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Original Article

Mid-Upper Arm Circumference vs. Quadriceps Muscle Layer Thickness as a Surrogate Measure of Fat Free Mass Index for GLIM Criteria Assessment among Head and Neck Cancer Patients

Mawaddah Azman [a *], Davina Stasia Teo [a], Mohd Razif Mohamad Yunus [a], Kew Thean Yean [b]

[a] *Department of Otorhinolaryngology and Head and Neck Surgery, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia,*
[b] *Department of Radiology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia*

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SUMMARY

Background: The objective assessment of phenotypic criteria for malnutrition requires tools which may be inaccessible to clinicians managing head and neck cancer (HNC) patients. The aim of this study was to measure the prevalence of malnutrition using Global Leadership Initiative on Malnutrition (GLIM) criteria, and evaluate the mid-upper arm circumference (MUAC) and quadriceps muscle layer thickness (QMLT) as a surrogate measure of fat free mass index (FFMI).
Methods: Fifty consecutive HNC patients were recruited in a cross-sectional study over a period of 18 months. QMLT was measured at three points using linear mode ultrasound. FFMI was determined using body impedance analysis. Blood samples were taken for serum albumin and C-reactive protein.
Results: The prevalence of malnutrition among HNC patients was 50.0%. MUAC was significantly correlated with FFMI, while QMLT significantly correlated with serum albumin ($p < 0.05$). The area under the curve of the MUAC measures obtained through the receiver operating characteristics was 0.9924, which was statistically significant ($p < 0.001$). Youden index revealed an optimal statistically derived MUAC cut-off of 23.5 cm (YI = 0.78; specificity 96; sensitivity 72) for detecting an abnormally low FFMI.
Conclusions: MUAC is superior to QMLT as a surrogate measure of FFMI. MUAC is a potentially useful phenotypic criteria for malnutrition in HNC.

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1. Introduction

Patients with head and neck cancer (HNC) are at high risk of developing malnutrition from a combination of tumour, host and immunological factors. Previous literature has linked malnutrition to increased length of hospital stay,[1–3] increased treatment-related complications,[1,2,4] reduced quality of life[5,6] and adverse survival outcomes.[2,3] Therefore, it is vital that clinicians assess patients with HNC to detect malnutrition and perform an early intervention.

In recent years, the Global Leader Initiatives for Malnutrition (GLIM) criteria has been adapted for the diagnosis of malnutrition.[7] A diagnosis of malnutrition is considered when a patient fulfils a combination of at least one phenotypic and one etiologic criterion. The three phenotypic criteria used include weight loss (either > 5% within past 6 months or > 10% over an indefinite duration), body mass index (BMI) (< 20 kg/m^2 if < 70 years or < 22 kg/m^2 if ≥ 70 years), and fat free mass index (FFMI), as measured by bioelectrical impedance analysis (< 17 fat free mass/m^2 for males and < 15 fat free mass/m^2 for females). The two etiologic criteria used are reduced food intake and elevated C-reactive protein (> 5 mg/L). Although this criterion has allowed standardization of the diagnosis of malnutrition, its practicality in a busy clinic remains questionable.

Ultrasonography is emerging as a promising bedside tool in measuring lean tissue. Campbell et al. showed that biceps, anterior forearm and anterior thigh muscle thicknesses as measured using ultrasound are correlated with gold standard dual x-ray absorptiometry.[8] However, further cross-sectional and validation studies have not only been heterogenous, but have lacked standardization on which anatomical point is best correlated with nutritional status.[9] The aim of this study was to measure the prevalence of malnutrition in HNC patients using the GLIM criteria, and to evaluate the mid-upper arm circumference (MUAC) and quadriceps muscle layer thickness (QMLT) as surrogate measures of FFMI. This being the case, MUAC or QMLT could potentially be utilized as a phenotypic measure of reduced muscle mass for diagnosis of malnutrition among HNC patients.

2. Materials and methods

This was a cross-sectional study conducted in the Department of Otorhinolaryngology, Universiti Kebangsaan Malaysia Medical Centre between October 2016 to March 2018 (18 months). The study was approved by the UKM Ethical Review Board and received funding from the fundamental grant of the University (Project code: FF-2016-354). The study was conducted according to the guidelines of the declaration of Helsinki and informed consent was obtained from all patients.

