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Review

# Are preoperative serum cancer antigen 125 levels a prognostic factor for outcome in epithelial ovarian cancer? A systematic review

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## Abstract

**Background**: Most patients with epithelial ovarian cancers (EOC) present with advanced-stage disease because of non-specific symptoms and lack of reliable strategies for early diagnosis. Cancer antigen 125 (CA-125) is suggested as a useful prognostic biomarker, its serum level is raised in over 80.0% of patients with EOC. Primary debulking surgery (PDS) followed by chemotherapy is the conventional treatment, but neoadjuvant chemotherapy followed by interval debulking surgery (NACT-IDS) is offered to patients with unresectable disease. There are inconsistencies regarding the role of preoperative CA-125 serum levels to adopt in stratifying patients for treatment choice that offers the most benefit. This review aimed to determine the role of preoperative CA-125 levels in predicting optimal cytoreduction and the association between optimal cytoreduction and survival outcome in patients with EOC.

**Methodology**: Three electronic databases CINAHL, Cochrane library and PubMed were searched for potentially relevant articles from 2016 to 2021 on the role of preoperative CA-125 levels in predicting optimal cytoreduction and survival in patients with epithelial ovarian carcinomas.

**Conclusion**: In patients who underwent NACT-IDS, a lower preoperative CA-125 value is a predictor of optimal cytoreduction and an increase in preoperative CA-125 value is consistently associated with a decrease in optimal cytoreduction. There was insufficient data to assess overall survival. However, a raised preoperative CA-125 level is poor predictor of chance of achieving optimal cytoreduction and the rate of optimal cytoreduction was a weak predictor of overall survival in women who had primary debulking surgery.

**Keywords**:

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**Quick Response Code:**

## Introduction

Ovarian cancer is the deadliest cancer of the female genital tract [1-3], with less than 30% of cases surviving beyond 5 years after diagnosis.[1, 4, 5] The main reason for the high death rate is that ovarian cancer presents mostly late due to lack of specific signs and symptoms with around 75.0% of patients presenting in stages III and IV disease. [6]Of these women presenting with stages III and IV disease, approximately 36.0% have had several clinic visitations before the diagnosis of ovarian cancer was made.[7] The 5-year survival is 90.0% for early stage, however, the overall survival is poor as only a quarter of the patients are diagnosed with such early-stage disease.[8]

Cancer antigen 125 (CA-125) is the most frequently evaluated tumour marker in ovarian carcinoma. [9, 10] It is also known as carbohydrate antigen 125 or MUC16 or mucin 16.

CA-125 value is considered elevated (abnormal) when it is ≥35.0U/ml and this is seen in 99.0%, 89.0% and 69.0% of serous, endometrioid and mucinous EOC respectively[11] and in 79.0% of clear cell cancers. [12] Strikingly, CA-125 serum value is elevated in about 50.0%, 90.0%, 92.0% and 94.0% of patients with stages I, II, III and IV of ovarian carcinomas respectively, underlining its lack of sensitivity in detecting ovarian cancer at its earliest stage. [12]

While the standard treatment for advanced EOC remains primary debulking surgery (PDS) and adjuvant chemotherapy, NACT-IDS is gradually increasing in popularity [13] and has been demonstrated to be similarly effective. [14] Treatment is associated with complete response in only about 20.0% ofpatients; the remaining 80.0% develop relapse to chemotherapy and the progression-free survival (PFS) is 12 to 18 months. [15] However, patients with early stage (International Federation of Obstetricians and Gynaecologists (FIGO) (stages I and II) disease have a better 5-year survival rate at around 90.0%. [16] Consequently, management approaches have been subject of much controversy as to which approach be given first consideration in patients with advanced-stage EOC. [9, 17]

Cancer antigen 125 enhances the replication of malignant cells by inhibiting the host's immunological response mechanisms thereby leaving the cancerous cellular proliferation unchecked. [6, 10] It achieves this by specifically inhibiting the destruction of cancer cells by Natural Killer (NK) cells. [10] It also interacts with mesothelin, and this association is reported to play a significant role in the metastasis of ovarian adenocarcinomas, with a CA-125-induced cellular migration mechanism that is thought to be mediated by the Wnt signal pathway. [18]Mesothelin has a unique binding site on CA-125 and this binding is thought to play an important role in metastasis. [19] Therefore, both inhibition of cell migration by Wnt inhibitor DKK-1 and DKK-1 dependent malignant cellular migration are reversible by CA-125NK cells incubated with CA-125 experienced a 50.0-70.0% reduction in ability to destroy cancer cells. [19] DMAN-1, an activator of NK cells is down-regulated, and this further diminishes their activation towards ovarian cancer cells. [20]

One of the important hallmarks of ovarian malignant cells is the capability to proliferate even in the absence of exogenous stimuli. [21] The CA-125 C-terminal domain stimulates clonal formation via cell-cell dependent and cell-cell independent mechanisms. [21] Evidence has also shown that CA-125 C-terminal domain expression facilitates growth, cellular migration, invasiveness, and metastasis of ovarian carcinomas. [22] Additionally, CA-125 has been demonstrated to regulate epithelial-mesenchymal transition of ovarian cancer cells, which is a critical step in ovarian carcinogenesis.[22] Therefore, CA-125 is not only a biomarker in oncogenesis, but also a valuable marker of ovarian cancer progression. [21] CA-125 also plays a significant role in regulation of glucose transporter 1, which enhances glycogen production and hence supplies the malignant cells with the required energy for continuous proliferation.

As ovarian cancer advances in stage and metastasizes, serum levels of CA-125 also increase and this has a positive correlation with tumour cell count and in situations where optimal treatment has been achieved, the serum level of CA-125 rapidly declines. [23] Consequently, serum levels of CA-125 can serve as a surrogate marker of tumour volume, [24] and this could assist in stratifying patients into those who optimal debulking may or may not be feasible**.** This would spare a significant number of patients with advanced-stage disease from undergoing debulking surgery with co-existing morbidities without a corresponding improvement in overall survival.

The CA-125 level could play a role as a prognostic biomarker in EOC as CA-125 level is elevated in greater than 85.0% of women with advanced-stage epithelial ovarian cancer. [3]

## Methodology

A comprehensive scoping search of the literature was carried out for the types of studies conducted on the topic to identify relevant keywords in databases and to get a clearer understanding of the topic. This was done to help develop an effective search strategy for the systematic review.

