Review Article
Clinicopathological and prognostic significance of serum interleukin-8 in ovarian cancer: a meta-analysis

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Abstract: To conduct a meta-analysis to clarify the association of elevated serum IL-8 levels with the clinicopathological features and survival outcomes of ovarian cancer patients. A search in PubMed, Embase was performed to identify eligible studies. Stata 12.0 software was used for meta-analysis. A total of 1456 ovarian cancer patients from 15 studies were included. The results indicated that serum IL-8 levels were elevated in ovarian cancer patients compared with patients with benign ovarian tumors (SMD = 0.35, 95% CI = 0.18-0.53, P < 0.001), or healthy women (SMD = 0.58, 95% CI= 0.40-0.76, P < 0.001). Moreover, elevated serum IL-8 was associated with tumor histology type (serous vs. nonserous: SMD = 1.03, 95% CI = 0.45-1.61, P < 0.001), high tumor grade (Grade 1 vs. Grade 2-3: SMD = -0.62, 95% CI = -0.86–0.38, P < 0.001), poor 5-year survival rates (HR = 2.06, 95% CI = 1.44-2.68, P < 0.001) and disease free survival rates (HR = 2.05, 95% CI = 1.31-2.80, P < 0.001). Whereas, serum IL-8 level was not significantly correlated with the advanced tumor stage. This meta-analysis indicates that elevated serum IL-8 level seems to be associated with advanced clinicopathological features and poor prognosis of ovarian cancer.

Keywords: Interleukin-8, ovarian cancer, meta-analysis, prognosis, clinicopathological features

Introduction

Ovarian cancer, the leading cause of death from gynecologic malignancies, is always diagnosed in an advanced clinical stage with poor prognosis [1]. Thus, it is necessary to identify effective and reliable prognostic factors to predict survival rates, identify vulnerable patients, facilitate treatment choices and improve the outcome of the patients.

It has been indicated that there is a strong association between inflammation and cancer prognosis [2]. Inflammatory cytokines are key players in regulating cancer inflammation [3, 4]. Easily detected in serum or plasma, these cytokines may serve as good prognostic tools in cancer patients. Interleukin-8 (IL-8), also called chemokine ligand 8 (CXCL8), is originally discovered as a chemotactic and inflammatory cytokine for leukocytes in 1987 [5]. Several studies have indicated that IL-8 may contribute to cancer progression through its potential function as a mitogenic, angiogenic, and motogenic factor [6-8]. In ovarian cancer, high levels of IL-8 have been found in the serum of patients with advanced cancer stages and unfavorable prognosis [9, 10]. Moreover, IL-8 has also been reported to promote ovarian cancer growth, angiogenesis and metastasis both in vitro and in vivo [11, 12], which supports that IL-8 is involved in ovarian cancer development. However, the clinicopathological and prognostic roles of serum IL-8 in ovarian cancer remain inconclusive.

In the current study, a meta-analysis of observational studies was carried out to evaluate the clinicopathological and prognostic value of serum IL-8 level in patients with ovarian cancer.

Materials and methods

Search strategy

A comprehensive literature search of the electronic databases, including PubMed and Embase was conducted up to August 1, 2016. Our search strategies included terms for inter-
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leukin-8 (interleukin-8, interleukin 8, IL8, IL-8 and CXCL8) and ovarian cancer (ovarian cancer, ovarian tumor, ovarian carcinoma and ovarian neoplasm).

Study selection

Studies meeting the following criteria were included: (1) IL-8 levels were measured in the pretreatment serum of patients with histologically proven ovarian cancer. (2) Correlation between pretreatment serum IL-8 and the clinicopathological parameters or prognosis of ovarian cancer patients was explored. (3) Studies regarding prognosis provided enough data to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Animal studies and studies published in languages other than English were excluded. Patients who had previously chemotherapy or radiotherapy were also excluded. If the study population was used in multiple articles, studies with larger sample size and more rigorous adjustment were included.

Data extraction and quality assessment

Two primary investigators independently extract the data from each publication, including first author, publication year, country, study population, IL-8 source, detection methods for serum IL-8, follow-up periods, clinicopathological parameters, and survival data. Disagreement in the extraction data were resolved by discussion and consensus. The quality of all studies was assessed by two investigators using Newcastle-Ottawa quality assessment scale (NOS). In this 9-score system, each study included in the meta-analysis was evaluated on three aspects: selection, comparability and outcome. Studies with scores higher than 6 were classified as “high” quality studies. Disagreement in the score was resolved through discussion and consensus.

