ejpmr, 2024, 11(7), 260-265

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

SARCOPENIA IS ASSOCIATED WITH SEVERE POSTOPERATIVE COMPLICATIONS IN COLORECTAL CANCER PATIENTS UNDERGOING SURGERY FOR COLORECTAL CANCER: A HOSPITAL BASED PROSPECTIVE OBSERVATIONAL STUDY IN SUB-HIMALAYAN REGION

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Article Received on 10/05/2024 **Article Revised on 01/06/2024** **Article Accepted on 21/06/2024**

ABSTRACT

Background: Malignancy is a secondary cause of sarcopenia, which is associated with impaired cancer treatment outcomes. The objective of this study was to examine the occurrence of postoperative complications in patients with resectable colorectal cancer, comparing those with sarcopenia to those without sarcopenia who underwent surgery for the disease. There is very limited data available from sub-Himalayan belt of northern India, hence the present study was planned to know the association of sarcopenia with postoperative complications in colorectal cancer patients undergoing surgery. **Methods:** A hospital based prospective observational study was conducted in the Department of General Surgery of a tertiary care hospital in Shimla, Himachal Pradesh. All patients who reported to Department of Surgery during the study period of 1st September 2021 to 30th September 2022 with diagnosis of colorectal cancer were considered for the study. **Results:** Thirty nine patients were included in the study and had a mean age of 57.59± 16.51 years. Sarcopenia was detected in 15(38.46%) patients based on EWGSOP2 (The European Working Group on Sarcopenia in Older People 2) recommendations. The mean age was 59.58 years in the sarcopenic group (SG) and 55.6 years in the non-sarcopenic group. The mean SMI(Skeletal Muscle Index) was 47.54±7.65cm²/m² and 49.248±8.44cm²/m² in the SG and NSG, respectively. The mean body mass index (BMI) was lower in the sarcopenic group than in the nonsarcopenic group (20.86 ± 2.34 vs. 21.90± 2.8 kg/m^2). Postoperative complications based on Clavien Dindo classification were significantly higher in the sarcopenic group than in the non-sarcopenic group (60 % vs. 33.33 %; P = 0.03). **Conclusions:** Preoperative sarcopenia as defined by the EWGSOP2 recommendations is a risk factor for severe postoperative complications in colorectal cancer patients undergoing surgery.

KEYWORDS: Sarcopenia _ Postoperative complications _ Colorectal cancer.

INTRODUCTION

Colorectal cancer (CRC) stands as the third most prevalent cause of cancer-related mortality worldwide.[1] While surgical resection plays a crucial role in treating this condition, certain patients encounter postoperative complications like surgical site infections and anastomotic leakage.[2–5] These complications are strongly linked to both cancer recurrence and reduced survival rates in CRC patients.[6–8]

Sarcopenia, initially conceptualized by Rosenberg and Roubenoff, characterizes a progressive and widespread decline in muscle mass and strength associated with aging.[9] It closely correlates with diminished muscle mass, which can be accurately assessed using computed tomography (CT) to measure skeletal muscle volume.[10] Sarcopenia often coincides with aging, sedentary behavior, and comorbidities such as chronic heart failure, pulmonary disease, cirrhosis, and renal failure.[11,12] Elevated rates of cancer recurrence and unfavorable outcomes have been observed when sarcopenia accompanies various cancer types.[13–15] It is yet unknown how much sarcopenia affects cancer patients, despite the fact that it is well known to be a risk factor for functional limitation, physical disability, a decline in quality of life, and eventually mortality.[2] Sarcopenia's impact on cancer patients' treatment outcomes has been the subject of extensive research recently; it has been shown that sarcopenia is independently linked to poor outcomes following surgery, both short- and long-term as well as

an increased risk of toxicity from chemotherapy. There is very limited data available from sub-Himalayan belt of northern India, hence the present study was planned to know the association of sarcopenia with postoperative complications in colorectal cancer patients undergoing surgery.