A thorough search was conducted on electronic databases using key terms from the research questions, after relevant keywords were identified. The databases CINHAL, Cochrane and PubMed were extensively searched for articles that are eligible from 2016 to 2022 for this systematic review initially on July 20, 2022, and an updated search was conducted on October 27, 2022.

Keywords used in the searches fell into three categories comprising ovarian cancer (the disease), CA-125 (the marker) and outcome and these three strings were combined to produce the final search string by use of the Boolean operator 'AND'. Details of the keywords and search strategy used are detailed separately and as appropriately for PubMed (Table 1) and CINHAL (Table 2), due to operational differences inherent in these databases. The systematic review was carried out in compliance with the Preferred Reporting item for Systematic review and Meta-analysis recommendation statement 2009 (PRISMA-2009). [25] The search results were imported into Endnote citation manager. The reference list of all returned articles was manually searched for relevant articles that met the inclusion criteria.

### Inclusion criteria

This systematic review was limited to only primary research papers that had abstracts or full texts available in English that were published from 2016 onwards. Only those papers which evaluated epithelial ovarian cancer were included. Furthermore, patients must have had a histologically confirmed diagnosis of ovarian cancer originating from the ovary, but no restrictions were placed on the histological type of epithelial ovarian cancer. Outcomes such as, overall survival (OS) and recurrence/relapse were included only if a primary research paper contained data on rate of optimal cytoreduction. Studies were included irrespective of whether patients had primary debulking surgery (PDS), secondary cytoreductive surgery (SCS) or NACT-IDS.

### Exclusion criteria

Excluded from the review were publications on benign ovarian tumours, germ cell and sex-cord stromal tumours and carcinomas originating from other sites and deposited on the ovaries as metastases. In addition, studies that assessed the role of changes in CA-125 such as longitudinal changes, nadir, or role of postoperative CA-125 on outcome of ovarian cancer were excluded from the systematic review because the review focused on preoperative CA-125 level. Studies that assessed the role of preoperative CA-125 together with other biomarkers, CA-125 values less than 35.0U/ml or inconsistent unit (mg/dl) of reporting were excluded because the authors did not use internationally acceptable value and unit; thus, it was not possible to consider their results in the context of this review. Primary research that evaluated the

role of preoperative CA-125 in combination with any form of radiological investigation such as transvaginal ultrasound scan, computerized tomography scan (CT scan) and positron emission tomographic scan (PET scan) were again excluded because it was not possible to extract from the various papers data on the role of CA-125 alone as a prognostic factor. Also excluded were theses, reports, reviews, personal views, case reports, and abstracts with insufficient data on intervention and outcomes.

Table 1. Keywords and search strategy on PubMed and date of search, October 27, 2022

| **Keyword** | **Synonyms** | **Search string** |
|---|---|---|
| Ovarian cancer | ovarian neoplasm<br>ovarian cancer<br>ovarian carcinoma<br>cancer of ovary<br>ovarian malignancy<br>epithelial ovarian cancer | ("ovarian neoplasm*"[All Fields] OR "ovarian cancer*"[All Fields] OR neoplasia OR "ovarian carcinoma*"[All Fields] OR "cancer of ovary"[All Fields] OR "ovarian malignancy"[All Fields] OR "epithelial ovarian cancer*"[All Fields]) |
| Cancer antigen 125 | preoperative CA-125<br>preoperative cancer antigen 125<br>mucin 16<br>pre-treatment CA-125<br>CA 125<br>ca-125<br>carbohydrate antigen 125 | ("preoperative CA-125"[All Fields] OR "preoperative cancer antigen 125"[All Fields] OR "mucin 16"[All Fields] OR "pre-treatment CA-125"[All Fields] OR "CA 125"[All Fields] OR ("ca 125 antigen"[MeSH Terms] OR ("CA 125"[All Fields] AND "antigen"[All Fields]) OR "ca 125 antigen"[All Fields] OR "CA 125"[All Fields]) OR "carbohydrate antigen 125"[All Fields]) |
| Outcome | survival<br>progression-free survival, overall survival<br>mortality<br>suboptimal debulking<br>lymph node metastasis<br>Optimal cytoreduction<br>suboptimal cytoreduction” | ("mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields] OR "progression-free survival"[All Fields] OR "overall survival"[All Fields] OR "mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading] OR "suboptimal debulking"[All Fields] OR "optimal cytoreduction"[All Fields] OR "suboptimal cytoreduction"[All Fields]) |

Table 2. Keywords and search strategy CINAHL and date of search, October 27, 2022

| **Keyword** | **Synonym** | **Search string** |
|---|---|---|
| Ovarian cancer | ovarian neoplasm<br>ovarian cancer<br>ovarian carcinoma<br>cancer of ovary<br>ovarian malignancy<br>epithelial ovarian cancer | (TI“ovarian neoplasm”) OR (AB“ovarian neoplasm”) OR (TI“Ovarian neoplasm”) OR (AB“Ovarian neoplasm”) OR (TI“ovarian cancer”) OR (AB“ovarian cancer”) OR (TI“Ovarian cancer”) OR (AB“Ovarian cancer”) OR (TI“ovarian carcinoma”) OR (AB“ovarian carcinoma”) OR (TI“Ovarian carcinoma”) OR (AB“Ovarian carcinoma”) OR (TI“cancer of ovary”) OR (AB“Cancer of ovary”) OR (TI“Cancer of ovary”) OR (AB“Cancer of ovary”) OR (TI“ovarian malignancy”) OR (AB“ovarian malignancy”) OR (TI“Ovarian malignancy”) OR (AB“Ovarian malignancy”) |
| Cancer antigen 125 | preoperative CA-125<br>preoperative cancer antigen 125<br>mucin 16<br>pretreatment CA-125<br>CA 125<br>ca-125<br>carbohydrate antigen 125 | (TI“preoperative CA-125”) OR (AB“preoperative CA-125”) OR (TI“Preoperative CA-125”) OR (AB“Preoperative CA-125”) OR (TI“preoperative cancer antigen 125”) OR (AB“preoperative cancer antigen 125”) OR (TI“Preoperative cancer antigen 125”) OR (AB“Preoperative cancer antigen 125”) OR (TI“mucin 16”) OR (AB“mucin 16”) OR (TI“Mucin 16”) OR (AB“Mucin 16”) OR (TI“pretreatment CA-125”) OR (AB“pretreatment CA-125”) OR (TI“Pretreatment CA-125”) OR (AB“Pretreatment CA-125”) OR (TI“CA 125”) OR (AB“CA 125”) OR (TI“cA 125”) OR (AB“cA 125”) OR (TI“ca-125”) OR (AB“ca-125”) OR (TI”Ca-125”) OR (AB”Ca-125”) |
| Outcome | survival progression-free survival, overall survival mortality suboptimal debulking lymph node metastasis Optimal cytoreduction suboptimal cytoreduction” | (TI“survival”) OR (AB“survival”) OR (TI“Survival”) OR (AB“Survival”) OR (TI“progression-free survival”) OR (AB“progression-free survival”) OR (TI“Progression-free survival”) OR (AB“Progression-free survival”) OR (TI“overall survival”) OR (AB“overall survival”) OR (TI“Overall survival”) OR (AB“Overall survival”) OR (TI“mortality”) OR (AB“mortality”) OR (TI“Mortality”) OR (AB“Mortality”) OR (TI“suboptimal debulking”) OR (AB“suboptimal debulking”) OR (TI“Suboptimal debulking”)OR (AB“Suboptimal debulking”) |

