Role of preoperative sarcopenia in predicting postoperative complications and survival after pancreatoduodenectomy for pancreatic cancer

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Vincenzo La Vaccara*, Chiara Cascone*, Alessandro Coppola*, Tommaso Farolfi*, Roberto Cammarata*, Sara Emerenziani**, Roberto Coppola*, Damiano Caputo*

**Department of General Surgery, "La Sapienza" University, Rome, Italy*
***Gastroenterology Unit, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy*

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AIM: *The aim of this monocentric retrospective study was to investigate the relation between sarcopenia, postoperative complications and survival in patients undergoing radical surgery for pancreatic ductal adenocarcinoma (PDAC).*
MATERIAL OF STUDY: *From a prospective collected database of 230 consecutive pancreatoduodenectomies (PD), data regarding patient's body composition, evaluated on diagnostic preoperative CT scans and defined as Skeletal Muscle Index (SMI) and Intramuscular Adipose Tissue Content (IMAC), postoperative complications and long-term outcomes were retrospectively analysed. Descriptive and survival analyses were performed.*
RESULTS: *Sarcopenia was found in 66% of study population. The majority of patients who developed at least one postoperative complication was sarcopenic. However, sarcopenia did not statistically significantly relate with the development of postoperative complications. However, all pancreatic fistula C occurs in sarcopenic patients. Moreover, there was no significant difference in median Overall Survival (OS) and Disease Free Survival (DFS) between sarcopenic and non-sarcopenic patients (31 versus 31.8 months and 12.9 and 11.1 months respectively).*
DISCUSSION: *Our results showed that sarcopenia was not related to short- and long-term outcomes in PDAC patients undergoing PD. However, the quantitative and qualitative radiological parameters are probably not enough to study the sarcopenia alone.*
CONCLUSIONS: *The majority of early stage PDAC patients undergoing PD were sarcopenic. Cancer stage was a determinant factor of sarcopenia while BMI seems less important. In our study, sarcopenia was associated with postoperative complications and in particular with pancreatic fistula. Further studies will need to demonstrated that sarcopenia can be considered an objective measure of patient frailty and strongly associated with short- and long-term outcomes.*

KEY WORDS: Pancreatic ductal adenocarcinoma, Pancretoduodenectomy, Sarcopenia

Introduction

Pancreatic cancer (PC) is the seventh leading cause of cancer-related death in the world [1]. Surgery represents the standard of care for pancreatic ductal adenocarcinoma (PDAC) even if postoperative course can be burdened by not negligible complications rate [2,3].
Furthermore, the prognosis is still poor even in patients eligible for radical surgery. It is therefore necessary to identify prognostic factors to correctly stratify patients and improve outcomes. Carbohydrate antigen Ca 19.9 plays an important role in predicting PDAC patients undergoing radical surgery [4,5].
Nutritional status, evaluated by standard laboratory tests such as haemoglobin [6] and albumin levels (prognostic nutritional index, PNI), has also been reported as useful, in predicting postoperative complications and assessing the prognosis of PDAC patients [7].
As known, hypoalbuminemia and >10% weight loss are important prognosatic factors in this patient setting [8].

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Correspondence to: Alessandro Coppola MD, PhD, FACS, FEBS(HPB), Department of General Surgery, "La Sapienza" University, Rome, 00161, Italy, (e-mail: a.coppola@policlinicocampus.it)

Frequently PDAC patients experience a marked and progressive weight loss and sarcopenia.
Rosemberg first describes sarcopenia in 1989 as an age-related involuntary loss of muscle mass. Currently, sarcopenia is defined as a complex syndrome characterized by progressive, generalized loss of skeletal muscle mass and strength [9].
Sarcopenia has recently been recognized as the main component of neoplastic cachexia [10,11], which occurs in up to 80% of deaths in patients with advanced PDAC. In Addition, sarcopenia has been considered as a prognostic biomarker able to predict poor treatments and survival outcomes in gastrointestinal and hepatopancreatobiliary cancer patients [12-14].
The malnourished phenotypes (sarcopenia and sarcopenic obesity) represent a significant prognostic factor in cancer patients undergoing radical surgery able to objectifying the patient's frailty and predicting short- and long-term outcomes [15]. However, the real prognostic role of preoperative sarcopenia has not been clearly defined [16].
The aim of this study was to investigate the correlation between sarcopenia, postoperative complications and survival in PDAC patients undergoing pancreatoduodenectomy (PD).

