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Diagnóstico nutricional de pacientes con carcinoma hepatocelular: ¿cuál es el mejor método?

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RESUMEN

Introducción: la desnutrición es un hallazgo frecuente entre pacientes oncológicos. A pesar de su significancia pronóstica, todavía son escasos los estudios que evalúan el estado nutricional de pacientes con carcinoma hepatocelular (CHC).

Objetivos: evaluar el estado nutricional de pacientes con CHC por diferentes métodos.

Métodos: se evaluaron pacientes con CHC en seguimiento ambulatorio en el Hospital Santa Casa de Misericordia de Porto Alegre. Los métodos empleados para la evaluación nutricional fueron índice de masa corporal (IMC), pliegue cutáneo tricipital (PCT), circunferencia del brazo (CB), circunferencia muscular del brazo (CMB), fuerza del apretón de manos (FAM), músculo aductor del pulgar (MAP), evaluación subjetiva global producida por el paciente (ASG-PPP) y ángulo de fase (AF).

Resultados: se evaluaron 43 pacientes con CHC, todos cirróticos. El promedio de edad fue de 64,0 ± 5,8 años y el sexo prevalente, el masculino (72,1%). MAP, AF, ASG-PPP y CMB fueron los métodos más sensibles para el diagnóstico de desnutrición. Se observó una correlación negativa entre la PCT y la puntuación Child-Pugh (p = 0,004) y una correlación positiva entre MAP y la estadificación BCLC (p = 0,006).

Conclusiones: hubo gran variación en el diagnóstico de desnutrición entre los métodos estudiados. MAP, CMB, AF y ASG-PPP se pueden indicar como herramientas de elección en la evaluación nutricional del paciente con CHC por haber sido los métodos más sensibles en el diagnóstico de desnutrición. PCT y MAP se correlacionan con la gravedad de la enfermedad.

Palabras clave: Carcinoma hepatocelular. Evaluación nutricional. Estado nutricional. Desnutrición.

ABSTRACT

Introduction: malnutrition is a frequent finding among cancer patients. Despite its prognostic significance, there are still few studies evaluating the nutritional status of patients with hepatocellular carcinoma (HCC).

Objectives: to evaluate the nutritional status of patients with HCC by different methods.

Methods: patients with HCC were evaluated in an outpatient clinic at the Hospital Santa Casa de Misericórdia de Porto Alegre. The methods used for the nutritional assessment were body mass index (BMI), tricipital skinfold (TSF), arm circumference (AC), arm muscle circumference (AMC), hand grip strength (HGS), adductor pollicis muscle (APM), patient-generated subjective global assessment (PG-SGA) and phase angle (PA).

Results: forty-three patients with HCC were evaluated; all of them were cirrhotic. The mean age was 64.0 ± 5.8 years and the prevalent gender was male (72.1%). APM, PA, PG-SGA and AMC were the most sensitive methods for the diagnosis of malnutrition. There was a negative correlation between TSF and Child-Pugh score ($p = 0.004$) and a positive correlation between APM and BCLC stage (Barcelona Clinic Liver Cancer Group) ($p = 0.006$).

Conclusions: there was high variation in the diagnosis of malnutrition among the methods studied. APM, AMC, PA and PG-SGA can be indicated as tools of choice in the nutritional assessment of the HCC patient because they were the most sensitive methods in the diagnosis of malnutrition. TSF and APM correlate with disease severity.

Key words: Hepatocellular carcinoma. Nutritional assessment. Nutritional status. Malnutrition.

INTRODUCTION

Cancer is a pathology that has serious implications on the health status of the individual, with nutritional aspects being one of the most compromised. Malnutrition is a frequent finding among oncology patients. Its prevalence can range from 30% to more than 70%, depending on the type of tumor, staging and profile of the patient (1-4).

Patients with hepatocellular carcinoma (HCC) are at increased risk of malnutrition because tumor progression can directly affect liver function, which plays a central role in nutrients metabolism (5).

Besides that, the majority of HCC cases occur in patients with underlying cirrhosis (6), which is, in turn, a disease that presents nutritional damage as a common complication (7).

