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Relationship Between Hemoglobin, Albumin, Lymphocyte and Platelet (HALP) Score and Geriatric Nutritional Risk Index (GNRI) and Prognosis in Patients Over 75 Years of Age with Metastatic Gastric Cancer

Yetmiş Beş Yaş Üstü Metastatik Mide Kanserli Hastalarda Hemoglobin, Albümin, Lenfosit, Platelet (HALP) Skoru ile Geriatrik Nütrisyonel İndeks (GNRI) ve Prognoz Arasındaki İlişki

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ABSTRACT

Aim: Gastric cancer (GC) is a common cancer with high mortality. Stage is the most important predictor of prognosis. But the clinical course of patients who are at the same stage may be different. Therefore, other prognostic markers other than stage are needed. Hemoglobin, albumin, lymphocyte and platelet (HALP) score and geriatric nutritional risk index (GNRI) related with prognosis in many malignancies, but their relationship to prognosis in patients with GC with advanced age is unknown. For this reason, we retrospectively analyzed patients older than 75 years, receiving chemotherapy, and metastatic GC.

Material and Methods: We retrospectively analyzed 145 patients with metastatic gastric cancer, older than 75 years, receiving chemotherapy in secondary level state hospital between 2009 and 2022. Patients' gender, age, Eastern Cooperative Oncology Group (ECOG) performance score, diagnosis dates, follow-up visits, albumin, hemoglobin, lactate dehydrogenase (LDH) levels, white blood cell, neutrophil, lymphocyte and platelet count, weight (kg), height (cm) values were examined. Using these values, HALP score, GNRI, and overall survival (OS) were calculated. Then, the relationship of these parameters with OS was analyzed retrospectively.

Results: The median overall survival (OS) was 8.1 (95% Confidence interval (CI), 7.07 – 9.13) months. In multivariate analysis, GNRI (0.035) and HALP (p<0.001) were associated with survival time. Median OS was 4.5 (95% C,3.77-5.24) months in the low HALP group, and 10.2 (95% CI, 9.04- 11.36) months in the high HALP group (p<0.001). Median OS was 6.2 (95% CI, 4.25-8.14) months in the low GNRI group and 8.6 (95% CI, 7.92-9.27) months in the high GNRI group.

Conclusion: GNRI and HALP score are associated with survival in metastatic GC patients older than 75 years. GNRI and HALP score can be used as an easy, cheap and practical method for follow-up, treatment and prognosis in elderly patients with metastatic GC.

Keywords: Elderly gastric cancer, HALP score, GNRI, Geriatric nutritional risk index, Prognosis

ÖZ

Amaç: Mide kanseri (MK) sık görülen ve mortalitesi yüksek bir kanserdir. Evre, prognozun en önemli belirleyicisidir. Ancak aynı evrede olan hastaların klinik seyri farklı olabilir. Bu nedenle evre dışında başka prognostik belirteçlere ihtiyaç vardır. Hemoglobin, albümin, lenfosit ve trombosit (HALP) skoru ve

geriatrik nütrisyonel risk indeksi (GNRI) birçok malignitede prognoz ile ilişkilidir, ancak ileri yaştaki mide kanserli hastalarda prognozla ilişkisi bilinmemektedir. Bu nedenle metastatik, 75 yaş üstü, kemoterapi alan mide kanserli hastaları retrospektif olarak inceledik.

Gereç ve Yöntemler: İkinci basamak bir devlet hastanesinde 2009-2022 yılları arasında kemoterapi alan, 75 yaş üstü metastatik mide kanserli 145 hasta retrospektif olarak incelendi. Hastaların cinsiyeti, yaşı, Eastern Cooperative Oncology Group (ECOG) performans skoru, tanı tarihleri, kontrole geliş tarihleri, albümin seviyeleri, hemoglobin, laktat dehidrogenaz (LDH), beyaz küre sayısı, nötrofil, lenfosit ve trombosit sayısı, ağırlık (kg), boy (cm) değerleri incelendi. Bu değerler kullanarak HALP skoru, GNRI, genel sağkalım (OS) hesaplandı. ardından bu parametrelerin OS ile ilişkisi retrospektif olarak analiz edildi.

