

Activation of *YAP1* Is Associated with Poor Prognosis and Response to Taxanes in Ovarian Cancer

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Abstract. Aim: We aimed to investigate the clinical significance of the activation of Yes-Associated Protein 1 (*YAP1*), a key downstream effector of Hippo tumor-suppressor pathway, in ovarian cancer. Materials and Methods: A gene expression signature reflecting activation of *YAP1* was developed from gene expression data of 267 samples from patients with ovarian cancer. A refined ovarian cancer *YAP1* signature was validated in an independent ovarian cancer cohort (n=185). Associations between the *YAP1* signature and prognosis were assessed using Kaplan–Meier plots, the log-rank test, and a Cox proportional hazards model. Results: We identified a 612-gene expression signature reflecting *YAP1* activation in ovarian cancer. In multivariate analysis, the signature was an independent predictor of overall survival (hazard ratio=1.66; 95% confidence interval=1.1 to 2.53; p=0.01). In subset analysis, the signature identified patients likely to benefit from taxane-based adjuvant chemotherapy.

Conclusion: Activation of *YAP1* is significantly associated with prognosis and the *YAP1* signature can predict response to taxane-based adjuvant chemotherapy in patients with ovarian cancer.

Ovarian cancer is the most lethal gynecological cancer, and has been predicted to account for an estimated 14,030 deaths in 2013 in the United States, making it the fifth most common cause of cancer death in women (1). The clinical approach to epithelial ovarian cancer is quite uniform, with all patients being treated with standard cytoreductive surgery and adjuvant chemotherapy. However, there is considerable clinicopathological heterogeneity and differential responses among patients (2). Tumors with similar histopathological appearance can follow significantly different clinical courses. Approximately 40 to 60% of patients with advanced ovarian cancer have complete response to adjuvant chemotherapy. However, disease in a significant proportion of patients with complete response will eventually recur. Disease in the remaining patients either does not respond or only responds transiently and subsequently progresses rapidly (3), suggesting heterogeneity of ovarian cancer.

The Hippo pathway represents a novel tumor-suppressor pathway. When Hippo signaling is active, Mammalian STE20-like kinase (*MST1/2*), Salvador Homolog 1 (*SAV1*), Large Tumor-Suppressor Kinase (*LATS1/2*), and Mps One Binder Kinase Activator-Like 1 (*MOBI*) form core complexes that inactivate the Yes-Associated Protein 1 (*YAP1*) and Transcriptional Coactivator With PDZ-Binding

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Motif (TAZ) oncogenes by phosphorylation (4, 5). When Hippo signaling is absent, unphosphorylated YAP1/TAZ enters the nucleus inducing the transcription of genes that promote cell growth and survival. *Sav1* and *Mst1/2* knockout in mouse leads to the development of liver cancer (6-9), indicating the importance of the Hippo pathway as a key tumor suppressor. Elevated YAP1 mRNA levels have been reported in colon, lung, and ovarian cancer (10, 11).

In this study, we undertook a systems level characterization of genomic data from multiple ovarian cancer cohorts to determine whether the Hippo pathway is a key tumor-suppressor pathway in the ovaries. This approach uncovered molecular classifiers that can stratify patients with ovarian cancer according to the absence or presence of active YAP1.

Materials and Methods

Gene expression and patient data. The gene expression and clinical data are available from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database (<http://www.ncbi.nlm.nih.gov/geo>). Gene expression data from MCF10A breast epithelial cells overexpressing human YAP1 were collected from two series of experiments (GSE10196 and GSE13218) using the U133 v2.0 platform (12). For discovery and validation of a YAP1-specific signature associated with prognosis of patients with ovarian cancer, gene expression data from two independent cohorts were used. Gene expression data from the Peter MacCallum Cancer Center (PMC cohort, GSE9891, n=267) were used as discovery cohort and for refining the prognostic gene expression signature (13). Gene expression data from the Memorial Sloan Kettering Cancer Center (MSKCC cohort, GSE26712, n=185) were used as the validation data set.

