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ORIGINAL ARTICLE

Prospective Study

Phase angle as a prognostic biomarker in metastatic colorectal cancer: A prospective trial

Domina Kekez, Juraj Prejac, Gordan Adžić, Nikša Librenjak, Irma Goršić, Danijela Jonjić, Željko Krznarić, Goran Augustin, Stjepko Pleština

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Domina Kekez, Juraj Prejac, Gordan Adžić, Nikša Librenjak, Irma Goršić, Danijela Jonjić, Stjepko Pleština, Department of Oncology, University Hospital Centre Zagreb, Zagreb 10000, Grad Zagreb, Croatia

Domina Kekez, Juraj Prejac, School of Dental Medicine, University of Zagreb, Zagreb 10000, Grad Zagreb, Croatia

Željko Krznarić, Department of Internal Medicine, University Hospital Centre Zagreb, Zagreb 10000, Grad Zagreb, Croatia

Željko Krznarić, Stjepko Pleština, School of Medicine, University of Zagreb, Zagreb 10000, Grad Zagreb, Croatia

Goran Augustin, Department of Surgery, University Hospital Centre Zagreb, Zagreb 10000, Grad Zagreb, Croatia

Corresponding author: Juraj Prejac, MD, PhD, Department of Oncology, University Hospital Centre Zagreb, Kišpatićeva 12, Zagreb 10000, Grad Zagreb, Croatia. jprejac@kbc-zagreb.hr

Abstract

BACKGROUND

Colorectal cancer (CRC) represents a major global public health issue, ranking as the third most common cancer worldwide. Given the substantial prevalence of CRC, there is a critical need to identify precise prognostic and predictive biomarker tools for better treatment outcomes. Phase angle (PA) has been proposed as a prognostic marker in various non-malignant and malignant clinical conditions.

AIM

To investigate the relationship between PA and survival outcomes in the first-line treatment of metastatic CRC (mCRC).

METHODS

In this prospective observational study, we obtained data on patients who started first-line systemic chemotherapy from the beginning of 2020 until the end of 2022. The PA, assessed by the bioelectrical impedance analysis scale, was evaluated as a possible prognostic factor for treatment outcomes, which were measured as progression-free survival (PFS) and objective response rate (ORR).

RESULTS
Using the cut-point value for PA set at 4.60°, 144 patients were divided into two cohorts. The high PA group of patients exhibited a significantly longer median PFS than the low PA group, 14.8 *vs* 10.5 months, respectively. No difference in ORR was observed. However, patients with PA ≥ 4.60° had a higher disease control rate.

CONCLUSION
PA represents a novel and objective pre-chemotherapy prognostic factor to identify mCRC patients who are at increased risk of a worse survival outcome.

Key Words: Phase angle; Bioimpedance scale; Metastatic colorectal cancer; Treatment outcomes; First-line chemotherapy

Core Tip: Most patients with metastatic colorectal cancer (mCRC) experience malnutrition during their illness, resulting from both the disease and the treatment. Assessing the nutritional status of these patients is crucial due to its negative impact on treatment outcomes. Our objective was to establish the phase angle (PA) as a prognostic indicator for survival in mCRC patients. Our findings indicate that patients with a high PA (≥ 4.60°) have a considerably longer median progression-free survival during first-line treatment. PA, assessed using a bioelectrical impedance analysis scale, is a non-invasive and easily obtainable measure that can serve as an independent prognostic factor for survival in managing mCRC.

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INTRODUCTION

Colorectal cancer (CRC) represents a major global public health issue, ranking as the third most common cancer worldwide, with the second-highest mortality in men and the third-highest in women among malignant diseases[1]. Although notable advancements in CRC treatment over the past decade have been made, the majority of patients with metastatic disease remain largely incurable, with a median survival of 30 months[2,3]. Given the substantial prevalence of CRC, there is a critical need to identify precise prognostic and predictive biomarker tools for better treatment outcomes.

Malnutrition is defined as a state resulting from insufficient intake or absorption of nutrients, which leads to changes in body composition, such as decreased fat-free mass and body cell mass, compromising both physical and mental functions and, ultimately, impacting clinical outcomes in the presence of disease[4]. The interplay between malnutrition and cancer is often reciprocal, particularly in patients with digestive tract cancers. The disease itself frequently contributes to nutritional deficiencies, further exacerbating the challenges posed by malnutrition and its impact on the course of cancer. Recognizing the nutritional status of these patients is of utmost importance.