* Corresponding author. Department of Otorhinolaryngology, Level 9, Clinical Block, UKM Medical Centre, Universiti Kebangsaan Malaysia Kuala Lumpur Campus, Jalan Yaakob Latif, 56000 Cheras, Kuala Lumpur, Malaysia.
E-mail address: mawaddah1504@yahoo.com (M. Binti Azman)

Consecutive adults presenting to the otorhinolaryngology department with pathologically proven HNC who agreed to participate were recruited into the study. Oedematous patients (e.g. nephrotic syndrome, renal or liver failure), those unable to stand unaided and those with chronic plantar lesions (e.g. eczema, venous or diabetic ulcer) were excluded. A dedicated researcher (M.A.) recorded the demographic characteristics, dietary history and stratified patients into well-nourished and malnourished categories based on the criteria adapted from the GLIM.[7]

Another researcher (D.S.T) performed the anthropometric measurements, ultrasound measurements of the QMLT and biochemical measurements. This researcher was blinded to the nutritional stratification of each patient. Anthropometric measurements performed included weight, height, FFMI and bilateral MUAC. Patient heights were recorded using SECA Body meter (SECA, Germany) to the nearest 0.1 cm. Weight and body composition were measured using TBF 300 – TANITA Body Composition Analyzer (TANITA Corporation, Japan). Patients were instructed to stand straight on the measuring electrodes so that their body weight would be distributed evenly on their feet. FFMI was calculated for all patients using the formula: FFMI = fat free mass [kg]/ (height [m])^2 as described by Lu et al.[10] MUAC was measured using a non-stretchable measuring tape to the nearest 1 mm. A point between the olecranon and the acromion was bilaterally marked using a surgical pen and MUAC was measured with a relaxed arm. An average of three measurements were taken as the MUAC for each arm.

A B-mode ultrasound using a linear array probe with transducer frequency of 6–13 MHz was used to determine the QMLT. We used a constant setting for gain, focus and contrast for all measurements. Three anatomical points were marked using a surgical pen and QMLT was recorded in centimetres (cm). Figure 1 illustrates the three points of measurement. Both the right and left QMLT were assessed for all patients.

Biochemical measurements taken from patients included serum albumin and C-reactive protein. The stratification of patients into the well-nourished and malnourished limb categories was performed upon completion of data collection to avoid investigator bias. All data were analysed using Statistical Products and Service Solution software version 23.0. For demographic data, percentage and Chi-square tests were used to compare different characteristics across the study limbs. A *t*-test was used to compare differences in quadriceps muscle thickness, albumin and fat free mass among the study limbs. Pearson correlation was used to evaluate the correlations among MUAC, QMLT, albumin and FFMI in all patients. The validity of the surrogate measure was established using the receiver operation characteristic (ROC) curve, area under the curve (AUC), specificity (%), sensitivity (%), accuracy, negative predictive value (NPV, %), and positive predictive value (PPV, %). A p value of < 0.05 was considered to be statistically significant. Sensitivity and specificity were calculated for all individual measurements in the dataset. Youden's Index (YI) was calculated as YI = sensitivity + specificity – 1. The MUAC cut-off with the highest YI-value was considered the optimal statistically-derived cut-off.

3. Results

3.1. Demographic characteristics

From October 2016 till March 2018, 50 patients with head and neck cancer who fulfilled the inclusion and exclusion criteria were recruited. Of these, 37 (74%) were male and 13 (26%) were female. The mean age for the study population was 58.54 ± 12.16 years (29,80). A comparison of specific demographic characteristics (sex, race, age group, stage and tumour subsite) between well-nourished and malnourished patients revealed no significant differences (p > 0.05) (Supplementary material Appendix 1, Table A1).

