

# 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 of 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.<sup>1</sup> 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.<sup>2,3</sup> Immunotherapy targeting programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1) has shown impressive antitumor efficacy in several solid cancers,<sup>4-6</sup> including advanced HCC.<sup>7</sup> Since response rates of various cancers to such immunotherapy appear to correlate with PD-L1 expression levels,<sup>8</sup> several studies have examined whether PD-L1 expression correlates with HCC pathology and patient prognosis. As the results obtained were inconsistent, Gu et al<sup>9</sup> initiated to perform the first meta-analysis that focused on the associations of PD-L1 with HCC characteristics and patient prognosis.<sup>9</sup> They concluded that higher PD-L1 levels predict poor differentiation, vascular invasion, higher levels of  $\alpha$ -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 studies<sup>10-13</sup> involving 384 patients that satisfied the inclusion criteria of this meta-analysis.<sup>9</sup> In addition, one study<sup>14</sup> 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,<sup>15-20</sup> 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 al<sup>9</sup> suggests that higher PD-L1 levels are associated with poorer clinicopathological characteristics of HCC. To extend this finding, we examined eleven

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**Table 1** Summary of studies examining potential associations of PD-L1 expression levels with HCC clinicopathological characteristics and patient prognosis

Study	Country	Sample size	P-value		AFP	Hepatitis history	Poor tumor differentiation	Tumor size	Satellite nodules	Vascular invasion	Tumor stage	OS	DFS/RFS
			Gender	Age									
Finkelmeier et al <sup>14</sup>	Germany	215	NR	NR	NR	>0.05	NR	NR	NR	NR	<0.05	<0.05	NR
Gabrielson et al <sup>15</sup>	USA	65	NR	NR	NR	>0.05	>0.05	NR	NR	>0.05	>0.05	0.353	NR
Gao et al <sup>16</sup>	People's Republic of China	240	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	<0.05	>0.05	<0.05	<0.05
Kan and Dong <sup>17</sup>	People's Republic of China	128	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	NR	<0.05	>0.05	<0.05	NR
Umemoto et al <sup>18</sup>	Japan	80	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	0.051	0.081
Wu et al <sup>19</sup>	People's Republic of China	71	NR	NR	NR	NR	NR	NR	NR	NR	NR	<0.05	NR
Zeng et al <sup>20</sup>	People's Republic of China	141	>0.05	>0.05	>0.05	NR	NR	<0.05	>0.05	<0.05	<0.05	<0.05	<0.05
Calderaro et al <sup>10</sup>	France	217	>0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	<0.05	NR	NR	<0.05
Jung et al <sup>11</sup>	Korea	85	>0.05	>0.05	>0.05	>0.05	>0.05	<0.05	NR	>0.05	>0.05	<0.05	<0.05
Shi et al <sup>12</sup>	People's Republic of China	56	NR	NR	NR	NR	NR	NR	NR	NR	<0.05	NR	<0.05
Wang et al <sup>13</sup>	People's Republic of China	26	>0.05	>0.05	NR	>0.05	>0.05	NR	NR	NR	<0.05	NR	NR

**Note:** Bold values are statistically significant.

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

studies and found that none of the studies reported gender, age, or hepatitis history to be associated with elevated PD-L1 expression (Table 1). Only one study associated high PD-L1 expression with higher preoperative serum levels of AFP, poor tumor differentiation, and satellite nodules;<sup>10</sup> two studies associated it with tumor size;<sup>11,20</sup> four studies associated it with vascular invasion;<sup>10,16,17,20</sup> and four studies<sup>12–14,20</sup> associated it with tumor stage. One study reported no significant association between high PD-L1 levels and overall survival,<sup>15</sup> while another study reported a nonsignificant trend that higher levels were associated with shorter overall survival.<sup>18</sup>

The results in Table 1 and those reported by Gu et al<sup>9</sup> suggest that elevated PD-L1 levels are associated with several HCC characteristics that are also risk factors for early tumor recurrence. Such recurrence can occur through two mechanisms: true metastasis due to primary HCC dissemination before surgery and multicentric occurrence (de novo) in remnant liver due to continuous viral infection and inflammation.<sup>21</sup> HCC treatments are usually effective against one or the other type of recurrence, but not both. In contrast, targeting PD-L1 may inhibit both types simultaneously, since reducing PD-L1 levels can strengthen T-cell responses to hepatitis virus infection.<sup>22,23</sup>

Despite its limitations, the meta-analysis of Gu et al<sup>9</sup> substantially strengthens the evidence that higher PD-L1 levels are associated with poorer clinicopathological characteristics of HCC and poorer prognosis of patients. Further phase I or phase II clinical trials should be performed to investigate anti-PD-L1 treatment for HCC.

## Acknowledgments

This work was funded by the National Natural Science Foundation of the People's Republic of China (81560460, 81060173), Guangxi University of Science and Technology Research Projects (KY2015LX056), the Self-Raised Scientific Research Fund of the Ministry of Health of Guangxi Province (Z2015621, Z2015601, GZZC15-34), and the Innovation Project of Guangxi Graduate Education (YCBZ2015030). The funding source had no role in the design or conduct of the study; in the collection, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

## Disclosure

The authors report no conflicts of interest in this work.

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