ORIGINAL RESEARCH

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# Ascites Fluid Interleukin-8 Level as a Predictor of Survival in Patients with Ovarian Cancer: Analytical Research-Cohort Research

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**ABSTRACT Objective:** Ovarian cancer is one of the most fatal gynaecological malignancies worldwide. In ovarian cancer patients, elevated interleukin-8 (IL-8) level was found in ovarian cyst fluid, ascites, serum, and tumour tissue. This study aimed to determine the relation between ascites' IL-8 level and progression-free survival (PFS) as well as overall survival (OS) in ovarian cancer patients. **Material and Methods:** This prospective cohort included ovarian cancer patients who underwent primary surgery at Sardjito General Hospital during the 2018-2021 period. Samples were taken from ascites fluid. Outcomes including PFS and OS were recorded at the end of this study. IL-8 level was measured with human cytokine magnetic 10-plex panel for luminex (commercial kit invitrogen). **Results:** The subjects of this study were 40 ovarian cancer patients. The median follow-up was 24 months. During follow-up, 22 participants (55%) were progression-free. Twenty participants (50%) survived at the end of the study. Patients with high IL-8 level significantly had 2.93 times more risk to develop disease progression (p=0.048) and shorter progression free survival time of 15.4 compared to 27.5 months (p log rank 0.02). High IL-8 also decreased OS time of 19.4 compared to 27.3 months but was not significant (p log rank 0.058). Older age significantly related to low overall survival (0% compared to 58.8%), p=0.003. **Conclusion:** IL-8 ascites increased the risk of disease progression significantly but did not lower overall survival significantly in ovarian cancer. Older age was found to be unbeneficial for overall survival in ovarian cancer patients.

**Keywords:** Interleukin-8; progression-free survival; overall survival; ovarian cancer; ascites

Ovarian cancer is one of the most fatal gynaecological malignancies worldwide.[1] It is more prevalent in elderly than young women. In Indonesia, ovarian cancer is the third most common cancer in females.[2] The majority of ovarian malignancies originate from the ovary's epithelial cells.[3] According to the appearance of the epithelium cells, ovarian cancer can be categorised into five major carcinoma histotypes: high-grade serous carcinoma, clear cell carcinoma, endometrioid carcinoma, mucinous carcinoma, and low-grade serous carcinoma.[3] Given its asymptomatic nature, ovarian cancer is commonly identified in advanced stages, even with advancements in diagnostic technologies, surgery, and chemotherapy.[4]

Interleukin 8 (IL-8) is a chemokine with defining Cysteine-X-Cysteine amino acid motif. As multifunctional chemokine, IL-8 is released by several cell types including monocytes, neutrophils, endothelial and mesothelial cells, and tumour cells. During immune system activation, IL-8 recruits neutrophils, T cells, and basophils.[5] In ovarian cancer patients, elevated IL-8 level was found in ovarian cyst fluid, ascites, serum, and tumour tissue.[6] Studies found that overexpression of IL-8 was associated with tumour progression, metastasis, poor prognosis, and chemosensitivity, high-grade and advanced-stage cancers and worse disease-related patient survival.[6-9] IL-8 secretion might enhance regulation of vascular endothelial growth factor (VEGF) ex-

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pression and result in increase of tumour microvessel density.[9] Our study aimed to determine the association between IL-8 level in ascites progression-free survival (PFS) and overall survival (OS) in ovarian cancer patients.

## MATERIAL AND METHODS

### PATIENTS

The sample size was calculated based on Freedman formula.[10]

$$Ntotal = (Z\alpha + Z\beta)^2 \left(\frac{1+HR}{1-HR}\right)^2$$

Ntotal=2n=n1+n2=total sample for both group.
$Z\alpha$=alpha standard deviation=1.96, alpha power 95%
$Z\beta$=beta standard deviation=0.84, beta power 20%
HR=hazard ratio from the previous study.

Based on a previous study, HR of IL-8 to survival in ovarian cancer was 3.6.[11] Therefore the N total is 25, and the minimal number of subject for each group is rounded to 13.