3.2. Quadriceps muscle layer thickness

At all points, mean QMLT taken on the right was similar to measurements on the left (p > 0.05) (Table 1). Patients with malnutrition showed a trend towards a lower mean QMLT measure at all points compared to well-nourished patients (Table 2). Comparing the three points used to measure QMLT, Point A bilaterally and Point C on the left showed a significant difference (p < 0.05). The QMLT measures at

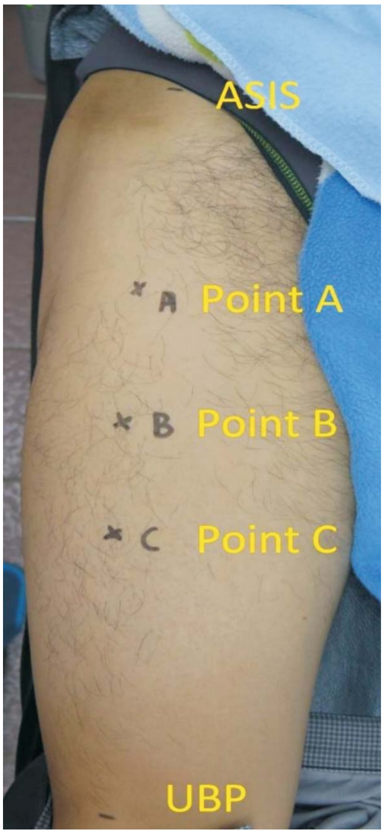

Figure 1. Anatomic reference points used for measurement of QMLT. A: Junction between upper 1/3 and lower2/3 of the distance between the anterior superior iliac spine and upper border of patella. B: Junction at the midpoint of the distance between the anterior superior iliac spine and upper border of patella. C: Junction between upper 2/3 and lower 1/3 of the distance between the anterior superior iliac spine and upper border of patella. ASIS: anterior superior iliac spine; QMLT: quadriceps muscle layer thickness; UBP: upper border of patella.

Table 1
Comparison of right and left quadriceps muscle thickness (QMLT) and mid-upper arm circumference (MUAC) taken at the same point.

Outcome measure		N	Mean (cm)	Standard deviation (cm)	*t*	p-value
QMLT	Right Point A	50	3.80	0.90	0.34	0.737*
	Left Point A	50	3.79	0.88		
	Right Point B	50	2.96	0.86	0.49	0.630*
	Left Point B	50	2.97	0.81		
	Right Point C	50	2.30	0.74	0.37	0.711*
	Left Point C	50	2.32	0.77		
MUAC	Right	50	27.14	3.51	1.27	0.209*
	Left	50	26.99	3.31		

* p-value > 0.05 using paired *t*-test.

Points A bilaterally and Point C on the left showed a significant low positive correlation with serum albumin and a non-significant correlation with FFMI (Supplementary material Appendix 1, Table A2). Using the ROC curve, the AUC for QMLT measures at all points were poor with FFMI.

3.3. Mid-upper arm circumference

MUAC was measured at bilateral upper arms in all patients. This study found no significant disparity between measurements taken on the right compared to the left side ($p > 0.05$) (Table 1). Patients who were malnourished typically had a lower MUAC compared to well-nourished patients i.e. 25.06 ± 2.65 cm and 28.80 ± 3.14, and the results were highly significantly different ($p < 0.001$) (Table 2). The MUAC measurements on the right and left sides showed a highly significant correlation with FFMI ($p < 0.001$). Mean MUAC for patients with normal FFMI was 28.80 ± 2.94 cm, while the mean MUAC for patients with malnourished FFMI was 25.23 ± 2.78 cm (Table 3). Using the ROC curve, the AUC for MUAC measures was 0.9924, which represents a statistically highly significant difference ($p \leq 0.001$). The cut-off value 23.5 cm recorded a high Youden's Index at 0.78. The sensitivity (1-false negative %) and specificity (1-false positive %) at the cut-off value of 23.5 cm were 72% and 96%, respectively. The PPV was 77.4%, the NPV was 94.7% and the accuracy of the MUAC measure was 84.0% (Figure 2).

