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Pre-treatment thrombocytosis and ovarian cancer survival: A meta-analysis

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ABSTRACT

An association between thrombocytosis and cancer progression and decreased survival has been observed for various forms of cancer. The aim of this study was to evaluate the impact of pre-treatment thrombocytosis on ovarian cancer survival. Medline, Scopus, Clinicaltrials.gov, Cochrane Central Register of Controlled Trials CENTRAL and Google Scholar were searched systematically for studies that compared survival outcomes of patients with ovarian cancer who had pre-treatment thrombocytosis with survival outcomes of patients with normal platelet counts. Fourteen articles were retrieved, with a total of 5414 patients with ovarian cancer. The methodological quality of included studies ranged between moderate and high. Patients with advanced stage disease were more likely to have pre-treatment thrombocytosis, and this was associated with lower rates of optimal debulking. Thrombocytosis was also associated with increased likelihood of recurrence of ovarian cancer [hazard ratio (HR) 2.01, 95 % confidence interval (CI) 1.34–3.01] and increased risk of death from ovarian cancer (HR 2.29, 95 % CI 1.35–3.90). The incidence of deep vein thrombosis was comparable in both groups (odds ratio 1.62, 95 % CI 0.48–5.46). Considering these findings, it is evident that pre-treatment thrombocytosis in patients with ovarian cancer is associated with increased risk of recurrence and death. Pre-treatment thrombocytosis is a potential sign of advanced stage disease, and may be predictive of suboptimal tumour debulking during surgery. Its association with other factors that affect survival, including platinum resistance and response to targeted therapy, remains poorly explored, although preliminary data suggest a potential correlation.

1. Introduction

Thrombocytosis is frequently observed in patients with cancer, and is believed to be the result of increased platelet production rather than altered platelet survival [1,2]. A large cohort study based on the Clinical Practice Research Datalink data in the UK revealed that thrombocytosis was significantly associated with the risk of cancer diagnosis [3]. The underlying pathophysiology has not been elucidated completely; however, it is believed that platelet activation is essential for tumour progression, as it is associated with the release of several platelet-derived growth factors that promote cellular proliferation, neovascularization and, ultimately, tumour growth, tissue invasion and metastasis [4–6].

Considering this, thrombocytosis may also regulate cancer progression as well as disease-specific survival. Large cohort studies have indicated that patients with high platelet counts have lower survival expectancy compared with patients with normal platelet counts [7]. A systematic review published in 2017 indicated that cancer patients with thrombocytosis had a higher incidence of cancer-related death, and the condition was indicative of an increased stage of disease at diagnosis [8].

The association between thrombocytosis and advanced stage ovarian cancer was first implied in 1994, when Zeimet et al. reported that thrombocytosis is frequently seen in patients with marked ascites [9]. Although the role of thrombocytosis in the progression of ovarian cancer has not been investigated fully, previous experimental studies linked thrombocytosis with chemotherapeutic response, and indicated that combined therapy with taxane-based regimens and platelet-depleting antibodies can help to reduce the tumour load significantly [10].

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2. Objectives

The aim of this systematic review was to summarise current evidence related to the incidence of thrombocytosis in patients with ovarian cancer, and investigate its association with factors that predispose to decreased survival, including advanced stage at diagnosis, presence of ascites and complete tumour reduction. Rates of venous thromboembolism have been compared between cases who develop thrombocytosis and those who do not, as well as the risks of disease recurrence and death.

3. Methods

This systematic review was registered in PROSPERO (International Prospective Register of Systematic Reviews) prior to its onset (Registration no. CRD42023433037), and was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. The review is based on aggregated data that have been published in the international literature. Patient consent and institutional review board approval were, therefore, waived.

3.1. Eligibility criteria, information sources and search strategy

The eligibility criteria for the inclusion of studies were predetermined. All studies that examined the impact of pre-treatment thrombocytosis on survival outcomes of patients with ovarian cancer were considered eligible for inclusion. Different cut-off values for the definition of thrombocytosis between the included studies were anticipated. Case reports, experimental studies and conference proceedings were excluded from this meta-analysis.