We obtained ethics approval (KE/FK/0749/EC/2018) from the ethics committee of the Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University at 20th July 2018. Our study inclusion criteria were patients with ovary carcinoma Stage I-IV based on histopathology findings by pathologists at the Anatomy Pathology Department, Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University/Sardjito General Hospital, underwent primary ovarian surgery at Sardjito General Hospital, and willing to participate in our study. The exclusion criteria were patients with a history of other malignancy, had previous ovarian cancer surgery, had previous chemotherapy, pregnant and breastfeeding women, or had infection during surgery. Using consecutive sampling technique, this prospective cohort obtained clinical data of 40 ovarian cancer patients who underwent primary surgery at Sardjito General Hospital from January 2018 to December 2021. This study was conducted in accordance with the principles of the Declaration of Helsinki, and informed consent was obtained from all participants prior to their inclusion in the study. The follow up median was 24 months with the longest follow up was 39 months. The study's samples were ascites fluid. IL-8 was measured with a human cytokine magnetic 10-plex panel for luminex (commercial kit invitrogen).

### ASCITES FLUID

During the operation, 10 mL of peritoneum fluid was taken. For patients who did not have sufficient peritoneal fluid, 20 mL NaCl 0.9% were used to wash the peritoneal cavity. From previous literature, this method was able to represent peritoneal fluid.[12] The sample was immediately taken to the molecular biology lab at 4°C and centrifuged at 1,200-1,400 rpm for 5 minutes. Supernatant component was collected and stored in Eppendorf. Freezing medium was added to the cellular component and stored inside cryovials. Temperature was being maintained at -80°C until samples were analysed.

### OPERATIONAL DEFINITION

Progression free survival was a duration from primary surgery until progression/relapse of the disease.[13] Overall survival was the period from the primary surgery to death or last follow-up, regarding the death cause. Histopathology type was categorised as Type 1 (low grade serous, low grade endometrioid, clear cell, mucinous, and transitional) and Type 2 (high grade serous, undifferentiated adenocarcinoma, and malignant mixed mesodermal) based on previous literature.[14] Cancer stage was considered as early for FIGO Stage I & II, and advance for FIGO Stage III & IV. Residual tumour was macroscopically seen, thus bigger from >1 centimetre in size.[15] Malignant ascites was defined by the presence of tumour cells and stromal cells in the ascitic fluid.[16] Total infiltrating leukocyte was obtained by using International Immuno-Oncology Biomarker Working Group method.[17] Lymph vascular space invasion (LVSI) was the presence of tumour cell in the lymphatic drainage system and or microvascular in the primary tumour.[18]

### STATISTICAL ANALYSIS

To describe subjects' characteristics, we used descriptive analysis including frequency, percentage, mean, and standard deviation. Using the statistical program SPSS 24.0 (IBM, USA), collected data were analysed for univariate and multivariate regression. Survival analysis was made using a log rank test, and

presented with Kaplan-Meier curves for bivariate analysis and Cox's regression for multivariate analysis. Statistical significance was p<0.05 and confidence interval (CI) 95%.

## RESULTS

We obtained informed consent from 58 patients with suspected ovarian cancer who underwent primary surgery at Sardjito General Hospital in the 2018-2021 period. From 58 patients, after pathological anatomy examination, 18 patients were excluded due to benign neoplasms (13), mature teratoma (2), infected cyst (2), and lymphangioma (1). No patients were lost to follow-up in this study.

The characteristics of a total of 40 epithelial ovarian cancer patients was analysed (Table 1). The mean age of the study group was 48.35 years old, with the domination of participants below 60 years old (85%). Most of the participants had multipara regarding their parity status (72.5%). The histopathology Type 1 (low grade serous, low grade endometrioid, clear cell, mucinous and transitional) was 42.5% and Type 2 (high grade serous, undifferentiated adenocarcinoma and malignant mixed mesodermal) was 57.5%. The majority of the participants presented with high grade cancer (72.5%). The early cancer stadium (I & II) was 40.0% and advanced cancer stadium (III & IV) was 60.0%. The tumour residual was not seen macroscopically in 62.5% of the participants. The median level of preoperative ca-125 was 839.7 U/mL with more than half having preoperative ca-125 level ≥500 (62.5%) and ascites fluid ≥500 (52.5%). Malignant ascites was found in 70% of the cases. The total infiltrating leukocyte was very low (55.0%), low (27.5%), and high (17.5%). The median of IL-8 in the ascites was 600.4 pg/mL. LVSI was found in 30% of the participants. Fifty-five percent of the participants were progression free during follow up. At the end of this study, half of the participants survived.