**Selection of studies**

The titles and abstracts of the identified articles were screened based on the inclusion and exclusion criteria and studies with no relevance to the research question removed by the reviewers. The selected articles were compared, duplicates removed using Endnote citation manager and visual scan, and discrepancies resolved. Articles which were not Open Access were accessed via the University of Chester library search portal and full texts obtained. The reference lists of selected articles were searched for additional publication that fulfilled the inclusion criteria and these were included in the review.

## Data Extraction

The reviewers extracted the data from the included studies into a Microsoft Excel spreadsheet in line with the PRISMA guidelines. These included: last name of first author, study design, the year of publication, number of patients, preoperative CA-125 value, FIGO stage of tumours in studies, histological types, rate of optimal cytoreduction, 5-year overall survival rate (OS), sensitivity, specificity, and p-value.

## Risk of Bias Assessment

This was assessed using the risk of bias assessment tool on non-randomized studies of interventions (ROBINS-I) tool [26] according to the guidelines supplied with the tool. ROBINS-I makes use of the Cochrane-endorsed risk of bias approach [27] and operates by visual demonstration of risk-of-bias assessment covering the following seven domains: confounding, selection of participants, classification of intervention, deviation from intended intervention, missing data, measurement of outcome, and in selection of the reported results. This tool is especially useful when undertaking systematic reviews that incorporate non-randomized studies [26, 27] . Each study was assessed and was rated as: low, moderate, serious, critical risk of bias or no information where applicable.

## Results

A search of the electronic databases produced 407 publications and two articles [28, 29] from additional sources. Fifty-eight duplicates were removed, and 351 articles were screened for relevance by reading their titles. Based on their titles, 309 articles were removed because they were irrelevant to the topic under review. The remaining forty-two full-text articles were retrieved for application of the inclusion and exclusion criteria. Thirty-three studies were excluded based on the following reasons: six articles predicted a role of CA-125 in prognosis together with HE4, two papers studied CA-125 with CA 19-9, two with other tumour markers, two studies with miRNAs and four studies with radiological investigations; in all cases, it was not possible to extract data on the role of CA-125 alone as a prognostic factor. Two studies evaluated preoperative CA-125 nadir, three studies investigated preoperative CA-125 for preoperative monitoring, and two studies examined CA-125 in non-epithelial ovarian cancers. A further nine articles which looked at changes in serum CA-125 levels as a prognostic factor but did not provide absolute levels of the analyte were excluded. One article [30] did not use internationally acceptable units of measure for CA-125 (used mg/dl instead of U/ml); thus, it was not possible to consider its result in the context of this review.

The nine primary research papers included in this systematic review were considered in two categories based on the intervention administered namely: NACT-IDS [28, 31, 32] and surgical treatment alone, PDS and SCS.[29, 33-36] (Table 3) This is because patients treated with NACT-IDS have unresectable tumour while patients offered surgical treatment had tumour that was resectable.