Medline (1966–2023), Scopus (2004–2023), Clinicaltrials.gov (2008–2023), Cochrane Central Register of Controlled Trials CENTRAL (1999–2023) and Google Scholar (2004–2023) were searched, along with the reference lists of electronically retrieved full-text papers. The date of the last search was 15 August 2023. The search strategy included the terms ‘thrombocytosis’, ‘ovarian cancer’ and ‘survival’, and is presented in Fig. 1.

3.2. Study selection

Retrieved studies were selected in three consecutive stages. The first stage involved deduplication of retrieved articles, followed by manual screening of titles and abstracts of all remaining electronic articles by two authors (LV and DEV) to evaluate their eligibility. Finally, studies

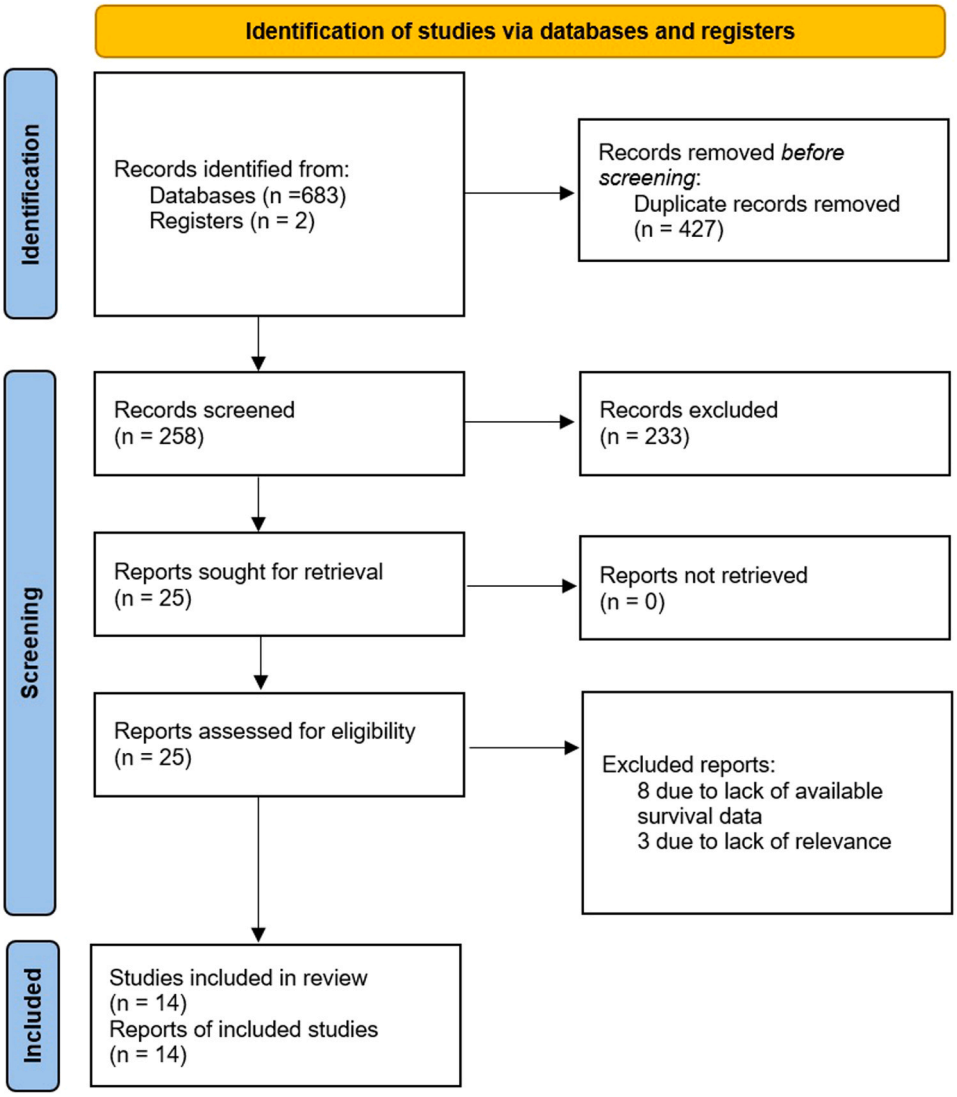

Fig. 1. Search plot diagram.

that were potentially eligible were selected for inclusion following retrieval and review of the full text. Discrepancies that arose in the latter stage were resolved by consensus.