Univariate analysis was performed for all variables. Using the logistic regression model, 1575.74 was the cut off for IL-8 level. We found IL-8 level, age, histopathology type, grading, stage, and residual tumour to be statistically significant variables for progression free survival in ovarian cancer. Patients with higher IL-8 level (HR 2.88; 95% CI 1.11-7.50; p=0.030), older age (HR 8.11; 95% CI 2.37-27.67; p=0.001), histology Type 2 (HR 8.77; 95% CI 1.99-38.59; p=0.004), high grade cancer (HR 8.26; 95% CI 1.09-62.20; p=0.040), advanced stage (HR 8.14; 95% CI 1.85-35.78; p=0.006), residual tumour Rx (HR 4.99; 95% CI 1.79-13.87; p=0.002) were found to have worse progression free survival (Table 2).

Regarding OS, age, histopathology type, stage, residual tumour and LVSI were significant variables.

**TABLE 1:** Characteristics of the study.

| | | $\bar{X}$±SD or Median (minimum-maximum) | n | % |
|---|---|---|---|---|
| Age (Year) | | 48.35±11.62 | | |
| Age | <60 | | 34 | 85.0% |
| | ≥60 | | 6 | 15.0% |
| Parity | Nullipara | | 11 | 27.5% |
| | Multipara | | 29 | 72.5% |
| Histopathology type | 1 | | 17 | 42.5% |
| | 2 | | 23 | 57.5% |
| Grade | Low | | 11 | 27.5% |
| | High | | 29 | 72.5% |
| Stage | Early | | 16 | 40.0% |
| | Advanced | | 24 | 60.0% |
| Tumour residual | R0 | | 25 | 62.5% |
| | Rx | | 15 | 37.5% |
| Pre-operative Ca125 | <500 | 839.7 (21.9-25000) | 15 | 37.5% |
| | ≥500 | | 25 | 62.5% |
| Ascites | <500 | | 19 | 47.5% |
| | ≥500 | | 21 | 52.5% |
| Ascites | Benign | | 12 | 30.0% |
| | Malignant | | 28 | 70.0% |
| Total TILs | Very low | | 22 | 55.0% |
| | Low | | 11 | 27.5% |
| | High | | 7 | 17.5% |
| LVSI | Negative | | 28 | 70.0% |
| | Positive | | 12 | 30.0% |
| IL-8 ascites | | 600.4 (5.5-4499.1) | | |
| Progression free survival | Sensor | | 22 | 55.0% |
| | Event | | 18 | 45.0% |
| Overall survival | Sensor | | 20 | 50.0% |
| | Event | | 20 | 50.0% |

IL-8: Interleukin-8; Histopathology Type 1: Low grade serous, low grade endometrioid, clear cell, mucinous and transitional; Histopathology Type 2: High grade serous, undifferentiated adenocarcinoma and malignant mixed mesodermal; Early stage: Stage I & II; Advanced Stage: Stage III & IV; Residual tumour R0: Tumour residual was not seen macroscopically; Residual tumour Rx: Tumour residual was seen macroscopically; LVSI: Lymph vascular space invasion; Total TILs: Total infiltrating leukocyte; SD: Standard deviation.

