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Systematic Evaluation of Serum Inflammatory Markers for Prognostication of Hepatocellular Carcinoma (HCC)

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BACKGROUND

It is evident that systemic inflammation plays a prognostic role in hepatocellular carcinoma (HCC). Different markers including C-reactive protein (CRP) and various interleukins have been shown to be prognostic factors for HCC. There have been no large scaled study to simultaneously evaluate the prognostications of multiple markers together.

OBJECTIVES

- To determine the individual ability of a panel of circulating inflammatory markers for prognostication of HCC.
- To study the additional prognostic value of these markers on existing tumor staging systems for HCC.

METHODOLOGY

- From Jan 2007 – Dec 2011, our group recruited a prospective cohort of 600 patients with HCC seen in the multi-disciplinary joint hepatoma clinic.
- Consented patients underwent evaluation by clinical investigators.
- Plasma samples and all clinical information including tumor staging were collected at the time of consent.
- The serum samples were then subjected to a multiplex cytokine assays testing 43 inflammatory cytokines and C-reactive protein (Eve Technologies, Alberta, Canada).
- All patients were followed up according to the standard local practice, and all the study-related procedures were endorsed by the ethics committee. The prognostications of baseline level of all inflammatory markers are evaluated by univariate and multivariate analyses.

RESULTS

Baseline Characteristics (Table 1)

Serum samples from 600 patients were analyzed, of which 560 of them are eligible for analyses. The median follow-up is 39 months and the median overall survival is 8.6 months (7.3-9.9 months).

- *Key features*
  - *The median age is 60 years (Range 18-88).*
  - *In the cohort, 443 patients (79.1%) and 74 (13.2%) have hepatitis B and C virus infection, respectively.*
  - *The mean tumor diameter was 8.55cm.*
  - *The BCLC Stage distribution of 0/A, B, C and D is 15.7%, 23.6%, 55.2% and 5.5%, respectively.*
  - *Total 102 patients underwent treatment of curative intent (64 surgery; 38 locoablation) while the remaining patients (n=458) received treatment of palliative intent.*

Table 1: Summary of the Baseline Characteristics of Patients (N=560)

Number of Eligible Cases	N=560		
Age:		First-line treatment:	
Median (Range)	60; (18-88)	*Curative intent*	102 (18.2)
Sex (Male: Female)	495:65	-Hepatectomy	64 (62.7)
ECOG:		-Liver transplantation	0
0	177 (31.6)	-Locoablative therapy	38 (37.3)
1	350 (62.5)	*Palliative intent*	458 (81.8)
2	25 (4.5)	-TACE or other transarterial therapy	124 (27.1)
3	8 (1.4)	-Systemic therapy (sorafenib, chemotherapy, clinical trial)	119 (26.0)
Etiology (%)		-Best supportive care	215 (46.9)
- HBV & HCV	6 (1.1)	Vascular Invasion (%)	187 (33.4)
- HBV	443 (79.1)	Tumor Staging	
- HCV	37 (6.6)	BCLC	
- Alcoholic	0 (0)	0/A	88 (15.7)
- other	74 (13.2)	B	132 (23.6)
Cirrhosis (%)	323 (57.7)	C	309 (55.2)
Ascites (%)	145 (25.9)	D	31 (5.5)
Symptomatic at presentation (%)	395 (70.5)	HBsAg positive	449 (80.3)
		Anti-HCV positive	43 (7.7)

(Abbreviations: ECOG: Eastern Cooperative Oncology Group; HBV: Hepatitis B virus; HCV: Hepatitis C virus; TACE, Transarterial Chemoembolization)

Univariate Analyses on Serum Inflammatory Factors (Table 2)

In the univariate analyses, TGFα, Factalkine, IFNα2, INFγ, Chemokine (C-X-C motif) ligand 1, Macrophage-derived chemokine (MDC), Interleukin (IL)-6, IL-7, IL-8, IL-10, IL-17A, IP-10, MIP-1α, TNF-α, VEGF-A, CRP are all prognostic factors for HCC.