Data analysis

The meta-analysis was performed by STATA 12.0 (Stata Corp, College Station, TX, USA). Survival data were presented as hazard ratio (HR) and continuous variables as Standardized mean difference (SMD), with 95% confidence interval (CI). Heterogeneity among the studies was estimated by I-square statistics, and P value more than 50% was recognized as significant heterogeneity. A random effects model was used in the presence of significant heterogeneity, otherwise a fixed effects model was used. The potential publication bias was assessed by funnel plots, Begg’s rank correlation test and Egger’s regression method.

Results

Study selection and characteristics

A total of 733 articles were identified using the search strategy described above. 234 duplicates were excluded using EndNote software. 484 articles were also excluded due to various reasons, such as being a review article, providing insufficient outcome data, being irrelevant to this study, and written in languages other than English. Finally, there were 15 studies included in this meta-analysis (Figure 1) [9, 10, 13-25]. The main characteristics of the 15 eligible publications were summarized in Table 1.
### Table 1. Characteristics of eligible studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Case/Control</th>
<th>FIGO stage</th>
<th>Historical subtype</th>
<th>Tumor Grade</th>
<th>IL-8 source</th>
<th>IL-8 detection methods</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasciani A</td>
<td>2001</td>
<td>Italy</td>
<td>9/53</td>
<td>III 7, IV 2</td>
<td>S 8, E 1</td>
<td>G2, G3</td>
<td>serum</td>
<td>ELISA</td>
<td>6</td>
</tr>
<tr>
<td>Darai E</td>
<td>2003</td>
<td>France</td>
<td>13/30</td>
<td>NA</td>
<td>S 8, M 5</td>
<td>NA</td>
<td>serum</td>
<td>immunoradiometric assay</td>
<td>7</td>
</tr>
<tr>
<td>Gorelik E</td>
<td>2005</td>
<td>USA</td>
<td>44/82</td>
<td>I/II 44</td>
<td>S 18, M 7, E 10, C 3, O 6</td>
<td>NA</td>
<td>serum</td>
<td>Multiplexed Immunobead-Based Cytokine Profiling</td>
<td>6</td>
</tr>
<tr>
<td>Lokshin AE</td>
<td>2006</td>
<td>USA</td>
<td>94/117</td>
<td>I/II 44, III/IV 50</td>
<td>NA</td>
<td>NA</td>
<td>serum</td>
<td>LabMAP assay</td>
<td>7</td>
</tr>
<tr>
<td>Lambeck AJ</td>
<td>2007</td>
<td>USA</td>
<td>187/95</td>
<td>I 44, II 23, III 96, IV 23, U 1</td>
<td>S 89, M 28, E 15, C 14, O 40, U 1</td>
<td>G1 72, G2/G3 83, U 32</td>
<td>serum</td>
<td>Cytometric Bead Array</td>
<td>7</td>
</tr>
<tr>
<td>Kavask PA</td>
<td>2008</td>
<td>Canada</td>
<td>45/33</td>
<td>I/II 28, III/IV 17</td>
<td>NA</td>
<td>NA</td>
<td>serum</td>
<td>cytokine array</td>
<td>6</td>
</tr>
<tr>
<td>Sadlecki P</td>
<td>2009</td>
<td>Poland</td>
<td>30/36</td>
<td>I/II 8, III/IV 22</td>
<td>S 21, M3, E 2, C 3, O 1</td>
<td>G1 6, G2 10, G3 14</td>
<td>serum</td>
<td>ELISA</td>
<td>7</td>
</tr>
<tr>
<td>Tsai-Turton M</td>
<td>2009</td>
<td>USA</td>
<td>130/84</td>
<td>I 10, II 7, III 79, IV 34</td>
<td>NA</td>
<td>NA</td>
<td>serum</td>
<td>Multiplex cytokine bioplex assays</td>
<td>6</td>
</tr>
<tr>
<td>Edgell T</td>
<td>2010</td>
<td>Australia</td>
<td>150/212</td>
<td>I 28, II 63, III 46, IV 7, U 6</td>
<td>S 99, M11, E 15, C 11, O 6, U 8</td>
<td>NA</td>
<td>serum</td>
<td>Multiplexed bead-based assays</td>
<td>7</td>
</tr>
<tr>
<td>Nowak M</td>
<td>2010</td>
<td>Poland</td>
<td>51/47</td>
<td>I 13, II 2, III 33, IV 3</td>
<td>S 22, M 7, E 11, C 2, O 9</td>
<td>G1 9, G2 14, G3 28</td>
<td>serum</td>
<td>ELISA</td>
<td>7</td>
</tr>
<tr>
<td>Autelitano DJ</td>
<td>2012</td>
<td>Australia</td>
<td>222/467</td>
<td>I 42, II 27, III 106, IV 14, U 33</td>
<td>S 130, M 16, E 19, C 16, O 41</td>
<td>NA</td>
<td>serum</td>
<td>Immulite assay</td>
<td>7</td>
</tr>
<tr>
<td>Aune G</td>
<td>2012</td>
<td>Norway</td>
<td>57/33</td>
<td>I 19, II 3, III 29, IV 6</td>
<td>S 28, M 2, E 13, C 6, O 8</td>
<td>G1 6, G2 12, G3 33</td>
<td>serum</td>
<td>Cytokine Human 25-plex panel</td>
<td>7</td>
</tr>
<tr>
<td>Dobrzynska B</td>
<td>2013</td>
<td>Poland</td>
<td>118/64</td>
<td>I 18, II 25, III 61, IV 14</td>
<td>S 57, M 18, E 12, C 8, O 23</td>
<td>G1 23, G2 46, G3 49</td>
<td>serum</td>
<td>ELISA</td>
<td>7</td>
</tr>
<tr>
<td>Kristjansdottir B</td>
<td>2014</td>
<td>Sweden</td>
<td>156/78</td>
<td>I 32, II 7, III 36, IV 3</td>
<td>S 48, M 7, E 16, C 6, O 8</td>
<td>G1 27, G2 17, G3 27</td>
<td>serum</td>
<td>ELISA</td>
<td>7</td>
</tr>
<tr>
<td>Block MS</td>
<td>2015</td>
<td>USA</td>
<td>150/50</td>
<td>I 36, II 14, III 83, IV 17</td>
<td>S 95, M 6, E 22, C 13, O 14</td>
<td>G1 23, G2/G3 123, U 4</td>
<td>serum</td>
<td>Electrochemiluminescence immunoassays</td>
<td>7</td>
</tr>
</tbody>
</table>

