Comparison of the prognostic value of inflammation-based prognostic scores in patients with hepatocellular carcinoma

A Kinoshita*,1, H Onoda1, N Imai1, A Iwaku1, M Oishi1, N Fushiya1, K Koike1, H Nishino1 and H Tajiri2

1Division of Gastroenterology and Hepatology, the Jikei University Daisan Hospital, 4-11-1 Izumihon-cho, Kamei-shi, Tokyo 201-8601, Japan; 2Division of Gastroenterology and Hepatology, Department of Internal Medicine, the Jikei University School of Medicine, 3-25-8 Nishishimbashi, Minato-ku, Tokyo 105-0003, Japan

BACKGROUND: Inflammation-based prognostic scores including the Glasgow Prognostic Score (GPS), neutrophil to lymphocyte ratio (NLR), and Prognostic Nutritional Index (PNI) are associated with survival in patients with hepatocellular carcinoma (HCC). The aim of this study was to investigate the prognostic value of these inflammation-based prognostic scores in patients with HCC.

METHODS: In total, 150 patients with newly diagnosed HCC were prospectively evaluated. Patients were divided according to the GPS, modified GPS, NLR, platelet to lymphocyte ratio (PLR), Prognostic Index (PI), and PNI. The area under the receiver operating characteristics curve (AUC) was calculated to compare the predictive ability of each of the scoring systems. A univariate and multivariate analysis were performed to identify the clinicopathological variables associated with overall survival.

RESULTS: The GPS consistently had a higher AUC value at 6 months (0.768), 12 months (0.787), and 24 months (0.758) in comparison with other inflammation-based prognostic scores. A multivariate analysis showed that the GPS was independently associated with overall survival.

CONCLUSION: This study demonstrates that the GPS, an inflammation-based prognostic score, is an independent marker of poor prognosis in patients with HCC and is superior to the other inflammation-based prognostic scores in terms of prognostic ability.

Keywords: inflammation-based prognostic score; the Glasgow Prognostic Score; hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the fifth most frequently diagnosed cancer worldwide, and the third leading cause of cancer-related deaths. An estimated 748,300 new liver cancer cases and 695,900 liver cancer-related deaths occurred in 2008, reflecting the poor prognosis of this disease (Jemal et al, 2011). In contrast to other cancers, the prognosis and treatment options for patients with HCC depend not only on the tumour progression but also on the extent of liver dysfunction (Huitzil-Melendez et al, 2010).

A number of staging systems have been proposed for HCC from independent groups, including the Barcelona Clinic Liver Cancer (Llovet et al, 1999), Cancer Liver Italian Programme (CLIP; CLIP investigators, 1998), and Japanese Integrated Staging (JIS) Score systems (Kudo et al, 2004). However, there is no worldwide consensus on which is the best system in staging and predicting the prognosis of patients with HCC.

In contrast, there is increasing evidence that the presence of a systemic inflammation response as evidenced by an elevated C-reactive protein (CRP) concentration, is associated with poor survival in patients with various malignancies, including HCC (Hashimoto et al, 2005; Kinoshita et al, 2012). Moreover, several studies have shown that inflammation-based prognostic scores including a combination of serum CRP and albumin as the Glasgow Prognostic Score (GPS), a combination of neutrophil and lymphocyte counts as the neutrophil to lymphocyte ratio (NLR), and a combination of albumin and lymphocyte counts as the Prognostic Nutritional Index (PNI) are associated with survival in patients with HCC (Gomez et al, 2008; Ishizuka et al, 2012; Pinato et al, 2012). Moreover, Smith et al (2009) have demonstrated that the platelet to lymphocyte ratio (PLR) is a significant prognostic marker in patients with pancreatic cancer, and Kasymjanova et al (2010) have shown that the Prognostic Index (PI) as evidenced by a combination of serum the CRP and white cell count is a significant prognostic marker in patients with lung cancer. Recently, in a Glasgow Inflammation Outcome Study, Proctor et al (2011a) compared the prognostic value of these inflammation-based prognostic scores (the modified GPS, NLR, PLR, PI, and PNI) in patients with a variety of cancers including ‘hepatopancreaticobiliary cancer’ and shown that modified GPS and PI have prognostic value in cancer independent of the tumour site. However, hepatopancreaticobiliary cancer includes pancreatic cancer and biliary tract cancer besides HCC in their study. Consequently, which inflammation-based prognostic scores is more suitable for predicting outcome in patients with HCC has not been fully elucidated.