Bulgular: Medyan genel sağkalım (OS) 8.1 (%95 Güven aralığı (GA), 7.07 – 9.13) aydı. Çok değişkenli analizde, GNRI (0.035) ve HALP skoru (p<0.001) sağkalım süresi ile ilişkiliydi. Medyan OS, düşük HALP grubunda 4,5 (%95 C,3.77-5.24) ay ve yüksek HALP grubunda 10.2 (%95 CI, 9.04- 11.36) ay saptandı (p<0.001). Medyan OS, düşük GNRI grubunda 6.2 (%95 GA, 4.25-8.14) ay ve yüksek GNRI grubunda 8.6 (%95 GA, 7.92-9.27) ay saptandı.

Sonuç: GNRI ve HALP skoru, 75 yaş üstü metastatik, mide kanserli hastalarda sağkalım süresi ile ilişkilidir. Metastatik mide kanserli yaşlı hastalarda takip stratejisi geliştirmek, tedavi planlamak ve prognoz belirlemek için kolay, ucuz ve pratik bir yöntem olarak kullanılabilir.

Anahtar Sözcükler: Yaşlı mide kanseri, HALP skoru, GNRI, Geriatrik nutrisyonel risk indeksi, Prognoz

INTRODUCTION

Gastric cancer (GC) is the sixth most common and third deadliest cancer according to GLOBOCAN' 2020 data (1). Although the incidence and mortality of GC vary considerably according to the region, it is generally seen in advanced ages. According to the 2017 data of cancer statistics in Turkey, it is seen at a rate of 14.3% in men and 6.4% in women, and 27.3% of them are metastatic at the time of diagnosis (2).

The most important standard marker in prognosis is stage. However, in daily practice, the clinical course of patients with the same stage and metastasis site may be different. Therefore, other prognostic factors are needed besides the stage. Age is one of these prognostic factors. However, physiologic changes that occur in patients with age and related changes in immune escape lead to decreased renal clearance, decreased organ reserves, and changes in drug clearance and metabolism. As a result of all these, drug tolerance in patients may decrease and accordingly, there may be differences in the clinical course of patients. Age-related cancer types and behaviors may also differ. For example, while GC screening programs in advanced ages tend to decrease in incidence and mortality in the last 1-2 decades due to easier access to endoscopy and advances in treatment, studies have reported an increase in incidence and mortality in non-cardiac tumors under the age of 50 (3).

Studies have reported an intertwined relationship between nutrition, immun system, inflamatuar system and cancer. There are many studies showing that nutrition, inflammation and immune system may be associated with cancer formation, progression and prognosis (4-6).

In recent years, a number of scores and indices have been developed that show inflammation, immune and nutritional status. A relationship has been reported between these scores, which provide information about the immune inflammation and nutritional status of the patients, and many cancers. Therefore, besides the stage of the disease, these scores can be used to determine the prognosis of the disease.

The HALP score and GNRI score show the inflammatory immune and nutritional status of patients and have been previously related with many cancers. However, its relationship with prognosis in advanced age GC patients is unknown. For this reason, we retrospectively analyzed patients older than 75 years with metastatic GC who were followed up in our center and received chemotherapy.

MATERIAL and METHODS

Patients aged 75 years and older, who have been diagnosed with metastatic GC in in the Medical Oncology division of Manisa State Hospital between 2009 and 2022, were examined retrospectively. The study was conducted by the principles of the Declaration of Helsinki (as revised in 2013) and reviewed and approved by the Health Sciences Ethics Committee of Manisa Celal Bayar University (Decision no: 20.478.486/1115, Date 28.12.2021).

Patients older than 18 years of age with GC, with metastasis at the time of diagnosis, with adenocarcinoma histology, who received at least one step of chemotherapy and who had a blood test at least one week before chemotherapy in our hospital were accepted in the study. Patients under the age of 18, who had never received chemotherapy, who did not have adenocarcinoma histology, and who did not have a blood test in our hospital before chemotherapy were considered as exclusion criteria.