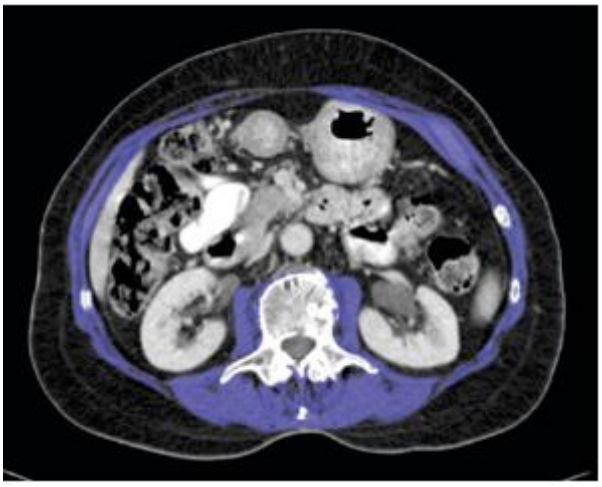
MATERIAL AND METHODS

A hospital based prospective observational study was conducted in the department of surgery of a tertiary care hospital in Shimla, Himachal Pradesh between September 2021 to September 2022., a total of 39 colorectal cancer patients reported to Department of General Surgery IGMC SHIMLA . We excluded patients who were not willing for surgery in surgical operable cases and patients with spinal deformity, quadriplegia, spinal muscular atrophy.

We investigated the postoperative complications between sarcopenic and non-sarcopenic patients. Postoperative complications were graded according to the Clavien–Dindo (CD) classification system.[24] Complications were defined as those that were CD grade II or higher.

Screening for sarcopenia

Sarcopenia was assessed by calculating Skeletal Muscle Index using CT scan at L3 vertebrae. In this study CECT ABDOMEN which is used for the diagnosis of the gastrointestinal malignancy was used for calculating the SMI. No separate CECT ABDOMEN was done for calculating SMI. In this study patients were subjected for CT scan in 64 slice MDCT (Light speed VLT –XTE Gc medial system) and the cross-sectional images at the level of L3 vertebral body at which both transverse processes were visualized. The area of the muscle's psoas, quadratus lumborum, erector spinae muscles, transversus abdominis, internal and external obliques and rectus abdominis muscles were evaluated manually by the area measurement tool using RadiAnt DICOM viewer. The threshold range for skeletal muscle was -30 to +150 Hounsfield units. The skeletal muscle area was normalized for height to calculate the skeletal muscle index.



The skeletal muscle index is calculated as follows:-

Cross-sectional area of the total skeletal muscles at L3 (psoas, quadratus lumborum, erector spinae, transversus abdominis, internal and external obliques and rectus abdominis muscles) in $[cm]^2$
Height $[m]^2$

Patients were categorized into sarcopenic and non-sarcopenic groups based on CT measurement of total skeletal muscle mass in cross sectional area at the level of L3. Based on EWGSOP2 (The European Working Group on Sarcopenia in Older People 2) recommendations, SMI < 55 cm^2/m^2 was considered the cutoff for men, compared to < 39 cm^2 for women.

Statistical analysis

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means ± SD and as median with 25th and 75th percentiles (interquartile range). The following statistical tests were applied for the results:

1. The association of the variables which were quantitative in nature were analysed using Independent t test (for two groups) and ANOVA (for more than two groups).
2. The association of the variables which were qualitative in nature were analysed using Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0. For statistical significance, p value of less than 0.05 was considered statistically significant. Ethical approval was obtained from institutional ethical committee.

RESULTS

Patient characteristics

Thirty nine patients were included in the study and had a mean age of 57.59 ± 16.51years.

Among the 39 patients with diagnosis of colorectal cancer; 15 patients (38.46 %) were diagnosed as sarcopenic and the remaining 24 patients (61.54%) were non sarcopenic based on EWGSOP2 (The European Working Group on Sarcopenia in Older People 2) recommendations. The mean age of patients with sarcopenia with colorectal malignancy was 59.58 years and the mean age of patients without sarcopenia with colorectal malignancy was 55.6 years. Clinicopathological features of the two groups are shown in Table 1.

Regarding gender, the proportion of men was higher in the sarcopenic group than women in the non-sarcopenic group (61.1% vs. 38.8 %). Of body weight and composition, mean body mass index (BMI) was lower in

the sarcopenic group than in the nonsarcopenic group (20.86 ± 2.34vs. 21.90± 2.8 kg/m^2). Nutritional parameters such as mean serum albumin was lower in the sarcopenic group than in the non sarcopenic group (sarcopenic, 3.22± .64g/dl vs. non-sarcopenic, 3.40± .63 g/dl). Mean skeletal muscle index (cm²/m²) in patients of gastric carcinoma in sarcopenic patients was 47.54±7.65cm²/m² while skeletal muscle index (cm²/m²) in patients of gastric carcinoma in non sarcopenic patients was 49.24±8.44cm²/m².

Table 1: Clinicopathological features of sarcopenic and non-sarcopenic patients.

