Research Article

Clinical Characteristics in the Prediction of Posttreatment Survival of Patients with Ovarian Cancer

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Received 17 March 2022; Accepted 15 April 2022; Published 5 May 2022

Academic Editor: Zhongjie Shi

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Objective. To determine the efficacy of clinical characteristics in the prediction of prognosis in patients with ovarian cancer.

Methods. Clinical data were collected from 3 datasets from TCGA database, including 1680 cases of ovarian serous cystadenocarcinoma, and were analyzed. Patients with ovarian cancer admitted to our hospital in 2016 were retrieved and followed up for prognosis analysis. Results. From the datasets, for patients > 75 years old at the time of diagnosis, histologic grade and mutation count were good predictors for disease-free survival, while for patients > 50 years old at the time of diagnosis, histologic grade, race, fraction genome altered, and mutation count were good predictors for overall survival. In the patients (n = 38) retrieved from our hospital, the longest dimension of lesion (cm) and body weight at admission were good predictors for overall survival. Conclusions. Those clinical factors, together with the two predictive equations, could be used to comprehensively predict the long-term prognosis of patients with ovarian cancer.

1. Introduction

Ovarian cancer is the third most common as well as the fifth cause of deaths of gynecologic cancers. The American Cancer Society estimates that in 2022, about 19,880 women will be newly diagnosed of ovarian cancer and about 12,810 women will die from it [1].

Patients with ovarian cancer have different clinical characteristics and prognosis. Based on data collected between 2010 and 2016, only about 20% of ovarian cancers were diagnosed at an early stage, which had a 5-year survival rate of 94%. In contrast, the 5-year relative survival rate of all SEER (Surveillance, Epidemiology, and End Results) stages combined invasive epithelial ovarian cancer patients was only 48%, with localized ones being 93% and distant ones being 31% [2]. Therefore, more efforts are needed to accurately predict the prognosis in later stage ovarian cancer in order to find clues to improve the prognosis.

In this study, we investigated into the clinical characteristics that could be used to effectively predict the prognosis of patients with ovarian cancer.

2. Materials and Methods

2.1. Patient Sources. Patient clinical data were obtained from the TCGA database (https://cancergenome.nih.gov), including the Firehose Legacy dataset (n = 606), the Nature 2011 dataset (n = 489), and the PanCancer Atlas dataset (n = 585). All cases were included for analysis when the corresponding parameter was available. Patients diagnosed with primary ovarian cancer admitted to our hospital from January 1, 2016, to December 31, 2016, were retrieved and followed up for prognosis analysis. The retrospective portion of this study was approved by our hospital’s ethical committee, and informed consents were obtained from the enrolled patients or their family member (if the patients died) during follow-up contact.

2.2. Data Extraction. Two authors independently extracted data and confirmed the accuracy of data. Clinical characteristics, such as age at diagnosis, disease-free survival, overall survival, clinical stages, histologic grades, race, fraction genome altered, Karnofsky performance score, longest dimension of lesion, lymphovascular invasion indicator, primary tumor site, neoplasm status, and mutation count were
2.3. Statistical Analyses. Statistical analyses were carried out by a third author. Measurement data were shown as mean ± standard deviation (SD). The Kaplan-Meier survival curve was used to analyze the associations between clinical characteristics and prognosis, including disease-free survival and overall survival. Receiver operating characteristic (ROC) curve was used to illustrate the predictive value of clinical characteristics on 5-year survival. Predictive equation for 5-year survival based on clinical factors was obtained using multinomial logistic regression. All statistical analyses were carried out using SPSS 24.0 (SPSS Inc., Chicago, USA). A p value < 0.05 (two-sided) was considered statistically significant.

