# Development and validation of an IGF-1-modified Child–Pugh score to risk-stratify hepatocellular carcinoma patients

Ahmed O. Kaseb[a], Lianchun Xiao[a], Rania Naguib[b], Wafaa El-Shikh[b], Manal Hassan[a], Hesham Hassabo[a], Jeong-Hoon Lee[c], Jung-Hwan Yoon[c], Hyo-Suk Lee[c], Young Kwang Chae[a], James L. Abbruzzese[a], Jeffrey Morris[a]

[a]Department of Cancer Center, UT MD Anderson Cancer Center Houston, Texas, USA, [b]Department of Medicine, Alexandria University, Alexandria, Egypt, [c]Department of Cancer Center, Seoul National University College of Medicine, Seoul, Republic of Korea

Correspondence to Rania Naguib, Assistant Professor, Internal Medicine, Alexandria University, Egypt
e-mail: ranianaguib2000@yahoo.com

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**Background**
The Child–Turcotte–Pugh (CTP) score inaccurately predicts survival in patients with chronic liver disease, including hepatocellular carcinoma (HCC), yet remains the standard tool for assessing hepatic reserve and guiding therapeutic decisions. CTP scoring relies on objective laboratory values for albumin, bilirubin, and prothrombin time and subjective clinical grading of hepatic encephalopathy and ascites. As liver production of insulin-like growth factor-1 (IGF-1) is significantly reduced in patients with cirrhosis, we hypothesized that IGF-1 could be a valid surrogate for hepatic reserve to replace the subjective parameters in CTP scores.

**Materials and methods**
We prospectively enrolled patients and collected data and retrospectively tested plasma IGF-1 levels in four independent cohorts: two HCC cohorts from the USA [$n = 310$ (training set) and $n = 99$ (validation set 1)]; one HCC cohort from Korea [$n = 188$ (validation set 2)]; and one cirrhosis cohort from Egypt [$n = 71$ (validation set 3)]. Recursive partitioning identified within the training set three optimal IGF-1 ranges that correlated with survival: >50 ng/ml = 1 point; 26–50 ng/ml = 2 points; and <26 ng/ml = 3 points. We modified the CTP score by replacing ascites and encephalopathy grading with IGF-1 values, subjected both the resulting IGF score and the CTP score to log-rank analysis, and quantified the prognostic values with *C*-statistics to compare the scores' performance in all cohorts.

**Results**
The IGF score was significantly more accurate in predicting survival and improved the stratification of all CTP classes in the training and validation cohorts.

**Conclusion**
The new IGF score is simple and blood-based, and validated well on multiple independent HCC cohorts. It could identify a subpopulation of patients who may benefit from active therapy because of their preserved hepatic reserve, as distinct from patients for whom therapy can be deferred or avoided.

**Keywords:**
hepatocellular carcinoma, IGF-1-modified Child–Pugh score, risk stratification

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## Introduction

Cirrhosis represents the final common pathway for a wide variety of chronic liver diseases (CLD). It is defined histologically as a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. The progression of liver injury to cirrhosis may occur over months to years [1]. Cirrhosis is often a silent disease, with most patients remaining asymptomatic until decompensation occurs. Early and well-compensated cirrhosis can manifest as anorexia and weight loss, weakness and fatigue.

Decompensated disease is the result of impaired hepatocellular function leading to complications such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and variceal bleeding. Clinical symptoms at presentation may include jaundice, gastrointestinal bleeding, coagulopathy, abdominal distension, and mental status changes [2,3]. To date, no single serologic test can diagnose cirrhosis or assess its phase of severity accurately [2]. ALT is still thought to be the most cost-effective screening test for identifying metabolic or drug-induced hepatic injury, but it is of limited use in predicting the degree of inflammation and of no use in estimating the severity of fibrosis [4]. The limitations of a single parameter to assess liver fibrosis have led to the development of algorithms or indices combining the results of different markers that substantially improve diagnostic accuracy.

Hepatic reserve is an important predictor of outcome in liver diseases. This necessitates an accurate assessment of the liver reserve to predict patients' morbidity and mortality.