All of gene expression data were generated by using Affymetrix microarray platforms (U133A or U133 v2.0). All data were normalized by using robust multi-array average method (14). All patients in the two cohorts had undergone cytoreductive surgery and subsequent platinum-based chemotherapy. Overall survival (OS) and chemotherapy response data are lacking for 7 and 10 patients, respectively. Out of the 275 patients with available chemotherapy response data, 192 had undergone both platinum and taxane treatment, while the remainder (n=65) did not receive taxane-based treatment. Treatment data were not available from the MSKCC cohort.

Patient and gene expression data in Cambridge Translational Cancer Research Ovarian Study 01(CTCR-OV01) are also publicly available from NCBI (accession ID, GSE15622) (15). Patients in CTCR-OV01 had been recruited from 2002 to 2004 and had histologically-confirmed advanced (stages III and IV) epithelial ovarian cancer. All tissues had been biopsied prior to the start of neoadjuvant chemotherapy. Patients had been randomly assigned to undergo either three cycles of carboplatin [area under the receiver operating characteristic (ROC) curve (AUC) 7] or paclitaxel (175 mg/m²). Treatment response had been estimated using serum Cancer Antigen 125 (CA125) levels after three cycles of single-agent treatment. Treatment-sensitive patients were defined as those who experienced more than a 50% decrease in serum CA125 level (15). The pathological and clinical characteristics of the patients in all three cohorts are shown in Table I.

Table I. *Clinical and pathological features of patients with ovarian cancer.*

| Variable | Cohort | | |
|----------------------|-------------|------------|-----------|
| | PMC | MSKCC | CTCR-OV01 |
| Number of patients | 267 | 185 | 35 |
| Age (years) | | | |
| Median | 59 | 63 | NA |
| Range | 22-80 | 26-84 | NA |
| FIGO stage | | | |
| I | 16 (6%) | 0 | |
| II | 14 (5%) | 0 | |
| III | 212 (79.5%) | 149 (80%) | |
| IV | 21 (8%) | 36 (20%) | |
| NA | 4 (1.5%) | 0 | 35 |
| Grade | | | |
| 1 | 11 (4%) | 0 | |
| 2 | 97 (36.5%) | 40 (22%) | |
| 3 | 155 (58%) | 145 (78%) | |
| NA | 4 (1.5%) | 0 | 35 |
| Histological subtype | | | |
| Serous | 246 (92%) | 185 (100%) | 35 (100%) |
| Endometrioid | 20 (7.5%) | | |
| Adenocarcinoma | 1 (0.5%) | | |
| Number of deaths | 103 | 129 | NA |

PMC, Peter MacCallum Cancer Center; MSKCC, Memorial Sloan Kettering Cancer Center; CTCR-OV1, Cambridge Translational Cancer Research Ovarian Study 01; NA: not available.

Statistical analysis of microarray data. BRB-ArrayTools were primarily used to statistically analyze gene expression data (16), and all other statistical analyses were performed in the R language environment (<http://www.r-project.org>). We identified genes that were differentially expressed among the two classes using a random-variance *t*-test (17); genes were considered statistically significant if their *p*-value was less than 0.001. Cluster analysis was performed using Cluster and Treeview (18).

The strategy used to develop and validate the prediction model on the basis of the gene expression signature and to estimate of predictive accuracy was adopted from previous studies (19-21). Briefly, using the expression patterns of the 612 genes included in the Affymetrix microarray, we used data from the PMC cohort as the training set and data from the MSKCC cohort as the validation set. In brief, expression patterns of the 612 genes from the PMC cohort were combined to form a classifier according to the compound covariate predictor (CCP) algorithm (22). This algorithm estimates the probability that a particular sample belongs to the YAP1 subgroup. The miscalculation rate in this training set was estimated by leave-one-out cross-validation during training. We then directly applied the developed classifier to gene expression data from the MSKCC cohort (test set).