Nutritional status can be assessed by a variety of parameters, both anthropometric and biochemical. Using anthropometric parameters such as weight and body mass index, arm muscle circumference, and triceps skinfold thickness may be unreliable, especially in cancer patients with excess body weight, as such measurement can lead to an underestimation of nutritional risk and risk of sarcopenia[5]. In a clinical setting, anthropometric methods are not ideal due to their time-consuming nature and the need for well-trained staff. Nutritional status was also linked to serum concentrations of liver proteins, such as albumin. However, the reliability of albumin as an indicator of malnutrition is compromised due to its extended half-life and susceptibility to inhibition by inflammatory cytokines, including tumor necrosis factor-α and interleukin-6, which are elevated in cancer patients[6].

To address these challenges, a tool called bioelectrical impedance analysis (BIA) can be used. BIA is a user-friendly, noninvasive, and reproducible technique that allows for the evaluation of changes in body composition by measuring resistance and reactance to the weak electrical current that flows through the body. Different tissues have different electric impedances (opposition to the flow of an electric current), which can be used to determine total body water and, therefore, fat-free mass and body fat[7]. Phase angle (PA) is defined as the ratio of resistance (both intracellular and extracellular) and reactance (cell membrane-specific resistance). PA is considered an indicator of cellular health, with elevated values reflecting increased cellularity, enhanced cell membrane integrity, and improved cell function. The PA falls within the 5° to 7° range in healthy individuals, although athletes may achieve values surpassing 9.5°[8].

PA has been identified as a prognostic marker in various non-malignant clinical conditions, including liver disease, human immunodeficiency virus infection, chronic kidney disease, pulmonary disease, amyotrophic lateral sclerosis, geriatric and surgical patients, hemodialysis, sepsis, and many more[9-13]. Because malnutrition is a prominent contributor to morbidity and mortality among cancer patients, the PA was investigated and established as a prognostic factor in advanced colorectal, pancreatic, breast, non-small cell lung cancer, and others[14-18]. The main disadvantage of these trials is that they were retrospective. The aim of our prospective study is to evaluate the association of the BIA-derived

PA with the duration of the first-line treatment in patients with metastatic CRC (mCRC).

MATERIALS AND METHODS

In this prospective, observational single-cohort study, we examined the PA as an independent prognostic factor in the first-line treatment of mCRC. Patients who started treatment for mCRC at our institution from January 1, 2020, until December 31, 2022, were included. All eligible patients had histologically confirmed disease and were ≥ 18 years old. The study was approved by the Ethical Committee of the University Hospital Centre Zagreb (No. 8.1-21/1281-2) and conducted under the guidelines of the Declaration of Helsinki. All patients provided their written informed consent before entering the study.

Standard chemotherapy for mCRC consisted of fluoropyrimidines, oxaliplatin, and/or irinotecan, with or without the addition of an anti-vascular endothelial growth factor or anti-epidermal growth factor receptor biological agent. Therapy was continued until clinical and/or radiological disease progression or unacceptable toxicity. Before each cycle, blood tests were performed, and treatment pauses and dose de-escalation due to toxicity were allowed. Objective response evaluation using computed tomography (CT) and carcinoembryonic antigen was routinely performed every 3 months.

Data on nutritional status and body composition were documented using the BIA scale. All treated patients received oral nutritional support and a high-calorie diet. Patients are weighed with a BIA scale (Tanita PRO Body Composition Analyzer MC-780MA-N, Tanita Corporation, Tokyo, Japan) before the start of chemotherapy as part of a complete physical examination. The scale features a multi-frequency 8-electrode measurement system with a 5 kHz/50 kHz/250 kHz measurement frequency and a 90 μA or less measurement current. Measurements are conducted while the patient stands, ensuring both feet are placed on the scale (foot electrodes). Also, measurements were done after 8 hours fasting, and patients with ascites or severe edema were excluded from the trial. Additionally, the patient firmly grasps the hand electrodes with both hands while keeping their hands resting alongside their body. Patients are required to stand calmly for 20 seconds until the measurements are completed. The scale measures the PA at 50 kHz. In addition to the PA, the scale also measures body weight (kg), extracellular water (kg), intracellular water (kg), body fat (% and kg), fat-free mass (kg), total body water (kg), muscle mass (kg), bone mass (kg), impedance (Ohm), and basal metabolism (kJ). PA was used as a biomarker to detect sarcopenia.