3.3. Data extraction

Outcome measures were pre-defined. Data extraction was performed using a modified data form based on Cochrane`s data collection form for intervention reviews for randomised controlled trials (RCTs) and non-RCTs [12]. The primary outcome of this review was the evaluation of differences in survival rates [overall survival (OS) and recurrence-free survival (RFS)] of patients with ovarian cancer. Differences in time intervals until disease relapse and death were considered as secondary outcomes. Other secondary outcomes included differences in rates of advanced stage disease, presence of ascites and optimal cytoreduction, as well as rates of development of deep vein thrombosis (DVT).

3.4. Assessment of risk of bias

The methodological quality of included studies was assessed by two authors (LV and VP) using the Newcastle–Ottawa scale, which assesses the risk of bias in observational studies by evaluating selection of study groups (maximum rating 4 points), comparability of groups (maximum rating 2 points), and ascertainment of exposure or outcome of interest (maximum rating 3 points) [13]. Comparability of groups was determined on the basis of cases with advanced stage disease (one star) and optimal debulking surgery (one star).

3.5. Data synthesis

Statistical meta-analysis was performed with RStudio using the *meta* function (http://www.rstudio.com/). Statistical heterogeneity was not considered during evaluation of the appropriate model (fixed effects or random effects) of statistical analysis, as considerable methodological heterogeneity (Table 1) did not permit the assumption of comparable effect sizes among studies included in the meta-analysis [14]. Confidence intervals (CI) were set at 95 %. Pooled risk ratios (RR), hazard ratios (HR), mean differences (MD) of survival, and pooled 95 % confidence intervals (CI) were calculated with the Hartung–-Knapp–Sidik–Jonkman random effects model, instead of the traditional Dersimonian–Laird random effects model. The decision to proceed with this type of analysis was taken after considering recent reports which support its superiority compared with the Dersimonian–Laird model when comparing studies of varying sample sizes and between-study heterogeneity [15]. Publication bias was considered using inspection of retrieved funnel plots for outcomes that included more than 10 studies, as well as with the Egger`s test which represents a linear regression analysis that takes into account the intervention effect estimates and their standard errors which are weighted by their inverse variance [16]. Duval and Tweedies' trim and fill test was then applied to evaluate the impact of a potentially unbiased meta-analysis and compare this with the findings of this study. The test first trims the studies responsible for funnel plot asymmetry, and then fills imputed missing studies using an assumption that supports a bias-corrected overall estimate [17].

The potential presence of small study effects was evaluated using Rücker's Limit Meta-Analysis, and the possibility of p-hacking was evaluated from the results of p-curve analysis.

3.5.1. Prediction intervals

Prediction intervals were calculated, using the *meta* function in RStudio, to evaluate the estimated effect that is expected to be seen by future studies in the field. The estimation of prediction intervals considers interstudy variation of the results, and expresses existing heterogeneity using the same scale as the examined outcome.

3.5.2. Trial sequential analysis

To evaluate information size, trial sequential analysis (TSA) was performed in all meta-analyses that involved binary of continuous outcomes. This permits the investigation of type I error in the aggregated results of meta-analyses performed for primary outcomes that were predefined in the present meta-analysis. A minimum of three studies was considered appropriate to perform the analysis. Repeated significance testing increases the risk of type I error in meta-analyses, and TSA has the ability to re-adjust the desired significance level by using the O`Brien-Fleming a-spending function. Therefore, during TSA, sequential interim analyses that permit investigation of the impact of each study on the overall findings of the meta-analysis are performed. Risks of type I and type II errors were set at 5 % and 20 %, respectively. TSA was not performed for pre-calculated effect size data, namely HRs, provided in this meta-analysis as no algorithm is available for this type of data at present. TSA analysis was performed using TSA v. 0.9.5.10 Beta software (http://www.ctu.dk/tsa/).

4. Results

4.1. Study selection

The full-text of 25 studies was retrieved; 11 of these studies were excluded due to lack of relevance or limited data [9,10,18–26]. Fourteen articles, with a total of 5414 patients with ovarian cancer, were selected for inclusion in this review [27–40].

Table 1
Methodological characteristics of included studies.