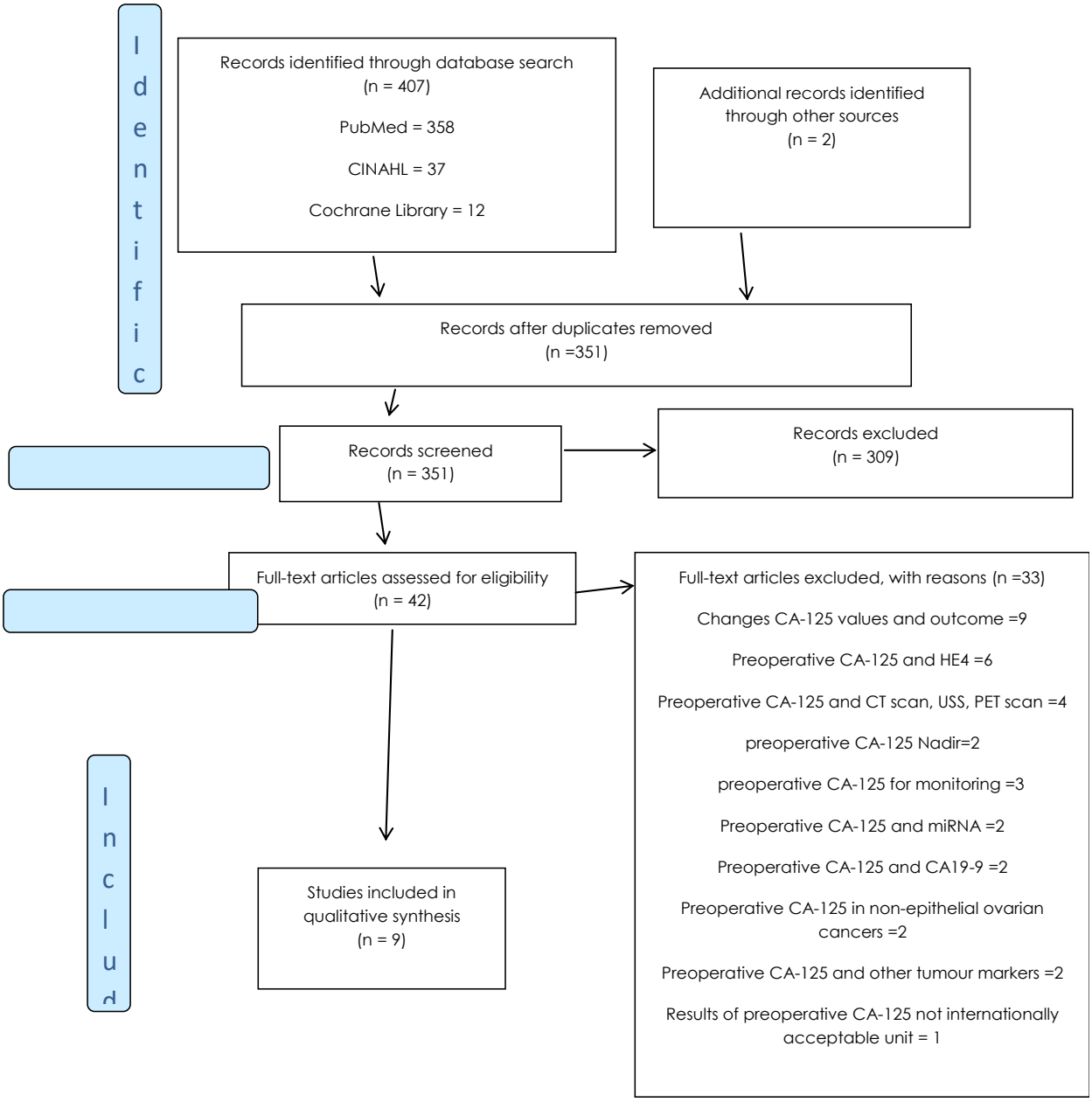



**Figure 1.** PRISMA flow diagram of study identification, screening and application of inclusion and exclusion criteria

The quality of the nine studies selected was assessed using the ROBINS-I tool and an Excel sheet template was imported into a web application package which generated a traffic light plot and a weighted summary bar plot that displays the overall risk of bias (RoB) assessment of each of the seven domains and overall RoB. The ROBINS-I tool was used instead of the Newcastle-Ottawa tool because the Newcastle-Ottawa tool lacks a comprehensive manual for interpretation and results are subject to inter-observer and intra-observer variations. [37] Overall, the studies scored differently with the prospective studies by Prajatmo H. [28] and Muallem et al. [35] having low RoB while the retrospective studies having

moderate RoB based on the colour codes of their seven and overall domains, making them eligible for inclusion in the systematic review (Figure 2).

There were nine studies with 2,122 patients with epithelial ovarian cancers stages I-IV (Table 3). The average preoperative CA-125 serum value was 321.5U/ml and the range are 35.0U/ml to 1066.1U/ml, optimal cytoreduction (the presence of residual tumour less than 10.0mm in diameter after surgical resection) ranges from 55.0-89.9% of patients, while OS rate is 46.3.0-86.0% of patients and varying ranges of sensitivity and specificity and p value (Table 4).

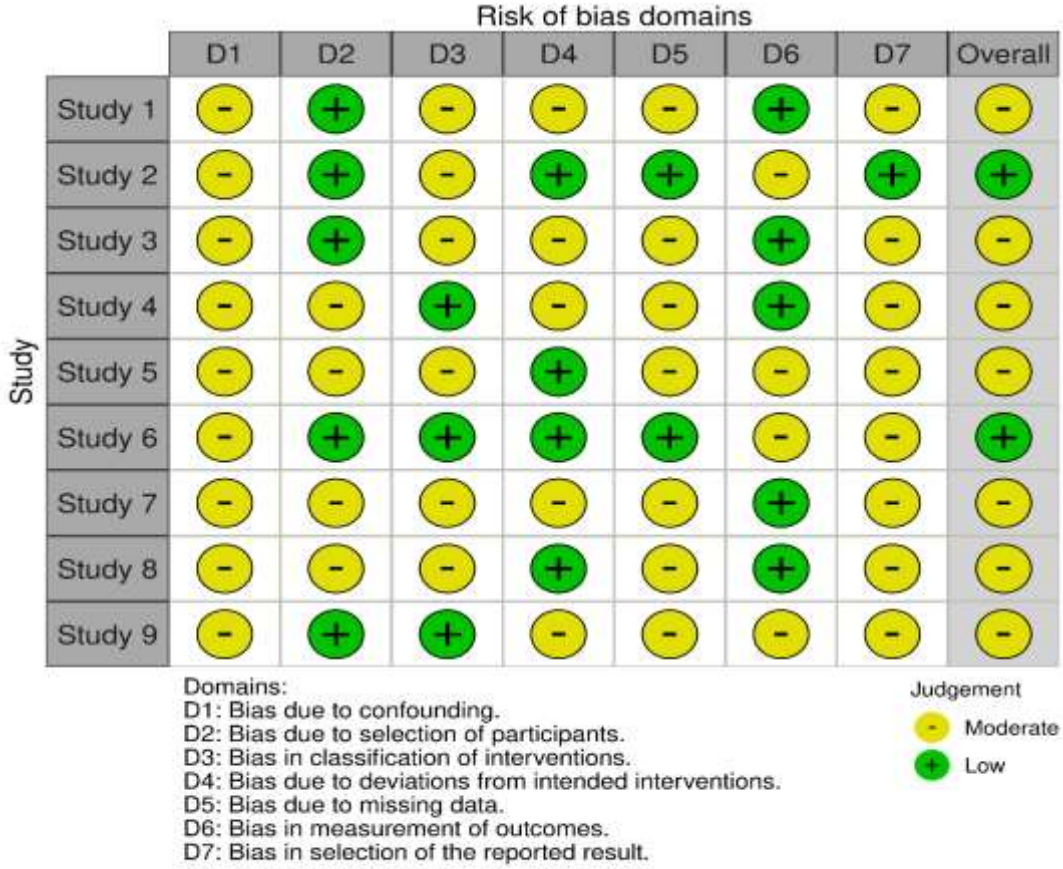



**Figure 2.** Pictorial representation of the domains assessed for risk-of-bias in the papers included in the systematic review

Figure 3. Summary plot of the seven domains of RoB and overall score of risk of bias.