Several studies have demonstrated the prognostic significance of malnutrition in cancer. Malnutrition is associated with an increased incidence of comorbidities, increased mortality, reduced survival time, reduced quality of life, longer hospitalization and consequent higher hospital costs (1,8-10). In addition, malnutrition has a negative impact on the efficacy of cancer therapy, resulting in low response, low tolerance and high toxicity to the treatment (9,11).

Despite the importance of malnutrition for the clinical evolution of cancer patients, there is no method of nutritional assessment considered as the gold standard (4,12). In the nutritional assessment of patients with HCC, it should be considered that the changes caused by hepatic dysfunction prevent the use of the more traditional tools (13).

Despite the wide range of scientific publications about the nutritional status of cancer patients, there are still few studies that specifically evaluate HCC patients. Therefore, the objective of this study was to evaluate the nutritional status of patients with hepatocellular carcinoma by different methods of nutritional assessment.

METHODS

This was a cross-sectional study conducted between November 2016 and May 2017. Adult patients (> 18 years) with HCC diagnosis due to different etiologies, who were being followed up at the Gastroenterology Outpatient Clinic, at the Liver Transplant Outpatient Clinic and at the Hepatopathy Outpatient Clinic of the Santa Clara Hospital of the Irmandade Santa Casa de Misericórdia de Porto Alegre were invited to participate in the study.

Patients who were participating in dietetic programs or physical activity for weight gain, patients with cancers other than HCC, those who did not present sufficient psychic and cognitive conditions to fill in the questionnaires, illiterates, and those who did not present physical and motor conditions for anthropometric evaluation were excluded from the study.

All participants agreed to participate in the study by reading and signing the informed consent form. This research protocol was approved by the Research Ethics Committee of the Irmandade Santa Casa de Misericórdia de Porto Alegre (protocol 1.780.500) and the Federal University of Health Sciences of Porto Alegre (UFCSPA) (protocol 1.827.929).

The study protocol included the assessment of nutritional status and functional assessment, both performed by a trained nutritionist, in addition to the collection of socio-demographic data. Directly from the patients’ records, data related to the diagnosis and treatment of HCC, Child-Pugh score, comorbidities, results of laboratory tests, imaging tests, anatomical pathology and clinical history were collected.

The HCC classification was defined by a hepatologist through the Barcelona Clinic Liver Cancer Group (BCLC) staging system. The Model for End Stage Liver Disease (MELD) score was calculated through the patient’s laboratory tests.

Anthropometry

Weight was measured using a Filizola 100 g resolution scale and height with a wall-mounted stadiometer. The body mass index (BMI) was calculated using the formula: weight (kg)/height^2 and classified according to World Health Organization (WHO) (14) cut-off points for adults or according to Lipschitz (15) for elderly.

The arm circumference (AC) was measured with an inelastic tape at the midpoint of the non-dominant arm. A scientific skinfold caliper (Cescorf®) was used for triceps skinfold measurement (TSF). To determine muscle mass, the anthropometric parameter used was the arm muscle circumference (AMC), which takes AC and TSF into account by the following equation: $AMC\ (cm) = AC\ (cm) - \pi \times [TSF\ (mm) \div 10]$. The results obtained were related to the default values shown in Frisancho's percentiles tables (16) and classified according to Blackburn BL and Thornton PA (17).

Functional assessment

A mechanical hand grip dynamometer of adjustable handle (Baseline®, Smedley Spring model) was used to assess the hand grip strength (HGS). The assessment was performed in the non-dominant hand, in triplicate, and highest value result was classified according to the cut-off points proposed by Budziareck MB et al. (18).

Assessment of adductor pollicis muscle

The thickness of the adductor pollicis muscle (APM) was measured using a scientific skinfold caliper (Cescorf®). The measurement was performed in triplicate and the final value obtained from the average of the three measurements was used. Patients with APM values below p5 as proposed by González et al. (19) were considered as undernourished.

Patient-Generated Subjective Global Assessment

The Patient-Generated Subjective Global Assessment (PG-SGA) was performed following the protocol validated by Ottery FD (20).

Bioelectrical impedance analysis (BIA)

For the assessment of the phase angle (PA), a bioelectrical impedance Biodynamic® model 450 device (Seattle, WA, USA) was used. The electrical current used in the measurement is 800 A and 50 kHz.