**Abbreviations:** NA, not available; S, serous; M, mucinous; E, endometrioid; C, clear cell; O, others; U, unknown; G1, Grade 1; G2, Grade 2; G3, Grade 3.
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Overall, 11 of 15 studies evaluate the association between serum IL-8 concentration and clinicopathological features of ovarian cancer. Overall survival (OS) was obtained from 3 studies while disease free survival (DFS) was obtained from 2 studies. The Newcastle-Ottawa scale (NOS) was used to assess the study quality and NOS scores were presented in Table 1.

Circulating IL-8 level between ovarian cancer group and control group

A total of eleven studies reported the serum expression level of IL-8 in ovarian cancer group and benign ovarian tumor group. Meta-analysis of random effect model indicated that the IL-8 levels in ovarian cancer group were higher than those in the control group. The difference was statistically significant (Figure 2A, SMD = 0.35, 95% CI = 0.18-0.53, P < 0.001). Eleven studies reported the serum expression level of IL-8 in ovarian cancer group and healthy control group. Meta-analysis of random effect model showed that the blood IL-8 levels were higher than those in the control group (Figure 2B, SMD = 0.58, 95% CI = 0.40-0.76, P < 0.001).

Correlation between circulating IL-8 and clinicopathological features of ovarian cancer

Three studies reported the association between IL-8 level and histological types. The outcomes are significantly heterogeneous so that a random effect model was used for meta-analysis. The combined SMD revealed that IL-8 levels in serous ovarian cancer group were higher than those in nonserous ovarian cancer group (Figure 3A, SMD = 1.03, 95% CI = 0.45-1.61, P < 0.001). Four studies described the serum IL-8 level according to tumor grade. It was found that IL-8 levels in G1 group were lower than those in G2-3 group. The difference between

![Figure 2. A. Meta-analysis of serum IL-8 level between ovarian cancer group and benign tumor group. B. Meta-analysis of serum IL-8 level between ovarian cancer group and healthy control group. I$^2$ was larger than 50% so that a random effects model was used.](image)
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Two groups was statistically significant (Figure 3B, SMD = -0.62, 95% CI = -0.86--0.38, P < 0.001). Nine studies investigated the relationship between IL-8 level and tumor stage. The outcomes are significantly heterogeneous so that a random effect model was used for meta-analysis. The combined SMD revealed that serum IL-8 level was not related to tumor stage (Figure 3C, SMD = -0.34, 95% CI = -0.77-0.10, P = 0.129).

Circulating IL-8 as a prognostic factor of ovarian cancer

Three studies estimated the relationship between OS and IL-8 level. The pooled hazard ratio (HR) showed high serum IL-8 level was significantly associated with poor OS in ovarian cancer (HR = 2.06, 95% CI =1.44-2.68, P < 0.001). Two studies investigated the relationship between DFS and IL-8 level. Meta-analysis
showed that high serum IL-8 group suffered with shorter DFS in ovarian cancer (HR = 2.05, 95% CI = 1.31-2.80, P < 0.001) (Figure 4).