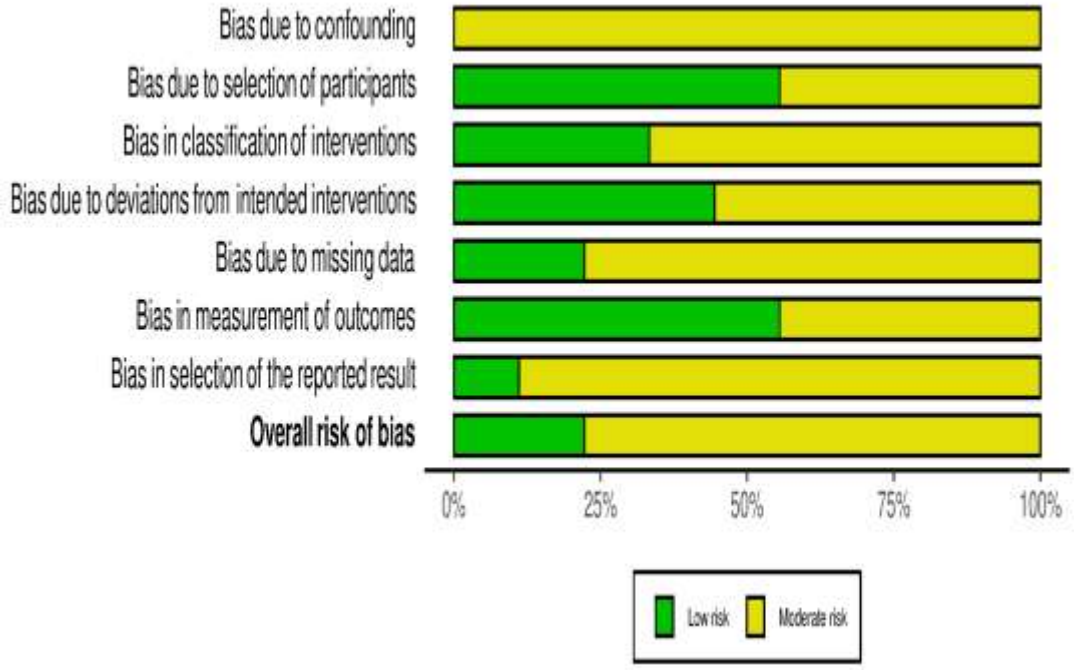



**Figure 3.** Summary plot of the seven domains of RoB and overall score of risk of bias.

**Table 3. Characteristics of studies included in the systematic review**

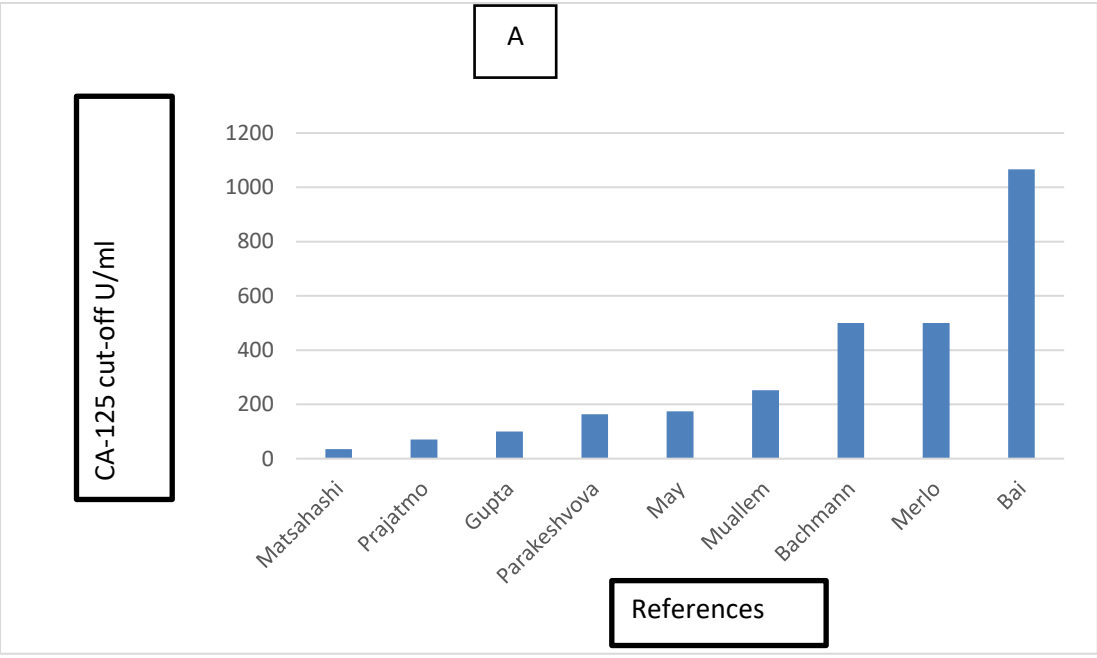
| Study | Reference | Year of publication | Study design | Patients number | FIGO Stage | Early stage (%) | Advanced stage (%) | Type of epithelial Ovarian cancer (%) | Intervention |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Matsuhashi *et al.*[31] | 2017 | Retrosp-ective | 110 | III-IV | 0 | 100.0 | Serous 78.5<br>Mucinous 2.8<br>Endometroid 4.7<br>Clear cell 11.2<br>Undifferentiated 4.7 | NACT-IDS |
| 2 | Prajatmo*et al.*[28] | 2016 | Prospect-ive | 90 | I-IV | 38.9 | 61.1 | Serous 27.8<br>Mucinous 48.9<br>Others 23.4 | NACT-IDS |
| 3 | Gupta *et al.*[38] | 2020 | Retrospe-ctive | 433 | III-IV | 0 | 100.0 | Serous 95.5<br>Others 4.5 | NACT-IDS |
| 4 | Parash-kevova*et al.*[36] | 2018 | Retrospe-ctive | 111 | II-IV | 3.6 | 96.3 | Serous 100.0 | SCS |
| 5 | May *et al.*[34] | 2017 | Retrospe-ctive | 212 | I-IV | 11.3 | 88.7 | Serous 100.0 | PDS |
| 6 | Muallem *et al.*[35] | 2017 | Prospect-ive | 277 | II-IV | 3.1 | 96.9 | Serous 100.0 | PDS |
| 7 | Bachmann *et al.*[29]) | 2020 | Retrospe-ctive | 261 | IIIA-IV | 0 | 100.0 | Serous 100.0 | PDS |
| 8 | Merlo *et al.*[32] | 2021 | Retrospe-ctive | 253 | IIIC-IV | 0 | 100.0 | Serous 92.5 | NACT-IDS |
| 9 | Bai *et al.*[33] | 2016 | Retrospe-ctive | 375 | I-IV | 56.5 | 43.5 | Clear cell 100.0 | PDS |