Kaplan–Meier plots and the log-rank test were used to estimate patient prognosis, and a multivariate Cox proportional hazard regression analysis was used to evaluate independent prognostic factors associated with survival. Overall survival (OS) was defined as the time interval between the date of histological

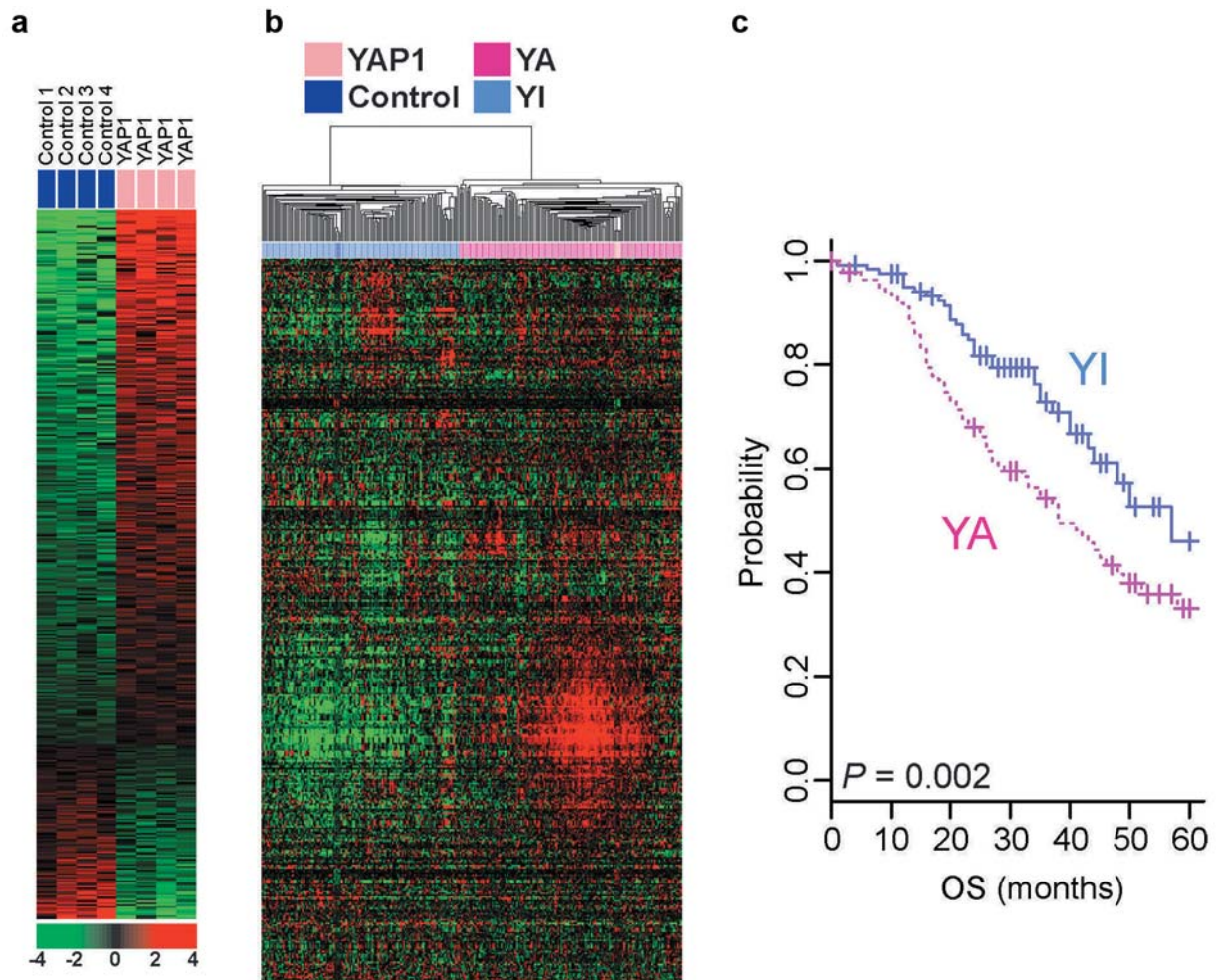


Figure 1. Hierarchical clustering analysis of gene expression data from patients with ovarian cancer and human mammary epithelial cells overexpressing Yes-Associated Protein 1 (YAP1). a: YAP1-specific gene expression signature from the MCF10A cell line. A two-sample *t*-test was applied to gene expression data from two sample groups ($p < 0.001$). b: Expression data from YAP1-specific 388 genes were used for clustering of 267 patients with ovarian cancer (Peter MacCallum Cancer Center cohort). Gene expression data from cell lines and human tissues were centralized by subtracting the median expression level across samples before pooling them together for clustering analysis. The data are presented in matrix format in which rows represent individual genes and columns represent individual tumor samples. Each cell in the matrix represents the expression level of a gene in an individual tumor. The red and green colors reflect high and low relative expression levels, respectively, as indicated in the scale bar (\log_2 -transformed scale). c: Kaplan-Meier plots of overall survival (OS). Patients were stratified into two subgroups by hierarchical clustering. Seven patients [four in the YAP1-active (YA) and three in the YAP1-inactive (YI) subgroup] with no survival data were excluded from the plot. *p*-Values were obtained using the log-rank test. +, Censored data.