Material and Method

Data collected between february 2004 and january 2016, from a prospective maintained database of 230 PDs for periampullary cancers at Campus Bio-Medico University of Rome, were retrospectively analysed.
Patients underdoing PD for PDAC with complete body composition data evaluated on diagnostic preoperative Computer Tomography scan (CT scan) were included in the study. Data regarding preoperative characteristics (sex, age, Body Mass Index (BMI), albumin, comorbidities, American Society of Anesthesiologists score (ASA), postoperative infectious complications (urinary tract infection, pneumonia, sepsis), postoperative surgical complications (pancreatic fistula, delayed gastric emptying (DGE), hemorrhage, enteric fistula, biliary fistula, abdominal collection), length of hospital stay, pathological staging, Overall Survival (OS) and Disease Free Survival (DFS) were collected.
The quantitative aspect of sarcopenia was measured by preoperative CT-based muscle analysis at lumbar vertebra L3 (L3 SMI, Lumbar Skeletal Muscle Index) normalized to each patient's height according to the radiological criteria proposed in 2008 [17]: males < 55,4 cm^2/m^2 and females < 38,9 cm^2/m^2.
According to Okumura [18], the qualitative aspect of sarcopenia was evaluated on the basis of the Intramuscular Adipose Tissue Content (IMAC).
The cut-off values for IMAC in males and females were – 0.343 (AUC=0.626) and – 0.256 (AUC=0.610), respectively.
Descriptive analyses were conducted. Survival analyses were performed using the Log-rank Test and the Kaplan-Meier method. The χ^2- test was used to investigate the association of sarcopenia to both pancreatic fistula and postoperative infectious complications.

Results

Eighty-two patients were found to be eligible for the analysis in the present study. Fifty (61%) patients were male and 32 (30%) female. Fifty-four (66%) were sarcopenic, 37 (69%) were male and 17 (31%) female. The median age was 66 years (range 42-83 years). All patients underwent PD for PDAC, 59 (72%) patients underwent to pylorus-preserving PD, while Whipple's procedures were performed in 28% of the cases. Demographic characteristics and intraoperative of this series are shown in (Table I). Patients underwent to neoadjuvant treatments were excluded.

Preoperative Sarcopenia and Comorbidities

Twenty-five (30%) patients had no preoperative comorbidities, 21 of them were sarcopenic. Fifty-sever (70%) patients had at least one preoperative comorbidity and 30 of them were sarcopenic: 21 (25%) cardiovascular disease; 8 (10%) respiratory disease; 48 (59%) hypertension; 26 (31.7%) diabetes mellitus and 26 (31.7%) kidney failure, respectively.

Table I - *Demographic characteristics of the study population.*

Demographic Characteristics	**N Patients (%)**
Study Population	82
GENDER	
Male	50 (61%)
Female	32 (39%)
AGE	
< 65 years	35 (43%)
≥ 65 years	47 (57%)
ASA SCORE	
1	3 (3,7%)
2	38 (46%)
3	38 (46%)
4	3 (3,7%)
COMORBIDITIES	
Hypertension	48 (59%)
Diabetes mellitus	26 (31.7%)
Kidney failure	26 (31.7%)
Cardiovascular disease	21 (25%)
Respiratory disease	8 (10%)

Preoperative Nutritional Assessment (BMI and Albumin)

The median preoperative BMI was 24.58 Kg/m^2 (range 17 - 34 Kg/m^2). Preoperative albumin values™ were stratified according to common clinical cut-offs. Preoperative nutritional assessment is shown in (Table II).
There was no statistically significant correlation between nutritional assessment and sarcopenia (p>0.05).

Sarcopenia and Short-Term Outcomes

The median length of hospital stay was 17.75 days (16 days in non sarcopenic and 21 days in sarcopenic patients, respectively) without significant difference (p>0.05). Seventy-six (93%) patients had early stage cancer. Our results have shown a higher prevalence of sarcopenia in pT > 2 tumors. On the contrary, there was no significantly difference with pathological lymph nodes. Fifty-nine (72%) patients developed at least one postoperative infectious and/or surgical complication; 51 (62%) patients; 33 (65%) of whom sarcopenic, developed at least one postoperative surgical complication; 21 (26%) patients, 14 (66%) of whom sarcopenic, developed at least one infectious complication (Table III).
The combined assessment of the quantitative and qualitative aspect of sarcopenia was conducted both in the group who developed at least one infectious complication (21 cases, 26%) and in the group who was not affected by any infectious complication (61 patients, 74%), with no significant differences (p>0.05).
Pancreatic fistula was diagnosed in 30 (36.59%) patients, however clinically relevant pancreatic fistula was recorded in 13 cases (12.2% grade B and 5.56% grade C, respectively). Moreover, grade C pancreatic fistula has only been documented in sarcopenic patients (Fig. 1).