Patients sex, age, Eastern Cooperative Oncology Group (ECOG) performance score, albumin levels (g/dL), hemoglobin (g/dL), lactate dehydrogenase (LDH) (U/L), white blood cell counts (10^3/μL), neutrophil (10^3/μL), lymphocyte (10^3/μL) and platelet counts (10^3/μL), weight (kg), height

(cm), tumor location, HALP score , GNRI , and overall survival (OS) and the relationschip between OS and these parameters was analyzed retrospectively. These values were examined from the blood samples taken 24-48 hours after the pathological diagnosis of the patients. The main evaluation criterion was overall survival and the secondary evaluation criterion was factors affecting overall survival. Overall survival time is the time between diagnosis and death of the patient. HALP score was calculated as hemoglobin (g/dL) x albumin (g/dL) x lymphocytes ($10^3/\mu L$) / platelets ($10^3/\mu L$). Albumin-to-globulin ratio (AGR) calculated with the albumin / (total protein - albumin). GNRI is calculated as 14.87 x serum albumin concentration (g/dL) + 41.7 x weight/ideal weight (kg) (ideal body weight calculated as: 22 × height squared (m)).

The median HALP score of the patients was 2.71, the median value of the GNRI score was 98, and the median albumin to globulin ratio was 1.1. Patients were grouped according to HALP score (>2.71 or 2.71), GNRI (>98 or ≤98), ECOG performance score (3> or 3≤), age (≤80 or >80), AGR (>1.10 or ≤1.10).

Statistical Analyses

Descriptive statistics were reported as median (minimum, maximum), mean (± standart deviation) values for numeric variables and numbers and percentages for categoric variables. Survival analyses and curves were conducted using the Kaplan-Meier method. Determinants were analyzed by Cox regression analysis. In all statistical analyzes, p< 0.05 was considered significant.

RESULTS

One hundred and forty-five patients, 60 (41.4 %) females and 85 (58.6%) males were examined retrospectively. Median patient age was 80 (75-88) years (Table 1 and Table 2).

The median OS time of the patients was 8.1 (95% CI, 7.07 - 9.13) months. The median OS time was 4.5 (95% C,3.77-5.24) months in the low HALP group, 10.2 (95% CI, 9.04-11.36) months in the high HALP group (p<0.001), (Table 3, Figure 1). The median OS time was 6.2 (95% CI, 4.25-8.14) months in the low GNRI group, 8.6 (95% CI, 7.92-9.27) months in the high GNRI group (Table 3, Figure 1).

Age (p=0.039), ECOG performance score (p=0.043), BMI (p=0.023), albumin (p=0.001), hemoglobin (p=0.001), platelet (p=0.036), lymphocyte (p=0.036) in univariance analysis 0.045), neutrophil (p=0.044), liver metastasis (p=0.037) bone metastasis (p=0.028), lung metastasis (p=0.045), pleura (p=0.042), peritoneum (p=0.034) LVI (p= 0.026), AGR (p=0.026), GNRI (p=0.013) HALP (p<0.001) were associated with OS. In multivariate analysis, GNRI (0.035) and HALP (p<0.001) were associated with overall survival (Table 3).

Table 1: Demographic and clinicopathological characteristics of the patients

Parameters*		Findings (n= 145)	
Age	<80 years	67	(46.2)
	≥80 years	78	(53.8)
Sex	Female	60	(41.4)
	Male	85	(58.6)
ECOG performance score	3≤	106	(71.2)
	3>	39	(38.8)
Metastasis site	Liver	77	(53.1)
	Bone	34	(23.4)
	Lung	28	(19.3)
	Ovary	2	(1.4)
	LN	71	(49.0)
	Peritoneum	51	(25.2)
Comorbidities	Diabetes mellitus	46	(31.7)
	Hypertension	48	(33.1)
	CAD	30	(20.7)
	CRF	3	(2.1)
	COPD	8	(5.5)
	CVD	3	(2.1)
Grade	Grade 1	21	(14.5)
	Grade 2	106	(73.1)
	Grade 3	18	(12.4)
PNI	Positive	118	(81.4)
LVI	Positive	102	(70.3)
Localisation	Corpus	48	(33.1)
	Antrum	45	(31)
	Cardia	31	(21.4)
	Pylorus	5	(3.4)
Gastrectomy	Yes	42	(29.0)
AGR	(>1.10)	61	(42.2)
	(≤1.10)	84	(57.8)
GNRI	(>98)	67	(46.2)
	(≤98)	78	(52.8)
HALP score	(>2.71)	73	(50.3)
	(≤2.71)	72	(49.7)

