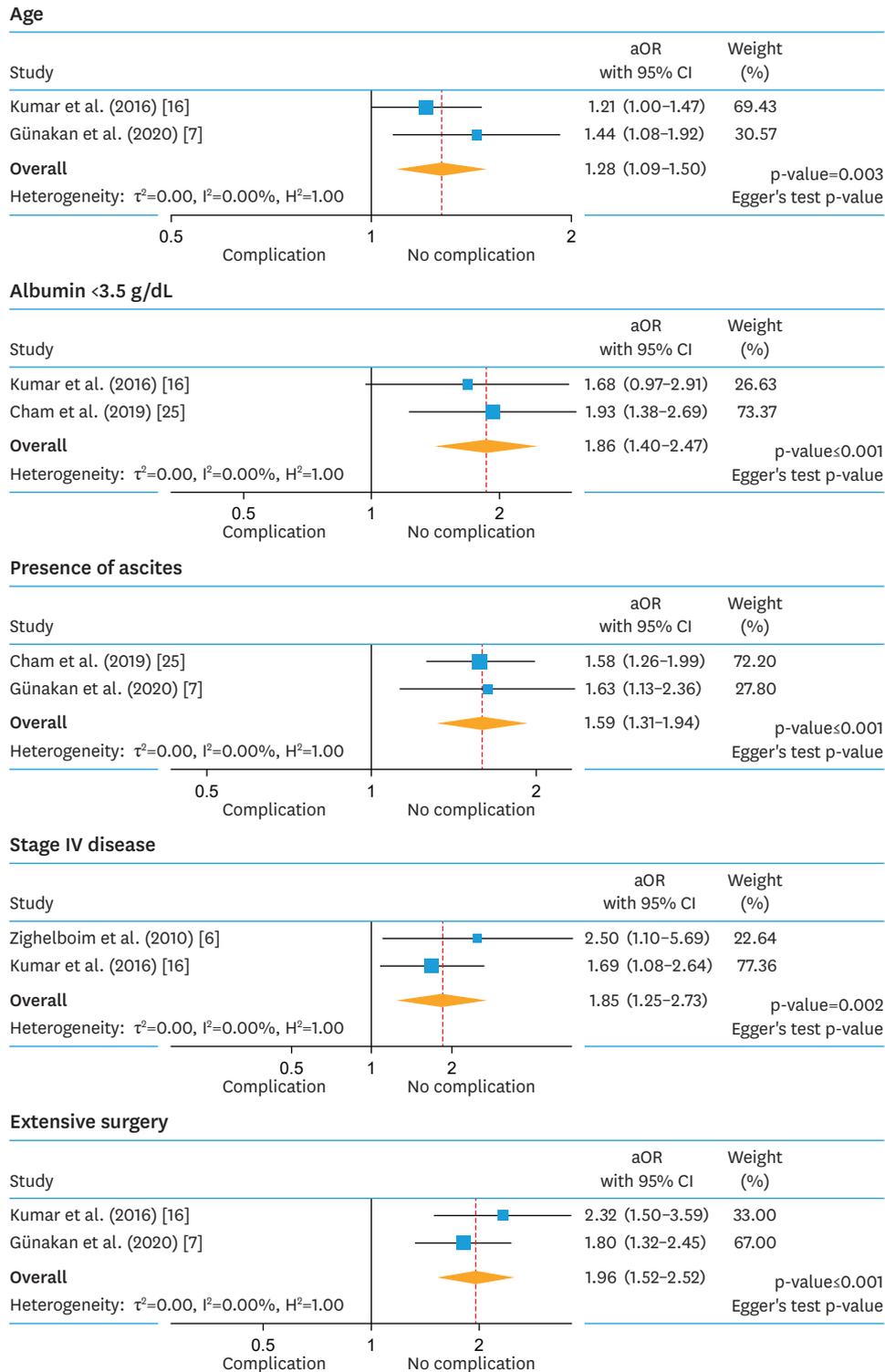


Fig. 1. Forest plots displaying pooled adjusted odds ratios of factors associated with postoperative complications (vs. no complications) from multivariate models. aOR, adjusted odds ratio; CI, confidence interval.

favor more aggressive surgery in order to achieve complete cytoreduction [29]. Nevertheless, postoperative morbidity and mortality should also be considered when aggressive cytoreductive surgery is undertaken [30]. A recent study on adjuvant chemotherapy delay

(ACD) after surgery reported that the threshold of 28 days was associated with adverse overall survival especially in patients with postoperative residual disease [31]. Additionally, Castro et al. [22], reported that ACD were significantly related to surgical complications and shorter progression free survival time in both PDS and IDS was observed in patients with ACD compared to those without ACD.

