Serum Insulin-Like Growth Factor-1 Levels Predict Outcomes of Patients with Advanced Hepatocellular Carcinoma Receiving Anti-Angiogenic Therapy

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Running title: IGF-1 Levels Predict HCC Treatment Outcomes

Key words: anti-angiogenic therapy, hepatocellular carcinoma, IGF, prognosis

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TRANSLATIONAL RELEVANCE

Although the insulin-like growth factor (IGF)-1 signaling network is associated with
carcinogenesis, IGF-1 may also serve as a surrogate for the liver function reserve
because it is mainly produced by the liver. IGF-1 levels have been found to decrease
in patients with liver cirrhosis or hepatocellular carcinoma (HCC). Here we
demonstrated that high pre-treatment IGF-1 levels were associated with better disease
control rates and can independently predicted better progression-free survival and
overall survival of patients with advanced HCC who received first-line antiangiogenic
therapy.
ABSTRACT

Purpose: Patients with liver cirrhosis or hepatocellular carcinoma (HCC) have decreased serum insulin-like growth factor (IGF)-1 levels. We evaluated whether IGF-1 levels were associated with the outcomes of patients with advanced HCC treated with systemic anti-angiogenic therapy.

Experimental Design: The study was based on patients with advanced HCC who were enrolled in 2 clinical trials evaluating first-line combination anti-angiogenic therapy. Serum samples were collected before treatment and 4 to 6 weeks after the start of treatment. The levels of IGF-1, IGF-2 and IGF binding protein-3 (IGFBP3) were analyzed for their associations with treatment outcomes.

Results: A total of 83 patients were included in the study. Patients who had high (≥ the median level) baseline IGF-1 levels had significantly higher disease control rate (DCR) than patients who had low (< the median level) levels (71% vs. 39%, p = 0.003). The levels of post-treatment IGF-1, and pre- or post-treatment IGF-2 and IGFBP3 were not associated with DCR. Patients with high baseline IGF-1 levels, compared to patients with low levels, had significantly longer progression-free survival (PFS) (median, 4.3 vs. 1.9 months, p = 0.014) and overall survival (OS) (median, 10.7 vs. 3.9 months, p = 0.009). The high baseline IGF-1 level remains an independent factor associated with favorable PFS and OS in multivariate analysis.
**Conclusions:** High pre-treatment IGF-1 levels were associated with better DCR, PFS and OS of patients who received anti-angiogenic therapy for advanced HCC. This finding warrants validation in large studies.
INTRODUCTION

Insulin-like growth factor (IGF) signaling pathways are key regulators of energy metabolism and growth (1, 2). Substantial evidence indicates that IGF-1 and its signaling networks play an important role in the carcinogenesis of many cancer types. Although the vast majority of the ligands in circulation, including IGF-1 and IGF-2, are synthesized by the liver,(3, 4) these ligands are frequently expressed in neoplastic tissues (1). Many cancer cells also overexpress the IGF-1 receptor (IGFR) (5).

Activation of IGF-1 signaling promotes mitogenesis and inhibits apoptosis (1, 2). In epidemiologic studies, high blood IGF-1 concentration was associated with an increased risk of breast cancer, prostate cancer, esophageal cancer, and colon cancer (6-9).

The relevance of IGF signaling to hepatocellular carcinoma (HCC) is unique. Unlike other cancer types, patients with HCC have lower circulating IGF-1 levels than healthy controls (10). Regular monitoring of serum IGF-1 levels in patients with chronic hepatitis C showed that patients with declining serum IGF-1 level were more likely to develop HCC (11). In addition, low serum IGF-1 levels were associated with extensive liver involvement and vascular invasion in patients with HCC (12, 13). The inclusion of serum IGF-1 level into the common HCC staging systems improves their prognostic stratification (13, 14).
In the past, advanced HCC was a disease with very poor prognosis and few treatment options. In 2007, sorafenib, a multi-targeted inhibitor with anti-angiogenic activity, became the first approved systemic therapy for HCC after it was demonstrated to provide survival benefit in patients with advanced HCC (15, 16). Many other anti-angiogenic compounds or combinations are under active investigation (17-19). However, biomarkers that predict the efficacy or prognosis of patients treated with these therapies for advanced HCC are still lacking.

Since serum IGF-1 has been shown to be associated with the risk and disease extent of HCC, we planned this study to explore the significance of serum factors related to IGF signaling in patients with advanced HCC, focusing on their association with treatment outcomes.