***Data are presented as n(%). ECOG:** Eastern Cooperative Oncology Group, **CAD:** Coronary artery disease, **CRF:** Chronic renal failure, **COPD:** Chronic obstrictive pulmonary disease, **CVD:** Cerebrovascular disease, **LVI:** Lymphovascular invasion, **PNI:** Perineural invasion, **GNRI:** Geriatric Nutritional Risk Index, **AGR:** Albumin-to-globulin ratio, **HALP:** Hemoglobin, albumin, lymphocyte ve platelet score

DISCUSSION

The purpose of this study was to examine the relation between HALP scores, GNRI scores and prognosis in patients older than 75 years with metastatic GC receiving chemoetherapy at diagnosis. In our study, we found that patients with low HALP scores and low GNRI values at the time of diagnosis had worse prognosis and shorter median survival times.

Immune, inflammatory, and nutritional status of patients are intertwined in many cancers, and studies have reported that immune,inflammation, and nutrition status are associated with carcinogenesis and post-carcinogenesis stages (4-7). For example, in patients with GC, lack of oral intake, malnutrition as a result of weight loss causes chronic inflammation, cytokine release, and ultimately cachexia. Cytokines and proinflammatory mediators released in this process cause changes in the immune system and inflammatory system, and a decrease in albumin, which is a negative acute phase reactant. These proinflammatory cytokines are also involved in malignant transformation, neoangiogenesis, and cancer progression. Lack of oral intake and malnutrition can lead to treatment toxicities, prolonged hospital stays, nosocomial infections and reduced quality of life in patients (8).

Table 2: Laboratory values of the patients

Parameters	Values (n=145)
Age (Year) (Median [min-max])	80 (65-88)
Hemoglobin (g/dL) (Median [min-max])	12.37 (11-15.5)
Albumin (g/dL) (Mean± SD)	3.66 ± 0.04
Platelet (10^3/µL) (Median [min-max])	265 (112-644)
Lymphocyt (10^3/µL) (Median [min-max])	1.7 (0.8-3.4)
Neutrophil (103/µL) (Median [min-max])	5.6 (1.5-14.6)
WBC (10^3/µL) (Median [min-max])	8.5 (4.00-18.6)
GNRI (Median [min-max])	98 (70-121)
AGR (Median [min-max])	1.1 (0.6-1.9)
HALP (Median [min-max])	2.71 (0.41-12.41)

Min: Minimum, **Max:** Maximum, **SD:** Standard deviation, **WBC:** Whole blood cell, **GNRI:** Geriatric Nutritional Risk Index, **AGR:** Albumin-to-globulin ratio, **HALP:** Hemoglobin, albumin, lymphocyte ve platelet score

In daily clinical practice, there is a need for prognostic indicators other than stage because the clinical course and survival time of patients with the same stage may be different. Peripheral blood-derived cells and biochemical parameters can provide simple and inexpensive practical information about prognosis by showing inflammation, immune status and malnutrition (9). Albumin is synthesized in the liver. Its production is arranged by proinflammatory cytokines like tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), interleukin-1 (IL-1) (10).

Platelets plays a role in hemostasis, thrombosis and inflammation by releasing pro-inflammatory cytokines such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). Platelets cause the movement of inflammatory cells into the inflammatory zone. As a result of these, the microenvironment of the tumor is formed. Tumor cells escape and evade the immune system and angiogenesis and progression occur, which are essential for the development of cancer and metastasis (11).

