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Paper number: HELIYON-D-23-53975R1

Heliyon

Title: Image Analysis Uncovers Associations between Immune Landscape, Collagen Structure, and Neoadjuvant Chemotherapy in High-Grade Serous Ovarian Carcinomas

## Dear Editor,

Please find enclosed a revised version of our manuscript “**Image Analysis Uncovers Associations between Immune Landscape, Collagen Structure, and Neoadjuvant Chemotherapy in High-Grade Serous Ovarian Carcinomas**”. We believe we have addressed the comments raised by the editor and have updated our manuscript accordingly. Detailed responses are outlined below. We hope that this new version satisfactorily addresses the concerns. Thank you for your consideration.

Best regards,

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**Editor**  
“Thank you for submitting your manuscript to Heliyon. In reviewing your manuscript, I discovered that your study uses the same samples and/ or data as that of your previous publication, available here:  
[<https://www.nature.com/articles/s43856-023-00428-0#Sec2>]  
  
The data sets used in this manuscript and the article submitted to Heliyon by the co-authors appear to be the same.  
We would require that you wait to publish all findings from the same dataset together in one publication. For this reason, we cannot consider your manuscript for publication in Heliyon.  
Thank you again for submitting your manuscript to this journal and for giving us the opportunity to consider your work. Please also note that the decision on this manuscript is final, and resubmissions of the same manuscript will not be considered.”

**Response**

We appreciate the opportunity to address the concerns you have raised regarding the use of datasets. Firstly, we would like to clarify that the hypotheses for the two studies in question are distinctly different. The study published in Nature Communications Medicine(1) investigates the interactions between immune cells and collagen and their association with clinical outcomes in ovarian, cervical, and endometrial cancers. Conversely, this manuscript submitted to Heliyon focuses on using image analysis and machine learning to explicitly tease apart the differences in immune response and collagen structure when comparing pre-treatment and post-treatment scans of ovarian cancer patients undergoing neoadjuvant chemotherapy. Specifically, we seek to understand the impact of chemotherapy on the changes in the tumor and tumor micro-environment in this study, a topic not addressed in(1). Further this publication is the first we are aware of that quantitatively assesses the changes in specific hallmarks of the TME including the collagen and immune architecture before and after treatment with chemotherapy.

To address the specific concern regarding dataset usage, we wish to assure you that the dataset utilized in this study is entirely separate from that used in the Nature Communications Medicine publication (1). This study uniquely leverages a dataset with both pre-treatment and post-treatment scans, which was not available for the Nature Communications Medicine study (1). The latter did not include any pre-treatment scans, thus precluding its use in the analysis presented in this submission.

Given these differences, there is no duplication of datasets or findings between the two publications. Each study stands on its own with its unique dataset and research questions. We have taken great care to ensure that our research complies with all ethical and publication standards, avoiding multiple publications from the same dataset.

**Datasets used in Nature Communications Medicine paper** (important to note that all patients diagnosed with ovarian cancer in this study underwent primary debulking surgery)