The Child–Turcotte–Pugh (CTP) classification (the Child score) has been the standard for evaluating cirrhotic patients, and it was originally intended as an assessment of life expectancy in cirrhotic patients with portal hypertensive variceal bleeding. Then the CTP score became the standard method for evaluating hepatic reserve in patients with cirrhosis and has been subject to many evaluations and modifications [5] (Table 1).

Furthermore, the model for end-stage liver disease (MELD) scoring system has received increasing attention and use in the last several years, especially in conjunction with liver transplantation. It has the advantage over the Child score of being dependent only on laboratory values rather than clinical evaluation, hence providing a more objective and unbiased report about liver function status [6]:

$$\text{MELD score} = 3.8 \times \log_e [\text{bilirubin (mg/dl)}] + 11.2 \times \log_e (\text{INR}) + 9.6 \log_e [\text{creatinine (mg/dl)}].$$

Because cirrhosis underlies most cases of hepatocellular carcinoma (HCC) and as advanced cirrhosis can, in fact, affect patients' survival to a greater degree than the carcinoma itself [7,8], the CTP score has become the standard prognostic tool for predicting survival to guide initial or subsequent therapy decisions by predicting the risk for liver failure and death after local and systemic therapies and for categorizing patients under HCC staging systems for trial entry [9].

The five CTP variables are each scored on a scale of 1–3; thus, the minimum score is 5 and the maximum score is 15 (Table 1). The lowest scores (scores 5 and 6) are considered CTP class A, which carries the best prognosis; the middle scores (scores 7–9) are class B, and the highest scores (scores 10–15) are class C. Because survival rates are universally low for CTP classes B and C compared with class A, multiple expert panels have reached the consensus that patients with HCC should have a CTP score of A to be considered for aggressive therapies to facilitate assessment of the effect of treatment without the confounding issues of liver failure and death as a result of underlying poor hepatic reserve [7,8]. However, clinical outcome can vary considerably among patients within the same CTP class. Furthermore, CTP is partially based on subjective assessment of empiric dynamic clinical parameters (hepatic encephalopathy and ascites) with arbitrary cutoff ranges that are difficult to grade subjectively and may vary in severity according to nutritional status, comorbidities, and in response to medical management [10–12]. Subsequently, the reliability of the CTP score for survival prediction and clinical decision-making was questioned, and more objective liver scores were introduced [13,14]. Also, no scoring system was developed for patients with HCC. Other limitations of the CTP score include the disproportionate number of patients under class A and its need for more accurate objective markers that reflect the hepatic reserve [10].

Growth hormone is released from the anterior pituitary gland and binds to its receptors on the liver. The liver in turn synthesizes insulin-like growth factors (IGF) [15]. The IGF system operates in anabolism and cell proliferation [16,17]. The liver is the predominant site of IGF production and thus the GH IGF system is adversely affected in liver cirrhosis.

IGF-I and IGF-II are the two major forms of the IGF family. They are single-chain molecules with three intrachain disulfide bridges [18,19]. Both of them may be considered as important anabolic hormones that are active throughout one's life, inducing anabolic metabolism, stimulation of DNA synthesis, cell proliferation, and meiotic division [17,18]. IGF-I is considered the most important member of this system. It is generally believed that IGF-I bioactivity is maintained primarily through free, unbound IGF-I [20,21].

The IGF family has recently been linked to the pathogenesis of several cancer types [22]. Results from early studies suggested higher plasma IGF-1 in patients with prostate cancer [23], breast cancer [24], colon cancer [25], and lung cancer [26]. However, circulating levels of IGF-1 decrease sharply in patients with CLD and HCC [27–32] because the liver synthesizes most of the circulating IGF-1. Subsequently, low IGF-1