NACT-IDS - neoadjuvant chemotherapy and Interval debulking surgery, PDS - primary debulking surgery, SCS - secondary cytoreductive surgery

Table 4. Preoperative CA-125 cut-off values, optimal cytoreduction rate and overall survival rate of all included studies

| Study | Author | Intervention | RoB | CA-125 cut-off value (U/ml) | Optimal cytoreduction rate (%) | OS rate (%) | Sensitivity for optimal cytoreduction (%) | Specificity for optimal cytoreduction (%) | p-value |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Matsahashi et al. [31] | NACT-IDS | M | 35 | 78.1 | 78 | 78.0 | 68.0 | 0.01 |
| 2 | Prajatmo et al.[28] | NACT-IDS | L | 70 | 65.5 | 86 | - | - | |
| 3 | Gupta et al. [38] | NACT-IDS | M | 100 | 55 | - | - | - | <0.001 |
| 4 | Merlo et al. [32] | NACT-IDS | M | 500 | 71.6 | - | 58.0 | - | 0.002 |
| 5 | Parakeshvova et al.[34] | SCS | M | 164 | 58.5 | 46.3 | 58.5 | 66.9 | 0,002 |
| 6 | May et al. [35] | PDS | M | 174 | 70.3 | 77.6 | - | - | 0.001 |
| 7 | Muallem et al.[35] | PDS | L | 252 | 79.1 | 62 | 79.1 | 55.1 | - |
| 8 | Bachmann et al. [29] | PDS | M | 500 | 74.3 | 74.3 | - | - | 0.023 |
| 9 | Bai et al.[33] | PDS | M | 1066 | 89.9 | 76.9 | - | - | 0.654 |

RoB - risk of bias, NACT-IDS - neoadjuvant chemotherapy and interval debulking surgery, PDS - primary debulking surgery, SCS - secondary cytoreductive surgery, L - low, M – moderate



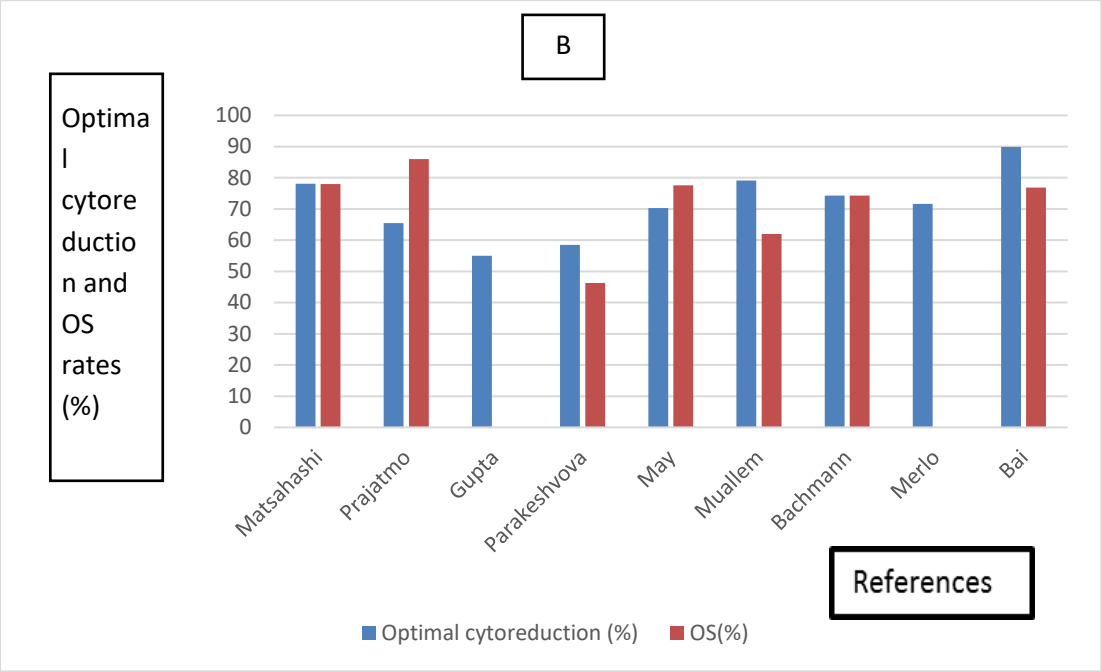



**Figure 4.** A. Bar chart representing studies, CA-125 level, optimal cytoreduction and overall survival rates, B. Bar chart of optimal cytoreduction rate and overall survival rate of the nine studies

In the first category of studies (NACT-IDS), Merlo et al. [32]analyzed the records of 253 patients with advanced EOC and stratified them into two categories based on their initial treatment in addition to their preoperative CA-125 cut-off values. Two hundred and fifteen patients received neoadjuvant chemotherapy before interval debulking surgery and 38 had primary debulking surgery. Approximately, 42.0% of the cases stratified for primary debulking surgery had optimal cytoreduction, while those offered neoadjuvant chemotherapy and subsequently interval debulking surgery had optimal cytoreduction rate of 71.6%. Preoperative cut-off level of ≤500U/ml was an independent predictor of optimal cytoreduction. Similarly, Gupta et al. [38] examined 406 patients with advanced epithelial ovarian cancer who received neoadjuvant chemotherapy and stratified them before surgical debulking into two groups according to their preoperative CA-125 levels in to patients with preoperative CA-125 serum levels ≤100.0U/ml and those with preoperative CA-125 level above100.0U/ml. Patients with preoperative CA-125 values ≤100U/ml had a significantly ($p<0.05$) higher chance of having optimal cytoreduction (55.0%) than those with CA-125 serum levels >100U/ml (40.0%).