The patient remains in supine position, comfortable and relaxed, with hands and feet parallel to the body. One electrode was placed on the dorsal hand, at the middle finger level, and one in the wrist joint, both on the right side. Another pair of electrodes was placed on the dorsal foot, at the middle toe level, and in the ankle joint, also on the right side.

The patients were classified according to the cut-off point proposed by Fernandes SA et al. (7).

Statistical analysis

Statistical analyses of the data were performed using the SPSS (Statistical Package for Social Sciences) software version 21.0 and a significance level of 5% ($p \leq 0.05$).

The quantitative variables were described by mean and standard deviation or median value and interquartile amplitude. The categorical variables were described using absolute and relative frequencies.

Pearson's Chi-square test was used to assess the association between categorical variables. The Cochran test was applied to compare the nutritional status among the methods of nutritional assessment.

Spearman's correlation test was used to assess the associations between nutritional assessment methods and disease staging.

RESULTS

The sample was composed of 43 patients, all with diagnosis of hepatocellular carcinoma associated with cirrhosis. The mean age was 64.0 ± 5.8 years, the prevalent sex was male (72.1%). The clinical characteristics of the sample studied are described in table I.

Regarding the HCC treatment, there were 13 patients (30.2%) in the transplant waiting list and concomitant indication for chemoembolization, 12 patients (27.9%) were exclusively indicated for treatment with chemoembolization, nine patients (20.9%) were on transplant waiting list, five patients (11.6%) were being treated with sorafenib, three patients (7%) had palliative treatment and one patient (2.3%) had indication for hepatectomy.

In the physical evaluation, it was observed that 44.2% of the patients presented fluid retention, three of them (7%) with ascites, ten patients (23.3%) with edema and five (11.6%) presented both.

The assessment of nutritional status according to the different methods presented discrepancies, ranging from 11.6% to 58.1% in the diagnosis of malnutrition. The nutritional assessment is described in table II.

As observed in figure 1, there was a statistical difference between the diagnoses of malnutrition by the different methods.

In the correlation analysis between the nutritional assessment methods and staging HCC and cirrhosis scores, a negative correlation was observed between TSF and Child-Pugh score (p = 0.004) and a positive correlation was found between APM and BCLC (p = 0.006) (Table III).

DISCUSSION

The nutritional diagnosis of the HCC patient is directly related to their prognosis, so an effective and individualized dietary therapy is essential. For this, identifying the nutritional assessment method characteristic for these patients becomes of paramount importance. Although liver cancer is one of the most prevalent cancers in the world (21), with HCC accounting for 70-85% of these cases (6), there are still few studies that evaluate the prevalence of malnutrition in this population.

Schütte K et al., in their study with 51 HCC patients, observed a prevalence of nutritional risk of 33.4 to 37%, assessed through Nutritional Risk Score (NRS) and Mini Nutritional Assessment (MNA), respectively. No patient was diagnosed as malnourished (12).

A similar finding was observed by Tsai AC et al. (2011), when assessing the nutritional status of 300 patients with HCC through two modified versions of the Mini Nutritional Assessment: a thai standard version (specific cut-off points for this population) and a thai version in which the BMI is replaced by AC and calf circumference. The prevalence of malnutrition was 2% and the risk of malnutrition ranged between 45 and 47% (22).

However, the present study identified a higher prevalence of malnutrition in HCC patients, greater than 50% according to PG-SGA and AMC. These differences can be justified according to the nutritional assessment tools used. In the studies by Schütte K et al. (12) and Tsai AC et al. (22), the individuals were assessed through MNA, a validated tool to the assessment of nutritional status of elderly patients, not being compatible with the population allocated in both studies.

When assessing the nutritional status of HCC patients by different methods, we found discrepancies in the diagnosis of malnutrition ranging from 11.6% to 58.1%.

According to BMI classification, we observed a low prevalence of malnutrition, 11.6%, and a high prevalence of overweight and obesity, 32.6% and 14%, respectively, being statistically different from the other methods (APM, PA, PG-SGA and AMC). BMI underestimates the prevalence of malnutrition in HCC patients because it reflects body weight, which in most cases presents significant alterations due to hydroelectrolytic disorders, which was observed in physical examination of more than 40% of our sample. This finding corroborates studies performed with cirrhotic (7,23-25) and oncological patients (12,26-28).