**Table 1 Child–Turcotte–Pugh scoring system to assess liver disease severity [5]**

| Clinical and laboratory measurements | Points scored for increased abnormality | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Encephalopathy (grade) | None | 1–2 | 3–4 |
| Ascites | None | Mild (or controlled by diuretics) | Moderate–severe despite diuretic treatment |
| Prothrombin time (seconds prolonged) or | <4 | 4–6 | >6 |
| INR | <1.7 | 1.7–2.3 | >2.3 |
| Albumin (g/dl) | >3.5 | 2.8–3.5 | <2.8 |
| Bilirubin (mg/dl) | <2 | 2–3 | >3 |

A score of 5–6 = grade A; 7–9 = grade B; 10 –15 = grade C; INR, international normalized ratio.

levels lead to bone loss and other metabolic changes in patients with cirrhosis [33–35]. In addition, circulating IGF-1 has been found to correlate with the status of liver disease, histologic grade of fibrosis, and liver reserve scores such as CTP and MELD [36–40], which is used to predict 3-month mortality risk to determine liver organ allocation priorities. Recent studies [41,42] showed that baseline plasma IGF-1 level was statistically significantly associated with patients' survival, synthetic function of the liver, and tumor parameters. However, few studies have assessed the role of integrating plasma IGF-1 into CTP parameters on patients' prognostication. Because HCC tumors act as space-occupying lesions that decrease the synthetic function of the liver and decrease hepatic IGF-1 production, we hypothesized that plasma IGF-1 could be used as a surrogate marker for hepatic reserve that can be replaced for the subjective variables (ascites and hepatic encephalopathy) in the CTP score to create a novel liver score based exclusively on objective variables with increased prognostic accuracy.

Our study aimed to:

(1) Determine whether IGF could further distinguish patients in terms of overall survival.
(2) Build up a new Child–Pugh (CP) score system by incorporating plasma IGF-1 level to the three parameters (PT%, bilirubin, and albumin) used for the original CP score to refine patients' stratification.
(3) Evaluate the prognostic performance of the new score system.

## Materials and methods

We prospectively enrolled patients and collected data and retrospectively tested plasma IGF-1 levels by ELISA in four independent cohorts: two HCC cohorts from the Anderson Cancer Center (Maryland, USA) [$n$ = 310 (training set) and $n$ = 99 (validation set 1)]; one HCC cohort from Korea [$n$ = 188 (validation set 2)]; and one cirrhosis cohort ($n$ = 71), as well as 21 patients with HCC from Alexandria University, Egypt (validation set 3). Recursive partitioning was used to identify optimal cutoff points and IGF-1 ranges within the training set, and established three distinct groups of IGF-1 that correlated with poor overall survival (OS) and advanced CLD parameters: IGF-1 levels more than 50 ng/ml, group A = 1 point; IGF-1 levels 26–50, group B = 2 points; and IGF-1 levels less than 26, group C = 3 points. We modified the CP scoring system by replacing ascites and encephalopathy with plasma IGF-1 (total point range: 4–11). Finally, we calculated the log-rank test for both systems and compared their prognostic accuracies with CP parameters to refine patient stratification. The prognostic values were quantified with *C*-statistics to compare the scores' performance in all cohorts.

Patients' blood samples and epidemiologic and clinical data were collected. This study was approved by the institutional review boards at MDACC and at the Faculty of Medicine, Alexandria, Egypt, and patients signed a written informed consent form. For the two HCC cohorts, the study involved pathologically or radiologically confirmed HCC; the diagnosis was based on the criteria set forth by the 2005 guidelines of the American Association for the Study of Liver Diseases [43] for patients enrolled after 2005 who did not have biopsy samples available.

For all patients, peripheral venous blood specimens (3–5 ml) were collected, anticoagulated by ethylenediaminetetraacetic acid, and subjected to centrifugation for 15 min at 3000 rpm. The plasma was then removed, aliquoted, and snap-frozen at –20°C until analysis. IGF-1 was tested by means of the enzyme-linked immunosorbent assay performed according to the manufacturer's directions (Quantikine Human IGF-1 ELISA Kit; R&D Systems, Minneapolis, Minnesota, USA).

### Statistical analysis

The data were collected and entered into a personal computer. Statistical analysis was conducted using the statistical package for social sciences (SPSS version 17).

