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Research Article

Prognostic Significance of the Gustave-Roussy Immune Score in Colon Cancer Patients Treated with Adjuvant CAPEOX Regimen

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Abstract

Objectives: The aim of this research was to assess the prognostic value of Gustave-Roussy immune score (GRIm-Score) in stage II and III colon cancer patients receiving capecitabine and oxaliplatin (CAPEOX).

Methods: Serum lactate dehydrogenase (LDH), neutrophil-to-lymphocyte ratio (NLR), and albumin levels were used to create the GRIm-Score. The GRIm-score was obtained with the sum of these three laboratory parameters, which were scored as 0 and 1 according to the cut-off values. A homogeneous patient group (high-risk stage II and stage III patients) was classified into two groups, one with a high GRIm-Score (score 2 and 3) and the other with a low GRIm-Score (score 0 and 1).

Results: The 4-year recurrence-free survival (RFS) was 60% in the GRIm-Score high group and 94.4% in the GRIm-Score low group (p<0.001). The 4-year overall survival (OS) was 78.1% in the GRIm-Score high group and 93.8% in the GRIm-Score low group (p<0.001). Additionally, multivariable analyses revealed that GRIm-Score (HR: 4.226, 95% CI: 1.953-9.143, p <0.001) was an independent prognostic marker for OS.

Conclusion: High GRIm-Score was significantly related to poor OS in stage II and III colon cancer patients who received CAPEOX.

Keywords: Colon cancer, survival, immune score, prognosis

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Improvements in colon cancer treatment have increased survival; however, a considerable proportion of individuals still experience disease recurrence. Previous studies have shown that nearly half of stage III colon cancer patients will relapse within 5 years following colectomy, whereas the 5-year recurrence rate for stage II colon cancer patients is between 12% and 38%.[1-3] Despite significant advancements in surgery and adjuvant treatment strategies, the search for biomarkers that can predict recurrence and survival for patients with early-stage colon cancer continues. Using prognostic indicators to identify patients with poor prognostic risk factors will be important for creating a personalized treatment plan and will increase overall survival (OS).

Inflammation has a significant impact on the formation and progression of cancer. Thanks to molecular advancements, inflammatory markers and scoring systems based on these markers have been created recently to predict prognosis

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in colon cancer patients.[4-6] Gustave-Roussy immune score (GRIm-Score) is one of these new scoring systems, and it was initially developed to improve patient screening in immunotherapy clinical trials,[7] and derived from serum lactate dehydrogenase (LDH), neutrophil to lymphocyte ratio (NLR), and albumin, was found to be a more reliable prognostic indicator for experimental trial participants. Additionally, researches on non-small cell lung cancer,[8, 9] gastric cancer,[10] and esophageal cancer[11] have demonstrated the effect of GRIm-Score on survival.

According to our knowledge, there has been only one study investigating the prognostic effect of the GRIm-Score in stage I-IV colon cancer patients; however, there has been no study investigating this score in patients who treated with the diagnosis of early-stage colon cancer.[12] The goal of this research was to assess the prognostic impact of the GRIm-Score in early-stage colon cancer patients receiving capecitabine and oxaliplatin (CAPEOX).

Methods

Patients were evaluated retrospectively from medical files and the hospital information system who treated between 2010 and 2019. The inclusion criteria were: 1) age >18 years; 2) histopathologically diagnosed with stage II or III colon adenocarcinoma after colectomy; 3) completed adjuvant capecitabine plus oxaliplatin chemotherapy; 4) continued their follow-up regularly; 5) had laboratory data such as neutrophils, lymphocytes, LDH, and albumin before chemotherapy initiation in the hospital information system. Patients whose laboratory data before starting chemotherapy could not be reached, had incomplete chemotherapy, had metastatic disease, were early-stage patients who received chemotherapy other than CAPEOX, and had additional comorbidities (congestive heart failure, chronic kidney disease, chronic liver disease, and nephrotic syndrome) that might affect OS, LDH, and albumin levels were excluded. We evaluated 262 patients, and 192 of them were included in the study. Considering that patients in different risk groups who received different adjuvant chemotherapy regimens might confuse the study results, a homogeneous patient group (high-risk stage II and stage III patients) treated with CAPEOX was selected. High-risk stage II was defined as pT4 stage or multiple intermediate risk factors (i.e., lymphatic, perineural or vascular invasion, tumor obstruction).

