Comprehensive cytokine, chemokine and immune marker evaluation in plasma samples of primary, non-metastatic high grade serous ovarian cancer patients to estimate outcome and platinum resistance.

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BACKGROUND and PURPOSE of the STUDY

- **Ovarian cancer** (**OC**) still has the **highest mortality rate** of all **gynecological malignancies**, diagnosed mostly at advanced stages, resulting in a **generally poor outcome**. **Radical tumor debulking**, followed by **platinum-based chemotherapy** with/without **bevacizumab** and with/without **PARP inhibitors** is the **standard of care** in advanced OC.
- Nevertheless, the majority of patients will ultimately **relapse due to the development of platinum resistance**. Efforts to apply **immunotherapy** has been **less successful**, however, **immunologic processes** play an important role in **tumorigenesis** and **therapy response**.

In view of biomarker research to identify patients at high risk for relapse,

we here determined cytokine/chemokine/immune-related marker levels in blood samples of primary, non-metastatic, high grade serous (HGS) OC patients before and after platinum-based chemotherapy to estimate their value with regard to overall survival (OS), progression-free survival (PFS), and platinum resistance.

PATIENTS and METHODS

- **Plasma** samples of **53 primary HGSOC patients,** the majority of them diagnosed between 2019 and 2022, were collected **prior** (**n=53**) **and following platinum-based chemotherapy (n=27) with/without bevacizumab**.
- **Cytokine/chemokine/immune-related marker levels** were quantified **using the Olink Target 48 Cytokine panel** and **Immune Surveillance Panel (LuminoDx, San Diego, USA**), which includes a total of **89 immune-related proteins** and requires **only 1 µL of sample.**
- **Correlation** between **cytokine/chemokine/immune-related marker levels** and **OS** as well as **PFS** was assessed using the **Cox proportional hazards model** and **Log-rank test**, and **platinum resistance** was evaluated using the **student's t-test.**

FIGURE 1. Patient Cohort

53 primary, non-metastatic HGSOC patients were enrolled.

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Exclusion criteria:
- Non-serous histology,
- Metastatic disease
- Insufficient sample quality
- Missing follow-up data

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Final cohort:
53 patients included
Baseline samples: n=53
Post-therapy samples: n=27

SUMMARY and CONCLUSION

Plasma cytokine profiling in HGSOC patients demonstrates prognostic value for OS, PFS and platinum resistance.

- ***Baseline Associations:***
  OS: Lower **IL17A, IL19, VEGFA, and IL27 levels, as well as higher FASLG levels, were significantly associated with a longer OS (*p* < 0.01), FIGURE 2.**
  PFS: Lower **IL19 levels and higher FASLG and CEACAM5 levels were significantly associated with an improved PFS (*p* < 0.01), FIGURE 3.**

- ***Platinum Response:***
  Higher baseline IL19 and IL6 levels were associated with *platinum resistance* (*p* < 0.05).
  Higher baseline CXCL12 and IL18 levels were associated with *platinum sensitivity* (*p* < 0.05), FIGURE 4.

- ***Longitudinal (Follow-up) Associations:***
  Increasing VEGFA levels over time were significantly associated with a longer OS, TABLE 1.
  Declining FASLG and CEACAM5 levels over the course of treatment correlated with a longer PFS, TABLE2.

Overall Conclusion

IL19 is the only marker demonstrating statistical significance for both, PFS and platinum resistance, highlighting its potential as a key prognostic and predictive biomarker in HGSOC.

RESULTS for Baseline Associations and Platinum Resistance

FIGURE 2. Cytokine/Chemokine/Immune-related marker that significantly correlate with OS