Patient-based management should be the goal of modern medical practice, and minimizing the postoperative healing period is important for the timely start of adjuvant treatment. In present study, we demonstrated factors associated with postoperative complications in both PDS and IDS in patients with EOC.

Overall, 30-day severe postoperative complications occurred in 2,357 (15.38%) patients and the postoperative mortality rate was 1.92%. These results are in concordance with a previous prospective study [30]. In our present meta-analysis, post-operative complications were classified based on several different classification systems, according to the intensity of the complication or complexity of the treatments. However, no study has demonstrated any classification system to be superior [15].

Surgical complexity is known to increase postoperative complications [30]. In the present study, extensive surgery was significantly associated with severe postoperative complications. Patients with extensive surgery had a 1.96-time increased odds of severe postoperative complications compared to those who underwent standard surgery (95% CI=1.52–2.52; p -value<0.001; $I^2=0\%$). Pepin et al. [24], retrospectively evaluated 635 ovarian cancer patients. The authors reported that the rate of intensive care unit (ICU) admission among patients undergoing PDS was higher than for those who received NACT followed by IDS. However, the indication for admission, length of stay and surgical complexity were similar between both groups. Another study suggested that the most important risk factors for major complications in advanced ovarian cancer surgery were >5 visceral resections, rectosigmoid resection, Glissonian (liver surgery) and pelvic peritonectomy. The authors proposed a model that predicted postoperative complications at nearly 70% [15]. The present meta-analysis also supports that patients who underwent peritonectomy, splenectomy or colon surgery had a significantly increased risk of postoperative complications compared to those who did not. We also found that patients who underwent liver surgery had a 10-time increase in the odds of postoperative complication, although this was not statistically significant.

Our meta-analysis demonstrated that ECOG performance status >0, presence of comorbidities, presence of ascites in preoperative imaging, and FIGO stage IV disease were the preoperative parameters that associated with postoperative complications (grade 1–5). In adjusted OR, age, presence of ascites, hypoalbuminemia <3.5 g/dL and stage IV disease were also the significant predictors for severe postoperative complications (grade 3–5).

It has been well recognized that advanced age carries an increased risk of mortality and morbidity after surgery [8]. A population-based study of 2,087 ovarian cancer patients reported that over 50% of patients who underwent cytoreductive surgery were older than 60 years. Among them, nearly 10% were ≥ 80 years [32]. The authors concluded that age was a significant predictor of 30-day postoperative mortality and morbidity and patients who were ≥ 80 years old were at 9-time increase risk of dying and were 70% more likely to develop 30-day post-operative complications [32]. In our review, patients with postoperative complications were significantly older than those without complications with WMD of 4.1

year (95% CI=2.6–5.6; p-value<0.001; I²=34.40%). Additionally, we found that patients with age ≥60 years had almost twice the odds of developing post-operative complication compared to those <60 years. The result from the pooled multivariate analyses also supported that age was a significant factor associated with postoperative complications (adjusted OR=1.28; 95% CI=1.09–1.50; p-value=0.003; I²=0%). However, a recent study has highlighted that frailty may be a more sensitive predictor of postoperative morbidity and mortality than age [33]. Frailty is a geriatric syndrome characterized with age-related cumulative decline in multiple physiological functions and reserve [34]. Recently, frailty assessment instruments have been developed that assess function across a variety of domains: physical status, cognitive function, comorbidities, self-reported activities and clinical judgment. Although there is scant evidence from gynecologic oncology about this issue, other disciplines have noted that patients with frailty should be carefully evaluated preoperatively by multidisciplinary teams [34].