Survival Analysis

Survival analysis was conducted using the Log-rank Test and the Kaplan-Meier method. The median OS in the study population was 31.2 months (range 0.1-150 months). The median OS was 31.8 months (range 0.1-115.8 months) and 31 months (range 0.2-150

Table II - *Preoperative nutritional assessment (BMI and albumin).*

Nutritional Assessment	N. patients (%)	N. sarcopenic patients (%)
BMI		
Underweight BMI ≤ 18,49 Kg/m2	5 (6%)	3 (60%)
Normal range ≤ 18,5 BMI ≤ 24,9 Kg/m2	40 (49%)	33 (82%)
Overweight BMI > 25 Kg/m2	37 (45%)	18 (48%)
ALBUMIN		
Severe hypoalbuminemia (< 2,5 g/dL)	21 (26%)	16 (76%)
Mild hypoalbuminemia(≥ 2,5 albumin < 3,5 g/dL)	31 (38%)	18 (58%)
Normal (≥ 3,5 g/dL)	30 (36%)	20 (67%)

Table III - *Sarcopenia and postoperative complications.*

Postoperative Complications	N patients * (%)	N sarcopenic patients (%)
INFECTIOUS COMPLICATIONS	21 (26%)	14 (66 %)
Urinary tract infection	7 (8,5%)	5 (71%)
Pneumonia	6 (7,3%)	5 (83%)
Sepsis	14 (17%)	9 (64%)
SURGICAL COMPLICATIONS	51 (62%)	33 (65%)
Early hemorrhage (< 24h)	2 (2,4%)	1 (50%)
Late hemorrhage (> 24h)	5 (6%)	4 (80%)
Delayed Gastric Emptying (DGE)	24 (29%)	16 (66%)
Abdominal Collection	18 (22%)	13 (72%)
Biliary Fistula	10 (12%)	9 (90%)
Enteric Fistula	30 (37%)	20 (66%)
Pancreatic Fistula	30 (37%)	20 (66%)
- Grade A	17 (21%)	12 (70,5%)
- Grade B	10 (12%)	5 (50%)
- Grade C	3 (3,6%)	3 (100%)

*Number of patients who developed at least one postoperative complication.

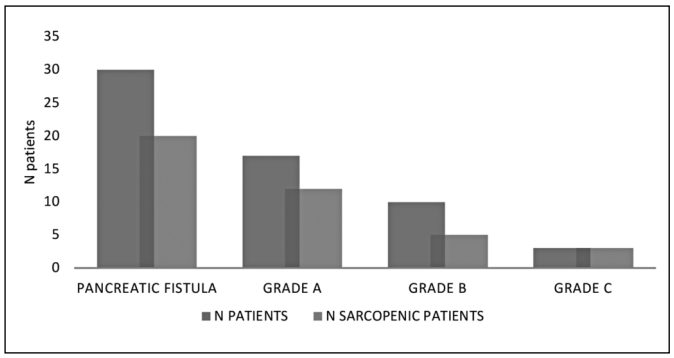

Fig. 1: Sarcopenia and grade A, B and C pancreatic fistula.

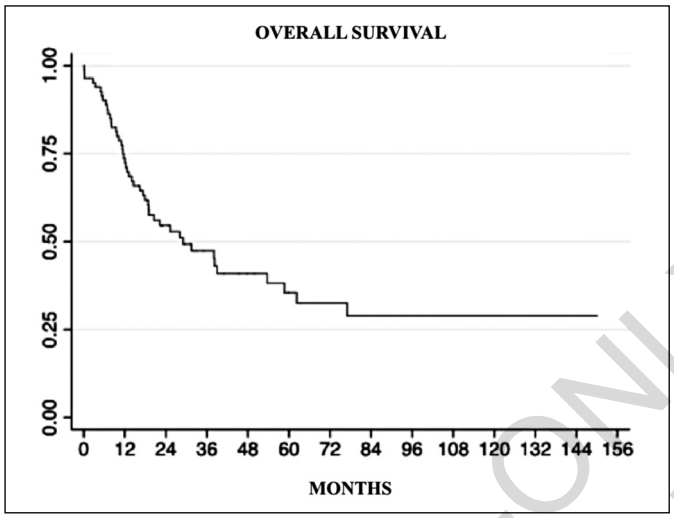

Fig. 2: Kaplan-Meier curve of OS of the study population.