Standard demographic, tumor- and treatment-related data were collected for each patient, including age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), sidedness and resection of the primary tumor, rat sarcoma (RAS) mutational status, type of chemotherapy and biological agent received, tumor involvement of the liver and/or peritoneum. Peritoneal carcinomatosis was diagnosed radiologically using the CT scan or the magnetic resonance imaging or surgically when exploration was performed during primary tumor resection or colostomy. No routine staging laparoscopy was performed.

This study aimed to define the PA as an independent prognostic factor for survival in patients with mCRC. Outcomes were measured as progression-free survival (PFS) and objective response rate (ORR). PFS was defined as the time from the start of first-line treatment until disease progression or death from any cause. Patients lost to follow-up were censored at their last hospital visit. ORR was defined as the percentage of patients having a partial or complete response.

Statistical analysis

The Shapiro-Wilk test was used to assess the normality of distribution. Age as a continuous variable was reported as median, and the difference was tested using the Mann-Whitney *U* test. Categorical variables were reported as absolute numbers and percentages, and the differences were tested using Pearson's χ^2 d test. Receiver operating characteristic (ROC) analysis was conducted for PA as the test value, and response to therapy in the dichotomized form (controlled or progressive disease) served as the outcome measure. The overall diagnostic accuracy was quantified using an analysis of the area under the curve.

Cox multiple regression analysis examined the association between PFS, PA, and patient- and tumor-specific variables listed above. The patients were divided into two groups based on the PA cut-off value obtained by the ROC curve analysis whose absolute value of the difference between the sensitivity and specificity values is minimal. PFS estimates were generated using the Kaplan-Meier method, presented as survival curves, and compared using the log-rank test. Data on PFS were censored at a 36-month cut-off.

Data was analyzed using statistical, TIBCO Software Inc. (2020), Data Science Workbench, version 14 (http://tibco.com).

RESULTS

Of 238 patients initially included in the study, 90 did not undergo BIA measurement before initiating the first chemotherapy cycle, 2 underwent secondary curative resection, and 2 withdrew informed consent. The final analysis included 144 patients (Figure 1). The median value of PA for the whole cohort was 4.70° (range: 2.90° to 8.40°). Simultaneous assessment of sensitivity and specificity, using ROC curve analysis, identified the cut-point value for PA as 4.60°. The patients were divided into two groups: The low PA group, defined by PA values < 4.60° (n = 63), and the high PA group with PA value ≥ 4.60° (n = 81).

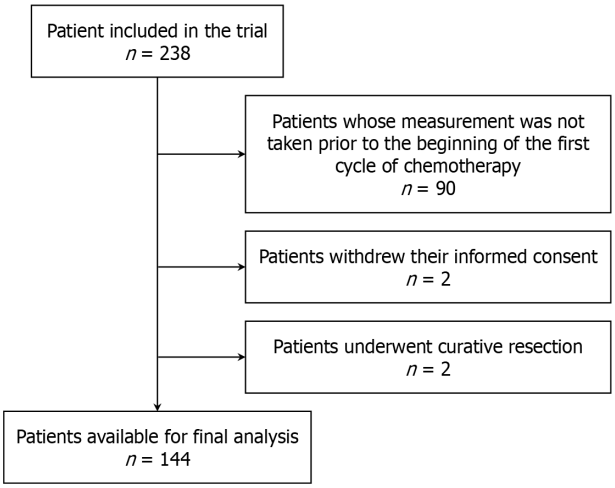

Figure 1 CONSORT diagram. Flowchart of patients' disposition for the study.

Baseline characteristics are detailed in Table 1. Differences in the number of subjects between the two defined groups were tested. The groups were numerically well-balanced, and no significant differences were observed between them except in the distribution by sex. Men had relatively higher PA values than women.

Cox multiple regression was employed to identify PA as an independent prognostic factor for PFS and to assess the impact of other specific variables, including demographic, tumor-related, and treatment-related factors: Age, sex, ECOG PS, RAS status, primary tumor location, primary tumor resection, liver metastases, and peritoneal carcinomatosis (Table 2).