Serum albumin has been traditionally used as a measurement for patient's nutritional status. Hypoalbuminemia commonly found in patients with advanced cancer disease and low performance status [35]. Approximately, 10%–30% of EOC patients have hypoalbuminemia [36]. In colorectal cancer patients, hypoalbuminemia significantly increases the length of hospital stay, rates of surgical site infections, enterocutaneous fistula risk, and deep vein thrombosis formation [37]. Similar findings have been observed among gynecological malignancy patients. Preoperative hypoalbuminemia defined as serum albumin <3.5 g/dL was associated with severe postoperative complications and poor overall survival in EOC patients [36]. Additionally, the delay of surgical procedures to allow for preoperative correction of albumin levels in hypoalbuminemia patients has been shown to improve morbidity and mortality in patients undergoing colorectal surgery [37]. However, there is no definitive evidence that the same is true in gynecological malignancies [35]. In the present study, the pooled adjusted OR for preoperative albumin <3.5 g/dL was 1.86 (95% CI=1.40–2.47; p-value<0.001; I²=0%). This finding supports the importance of preoperative assessment of serum albumin levels. We propose that serum albumin should be routinely evaluated in patients who are candidates for cancer surgery and should be added to future complication risk assessment tools.

Malignant ascites is often found in advanced stage in ovarian cancer and significantly contributes to poor quality of life and mortality. Ascites is highly correlated with disseminated peritoneal carcinomatosis. Moreover, patients with malignant ascites commonly also present with abdominal distension, anorexia, dyspnea, insomnia, and fatigue which associated with low functional capacity [38]. A study of the impact of ascites on surgical outcomes reported that the presence of a high amount of ascites at cytoreductive surgery is associated with higher blood transfusion requirements, prolonged hospital stays and postoperative ICU treatment compared to patients without ascites [39]. This finding is in concordance with our analysis that patients with ascites had a 1.59 increase in the odds of postoperative morbidity compared with those without ascites (95% CI=1.31–1.94; p-value<0.001; I²=0%).

Patients with stage IV disease carry a large intra or extra abdominal tumor burden, and therefore require more extensive surgery. At present, patients who are not candidates for PDS are alternatively treated with NACT follow with IDS. However, our study demonstrated that FIGO stage IV disease was an important prognostic factor for postoperative complication in patients who underwent both PDS and IDS. A univariate analysis of Castro et al. [22] reported that surgical time >300 minutes was related to major complications in IDS patients.

Over the past decade, the concept of NACT followed by IDS has been accepted as an alternative treatment for patients who were inoperable for PDS. Several studies demonstrated that patients in the NACT group had a lower rate of serious adverse events, post-operative mortality and need for stoma formation [40,41]. Our study also supports those patients who received NACT followed by IDS had half of the odds of developing post-operative complications compared to those who underwent PDS. However, the evidence from meta-analysis has shown an inconclusive primary survival difference between PDS and IDS [40]. As a result, patients treated with IDS should be continuously monitored since emerging studies suggest that complete cytoreduction at time of PDS carries a more favorable prognosis [42,43]. Choosing the most appropriate treatment to balance the benefits and risk of cytoreductive surgery in EOC remains a challenging issue for gynecologic oncologists.

We know that patients undergoing major surgery will develop surgical stress which could delay postoperative recovery, even in patient without complications. During the last several years, Enhanced Recovery After Surgery (ERAS) programs have been introduced. In patients with gynecologic malignancies, the use of ERAS protocols have been shown to reduce the postoperative length of hospital stay as well as the incidence of postoperative complications [44]. However, the program is inhomogeneous between institutes and mainly focuses on the perioperative and immediate postoperative period. Our study demonstrated that preoperative hypoalbuminemia and performance status are potential modifiable risk factors for post-operative complications. More recent evidence indicates that improvements in preoperative physical fitness and nutrition through prehabilitation programs added to ERAS perioperative care have a promising result in other malignancies [45]. However, these studies are still limited in gynecological malignancy.

The present meta-analysis demonstrated factors associated with postoperative complications after both PDS and IDS for primary EOC. The individual studies included high-volume single center, multicenter and population-based cohorts. All included studies were high quality studies according to Newcastle-Ottawa Quality Assessment Scale. Nevertheless, most of studies were retrospective cohort studies, which may carry the risk of missing data, selection bias and other possible unobserved confounding. Secondly, all summary data were extracted from published scientific journals, and individual patient data were not available for analysis.