Arithmetic mean and SD were computed; the $\chi^2$-test was used for categorized parameters, and the $t$-test for numerical data to compare two groups. The level of significance was 0.05. We compared the prognostic scales using the *C*-index, which yields values ranging from 0 (no discrimination) to 1 (perfect separation) to compare both scores. The *C*-index analysis shows the prognostic stratification provided by the new Child-Pugh-IGF (CPG) compared with the original CP classification.

The log-rank test was used for both systems; their prognostic accuracies were compared with CP parameters to refine patient stratification.

## Results

Most patient characteristics were similar; we found no statistically significant differences regarding age and sex between the studied groups (all $P > 0.05$) (Table 2).

Among patients with CP score grade 'A', there were no cases of mortality, whereas among patients with CP

score grade 'B' seven of 26 patients died and among patients with CP score grade 'C' 29 of 39 patients died. Among patients with CP grade B, six patients had IGF-1 levels less than 26 ng/ml, whereas 20 patients had IGF-1 levels more than 26 ng/ml. Among patients with CP score grade 'C', 18 patients had IGF-1 levels less than 26 ng/ml and 21 patients had IGF-1 levels more than 26 ng/ml.

In each of the CP 'B' and 'C' categories, patients with IGF less than 26 ng/ml had a shorter median OS time compared with patients with IGF more than 26 ng/ml. In CP 'B' category, this difference was statistically significant (Table 3).

Patients were classified by both the IGF-incorporated new score system and the original CP score system. Twenty-seven patients were classified as grade A in the original CP score, whereas in the new IGF-1-incorporated score, one patient was downgraded from grade A to grade B. The biggest shift was that six patients who were scored 'B' by the original CP score system were classified as 'C' in the new score system. Thus, between the two score systems, 7/92 patients had different scores and 85/92 patients had the same scores (Table 4).

**Table 2 Comparison between baseline characteristics of the studied groups**

| Parameters | Child A | Child B | Child C | *P*-value |
|---|---|---|---|---|
| Age (years) | 53.0 ± 3.0 | 55.0 ± 4.5 | 52.5 ± 7.0 | 0.02 |
| Sex | | | | |
| Males | 18 | 15 | 21 | 0.1 |
| Females | 9 | 11 | 18 | |

Tables 5 and 6 show how the original CP score system and the IGF-incorporated new system classify patients with cirrhosis and HCC, respectively.

Five of the six patients who were grade B in the original CP score but were reclassified as grade C in the IGF-1-incorporated score died. This shows that these six patients (old B, new C) had a shorter OS and a higher risk of death and a statistically significantly worse prognosis ($P < 0.005$) compared with patients who were scored as 'B' in both score systems (hazard ratio = 7.3; 95% confidence interval = 1.4–37.8) (Table 7 and 8).

In the current study, in all of the studied groups, patients with high serum IGF levels showed statistically significantly better prognosis than those with low IGF levels ($P < 0.001$), whereas patients with low IGF had worse prognosis than intermediate IGF levels.

IGF-1 levels significantly correlated with poor OS and advanced CLD parameters. Compared with CP, the IGF-modified CP score was significantly more accurate in predicting OS and improved the stratification of all classes of CP, in both the training cohort ($P < 0.0001$) and the validation cohort ($P < 0.0001$).

Both scores stratified patients into low-risk (A), intermediate-risk (B), and high-risk (C) groups that differed in OS ($P < 0.001$).

