Strengthening the case that elevated levels of programmed death ligand 1 predict poor prognosis in hepatocellular carcinoma patients

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Abstract: Immunotherapy targeting programmed death receptor 1 and programmed death ligand 1 (PD-L1) has shown impressive antitumor efficacy in several solid cancers, including advanced hepatocellular carcinoma (HCC). Since response rates of various cancers to such immunotherapy appear to correlate with PD-L1 expression levels, several studies have examined whether PD-L1 expression correlates with HCC pathology and patient prognosis. In this paper, we analyzed the strength and limitations of a recent meta-analysis that focused on the associations of PD-L1 with HCC characteristics and patient prognosis.

Keywords: hepatocellular carcinoma, programmed death ligand 1, hepatic resection, prognoses

Hepatocellular carcinoma (HCC) is a malignant disease with poor prognosis.1 Its officially recommended treatment is by sorafenib therapy, which is extremely expensive, often causes adverse events, and prolongs overall survival by only 3 months in patients with advanced disease.2,3 Immunotherapy targeting programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1) has shown impressive antitumor efficacy in several solid cancers,4–6 including advanced HCC.7 Since response rates of various cancers to such immunotherapy appear to correlate with PD-L1 expression levels,8 several studies have examined whether PD-L1 expression correlates with HCC pathology and patient prognosis. As the results obtained were inconsistent, Gu et al9 initiated to perform the first meta-analysis that focused on the associations of PD-L1 with HCC characteristics and patient prognosis.9 They concluded that higher PD-L1 levels predict poor differentiation, vascular invasion, higher levels of α-fetoprotein (AFP), and poorer survival. While these results are clinically useful, they should be interpreted with several limitations in mind.

One of the limitations is that the meta-analysis did not include four studies10–13 involving 384 patients that satisfied the inclusion criteria of this meta-analysis.9 In addition, one study14 included in this meta-analysis was based on PD-L1 assays in serum but not in tumor samples. The patients included in this study received both surgery and palliative therapies, while in other studies,15–20 patients received only surgery. These issues may increase heterogeneity in the pooled data, undermining the reliability of the results. In addition, it is unclear to us how this meta-analysis was able to report survival hazard ratios for the pooled patient population with tumors of any stage, when most studies in the meta-analysis reported survival separately by tumor stages but not in the population as a whole.

The work of Gu et al9 suggests that higher PD-L1 levels are associated with poorer clinicopathological characteristics of HCC. To extend this finding, we examined eleven...
**Table 1** Summary of studies examining potential associations of PD-L1 expression levels with HCC clinicopathological characteristics and patient prognosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sample size</th>
<th>Gender</th>
<th>Age</th>
<th>AFP</th>
<th>Hepatitis</th>
<th>Poor tumor</th>
<th>Tumor size</th>
<th>Satellite nodules</th>
<th>Vascular invasion</th>
<th>Tumor stage</th>
<th>OS</th>
<th>DFS/RFS</th>
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<tbody>
<tr>
<td>Finkelmeier et al³⁴</td>
<td>Germany</td>
<td>215</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
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<td>NR</td>
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<td>&lt;0.05</td>
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<tr>
<td>Gabrielson et al³⁵</td>
<td>USA</td>
<td>65</td>
<td>NR</td>
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<td>NR</td>
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<td>&gt;0.05</td>
<td>0.333</td>
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<tr>
<td>Gao et al³⁶</td>
<td>People's Republic of China</td>
<td>240</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
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<tr>
<td>Kan and Dong⁷³⁷</td>
<td>People's Republic of China</td>
<td>128</td>
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<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
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<tr>
<td>Umemoto et al³⁸</td>
<td>Japan</td>
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<td>0.051</td>
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<td>Wu et al³⁹</td>
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<td>NR</td>
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<td>&lt;0.05</td>
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<tr>
<td>Zeng et al⁴⁰</td>
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<td>141</td>
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<tr>
<td>Calderaro et al¹⁰</td>
<td>France</td>
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<td>Jung et al¹¹</td>
<td>Korea</td>
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<td>Shi et al¹²</td>
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<td>Wang et al¹³</td>
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<td>&lt;0.05</td>
<td>NR</td>
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</tbody>
</table>

Note: Bold values are statistically significant.

Abbreviations: AFP, α-fetoprotein; DFS, disease-free survival; HCC, hepatocellular carcinoma; OS, overall survival; PD-L1, programmed death ligand 1; RFS, recurrence-free survival; NR, not reported.

**Acknowledgments**

Despite its limitations, the meta-analysis of Gao et al.⁶⁶ suggests that higher PD-L1 levels are associated with poorer clinicopathological characteristics of HCC and poorer prognosis of patients. Further phase II clinical trials should be performed to investigate anti-PD-L1 treatment for HCC.

**References**