Therefore, this study compared the prognostic value of these inflammation-based prognostic scores (the GPS, mGPS, NLR, PLR, PI, and PNI) in patients with HCC in various stages of disease and different liver functional status.

MATERIALS AND METHODS

Patients

In total, 208 patients with newly diagnosed HCC that had been treated at the Department of Gastroenterology and Hepatology,
The diagnosis of HCC was confirmed pathologically or based on imaging techniques obtained by 4-phase multidetector computed tomography (CT), or dynamic contrast-enhanced magnetic resonance imaging. Diagnosis should be based on the typical hallmark of HCC (hypoechoic in the arterial phase with washout in the portal venous or delayed phases; European Association For The Study Of The Liver and European Organisation For Research And Treatment Of Cancer, 2012). Tumour-related variables such as maximal tumour diameter, tumour number, vascular invasion, and extra hepatic metastases were evaluated by these imaging techniques. The clinical stage (TNM classification) was determined according to the Liver Cancer Study Group of Japan (Minagawa et al, 2007).

This study complied with the standards of the Helsinki Declaration and current ethical guideline and was approved by the Institutional Ethical Board.

Inflammation-based prognostic scores and other variables

Blood samples were obtained before initial treatment for measurement of CRP, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, white blood cell count, neutrophil, lymphocyte, platelet (Plt) count, prothrombin time, and α-fetoprotein level (AFP). Cancer Liver Italian Programme was calculated based on these variables and imaging techniques.

The GPS, mGPS, NLR, PLR, PI, and PNI were constructed as described in Table 1.

| Scoring systems | Score |
|-----------------|-------|
| The GPS         |       |
| CRP (≤10mg/l−1) and albumin (≥35g/l−1) | 0     |
| CRP (≤10mg/l−1) and albumin (≥35g/l−1) | 0     |
| CRP (≥10mg/l−1) and albumin (≤35g/l−1) | 1     |
| CRP (≥10mg/l−1) and albumin (≤35g/l−1) | 1     |
| The modified GPS |       |
| CRP (≤10mg/l−1) and albumin (≥35g/l−1) | 0     |
| CRP (≤10mg/l−1) and albumin (≥35g/l−1) | 0     |
| CRP (≥10mg/l−1) and albumin (≤35g/l−1) | 2     |
| Neutrophil lymphocyte ratio          |       |
| Neutrophil count : lymphocyte count < 5 : 1 | 0     |
| Neutrophil count : lymphocyte count ≤ 5 : 1 | 1     |
| Plt lymphocyte ratio                |       |
| Plt count : lymphocyte count < 150 : 1 | 0     |
| Plt count : lymphocyte count ≥ 150 : 1 | 1     |
| Plt count : lymphocyte count > 300 : 1 | 2     |
| Prognostic index                    |       |
| CRP (≤10mg/l−1) and white cell count (≤11×109/l−1) | 0     |
| CRP (≤10mg/l−1) and white cell count (≤11×109/l−1) | 0     |
| CRP (≥10mg/l−1) and white cell count (≥11×109/l−1) | 1     |
| CRP (≥10mg/l−1) and white cell count (≥11×109/l−1) | 1     |
| PNI                              |       |
| Albumin (g/l−1) + 5 × total lymphocyte count × 109/l−1 ≥ 45 | 0     |
| Albumin (g/l−1) + 5 × total lymphocyte count × 109/l−1 < 45 | 1     |