We compared the prognostic scales using the *C*-index, which yields values ranging from 0 (no discrimination) to 1 (perfect separation) to compare both scores. The *C*-index analysis shows the prognostic stratification

**Table 3 Log-rank test to compare overall survival between various insulin-like growth factor levels within each Child–Pugh score category**

| Child–Pugh | Level | *N* | Event | Median OS time (95% CI) | OS rate at 1 years (95% CI) | *P*-value |
|---|---|---|---|---|---|---|
| CPG = A | | | | | | |
| | CPG 'A' patients | 27 | 0 | NA | 1 (1–1) | |
| IGF score1 | ≤26 | 1 | 0 | NA | 1 (1–1) | 1 |
| | >26 | 26 | 0 | NA | 1 (1–1) | |
| IGF score | 1 (>50) | 26 | 0 | NA | 1 (1–1) | 1 |
| | 3 (≤26) | 1 | 0 | NA | 1 (1–1) | |
| CPG = B | | | | | | |
| | CPG 'B' patients | 26 | 7 | NA (22.86–NA) | 0.87 (0.75–1) | |
| IGF score 1 | ≤26 | 6 | 5 | 21.89 (13.59–NA) | 0.83 (0.58–1) | 0.0055 |
| | >26 | 20 | 2 | NA | 0.88 (0.74–1) | |
| IGF score | 1 (>50) | 9 | 0 | NA | 1 (1–1) | 0.0163 |
| | 2 (26–50) | 11 | 2 | NA | 0.8 (0.58–1) | |
| | 3 (≤26) | 6 | 5 | 21.89 (13.59–NA) | 0.83 (0.58–1) | |
| CPG = C | | | | | | |
| | CPG 'C' patients | 39 | 29 | 6.88 (5.92–10.82) | 0.21 (0.11–0.43) | |
| IGF score 1 | ≤26 | 18 | 17 | 5.99 (2.89–15.1) | 0.22 (0.09–0.53) | 0.2244 |
| | >26 | 21 | 12 | 9.7 (6.71–NA) | 0.17 (0.05–0.59) | |
| IGF score | 2 (26–50) | 21 | 12 | 9.7 (6.71–NA) | 0.17 (0.05–0.59) | 0.2244 |
| | 3 (≤26) | 18 | 17 | 5.99 (2.89–15.1) | 0.22 (0.09–0.53) | |

CI, confidence interval; IGF, insulin-like growth factor; OS, overall survival.

**Table 4 All patients (*N* = 92)**

| New CPG | Child–Pugh score | | |
|---|---|---|---|
| | A | B | C |
| A (4–5) | 26 | 0 | 0 |
| B (6–7) | 1 | 20 | 0 |
| C (>7) | 0 | 6 | 39 |

New CPG score by A (4–5), B (6–7), and C (>7).

**Table 5 Hepatocellular carcinoma patients (*N* = 21)**

| New CPG | Child–Pugh score | | |
|---|---|---|---|
| | A | B | C |
| A (4–5) | 0 | 0 | 0 |
| B (6–7) | 1 | 2 | 0 |
| C (>7) | 0 | 2 | 16 |

New CPG scores A (4–5), B (6–7), and C (>7).

**Table 6 Cirrhosis patients (*N* = 71)**

| New CPG | Child–Pugh score | | |
|---|---|---|---|
| | A | B | C |
| A (4–5) | 26 | 0 | 0 |
| B (6–7) | 0 | 18 | 0 |
| C (>7) | 0 | 4 | 23 |

New CPG score by A (4–5), B (6–7), and C (>7).

**Table 7 Log-rank test to compare overall survival among patients with new CPG scores A (4–5), B (6–7), and C (>7)**

| New CPG | Level | *N* | Event | Median OS time (95% CI) | *P*-value |
|---|---|---|---|---|---|
| Group 1 | NewAoldA | 26 | 0 | NA | <0.0001 |
| | NewBoldB | 20 | 2 | NA | |
| | NewColdB | 6 | 5 | 21.89 (13.59–NA) | |
| | NewColdC | 39 | 29 | 6.88 (5.92–10.82) | |

CI, confidence interval; HR, hazard ratio.

**Table 8 Univariate Cox model to determine whether the overall survival and hazard ratio for six patients switched from old B to new C were significantly different from the newboldB patients**

| Group | HR (95% CI) | *P*-value |
|---|---|---|
| NewBoldB | Baseline | |
| NewColdB | 7.33 (1.42–37.8) | 0.017 |
| NewColdC | 15.01 (3.55–63.5) | 0.0002 |

CI, confidence interval; HR, hazard ratio.

provided by the new CPG compared with the original CP classification. The *C*-index analysis demonstrated that the prognostic stratification provided by IGF-CTP was statistically significantly better than the CTP in both the training cohort ($P = 0.003$) and the validation cohort ($P = 0.005$).