Prajatmo H. [28] conducted a prospective cohort study including 90 patients with EOC stage II-IV who were administered neoadjuvant therapy prior to interval debulking surgery and evaluated the association between preoperative CA125 values, rate of optimal cytoreduction and overall surgery. Preoperative CA-125 level <70U/ml independently predicted optimal cytoreduction in 65.6% and suboptimal cytoreduction in 34.5% of patients who received neoadjuvant chemotherapy before interval debulking surgery. The 5-year OS rate in patients who underwent optimal cytoreduction was 86.0% ($p=0.003$). In patients with preoperative cut-off value >70.0U/ml, the result indicated a poor overall survival (crude hazard ratio 5.13, $p<0.01$) Likewise, Matsuhashi et al. [43]analyzed 107 patients with serous EOC and reported that patients with CA-125 values ≤35.0U/ml had a better chance of achieving optimal cytoreduction (78.1%, $p<0.01$) than patients with values >35.0U/ml (33.3%) and also better 5-year survival (43.0% versus 0).

In the second category with surgical treatment (PDS and SCS), Muallem et al.prospectively analyzed 277 cases of FIGO stage II-IV serous EOC in which only 3.1% were early-stage carcinomas. [35] They compared high-grade serous cancers with median preoperative CA-125 cut-off value of 636U/ml with low-grade serous EOC with median preoperative CA-125 cut-off value of 284U/ml separately because high-grade tumours are poorly differentiated and aggressive while low-grade tumours are well-differentiated and slow-growing. They determined the association between preoperative CA-125 serum level and optimal cytoreduction, OS rates. The patients were further stratified based on three CA-125 levels; ≤252U/ml, 252-475U/ml and >475U/ml based on different sensitivities of the values. Preoperative CA-125 was predictive of optimal cytoreduction in 79.1% of women with CA-125 values ≤252U/ml and values < 475U/ml could predict optimal cytoreduction in 65.9% of cases before surgery. In addition, the specificity was 41.9% and 55.1% respectively. There was no significant disparity between OS and PFS rates in the three groups of patients (preoperative CA-125 ≤252U/ml, 252-475U/ml and >475U/ml).

Furthermore, a report from a retrospective study by May et al.[34] that analyzed patients with epithelial ovarian cancer (serous cancer 100%) FIGO stages I-IV who underwent surgery divided them into those with preoperative CA-125 levels ≤174U/ml and those with values above 174U/ml. in the study, preoperativeCA-125 value ≤174U/ml predicted optimal cytoreduction in 70.3% of cases after controlling for variables like stage, residual tumour, and age. The 5-year overall survival rate was 55.0%, and when patients were stratified based on residual tumour size at the end of debulking surgery,5-year survival likelihood of cases with residual tumour 0mm, 1-9mm and ≥10mm were 77.6%, 39.3% and 29.0% respectively. A preoperative CA-125 value ≥174 was associated with worse overall survival, however, rate of optimal cytoreduction in those patients is missing in the report. Thus, the conclusion was preoperative CA-125 is an independent predictor of optimal cytoreduction.

Conversely, Bachmann et al. [29] reported that the rate of optimal cytoreduction when preoperative CA-125 level was ≤500.0U/ml was 74.3% compared with 74.2% when the preoperative CA-125 value was >500.0U/ml, demonstrating no statistically significant difference in rate of optimal cytoreduction. Therefore, preoperative CA-125 is not an independent predictor of optimal cytoreduction, however, OS (p=0.023) and PFS (p=0.01) were significantly reduced when the preoperative CA-125 serum level was >500U/ml. Another retrospective study [33] by Bai et al. that evaluated 375 patients with clear cell cancers of the ovary (100.0%) to ascertain the relationship between preoperative CA-125 level and rate of cytoreduction with pre-treatment CA-125 cut-off of 1066.1U/ml. Among the patients, 10.1% had residual disease >10.0mm, meaning the rate of optimal cytoreduction was 89.9%. However, the authors reported no statistically significant association between a preoperative CA-125 value and OS or residual disease in patients with clear cell cancers of the ovary, suggesting preoperative CA-125 level is not a reliable predictor of overall survival and residual tumour.

Parashkevova et al. [36] obtained the records of 111 patients with serous epithelial cancers (serous 100.0%) FIGO stage II-IV from the cancer database of his institution and investigated the association between preoperative CA-125 levels and extent of secondary cytoreductive surgery in patients with relapse and used a preoperative CA-125 cut-off value of ≤164.5U/ml**.** Preoperative CA-125 level ≤164.5U/ml predicted 58.8% of patients who had optimal cytoreduction and the OS for patients with preoperative CA-125 levels ≤164.5U/ml were significantly better compared with those with CA-125 levels >164.5U/ml, implying preoperative CA-125 levels ≤164.5U/ml is not a predictive of extent of cytoreduction, but can predict better OS in patients with first-time relapse.

## Discussion

All the papers included in the review are non-randomized studies (NRS) of interventions and their quality was assessed with ROBINS-I tool. [26] Seven of the papers [29, 31-34, 36, 38] were at moderate RoB and two [28, 35] were judged to be at low ROB according to the overall scores of the seven domains of individual studies (Figure 1) and the overall ROB of all the studies (Figure 2). The ROBINS-I is a new instrument published by Sterna et al. in 2016 and uses the Cochrane RoB strategy to evaluate internal validity [26, 27], and distinguishes objective responses to signaling questions from subjective perception about RoB as this will improve reliability of the 7 domains and overall RoB assessment. [39] It is recommended that papers judged to be at critical RoB should be included and those at serious RoB be included with caution. [26] Low RoB corresponds to a high-quality study while moderate RoB corresponds to a good quality study [26], hence the ground for inclusion of the nine papers. An important strength of use of ROBINS-I tool is it addresses a common obstacle that NRS are graded as 'low' because of lack of randomization without considering the types of bias in such studies. [40] ROBINS-I tool has the advantages of low inter-observer reliability and concurrence[41] and variability. [42]