Inflammation-based prognostic scores in HCC

A Kinoshita et al

Treatment and patient’s follow-up

The indications for surgical resection were patients with solitary lesion, Child-Pugh grade A, no main portal vein trunk involvement, or distant metastasis. Radiofrequency ablation (RFA) or percutaneous ethanol injection was performed for patients with lesions <3 cm in size and <3 in number. Transcatheter arterial chemoembolisation (TACE) or lipiodol-transcatheter arterial infusion (TATI) was performed for patients with >4 multiple lesions or those >3 cm in size. Systemic chemotheraphy or targeted therapy including sorafenib was performed for patients with distant metastasis and preserved liver function. Only the best supportive care (BSC) was given for patients with Child-Pugh grade C or distant metastasis.

Patients were followed carefully after the initial treatment. The serum AFP was measured once every month. US and dynamic CT were performed every 3 months. A selective hepatic arterial angiography or a percutaneous biopsy was performed in patients with suspected tumour recurrence. The start date of follow-up was the date of initial diagnosis of HCC. The end of follow-up was the time of last follow-up (October 2011) or death.

Statistical analysis

Continuous variables are presented as the median and range. Categorical variables are presented as the number and percentages. The overall survival rates were calculated using the Kaplan–Meier method, and differences in the survival rates between the groups were compared by the log-rank test. A receiver operating characteristics (ROC) curve was also generated and the area under the curve (AUC) was calculated to evaluate the discriminatory ability.
of each scoring systems. A univariate and multivariate analysis was performed for the prognostic factors using the Cox proportional hazard model. Variables that proved to be significant in the univariate analysis were tested subsequently with the multivariate Cox proportional hazard model. The forward selection method was used for multivariate Cox proportional analysis. A $P$-value $<0.05$ was considered to be significant. All statistical analysis was performed using the IBM SPSS Statistics software package v.19.0 (IBM SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

The baseline characteristics of the patients are shown in Table 2. The median age of the patients was 72 (range 43–91) years. One hundred and six (70.7%) patients were males and 44 (29.3%) patients were females. Eighty-four (56%) patients were positive for antibodies to hepatitis C virus (anti-HCV), 20 (13.3%) patients were positive for hepatitis B surface antigen. One hundred and seven patients (71.3%) had preserved liver function (Child-Pugh A grade), and 78 patients (52%) were classified as stage I or II. Surgical resection was performed in 9 (6%) patients, TACE or RFA were administered in 134 (89.3%) patients. The remaining 7 (4.7%) patients received BSC.

Thirty-one (20.7%) patients had an elevated CRP level ($>10$ g/l) and 58 (38.7%) patients had hypoalbuminemia ($<3.5$ g/l). Twenty (13.3%) patients had both elevated CRP level and hypoalbuminemia. Eighty-one (54%) patients were allocated to GPS 0, 49 (32.7%) patients were allocated to GPS 1, and 20 (13.3%) patients were allocated to GPS 2, respectively. In contrast, 119 (79.3%) patients were allocated to mGPS 0, 11 (7.3%) patients were allocated to mGPS 1, and 20 (13.3%) patients were allocated to mGPS 2, respectively. Three (0.02%) patients had an elevated white cell count ($>11 \times 10^9$ l$^{-1}$), 5 (3.3%) patients an elevated neutrophil count ($>7.5 \times 10^9$ l$^{-1}$), 29 (19.3%) patients a lowered lymphocyte count ($<1.0 \times 10^9$ l$^{-1}$), and 2 (1.3%) patients an elevated platelet count ($>400 \times 10^9$ l$^{-1}$). Fifteen patients (10%) had NLR $>5$, 32 patients (21.3%) had PLR $>150$, and 78 patients (52%) had PNI $<45$. Thirty-three patients (22%) were allocated to PI1 or 2.

Survival

The median duration of follow-up was 18 (range 1–80) months. Seventy-seven (51.3%) patients were alive at the end of the follow-up period, and 73 (48.7%) patients had died. The 1-year, 3-year, and 5-year overall survival rates were 74.1%, 53.3%, and 28.4%, respectively.