4. Discussion

4.1. Malnutrition among head and neck cancer patients

Malnutrition is defined as a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass, further leading to diminished physical and mental function and impaired clinical outcome from disease.[11] Recent studies have since then reflected on these recommendations by ESPEN, such that the diagnosis of malnutrition encompasses not only the history of reduced nutritional intake, but also validated measures of decreased body cell mass.[7,12,13]

The present study reported a higher prevalence of malnutrition of 50% among a cohort of 50 HNC patients presenting at various stages of treatment. Despite using the same objective measures (FFMI and C-reactive protein) to determine a diagnosis of malnutrition using the GLIM criteria, our prevalence was higher compared to a recently published study by Einarsson et al.[7] Yet, another study by Steer et al. reported an even lower prevalence of 22.6%.[13] In this study, a validated subjective measure of muscle loss was used in the GLIM diagnosis of malnutrition, leading to minor limitations. The higher number of patients recruited from multiple centres and ongoing nutritional interventions may have contributed to the lower frequency of malnutrition among HNC patients reported in these two studies.

4.2. Measures of reduced muscle mass as a phenotypic criterion for malnutrition

Many studies have described the objective measurement of muscle mass in clinical assessment of nutrition status, ranging from bioelectrical impedance studies,[7] mid-arm muscle circumference,[14] computed tomography, dual-energy X-ray absorptiometry[15] to magnetic resonance imaging.[16] This is the first study to compare measures of muscle mass using the GLIM criteria for malnutrition. Each measure was compared against FFMI, a widely used objective measure of malnutrition among head and neck cancer patients. This study demonstrated no significant difference between the right and

Table 2
Comparison of outcome measures across well-nourished and malnourished limbs (based on the GLIM criteria).

Outcome measure		Limb	N	Mean	Standard deviation	p-value
QMLT (cm)	Right Point A	Well-nourished	25	4.02	0.96	0.033*
		Malnourished	25	3.56	0.82	
	Left Point A	Well-nourished	25	3.14	0.90	0.065
		Malnourished	25	2.77	0.80	
	Right Point B	Well-nourished	25	2.46	0.77	0.074
		Malnourished	25	2.16	0.67	
	Left Point B	Well-nourished	25	4.03	0.91	0.022*
		Malnourished	25	3.53	0.81	
	Right Point C	Well-nourished	25	3.13	0.84	0.085
		Malnourished	25	2.81	0.77	
	Left Point C	Well-nourished	25	2.52	0.78	0.035*
		Malnourished	25	2.13	0.71	
MUAC (cm)	Right	Well-nourished	25	28.80	3.11	0.0001*
		Malnourished	25	25.40	3.14	
	Left	Well-nourished	25	28.80	3.14	0.0001*
		Malnourished	25	25.06	2.65	
Serum albumin (g/L)		Well-nourished	25	36.32	3.64	0.343
		Malnourished	25	35.84	4.38	

* p-value < 0.05 using independent *t*-test.
GLIM: Global Leader Initiatives for Malnutrition; MUAC: mid-upper arm circumference; N: patient numbers; QMLT: quadriceps muscle layer thickness.

Table 3
A comparison of MUAC between well-nourished and malnourished limbs.

Outcome measure		Total (n = 100)		p-value
		Well-nourished (FFMI ≥ 17 kg/m² in males and ≥ 15 kg/m² in females)	Malnourished (FFMI < 17 kg/m² in males and < kg/m² in females)	
MUAC	(Mean ± SD)	28.80 ± 2.94	25.23 ± 2.78	< 0.001*
	MUAC ≤ 23.5 cm	48	14	< 0.001*
	MUAC > 23.5 cm	2	36	

* Significant p-value < 0.05.
FFMI: fat free mass index; MUAC: mid-upper arm circumference; n: patient numbers; SD: standard deviation.