In view of these difficulties related to the actual body weight of the chronic hepatopathic patient, a method of nutritional diagnostic with great value is the HGS, which indirectly reflects the muscular functionality of the individual (29).

Despite the high prevalence of muscle depletion identified through APM and AMC, only 23.3% of the patients presented functionality loss according to the HGS. Although we can’t asset, since we did not use all the criteria indicated by the European Working Group on Sarcopenia in Older People (EWGSOP) (30) in the evaluation of sarcopenia, we believe that the observed difference between the percentage of patients with reduced functionality and patients with loss of muscle mass is due to the fact that many of these were still in the pre-sarcopenia stage. In the pre-sarcopenia stage there is loss of muscle mass but without impairment of muscle strength or physical performance (30).

Through APM, malnutrition was identified in 48.8% of patients and a significant positive correlation with BCLC staging was observed. This means that, in our study, patients in the more advanced stages of the disease presented higher APM values, in agreement with other authors who showed that this is a poorly sensitive method in the assessment of liver disease patients (23-25).

With regard to arm measurements, 30.2% of the patients were classified as malnourished by TSF, 39.5% by AC and 58.1% by AMC. These findings are consistent with a greater mobilization of muscle mass in the assessed patients. Silva et al. also observed a higher prevalence, 74.4% of the sample, of muscle mass loss in the arm measurements of patients with esophageal and stomach cancer (31).

In this study, TSF was the only method showing a significant negative correlation with Child-Pugh score. In line with these findings, other authors observed correlation between Child-Pugh score and TSF (32,33). According to Alberino F et al., malnutrition is an independent risk factor for mortality and the inclusion of TSF and AMC improves the prognostic accuracy of Child-Pugh score (34).

Through PA, 48.8% of the patients were diagnosed with nutritional risk. These findings are in agreement with the literature, which defines PA as a good nutritional marker in liver disease, since it reflects the integrity of cell membranes and tissue homeostasis (35). According to Fernandes SA et al., 34.1% of the cirrhotic patients evaluated were malnourished according to PA and this was the only method capable of correlating malnutrition with Child-Pugh score (7). In Schütte study, 58.8% of patients had PA below 4.8° and this cut-off point was a predictor of mortality (12).

Several studies report PA as a clinically relevant indicator, predicting not only mortality (12,26,36), but also a reduction in muscle strength and quality of life (36). However, in our study we did not observe a correlation between PA and Child-Pugh, MELD or BCLC scores. Nevertheless, we believe that this absence of correlation was due to the sample size.

Some authors affirm that the nutritional assessment through Global Subjective Assessment (SGA) underestimates the prevalence and severity of malnutrition among cirrhotic patients (7,23,24). However, in our study, we chose to use PG-SGA, which is an adaptation of the original SGA proposed by Detsky et al., developed specifically for cancer patients (20).

Its seems to us that PG-SGA is a more comprehensive nutritional assessment method, since it encompasses both objective and subjective parameters, allowing an anthropometric analysis not only through weight, height and percentage of weight loss, but also of food consumption, symptoms of nutritional impact, physical examination, functionality and metabolic stress. This justifies that PG-SGA was one of the methods capable of identifying the highest percentage of malnourished patients (51.2%) in our sample. Even higher malnutrition rates were identified through the application of PG-SGA in other oncological populations, reaching 66% among patients with upper gastrointestinal tumors, correlating with mortality (37), 81% among patients with lung cancer (38) and up to 94.2% among palliative cancer patients (39). According to our experience, PG-SGA is a simple, easy-to-apply tool that requires 10-15 minutes to fulfill.

Recently, the Global Leadership Initiative on Malnutrition (GLIM) was convened by several of the major global clinical nutrition societies with the intent to build a global consensus about the diagnostic criteria for malnutrition in adults in clinical settings (40). The malnutrition classification criteria is divided into phenotypic criteria (non-voluntary weight loss, BMI and reduced muscle mass) and etiological criteria (reduced dietary intake and inflammation or disease severity). To diagnose malnutrition, at least one phenotypic criterion and one etiologic criterion should be present (40). Since the GLIM consensus was published in the second semester of 2018 and our study was developed between 2016 and 2017, we did not use its criteria for the diagnosis of malnutrition, which may be a limitation of our study.