MATERIALS AND METHODS

Study Population

This study was based on patients who were enrolled in 2 phase II clinical trials at the National Taiwan University Hospital (NTUH), Taipei, Taiwan. Both studies tested first-line combination systemic therapy for advanced HCC using an anti-angiogenic targeted agent plus metronomic chemotherapy, which was defined as the uninterrupted administration of low-dose chemotherapeutic agents for a prolonged
Metronomic chemotherapy was found with anti-angiogenic activity, rather than cytotoxicity to the tumor cells. One clinical trial studied sorafenib plus metronomic tegafur/uracil (S + T), and the other studied bevacizumab plus capecitabine (B + C). The eligibility criteria for both trials were similar. Patients were required to have pathologically proven or clinically diagnosed (typical imaging plus high serum alpha-fetal protein) metastatic or locally advanced HCC not amenable to loco-regional therapies, with adequate liver reserve (Child-Pugh Class A, liver transaminases levels ≤ 5 × upper limit of normal [ULN]) and organ functions (serum creatinine level ≤ 1.5 × ULN; platelet counts ≥ 100,000/μl for the study with S + T and ≥ 150,000/μl for the study with B + C). Tumor assessment was performed every 6 to 8 weeks following RECIST 1.0. The results of the 2 clinical trials have been published.

**Measurement of IGF-1, IGF-2, and IGF Binding Protein-3**

Patients who were enrolled in the clinical trials could choose whether or not to participate in the current biomarker study. Those patients who provided written informed consent had serum samples collected before treatment started and again at 4 to 6 weeks after the start of therapy. All sera were aliquoted and stored at -80°C. Measurement of serum levels of IGF-1 (R&D, Minneapolis, MN, USA), IGF-2 (Diagnostic Systems Laboratories, Webster, TX, USA), and IGF binding protein-3
(IGFBP3; R&D) were performed by enzyme-linked immunosorbant assay (ELISA) following the manufacturers’ instructions. This biomarker study was approved by the Research Ethical Committee of NTUH.

Statistical Methods

Statistical analyses were performed with SAS statistical software (version 9.1.3, The SAS Institute, Cary, NC, USA). A two-sided $p$ value $\leq 0.05$ was considered statistically significant. The associations between IGF-1, IGF-2, or IGFBP3 levels and disease control rate (DCR), which was defined as complete response, partial response or stable disease, were examined by the independent $t$ test. This test was also applied to examine the associations between IGF-1 levels and patient characteristics. Baseline IGF-1 levels were further dichotomized into high ($\geq$ median levels) and low ($<$ median levels) for further analysis. The association between disease control and high or low IGF-1 was examined by the Chi-square test or by Fisher’s exact test if any expected values of cells were less than 5. The Kaplan-Meier method was utilized to estimate survival. The survival of patients with high and low IGF-1 levels was compared by the log-rank test.

The Cox’s proportional hazards model was utilized to calculate the hazard ratios (HR) of baseline IGF-1, IGF2 and IGFBP3 levels, and other potential clinico-pathologic parameters including treatment regimens, gender, age, BMI, hepatitis etiologies,
macrovascular invasion, extrahepatic metastasis, α-fetoprotein > 400 ng/mL, Barcelona Clinic Liver Cancer stage, Cancer of the Liver Italian Program (CLIP) scores, Eastern Cooperative Oncology Group (ECOG) performance status and prior treatment in univariate and multivariate analyses. In the stepwise variable selection procedure during multivariate analysis, all the significant and non-significant covariates were considered by their $p$ values. The significance levels for entry and for stay were set as $p < 0.15$.

RESULTS

Patient Characteristics and Treatment Outcomes

A total of 83 patients were enrolled into the current study; 64 received S+T, and 19 received B+C. The median age was 54 years; 75% had chronic hepatitis B virus infection, and 90% had either extrahepatic metastasis (60%) or macrovascular invasion (59%) (Table 1). The basic characteristics of these patients were similar to the entire groups in the 2 clinical trials (17, 18). All patients in the current study had Child-Pugh class A liver cirrhosis, bilirubin level < 2 mg/dL, platelet counts > 100,000, and INR < 1.5. Eleven patients had mild ascites, and the other 72 patients had no ascites.
There were no complete responses, but 7 (8%) patients had partial responses to treatment (Table 2). Another 39 patients had stable disease, yielding a DCR of 55%. Median progression-free survival (PFS) was 3.3 months (95% confidence interval [CI], 2.2–4.3), and median overall survival (OS) was 6.3 months (95% CI, 4.1–8.5).