Date; Author	Study type	Country	Number of patients	Stage	Cut-off (% above)	Follow-up
2004; Li	Retrospective	USA	183	III–IV	> 400 (22.4 %)	Not reported
2014; Cohen	Retrospective	USA	107	I–IV	> 350 (12 %)	Not reported
2008; Gungor	Retrospective	Turkey	292	I–IV	> 400 (42.5 %)	Not reported
2010; Kuyumcuoglu	Retrospective	Turkey	51	I–IV	> 400 (50.9 %)	Not reported
2011; Lee	Retrospective	Korea	179	III–IV	> 400 (34.6 %)	Not reported
2012; Qiu	Retrospective	China	282	I–IV	> 300 (22.8 %)*	Not reported
2013; Allensworth	Retrospective	USA	587	I–IV	> 450 (22.3 %)	Not reported
2013; Ma	Retrospective	China	454	I–IV	> 400 (24.73 %)*	Not reported
2014; Digklia	Retrospective	Switzerland	91	III–IV	> 350 (42.9 %)	Not reported
2015; Chen	Retrospective	China	816	I–IV	> 400 (22.8 %)	Not reported
2015; Man	Retrospective	China	190	I–IV	> 300 (45.26 %)	Not reported
2016; Cozzi	Retrospective cohort	USA	304	I–IV	> 350 (52.3 %) > 400 (37.5 %) > 450 (25 %)	Not reported
2018; Hefler	Retrospective cohort	Austria	498	I–IV	> 450 (17.7 %)	Not reported
2020; Matsuo	Retrospective	USA, Japan, UK	1308	I–IV	> 400 (33.18 %)	Not reported
2020; Okunande	Retrospective cohort	Nigeria	72	I–IV	> 450 (41.7 %)	Not reported

4.2. Study characteristics

Most studies included cases with ovarian cancer of any stage, whereas three studies only included patients with advanced stage ovarian cancer [27,30,35]. Significant heterogeneity was noted in the proposed cut-off value for the definition of thrombocytosis (Table 1).

4.3. Risk of bias of included studies

The Newcastle–Ottawa scale revealed that the methodological quality of included studies ranged between moderate and high, with comparability being the main issue encountered in approximately half of studies which either under-reported differences in stage of disease and optimal radicality of the procedure, or reported significant differences in these factors between cases with and without thrombocytosis (Table 2).

4.4. Synthesis of results

The meta-analysis of seven studies revealed that pre-treatment thrombocytosis was significantly associated with increased likelihood of recurrence of ovarian cancer (HR 2.01, 95 % CI 1.34–3.01) (Fig. 2). Sensitivity analysis indicated that the study by Okunade et al. was an outlier, influencing the results of the analysis [40]. Its exclusion revealed a somewhat lower effect estimate, with narrower CI (HR 1.67, 95 % CI 1.25–2.53). The adjusted estimate that was provided after analysis for small study effects revealed that the association between thrombocytosis and risk of disease recurrence remained significant (HR 1.89, 95 % CI.74–1.97). The possibility of p-hacking was low, as p-curve analysis indicated the presence of evidential value for the investigated outcome. The interval to recurrence was shorter in patients with thrombocytosis, although the result did not reach significance (MD − 6.61 months, 95 % CI − 14.65 to 1.41; $p = 0.079$, four studies). TSA revealed that the sample size required for firm evaluation of the impact of thrombocytosis on recurrence-free interval was not reached (506/713 women).

The meta-analysis of 11 studies revealed that overall survival was significantly associated with higher risk of death from ovarian cancer (HR 2.29, 95 % CI 1.35–3.90) (Fig. 3). Outlier analysis revealed two studies as potential outliers [34,40], so these were removed. The remaining studies provided a similar summary effect estimate (HR 2.08, 95 % CI 1.49–2.90). However, funnel plot analysis revealed the existence of potential publication bias, which was also confirmed by Egger`s test analysis (Egger test 3.64, 95 % CI 2.46–4.82, $p < 0.001$). The trim and fill analysis required the addition of seven studies, which provided a summary effect estimate that indicated a non-significant association between thrombocytosis and overall survival (HR 1.13, 95 % CI 0.53–2.34). A small study effect analysis was performed to further evaluate if the aggregated effect estimate was influenced by smaller studies. This provided a mean summary effect estimate that was significant, although somewhat smaller compared with that of the primary analysis (HR 1.49, 95 % CI 1.49–1.50). Residual heterogeneity remained significant following this adjustment ($p < 0.001$), indicating the presence of other factors that may influence the overall result. p-curve analysis was performed to evaluate the possibility of p-hacking among different studies; this revealed that this was not possible. The interval to death did not differ between cases with and without thrombocytosis (MD − 0.26 months, 95 % CI − 6.89 to 6.36, $p = 0.908$, four studies). TSA revealed that the sample size was too small (0.14 %) to reach firm conclusions.