Based on the results presented, it can be concluded that there was great variance in the malnutrition diagnosis among the methods studied. We believe that APM, AMC, PA and PG-SGA can be indicated as tools of choice in the nutritional assessment of HCC patients because they were the most sensitive methods in malnutrition diagnosis. These are simple, quick and inexpensive methods that can be used in clinical practice. It should be emphasized that a method may not meet the objective needs for the nutritional assessment of HCC patients, which is why we consider that the adoption of two or three methods that evaluate different situations can be complementary and more precise. We recommend further studies with a larger number of patients to confirm our findings and to identify a method that may be ideally considered as a golden standard in the assessment of HCC patients and that correlates with their clinical condition.

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Table I. Sample characterization

Variables	*n = 43*
Age (years) - mean ± SD	64.0 ± 5.8
Gender - n (%)	
Male	31 (72.1)
Female	12 (27.9)
Number of nodules - median (P25-P75)	2 (1-2)
Etiology of cirrhosis - n (%)	
Alcohol	9 (20.9)
HCV	24 (55.8)
HBV	4 (9.3)
HCV+ alcohol	4 (9.3)
NAFLD	2 (4.7)
Child-Pugh - n (%)	
A	25 (58.1)
B	16 (37.2)
C	2 (4.7)
Meld - mean ± SD	11.2 ± 3.3
BCLC stage - n (%)	
0	4 (9.3)
A	13 (30.2)
B	17 (39.5)
C	8 (18.6)
D	1 (2.3)
Diagnostic time (months) - median (P25-P75)	12 (6-24)
Comorbidities - n (%)	
SAH	18 (41.9)
DM2	12 (27.9)
Smoking - n (%)	
Active smoker	6 (14.0)
Ex-smoker	30 (69.8)
Alcoholism - n (%)	
Active alcoholism	2 (4.7)
Ex-alcoholic	20 (46.5)
Physical activity - n (%)	
Active	5 (11.6)
Inactive	38 (88.4)

SD: standard deviation; HCV: hepatitis C virus; HBV: hepatitis B virus; NAFLD: non-alcoholic fatty liver disease; MELD: Model for End Stage Liver Disease; BLCL: Barcelona Clinic Liver Cancer Group; SAH: systemic arterial hypertension; DM2: type 2 diabetes mellitus.

Table II. Nutrition status assessment

Variables	*n = 43*
BMI - n (%)	
Malnutrition	5 (11.6)
Eutrophy	18 (41.9)
Overweight	14 (32.6)
Obesity	6 (14.0)
AC - n (%)	
Severe malnutrition	2 (4.7)
Moderate malnutrition	5 (11.6)
Mild malnutrition	10 (23.3)
Eutrophy	20 (46.5)
Overweight	4 (9.3)
Obesity	2 (4.7)
TSF - n (%)	
Severe malnutrition	7 (16.3)
Moderate malnutrition	2 (4.7)
Mild malnutrition	4 (9.3)
Eutrophy	10 (23.3)
Overweight	2 (4.7)
Obesity	18 (41.9)
AMC - n (%)	
Severe malnutrition	0 (0.0)
Moderate malnutrition	5 (11.6)
Mild malnutrition	20 (46.5)
Eutrophy	18 (41.9)
HGS - n (%)	
Eutrophy	33 (76.7)
Malnutrition	10 (23.3)
APM - n (%)	
Eutrophy	22 (51.2)
Malnutrition	21 (48.8)
PA - n (%)	
Eutrophy	22 (51.2)
Malnutrition	21 (48.8)
PG-SGA - n (%)	
Eutrophy	21 (48.8)
Moderate malnutrition	13 (30.2)
Mild malnutrition	9 (20.9)

BMI: body mass index; HGS: hand grip strength; TSF: tricipital skinfold; AC: arm circumference; APM: adductor pollicis muscle; PA: phase angle; PG-SGA: patient-generated subjective global assessment; AMC: arm muscle circumference.