3. Results

3.1. Clinical Characteristics of Enrolled Patients. There were 1692 patients retrieved from the three TCGA database (Table 1). The mean age at diagnosis was 59.6 years old. Disease-free survival and overall survival were shown using mean ± SD. Clinical stages, histologic stages, race, fraction genome altered, longest dimension of lesion, primary tumor site, and mutation count were further analyzed in corresponding subgroups. There were 38 cases with available data during our follow-up contact, with an average age of 49.8 ± 14.4 years old.

3.2. Value of Clinical Predictive Factors for Disease-Free Survival. Age at diagnosis > 75 years old (p = 0.021), clinical stages (p < 0.01 for overall and subgroups), histologic stage (p = 0.01 for overall and and p = 0.014 for stage III), longest dimension of lesion > 3 cm (p = 0.007), neoplasm status (p < 0.001), and mutation count (p = 0.004 when > 30 and p < 0.001 when > 50) were significantly associated with disease-free survival (Table 2). The Kaplan-Meier survival curves and ROC curves of corresponding factors are shown in Figures 1 and 2, respectively. According to the area under the curve, neoplasm status showed the best value (0.878) in prediction of long-term disease-free survival.
Figure 1: Continued.
Figure 1: Kaplan-Meier survival curve of clinical factors for disease-free survival. (a) Age > 75 years old. (b) Clinical stage over II. (c) Histologic grade over III. (d) Longest dimension of lesion (>3 cm). (e) Neoplasm status (with tumor). (f) Mutation count (>30).
Figure 2: Continued.
Figure 2: ROC curve of predictive value of clinical factors for disease-free survival. (a) Clinical stage. (b) Neoplasm status (with tumor). (c) Mutation count.
Table 3: Summary of value of predictive factors for overall survival from database.

| Variable                        | Cutoff | p value |
|---------------------------------|--------|---------|
| Age at diagnosis (years)        | Overall | <0.001  |
|                                 | 50     | 0.003   |
|                                 | 60     | <0.001  |
|                                 | 70     | <0.001  |
|                                 | 75     | <0.001  |
| Clinical stage                   | Overall | 0.121   |
|                                 | II     | 0.201   |
|                                 | IIC    | 0.017   |
|                                 | IIIA   | <0.001  |
|                                 | IIIB   | <0.001  |
|                                 | IIIC   | <0.001  |
|                                 | IV     | <0.001  |
| Histologic grade                | Overall | 0.009   |
|                                 | II     | 0.222   |
|                                 | III    | 0.037   |
| Race                            | Overall | 0.004   |
| Fraction genome altered         | 0.4    | 0.032   |
|                                 | 0.5    | 0.03    |
|                                 | 0.6    | 0.001   |
| Karnofsky performance score     | Overall | 0.37    |
| Longest dimension of lesion (cm)| 3      | 0.091   |
| Lymphovascular invasion indicator| Overall | 0.064   |
| Primary tumor site              | Overall | 0.825   |
| Neoplasm status                 | Overall | <0.001  |
| Mutation count                  | 10     | <0.001  |
|                                 | 20     | <0.001  |
|                                 | 30     | <0.001  |
|                                 | 50     | <0.001  |

3.3. Value of Clinical Predictive Factors for Overall Survival. Age at diagnosis ($p < 0.01$ for overall and subgroups), clinical stages ($p = 0.017$ for IIC and $p < 0.01$ for IIIA and above), histologic grade ($p = 0.009$ for overall and $p = 0.037$ for grade III), race ($p = 0.004$), fraction genome altered ($p = 0.032$ for the 0.4 and above group, $p = 0.03$ for the 0.5 and above group, and $p = 0.001$ for the 0.6 and above group), neoplasm status ($p < 0.001$), and mutation count ($p < 0.001$ for all subgroups) were significantly associated with overall survival (Table 3). The Kaplan-Meier survival curves and ROC curves of corresponding factors are shown in Figures 3 and 4, respectively. According to the area under the curve, clinical stage above III showed the best value (>0.64) in prediction of long-term overall survival. In the patients ($n = 38$) retrieved from our hospital, the longest dimension of lesion (cm, $p = 0.001$) and body weight at admission ($p < 0.001$) were good predictors for overall survival (Table 4).