In conclusion, in the era of platinum-based chemotherapy, maximal cytoreductive to no gross residual tumor is the state of art for advanced stage EOC. However, extensive surgery strongly correlates with postoperative morbidity and mortality. Patients-based treatment is essential in order to balance the benefit of aggressive cytoreductive surgery and postoperative morbidity. Patients with advanced age, presence of ascites, preoperative albumin <3.5 g/dL, FIGO stage IV and extensive surgery, were at higher risk of developing severe postoperative complications. Patients who received NACT followed by IDS had a lower risk of developing postoperative complications. Nevertheless, the survival benefit after NACT for EOC remains inconclusive. Our findings highlight the importance of preoperative patients' performance and albumin status as adjustable preoperative factors. These findings could be useful in developing patient based preoperative protocols to reduce postoperative complications in the future. A multidisciplinary team approached should be instituted preoperatively to tailor treatment programs for these specific patients. Moreover, physicians should pay attention to patient's performance and nutritional status since they were the only significant adjustable preoperative risk factors associated with postoperative complications. We suggested that all EOC should undergo routine preoperative serum albumin testing and nutritional status assessment and counselling.

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SUPPLEMENTARY MATERIALS

Table S1

The search strings

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Table S2

Review of literatures

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Table S3

Quality assessment of the included studies using the Newcastle-Ottawa Quality Assessment Scale

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Fig. S1

Flow diagram of study selection.

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REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209-49.
[PUBMED](#) | [CROSSREF](#)
2. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol* 2002;20:1248-59.
[PUBMED](#) | [CROSSREF](#)
3. Gerestein CG, Damhuis RA, de Vries M, Reedijk A, Burger CW, Kooi GS. Causes of postoperative mortality after surgery for ovarian cancer. *Eur J Cancer* 2009;45:2799-803.
[PUBMED](#) | [CROSSREF](#)
4. Di Donato V, Kontopantelis E, Aletti G, Casorelli A, Piacenti I, Bogani G, et al. Trends in mortality after primary cytoreductive surgery for ovarian cancer: a systematic review and metaregression of randomized clinical trials and observational studies. *Ann Surg Oncol* 2017;24:1688-97.
[PUBMED](#) | [CROSSREF](#)
5. Rafii A, Stoeckle E, Jean-Laurent M, Ferron G, Morice P, Houvenaeghel G, et al. Multi-center evaluation of post-operative morbidity and mortality after optimal cytoreductive surgery for advanced ovarian cancer. *PLoS One* 2012;7:e39415.
[PUBMED](#) | [CROSSREF](#)

6. Zigelboim I, Kizer N, Taylor NP, Case AS, Gao F, Thaker PH, et al. "Surgical Apgar Score" predicts postoperative complications after cytoreduction for advanced ovarian cancer. *Gynecol Oncol* 2010;116:370-3.
[PUBMED](#) | [CROSSREF](#)
7. Günakan E, Tohma YA, Tunç M, Akıllı H, Şahin H, Ayhan A. Factors associated with surgical morbidity of primary debulking in epithelial ovarian cancer. *Obstet Gynecol Sci* 2020;63:64-71.
[PUBMED](#) | [CROSSREF](#)
8. Gerestein CG, Nieuwenhuyzen-de Boer GM, Eijkemans MJ, Kooi GS, Burger CW. Prediction of 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer. *Eur J Cancer* 2010;46:102-9.
[PUBMED](#) | [CROSSREF](#)
9. Rausei S, Uccella S, D'Alessandro V, Gisone B, Frattini F, Lianos G, et al. Aggressive surgery for advanced ovarian cancer performed by a multidisciplinary team: A retrospective analysis on a large series of patients. *Surg Open Sci* 2019;1:43-7.
[PUBMED](#) | [CROSSREF](#)
10. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006-12.
[PUBMED](#) | [CROSSREF](#)
11. Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. *Syst Rev* 2021;10:39.
[PUBMED](#) | [CROSSREF](#)
12. Harzing AW. Publish or perish [Internet]. Rotterdam: Harzing.com; 2021 [cited 2021 Aug 1]. Available from: <https://harzing.com/resources/publish-or-perish>.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344-9.
[PUBMED](#) | [CROSSREF](#)
14. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205-13.
[PUBMED](#) | [CROSSREF](#)
15. Lluca A, Serra A, Maiocchi K, Delgado K, Jativa R, Gomez L, et al. Predictive model for major complications after extensive abdominal surgery in primary advanced ovarian cancer. *Int J Womens Health* 2019;11:161-7.
[PUBMED](#) | [CROSSREF](#)
16. Kumar A, Janco JM, Mariani A, Bakkum-Gamez JN, Langstraat CL, Weaver AL, et al. Risk-prediction model of severe postoperative complications after primary debulking surgery for advanced ovarian cancer. *Gynecol Oncol* 2016;140:15-21.
[PUBMED](#) | [CROSSREF](#)
17. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603-5.
[PUBMED](#) | [CROSSREF](#)
18. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135.
[PUBMED](#) | [CROSSREF](#)
19. Inci MG, Rasch J, Woopen H, Mueller K, Richter R, Sehouli J. ECOG and BMI as preoperative risk factors for severe postoperative complications in ovarian cancer patients: results of a prospective study (RISC-GYN-trial). *Arch Gynecol Obstet* 2021;304:1323-33.
[PUBMED](#) | [CROSSREF](#)
20. Sharma S, Driscoll D, Odunsi K, Venkatadri A, Lele S. Safety and efficacy of cytoreductive surgery for epithelial ovarian cancer in elderly and high-risk surgical patients. *Am J Obstet Gynecol* 2005;193:2077-82.
[PUBMED](#) | [CROSSREF](#)
21. Benedetti Panici P, Di Donato V, Fischetti M, Casorelli A, Perniola G, Musella A, et al. Predictors of postoperative morbidity after cytoreduction for advanced ovarian cancer: analysis and management of complications in upper abdominal surgery. *Gynecol Oncol* 2015;137:406-11.
[PUBMED](#) | [CROSSREF](#)
22. Castro BGR, Dos Reis R, Cintra GF, Sousa MMA, Vieira MA, Andrade CEMDC. Predictive factors for surgical morbidities and adjuvant chemotherapy delay for advanced ovarian cancer patients treated by primary debulking surgery or interval debulking surgery. *Int J Gynecol Cancer* 2018;28:1520-8.
[PUBMED](#) | [CROSSREF](#)