The median PFS for the entire cohort was 12.6 months (range: 0.7 to 49.4). A significantly shorter PFS was observed in the low PA group [hazard ratio (HR) = 0.64, 95% confidence interval (CI): 0.42-0.98]. Additionally, the metastasis site has a notable effect on survival. Patients without peritoneal metastases experienced longer PFS in comparison to patients with involvement of the peritoneum, 12.9 *vs* 11.7 months (HR = 0.57, 95%CI: 0.37-0.87), respectively. Furthermore, patients who underwent primary tumor resection had a longer PFS of 13.6 months compared to 10.5 months for those with primary tumor in situ (HR = 0.57, 95%CI: 0.37-0.87). No significant influence on PFS was found for other tested variables.

Survival outcomes for the low and high PA groups were depicted using the Kaplan-Meier curve (Figure 2). The high PA group exhibited a significantly longer median PFS than the low PA group, 14.8 *vs* 10.5 months.

At the time of data collection, 95 patients have died, and 121 have experienced disease progression after first-line treatment. Using RECIST1.1, 4 complete responses were achieved, and 69 patients had tumor reduction (partial response) on first-line treatment, with no significant statistical difference between the groups. The total disease control rate (DCR) was recorded in a total of 125 patients, and patients in the group with PA ≥ 4.60° exhibited significantly higher DCR (Table 3).

DISCUSSION

Although several well-known prognostic factors for survival in mCRC exist, including primary tumor sidedness, microsatellite instability, RAS/*BRAF* status, age, and performance score, given the prevalence and epidemiology of the disease, the identification of new prognostic factors remains of utmost importance[19]. Nutritional status, *i.e.*, its specific biological indicators, is often omitted when examining cancer patients' treatment outcomes. Even despite the oncologists' awareness of cancer-related malnutrition, in the actual clinical practice setting, there is an insufficient active approach to its early recognition and prevention[20]. Due to its proven prognostic value for survival, ECOG status is used as a robust and comprehensive indicator of the patient's general condition[21]. Our earlier study based on the simple dynamics of body mass change indicated that a higher rate of weight loss is also an independent prognostic factor for outcome in first-line treatment of mCRC[22].

PA serves as an indicator of cell membrane health and integrity. Elevated PA values indicate increased cellularity, enhanced cell membrane integrity, and improved cell function, while lower values suggest cell deterioration, compromised cell membrane integrity, and impaired cell function[8]. PA is also considered a proxy for fluid distribution (extracellular water/intracellular water) and body cell mass[23]. Higher PA values are linked to greater muscle mass, reduced fat mass, and decreased fluid retention. In contrast, lower values are associated with diminished muscle mass, increased fat mass, and heightened fluid retention. The association between PA and sarcopenia in patients with cancer has been extensively investigated. Many studies of BIA focused on the relationship between PA and sarcopenia. Indeed, PA can indicate body composition, encompassing factors like visceral proteins and body cell mass. In a study by Ji *et al* [24], the relationship between PA and sarcopenia was explored in 445 men older than 65 years diagnosed with non-small cell lung or digestive tract cancers. It was categorized into two groups depending on the presence of sarcopenia. Significant variance in PA levels between the sarcopenic and non-sarcopenic patients was found, and there was a strong

Table 1 Patients' characteristics at baseline, *n* (%)

Characteristic		*n* = 144	PA < 4.60° (*n* = 63)	PA ≥ 4.60° (*n* = 81)	*P* (χ^2, *U*)[1]
Age (years)	Median	62	64	62	0.336
	Range	22-82	35-82	22-78	
Sex	Men	79 (54.9)	24 (38.1)	55 (67.9)	< 0.001
	Women	65 (45.1)	39 (61.9)	26 (32.1)	
ECOG PS	0	133 (92.4)	56 (88.9)	77 (95.1)	0.167
	1	11 (7.6)	7 (11.1)	4 (4.9)	
Sidedness	Left	123 (85.4)	57 (90.5)	66 (81.5)	0.129
	Right	21 (14.6)	6 (9.5)	15 (18.5)	
Mutation status	Wild type	60 (41.7)	22 (34.9)	38 (46.9)	0.211
	RAS mutated	79 (54.9)	37 (58.7)	42 (51.9)	
	BRAF mutated	4 (2.8)	3 (4.8)	1 (1.2)	
	Unknown	1 (0.7)	1 (1.6)	0	
Biological agent	anti-EGFR	59 (41.0)	23 (36.5)	36 (44.4)	0.324
	bevacizumab	81 (56.3)	37 (58.7)	44 (54.3)	
	None	4 (2.8)	3 (4.8)	1 (1.2)	
Primary tumor resection	Yes	117 (81.3)	49 (77.8)	68 (84.0)	0.346
	No	27 (18.8)	14 (22.2)	13 (16.0)	
Liver metastases	Yes	102 (70.8)	43 (68.3)	59 (72.8)	0.548
	No	42 (29.2)	20 (31.7)	22 (27.2)	
Peritoneal metastases	Yes	46 (31.9)	15 (23.8)	31 (38.3)	0.065
	No	98 (68.1)	48 (76.2)	50 (61.7)	