diagnosis and the date of death from any cause. Gene signature, tumor stage, and pathological characteristics were used as covariates.

To evaluate the usefulness of dichotomized stratification by the YAP1 signature for predicting sensitivity to each neoadjuvant chemotherapy, we used ROC curve analysis. For each ROC curve, we calculated the AUC, which ranges from 0.5 (for a noninformative predictive marker) to 1 (for a perfect predictive marker). A bootstrap method was used to calculate the confidence interval (CI) for the AUC. A *p*-value of less than 0.05 was considered to indicate statistical significance, and all tests were two-tailed.

Results

Activation of YAP1 is significantly associated with prognosis of ovarian cancer. Since YAP1 is the most well-known activated oncogene in the Hippo pathway (23), we analyzed gene expression data generated from MCF10A cells overexpressing human YAP1 to identify genes whose expression is significantly associated with activation of YAP1. This analysis revealed 388 genes under stringent statistical cut-off ($p < 0.001$) (Figure 1a). We next sought to

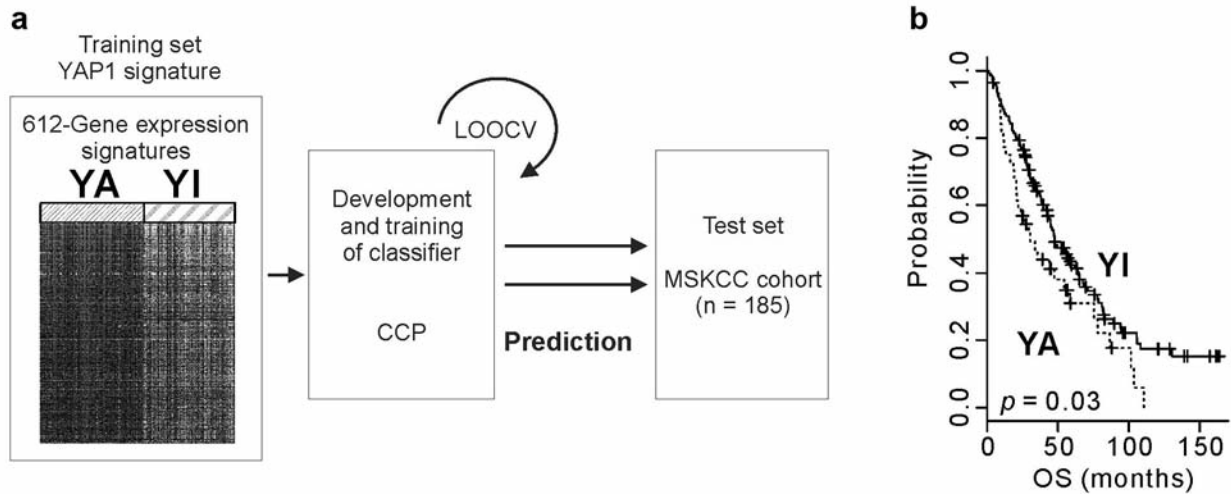


Figure 2. Validation of the Yes-Associated Protein 1 (*YAP1*) signature with prognosis in an independent cohort. a: A schematic overview of the strategy used for constructing predictive models and evaluating predicted outcomes based on gene expression signatures. CCP, Compound covariate predictor; LOOCV, leave-one-out cross-validation. b: Kaplan–Meier plots of overall survival (OS) in the Memorial Sloan Kettering Cancer Center cohort. Patients were stratified into two subgroups, as predicted by the CCP predictor algorithm. p-Values were obtained using the log-rank test. +, Censored data.