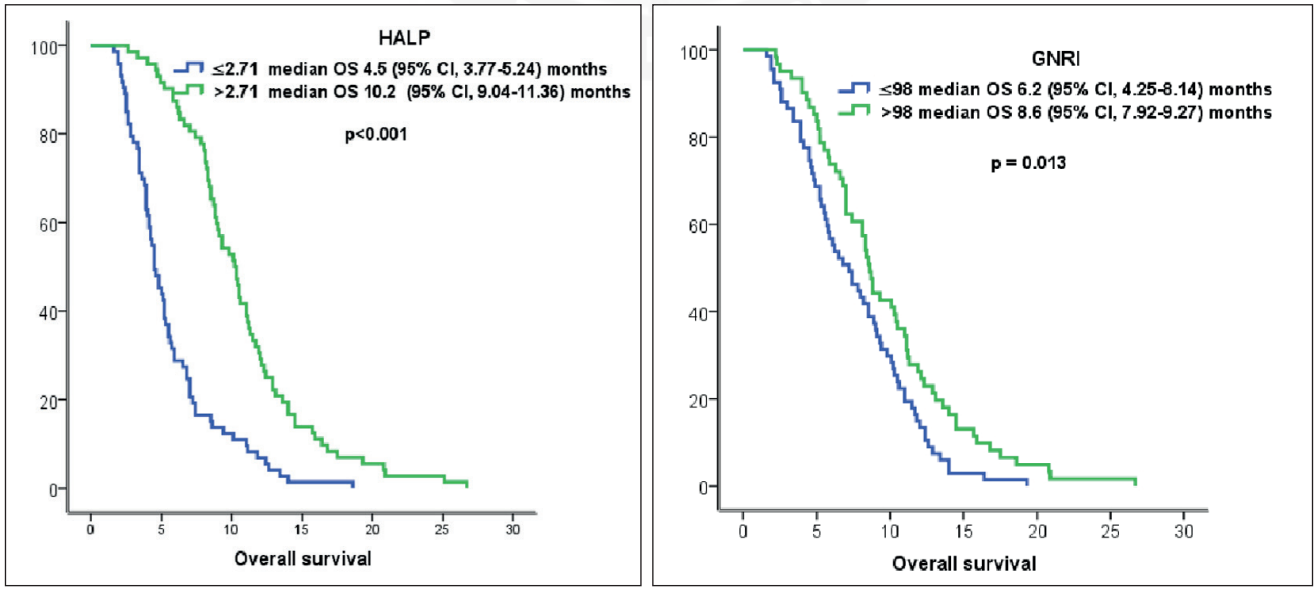

Figure 1: Kaplan-Meier curves of hemoglobin, albumin, lymphocyte and platelet (HALP) score and geriatric nutritionel risk index (GNRI), for overall survival.

Table 3: Univariate and multivariate analyses of overall survival

	Univariate analysis (HR, 95% CI)	p	Multivariate analysis (HR, 95% CI)	p
Age (80< vs 80≥)	1.76 (1.25-2.46)	0.039	0.68 (0.45-1.04)	0.761
Sex	1.20 (0.86-1.68)	0.281		
ECOG (<3 vs 3≤)	3.92 (2.19-7.05)	0.043	-0.96 (0.28-3.38)	0.962
BMI(kg/m^2)	-0.909 (0.87-.95)	0.023	-0.95 (0.89-1.02)	0.140
Diabetes Mellitus	1.05 (0.74-1.49)	0.760		
Hypertension	0.99 (.70-1.40)	0.973		
CAD	1.32 (0.88-1.97)	0.192		
CRF	1.78 (0.56-5.60)	0.384		
COPD	2.58 (0.54-30.40)	0.170		
CVD	-.0408 (0.28-0.95)	0.050	1.18 (0.80-16)	0.513
Albumin(g/dL)	-0.34 (0.25-0.49)	<0.001	-0.55 (0.29-1.04)	0.642
Hemoglobin(g/dL)	-0.78 (0.71-0.86)	<0.001	1.15 (0.97-1.37)	0.121
Platelet(10^3/µL)	1.02 (1.00-1.03)	0.036	1.15 (0.62-2.10)	0.664
Lymphocyte(10^3/µL)	-0.99 (0.99-0.99)	0.045	-0.89 (0.54-1.45)	0.652
Neutrophil(10^3/µL)	1.00 (1.00-1.01)	0.014	1.26 (0.82-1.96)	0.290
WBC(10^3/µL)	1.00 (1.00-1.01)	0.760		
Liver metastasis	1.89 (1.35-2.64)	0.037	1.41 (0.92-2.18)	0.121
Bone metastasis	-0.42 (0.28-0.62)	0.028	1.28 (.073-2.729	0.392
Lung metastasis	1.98 (1.36-2.90)	0.045	1.23 (0.74-2.07)	0.413
Pleura metastasis	-0.65 (0.43-0.98)	0.042	-0.62 (0.33-1.19)	0.151
Peritoneal metastasis	1.72 (1.20-2.44)	0.034	0.92 (0.57-1.49)	0.750
LN	1.12 (0.80-15)	0.504		
AGR	1.59 (1.15-2.25)	0.026	1.10 (0.83-1.45)	0.055
GNRI	1.57 (1.10-2.25)	0.013	1.22 (1.03-1.78)	0.035
HALP	3.121 (2.20-4.42)	<0.001	2.07 (1.40-3.05)	<0.001
LVI	-0.66 (0.46-0.95)	0.026	-0.82 (0.51-1.299	0.381
PNI	-0.76 (0.66-1.075)	0.132		
Grade	-0.77 (0.55-1.09)	0.153		