Ovarian cancer cohorts used in study from TCGA, Memorial Sloan Kettering Cancer Center, and Cleveland Clinic.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cohort (N)** | **Therapy** | **Cancer** | **#slides per patient** | **Histology**  **(FIGO Stage I, II, III, IV, missing)** | **#Censored** | **Mean age ± std (years)** | **Site** | **Clinical endpoint of interest** |
| D0 (95),  Training | Chemotherapy | HGSOC | 1 | High-grade serous ovarian carcinoma  (Stage I: 2,  Stage II: 4,  Stage III: 68,  Stage IV: 20,  Missing: 1) | 32 (33.7%) | 60.28  ± 14.23 | TCGA | OS |
| D1 (134),  Validation | Chemotherapy | CSCC | 1 | Squamous cell carcinoma  (Stage I: 72,  Stage II: 30,  Stage III: 22,  Stage IV: 8,  Missing: 2) | 106 (79%) | 48.39  ± 13.35 | TCGA | OS |
| D2 (128),  Validation | Radiotherapy | CSCC | 1 | Squamous cell carcinoma  (Stage I: 65,  Stage II: 30,  Stage III: 19,  Stage IV: 11,  Missing: 3) | 92 (71.9%) | 48.27  ± 13.39 | TCGA | OS |
| D3 (32),  Validation | Chemotherapy | EC | 1-4 | Endometroid, Serous, Mixed, Clear cell  (Stage I: 14,  Stage II: 2,  Stage III: 10,  Stage IV: 6,  Missing: 0) | 13 (40.6%) | 62.19  ± 4.5 | UH | OS |
| D4 (26),  Validation | No therapy | EC | 1-4 | Endometroid, Clear cell  (Stage I: 26,  Stage II: 0,  Stage III: 0,  Stage IV: 0,  Missing: 0) | 18 (69.2%) | 61.15  ± 4.9 | UH | OS |
| D5 (14),  Validation | Immunotherapy  (recurrent setting) | HGSOC | 1 | High-grade serous ovarian cancer  (Stage I: 1,  Stage II: 2,  Stage III: 5,  Stage IV: 5,  Missing: 1) | 3 (21.43%) | 63.3  ± 13.1 | CCF | PFS |
| D6 (7),  Validation | Immunotherapy  (recurrent setting) | CSCC | 1 | Squamous cell carcinoma  (Stage I: 0,  Stage II: 0,  Stage III: 4,  Stage IV: 3,  Missing: 0) | 3 (42.86%) | 63.1  ± 13.7 | CCF | PFS |
| D7 (27),  Validation | Immunotherapy  (recurrent setting) | EC | 1 | Endometrioid, Serous, Clear cell  (Stage I: 12,  Stage II: 0,  Stage III: 8,  Stage IV: 5,  Missing: 2) | 12 (44.4%) | 71.3  ± 9.1 | CCF | PFS |
| D8 (30),  Validation | Chemotherapy | HGSOC | 1 | High-grade serous ovarian cancer  (Stage I: 0,  Stage II: 0,  Stage III: 17,  Stage IV: 13,  Missing: 0) | 18 (60%) | 60.73  ± 8.64 | MSKCC | PFS |

#### \*TCGA, The Cancer Genome Atlas; UH, University Hospitals; CCF, Cleveland Clinic; MSKCC, Memorial Sloan Kettering Cancer Center; EC, endometrial carcinoma; HGSOC, high grade serous ovarian carcinoma; CSCC, cervical squamous cell carcinoma; FIGO, International Federation of Gynecology and Obstetrics; OS, overall survival; PFS, progression-free survival.

#### \*For D3 and D4 cohorts having multiple tissue slides per patient, the most representative tissue slide selected by the pathologist (Dr. Stefanie Avril) was used for analysis.

**Dataset used in this manuscript** (important to note that all patients diagnosed with ovarian cancer in this study underwent neoadjuvant chemotherapy followed by interval debulking surgery)

Ovarian cancer cohort used in this study from University of Pittsburgh Medical Center

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Patient (ID)** | **Age**  **(in years)** | **Death** | **Tumor Stage** | **Overall survival (in months)** | **Debulking status** | **Chemo cycles** |
| 1 | 61 | True | 3 | 16.83333333 | Suboptimal | 6 |
| 2 | 61 | True | 4 | 12.43333333 | Optimal | 3 |
| 3 | 71 | True | 3 | 17.8 | Optimal | 4 |
| 4 | 75 | True | 3 | 19.86666667 | Optimal | 6 |
| 5 | 47 | True | 4 | 42.93333333 | Optimal | 6 |
| 6 | 77 | True | 3 | 28.93333333 | Optimal | 5 |
| 7 | 67 | True | 3 | 55.1 | Optimal | 3 |
| 8 | 80 | True | 3 | 46.56666667 | Optimal | 5 |
| 9 | 67 | False | 3 | 52.46666667 | Optimal | 5 |
| 10 | 58 | False | 3 | 50.56666667 | Optimal | 3 |
| 11 | 59 | False | 3 | 42.5 | Optimal | 4 |
| 12 | 73 | False | 3 | 39.86666667 | Optimal | 4 |

**References**

1. Aggarwal A, Khalighi S, Babu D, Li H, Azarianpour-Esfahani S, Corredor G, et al. Computational pathology identifies immune-mediated collagen disruption to predict clinical outcomes in gynecologic malignancies.