test the clinical relevance of *YAP1* activation in human ovarian cancer by cross-comparing the data for 388 genes from the MCF10A cell line with expression data from human ovarian cancer. Gene expression data of 267 ovarian cancer tissues from the PMC cohort were used for this analysis, and hierarchical clustering analysis was applied to stratify patients according to overlap with the *YAP1*-activated gene expression signature (Figure 1b). When the gene expression data were analyzed, data for 138 patients were tightly co-clustered with that for *YAP1*-overexpressing cells (hereafter referred to as the *YAP1*-active or YA-subgroup), while the rest lacked the *YAP1*-specific signature (hereafter referred to as *YAP1*-inactive or YI subgroup). Kaplan–Meier plots revealed that the duration of OS of the YA-subgroup was significantly shorter ($p=0.002$) than that of the YI-subgroup (Figure 1c).

The 388-gene expression signature reflects *YAP1* activation in the cell culture condition but may lack the biological characteristics associated with ovarian cancer because it was generated from MCF10A human mammary epithelial cells. Therefore in order to identify genes whose expression is tightly associated with *YAP1* activation in ovarian cancer, we used the two-sample *t*-test with stringent threshold cut-off ($p<0.001$ and two-fold difference) to evaluate gene expression data from 267 patients in the PMC cohort. This approach revealed 612 genes that were differentially expressed between the YA- and YI-subgroups of ovarian cancer in the PMC cohort (Figure 2a). As an example of the utility of this approach, expression of

connective tissue growth factor (*CTGF*), a well-known downstream target of *YAP1* (24), was elevated (>2-fold) in the YA subgroup.

Validation that the *YAP1* signature is significantly associated with prognosis in an independent ovarian cancer cohort. We next used the 612-gene signature to validate the association between the YA-subgroup with the poorer ovarian cancer prognosis in the MSKCC cohort ($n=185$). The expression signature of 612 genes from the PMC cohort and CCP algorithm were used to build and train the predictive model. When patients in the MSKCC cohort were stratified according to the refined *YAP1* signature, the duration of OS for patients in the YA subgroup was significantly shorter ($p=0.03$ by log-rank test) than those in the YI subgroup (Figure 2b). Specificity and sensitivity for correctly predicting subgroup YA during leave-one-out cross-validation in the PMC cohort were 0.88 and 0.73, respectively.

To estimate the prognostic value of the *YAP1* signature with other clinical variables, including patient age at diagnosis, Fédération Internationale de Gynécologie et d’Obstétrique (FIGO) stage and grade, univariate and multivariate Cox proportional hazards regression analysis was undertaken in the PMC cohort, because only in this cohort were all clinical variables available for analysis. On univariate analysis, FIGO stage and the *YAP1* signature were significant predictors of OS ($p<0.0001$ and $p=0.003$, respectively). On multivariate analysis, FIGO stage and the *YAP1* signature retained significance ($p=0.001$ and 0.01) (Table II).