Clinicopathological features	Sarcopenic group(n=15)	Non Sarcopenic group(n=24)
Mean age(years)	59.58	55.6
Gender Men Women	 8(61.1%) 7(31.8%)	 14(52.17%) 10(47.82%)
BMI (kg/m ^{2})	20.86 ± 2.34	21.90± 2.8
Serum albumin(g/dl)	3.22± .64	3.40± .63
SMI(cm²/m²)	47.54±7.65	49.24±8.44

Table 2: Association of complications in operable cases in sarcopenic and non-sarcopenic patients.

Colorectal Cancer(n=11)			
	Sarcopenic Group (n=3)	Non Sarcopenic Group (n=5)	P value
Complications	Frequency	Frequency	
No Complications	2(40%)	4(66.66%)	.07
Total Complications(>=grade2)	3(60%)	2(33.33%)	.03
Grade 2	3(60%)	2(33.33%)	

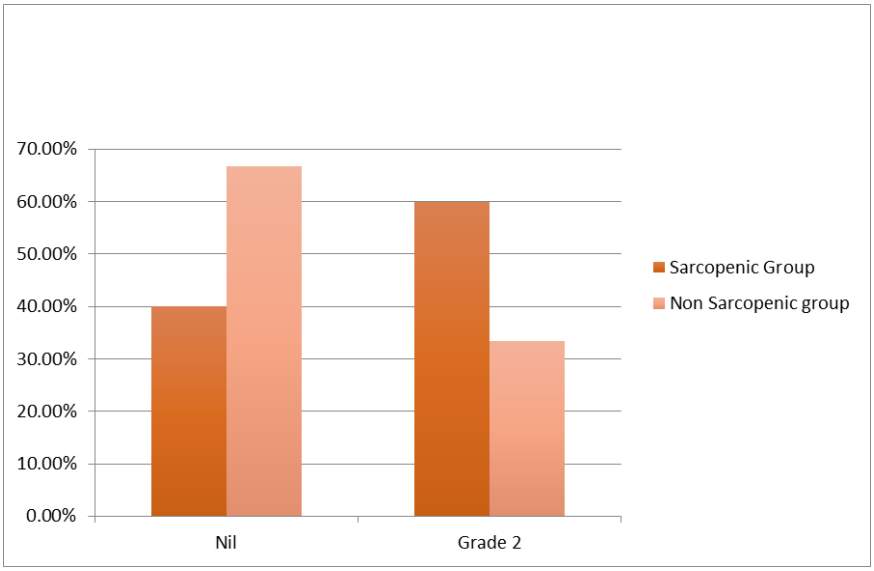


Figure 2: Association of complications in operable cases in sarcopenic and non-sarcopenic patients.

Impact of sarcopenia on postoperative complications in operable cases

Of 39 patients who were diagnosed with colorectal cancer 11 patients were operable and they underwent surgery. Out of these 11 patients, 5 patients were sarcopenic and 6 were non sarcopenic.5 patients developed postoperative complications. In patients without sarcopenia there were no complications in four (66.66%) patients followed by grade 2 complications in two(33.33%) patients according to Clavien Dindo classification and in patients with sarcopenia there were grade 2 complications in three (60%) patients followed by no complications in two(40%) patients according to Clavien Dindo classification. Table 2 and figure 2 shows the association of postoperative complications in operable cases in the two groups. Although there significant difference in the overall complication rate (sarcopenic, 60%, vs. non-sarcopenic, 33.33%; P = 0.03).

DISCUSSION

Surgery remains the predominant form of curative therapy for gastrointestinal cancers. Apart from diminishing adherence to postoperative care and increasing healthcare costs, the challenges following surgery can exacerbate oncological results by impeding the maintenance of healthy lifestyles Sarcopenia is a disease characterized by age-related muscle loss; its definition and standards have changed throughout

