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Research Article

Prognostic value of the Gustave Roussy immune score across etiological subtypes in hepatocellular carcinoma

Hepatoselüler kanserde etiyolojik alt tiplere göre Gustave Roussy immün skorunun prognostik değeri

İlknur Deliktaş Onur [1*], Hatice Gülgün Fırat [2], Alper Türkel[1], Elif Sertesen Çamöz[1], Necla Demir[1], Fatih Yıldız [1]

[1]Department of Medical Oncology, Dr. Abdurrahman Yurtaslan Ankara Oncology Education and Research Hospital, Health Sciences University, Ankara, Turkey.

[2]Department of Internal Medicine, Dr. Abdurrahman Yurtaslan Ankara Oncology Education and Research Hospital, Health Sciences University, Ankara, Turkey.

Abstract

Aim: The prognostic efficiencies of Gustave Roussy immune (GRIm) and HCC-GRIm scores in hepatocellular carcinoma (HCC) have been determined in previous studies. However, there is no study evaluating them according to etiological subtypes in the literature yet. This study aimed to investigate the prognostic efficacy of GRIm in HCC etiological subgroups.

Material and Methods: The study was conducted on patients aged 18 years and older with unresectable/metastatic HCC diagnosed between 2017 and 2023. One hundred twenty-four patients were included in the study. GRIm scores were calculated, and their prognostic efficiencies were evaluated.

Results: Sixty-seven (54%) of the patients had low GRIm scores, while 68 (54.8%) had low HCC-GRIm scores. Median overall survival (OS) was 17.2 months in patients with low-viral GRIm scores, while median OS was 2.1 months in patients with high-viral GRIm scores. Median OS was 12.6 months in patients with low nonviral GRIm scores, and 3.3 months in patients with high nonviral GRIm scores (HR: 2.4; 95% CI: 1.3-4.7; $p < 0.001$).

Conclusions: We found that GRIm score was prognostic in terms of OS in HCC. GRIm scores were higher in patients with viral etiology. However, when we evaluated the patients with low/high GRIm scores in terms of viral/nonviral etiology, there was no significant difference in OS. We believe that the GRIm score may assist clinicians in stratifying prognosis among unresectable/metastatic HCC patients regardless of etiology. Larger-scale studies investigating prognosis and treatment efficacies in etiological subtypes of HCC are needed.

Keywords: HCC-GRIm score, GRIm score, HCC, HCC etiology, HCC prognostic score

Corresponding Author*: İlknur Deliktaş Onur, MD. Dr. Abdurrahman Yurtaslan Ankara Oncology Education and Research Hospital, Department of Medical Oncology, 06200 Yenimahalle/Ankara, Turkey.
E-mail: ilknurdeliktas382@gmail.com
Orcid: 0000-0001-9884-5789
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Öz

Amaç: Hepatoselüler kanserde (HCC) Gustave Roussy immün (GRIm) skorunun prognostik etkinliği önceki çalışmalarla belirlenmiştir. Ancak literatürde henüz bu skoru etiyolojik alt tiplere göre değerlendiren bir çalışma bulunmamaktadır. Bu çalışmanın amacı, HCC etiyolojik alt gruplarında GRIm skorunun prognostik etkinliğini araştırmaktır.

Gereç ve Yöntemler: Çalışmaya, 2017-2023 yılları arasında tanı almış, rezeke edilemeyen/metastatik HCC tanılı 18 yaş ve üzeri 124 hasta dahil edildi. Hastaların tanı anındaki GRIm skorları hesaplandı ve bu skorların prognostik etkinlikleri değerlendirildi.

Bulgular: Hastaların 67'sinde (%54) düşük GRIm skoru, 68'inde (%54,8) ise düşük HCC-GRIm skoru saptandı. Düşük GRIm skorlu viral etiyolojili hastalarda ortanca genel sağkalım (OS) 17,2 ay iken, yüksek GRIm skorlu viral etiyolojili hastalarda ortanca OS 2,1 ay olarak bulundu. Düşük GRIm skorlu nonviral etiyolojili hastalarda ortanca OS 12,6 ay iken yüksek GRIm skorlu nonviral hastalarda ortanca OS 3,3 ay olarak bulundu (HR: 2,4; %95 GA: 1,3-4,7; $p < 0,001$).