[1]Differences between groups were tested using the χ^2 test for categorical and *U* test for continuous variables.
ECOG: Eastern Cooperative Oncology Group; PS: Performance status; RAS: Rat sarcoma; EGFR: Epidermal growth factor receptor; PA: Phase angle.

correlation between PA and sarcopenia. Moreover, PA exhibited connections with specific diagnostic factors of sarcopenia, such as handgrip strength and skeletal muscle mass index. A similar correlation was found in patients with hepatobiliary and pancreatic cancers and patients with cancer in palliative care[25,26]. Two prospective trials in patients with pancreatic head cancer undergoing pancreaticoduodenectomy and patients with breast cancer undergoing first-line chemotherapy have shown that PA was associated with an increased risk of malnutrition[27,28]. Considering the influence of malnutrition and sarcopenia on the survival rates of cancer patients, it is probable that PA carries prognostic significance. PA holds promise in enhancing current prognostic methodologies aimed at recognizing patients who are susceptible to the adverse effects of cancer treatments and increased overall mortality risk[29].

Several studies have also demonstrated that a low PA is a significant predictor of adverse outcomes in patients with various chronic diseases, not just cancer patients. In a study of cirrhotic patients, a PA cutoff of ≤ 4.9° was independently associated with increased mortality. Patients with this low PA exhibited poorer metabolic health, worse nutritional status, and more rapid disease progression[30]. In another study of chronic obstructive pulmonary disease patients, low PA was significantly correlated with sarcopenia and malnutrition. Cutoff values of 4.75° and 4.25° for PA were identified as predictors of sarcopenia and malnutrition, respectively[31]. A retrospective study of adult human immunodeficiency virus patients found that low PA was an independent predictor of malnutrition. Cutoff values of 5.45° for men and 4.95° for women demonstrated high sensitivity and specificity in predicting malnutrition[32].

To our knowledge, this is the first prospective study investigating the link between PA and survival in the first-line setting of mCRC. Multiple studies consistently emphasize the strong predictive link not only between the PA and nutritional status and functional condition but also between the PA and survival in various diseases, especially cancer. However, many studies were conducted retrospectively, introducing a potential bias to the results. Additionally, most studies commonly establish PA cut-offs based on the study population, often using the median or lowest quartile or by comparing with a healthy control group. This approach lacks generalizability, making these cut-offs potentially inapplicable in broader clinical settings[8]. Although several reference values for PA have been published for the healthy population, there is no consensus on an adequate cut-off for patients with cancer[33,34]. Due to metabolic disruptions linked to malnutrition and cancer cachexia, individuals with advanced cancer may exhibit a lower PA compared to the levels observed in the healthy population[35].

Table 2 Cox multiple regression model for progression-free survival as outcome

		Hazard ratio	95%CI		*P* value
			Lower	Upper	
Age		1.00	0.98	1.02	0.840
Sex	Women	1.18	0.42	1.81	0.437
	Men	1 (Ref.)			
ECOG PS	0	0.74	0.37	1.51	0.414
	1	1 (Ref.)			
Phase angle	≥ 4.60°	0.64	0.42	0.98	0.040
	< 4.60°	1 (Ref.)			
Primary tumor sidedness	Left	1.13	0.65	1.94	0.668
	Right	1 (Ref.)			
Resection of the primary tumor	No	1.86	1.16	2.98	0.010
	Yes	1 (Ref.)			
RAS status	Mutated	1.16	0.78	1.71	0.462
	Wild type	1 (Ref.)			
Liver metastases	Absent	0.77	0.50	1.17	0.223
	Present	1 (Ref.)			
Peritoneal metastases	Absent	0.57	0.37	0.87	0.009
	Present	1 (Ref.)			

