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Systematic Review

Determinants of Mortality in Epithelial Ovarian Cancer: Systematic Review and Meta-analysis (Last 5 Years)

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ABSTRACT

Background: *Ovarian cancer poses a significant global health challenge, affecting over 239,000 annually and causing 150,000 deaths, the overall survival rate is 45.6%. Variability in survival rates across different stages necessitates a detailed understanding of contributing factors. This review explores recent research to illuminate crucial aspects influencing epithelial ovarian cancer (EOC) patient outcomes.*

Methods: *A protocol registered in PROSPERO guided this systematic review, focusing on cohort studies examining prognostic factors for EOC mortality. Eligibility criteria included relevance to mortality risk, clear extraction methods, and English language. A PRISMA-guided search with the keywords "((Ovarian Cancer) AND (Mortality) AND (Risk)" across Scopus, PubMed, and Cochrane. Evaluation of 66,191 samples from 16 cohort studies identified several key prognostic factors for mortality in epithelial ovarian cancer (EOC).*

Results: *Advanced FIGO stage (III-IV) and high-grade serous histology were significant predictors of higher mortality, with stage III-IV showing a risk ratio of 3.62 (95% CI 3.35–3.91). Older age, greater inflammation, and bilateral tumors also increased mortality risk. Reduced physical activity and rural living, as well as treatment-related factors such as perioperative red blood cell transfusion, were associated with poorer survival outcomes. Key prognostic factors for mortality in EOC patients include advanced cancer stage, high-grade serous histology, older age, inflammation, and bilateral tumors. Treatment factors such as perioperative transfusion and neoadjuvant chemotherapy intensity also play a critical role.*

Conclusion: *These findings highlight the need for personalized treatment strategies based on these factors to improve survival outcomes for EOC patients.*

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INTRODUCTION

Ovarian cancer is a significant issue among women, ranking as the third most common gynecologic cancer after cervical and uterine cancers (Andreou et al., 2023). Annually, it affects about 239,000 new people worldwide and leads to over 150,000 deaths, making up 4.3% of all cancer-related deaths globally(Sait et al., 2022). Despite medical progress, the overall survival rate for ovarian cancer is at 45.6%, emphasizing the need for better understanding and research (Momenimovahed et al., 2019). Looking closely at the stages of ovarian cancer, we find a stark contrast in survival rates. Stage I patients have a promising 92.1% chance of surviving for five years, which is good news when caught early. However, this positivity drops significantly for those diagnosed at stages III and IV, with a survival rate plummeting to just 25% (Ali et al., 2023). Understanding the factors contributing to these different outcomes is essential for improving interventions and patient outcomes. The tricky part about ovarian cancer is that it often goes unnoticed in its early stages due to a lack of obvious symptoms. This delayed diagnosis is made worse by the vague nature of the symptoms, which can be wrongly attributed to normal changes related to pregnancy, menopause, or aging (Kim et al., 2017).

In this systematic review and meta-analysis, we aim to make sense of the research from the last five years to understand the factors affecting the survival of epithelial ovarian cancer patients. Key strenght of this study is that no previous meta-analysis has included a sample size as large as this study while focusing exclusively on evidence from the most recent five years. By exploring recent findings, our goal is to highlight crucial aspects influencing patient outcomes and set the stage for improvements in diagnosis, treatment, and overall survival rates.

MATERIALS AND METHOD

We registered a protocol before composing this review and meta-analysis, and it was entered into the International prospective register of systematic reviews (PROSPERO) on 26th of January 2024, with the registration number CRD42024502616. Our research employs a systematic review approach on cohort studies. The clinical investigation in this study centers on prognostic factors, specifically examining those that influence mortality among ovarian cancer patients. Cohort studies were the chosen study type as they provide superior evidence compared to other prognostic studies, aligning with the standards of evidence-based medicine. The criteria for inclusion in this study were: (a) cohort studies, (b) possesses relevance regarding mortality risk in ovarian cancer patients, (c) having at least one control group and one exposure group, and (d) demonstrates a clear extraction and statistical analysis method. Exclusion criteria for this systematic review includes : (a) inaccessible full text, and (b) articles in languages other than English.