DCR, PFS, and OS were not significantly different between patients who were enrolled in the biomarker study and those who were not. In addition, within the current study population, patients who received different treatment regimens had similar DCR ($p = 0.421$), PFS ($p = 0.141$), and OS ($p = 0.218$).

**IGF-1 Levels and Treatment Outcomes**

Patients with disease control had significantly higher baseline IGF-1 levels than did patients without disease control (mean 78.2 vs. 56.5 ng/mL, $p = 0.006$; Fig. 1A).

When baseline IGF-1 levels were dichotomized to high ($\geq$ median level [63.6 ng/mL]) or low (< median level), patients with high IGF-1 levels had significantly higher DCR than patients with low IGF-1 levels (71% vs. 39%, $p = 0.003$). The higher DCR in patients with high IGF-1 levels could be attributed to more stable diseases compared to patients with low IGF-1 levels (62% vs. 32%). The baseline levels of IGF-2 and IGFBP3 were not associated with DCR (Fig. 1B & C). Post-treatment changes in the IGF-1, IGF2 and IGFBP3 levels were not associated with DCR ($p = 0.415$, 0.295 and 0.099, respectively), either.
Patients with high baseline IGF-1 levels, compared to patients with low levels, had significantly longer PFS (median, 4.3 vs. 1.9 months, \( p = 0.014 \); Fig. 2A) and OS (median, 10.7 vs. 3.9 months, \( p = 0.009 \); Fig. 2B). All the variables in Table 1, along with the baseline levels of IGF-1, IGF-2 and IGFBP3 were then analyzed in the Cox’s proportional hazard model. Treatment regimens, body mass index (BMI) and prior treatment were also included. Univariate analysis results were listed in the supplement Table 1. In multivariate analysis, high baseline IGF-1 remained an independent predictor for better PFS (hazard ratio [HR], 0.375; \( p < 0.001 \)) and OS (HR, 0.577, \( p = 0.029 \); Table 3) in the final fitting model.

**IGF-1 Levels and Patient Characteristics**

Patients with low baseline IGF-1 levels were more likely to have chronic hepatitis C (\( p = 0.028 \)), macrovascular tumor invasion (\( p = 0.002 \)), CLIP scores \( \geq 3 \) (\( p = 0.021 \)), or ECOG =1 (vs. 0, \( p = 0.027 \), Table 1). Baseline IGF-1 levels were not associated with the body mass index, bilirubin level and the presence of ascites or encephalopathy. As discussed above, these and other potential prognostic factors were adjusted in the multivariate analysis for PFS and OS, and the baseline IGF-1 level remained an independent predictor.
DISCUSSION

In the current study, we found that high pre-treatment serum IGF-1 levels were associated with better DCR, PFS, and OS in patients who received first-line systemic therapy for advanced HCC. The associations were independent of other clinicopathologic variables such as hepatitis etiologies, performance status, α-fetoprotein levels, and CLIP scores. Although previous studies have demonstrated that blood IGF-1 levels are a prognostic marker for HCC (13, 14, 22), this is the first study showing the potential association between serum IGF-1 levels and the efficacy of systemic therapy for advanced HCC. The study was a retrospective analysis and did not include a control group of patients who did not receive therapy. However, the adherence of this study to clinical trials ensured the accuracy of the clinicopathologic variables and the treatment outcomes, which were all prospectively collected.

The finding that high IGF-1 levels were associated with better treatment efficacy and patient outcomes may be counterintuitive because elevated IGF-1 levels and activation of the IGFR signaling pathway have been linked to tumorigenesis and the development of many cancer types (1, 2). However, patients with HCC had lower circulating IGF-1 levels than healthy controls (10). Based on an HCC patient cohort with heterogeneous disease status and treatment, Kaseb et al. found that low plasma
IGF-1 levels were associated with extensive liver involvement, vascular invasion, and poorer OS (13, 14). Most circulating IGF-1 is produced in the liver (3, 4). It was therefore postulated that IGF-1 levels reflect the functional reserve of the liver. We also found the correlation between high IGF-1 levels and less advanced disease status (CLIP score <3) or better performance status, which may contribute to the better PFS and OS of patients with high-IGF-1 levels.