Table 2: Univariate Analyses on All the Prognostic Factors for HCC

Marker	N	p-value	Hazard Ratio	95% CI for HR
Transforming growth factor-alpha (TGFα)	555	0.0042	1.253	1.074-1.463
Factalkine	558	<0.0001	1.346	1.163-1.557
Interferon, alpha 2 (IFNα2)	554	0.0074	1.184	1.046-1.340
Interferon-gamma (INFγ)	560	0.0297	1.138	1.013-1.278
Chemokine (C-X-C motif) ligand 1 (GRO pan)	560	0.0007	1.495	1.184-1.888
Interleukin-10 (IL-10)	500	0.0003	1.323	1.137-1.539
Macrophage-derived chemokine (MDC)	560	0.0380	0.724	0.534-0.982
Interleukin-17A (IL-17A)	553	0.0019	1.212	1.074-1.368
Interleukin-6 (IL-6)	509	<0.0001	1.453	1.283-1.646
Interleukin-7 (IL-7)	515	0.0048	1.258	1.073-1.475
Interleukin-8 (IL-8)	558	<0.0001	2.665	2.263-3.138
Interferon gamma-induced protein 10 (IP-10)	560	<0.0001	2.147	1.678-2.748
Macrophage inflammatory protein 1 alpha (MIP-1α)	484	0.0419	1.229	1.008-1.498
Tumor necrosis factor alpha (TNF-α)	560	0.0069	1.345	1.085-1.668
Vascular endothelial growth factor-A (VEGF-A)	544	0.0285	1.205	1.020-1.423
C-reactive protein (CRP)	560	<0.0001	4.132	3.166-5.392

Multivariate Analyses (Table 3 & 4)

•Multivariate analyses idenfitied four serum inflammatory markers, namely IL-8 (HR=2.62), CRP (HR=2.895), IP-10 and MDC, to be independent prognostic factors for HCC (all p<0.0001). The prognostications of these markers are independent of BCLC staging system. (Table 3)

•It is found that the 4 inflammatory markers confer additional prognostic value on existing tumor staging systems including BCLC, CLIP and CUPI. These findings indicate a role of combining inflammatory markers and staging systems. (Table 4)

Table 3: Multivariate Analysis on All Serum Inflammatory Markers

Marker	N	p-value	Hazard Ratio (HR)	95% CI for HR
IL-8	527	<0.0001	2.616	2.156-3.173
CRP	527	<0.0001	2.895	2.172-3.858
IP-10	527	<0.0001	2.193	1.709-2.815
MDC	527	<0.0001	0.408	0.298-0.560

Table 4: Multivariate Analysis of Serum Inflammatory Markers and Staging System

a.BCLC plus four markers. (N=558)

Label	N	p-value	HR	95% CI for HR
BCLC staging	558	<0.0001	1.994	1.702-2.336
IL-8	558	<0.0001	2.297	1.895-2.786
MDC	558	<0.0001	0.450	0.334-0.606
CRP	558	<0.0001	1.780	1.387-2.285
IP-10	558	<0.0001	1.780	1.702-2.336

AIC = 4567.099

b. CLIP plus four markers. (N=558)

Label	N	p-value	HR	95% CI for HR
CLIP staging	558	<0.0001	1.627	1.496-1.770
IL-8	558	<0.0001	2.096	1.690-2.599
MDC	558	<0.0001	0.531	0.389-0.725
CRP	558	0.0002	1.733	1.297-2.316
IP-10	558	0.0004	1.586	1.231-2.043

AIC = 4512.453

c. CUPI plus four markers. (N=558)

Label	N	p-value	HR	95% CI for HR
CUPI staging	558	<0.0001	2.062	1.755-2.422
IL-8	558	<0.0001	1.910	1.553-2.349
MDC	558	<0.0001	0.542	0.399-0.735
CRP	558	<0.0001	2.092	1.580-2.769
IP-10	558	<0.0001	1.818	1.755-2.422

AIC= 4571.093

CONCLUSIONS

Four serum markers reflective inflammation, namely IL-8, CRP, IP-10 and MDC, are independent prognostic factors. This panel of markers could add additional prognostic information on existing staging system. (Supported by Hong Kong Research Grants Council General Research Fund [No. 462013])

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