The investigation followed the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). Three electronic databases, comprising Scopus, PubMed, and Cochrane were used to search for relevant literature. The search term utilized was "((Ovarian Cancer) AND (Mortality) AND (Risk))". Five researchers independently reviewed titles and abstracts, excluding irrelevant studies. Following this screening, five authors (FK, KAS, GS, KPIS, ASW) individually assessed each entry based on inclusion and exclusion criteria, with four possible responses of 'Yes,' 'No,' or 'Maybe.' Discussion to achieve mutual agreement were carried out to resolve any discrepancies.

The use of an electronic bibliography manager (EndNote) were used to remove duplicate studies. Following duplicate exclusion, studies were systematically evaluated according to the inclusion and exclusion criteria established above. Full-text articles were retrieved for studies relevant to the said inclusion and exclusion criteria, and the five authors independently assessed subject characteristics (ovarian cancer), prognostic factors, and study outcomes (mortality

risk), as well as other relevant information. Bias and certainty evaluations were performed after synthesizing the factors influencing mortality in epithelial ovarian cancer. A meta-analysis was conducted by creating a forest plot for factors with more than one study comparing mortality rates with the same outcome using the ReviewManager application RevMan 5.4 (RRID:SCR_003581), while the risk of bias was assessed with the Newcastle-Ottawa Scale tool for non-randomized studies.

RESULTS

A total of 446 studies were retrieved based on the keywords from 3 databases PubMed (n = 244), Scopus (n=190) and Cochrane (n = 12). Abstract and title of 173 studies were screened after duplicate records were removed, and irrelevant search results were removed by automation tools. 152 articles with irrelevant title and abstracts were excluded. The full-text of the remaining 21 studies were screened, and results in 16 studies that met the inclusion and exclusion criteria of this study. Figure 1. visualizes the study selection flowchart.

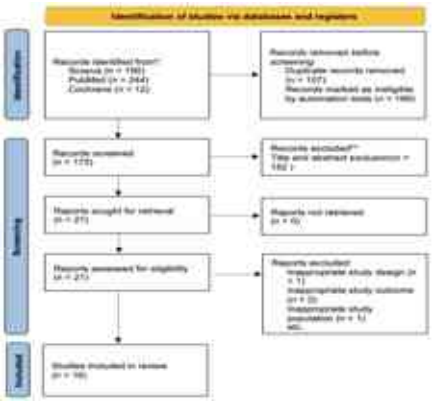

Figure 1. Study search and selection flowchart

A total of 66191 samples were collected from 16 included cohort studies, of which 11 of the studies were retrospective and 5 were prospective in manner. Outcomes that were measured for this study include odds ratios (ORs), hazard ratios (HRs), relative risks (RRs), p-values and comparisons associating risk factors to prognostic factors for mortality among EOC patients. Detailed characteristics of the included studies can be found in **Table 1.**

Table 1. study characteristics and outcome

Author (Year)	Research Design	Location	Study Population	Factors Measured	Main Results
Brieger et al. (2022)	Retrospective cohort	USA	8,147 patients with invasive EOC from the Ovarian Cancer Association Consortium	IRRS score components: pre-diagnosis inflammation-related exposures (e.g., alcohol, BMI, tobacco smoke, PCOS, endometriosis)	Higher IRRS score increased mortality risk (HR=1.09, 95% CI: 1.03–1.14).
Gaitskell et al. (2022)	Prospective cohort	England and Scotland	13,222 women with EOC	FIGO stage, age, BMI, smoking status	Stage IV vs I (RR=10.54, 95% CI: 9.16–12.13); age (per 5 years: RR=1.19, 95% CI: 1.15–1.22); BMI (per 5-unit:

					RR=1.06, 95% CI: 1.02–1.11).
Lutgendorf et al. (2021)	Prospective cohort	USA	342 women with histologically confirmed high-grade primary EOC	Rural vs urban residency	Rural residency increased mortality risk (HR=1.39, 95% CI: 1.04–1.85, p=0.026).
Wang et al. (2021)	Prospective cohort	USA	1,461 women with confirmed invasive EOC	Physical activity before and after diagnosis	Reduced activity increased mortality risk (HR=1.49, 95% CI: 1.07–2.08).
Zheng et al. (2023)	Retrospective cohort	China	314 women diagnosed with EOC	PRBCT transfusion during PDS	PRBCT transfusion increased mortality risk (HR=1.59, 95% CI: 1.12–2.25).
Birge et al. (2022)	Retrospective cohort	Turkey	66 patients with early-stage EOC	Fertility-sparing surgery (FSS) vs radical surgery (RS)	No increased mortality with FSS vs RS after 15 years (p=0.668).
Okunade et al. (2022)	Prospective cohort	Nigeria	93 EOC patients receiving standard treatment	Early tumor relapse	Early relapse (<6 months) significantly increased mortality risk (RR=8.6, 95% CI: 3.3–24.5, p<0.01).
Huang et al. (2023)	Retrospective cohort	China	323 ethnic Chinese patients diagnosed with epithelial ovarian cancer	Age, primary tumor laterality, FIGO stage	Age ≥70 (HR=1.967, p=0.007); laterality (HR=1.849, p=0.009); FIGO stage III vs I (HR=3.588, p=0.001), IV vs I (HR=4.382, p=0.001).
Ekmann-Gade et al. (2022)	Retrospective cohort	Denmark	7,522 patients aged ≥18 years with EOC	Age	Age >70 increased cancer-specific death risk (HR=1.4, 95% CI: 1.2–1.5).
Huepenbecker et al. (2022)	Retrospective cohort	USA	13,872 patients with outpatient diagnosis of ovarian cancer symptoms	Time from symptom presentation to diagnosis and diagnosis to treatment	Longer time improved survival: OS (HR=0.95, 95% CI: 0.94–0.95); cancer-specific survival (HR=0.95, 95% CI: 0.94–0.96).
Piatek et al (2020)	Retrospective cohort	Poland	168 patients with epithelial ovarian cancer (EOC), achieving complete remission after first-line treatment.	CA-125 concentration at 3 and 6 months post-therapy.	Increased CA-125 levels by 5 U/ml significantly reduced 5-year survival: 3 and 6 months after therapy (56.79% vs 0 (p<0.05) and 50.62% vs 15.55% (p<0.05)).

Melamed et al (2021)	Prospective cohort	USA	19,562 patients with stage IIIC or IV EOC diagnosed between 2004–2015.	One-year mortality based on neoadjuvant chemotherapy usage.	Higher neoadjuvant chemotherapy use reduced mortality: risk difference (RD)=−5.2%, 95% CI=−6.4 to −4.1; lower use: RD=−3.2%, 95% CI=−4.3 to −2.0.
Dilley et al (2020)	Retrospective cohort	UK	574 women from the UKCTOCS database with no significant ovarian cancer history.	NICE symptoms, modified Goff Index, number of presenting symptoms.	NICE symptoms: HR=1.48, 95% CI=1.16–1.89, p=0.001; Modified Goff Index: HR=1.68, 95% CI=1.32–2.13, p<0.0001; Additional symptoms: HR=1.20, 95% CI=1.12–1.28, p<0.0001.
Kajiyama et al (2019)	Retrospective cohort	Japan	285 patients with stage I EOC at reproductive age.	OS and RFS between FSS and RS groups.	No significant difference: RFS (HR=1.262, 95% CI=0.559–2.852, p=0.575); OS (HR=1.206, 95% CI=0.460–3.163, p=0.704).
Calvillo-Robledo et al (2021)	Retrospective cohort	Mexico	154 samples of ovarian tumors diagnosed over 10 years (2008–2018).	AR immunoreactivity, STS expression.	AR+STS associated with reduced survival: Univariate: HR=3.46, 95% CI=1.00–11.92, p=0.049; Multivariate: HR=5.92, 95% CI=1.34–26.09, p=0.019.
Zhu et al (2021)	Retrospective cohort	China	86 patients with primary ovarian clear cell carcinoma (OCCC) between 2010–2020.	CA19-9, HE4, ascites, lymph node involvement, OS and PFS.	OS: CA19-9 (p=0.025), ascites (p=0.001), lymph node involvement (p=0.001); PFS: HE4 (p=0.027), ascites (p=0.001).