Although we identified the high IGF-1 levels were associated with better DCR, PFS and OS, we did not find associations between IGF-1 levels and response rates. This observation may imply that better survival outcomes in HCC patients with high IGF-1 levels may derive from better tumor behavior or prognosis, rather than from better therapeutic efficacy. Alternatively, this may be attributed to the low response rate (8%) determined by RECIST. Recent data indicated that RECIST may not be adequate in evaluating the efficacy of systemic therapy, especially anti-angiogenic agents, in patients with advanced HCC (23, 24). Modified RECIST, which incorporates the measurements of viable tumors in liver, could identify more responders and have improved prognosis prediction for patients with advanced HCC (23, 24). If the two phase II clinical trials our study had adopted modified RECIST for tumor assessment, the probable association between response rates and IGF-1 levels might have been found.
The other potential mechanism underlying the associations between treatment outcomes of anti-angiogenic therapy and serum IGF-1 levels is the crosstalk between the IGF pathway and tumor angiogenesis. IGF-1 has been shown to stimulate hypoxia-inducible factor-1α activity and vascular endothelial growth factor (VEGF) expression in several cancer models (25-28). Blockade of the IGF-1 pathway inhibited angiogenesis and tumor growth in experimental animals (29-32). It is plausible that our HCC patients who had high serum IGF-1 levels might have tumors with higher angiogenic activity, which renders them more likely to benefit from anti-angiogenic therapy. We also found that the association of IGF-1 levels with DCR, PFS and OS held true for patients receiving either bevacizumab or sorafenib-based regimens. This implies that the mechanism underlying the predictive values of IGF-1 levels is possibly linked to anti-angiogenesis, the common mechanism of action shared by bevacizumab and sorafenib. However, because the lack of a control group not receiving anti-angiogenic therapy, this hypothesis awaits further exploration.

Approximately 99% of IGF-1 circulates bound to IGFBPs, with most bound to IGFBP3. Less than 1% of IGF-1 circulates unbound (1). In our analysis, serum levels of IGFBP3 had no association with the treatment outcomes. We measured free serum IGF-1 levels and found them also to be associated with DCR. Patients with high levels of free serum IGF-1 had better PFS and OS, although this was not statistically
significant (data not shown).

In conclusion, we have demonstrated that high pre-treatment serum IGF-1 levels were associated with better DCR, PFS and OS of patients who received systemic therapy for advanced HCC. These findings warrant validation in large studies.

GRANT SUPPORT

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hypoxia-inducible factor-1alpha by transcriptional and translational mechanisms.


FIGURE LEGENDS

**Fig. 1** Baseline levels of (A) insulin-like growth factor (IGF)-1, (B) IGF-2, and (C) IGF binding protein-3 (IGFBP3), grouped by disease control or not. The lines marked mean levels and 95% confidence intervals. *P* values were calculated by independent t test to compare the mean levels of biomarker between patients with disease control and with disease progression.

**Fig. 2** Kaplan-Meier analysis of (A) progression-free survival (PFS) and (B) overall survival (OS), grouped by high (≥ median level) and low (< median level) baseline insulin-like growth factor (IGF)-1 levels. *P* values were conducted by log-rank tests.
### Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>N (%)</th>
<th>Baseline IGF-1</th>
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<tr>
<td></td>
<td>Total</td>
<td>High</td>
<td>Low</td>
<td></td>
<td></td>
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<tr>
<td>Total</td>
<td>83 (100)</td>
<td>42 (100)</td>
<td>41 (100)</td>
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<tr>
<td>Median age (range, yrs)</td>
<td>54 (24-83)</td>
<td>52 (24-73)</td>
<td>56 (28-83)</td>
<td>0.065</td>
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<td>Gender</td>
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<td>Female</td>
<td>9 (11)</td>
<td>5 (12)</td>
<td>4 (10)</td>
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<td>Male</td>
<td>74 (89)</td>
<td>37 (88)</td>
<td>37 (90)</td>
<td></td>
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<tr>
<td>Hepatitis virus</td>
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<td></td>
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<tr>
<td>HBsAg positive</td>
<td>62 (75)</td>
<td>33 (79)</td>
<td>29 (71)</td>
<td>0.411</td>
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<td>Anti-HCV positive</td>
<td>16 (19)</td>
<td>4 (10)</td>
<td>12 (29)</td>
<td>0.028</td>
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<td>Extrahepatic metastasis</td>
<td>50 (60)</td>
<td>26 (62)</td>
<td>24 (59)</td>
<td>0.754</td>
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<tr>
<td>Macrovascular invasion</td>
<td>49 (59)</td>
<td>18 (43)</td>
<td>31 (76)</td>
<td>0.002</td>
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<td>AFP &gt; 400 ng/mL</td>
<td>45 (54)</td>
<td>21 (50)</td>
<td>24 (59)</td>
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<td>BCLC stage</td>
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<td></td>
</tr>
<tr>
<td>B</td>
<td>5 (6)</td>
<td>4 (10)</td>
<td>1 (2)</td>
<td>0.360</td>
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<tr>
<td>C</td>
<td>78 (94)</td>
<td>38 (90)</td>
<td>40 (98)</td>
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### CLIP score