Serum LDH, NLR, and albumin levels were used to create the GRIm-Score. Serum albumin level, LDH level, absolute lymphocyte count, and neutrophil count before starting chemotherapy were obtained from the patient's file. The optimal cut-off values of these GRIm-Score components were obtained from the original research.[7] The optimal cut-off values were 6 for NLR, 3.5 g/dL for albumin, and 220 U/L for LDH. If NLR≤ 6, it was evaluated as NLR score: 0, if NLR> 6, it was accepted as NLR score:1. For albumin ≤ 3.5 gr/dL, it was evaluated as albumin score: 0, and for albumin >3.5 gr/dL it was assessed as albumin score:1. Similarly, whether LDH ≤ 220 U/L it was scored as 0, and LDH> 220 U/L it was defined as score 1. Afterwards, the NLR, albumin, and LDH scores were added to obtain the total GRIm-Score. While GRIm-Scores 0 and 1 were counted as low-GRIm-Score, GRIm-Scores 2 and 3 were counted as high-GRIm-Score. We classified 192 colon cancer patients into two groups, those who had a high GRIm-Score (scores 2 and 3) and those who had a low GRIm-Score (scores 0 and 1). Figure 1 illustrates the GRIm-Score classification and definition.

Statistical Analysis

The majority of continuous variables were turned into categorical categories and analyzed using Chi-squared or Fisher exact analysis. An evaluation of the relationship between NLR, albumin, and LDH was performed using the Spearman correlation method. The time between colectomy and death was defined as the OS. The time from colectomy to radiologically verified disease recurrence was used to calculate the RFS. Patients alive and recurrence-free at the time of the analysis were censored for RFS at the time of last patient contact. Survival assessments of histologic variables and prognostic markers were calculated using the Kaplan–Meier and long-rank tests. Univariate Cox regression analysis was used to investigate the relationship between OS, RFS, and variables. In order to analyze the association between prognostic markers and survival, variables with p< 0.05 in the univariate analysis were analyzed using Cox regression analysis with a backward LR method. All analyses were conducted with version 22.0 of SPSS statistics.

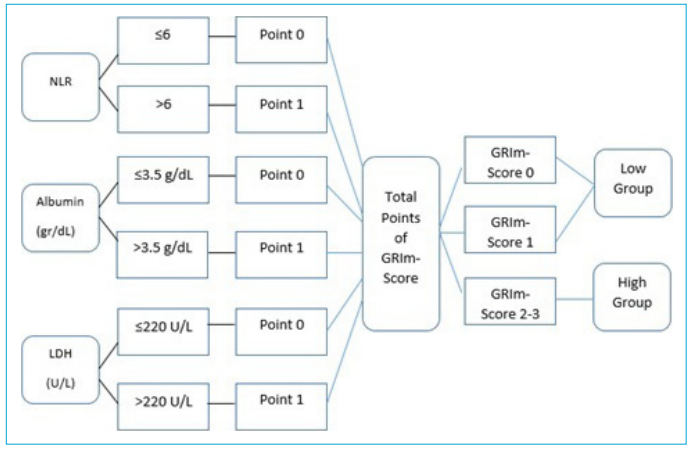

Figure 1. Definition and classification of GRIm-Score Points. (Abbrevations: GRIm-Score: Gustave Roussy Immune Score; LDH: Lactate dehydrogenase; NLR: Neutrophil-to-lymphocyte ratio).

Results

Patient Characteristics

A total of 192 patients were included in the study. The median age was 53 (22-74). Eighty-nine (46.4%) of the patients were women. Of the patients, 97 (50.6%) were in stage II. All the patients received adjuvant chemotherapy after surgical resection. The baseline characteristics of the patients according to GRIm-Score are demonstrated in Table 1.

Negative correlations were observed between albumin and NLR (r= -0.218, p= 0.002). There was a positive correlation between LDH and NLR (r= 0.22, p= 0.002). However, there was no correlation between albumin and LDH (r= 0.112, p= 0.123).

Recurrence-free Survival Analysis

At the end of the follow-up period, 29 (15.1%) patients had relapsed, and 20 of them were in the GRIm-Score high group. The median RFS was not reached in both groups; the 4-year RFS was 60% in the GRIm-Score high group and 94.4% in the GRIm-Score low group (p<0.001). According to univariate analyses, a high GRIm-Score was associated with a lower RFS (94.4% vs. 60%, p<0.001). However, multivariable analyses showed that GRIm-Score was not a prognostic marker for RFS (HR: 2.50, 95 CI%: 0.95-6.57, p=0.062). Univariate and multivariate analyses for RFS were shown in Table 2, and the Kaplan-Meier curve for RFS according to GRIm-Score was demonstrated in Figure 2.