The relationship between the inflammation-based prognostic scores and overall survival is shown in Figures 1A–F. An elevated GPS, mGPS, NLR, PLR, PI, and PNI were associated with a reduced overall survival ($\forall P<0.05$). Receiver operating characteristic curves were constructed for survival status at 6-month, 12-month, and 24-month follow-up, and the area under the ROC curve (AUC) was compared (Table 3, Figures 2A–C) to assess the discrimination ability of each scoring

![Figure 1](image)

The relationship between the inflammation-based prognostic scores and overall survival in patients with HCC. (A) GPS, (B) modified GPS, (C) NLR, (D) PLR, (E) PI, and (F) PNI.
system. The GPS consistently had a higher AUC value at 6 month (0.768), 12 month (0.787), and 24 month (0.758) in comparison with other inflammation-based prognostic scores.

**Prognostic factors**

The univariate analysis showed that AST (P = 0.001), total serum bilirubin (P < 0.0001), albumin (P < 0.0001), pretreatment serum CRP level (P < 0.0001), AFP (P < 0.0001), Child-Pugh grade, CLIP (P < 0.0001), TNM (P < 0.0001), maximal tumour diameter (P < 0.0001), multiple nodules (P < 0.0001), vascular invasion (P < 0.0001), extrahepatic metastasis (P = 0.001), GPS (P < 0.0001), mGPS (P < 0.0001), NLR (P = 0.01), PLR (P = 0.01), PI (P < 0.0001), and PNI (P < 0.0001) were associated with overall survival (Table 4).

**Table 3** Comparison of the AUC between inflammation-based prognostic scores

| Period    | AUC     | 95% CI      | P-value |
|-----------|---------|-------------|---------|
| 6-Month   |         |             |         |
| GPS       | 0.768   | 0.655–0.882 | <0.0001 |
| Modified GPS | 0.734 | 0.604–0.864 | <0.0001 |
| NLR       | 0.628   | 0.487–0.769 | 0.056   |
| PLR       | 0.697   | 0.565–0.830 | 0.003   |
| PI        | 0.747   | 0.622–0.873 | <0.0001 |
| PNI       | 0.675   | 0.562–0.787 | 0.009   |
| 12-Month  |         |             |         |
| GPS       | 0.787   | 0.699–0.876 | <0.0001 |
| Modified GPS | 0.752 | 0.650–0.855 | <0.0001 |
| NLR       | 0.592   | 0.480–0.703 | 0.092   |
| PLR       | 0.694   | 0.588–0.801 | <0.0001 |
| PI        | 0.759   | 0.659–0.860 | <0.0001 |
| PNI       | 0.663   | 0.566–0.760 | 0.003   |
| 24-Month  |         |             |         |
| GPS       | 0.758   | 0.667–0.848 | <0.0001 |
| Modified GPS | 0.695 | 0.595–0.795 | <0.0001 |
| NLR       | 0.552   | 0.445–0.659 | 0.344   |
| PLR       | 0.63    | 0.526–0.735 | 0.018   |
| PI        | 0.695   | 0.595–0.795 | <0.0001 |
| PNI       | 0.699   | 0.601–0.798 | <0.0001 |

Abbreviations: AUC = area under the curve; CI = confidence interval; GPS = Glasgow prognostic score; NLR = neutrophil/lymphocyte ratio; PI = prognostic index; PLR = platelet (Plt)/lymphocyte ratio; PNI = prognostic nutritional index.