**TABLE 2:** Univariate and multivariate logistic regression of variables with progression-free survival and overall survival in ovarian cancer patients.

| Variable | Progression free survival | | | | | | | | Overall survival | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Sensor | Event | Univariate | | | Multivariate | | | Sensor | Event | Univariate | | | Multivariate | | |
| | n (%) | n (%) | p value | HR | CI 95% | p value | HR | CI 95% | n (%) | n (%) | p value | HR | CI 95% | p value | HR | CI 95% |
| IL-8 ascites (cut off) | | | | | | | | | | | | | | | | |
| <1575.74 | 20 (64.5) | 11 (35.5) | 0.030* | 2.88 | 1.11-7.50 | 0.048* | 2.93 | 1.01-8.53 | 18 (58.1) | 13 (41.9) | 0.070 | 2.37 | 0.93-6.06 | 0.138 | 2.19 | 0.78-6.17 |
| ≥1575.74 | 2 (22.2) | 7 (77.8) | | | | | | | 2 (22.2) | 7 (77.8) | | | | | | |
| Age | | | | | | | | | | | | | | | | |
| <60 | 21 (61.8) | 13 (38.2) | 0.001* | 8.11 | 2.37-27.67 | 0.085 | 3.48 | 0.84-14.41 | 20 (58.8) | 14 (41.2) | 0.001* | 11.00 | 3.39-35.99 | 0.003* | 7.67 | 1.99-29.46 |
| ≥60 | 1 16.7% | 5 (83.3) | | | | | | | 0 (0.0) | 6 (100.0) | | | | | | |
| Histopathology type | | | | | | | | | | | | | | | | |
| 1 | 15 (88.2) | 2 (11.8) | 0.004* | 8.77 | 1.99-38.59 | 0.061 | 5.75 | 0.92-35.93 | 12 (70.6) | 5 (29.4) | 0.021* | 3.36 | 1.20-9.39 | 0.316 | 1.87 | 0.55-6.41 |
| 2 | 7 (30.4 | 16 (69.6) | | | | | | | 8 (34.8) | 15 (65.2) | | | | | | |
| Grade | | | | | | | | | | | | | | | | |
| Low | 10 (90.9) | 1 (9.1) | 0.040* | 8.26 | 1.09-62.20 | 0.893 | 0.85 | 0.08-9.29 | 6 (54.5) | 5 (45.5) | 0.410 | 1.54 | 0.55-4.26 | | | |
| High | 12 (41.4) | 17 (58.6 | | | | | | | 14 (48.3) | 15 (51.7) | | | | | | |
| Stage | | | | | | | | | | | | | | | | |
| Early | 14 (87.5) | 2 (12.5) | 0.006* | 8.14 | 1.85-35.78 | 0.176 | 3.24 | 0.59-17.77 | 11 (68.7) | 5 (31.3) | 0.040 | 2.92 | 1.05-8.14 | 0.783 | 1.21 | 0.32-4.55 |
| Advanced | 8 (33.3) | 16 (66.7) | | | | | | | 9 (37.5) | 15 (62.5) | | | | | | |
| Residual tumour | | | | | | | | | | | | | | | | |
| R0 | 18 (72.0) | 7 (28.0) | 0.002* | 4.99 | 1.79-13.87 | 0.069 | 9.94 | 0.83-118.5 | 15 (60.0) | 10 (40.0) | 0.025* | 2.86 | 1.14-7.16 | 0.250 | 1.84 | 0.65-5.19 |
| Rx | 4 (26.7) | 11 (73.3) | | | | | | | 5 (33.3) | 10 (66.7) | | | | | | |
| Parity | | | | | | | | | | | | | | | | |
| Nullipara | 6 (54.5) | 5 (45.5) | 0.859 | 1.09 | 0.39-3.10 | | | | 6 (54.5) | 5 (45.5) | 0.477 | 1.45 | 0.52-4.04 | | | |
| Multipara | 16 (55.2) | 13 (44.8) | | | | | | | 14 (48.3) | 15 (51.7) | | | | | | |
| LVSI | | | | | | | | | | | | | | | | |
| Negative | 17 (60.7) | 11 (39.3) | 0.075 | 2.46 | 0.92-6.59 | | | | 16 (57.1) | 12 (42.9) | 0.025* | 2.91 | 1.15-7.37 | 0.612 | 1.34 | 0.44-4.12 |
| Positive | 5 (41.7) | 7 (58.3) | | | | | | | 4 (33.3) | 8 (66.7) | | | | | | |
| Preoperative Ca-125 | | | | | | | | | | | | | | | | |
| <500 | 9 (60.0) | 6 (40.0) | 0.704 | 1.21 | 0.45-3.24 | | | | 6 (40.0) | 9 (60.0) | 0.466 | 0.72 | 0.29-1.75 | | | |
| ≥500 | 13 (52.0) | 12 (48.0) | | | | | | | 14 (56.0) | 11 (44.0) | | | | | | |
| Ascites volume | | | | | | | | | | | | | | | | |
| <500 | 10 (52.6) | 9 (47.4) | 0.821 | 0.89 | 0.36-2.26 | | | | 7 (36.8) | 12 (63.2) | 0.240 | 0.58 | 0.24-1.43 | | | |
| ≥500 | 13 (52.0) | 12 (48.0) | | | | | | | 14 (56.0) | 11 (44.0) | | | | | | |
| Ascites | | | | | | | | | | | | | | | | |
| Benign | 10 (83.3) | 2 (16.7) | 0.056 | 4.21 | 0.96-18.39 | | | | 8 (66.7) | 4 (33.3) | 0.197 | 2.07 | 0.68-6.22 | | | |
| Malignant | 12 (42.9) | 16 (57.1) | | | | | | | 12 (42.9) | 16 (57.1) | | | | | | |
| Total TILs | | | | | | | | | | | | | | | | |
| Very low | 13 (59.1) | 9 (40.9) | | | | | | | 12 (54.5) | 10 (45.5) | | | | | | |
| Low | 6 (54.5) | 5 (45.5) | 0.943 | 1.04 | 0.35-3.11 | | | | 5 (45.5) | 6 (54.5) | 0.808 | 1.13 | 0.41-3.13 | | | |
| High | 3 (42.9) | 4 (57.1) | 0.280 | 1.93 | 0.58-6.34 | | | | 3 (42.9) | 4 (57.1) | 0.253 | 1.98 | 0.61-6.43 | | | |