Overall Survival Analysis

While the median OS was not met in both groups, the 4-year OS was 78.1% in the GRIm-Score high group and 93.8% in the GRIm-Score low group (p<0.001). According to univariate analyses, a high GRIm-Score was related to a worse OS (HR: 2.633, 95% CI: 1.295-5.351, P< 0.001). Additionally, multivariable evaluation revealed that GRIm-Score (HR: 4.226, 95% CI: 1.953-9.143, p<0.001) was a prognostic

Table 1. Demographic and pathological features of the patients with early-stage colon cancer.

Features	Total (n=192)	GRIm-Score (0-1) (=142)	GRIm-Score (1-2) (=50)	p
Age (years)				
<65	169 (88%)	123 (64.1%)	46 (24%)	0.23
≥65	23 (12%)	19 (9.9%)	4 (2.1%)	
Gender				
Female	89 (46.4%)	62 (32.3%)	27 (14.1%)	0.24
Male	103 (53.6%)	80 (41.7%)	23 (12%)	
Tumor sidedness				
Right	67 (34.9%)	49 (25.5%)	18 (9.4%)	0.86
Left	125 (65.1%)	93 (48.4%)	32 (16.7%)	
PNI				
Yes	27 (14.1%)	24 (12.5%)	3 (1.6%)	0.13
No	147 (76.6%)	104 (54.2%)	43 (22.4%)	
LVI				
Yes	62 (32.3%)	45 (23.4%)	17 (8.9%)	0.90
No	120 (62.5%)	90 (46.9%)	30 (15.6%)	
TNM Stage				
Stage 2	97 (50.5%)	73 (38%)	24 (12.5%)	0.67
Stage 3	95 (49.5%)	69 (35.9%)	26 (13.5%)	
NLR				
<6	120 (62.5%)	117 (60.9%)	3 (1.6%)	<0.001
≥6	72 (37.5%)	25 (13%)	47 (24.5%)	
LDH				
<240 U/L	39 (46.4%)	17 (42.7%)	22 (3.6%)	<0.001
≥240 U/L	153 (53.6%)	125 (31.3%)	28 (22.4%)	
Albumin				
<3.5 g/dL	39 (20.3%)	17 (8.9%)	22 (11.5%)	<0.001
≥3.5 g/dL	153 (79.7%)	125 (65.1%)	28 (14.6%)	

GRIm-Score: Gustave Roussy Immune Score; LDH: Lactate dehydrogenase; LVI: Lymphovascular Invasion; NLR: Neutrophil-lymphocyte Ratio; PNI: Perineural Invasion; TNM: Tumor Node Metastases.

Table 2. Univariate and multivariate analyses of 4-year recurrence-free survival in patients with early-stage colon cancer.

Features	Univariate analyses			Multivariate analyses	
	4-year RFS (%)	HR (95% CI)	p	HR (95% CI)	p
Age(years)			0.418		
<65	84.6	1			
≥65	91.3	0.552 (0.131-2.325)			
Gender			0.831		
Female	85.4	1			
Male	85.4	1.08 (0.515-2.281)			
Tumor sidedness			0.899		
Right	85.1	1			
Left	85.6	0.951 (0.439-2.061)			
TNM stage			0.029		
Stage 2	90.7	1		1	0.011
Stage 3	80	2.425 (1.096-5.365)		2.82 (1.26-6.29)	
LVI			0.948		
Yes	83.9	1			
No	87.5	1.023 (0.511-2.049)			
PNI			0.942		
Yes	81.5	1			
No	87.1	1.030 (0.465-2.282)			
Albumin			0.09		
<3.5 g/dL	76.9	1			
≥3.5 g/dL	87.6	0.503 (0.228-1.114)			
NLR			<0.001		
<6	97.5	1		1	0.002
≥6	65.3	15.86 (4.78-52.55)		9.17 (2.25-37.32)	
LDH			0.06		
<240 U/L	91	1		1	
≥240 U/L	80.6	2.155 (0.949-4.893)			
GRIm-Score			<0.001		
Low	94.4	1		1	0.062
High	60	8.82 (3.87-20.09)		2.50 (0.95-6.57)	

CI: Confidence Interval; GRIm-Score: Gustave Roussy Immune Score; HR: Hazard Ratio; LDH: Lactate dehydrogenase; LVI: Lymphovascular Invasion; NLR: Neutrophil-lymphocyte Ratio; PNI: Perineural Invasion; TNM: Tumor Node Metastase.

marker for OS. Univariable and multivariable analyses for OS were shown in Table 3, and Figure 3 demonstrated the Kaplan-Meier curve for OS according to the GRIm-Score.