The analysis of secondary outcomes revealed a significant association between thrombocytosis and advanced stage disease, as well as increased risk of suboptimal debulking surgery in this group of patients (Table 3). However, the summary effect estimates were influenced by small study effects, although the possibility of p-hacking was ruled out with p-curve analysis. The incidence of ascites and DVT did not differ between cases with thrombocytosis and those with normal platelet counts. TSA revealed that the sample size required to reach robust conclusions was reached for the advanced stage and DVT outcomes, but not for the optimal debulking and prevalence of ascites outcomes.

5. Comment

5.1. Principal findings

This review found that pre-treatment thrombocytosis significantly affects the risk of recurrence and death of patients with ovarian cancer. However, it should be noted that the risk of publication bias cannot be ruled out entirely, as the findings of the respective analysis in the case of overall survival suggest that the literature may be skewed, therefore providing a false-positive association between thrombocytosis and survival outcomes. Sensitivity analyses for potential outliers, manipulation of data analysis (p-hacking) and small study effects revealed that the results of this review were not subject to any of these causes of misinformation, as significance remained unaffected and residual heterogeneity continued to be present.

Table 2
Methodological quality assessment of included studies using the Newcastle–Ottawa scale.

Study	Selection				Comparability	Exposure		
	Definition of cases	Representativeness of case	Selection of controls	Definition of controls	Comparable factors	Ascertainment of exposure	Comparability of methods	Non-response rate
2004; Li	√	√	√	√	–	√	√	√
2008; Gungor	√	√	√	√	√	√	√	√
2010; Kuyumcuoglu	√	√	√	√	–	√	√	√
2011; Lee	√	√	√	√	√√	√	√	√
2012; Qiu	√	√	√	√	–	√	√	√
2013; Allensworth	√	√	√	√	–	√	√	√
2013; Ma	√	√	√	√	–	√	√	√
2014; Cohen	√	√	√	√	√	√	√	√
2014; Digklia	√	√	√	√	√	√	√	√
2014; Chen	√	√	√	√	–	√	√	√
2015; Man	√	√	√	√	√	√	√	√
2016; Cozzi	√	√	√	√	–	√	√	√
2020; Matsuo	√	√	√	√	–	√	√	√
2020; Okunade	√	√	√	√	√	√	√	√

Factors assessed for comparability included percentages of patients with advanced stage disease, as well as patients subjected to optimal debulking.

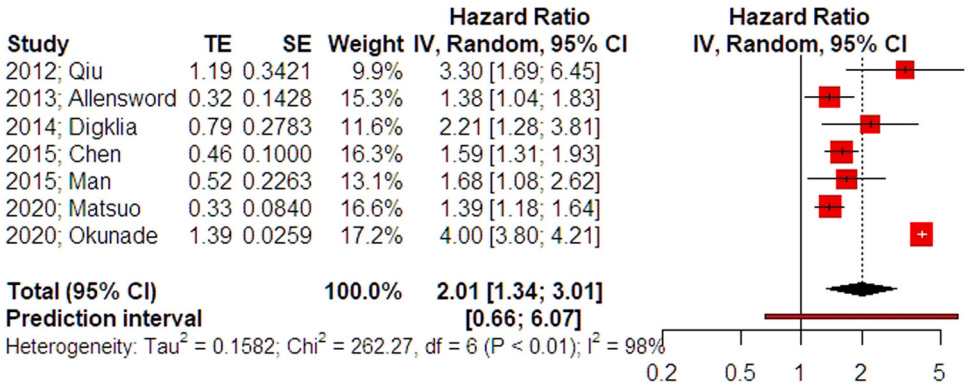

Fig. 2. Hazard ratios (HR) of recurrence-free survival. Forest plot analysis: vertical line, 'no difference' point between the two groups; red squares, HR; diamond, pooled HR and 95 % confidence interval (CI) for all studies; horizontal black lines, 95 % CI; horizontal red line, prediction interval.