3.4. Predictive Equations for Disease-Free and Overall Survival. In order to obtain a more practical way to predict the prognosis and to test if all factors based on Kaplan-Meier survival curves and ROC curves are good predictors for prognosis, a predictive equation for disease-free survival based on clinical factors was obtained using multinomial logistic regression: 

\[
\log \left( \frac{p}{1-p} \right) = 18.972 - 14.568 \text{Longest Dimension of lesion} - 3.593 \text{Neoplasm Status}
\]

where $p$ is the probability of death within 5 years, Shortest Dimension of lesion = 2 if $>3$ cm and =1 if $\leq 3$ cm, and Neoplasm Status = 2 if cancer lesion remained and =1 if cancer lesion was removed completely.

A predictive equation for overall survival based on clinical factors was obtained using multinomial logistic regression:

\[
\log \left( \frac{p}{1-p} \right) = -3.152 \text{Neoplasm Status} - 0.872 \text{Diagnosis Age} + 12.819 \text{Mutation count}
\]

where $p$ is the probability of death within 5 years, Neoplasm Status = 1 if cancer lesion remained and =0 if cancer lesion was removed completely, Diagnosis Age = 2 if $>50$ years old and =1 if $\leq 50$ years old and Mutation count = 2 if counted $>10$ and =1 if counted $\leq 10$.

4. Discussion

In the present study, there were 17 patients diagnosed at clinical stage I, 57 patients diagnosed at clinical stage II, 841 patients diagnosed at clinical stage III, and 168 patients diagnosed at clinical stage IV. The majority of late stage cases showed the importance of identifying accurate predictive factors for prognosis and the possibility of improving the life expectancy and quality based on those important factors.

There have been reports of various biological prognostic biomarkers for ovarian cancer [3–7]. Interestingly, Yang et al. showed that some clinical variables were good predictors [8]. Their findings were based on TCGA OvCa cohort ($n = 552$), and they found that age ($>60$ years old), nodule of residual disease, tumor status, and clinical stage could significantly predict the prognosis. Our findings, based on 1692 cases from the updated TCGA OvCa cohort, showed that patients $>75$ years old had a significantly shorter disease-free survival, while patients $>50$ years old had a significantly shorter overall survival, which showed more challenges for the prognosis of patients diagnosed at a younger age. We also showed that histologic grade and mutation count were good predictors for disease-free survival, while histologic grade, race, fraction genome altered, and mutation count were good predictors for overall survival. The above parameters coincide with some recent reports [9].

Our study also showed that the total number of mutations, when considered as a whole, contributed positively to the long-term survival of ovarian cancer patients, which is consistent with previous studies including only BRCA1 or BRCA2 mutant cases [10]. The underlying mechanisms include different pathways of DNA repair, and more studies are needed when considering all patients not restricted to BRCA1 or BRCA2 mutant cases.

In the data extracted from patients admitted to our hospital, some parameters which were good predictors for prognosis in the published datasets seems to be invalid. This may be due to the smaller number of cases enrolled, the
Figure 3: Continued.
difference in race between the datasets and our own data, and the unavailability of certain parameters in our data. With the development of big data techniques, data mining from available database has received more and more attention [11, 12]. Therefore, an updated analysis with more available datasets is beneficial in discovery of more valuable predictive factors. Due to the limitation in study design and retrospective manner of data retrieval, details in treatment methods [13, 14], psychological factors, and social-economical factors were missing from the available databases, such as anxiety or depression [15], income, nutrient conditions, and living habits, which could also contribute to the prognosis.