23. Yalcin Y, Tatar B, Erdemoglu E, Erdemoglu E. The parameters to estimate postoperative severe complications classified through Clavien-Dindo after upper abdominal surgery in patients with primary and recurrent ovarian cancer. *Ginekol Pol* 2019;90:557-64.
[PUBMED](#) | [CROSSREF](#)
24. Pepin K, Bregar A, Davis M, Melamed A, Hinchcliff E, Gockley A, et al. Intensive care admissions among ovarian cancer patients treated with primary debulking surgery and neoadjuvant chemotherapy-interval debulking surgery. *Gynecol Oncol* 2017;147:612-6.
[PUBMED](#) | [CROSSREF](#)
25. Cham S, Chen L, St Clair CM, Hou JY, Tergas AI, Melamed A, et al. Development and validation of a risk-calculator for adverse perioperative outcomes for women with ovarian cancer. *Am J Obstet Gynecol* 2019;220:571.e1-8.
[PUBMED](#) | [CROSSREF](#)
26. Xu Z, Becerra AZ, Justiniano CF, Aquina CT, Fleming FJ, Boscoe FP, et al. Complications and survivorship trends after primary debulking surgery for ovarian cancer. *J Surg Res* 2020;246:34-41.
[PUBMED](#) | [CROSSREF](#)
27. Chang SJ, Hodeib M, Chang J, Bristow RE. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis. *Gynecol Oncol* 2013;130:493-8.
[PUBMED](#) | [CROSSREF](#)
28. Eisenhauer EL, Abu-Rustum NR, Sonoda Y, Levine DA, Poynor EA, Aghajanian C, et al. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. *Gynecol Oncol* 2006;103:1083-90.
[PUBMED](#) | [CROSSREF](#)
29. Chi DS, Eisenhauer EL, Zivanovic O, Sonoda Y, Abu-Rustum NR, Levine DA, et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. *Gynecol Oncol* 2009;114:26-31.
[PUBMED](#) | [CROSSREF](#)
30. Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. *Am J Obstet Gynecol* 2007;197:676.e1-7.
[PUBMED](#) | [CROSSREF](#)
31. Hofstetter G, Concin N, Braicu I, Chekеров R, Sehouli J, Cadron I, et al. The time interval from surgery to start of chemotherapy significantly impacts prognosis in patients with advanced serous ovarian carcinoma - analysis of patient data in the prospective OVCAD study. *Gynecol Oncol* 2013;131:15-20.
[PUBMED](#) | [CROSSREF](#)
32. Mahdi H, Wiechert A, Lockhart D, Rose PG. Impact of age on 30-day mortality and morbidity in patients undergoing surgery for ovarian cancer. *Int J Gynecol Cancer* 2015;25:1216-23.
[PUBMED](#) | [CROSSREF](#)
33. Lin HS, Watts JN, Peel NM, Hubbard RE. Frailty and post-operative outcomes in older surgical patients: a systematic review. *BMC Geriatr* 2016;16:157.
[PUBMED](#) | [CROSSREF](#)
34. Nidadavolu LS, Ehrlich AL, Sieber FE, Oh ES. Preoperative evaluation of the frail patient. *Anesth Analg* 2020;130:1493-503.
[PUBMED](#) | [CROSSREF](#)
35. Bekos C, Polterauer S, Seebacher V, Bartl T, Joura E, Reinthaller A, et al. Pre-operative hypoalbuminemia is associated with complication rate and overall survival in patients with vulvar cancer undergoing surgery. *Arch Gynecol Obstet* 2019;300:1015-22.
[PUBMED](#) | [CROSSREF](#)
36. Ayhan A, Günakan E, Alyazıcı İ, Haberal N, Altundağ Ö, Dursun P. The preoperative albumin level is an independent prognostic factor for optimally debulked epithelial ovarian cancer. *Arch Gynecol Obstet* 2017;296:989-95.
[PUBMED](#) | [CROSSREF](#)
37. Truong A, Hanna MH, Moghadamyeghaneh Z, Stamos MJ. Implications of preoperative hypoalbuminemia in colorectal surgery. *World J Gastrointest Surg* 2016;8:353-62.
[PUBMED](#) | [CROSSREF](#)
38. Penet MF, Krishnamachary B, Wildes FB, Mironchik Y, Hung CF, Wu TC, et al. Ascites volumes and the ovarian cancer microenvironment. *Front Oncol* 2018;8:595.
[PUBMED](#) | [CROSSREF](#)
39. Feldheiser A, Braicu EI, Bonomo T, Walther A, Kaufner L, Pietzner K, et al. Impact of ascites on the perioperative course of patients with advanced ovarian cancer undergoing extensive cytoreduction: results of a study on 119 patients. *Int J Gynecol Cancer* 2014;24:478-87.
[PUBMED](#) | [CROSSREF](#)

40. Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P, Bryant A. Interval debulking surgery for advanced epithelial ovarian cancer. *Cochrane Database Syst Rev* 2016;2016:CD006014.
[PUBMED](#) | [CROSSREF](#)
41. Coleridge SL, Bryant A, Kehoe S, Morrison J. Neoadjuvant chemotherapy before surgery versus surgery followed by chemotherapy for initial treatment in advanced ovarian epithelial cancer. *Cochrane Database Syst Rev* 2021;7:CD005343.
[PUBMED](#) | [CROSSREF](#)
42. Narasimhulu DM, Thannickal A, Kumar A, Weaver AL, McGree ME, Langstraat CL, et al. Appropriate triage allows aggressive primary debulking surgery with rates of morbidity and mortality comparable to interval surgery after chemotherapy. *Gynecol Oncol* 2021;160:681-7.
[PUBMED](#) | [CROSSREF](#)
43. May T, Comeau R, Sun P, Kotsopoulos J, Narod SA, Rosen B, et al. A comparison of survival outcomes in advanced serous ovarian cancer patients treated with primary debulking surgery versus neoadjuvant chemotherapy. *Int J Gynecol Cancer* 2017;27:668-74.
[PUBMED](#) | [CROSSREF](#)
44. Tankou JI, Foley O, Falzone M, Kalyanaraman R, Elias KM. Enhanced recovery after surgery protocols improve time to return to intended oncology treatment following interval cytoreductive surgery for advanced gynecologic cancers. *Int J Gynecol Cancer* 2021;31:1145-53.
[PUBMED](#) | [CROSSREF](#)
45. Cuijpers ACM, Heldens AFJM, Bours MJL, van Meeteren NLU, Stassen LPS, Lubbers T, et al. Relation between preoperative aerobic fitness estimated by steep ramp test performance and postoperative morbidity in colorectal cancer surgery: prospective observational study. *Br J Surg* 2022;109:155-9.
[PUBMED](#) | [CROSSREF](#)