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<th>Count</th>
<th>Percent</th>
<th>Count</th>
<th>Percent</th>
<th>P-value</th>
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<td>0-2</td>
<td>43 (52)</td>
<td>27 (64)</td>
<td>16 (39)</td>
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<tr>
<td>3-4</td>
<td>40 (48)</td>
<td>15 (36)</td>
<td>25 (61)</td>
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### ECOG PS

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<th>Count</th>
<th>Percent</th>
<th>Count</th>
<th>Percent</th>
<th>Count</th>
<th>Percent</th>
<th>P-value</th>
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<tr>
<td>0</td>
<td>70 (84)</td>
<td>39 (93)</td>
<td>31 (76)</td>
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<tr>
<td>1</td>
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<td>3 (7)</td>
<td>10 (24)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: IGF = insulin-like growth factor; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; AFP = \( \alpha \)-fetoprotein; BCLC = Barcelona Clinic Liver Cancer; CLIP = Cancer of the Liver Italian Program; ECOG PS = Eastern Cooperative Oncology Group performance status
Table 2 Treatment response of studied patients according to RECIST

<table>
<thead>
<tr>
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<th>Total</th>
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<th>Low</th>
<th>P value</th>
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<td>Total</td>
<td>83 (100)</td>
<td>42 (100)</td>
<td>41 (100)</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>Partial response</td>
<td>7 (8)</td>
<td>4 (10)</td>
<td>3 (7)</td>
<td></td>
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<tr>
<td>Stable disease</td>
<td>39 (47)</td>
<td>26 (62)</td>
<td>13 (32)</td>
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<tr>
<td>Progressive disease</td>
<td>33 (40)</td>
<td>10 (24)</td>
<td>23 (56)</td>
<td></td>
</tr>
<tr>
<td>Not evaluable</td>
<td>4 (5)</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Response rate*</td>
<td>7 (8)</td>
<td>4 (10)</td>
<td>3 (7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Disease control rate#</td>
<td>46 (55)</td>
<td>30 (71)</td>
<td>16 (39)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*defined as the percentage of patients with complete response or partial response

#defined as the percentage of patients with complete response, partial response or stable disease
Table 3 Cox’s proportional hazards model for predictors of progression-free survival and overall survival

<table>
<thead>
<tr>
<th>Variables</th>
<th>P value</th>
<th>Hazard ratio</th>
<th>95% CI</th>
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<td><strong>Progression-free survival</strong></td>
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</tr>
<tr>
<td>Male (vs. female)</td>
<td>&lt; 0.001</td>
<td>5.294</td>
<td>2.172-12.903</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 0.001</td>
<td>0.958</td>
<td>0.941-0.974</td>
</tr>
<tr>
<td>High baseline IGF-1 levels</td>
<td>&lt; 0.001</td>
<td>0.375</td>
<td>0.230-0.612</td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (vs. female)</td>
<td>0.047</td>
<td>2.557</td>
<td>1.012-6.461</td>
</tr>
<tr>
<td>HBsAg positive</td>
<td>0.014</td>
<td>2.087</td>
<td>1.157-3.763</td>
</tr>
<tr>
<td>CLIP score ≥ 3</td>
<td>&lt; 0.001</td>
<td>2.821</td>
<td>1.674-4.754</td>
</tr>
<tr>
<td>High baseline IGF-1 levels</td>
<td>0.029</td>
<td>0.577</td>
<td>0.352-0.945</td>
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</tbody>
</table>

Abbreviations: CI = confidence interval; IGF = insulin-like growth factor; HBsAg = hepatitis B virus surface antigen; CLIP = Cancer of the Liver Italian Program
B

$P = 0.432$

IGF-2 (ng/mL)

Disease control Disease progression

3500 3000 2500 2000 1500 1000 500 0
Clinical Cancer Research

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