HR: Hazard ratio, **CI:** Confidence interval, **ECOG:** Eastern Cooperative Oncology Group, **BMI:** Bady mass index, **CAD:** Coronary artery disease, **CRF:** Chronic renal failure, **COPD:** Chronic obstrictive pulmonary disease, **CVD:** Cerebrovascular disease, **LN:** Lymphadenopathy, **WBC:** Whole blood cell, **AGR:** Albumin-to-globulin ratio, **GNI:** Geriatric Nutritional Risk Index, **HALP:** Hemoglobin, albumin, lymphocyte ve platelet score **LVI:** Lymphovascular invasion, **PNI:** Perineural invasion.

Lymphocytes are immune system elements that play an important role in host defense. They inhibit proliferation and metastasis of tumor cells. In their deficiency, tumor cells escape immune elimination. Lymphocyte levels have been associated with many cancers (12). Anemia reduces the oxygen capacity of the blood, that caues hypoxia. Chronic hypoxia can lead to an increase in VEGF secretion, neovascularization and prognosis in cancer (13). In addition to malnutrition, changes in the microbiota, increase in adipose tissue, increase in inflammatory mediators and free oxygen radicals, chronic inflammatory condition and DNA damage may be associated with carcinogenesis and subsequent stages in obesity-related carcinogenesis (14).

The HALP score consists of hemoglobin, albumin, lymphocyte and platelet values of patients and is an indicator of nutritional and systemic inflammation and can be used as a prognostic marker (15-17). Studies have found that it is associated with prognosis with many cancers such as colorectal cancers, bladder cancers, kidney cancers, pancreatic cancers, esophageal cancers, and small cell lung cancers (18-23). However, its relationship with prognosis in patients older than 75 years with metastatic GC is unknown. In our study, we found that patients with low HALP values in this group had a shorter median life expectancy and this value was statistically significant (p< 0.001).

GNRI shows the nutritional status . The GNRI consists of two parameters: serum albumin level and comparison of current body weight with ideal body weight (24). It has also been found to be associated with prognosis in previous studies in the literature (12). However, its relationship with prognosis in patients older than 75 years with metastatic GC was unknown. In our study, we found that the survival time of patients with low GNRI in this group of patients was low as in other cancers and this value was statistically significant.

Although the retrospective, single-center and small number of patients constitute the weaknesses of the study, our study is important because it is the first study to show the relationship between GNRI, HALP and prognosis in patients older than 75 of age with metastatic GC.

In metastatic gastric cancer patients older than 75 years, GNRI and HALP scores are associated with survival time. In addition, GNRI and HALP scores can be used as an easy and inexpensive practical method in daily practice for follow-up treatment and prognostic determination as well as the stage in elderly metastatic GC patients.

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Author Contributions

Concept: **Serkan Menekşe,** Design: **Engin Kut,** Data collection or processing: **Serkan Menekşe,** Analysis or Interpretation: **Engin Kut,** Literature search: **Engin Kut, Serkan Menekşe,** Writing: **Serkan Menekşe,** Approval: **Serkan Menekşe.**

Conflicts of Interest

There is no conflict of interest in our study.

Financial Support

There is no financial support.

Ethical Approval

The study was conducted by the principles of the Declaration of Helsinki (as revised in 2013) and reviewed and approved by the Health Sciences Ethics Committee of Manisa Celal Bayar University (Decision no: 20.478.486/1115, Date 28.12.2021).

Review Process

Extremely peer-reviewed and accepted.

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