ECOG: Eastern Cooperative Oncology Group; PS: Performance status; RAS: Rat sarcoma; CI: Confidence interval.

Table 3 Best response, *n* (%)

		PA < 4.60° (*n* = 63)	PA ≥ 4.60° (*n* = 81)	*P* (χ^2) value
CR	4 (2.8)	2 (3.2)	2 (2.5)	
PR	69 (47.9)	25 (39.7)	44 (54.3)	
SD	52 (36.1)	20 (31.7)	32 (39.5)	
PD	19 (13.2)	16 (25.4)	3 (3.7)	
CR + PR	73 (50.7)	27 (42.9)	46 (56.8)	0.097
DCR (CR + PR + SD)	125 (86.8)	47 (74.6)	78 (96.3)	< 0.001

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; DCR: Disease control rate; PA: Phase angle.

Using the ROC analysis, our study identified a PA of 4.60° as a cut-off point for this analysis. A statistically significant decrease in PFS among patients with a PA < 4.60° compared to those with a PA ≥ 4.60° was observed. Previous studies on this topic have confirmed comparable findings. One retrospective study on patients with CRC found that patients with a PA of ≤ 5.57° have a median odds ratio of 8.6 compared to 40.4 months in patients with a PA of > 5.57°[16]. A similar study was conducted involving patients with metastatic pancreatic cancer, and it demonstrated a statistically significant association between the values of PA below 5 and survival[15]. Besides PA, the sites of metastases, specifically liver and peritoneal dissemination, showed a statistically significant negative association with PFS. Within our cohort, 70.8% and 31.9% were found to have liver and peritoneal involvement, respectively. Liver metastases are the most common site in mCRC, followed by lungs and peritoneum[36,37]. They are recognized to have a detrimental effect on survival, with the number of lesions influencing survival[38]. Less frequent than the liver, peritoneal dissemination is generally present in about a fifth of patients[39]. Similarly, these patients also have a significantly worse survival compared to those whose peritoneum is not affected by the tumor. In itself, peritoneal metastases represent both negative prognostic and predictive factors, given that even systemic chemotherapy is less effective in these patients[39,40]. However, our study did not find a significant independent impact of liver metastases on survival. Regarding the impact of primary tumor resection on the

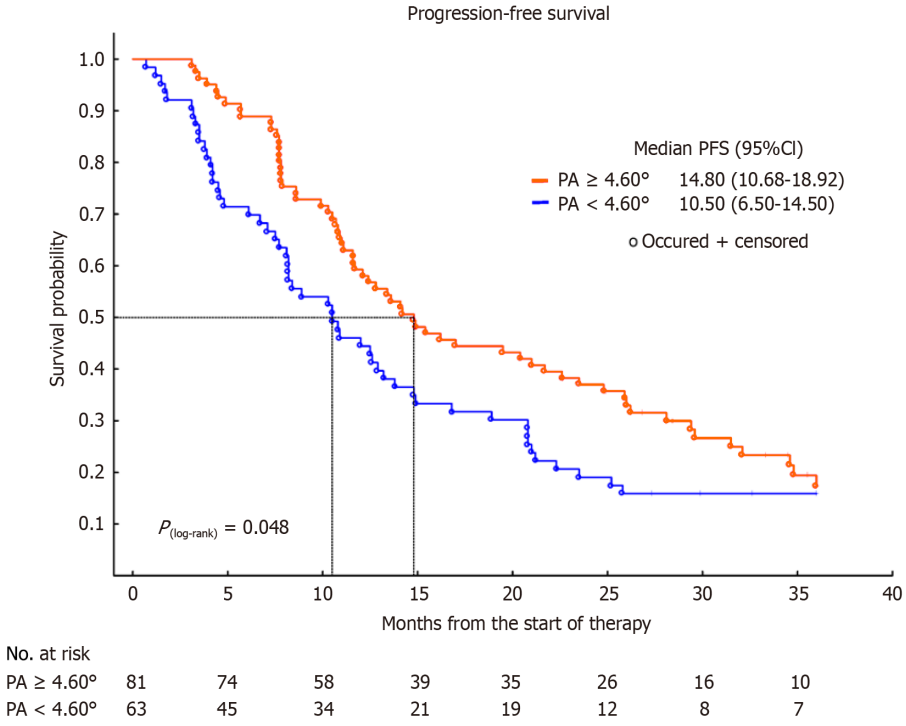

Figure 2 Kaplan-Meier curves demonstrating progression-free survival in metastatic colorectal cancer patients stratified by phase angle.
The numbers of patients at risk for each group are shown in the table below. PFS: Progression-free survival; CI: Confidence interval; PA: Phase angle.