*p<0.05: Statistically significant; IL-8: Interleukin-8; Histopathology Type 1: Low grade serous, low grade endometrioid, clear cell, mucinous and transitional; Histopathology Type 2: High grade serous, undifferentiated adenocarcinoma and malignant mixed mesodermal; Early stage: Stage I & II; Advanced stage: Stage III & IV; Residual tumour R0: Tumour residual was not seen macroscopically; Residual tumour Rx: Tumour residual was seen macroscopically; LVSI: Lymph vascular space invasion; Total TILs: Total infiltrating leukocyte; Sensor: Patient had progression free survival or survive; Event: Patient had disease progression or had not survived.

Patients with older age (HR 11.00; 95% CI 3.39-35.99; p=0.001), histology Type 2 (HR 3.36; 95% CI 1.20-9.39; p=0.021), advanced stage (HR 2.92; 95% CI 1.05-8.14; p=0.040), residual tumour Rx (HR 2.86; 95% CI 1.14-7.16; p=0.025), and positive LVSI (HR 2.91; 95% CI 1.15-7.37; p=0.025) had lower OS

(Table 2). Significant variables (p<0.05) including IL-8, age, histopathology type, cancer grading, stage, and residual tumour were assessed for multivariate analysis. IL-8 (HR 2.93; 95% CI 1.01-8.53; p=0.048) remained to be the only significant variable to predict progression free survival. High IL-8 level (>1575.74) had 2.93 more risk to develop disease progression. More than third quarter (77.8%) patients had disease progression in the higher IL-8 group compared to less than half (35.5%) patients in the lower IL-8 group (Table 2).

As for OS, although IL-8 was not statistically significant, it was analysed together with age, histopathology type, stage, residual tumour and LVSI. Older age was found to be the only significant variable related to poor OS in ovarian cancer patients. All patients aged at least 60 years old did not survive at the end of our study, while 57.8% had survived in the age group below 60 (HR 7.67; 95% CI 1.99-29.46; p=0.003). Our study also found that the percentage of patients who survived in the high IL-8 group (22.2%) was lower than the low IL-8 group (58.1%) (HR 2.19; 95% CI 0.78-6.17; p=0.138) (Table 2).