In this study, the meta-analysis was conducted on two factors. Further analysis was performed using the RevMan 5.4 application to create forest plots. The first factor, cancer stage, involved a forest plot based on 2 studies comparing 5,486 patients with stages 3-4 to 2,422 patients with stages 1-2. The results showed higher mortality rates in stages 3-4 with a risk ratio of 3.62 (95% CI 3.35–3.91) and heterogeneity ($I^2 = 62\%$). The second factor involved a forest plot based on 3 studies comparing histological types in 7,071 patients with high-grade serous histology to 7,600 patients with other histological types. The results indicated higher mortality rates in high-grade serous histology with a risk ratio of 1.25 (95% CI 1.22–1.28) and heterogeneity ($I^2 = 67\%$). The forest plot is presented in **Figure 2.**

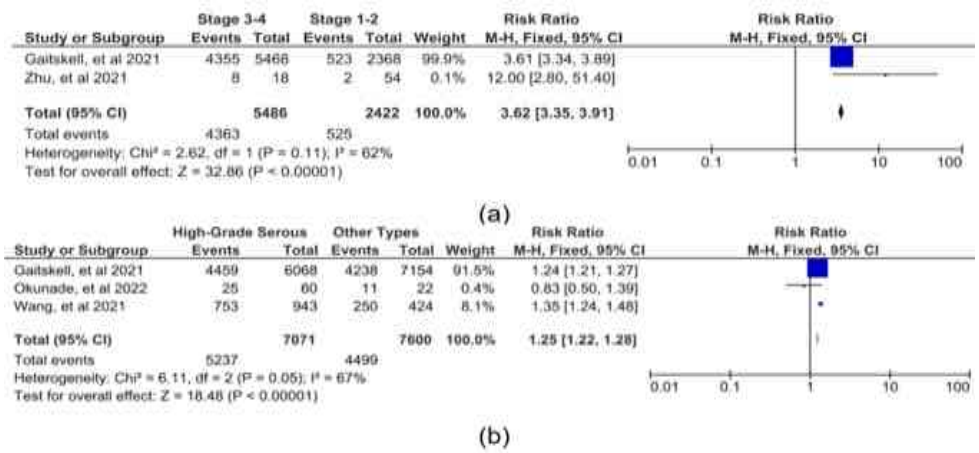

Figure 2. Forrest Plot of: (a) Cancer Grades as Mortality Factor of EOC Patients, (b) Histological Type as as Mortality Factor of EOC Patients.

The results of the risk of bias assessment are depicted in **Appendix 1** using Newcastle-Ottawa Scale tool. All of the studies had shown low risk of bias due to the majority of studies drawing groups from the same respective cohorts, controlling or adjusting for potential confounders, and conducting match analyses.

DISCUSSION

In this systematic review, sixteen studies were identified that explored various prognostic factors for mortality among EOC patients. The 16 studies used a total of 66,191 patients from Europe , Asia America, Africa. Three studies demonstrated that a higher FIGO stage is a significant predictor for mortality among EOC patients (Gaitskell et al., 2022, Huang et al.,2023,Zhu et al., 2021). Two stuides demonstrated the association between high degree of inflammation as a predictor for mortality among EOC patients which the increase in IRRS score,increasing BMI, and history of smoking significantly increased risk of mortality (Gaitskell et al.,2022, Brieger et al.,2022). Three studies review identified older age at diagnosis as a significant risk factor for mortality(Gaitskell et al., 2022, Huang et al.,2023, Ekmann et al., 2022). Two studies reported the role of lifestyle choices (decrease in physical activity) and socioeconomic factors (patient living in rural areas dan have lower education level) as a prognostic factor for mortality among EOC patients (Lutgendorf et al., 2021,Wang et al., 2021).The results of this systematic review also identified several EOC treatment related characteristics such as perioperative red blood cell transfusion (PRBCT) andthe intensity of neoadjuvant chemotherapy has been documented as significant prognostic factors for mortality (Zheng et al., 2023, Melamed et al.,2021).