Table III. Correlation between the methods of nutritional assessment and disease staging

Variables	*Child*	*BCLC*	*Meld*
BMI	r_s = 0.100 (p = 0.523)	r_s = -0.195 (p = 0.290)	r_s = 0.233 (p = 0.133)
AC	r_s = -0.268 (p = 0.083)	r_s = -0.234 (p = 0.132)	r_s = -0.152 (p = 0.332)
TSF	*r_s = -0.430 (p = 0.004)*	r_s = -0.172 (p = 0.269)	r_s = -0.109 (p = 0.488)
AMC	r_s = -0.096 (p = 0.542)	r_s = -0.293 (p = 0.057)	r_s = -0.072 (p = 0.645)
HGS	r_s = 0.064 (p = 0.684)	r_s = 0.124 (p = 0.430)	r_s = 0.040 (p = 0.798)
PA	r_s = 0.104 (p = 0.506)	r_s = 0.229 (p = 0.140)	r_s = 0.175 (p = 0.261)
PG-SGA	r_s = 0.289 (p = 0.060)	r_s = 0.235 (p = 0.128)	r_s = 0.098 (p = 0.532)
APM	r_s = 0.285 (p = 0.064)	*r_s = 0.412 (p = 0.006)*	r_s = 0.100 (p = 0.524)

BMI: body mass index; HGS: hand grip strength; TSF: tricipital skinfold; AC: arm circumference; APM: adductor pollicis muscle; PA: phase angle; PG-SGA: Patient-Generated Subjective Global Assessment; AMC: arm muscle circumference; MELD: Model for End Stage Liver Disease; BLCL: Barcelona Clinic Liver Cancer Group: r: Spearman’s correlation coefficient.

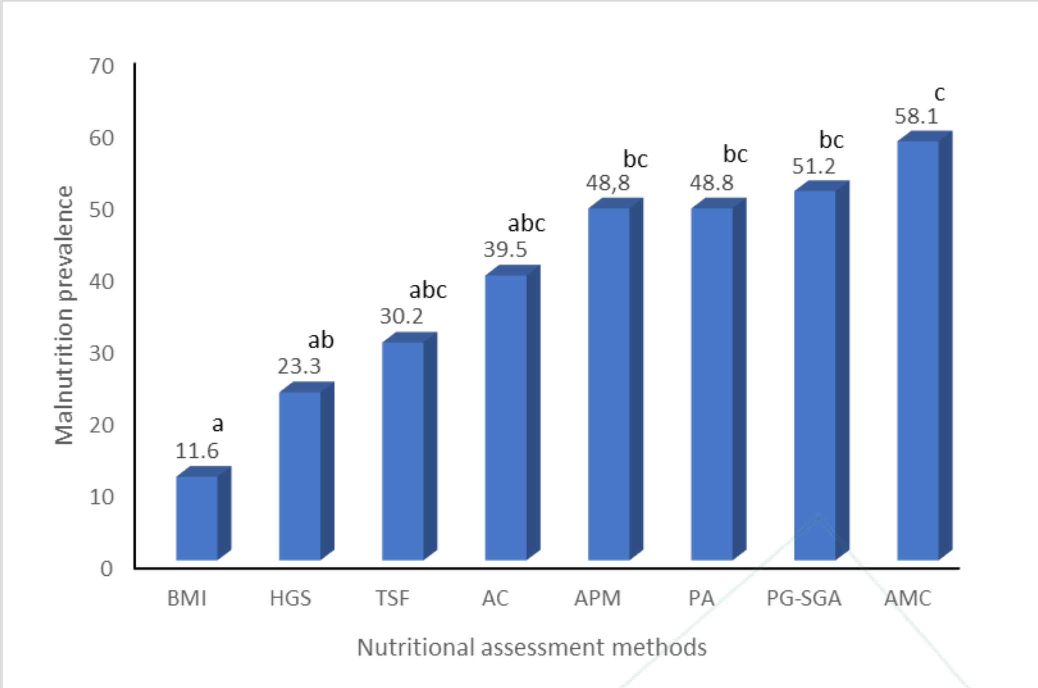

Fig. 1. Comparison of the percentage of malnutrition of the sample according to the different methods of nutritional assessment. BMI: body mass index; HGS: hand grip strength; TSF: tricipital skinfold; AC: arm circumference; APM: adductor pollicis muscle; PA: phase angle; PG-SGA: Patient-Generated Subjective Global Assessment; AMC: arm muscle circumference. Equal letters (a, b, c, d) do not differ by the multiple comparisons Cochrane's test at 5% significance.