time.[17,20] Sarcopenia is thought to be a syndrome in which a decrease in skeletal muscle mass linked to a reduction in muscular strength or function increases the probability of unfavorable occurrences.[20] CT is regarded as the "gold standard" for measuring muscle mass because of its objectivity, repeatability, and precision, with errors ranging from 1 to 4%.[19,21] Usually, the L3 muscle area is measured due to its accuracy reflecting the "real" muscle mass and fat volume.[22] Patients undergoing elective GI cancer surgery routinely undergo abdominal CT assessment of the patient's tumor staging without additional costs. The process of aging involves a decline in every bodily function. Skeletal muscle mass starts to decrease around the age of 30, and the number of motor neurons in those over 70 years old is significantly decreased.[16] According to studies, the primary cause of sarcopenia is a reduction in type II muscle fiber count, which can occur in patients older than 70 by as much as 40%. This may help to explain why older people are more likely to fall.[18] In our study, we found that preoperative sarcopenia increases the risk of total and major complications in colorectal cancer patients undergoing surgery. Sarcopenia patients may have weakness and decreased mobility, which might impact their ability to recuperate after surgery. Nevertheless, there was no proof up until this point that a preoperative increase in muscle mass could enhance the prognosis of patients with colorectal cancer. One explanation for this could be that improving nutritional condition during the brief time between cancer diagnosis and surgery may not be possible. The majority of elderly individuals have inadequate protein consumption or absorption problems. Furthermore, patients with colorectal cancer frequently experience malnutrition and weight loss due to the nutrient consumption in tumors. Therefore, preoperative sarcopenia may be associated with postoperative complications. Early identification of the onset of sarcopenia in the elderly population and early intervention may help the patient maintain muscle mass and improve patient outcomes during treatment. Nutritional support therapy holds promise for enhancing the prognosis of hospitalized patients, yet there's ongoing debate regarding its impact on muscle mass and function. Meanwhile, exercise is recognized as beneficial for maintaining overall physiological health.[23] The American Cancer Society (ACS) has endorsed specific clinical practices for all cancer patients, drawing from recent decades of research on aerobic exercise and resistance training. Factors contributing to age-related muscle decline include individual health, genetics, activity levels, muscle training, and nutritional intake.[16] Notably, individuals with sedentary lifestyles exhibit a more pronounced decline in muscle fibers compared to those with regular activity, highlighting the potential of exercise in mitigating muscle atrophy. Combining active exercise with essential amino acid nutrition support presents a promising approach to improving muscle condition and addressing muscle deficiency.[24] Most current studies primarily examine the correlation between sarcopenia and clinical outcomes, often neglecting to delve into its underlying causes. Research indicates that muscle depletion may signify heightened metabolism in malignant tumors, leading to increased systemic inflammation and muscle consumption.[96] Furthermore, several studies have highlighted the detrimental impact of systemic inflammation on patient outcomes.[26,27] For instance, Richards et al. observed a clear association between muscle loss in patients with resectable primary colorectal cancer (CRC) and systemic inflammatory response.[25] Aleman et al. suggested that inflammatory cells might play a role in triggering sarcopenia by interfering with the skeletal muscle insulin-like growth factor-I pathway.[26] This could elucidate the connection between sarcopenia's poor prognosis and the escalation of systemic inflammation. Additionally, genetic factors may influence sarcopenia. A genome-wide association study identified genes linked to sarcopenia and osteoporosis, such as growth differentiation factor 8, myocyte enhancer factor 2C, and peroxisome proliferator-activated receptor gamma coactivator 1a. However, research on the genetics of sarcopenia remains limited, necessitating further investigation.[27]

Undoubtedly, the incidence of sarcopenia depends mostly on how to define the diagnostic cut-off point for sarcopenia. In this study, cutoff introduced by EWGSOP2 (The European Working Group on Sarcopenia in Older People 2) which defines sarcopenia when Lumbar skeletal muscle index by CT imaging (3rd lumbar vertebra) in Men < 55 cm^2/m^2 and in Women < 39 $cm^2/m^2$was used. In the current investigation, we showed that elderly patients with colorectal cancer had a greater frequency of severe postoperative sequelae and a higher prevalence of sarcopenia prior to surgery. The cross-sectional area of skeletal muscle at the level of the third lumbar vertebra is directly correlated with whole-body SM in cancer patients, as per the findings of research by Mourtzakis and colleagues.[34] Sarcopenia is a crucial component of cachexia, according to Fearon et al.'s[35] classification of malignant cachexia, which includes precachexia, cachexia, and refractory cachexia. Preoperative sarcopenia was, in fact, linked to lower BMI in both the current study and earlier research.[28–31,32] It may also have been linked to a more advanced state of the disease and reduced food intake in the former study. Serum albumin, which is frequently measured as a nutritional metric, was shown to be lower in both the sarcopenic and non-sarcopenic groups. Consistent with our findings in this investigation, a number of studies have revealed that sarcopenia is independently linked with postoperative complications (CD grade IIa or above).[31,32,33] This study has a number of limitations. The sample size was modest for this single-center prospective observational study. Verification of the effect of preoperative sarcopenia on postoperative complications will require a validation research with a sizable sample size.

CONCLUSION

Sarcopenia, as assessed by the EWGSOP 2 recommendations, is prevalent among colorectal cancer patients. Sarcopenia is associated with the development of severe postoperative complications.

Compliance with ethical standards

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for inclusion in the study.

Funding: No funding sources.

Conflict of interest: We declare that we have no conflicts of interest.

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