Two studies within this systematic review compared mortality levels between patients receiving fertility sparing surgery (FSS) and radical surgery (RS). The studies reported that there were no significant differences in terms of overall survival between patients receiving FSS and RS (Birge et al.,2022, Kajiyama et al.,2019). There are several different patient characteristics as prognostic factors for mortality such as tumour relapse within 6 months of treatment completion, the presence of a bilateral tumour and the presence of ascites with ≥2000 mL is an independent prognostic factor for mortalit (Huang et al.,2023,Zhu et al 2021.,Okunade et al.,2022).In addition, it was found that classical symptoms listed within the NICE guidelines (pelvic or abdominal pain,bloating, reduced feeding and increased urinary frequency urgency), are at a greater risk for mortality (Dilley et al.,2020).

In this study, we performed a meta-analysis to assess the impact of two key factors—cancer stage and histological type—on mortality in epithelial ovarian cancer (EOC) patients. Using the RevMan 5.4 application, we created forest plots to illustrate the findings. The first

factor analyzed was cancer stage. A comparison of 5,486 patients in stages 3-4 with 2,422 patients in stages 1-2 revealed a significantly higher mortality rate in the advanced stages (3-4), with a risk ratio of 3.62 and moderate heterogeneity. This highlights the critical role of cancer stage in determining survival outcomes for EOC patients. The second factor examined was histological type. A comparison of 7,071 patients with high-grade serous histology and 7,600 patients with other histological types showed that high-grade serous histology was associated with a higher mortality rate, with a risk ratio of 1.25 and considerable heterogeneity. This emphasizes the aggressive nature of high-grade serous ovarian cancer, which contributes to worse survival outcomes.

Overall, the results show the importance of both cancer stage and histological subtype in determining mortality, supporting the need for better treatment approaches based on these factors to optimize survival for EOC patients. Factors that can increase the mortality of epithelial ovarian cancer patients based on this systematic review and meta-analysis can be seen in **Figure 3.**

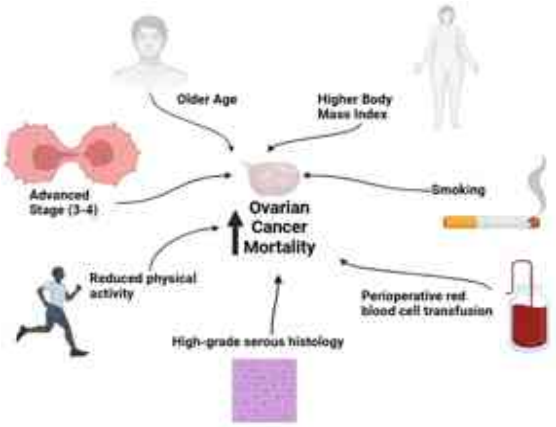

Figure 3. Factors influencing the increase in mortality from epithelial ovarian cancer

This systematic review identified several studies that investigated common prognostic factors for mortality among EOC patients. Older age at diagnosis and higher tumour FIGO stage at time of diagnosis has been identified as a common prognostic factor for mortality among EOC patients. This association may be explained as older stage and higher FIGO stage at diagnosis suggests a more complex and extensive disease progression that has taken place, reducing survival of said EOC patients(Elias et al.,2018). This systematic review reveals a statistically significant association between inflammation related exposure and mortality among EOC patients such as both active smokers and those with history of smoking are at an increased risk of mortality from ovarian cancers(Præstegaard et al., 2017). The findings of tumor relapse, symptoms listed in the NICE guidelines and bilateral tumor presence may also signify the failure of early detection and initiation of prompt treatment among said EOC patients, which results in a highly extensive disease progression that is more challenging to treat (Elias et al., 2018).