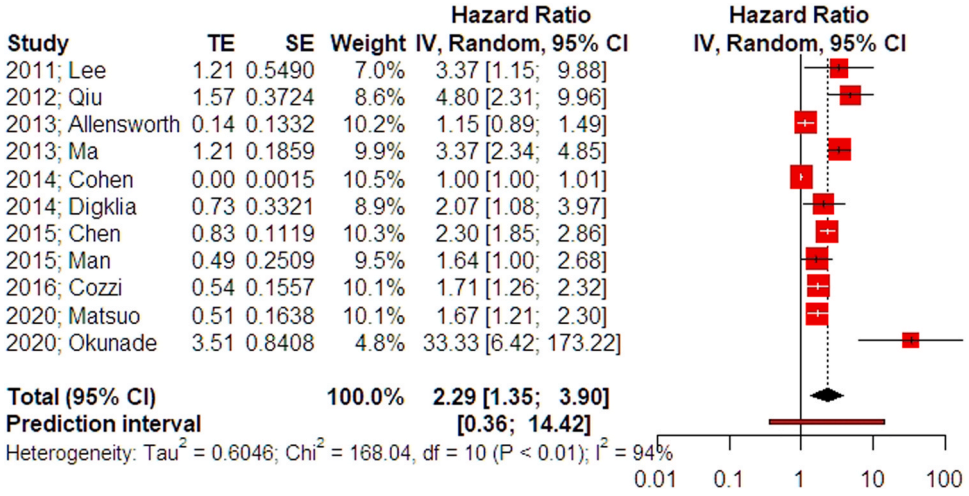

Fig. 3. Hazard ratios (HR) of overall survival. Forest plot analysis: vertical line, 'no difference' point between the two groups; red squares, HR; diamond, pooled HR and 95 % confidence interval (CI) for all studies; horizontal black lines, 95 % CI; horizontal red line, prediction interval.

Table 3
Outcomes of meta-analysis for secondary outcomes.

Outcome	Number of studies	Primary analysis	Outlier analysis	Limit meta-analysis	p-curve	TSA analysis
Advanced stage	7	2.88 (1.90–4.37)	-	1.81 (0.95–3.43)	Evidential value	Reached (566)
Optimal debulking	8	3.45 (1.40–8.49)	2.63 (1.28–5.40)	1.27 (0.73–2.22)	Evidential value	Not reached (2863)
Ascites	3	2.50 (0.30–20.66)	-	0.96 (0.33–2.78)	-	Not reached (1291)
Deep vein thrombosis	4	1.62 (0.48–5.46)	-	0.04 (0.0002–10.11)	-	Reached (515)

TSA, trial sequential analysis.

5.2. Comparison with existing literature

Several studies have indicated that thrombocytosis increases the risk of recurrence and death in various forms of cancer [41–44]. The proposed underlying mechanism seems to be primarily related to the onset of a cancer-induced inflammatory cascade that triggers the release of several inflammatory factors which, in turn, promote cancer progression by enhancing malignant conversion, invasion and metastasis [4]. Paraneoplastic thrombocytosis is part of this inflammatory process, as the release of cytokines in patients with ovarian cancer triggers thrombopoiesis [25]. The cause of death in these patients does not seem to be increased risk of fatal cardiovascular incidents, including DVT and pulmonary embolism; this was confirmed by the findings of the present meta-analysis, which seem to be based on an adequate sample size, according to the results of the TSA analysis.

This information implies that thrombocytosis may be associated with aggressive tumour biology [45]. This is supported by this review, as patients with a higher tumour load (advanced stage disease) seemed to be at higher risk of developing thrombocytosis. To date, it remains unclear if this finding should be considered the result of tumour progression or if it actually denotes a more aggressive pathophysiology. Although it seems reasonable to assume a correlation between tumour progression and the release of thrombopoietic factors, one cannot underestimate the potentially significant effect of platelet inhibition on the control of cancer progression [46]. Limited evidence suggests that patients who have pre-treatment thrombocytosis may develop chemoresistance, which directly affects overall survival and recurrence-free survival of patients [47]; however, more studies are needed to corroborate these findings. One could assume that these patients might benefit from primary debulking surgery; however, there are no relevant data to show that upfront surgery may be better than interval debulking procedures.