Sonuç: HCC'de GRIm skorunun OS açısından prognostik olduğu tespit edildi. Viral etiyolojili hastalarda GRIm skorları daha yüksekti. Ancak düşük/yüksek GRIm skorlu hastalar viral/nonviral etiyoloji açısından değerlendirildiğinde OS açısından anlamlı bir fark bulunamadı. GRIm skorunun, etiyolojiden bağımsız olarak, rezeke edilemeyen/metastatik HCC hastalarında prognozu belirlemede klinisyenlere yardımcı olabileceği düşünülmektedir. HCC'nin etiyolojik alt tiplerinde prognoz ve tedavi etkinliğini araştıran daha geniş ölçekli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: HCC-GRIm skoru, GRIm skoru, HCC, HCC etiyolojisi, HCC prognostik skoru

Introduction

Hepatocellular carcinoma (HCC) is a malignant tumor of the liver and has a poor prognosis. [1] Although systemic treatment options for HCC have been developed, especially in the last decade [3], sorafenib has been used in systemic treatment for a long time [4]. Recent studies have shown that atezolizumab-bevacizumab combination [5] and durvalumab-tremelimumab combination [6] are superior to sorafenib. However, the response rates of these treatments are not very high. In this disease with a poor prognosis, markers that will predict both prognosis and treatment response are the subject of research. Although it is known that the prognosis and treatment responses of HCC differ according to its etiology, prognostic markers have not yet been evaluated separately in etiological subtypes.

Gustave Roussy Immun Score (GRIm score) is a score that is an indicator of nutrition and inflammation. [7] Studies have shown that it is prognostic for survival in some cancer subtypes, regardless of treatment. [8-9]. There is no study yet showing the effectiveness of the GRIm score in etiological differences.

The relationship between GRIm score and OS in etiological subgroups of HCC patients was evaluated. We hypothesized that GRIm score would retain prognostic significance independent of HCC etiology.

Materials and Methods

The study was conducted with 124 HCC patients aged 18 years and over, diagnosed from February 2017 to October 2023. Patients with unresectable/metastatic. The study was conducted with patients with HCC who were not suitable for curative treatment; BCLC stage A patients who underwent curative treatment with surgical resection or local ablative methods and patients who underwent transplantation were excluded from the study.

Patients' diagnosis and treatment information from hospital records were retrospectively reviewed. Patients' gender, date of diagnosis, age at diagnosis, HCC etiology, whether they received systemic treatment, Child Pugh score, Barcelona stage, Meld score, and ECOG PS scores were recorded. All our patients diagnosed with HCC are evaluated for chronic viral hepatitis. Viral hepatitis evaluation of all our patients was available in our database. Patients diagnosed with hepatitis B and C were grouped as patients with HCC due to viral etiology. NASH (non-alcoholic fatty liver) and other factors were grouped as

HCC patients with nonviral etiology. For the diagnosis of HCC developing on the basis of chronic HBV, HBV DNA level above 2000 units in addition to HBSAG positivity was considered significant. HCV RNA positivity as well as anti-HCV positivity were considered significant for the diagnosis of HCC developing on the basis of chronic HCV. All patients whose files did not contain sufficient data to calculate the GRIm score, and whose etiological subtype could not be determined, were excluded from the study. All patients with missing data were removed from the analysis using listwise deletion.

GRIm score was calculated by serum albumin level (<3.5 = 1 point), serum LDH level (>220 = 1 point), and serum NLR (>6 = 1 point). 0-1 points were low risk; 2-3 points were high risk.