In summary, we showed from published datasets that for patients >75 years old at the time of diagnosis, histologic grade and mutation count were good predictors for disease-free survival, while for patients >50 years old at the time of diagnosis, histologic grade, race, fraction genome altered, and mutation count were good predictors for overall survival. On the other hand, the longest dimension of lesion and body weight at admission were good predictors for overall survival in our own retrieved data. Those clinical factors,
Source of the curve
- Diagnosis age
- Diagnosis age 40
- Diagnosis age 50
- Diagnosis age 60
- Diagnosis age 70
- Diagnosis age 75
- Reference line

Diagonal segments are produced by ties.

Area under the curve

| Test result variable (s) | Area   | Std. error | Asymptotic Sig. | Asymptotic 95% confidence interval | Lower bound | Upper bound |
|--------------------------|--------|------------|-----------------|-----------------------------------|-------------|-------------|
| Diagnosis age            | .587   | .018       | .000            | .553                              | .533        | .622        |
| Diagnosis age 40         | .508   | .018       | .009            | .479                              | .473        | .543        |
| Diagnosis age 50         | .559   | .018       | .001            | .524                              | .509        | .578        |
| Diagnosis age 60         | .549   | .018       | .006            | .515                              | .515        | .584        |
| Diagnosis age 70         | .543   | .018       | .015            | .509                              | .509        | .578        |
| Diagnosis age 75         | .509   | .018       | .610            | .474                              | .474        | .544        |

The test result variable (s): Diagnosis age, Diagnosis age 40, Diagnosis age 50, Diagnosis age 60, Diagnosis age 70, Diagnosis age 75 has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

(a)

**Figure 4**: Continued.
ROC curve

Diagonal segments are produced by ties.

Source of the curve
- Clinical stage 2
- Clinical stage 2c
- Clinical stage 3a
- Clinical stage 3b
- Clinical stage 3c
- Clinical stage 4
- Reference line

Area under the curve

| Test result variable(s) | Area | Std. error | Asymptotic Sig. | Asymptotic 95% confidence interval |
|-------------------------|------|------------|----------------|-----------------------------------|
| Clinical stage 2        | 0.536| 0.033      | 0.270          | 0.472                             |
| Clinical stage 2c       | 0.568| 0.033      | 0.036          | 0.494                             |
| Clinical stage 3a       | 0.640| 0.032      | 0.000          | 0.578                             |
| Clinical stage 3b       | 0.644| 0.032      | 0.000          | 0.581                             |
| Clinical stage 3c       | 0.663| 0.031      | 0.000          | 0.603                             |
| Clinical stage 4        | 0.654| 0.031      | 0.000          | 0.593                             |

The test result variable(s): Clinical stage 2, Clinical stage 2c, Clinical stage 3a, Clinical stage 3b, Clinical stage 3c, Clinical stage 4 has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

- Under the nonparametric assumption
- Null hypothesis: true area = 0.5

Figure 4: Continued.
Source of the curve

- Mutation count
- Mutation count 10
- Mutation count 20
- Mutation count 30
- Mutation count 50

Reference line

Area under the curve

| Test result variable | Area  | Std. error | Asymptotic Sig. | Asymptotic 95% confidence interval |
|----------------------|-------|------------|-----------------|-------------------------------------|
| Mutation count       | 0.417 | 0.018      | .000            | .382 - .452                         |
| Mutation count 10    | 0.499 | 0.018      | .944            | .463 - .535                         |
| Mutation count 20    | 0.481 | 0.018      | .293            | .442 - .516                         |
| Mutation count 30    | 0.465 | 0.018      | .037            | .430 - .501                         |
| Mutation count 50    | 0.446 | 0.018      | .063            | .419 - .482                         |

The test result variable (s): Mutation count, Mutation count 10, Mutation count 20, Mutation count 30, Mutation count 50 has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

c. Figure 4: ROC curve of predictive value of clinical factors for overall survival. (a) Age. (b) Clinical stage. (c) Mutation count.
together with the two predictive equations, could be used to comprehensively predict the long-term prognosis of patients with ovarian cancer.

**Data Availability**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Conflicts of Interest**

The authors declare that they have no conflicts of interest.

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