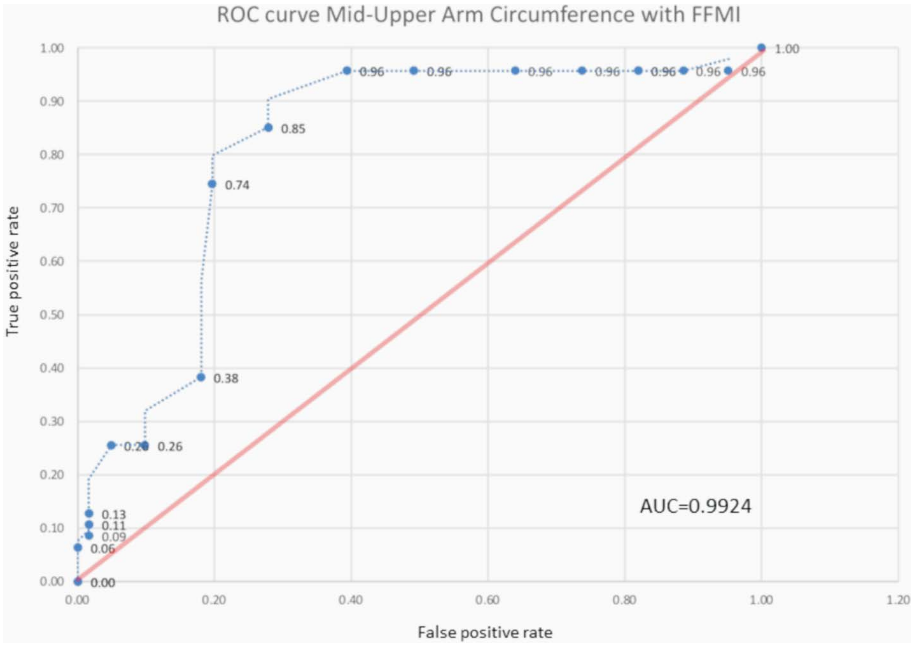

Figure 2. Receiver operating characteristics curve of mid-upper arm circumference based on FFMI < 17 kg/m^2 in males and < 15 kg/m^2 in females. AUC: area under curve; FFMI: fat free mass index; MUAC: mid-upper arm circumference; ROC: receiver operating characteristics.

left MUAC and QMLT values measured at the same point (p value > 0.05). This finding was supported by other published literatures on QMLT measurements, but no other studies have reported similar findings for MUAC.[17]

Earlier published studies have failed to clearly define standard anatomical reference points for measurement of QMLT.[18,19] Our findings show that the anatomical reference point used to measure QMLT is of clinical significance as a measure of nutritional status. Of all three points measured, Points C was found to be significantly different between well-nourished and malnourished patients based on the GLIM criteria, consistent through both thighs. The results indicate that the point between upper 1/3 and lower 2/3 of the distance between the upper border of patella and anterior superior iliac spine is a better reference point for measurement of quadriceps muscle thickness as an auxiliary tool for nutritional assessment. This finding must be interpreted with caution, as earlier validity studies with computed tomography used QMLT taken at mid-point and a point between upper 2/3 and lower 1/3 of the distance between the upper border of patella and anterior superior iliac spine.[20] In the present study, measurements taken at these points were found to be a less reliable measure of malnutrition according to the GLIM criteria. This is of great concern as validity and reliability on QMLT measurements undertaken at the point between upper 1/3 and lower 2/3 of the distance between the upper border of patella and anterior superior iliac spine has not been previously examined in earlier studies. Findings from this study may suggest the best reference point to measure QMLT and pave future directions to standardize QMLT measurements.

The MUAC is a simple tool used in the rural population for determining undernutrition among adults.[21] In the present study, MUAC has indicated a highly significant difference between well-nourished and malnourished patients based on the GLIM criteria. Additionally, the MUAC measurements showed a significant correlation with FFMI, a widely used phenotypic measure of malnutrition.[7,13,22]

4.3. MUAC as a surrogate measure of FFMI

The FFMI phenotypic criteria has been used widely in head and neck cancer and many other study populations utilizing the GLIM criteria for the diagnosis of malnutrition.[7,23] However, routine measurements of FFMI may not be possible in a busy outpatient clinic with no body impedance analysis machine, or among non-ambulant, oedematous patients.[23] Therefore, simpler and more readily available tool is required as a surrogate measure of FFMI. The MUAC measures obtained among our patients with head and neck cancer significantly correlated with FFMI measures. Additionally, further analysis using ROC curves showed a highly significant AUC of 0.9924, indicating the possibility of accurately determining the FFMI by measuring MUAC.