Discussion

Even patients with colon cancer at the same stage have different OS and RFS.In order to identify poor-prognostic patient groups, the search for prognostic markers continues. Our study examined the parameters influencing survival in co-stage patients receiving the same adjuvant chemotherapy and showed that a high GRIm-Score was associated with worse OS and RFS.

Previous studies have shown that the immunoscore predicts the duration of adjuvant chemotherapy in colorectal cancer.[13, 14] The immunoscore showed that in addition to tumor-related factors, host-related factors also affect the course of the disease. Although the relationship between the immunoscore and prognosis of colon cancer is very clear, it is difficult to measure, expensive, and requires standardization in pathological evaluation. Parameters like NLR, platelet to lymphocyte ratio (PLR), and systemic immune inflammation index (SII), which can be taken from peripheral blood and show how the immune system works, can be used as an easier method. Inflammatory indices, including NLR[15], PLR[16], and the lymphocyte to monocyte ratio (LMR)[17] have been identified as potential biomarkers for prognosis. In addition, combined scores, such as the SII[18] and the prognostic nutritional index (PNI)[19] are related to

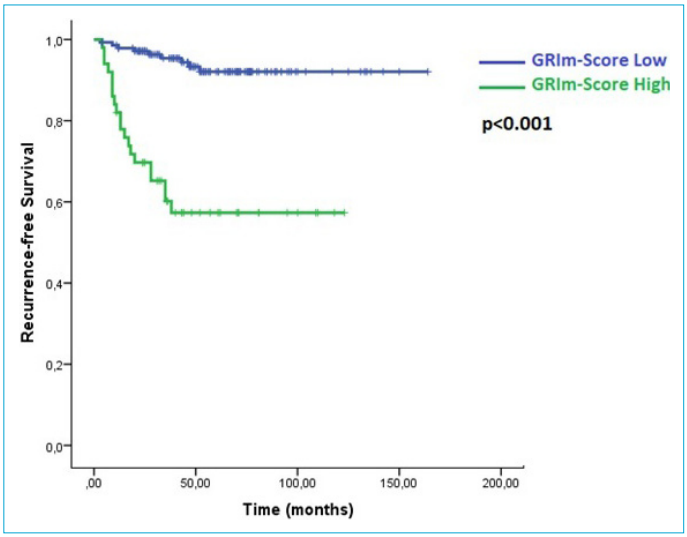

Figure 2. Kaplan-Meier for Recurrence-free Survival grouped by GRIm-Score.

poor outcomes in colon cancer patients. Albumin, an essential dietary component, indicates the nutritional status of a number of malignancies. Recent investigations have demonstrated that albumin is still a disputed prognostic factor in patients with colorectal cancer.[20, 21] LDH has been reported to be a marker of tumor load.[22] Patients with a high serum LDH level have a poor outcome, although this remains debatable in colorectal cancer.[23, 24]

All of these data inspire the development of a revolutionary risk score system that gives accurate information to clinicians for prognostic prediction. Bigot et al. demonstrated that the GRIm-Score is a strong prognostic indicator for immunotherapy response in trial participants.[7] Additionally, subsequent retrospective studies have verified the prognostic significance of the GRIm-Score in lung cancer and resected early-stage esophageal cancer in recent years.

Table 3. Univariate and multivariate analyses of 4-year overall survival in patients with early-stage colon cancer.

	Univariate analyses			Multivariate analyses	
Features	**4-year OS (%)**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age (years)			0.203		
<65	89.3	1			
≥65	82.6	1.784 (0.732-4.350)			
Gender			0.323		
Female	91	1			
Male	86.4	1.430 (0.700-2.924)			
Tumor sidedness			0.091		
Right	82	1		1	0.026
Left	92	0.541 (0.267-1.094)		0.431 (0.206-0.904)	
TNM stage			0.001		
Stage 2	96.8	1		1	0.001
Stage 3	80.4	3.954 (1.703-9.183)		4.117 (1.763-9.611)	
LVI			0.168		
Yes	85.5	1			
No	90.8	0.631 (0.328-1.214)			
PNI			0.305		
Yes	81.5	1			
No	90.5	0.678 (0.323-1.424)			
Albumin			0.022		
<3.5 g/dL	79.5	1		1	0.075
≥3.5 g/dL	90.8	0.412 (0.194-0.878)		0.484 (0.218-1.076)	
NLR			0.001		
<6	81.9	1		1	0.404
≥6	92.5	3.559 (1.675-7.561)		1.739 (0.473-6.389)	
LDH			0.009		
<240 U/L	96.5	1		1	0.165
≥240 U/L	82.1	3.074 (1.324-7.138)		1.910 (0.765-4.767)	
GRIm-Score			<0.001		
Low	91.5	1		1	<0.001
High	80	2.633 (1.295-5.351)		4.226 (1.953-9.143)	

CI: Confidende Interval; GRIm-Score: Gustave Roussy Immune Score; HR: Hazard Ratio; LDH: Lactate dehydrogenase; LVI: Lymphovascular Invasion; NLR: Neutrophil-lymphocyte Ratio; PNI: Perineural Invasion; TNM: Tumor Node Metastasis.