The IL-8 risk score had sensitivity 38.9% and specificity 90.9% with fair accuracy (area under the curve=0.591) in predicting PFS (Figure 1A). The sensitivity 35.0% and specificity 90.0% with fair accuracy (area under the curve=0.567) for OS in ovarian cancer patients (Figure 1B). The mean PFS time was significantly shorter for patients with IL-8>1575.74 (15.4 months) compared to <1575.74 (27.5 months), p log rank 0.02 (Figure 2A). Although the mean OS was longer in the low IL-8 group (27.3 compared to

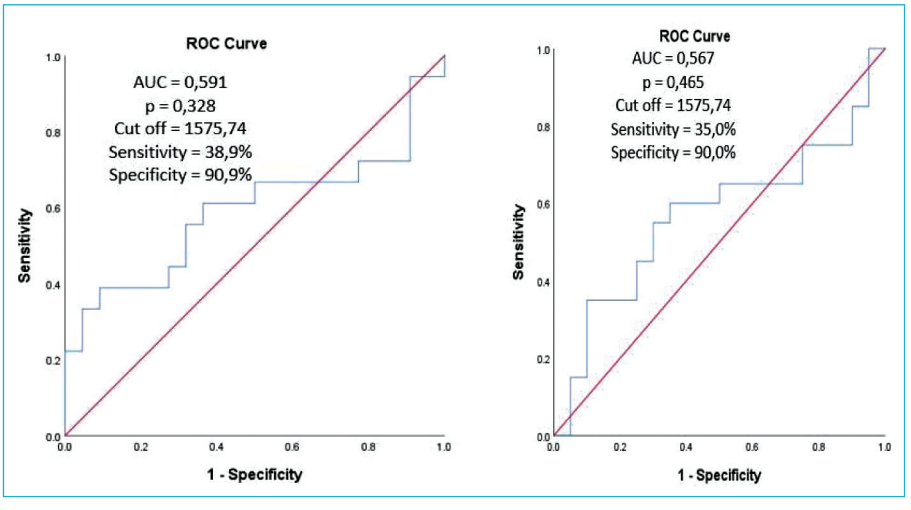


**FIGURE 1: A)** ROC IL-8 ascites curve for progression-free survival; **B)** ROC IL-8 ascites curve for overall survival.
IL: Interleukin.

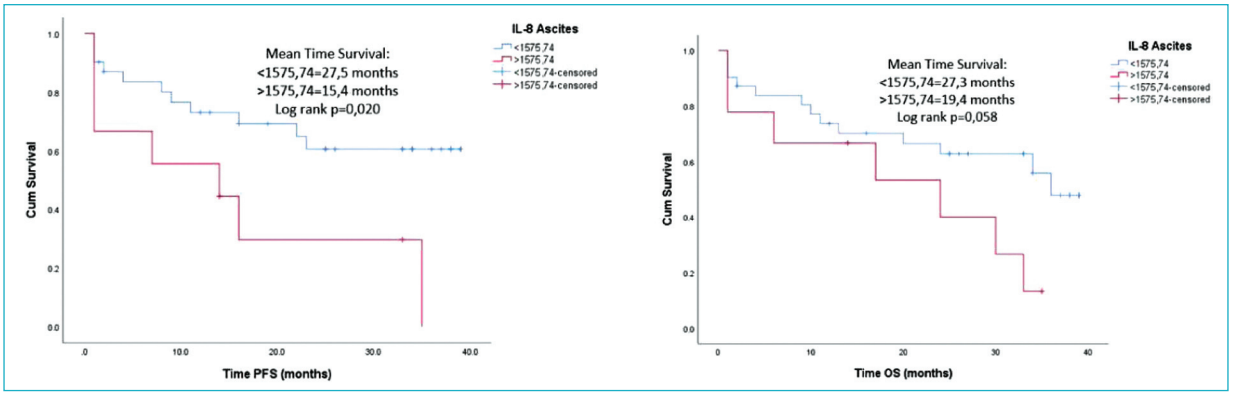


**FIGURE 2: A)** Kaplan Meier curve IL-8 and ovarian cancer for PFS; **B)** Kaplan Meier curve IL-8 and ovarian cancer for OS.
PFS: Progression-free survival; OS: Overall survival; IL: Interleukin.