Sensitivity analysis and publication bias

Egger’s and Begg’s tests showed no publication bias among included studies, with p values of 0.755 (Begg’s analysis) and 0.719 (Egger’s analysis) in Figure 5A and p values of 0.087 (Begg’s analysis) and 0.081 (Egger’s analysis) in Figure 5B. The symmetric funnel plots also suggest the publication bias was little (Figure 5).

Discussion

This meta-analysis presents the results of 15 studies and indicates that the serum IL-8 level in ovarian cancer group is higher than that in benign gynecologic tumor or healthy control group. Moreover, elevated serum IL-8 level is related to tumor stage as well as tumor type. Further, high serum IL-8 concentration was significantly associated with poor OS and DFS in patients with ovarian cancer. These results suggest the likelihood that serum IL-8 may become a valuable prognostic biomarker for ovarian cancer.

Tumor-promoting inflammation is one of the hallmarks of cancer [2], and several inflammatory cytokines, including IL-8, have been investigated in cancer clinical trials [26, 27]. The prognostic roles of IL-8 over-expression have been reported in various kinds of cancers, such as lung cancer [28], renal cell carcinoma [29] and urothelial carcinoma [30]. Moreover, higher IL-8 level has also been reported to be associated with some clinical parameters of cancer, including advanced stage, poor differentiation and lymphatic metastasis [31, 32]. Although several studies have been carried out to evaluate the clinical and prognostic value of IL-8 in ovarian cancer, the results are not consistent. This meta-analysis combined the data of 15 studies investigating circulating IL-8 level and revealed that increased serum IL-8 concentration is associated with poor OS, DFS, and important prognostic factors of ovarian cancer, such as tumor histology and tumor grade.
These results suggest that testing circulating IL-8 level may help to identify more vulnerable patients who may need closer follow-up to detect recurrence and more aggressive intervention to improve outcome. However, due to the small number of included studies, we failed to evaluate the relationship between IL-8 level and other essential prognostic factors, such as tumor size and lymphatic metastasis. Thus, prospective and high quality studies are needed in the future.

The rationale behind the clinical and prognostic role of serum IL-8 is partly based on its frequent elevation in advanced ovarian cancer. A number of studies have shown that the serum IL-8 level is much higher in ovarian cancer patients than in patients with benign ovarian tumors or healthy women [9, 10]. IL-8, an inflammatory and chemotactic cytokine, could be stimulated by inflammation. In ovarian cancer, the repeated inflammatory process during the damage and repair of the ovarian surface epithelium induced by incessant ovulation has been considered to be one of the major causes of the disease [33]. Moreover, the tumor milieu of ovarian cancer is enriched with pro-inflammatory cytokines and chemokines [34]. In addition, inflammation may contribute to ovarian cancer progression by supplying bioactive molecules facilitating tumor proliferation, angiogenesis, migration and invasion [2, 34]. This inflammatory process throughout ovarian tumorigenesis and cancer progression may cause the extensive alteration of serum inflammatory cytokines, including IL-8. Therefore, serum IL-8 level could be valuable in predicting tumor prognosis. However, more studies are needed to confirm the clinical value of IL-8.

Besides the predictive role of IL-8 in ovarian cancer prognosis, IL-8 level has also been found to be correlated with poor response to paclitaxel or carboplatin in ovarian cancer treatment [35, 36]. This prompts us to consider whether IL-8 expression level could also be used as predictors of chemoresistance. However, the small sample sizes are insufficient for us to conduct a meta-analysis and draw solid conclusions so that further studies in this area are needed.

There are several limitations to our study. First, heterogeneity was found in the analysis which may rise from the different characteristics of the investigated objects. Secondly, the methods used to test IL-8 level varied among included studies which prevents standardization of serum IL-8 measurements. Furthermore, the number of studies included in this meta-analysis is relatively small. Finally, retrospective studies included in this study provide a relatively lower level of evidence. In virtue of the limitations listed above, further large prospective cohort studies are needed to validate our results and provide a higher level of evidence.

In conclusion, we found that serum IL-8 level is much higher in ovarian cancer patients than in patients with benign ovarian tumors or healthy women. Moreover, circulating IL-8 level appeared to correlate with some clinical features and survival rates of ovarian cancer patients. Therefore, circulating IL-8 could be considered as an important factor of prognos-
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tic estimation and clinical intervention of ovari-an cancer patients.

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Disclosure of conflict of interest

None.

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