The study, approval was obtained from the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Education and Research Hospital (2023-11/116). Since it was a retrospective file study; the ethics committee did not require consent from the patients. The study was conducted ethically in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analysis was performed using IBM-SPSS version 23.0. Comparisons of categorical data between two independent groups were made using the chi-square test. Overall survival (OS) was calculated by the Kaplan-Meier method. Age, gender, ECOPG PS, BCLC stage, whether TACE-TARE was performed or not, whether the patient received systemic treatment or not, Child Pugh stage, etiology of the disease, GRIM score were evaluated in univariate analysis. Some of these factors are known to be prognostic in HCC, and as we hypothesized, we investigated the relationship between etiology and GRIm score and survival. Variants with $p < 0.05$ in univariate analysis were considered significant and were evaluated in multivariate analysis. In multivariate analysis, Cox regression was used.

Results

Seventy-seven (62.1%) of the patients developed HCC with viral etiology, while 47 (37.9%) had non-viral HCC. All patients receiving systemic therapy received sorafenib.

GRIm score of 67 (54.0%) of the patients was calculated to be low, the GRIm score of 57 (46.0%) was calculated to be high. Demographic characteristics are shown in Table 1.

Table 1. Demographic characteristics of patients.

	N(%):124(100)
Age(median) (mın-max)	64(22-82)
Sex	
Female	20 (16.1)
Male	104(83.9)
Comorbidity	
Yes	112(90.3)
No	12(9.7)
ECOG PS	
0-1	85(68.5)
≥2	39(31.5)
BCLC	
B	45(36.3)
C	69(55.6)
D	10(8.1)
TACE-TARE	
Yes	68(54.8)
No	56(45.2)
Systemic Treatment (Sorafenib)	
Yes	80(64.5)
No	44(35.5)
Child Pugg Score	
A	57(46.0)
B	57(46.0)
C	10(8.0)
Etiology	
Viral	77(62.1)
Nonviral	47(37.9)
GRIm score	
Low (0-1)	67(54.0)
High (2-3)	57(46.0)

ECOG PS: Eastern Cooperative Oncology Group Performans Status, BCLC: Barcelona Clinic Liver Cancer, HCC: Hepatocellular cancer, TACE: Transarterial Chemoembolization, TARE: Transarterial GRIm score: Gustave Roussy Immun Score.

The GRIm ($p = 0.018$) score was higher in patients with ECOG PS 2-3. GRIm score ($p < 0.001$) was higher in those with BCLB stage C. GRIm score was significantly higher in those with Child-Pugh scores B and C compared to those with Child-Pugh scores A ($p = 0.001$). There was a significant relationship between etiology and GRIm score ($p = 0.03$). GRIm score was higher in viral etiology. Characteristics of the patients according to GRIm score are summarized in Table 2.

Median follow-up was 31 months. Median OS was 7.8 (95% CI 5.2-10.4) months in all patients, 13.6 (95% CI 5.8-21.4) months in the low GRIm score group, and 2.4 (95% CI 1.2-3.6) months in the high GRIm score group. We also evaluated OS in etiological subgroups. As shown in Table 3, OS in the group

with low GRIm score-viral etiology was significantly better than the group with high GRIm score-viral etiology (17.2 months vs 2.1 months, p < 0.001). OS in the group with low GRIm score nonviral etiology was significantly better than the group with high GRIm score nonviral etiology (12.6 months vs 3.3 months p < 0.001) (Figure 1).

In univariate analysis, ECOG PS (p < 0.001), BCLC (p < 0.001) stage, Child Pugh stage (p < 0.001), GRIm score (p < 0.001), receiving systemic treatment (p > 0.01), and performing the TACE-TARE (p < 0.001) were significant prognostic variables for OS. In multivariate analysis, ECOG PS (p = 0.014), GRIm score (p = 0.005), Child Pugh stage (p = 0.020), and receiving systemic treatment (p = 0.013) were independent for OS was prognostically variable. Results of univariate and multivariate analyses to predict survival are presented in Table 4.

Table 2. Patient characteristics according to GRIm score.