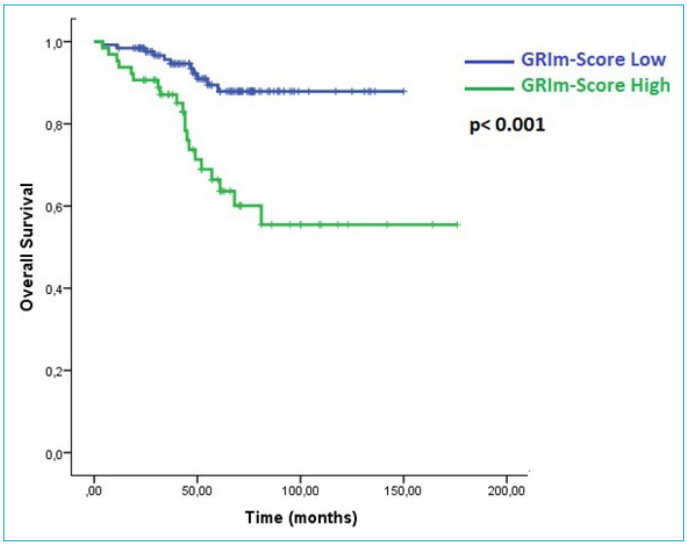

Figure 3. Kaplan-Meier for Overall Survival grouped by GRIm-Score.

Feng et al. discovered that early-stage esophageal cancer patients with a high GRIm-Score had a poorer OS than those with a low GRIm-Score (10.3% vs. 35.0%, p<0.001).[11] Furthermore, Li et al. demonstrated that GRIm-Score can be used as an efficient indicator to improve prognostic assessment for stage I and II non-small cell lung cancer.[25] A similar result was obtained in our study as well. We think that our study of early-stage colon cancer, which is a patient group in which there is debate about how long adjuvant therapy should be given, will contribute to our practice. It is still unproven that administration of the CAPEOX regimen for 3 months is non-inferior to administration of the CAPEOX regimen for 6 months in the T4 or N2 patient groups, defined as high-risk stage III colon cancer.[26, 27] In high-risk stage III patients (T4 and N2 positive), ifthere were poor prognostic markers such as GRIm-Score, a 6-month CAPEOX instead of a 3-month CAPEOX may improve survival. To be able to suggest it, prospective studies with more prognostic markers and larger number of patients are needed.

This study, according to our knowledge, is the second study that assess the prognostic impact of the GRIm-Score in colon cancer. The first study reported by Tian et al. included patients from all stages.[12] In this respect, we formed a more homogeneous group by including only stage II and stage III patients who received adjuvant chemotherapy. In addition, we tried to minimize the effect of chemotherapy type and cycle on relapse by including patients who received only CAPEOX regimen as adjuvant treatment with a minimum of 4 cycles of oxaliplatin.

This study has a number of limitations that need to be highlighted. Firstly, clinical data was obtained from a retrospective cohort at a single hospital. Furthermore, the GRIm-Score was evaluated once before the start of chemotherapy. As a result, the predictive value of the dynamic change in GRIm-Score remained unknown. Thirdly, chemotherapy completion rates could not be reached due to the lack of retrospectice data. As a result, comparing 3 versus 6-month CAPEOX was impossible. However, we included patients who received at least 4 cycles of oxaliplatin in order to minimize the effect of chemotherapy on survival. Consequently, the prognostic significance of the GRIm-Score can be confirmed with prospective cohort studies involving large sample of patients.

Conclusion

In conclusion, our study reported that a high GRIm-Score was associated with worse OS in stage II and III colon cancer patients who received CAPEOX. Furthermore, the GRIm-Score was a prognostic indicator for OS in the same patient group. For the prognostic prediction of patients with early-stage colon cancer, the GRIm-Score can be used as a simple, practical, and efficient assessment. More extensive prospective validation analyses are required to further support and validate our results.

Disclosures

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. The institutional ethics committee approved the study (16.12.2022-9c58eb3c-3ad1-4352-9194) and conducted it by the related privacy statements and applicable regulatory requirements.

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