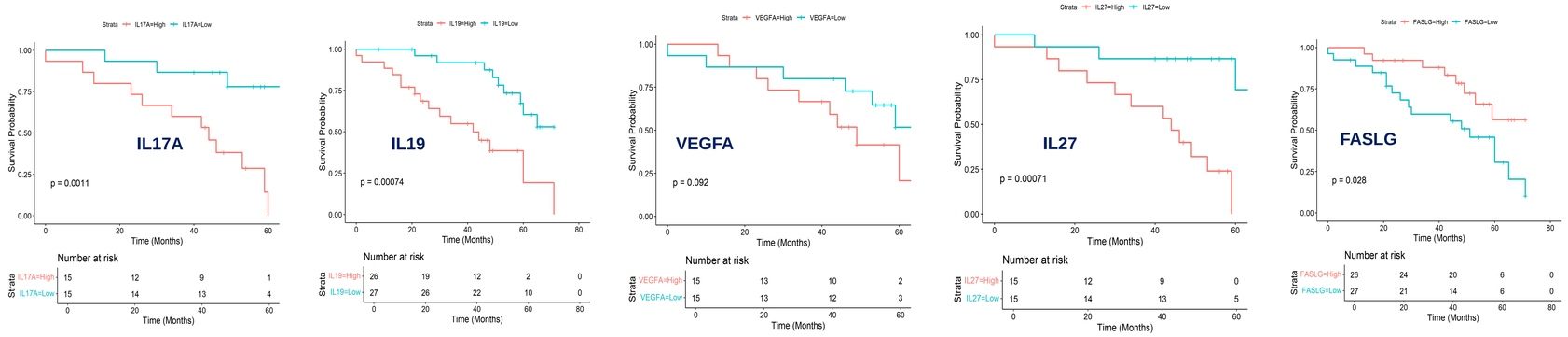


FIGURE 3. Cytokine/Chemokine/Immune-related marker that significantly correlate with PFS

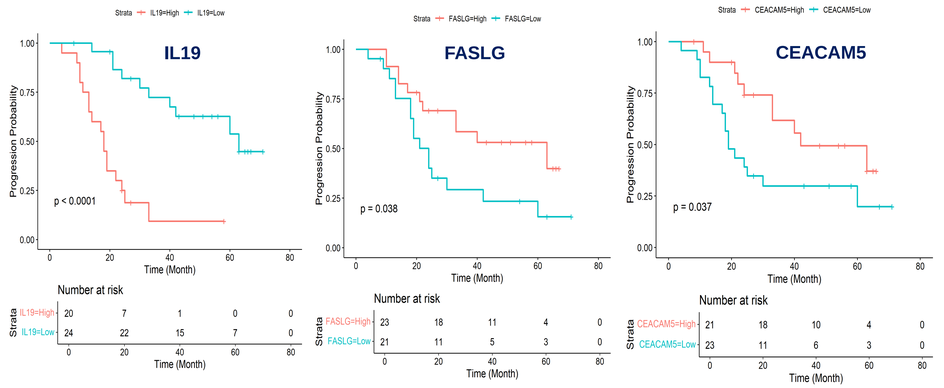
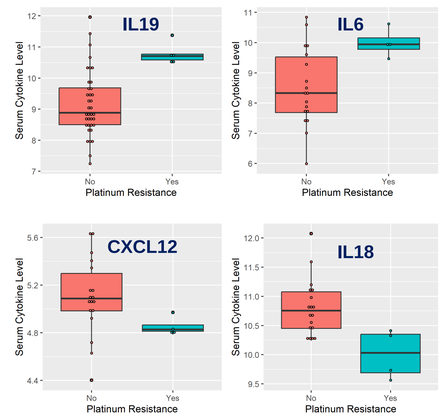


FIGURE 4. Cytokine/Chemokine/Immune-related marker that significantly correlate with platinum resistance



RESULTS for Longitudinal (Follow-up) Associations

TABLE 1. Association of Longitudinal Changes in Cytokine, Chemokine, and Immune-Related Markers with OS

Top six genes (p < 0.05) identified by Cox proportional hazards model

Gene Symbol	Hazard Ratio	*p*
FLT1	**2.50**	**0.013**
LTA	**4.40**	**0.013**
VEGFA	**0.37**	**0.022**
LAG3	**3.07**	**0.034**
CCL19	**2.07**	**0.042**
IL4R	**0.53**	**0.048**

Increasing plasma levels of **FLT1, LTA, LAG3**, and **CCL19** levels during **therapy** were associated with a **shorter OS,** whereas **increasing VEGFA** and **IL4R** levels were associated with a **longer OS.**

TABLE 2. Association of Longitudinal Changes in Cytokine, Chemokine, and Immune-Related Markers with PFS

Top seven genes (p < 0.05) identified by Cox proportional hazards model

Gene Symbol	Hazard Ratio	*p*
LAG3	**4.22**	**0.004**
FASLG	**3.31**	**0.029**
IL25	**1.78**	**0.029**
LTA	**3.38**	**0.030**
IL17F	**2.52**	**0.040**
CSF2	**3.50**	**0.045**
CEACAM5	**2.68**	**0.047**

Increasing plasma levels of **LAG3, FASLG, IL25, LTA, IL17F, CSF2**, and **CEACAM5 during therapy** were associated with a **shorter PFS.**

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