	GRIm score n (%)		
	Low	High	P*
Age			0.27
<65	29(43.2)	36(63.2)	
≥65	38(56.8)	21(36.8)	
Sex			0.69
Female	10(14.9)	10(17.5)	
Male	57(85.1)	47(82.5)	
Comorbidity			0.76
Yes	61(91.2)	51(89.5)	
No	6(8.9)	6(10.5)	
ECOG PS			0.018
0-1	52(77.6)	33(57.8)	
≥2	15(22.4)	24(42.2)	
BCLC			<0.001
B	32(47.8)	13(22.8)	
C	34(50.7)	35(61.4)	
D	1(1.5)	9(15.8)	
TACE-TARE			<0.001
Yes	50(74.6)	18(31.5)	
No	17(25.4)	39(68.5)	
Systemic treatment (Sorafenib)			0.072
Yes	48(71.6)	32(56.2)	
No	19(28.4)	25(43.8)	
Child Pugg Score			0.001
A	43(64.2)	14(24.5)	
B	23(34.3)	34(59.7)	
C	1(1.5)	9(15.8)	
Etiology			0.03
Viral	36(53.7)	41(71.9)	
Nonviral	31(46.3)	16(28.1)	

* Chi-square test ECOG PS: Eastern Cooperative Oncology Group Performance Status, BCLC: Barcelona Clinic Liver Cancer, HCC: Hepatocellular cancer, Tace: Trans arterial Chemoembolization, Tare: Trans arterial Radioembolization, GRIm score: Gustave Roussy Immun Score, HCC-GRIm score: HCC-Gustave Roussy Immun Score

Table 3. Overall survival analysis according to GRIm score.

Groups	Median OS (months) (%95 CI)	
GRIm score	Viral	Nonviral
Low	17.2(10.6-23.8)	12.6(2.7-22.5)
High	2.1(0.5-3.6)	3.3(0.8-5.9)
P*	<0.001	<0.001

Abbrev.: GRIm score: Gustave Roussy Immun Score, CI: Confidence Interval *Log Rank Test

Table 4. Univariate and multivariate analyses of factors related to overall survival.

Factor	Univariate analysis	Multivariate analysis	
	P	HR (%95 CI)	P*
Age (<65 vs ≥65)	0.39		
Sex	0.80		
ECOG PS	<0.001	1.8(1.1-3.0)	0.014
BCLC stage	<0.001	1.4(0.9-2.2)	0.099
TACE-TARE	<0.001	1.1(0.6-1.7)	0.68
Systemic treatment	<0.001	0.5(0.3-0.8)	0.013
Child Pugg Stage	<0.001	1.7(1.0-2.6)	0.020
Etiology	0.42		
GRIm Score	<0.001	2.4(1.3-4.7)	0.005

Abbrev.: ECOG PS: Eastern Cooperative Oncology Group Performance Status, BCLC: Barcelona Clinic Liver Cancer, TACE: Trans arterial Chemoembolization, TARE: Trans arterial Radioembolization, GRIm score: Gustave Roussy Immun Score, CI: Confidence Interval, HR: Hazard Ratio * Multivariant Cox regression

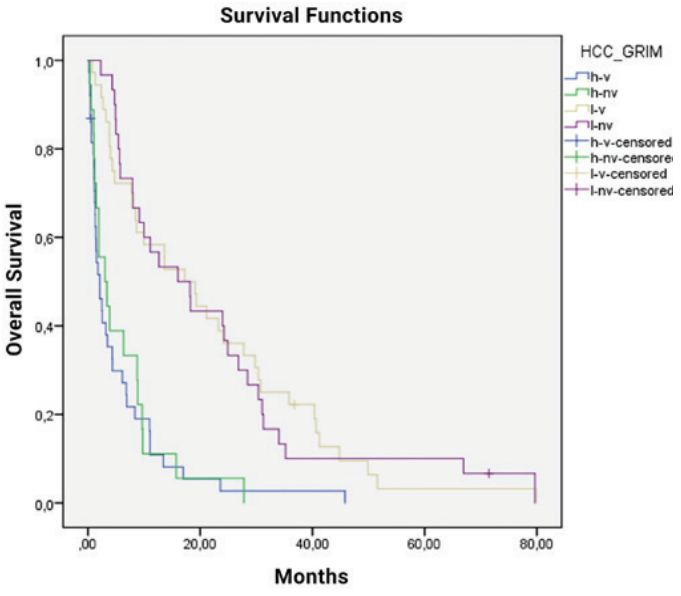

Figure 1. Kaplan-Meier curve according to GRIm score.