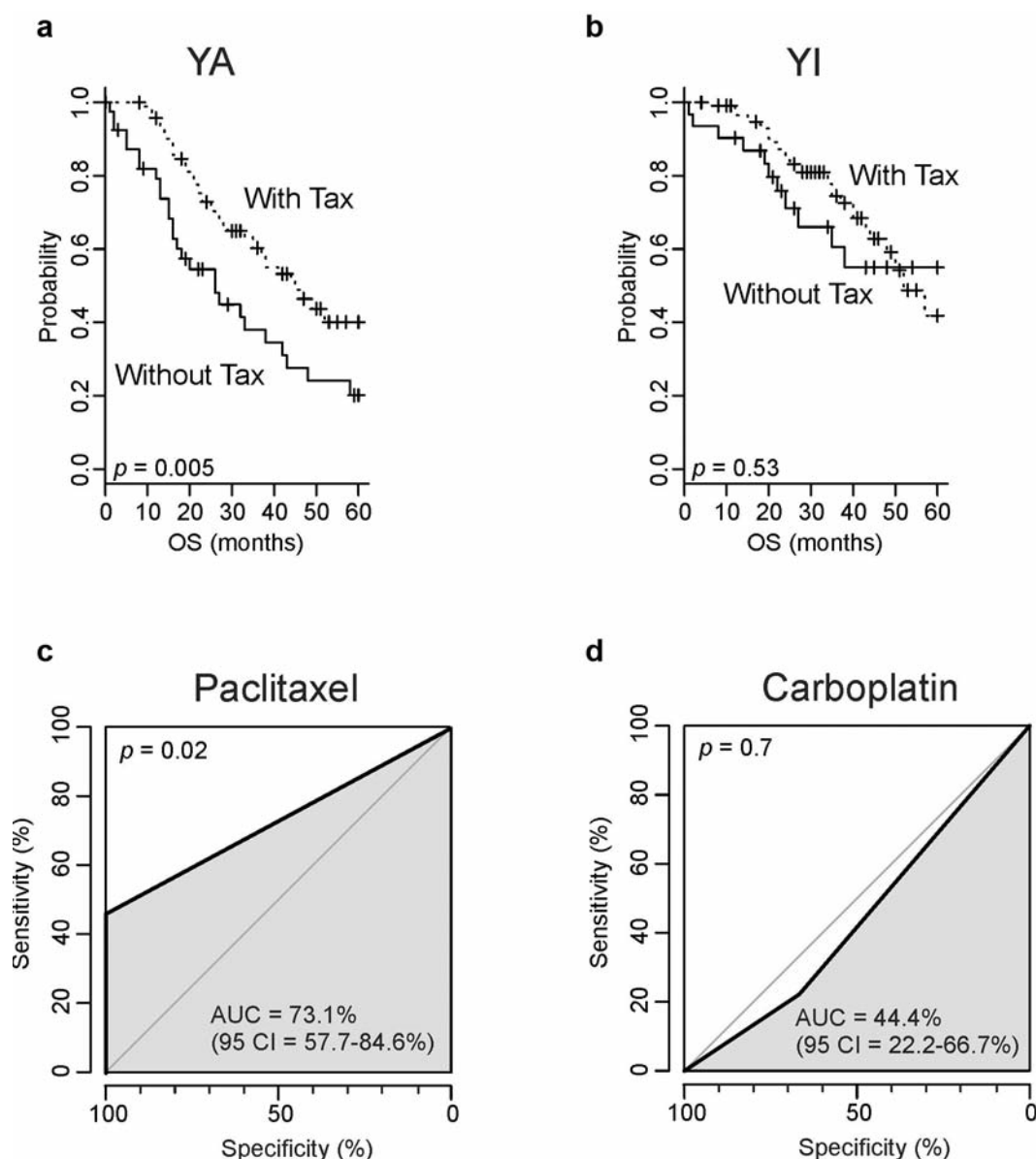


Figure 3. Sensitivity of Yes-Associated Protein 1 (YAP1) subgroups to taxane-based treatment. Kaplan–Meier plots of patients in the YAP1-Active, YA (a) and YAP1-inactive, YI (b) subgroups. Data were plotted according to taxane use. Chemotherapy data were not available for 10 patients. Receiver operating characteristic (ROC) analyses for the discriminatory value of the YAP1 signature in the paclitaxel- (c) and carboplatin-treated arms (d).

Sensitivity to taxane treatment. We next carried out a subset analysis in the PMC cohort, for which adjuvant chemotherapy treatment information was available for 257 out of the 267 patients. All patients underwent platinum-based treatment, 192 patients received additional taxane-based treatment. To determine the association between the signature and benefit of taxane-based treatment, we categorized the 257 patients into two subgroups (YA and YI), and independently assessed the OS rate. Taxane-based

treatment significantly affected OS for patients in the YA-subgroup (3-year rate: 60.3% with taxane vs. 37.9% without taxane, $p=0.005$ by log-rank test; Figure 3a). However, no significant benefit was found for patients in the YI subgroup (3-year rate: 74.4% vs. 60.5%, respectively, $p=0.53$ by log-rank test, Figure 3b). Consistent with the Kaplan–Meier plots, the estimated hazard ratio for death after taxane-based treatment in the YA subgroup was 0.5 (95% CI=0.31-0.82; $p=0.005$).