The history of PRBCT during surgery for ovarian cancer has been acknowledged as a potential prognostic factor for poor outcomes by other studies. Cytoreductive surgery employed in EOC treatment is known to be extensive in nature, and carries a great risk for major blood loss, which is known to cause anemia, and various postoperative hematologic complications that may reduce the overall survival of EOC patients following surgery (Dou et al.,2022). The detection of EOC at a relatively earlier stage would provide patients with more treatment options. The results of this systematic review demonstrated that the provision of FSS instead of RS among early stage EOC patients does not reduce overall survival, providing evidence that allows patients to have better post-operative quality and the option to preserve

fertility if desired (Crafton et al.,2020). This meta-analysis reveal that individuals diagnosed at advanced stages (3-4) face a markedly higher risk of mortality, with a risk ratio of 3.62, when compared to those diagnosed at earlier stages (1-2). This highlights the critical importance of early detection and timely intervention in improving patient prognosis. Moreover, high-grade serous histology was found to be strongly linked to an increased risk of mortality, underscoring the aggressive nature of this subtype. Taken together, these results support the need for personalized treatment plans that take into account both the stage of cancer and its histological type to enhance survival outcomes for EOC patients.

As the 16 studies in this review were cohort studies, it can be said that these studies are great for analysing and determining prognostic factors, in this case for EOCs. The risk of bias analyses for this review had shown that overall, all studies included in this review were at low risk of bias. The evidence provided in this review certainly has greater implications and applicability in clinical settings. From this review, it is found that prognostic factors such as older ages, FIGO staging, inflammatory related exposures, smoking habits and other factors play important roles towards the eventual increased chances for mortality in patients with EOCs. The knowledge regarding the prognostic factors may help clinicians by focusing more on these factors and hopefully intervene quicker to increase chances of survival for EOC patients. This review comes with a set of limitations, knowing that although all studies were overall at low risk of bias, some domains did not fulfill the low risk of bias criteria. The domains that were not fulfilled include the assessment of the exposure as well as match adjustments which were questionable, however leaned towards a higher risk of bias.

CONCLUSION

In conclusion, this systematic review and meta-analysis emphasize the critical prognostic factors for mortality in patients with epithelial ovarian cancer (EOC). The findings indicate that a higher FIGO stage significantly increases the risk of mortality. Similarly, high-grade serous histology was found to be a key factor, contributing to poorer survival outcomes. Other notable risk factors include older age at diagnosis, greater inflammation (as reflected by increased BMI, smoking, and other inflammation-related exposures), and the presence of bilateral tumors. Lifestyle factors, such as physical activity levels and socioeconomic determinants like rural living, were also associated with increased mortality. Additionally, treatment-related factors like perioperative red blood cell transfusion and the intensity of neoadjuvant chemotherapy were identified as significant contributors to mortality risk. The type of surgery, specifically fertility-sparing surgery, did not show an increased risk of mortality compared to radical surgery. Further research is needed to refine these prognostic factors and optimize therapeutic interventions for better patient management.

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Appendix 1

Table 2. Risk of Bias for Included Studies

Studies	Selection of exposed and non- exposed cohorts drawn from the same population	Assessment of exposure	Outcome of interest was not present at start of study	Match variables, adjust analysis	Assessment of the presence or absence of prognostic factors	Assessment of outcome	Follow-up of cohorts	Similar co-interventions	Study Quality
Brieger et al (2022)	1	3	1	1	1	1	1	2	Low risk
Gaitskell et al (2022)	1	1	1	1	1	1	1	1	Low risk
Lutgendorf et al (2021)	1	1	1	1	1	1	1	1	Low risk
Wang et al (2021)	1	1	1	1	1	1	1	1	Low risk
Zheng et al (2023)	1	1	1	1	1	1	1	1	Low risk
Birge et al (2022)	1	1	1	1	2	1	1	1	Low risk
Okunade et al (2022)	1	1	1	1	1	1	1	1	Low risk
Huang et al (2023)	1	1	1	1	1	1	1	1	Low risk
Ekmann-Gade et al (2022)	1	1	1	1	1	1	1	1	Low risk
Huepenbecker	1	1	1	1	1	1	1	1	Low risk

et al (2022)									
Piatek et al (2020)	1	1	1	1	2	1	1	1	Low risk
Melamed et al (2021)	1	1	1	1	1	1	1	1	Low risk
Dilley et al (2020)	1	1	1	1	1	1	1	1	Low risk
Kajiyama et al (2019)	1	1	1	1	1	1	1	1	Low risk
Calvillo-Robledo et al (2021)	1	1	1	3	1	1	1	1	Low risk
Zhu et al (2021)	1	1	1	1	1	1	1	1	Low risk