**Table 4** Prognostic factors for overall survival in patients with HCC. Univariate and multivariate analyses

| Variable                        | Univariate analysis | Multivariate analysis |
|---------------------------------|---------------------|-----------------------|
|                                 | P-value             | Hazard ratio (95% CI) | P-value |
| Age                             | 0.776               | 0.8                 | 0.01    |
| Sex (male/female)               | 0.352               | 0.6                 | 0.50    |
| AST (IU/L)                      | 0.001               | 0.001               | 0.001   |
| ALT (IU/L)                      | 0.053               | 0.6                 | 0.50    |
| Total serum bilirubin (mg/dL)   | <0.0001             | 1.777               | 1.242–2.545 | 0.002 |
| Albumin (g/L)                   | <0.0001             | 2.246               | 1.786–2.824 | 0.0001|
| CRP (mg/L)                      | <0.0001             | 0.112               | 0.089   |
| WBC (×10^3/μL)                  | 0.0001              | 0.0001              | 0.0001  |
| Platelet count (×10^3/μL)       | 0.12                | 0.0001              | 0.0001  |
| AST (IU/L)                      | 0.001               | 0.0001              | 0.001   |
| ALT (IU/L)                      | 0.001               | 0.0001              | 0.001   |
| Child-Pugh grade (A/B/C)        | <0.0001             | 0.0001              | 0.0001  |
| CLIP score (0/1/2/3/4/5/6)      | <0.0001             | 0.0001              | 0.0001  |
| Tumour stage (I/II/III/IV)      | <0.0001             | 0.0001              | 0.0001  |
| Maximal tumour diameter (mm)    | <0.0001             | 0.0001              | 0.0001  |
| Tumour number (solitary/multiple)|<0.0001             |<0.0001             |<0.0001  |
| Vascular invasion (absent/present)|<0.0001             |<0.0001             |<0.0001  |
| Extrahepatic metastasis (absent/present)|<0.0001       |<0.0001             |<0.0001  |
| GPS (0/1/2)                     | <0.0001             | 0.0001              | 0.0001  |
| Modified GPS (0/1/2)            | <0.0001             | 1.777               | 1.242–2.545 | 0.002 |
| NLR (0/1)                       | <0.0001             | 0.0001              | 0.0001  |
| PLR (0/1/2)                     | 0.001               | 0.0001              | 0.0001  |
| PI (0/1/2)                      | <0.0001             | 0.0001              | 0.0001  |
| PNI (0/1)                       | 0.0001              | 0.0001              | 0.0001  |

Abbreviations: AFP = a-fetoprotein level; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CLIP = the Cancer of the Liver Italian Programme; CRP = C-reactive protein; GPS = Glasgow prognostic score; HCC = hepatocellular carcinoma; NLR = neutrophil/lymphocyte ratio; PI = prognostic index; PLR = platelet (Plt)/lymphocyte ratio; PNI = prognostic nutritional index.

A multivariate analysis of these significant variables showed that only the GPS (HR 1.777, 95% CI 1.242–2.545, P = 0.002) and CLIP (HR 2.246, 95% CI 1.786–2.824, P < 0.0001) were independently associated with overall survival (Table 4).

**Figure 2** Comparison of the area under the ROC for outcome prediction between the inflammation-based prognostic scores at (A) 6 months, (B) 12 months, and (C) 24 months in patients with HCC.
DISCUSSION

This study has demonstrated that the GPS, an inflammation-based prognostic score, is an independent marker of poor prognosis in patients with HCC and is superior to the mGPS, NLR, PLR, PI, and PNI in terms of prognostic ability.

The host inflammatory response has an important role in the development and progression of cancer (Mantovani et al., 2008). Inflammation promotes tumour angiogenesis, invasion, and metastasis through recruitment of regulatory T lymphocytes and chemokines, activation of interleukin-6 and tumour necrosis factor alpha, secretion of CRP, induction of neutrophilia, subversion of adaptive immune response, and aberration of response to hormones and chemotherapeutic agents (Heikkinen et al., 2007; Mantovani et al., 2008; Wang et al., 2012).

Furthermore, the presence of an inflammatory response is proposed to be pathogenic in the development of cancer-associated malnutrition, resulting in poor performance status and increased mortality in patients with cancer (Argiles et al., 2003). This is of particular concern in patients with HCC, given the concomitant underlying illness and possible impaired nutritional status secondary to cirrhosis (Meng et al., 2010; Pinato et al., 2012).