Thrombocytosis has been linked to perioperative morbidity in surgical operations which, in turn, increases the duration of hospitalisation and return to daily activities [48,49]. In patients with cancer, this may result in significant prolongation of the interval to adjuvant treatment, which may explain the reduced survival rates of these patients. However, to date, this remains unproven as there is no published evidence.

In patients with ovarian cancer, recent experimental and clinical data suggest that platelets may increase the expression of immune checkpoint (PD-L1), therefore dampening the antitumour immune response, an effect that may result in more aggressive phenotypes [50]. Considering this, one may assume that the combination of antiplatelet agents, including aspirin and non-steroidal anti-inflammatory drugs, with chemotherapy may help attenuate the course of the disease and increase the intervals to recurrence and death. However, current data do not seem to support this [51]. Considering the limited effect of antiplatelet agents on the course of cancer progression, researchers targeted the pathways of interaction between platelets and tumours and observed that glycoprotein VI (GPVI) and tumour galectin-3 may link thrombocytosis to aggressive cancer phenotypes [52]. With this information in mind, they also experimented with Revacept, a competitive antagonist of GPVI that inhibits platelet adhesion, in an experimental in-vitro model and observed that its use was associated with decreased cancer cell invasion [52].

5.3. Study limitations

Despite the fact that this systematic review included an adequate number of studies, the heterogeneity between them suggests that the impact of thrombocytosis on specific subgroups may differ significantly. This is reflected by the observed skewed distribution of studies in the publication bias analysis, which does not seem to be attributed to small study effects or p-hacking. The residual heterogeneity that was reported following sensitivity analysis for these factors suggests that the summary effect estimate of HRs of overall and disease-free survival may differ substantially in selected subgroups of patients with ovarian cancer. Considering the potential effect of thrombocytosis on the chemotherapeutic response, one could assume that it could also be used as a predictive factor of platinum sensitivity. To date, relevant information on the diagnostic accuracy of thrombocytosis to detect poor responders to chemotherapy remains unavailable, therefore limiting the clinical implications of this systematic review. Another issue that requires further investigation is the response of thrombocytosis to the surgical and chemotherapeutic treatment of patients with ovarian cancer, as this might also serve as a biomarker of the chemotherapeutic response.

5.4. Conclusions and implications

The findings of this study suggest that pre-treatment thrombocytosis is associated with increased rates of disease recurrence and death. Thrombocytosis is encountered more frequently in patients with advanced stage disease, and it may be predictive of suboptimal tumour debulking. Although cancer-specific overall survival was not available in studies included in this systematic review, thromboembolic disease was not increased significantly in patients with thrombocytosis, partially precluding the possibility of attributing the increased risk of mortality to cardiovascular incidents.

Considering the significant effect of thrombocytosis on survival rates and the limited amount of evidence that suggests a potential association between the chemotherapeutic response and poly ADP ribose polymerase inhibitors, further research is needed to evaluate whether this factor may strongly predict those patients at risk of developing platinum resistance, as well as those that are more likely to respond poorly to maintenance therapy. Specific subgroups of patients with ovarian cancer should be considered, namely patients with advanced stage disease, as these patients are more likely to develop thrombocytosis. Establishment of an ideal threshold is of paramount importance, and in order to accomplish this, future research should focus on pre-determined values rather than optimal cut-offs.

Informed consent statement

Patient consent was obtained prior to the inclusion of patients in the study.

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CRediT authorship contribution statement

Nikolaos Thomakos: Writing – review & editing. **Lito Vogiatzi Vokotopoulou:** Writing – original draft, Data curation. **Dimitrios Efthimios Vlachos:** Writing – original draft, Conceptualization. **Michalis Liontos:** Writing – original draft. **Emmanuel Kontomanolis:** Writing – review & editing, Methodology, Data curation. **Vasilios Pergialiotis:** Writing – review & editing, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they do not have conflicts of interest.

Data availability statement

Data available upon reasonable request.

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