Interestingly, the review examined primary studies with patients having different subtypes of epithelial ovarian cancers despite the difference in expression of CA-125 in the serum by the different histological types. [11, 12]

Four of the included primary studies [28, 31, 32, 38] exclusively analyzed patients who were treated with NACT-IDS. Primary research with preoperative CA-125 serum cut-off level greater than ≥500U/ml[32] reported higher chance of accomplishing optimal cytoreduction compared with those with preoperative CA-125 levels less than 500U/ml [28, 38] except on one occasion.[31] (Table 4) This finding is in tandem with the result of Rodriguez et al. [57] that reported a low preoperative CA-125 serum level predicted a high rate of optimal cytoreduction (75.0%) in patients treated with NACT-IDS and the patients had a high chance of having no residual tumour. Again, the result is in keeping with another report that indicated even lower preoperative CA-125 values independently predicted high optimal cytoreduction rate in patients who underwent NACT-IDS, with 62.8% achieving optimal cytoreduction with no gross residual tumour mass. [43] This might be attributed to the difference in proportion of the various subtypes of EOC across the studies. In the reports, conclusion cannot be drawn in terms of overall survival, as the data wasavailable from only two of the four papers in NACT-IDS category.

In this review, the studies [33, 35] that considered surgery as primary treatment, preoperative CA-125 was observed to be a poor predictor of optimal cytoreduction and OS rate. These results fall in tandem with the much earlier reports of Mury et al. [44] that evaluated the prognostic value of preoperative CA-125 serum levels in 231 patients with different histological types of ovarian cancer that indicated that despite some association with surgical findings, a preoperative CA-125 cut-off value could not prediction of surgical results. The results again align with the findings of Memezadeh and colleagues [45] that examined the usefulness of preoperative CA-125 serum value to predict optimal cytoreduction. A cytoreduction rate of 73.0% was achieved in patients with ovarian carcinoma using CA-125 cut-off value above ≥500.0U/ml and concluded that preoperative CA-125 serum value is a weak predictor of optimal cytoreduction.

A much earlier report [46] indicated that there is no preoperative CA-125 serum cut-off value at which cytoreduction can be accurately predicted. On the contrary, in patients who underwent primary debulking surgery alone preoperative CA-125 serum value ≥500U/ml correlated with advanced ovarian carcinoma and was an independent predictive factor in achieving optimal cytoreduction in about 20.0% of patients. [47] It was also demonstrated in this review [29] that no statistically significant difference exists in the rate of optimal cytoreduction between patients with preoperative CA-125 serum levels less than 500.0U/ml and with preoperative serum levels ≥500U/ml, (rates were 74.3% and 74.2% respectively). Therefore, CA-125 cannot reliably predict which category of patients can be optimally cytoreduced. Patients optimally cytoreduced and having preoperative CA-125 value less than 500U/ml had more favourable OS

rate. The findings in the systematic review contrasted with the report of Cooper et al. [48] They suggested that a preoperative CA-125 value below 500U/ml predicted 82.0% of patients who were optimally cytoreduced, however, they concluded that even-though preoperative CA-125 serum level is an independent predictor of survival, it could not be relied upon to predict optimal cytoreduction.

With regards to recurrent ovarian cancer management, the review suggested preoperative cut-off value had no prognostic significance in patients with recurrent EOC. This report is consistent with the findings of earlier study [49] that preoperative CA-125 level was abnormal in about 80.0% of the patients at the time of first recurrence and that CA-125 value has no relevance in predicting ovarian cancer recurrence. This finding was also corroborated by report that indicated preoperative CA-125 level was not a predictive variable for optimal cytoreduction in primary and secondary cytoreductive surgery for recurrent disease. [50]

An evaluation of the studies in which surgery was the primary treatment option did not show a consistent relationship between CA-125 and optimal cytoreduction and overall survival. This might be a result of the differences in proportion of patients with early-stage and advanced-stage cancers across the studies and inclusion of papers with different proportions of subtypes of EOC (Table 3) which do not secrete CA-125 in equal proportion. [11, 12] This could have confounded the data, interpretation of results and conclusions of the findings of this review, a concern expressed by Makar et al. [51] that analysing a data with the various subtypes of EOC could confound the data. Furthermore, expression of CA-125 is lacking in the late stage of primary EOC, thus, relying on its values alone may make selection of patients for a particular treatment difficult. [52]

Based on the foregoing, in future studies, additional stratification of patients not only based on preoperative CA-125 serum levels but also according to tumour grade, patients' age, other parameters such as clinical, laboratory, pathological and radiological findings performance status and presence of co-morbidities might offer better prediction model for achieving optimal cytoreduction in patients with epithelial ovarian cancers

There are limitations to this systematic review among which are lack of clearly defined selection criteria for cases as candidates for neoadjuvant chemotherapy followed by interval debulking surgery or primary debulking surgery.

## Conclusion

This systematic review revealed inconsistent data on the impact of preoperative CA-125 serum level in predicting optimal cytoreduction and on optimal cytoreduction predicting overall survival. This lack of consistency shows that even-though lower preoperative CA-125 serum values predicted a higher likelihood of optimal cytoreduction in patients who received neoadjuvant chemotherapy followed by interval debulking surgery, there was no correlation between preoperative CA-125 and optimal cytoreduction at any preoperative CA-125 cut-off. The Impact of optimal cytoreduction on the overall survival in patients who received neoadjuvant chemotherapy before interval debulking surgery could not be assessed due to insufficient data. The review observed that these studies had a diverse proportion of patients with different subtypes of early-and advanced-stages epithelial ovarian cancers with each study adopting a different preoperative CA-125 cut-off value. Similarly, preoperative CA-125 serum value has no relevance in predicting optimal cytoreduction in patients with ovarian cancer recurrence.

With these discordant results on the role of preoperative CA-125 serum level in predicting optimal cytoreduction, use of other parameters such as clinical, laboratory, pathological and radiological findings in combination with preoperative CA-125 serum value might help define an ideal treatment approach to help solve this dilemma and predict before treatment which cases of EOC could be optimally cyto reduced.

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