These theoretical backgrounds have led to the proposal of several inflammation-based prognostic scores in patients with cancer over the last 10 years.

Several studies have shown that an elevated NLR is associated with poor prognosis in patients with HCC undergoing surgical resection (Gomez et al., 2008), transplantation (Halazun et al., 2009), transarterial chemoembolisation (Huang et al., 2011), and RFA (Chen et al., 2012). However, the cutoff points of NLR in these studies were different (2.4, 3.3, and 5) and non-optimal cutoff point has been determined. This study evaluated cutoff levels of NLR at 2.4, 3.3, and 5 and revealed that the NLR was not independently associated with survival at any of the cutoff levels (data not shown). Moreover, these studies did not compare the NLR to the GPS, mGPS, PNI, PLR, and PI.

Pinato et al. (2012) demonstrated that the PNI is an independent predictor of poor overall survival in patients with HCC in various stages of the diseases and different liver functional status. However, their study did not compare the PNI with the GPS, mGPS, NLR, PLR, and PI.

The univariate analysis in this study demonstrated that the GPS, mGPS, NLR, PLR, PNI, and the PI were significantly associated with overall survival. However, the multivariate analysis showed that only the GPS was independently associated with overall survival. Moreover, the AUC analysis has shown that the GPS was superior to other inflammation-based prognostic scores in terms of predictive accuracy. These results confirm Ishizuka’s study demonstrating the predictive usefulness of the GPS on survival in patients with HCC after surgical resection (Ishizuka et al., 2012). In addition to their study, this study showed the superior prognostic ability of the GPS over the mGPS, NLR, PLR, PI, and PNI. This study is the first to show the GPS to be superior to other inflammation-based prognostic scores for the prediction of prognosis in patients with HCC.

A Glasgow Inflammation Outcome Study conducted by Proctor et al. (2011a) showed that mGPS has prognostic value in cancer independent of the tumour site and was superior to other inflammation-based prognostic scores in terms of differentiating good from poor prognostic groups. Proctor et al. (2011b) also indicated that mGPS is superior to the original GPS and has greater consistency and is more useable. Their observations were based on the results that a low albumin concentration alone was uncommon (<10% of all patients) and was not significantly associated with cancer-specific survival in many cancers including hepatopancreatobiliary cancer (P = 0.209). In contrast, this study included 38 (25.3%) patients with low albumin concentration alone and the serum albumin level is one of the components of the Child-Pugh classification. In fact, hypoalbuminemia is reported to as an independent poor prognostic factor in patients with HCC (Cho et al., 2008). Moreover, “hepatopancreatobiliary cancer” includes pancreatic cancer and biliary tract cancer besides HCC in a Glasgow Inflammation Outcome Study. Therefore, the GPS may be more suitable than mGPS for patients with HCC.

Impaired nutritional status and elevated levels of acute-phase plasma proteins have been associated with increased toxicity from chemotherapy. There is evidence from preclinical and clinical studies in cancer and other inflammatory diseases that disease-associated cytokines responsible for the hepatic acute-phase response may also reduce the expression and protein levels of a number of drug-metabolising enzymes and transporters, especially cytochrome P450 3A4. This results in increased toxicity during chemotherapy (Kasymjanova et al., 2010; Clarke et al., 2011). Accordingly, the GPS reflecting both the presence of the systemic inflammatory response and the progressive nutritional decline might provide substantial opportunities for clinicians to predict and reduce toxicities in HCC patients undergoing transarterial chemoembolisation or sorafenib treatment (Clarke et al., 2011). Further evaluation is required to confirm this hypothesis.

A potential limitation of this study is that is a retrospective, single-centre study. Therefore, a large-scale prospective validation study is needed to confirm the results.

In conclusion, our study has demonstrated that the GPS, an inflammation-based prognostic score, is an independent marker of poor prognosis in patients with HCC and is superior to the other inflammation-based prognostic scores in terms of prognostic ability.

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