## Discussion

The CP score (range: 5–15; groups: A, B, C) is currently the standard method to stratify the severity of decompensated liver disease in patients with HCC, which in turn helps to stratify them in clinical trials and guide their treatment decisions.

As the CP score depends on two clinically subjective parameters – namely, degree of ascites and encephalopathy – which are clinically difficult to grade and may vary in severity in response to medical therapies, the need for an objective and more reliable parameter that depends on laboratory results arose.

Recent studies have shown that plasma IGF-1 is significantly reduced in CLD and that plasma IGF-1 level is a surrogate marker for functional liver reserve in HCC [36].

Thus, a new scoring system in which plasma IGF-1 is integrated to replace both ascites and encephalopathy is now developing [42].

The objective of the current study was to determine whether IGF could further distinguish patients in terms of overall survival, to build up a new CP score system by incorporating IGF expressions into three parameters (PT%, bilirubin, and albumin) used for the original CP score, and to evaluate the prognostic performance of the new scoring system.

In our study, patients with high serum IGF levels showed statistically significantly better prognosis than those with low IGF levels, whereas patients with low IGF had worse prognosis than intermediate IGF levels. These results agree with the results obtained by a recent study [41].

This can be explained by the fact that the IGF level negatively correlates with the degree of cirrhosis because of derangement of the synthetic liver function due to decreased hepatic reserve, caused by the underlying liver disease in addition to the HCC space-occupying tumors. Also serum IGF level correlates negatively with the stage of HCC and tumor size. This could be explained by the HCC space-occupying effect. All of these affect the prognosis and overall survival.

In the present study, patients were classified by both the IGF-incorporated new score system and the original CP score system and the results were compared.

Of the 27 patients classified as CP score A, 26 were reclassified as grade A in the IGF-incorporated CP score, whereas one patient was reclassified as having intermediate (IGF-CP-B) risk and had lower median OS. Also 20 patients classified as CP score B were

reclassified as grade B in the IGF-incorporated CP score, whereas six patients were reclassified as IGF-CP-C and had lower median OS but similar prognosis as other intermediate-risk (IGF-CP-B) patients who were CP-B.

This group of patients who were reclassified and downgraded had statistically significantly worse prognosis compared with their comparable group in the original CP score.

These results agree with those of Kaseb *et al*. [41] and help offer statistically significantly more accurate survival prediction and prognostic stratification than the CP score and helps re-evaluate patients regarding their therapeutic modality.

Both scores were compared regarding their prognostic scales using the *C*-index. For all patients, there was a statistically significant difference regarding the estimated *C*-index for the IGF-incorporated score system (A = 4–5, B = 6–7, and C > 7) and the original CP score system.

These results are in agreement with the results obtained by other studies [41,42,44]; although the difference between *C*-indices was not large, it was statistically significant [35].

Thus, the current study aims at applying a new score incorporating IGF-1 serum levels as a more accurate laboratory marker to help obtain a more accurate prediction of the overall survival and helps in reclassification of a good proportion of cirrhosis and HCC patients, which will assist in the decision regarding the plan of management. Therefore, further validation studies are warranted and future studies evaluating the replacement of CP scores with the IGF-CP score in HCC staging systems may lead to a more accurate approach to patient stratification and treatment assignment.

## Conclusion

The new IGF score is simple and blood-based, and validated well on multiple independent HCC cohorts. It could identify a subpopulation of patients who may benefit from active therapy because of their preserved hepatic reserve, as distinct from patients for whom therapy can be deferred or avoided. Replacing the clinical assessment of ascites and encephalopathy in the CP score with the objectively quantified IGF-1 significantly improved the prediction of OS and stratification of HCC patients. A prospective comparison of the performance of both systems is warranted.

## Acknowledgements

### Conflicts of interest

None declared.

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