survival of patients with mCRC, the literature data are contradictory, likely due to the heterogeneity of the populations included in the studies[41,42]. In our study, primary tumor resection proved relevant for first-line treatment outcomes. However, this result should be regarded, keeping in mind, that data on the potential resectability or the necessity of resecting the primary tumor were not collected.

Other monitored variables did not exhibit statistical significance, which aligns with previously established data on predictive factors in patients with CRC[19]. Our study patients were almost all in good general condition, expressed as ECOG PS 0. This is important as poor ECOG PS has been shown to be a risk factor for poor survival and increased toxicity, leading to its inclusion in mCRC treatment guidelines[43]. However, most studies include ECOG PS 0 and 1 patients pooled together as having good general condition, although ECOG PS 0 patients have significantly better treatment outcomes, both in terms of survival and fewer serious adverse events[44]. We can argue that the additional value of our research is that only 7.6% of patients had ECOG PS > 0, thus ruling out the possibility of the influence of PS on PA and treatment outcomes.

Although our results indicate a significant difference in PFS between the high and the low PA groups, no difference in the ORR was found. This discrepancy can stem from several potential causes. If we hypothesize that PA could indicate better organ physiology, such as improved organ function, enhanced nutrition, or reduced inflammation, this may affect the ability to maintain disease control rather than reflecting the tumor's inherent sensitivity to treatment. As a result, it could lead to a longer PFS than the ORR. A higher PA might be linked to characteristics such as better vascularization, lower levels of hypoxia, or lower systemic inflammation. These factors can contribute to slower disease progression but may not necessarily lead to a better tumor shrinkage response. Similarly, patients with higher PA might better tolerate treatment due to their overall health, enabling longer disease control. This could improve PFS without necessarily enhancing the ORR.

This study focused on a homogenous population of patients with mCRC before initiating first-line treatment. While traditional randomization was not employed, the investigated variable (PA values impacting treatment outcomes) was unknown, and previous studies in this area have been retrospective. Therefore, a key strength of our study lies in its inclusion of patients with uniformly staged disease, allowing for the control of disease characteristics and enhancing the robustness of our findings. It is crucial to highlight that the PA value of 4.6° was utilized to demonstrate that it can serve as a prognostic parameter when considered independently. Building on this, we believe it paves the way for further prospective research to establish specific prognostic cut-off values for different patient populations.

Single-center studies can have limitations, such as potential biases due to including patients from a specific geographic area, which may not represent the broader population. Additionally, treatment practices and resource availability can vary between institutions, potentially influencing study outcomes. Our study mitigated these concerns by including patients from across the country and adhering to international treatment guidelines for CRC. The main limitations of our study are its single-institution design and the limitations of the BIA method itself, where measurement errors can be influenced by factors such as recent food and beverage consumption, variations in air and skin temperature, and recent exercise[45].

CONCLUSION

PA is an objective, noninvasive, and easy-to-obtain pre-treatment measure that can be regarded as an independent prognostic factor for PFS in the first-line setting of mCRC. Further research is warranted to establish appropriate or even multiple cut-off values to clarify the overall prognosis of these patients. Also, studies investigating whether nutritional intervention during first-line therapy can change the PA value and/or treatment outcomes are needed.

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FOOTNOTES

Author contributions: Kekez D and Prejac J designed the study; Kekez D, Librenjak N, Goršić I, and Jonjić D participated in collecting data and drafting the manuscript; Adžić G and Prejac J did a statistical analysis and revised the manuscript; Pleština S helped design the study and revised the manuscript; Krznarić Ž and Augustin G revised the manuscript.

Institutional review board statement: The study was approved by the Ethical Committee of the University Hospital Centre Zagreb (No. 8.1-21/1281-2) and conducted under the guidelines of the Declaration of Helsinki.

Clinical trial registration statement: Given that this is a prospective study and no experimental drug was investigated, registration on ClinicalTrials.gov is not required.

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ORCID number: Juraj Prejac 0000-0003-1981-9369.

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