19.4 months), it was not statistically significant, p log rank 0.058 (Figure 2B).

## DISCUSSION

Our study found that higher IL-8 level, older age, histology Type 2, advanced stage, residual tumour Rx had worse progression free survival. The mean progression free survival time was significantly shorter for patients with IL-8>1575.74 (15.4 months) compared to <1575.74 (27.5 months), p log rank 0.02. We concluded that higher IL-8 ascites level is associated with poor PFS significantly. Previous studies concluded that ovarian cancer patients with high levels of IL-8 had a worse OS rate and shorter survival time.[19-21] In line with our findings, Ford et al. found the same findings.[22] Lane et al. on the contradictory, concluded that IL-8 did not significantly shorten the length of PFS.[13] However, from previous studies, IL-8 contributed to cell proliferation in ovarian cancer. IL-8 altered cell cycle distribution, promoted progression as well as metastasis.[9,23] In ovarian cancer, the expression of IL-8 promoted anchorage-independent growth and therefore cell behaviour was transformed and proliferated. Tumour angiogenesis was accelerated. By upregulating VEGF expression, IL-8 might also increase the tumour's microvessel density and accelerate tumour angiogenesis.[9,24]

As for OS in ovarian cancer patients, it decreased with older age, histology Type 2, residual tumour rx, and positive LVSI. The mean OS in the high IL-8 ascites group (19.4 months) was lower than the low IL-8 group (27.3 months) although it was not statistically significant, p log rank 0.058. Other studies had independent correlation between high IL-8 level and low OS. High IL-8 level decreased disease specific survival in ovarian cancer.[25] However, these findings measure serum levels.[20,21] Nevertheless, OS could be influenced by several factor including age, residual disease, tumour characteristic, and duration of PFS.[26,27]

Ovarian cancer incidence increased with older age.[28-30] Older age was reported to be an independent factor to have lower PFS and OS.[31] In line with previous studies, we found older age group had lower PFS and OS. We found that histology Type 2 decreased PFS and OS. Studies reported that histology Type 2 had low survival.[32,33] Another study reported that high grade ovarian cancer's PFS significantly lower compared to lower grade ovarian cancer.[34] Advanced ovarian cancer stadium had worse PFS. Arora et al. stated that survival decreased as cancer stadiums got more advanced.[35] Both PFS and OS increased in patients without residual tumour which was in accordance with literature.[34] Positive LVSI tended to decrease OS in our report. The present study found that positive LVSI could predict worse survival in patients with early stage of ovarian cancer.[18]

### LIMITATION

We conducted a single-centre prospective study with small study samples. In addition, the follow-up time could have been extended to see other possible outcomes. Nevertheless, to the best of our knowledge, this was the first study to examine IL-8 ascites level relation to OS. For further studies, we would recommend multi-center studies with a larger study population, and a longer follow up time to support the current evidence.

## CONCLUSION

IL-8 in ascites had a significant negative correlation with progression free survival, however, it did not relate significantly with overall survival in ovarian cancer patients. Older age (>60 year old) was related to overall survival in ovarian cancer patients.

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***Conflict of Interest***

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

***Authorship Contributions***

***Idea/Concept:*** *Moh Nailul Fahmi;* ***Design:*** *Moh Nailul Fahmi;* ***Control/Supervision:*** *Moh Nailul Fahmi;* ***Data Collection and/or***

***Processing:*** *Moh Nailul Fahmi, Patricia Alika Kurniawan;* ***Analysis and/or Interpretation:*** *Moh Nailul Fahmi, Patricia Alika Kurniawan;* ***Literature Review:*** *Moh Nailul Fahmi, Patricia Alika Kurniawan;* ***Writing the Article:*** *Moh Nailul Fahmi, Patricia Alika Kurniawan;* ***Critical Review:*** *Moh Nailul Fahmi, Patricia Alika Kurniawan;* ***References and Fundings:*** *Moh Nailul Fahmi, Patricia Alika Kurniawan;* ***Materials:*** *Moh Nailul Fahmi, Patricia Alika Kurniawan.*

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