Discussion

We evaluated the prognostic efficacy of GRIm score in HCC etiological subgroups. We found that the GRIm score was prognostic in HCC, independent of etiological subtypes. HCC is a very complex and difficult disease to manage, and various markers are needed to predict prognosis. GRIM score is associated with survival in various solid tumors, particularly NSLC [10], resectable oesophageal cancer [11], resectable gastric cancer [12], and resectable pancreatic cancer [13]. In a meta-analysis, the relationship between GRIm score and survival was evaluated in all cancer types, grouped as gastrointestinal cancers, lung cancer, and mixed other tumors. In this meta-analysis, it was found that GRIm score was associated with survival in gastrointestinal cancers, including HCC patients [8]. In addition, in a study in which serum and ascites GRIm score was calculated in HCC patients with malignant ascites and their relationships with survival were evaluated, it was found that the relationship of ascites GRIm score with survival was superior to that of serum GRIm score [14].

The hypothesis that prognosis and treatment efficacy vary according to etiological subtypes in HCC is a subject of research in recent years. There are not enough studies evaluating it. After a meta-analysis [15-16] showed that immunotherapy efficacy was low in the non-viral group, this hypothesis was also supported in a preclinical study [17]. Prospective studies comparing treatment efficacy according to etiological subtypes in HCC are needed to clarify this issue. In addition, prognostic markers according to etiological subtypes are also needed. We evaluated whether the relationship between this score and survival in HCC patients differed according to etiological subtypes. We found a significant relationship between GRIm scores and etiology ($p = 0.03$). GRIm scores were higher in patients with viral etiology. However, when we evaluated patients with low GRIm scores in terms of viral/nonviral etiology, no significant difference was found in OS. In addition, when we evaluated the patients with high GRIm scores in terms of viral/nonviral etiology, there was no difference in OS. As a result, the GRIm score tended to be higher in patients with viral etiology, but this had no relationship with survival (Figure 1). We think that larger-volume studies are needed on this subject.

Prognostic factors for survival in HCC have been evaluated in various studies and various staging systems have been developed [18-22]. This study showed that both BCLC staging and Child-Pugh score were associated with prognosis. In addition, we found in this study that non-immunotherapy treatments, especially sorafenib, were also prognostic.

Limitations of the study

The study had limitations because it was retrospective, and the number of patients was small. Nevertheless, we believe that the number of 124 patients is sufficient for a relatively low-frequency cancer such as HCC. Another limitation is that the patients in this study group did not receive the immunotherapy-VEGF combination therapy recommended as the optimal treatment for HCC [3]. However, there are studies showing that the GRIm score is associated with survival for both HCC and other solid tumors, regardless of treatment. We also believe that this study is a valuable one, as there is no other study evaluating the relationship between GRIM score and survival in HCC etiological subtypes. External validation in an independent cohort may generalize and strengthen the findings.

In conclusion, in this study, we found that the GRIm score was prognostic in HCC, who were not suitable for definitive treatment. When we evaluated it in etiological subgroups, we found that the GRIm score was higher in viral etiology, but this was not associated with OS. We believe that further studies are needed to make this score more widely used in clinical practice. We also believe that studies are needed to predict prognosis and treatment response according to etiologic subtypes in HCC.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Ethics approval

The Clinical Research Ethics Committee of Ankara Oncology Education and Research Hospital approved the study, prior to initiation of the research work. Ethics committee code: 2023-11/116.

Authors' contribution

İDO: Conception, design, resources, materials, data collection and processing, analysis and interpretation, literature search, writing manuscript. HGF: Data collection. AT: Data collection. ESÇ: Data collection, analysis and processing. ND: Data collection. FY: Supervision, resources, materials, literature search, writing manuscript, critical review.

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