Table II. Univariate and multivariate Cox proportional hazard regression analyses of overall survival in the Peter MacCallum Cancer Center cohort (n=267).

| | Univariate | | Multivariate | |
|---------------------------------------|-----------------------|-----------------------|-----------------------|---------|
| | Hazard ratio (95% CI) | p-Value | Hazard ratio (95% CI) | p-Value |
| Age (>50 years) | 1.26 (0.72-2.17) | 0.41 | 1.11 (0.78-1.59) | 0.54 |
| Stage (I, II, III, IV) | 2.15 (1.45-3.2) | 1.47×10 ⁻⁴ | 1.95 (1.3-2.92) | 0.001 |
| Grade (1, 2, 3) | 1.27 (0.89-1.79) | 0.17 | 1.29 (0.74-2.23) | 0.36 |
| YAP1 signature (presence vs. absence) | 1.87 (1.23-2.8) | 0.003 | 1.66 (1.1-2.53) | 0.01 |

To further test the association between the YA subgroup and benefit of taxane treatment, we evaluated gene expression data from advanced ovarian cancer tissues prospectively collected in a randomized phase II clinical trial, CTCR-OV01, that was designed to determine the response to neoadjuvant carboplatin (n=15) or paclitaxel (n=21) monotherapy. The *YAP1* signature was highly predictive of sensitivity to paclitaxel, with an AUC of 73.1% (p=0.02; 95% CI=54.9-92.3%) (Figure 3c), but not significantly predictive of sensitivity to carboplatin, with an AUC of 44.4% (p=0.7; 95% CI=22.2-66.7%) (Figure 3d). Together, these results strongly indicate that patients with the *YAP1* signature are significantly more sensitive to taxane-based treatment.

Discussion

By incorporating a well-defined gene expression signature reflecting activation of *YAP1*, we identified a novel subgroup of patients with ovarian cancer with a prognostic gene expression signature. The newly-identified *YAP1* gene expression signature was an independent and significant predictor of poor prognosis as evidenced by multivariate analysis (Table II). The clinical significance of *YAP1* activation observed in current study is in good agreement with biological characteristics of *YAP1*. *YAP1* and *TAZ* play key roles in lysophosphatidic acid-induced migration and proliferation of epithelial ovarian cancer cells (25, 26). Mice lacking *LATS1*, key upstream negative regulator of *YAP1* (4, 5), spontaneously developed ovarian cancer (27), further supporting the roles of *YAP1* as major oncogene and poor prognostic gene in ovary.

A subset analysis of patients in the PMC cohort revealed significant association between the *YAP1* signature and taxane-based chemotherapy; this finding was validated in a prospectively collected independent data set (CTCR-OV01). While these data are potentially interesting, the significance and robustness of the *YAP1* signature as a predictive marker for taxane-based chemotherapy response should be evaluated in large-scale data sets and prospective trials and the

molecular mechanisms associated with activation of *YAP1* and paclitaxel sensitivity remain to be elucidated.

The standard treatment for patients with ovarian cancer consists of maximal cytoreductive surgery followed by chemotherapy (28). However, 5-year OS durations remain very low. Therefore, alternative therapeutic strategies including novel cytotoxic drugs or targeted therapies are needed. Our results indicated that down-stream effectors of the Hippo pathway such as *YAP1* and *TAZ* might represent good therapeutic targets and the feasibility of targeting *YAP1* and *TAZ* should be tested in future investigations.

In conclusion, we have identified two new prognostic subgroups of ovarian cancer with significant survival differences. Our results clearly demonstrate that the *YAP1* signature can identify patients with ovarian cancer who have a poor prognosis, particularly in the subset that achieve complete response. Further validation of the signature will be necessary before implementation in clinical practice, but the fact that the signature was validated in two independent patient cohorts suggests that it can contribute to the rational design of future clinical trials by identifying high-risk patients.

Disclosure Statement

The Authors declare that there are no conflicts of interest.

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