This promising result shows that MUAC measures can potentially serve as a surrogate measure to FFMI. Using the Youden's Index, an MUAC cut off point value of 23.5 cm was able to predict an abnormally low FFMI with a sensitivity of 72% and specificity of 96%. The reference values for MUAC in children have been described in large population-based study by Addo et al.[24] In adults, the reference values are less established and there is still no consensus for a specific cut-off in adults. A recent study by Thorup et al. among Nepalese patients suggested a cut-off of 24.5 am, best associated with BMI of less than 18.5 kg/m^2, regardless of sex.[25] Other studies using Youden's Index have reported MUAC cut-off between 21.9–25.1 cm in predicting low BMI.[21,26–28]

To the best of our knowledge, this study is the first to propose an MUAC cut-off point value to best predict an abnormally low FFMI. We believe this value is clinically relevant, as FFMI is a better predictor of reduced muscle mass compared to BMI, especially in the context of cancer. Additionally, BMI can be easily measured in any outpatient or inpatient setting, hence a need for a surrogate measure is less justified. The optimal cut-off was not determined strictly based on an equation, but instead takes into account its context. Considering the high prevalence of malnutrition among patients with head and neck cancer, it is paramount to have a sufficiently high sensitivity not to miss any patients. At the same time, choosing a cut-off with low specificity may cause unnecessary strain on already burdened nutritional support services. However, in the specific context of head and neck cancer, the impact of missing a patient who needs nutritional intervention would outweigh the cost of low specificity. Based on our analysis, we suggest a MUAC cut-off of 23.5 cm to be ideal in a South-East Asian head and neck cancer population, as this offers the highest possible sensitivity, with a specificity of more than 80%. The MUAC criterion, if used as part of longitudinal evaluation in HNC patients, may enable early nutritional intervention and better prediction of disease-specific outcomes.

5. Conclusions

The prevalence of malnutrition using GLIM criteria among head and neck cancer patients was 50%. MUAC and QMLT measurements taken at Points A and C were significantly different among well-nourished patients as compared to malnourished patients diagnosed using the GLIM criteria. The anatomical site used to measure QMLT is of clinical significance when used as a measure of nutritional status. MUAC measurements significantly correlated with FFMI measurements and MUAC of 23.5 cm and less predicted an abnormally low FFMI. MUAC is a better surrogate measure of FFMI compared to QMLT. MUAC is therefore a potentially useful phenotypic criteria for malnutrition in HNC.

Conflict of interest statement

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Appendix

Table A1
Demographic data of study population.

Demographic characteristic	No. of patients (%)			p-value
	Well-nourished (n = 25)	Malnourished (n = 25)	Overall (n = 50)	
Gender				1.000*
Male	19 (38%)	19 (38%)	38 (76%)	
Female	6 (12%)	6 (12%)	12 (24%)	
Ethnic				0.709*
Chinese	14 (28%)	12 (24%)	26 (52%)	
Malay	9 (18%)	7 (14%)	16 (32%)	
Indian	2 (4%)	4 (8%)	6 (12%)	
Others	0 (0%)	2 (4%)	2 (4%)	
Age group				1.000*
Young adult	2 (4%)	2 (4%)	4 (8%)	
Middle adult	14 (28%)	14 (28%)	28 (56%)	
Elderly	9 (18%)	9 (18%)	18 (36%)	
Stage				0.089*
Early stage (stage I and II)	9 (18%)	8 (16%)	17 (34%)	
Late stage (stage III and IV)	16 (32%)	17 (34%)	33 (66%)	
Primary				0.549*
Nasopharynx	12 (24%)	10 (20%)	22 (44%)	
Larynx and hypopharynx	7 (14%)	5 (10%)	12 (24%)	
Oral cavity	3 (6%)	7 (14%)	10 (20%)	
Others	3 (6%)	3 (6%)	6 (12%)	

* p-value > 0.05 using chi-square test.

Table A2
Correlation studies between study outcome measures.

Outcome measure		Serum albumin		Fat free mass index	
		r	p-value	r	p-value
QMLT	Right Point A	0.46	0.006*	0.14	0.323
	Left Point A	0.45	0.001*	0.20	0.156
	Left Point C	0.37	0.007*	0.14	0.341
MUAC	Right	0.18	0.202	0.39	0.005*
	Left	0.14	0.329	0.42	0.003*

* Significant p-value < 0.05 using paired Pearson correlation.