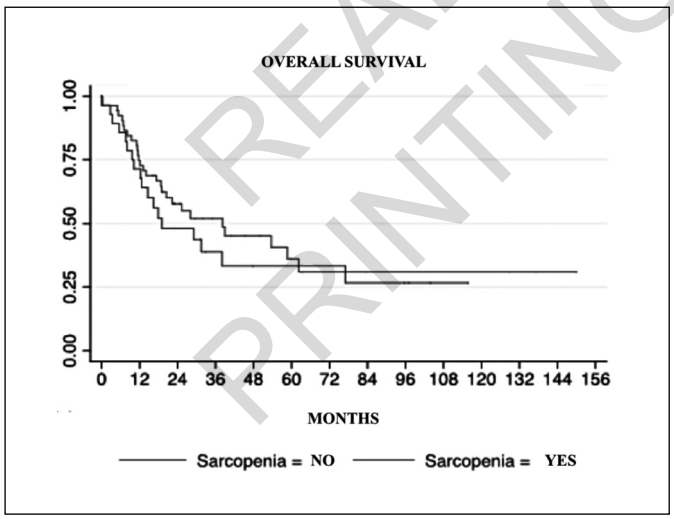

Fig. 3: Kaplan-Meier curves of OS of sarcopenic and non-sarcopenic patients.

months) in non-sarcopenic and sarcopenic patients respectively, with no significant differences between the two groups (p=0.43) (Figs. 2, 3). The same result

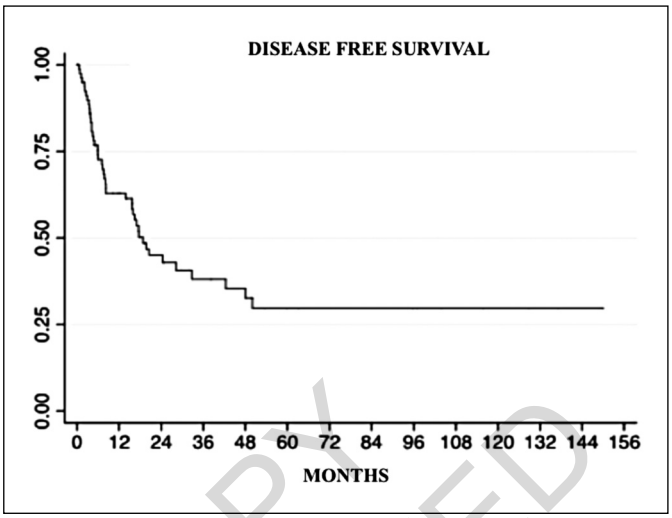

Fig. 4: Kaplan-Meier curve of DFS of the study population.

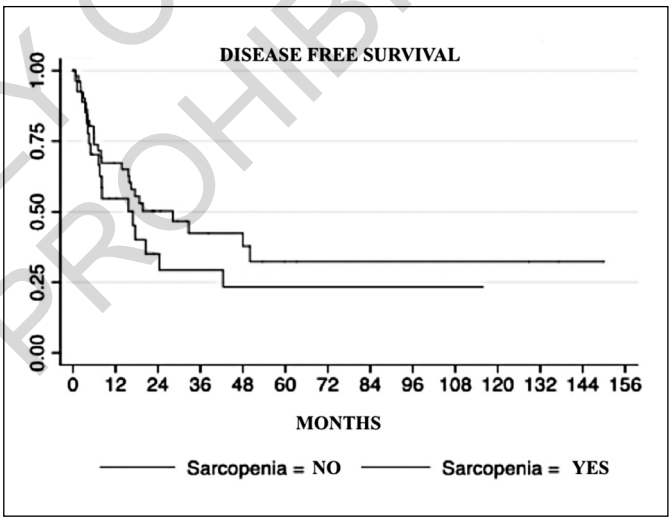

Fig. 5: Kaplan-Meier curves of DFS of sarcopenic and non-sarcopenic patients.

emerged from the OS analysis of the absolute value L3 SMI (cm^2) (p=0.79).

In the study population, 45 (55%) patients developed disease recurrence with a median DFS of 12.1 months (range 0.7 - 50 months) (Fig. 4). Survival analyses were performed in both sarcopenic (27/45 patients) and non-sarcopenic patients (18/45 patients), the median DFS was 12.9 months and 11.1 months respectively, with no significant differences between the two groups (p=0.27) (Fig. 5).

The pT stage in sarcopenic patients showed no statistically significant correlation either in terms of OS (p=0.2) or DFS (p=0.1). Also from the study of the pT in relation to the IMAC value, no significant differences were reached between the sarcopenic and non-sarcopenic group (p=0.23).

Discussion

PD still remains the standard of care for patients affected by PDAC arise from the head of the pancreas. Over the last few decades, the centralization of pancreatic surgery in high-volume centres had radically changed the short and long-terms outcomes. However, also in high volume centres mortality and morbidity rate still reach 5% and 30-50%, respectively [19,20].

The prognosis, still poor in these patients, is multifactorial and determined not only by tumor-specific factors, but also by the patient's characteristics. Currently, the alteration of metabolic-nutritional assessment is considered an important factor related with the development of postoperative complications, the prolongation of hospital stay and the reduction of overall survival [21].

The alterations of the nutritional status of the cancer patient undergoing radical surgery can be characterized by both underweight and overweight-obesity. However, according to the literature [22], in our experience BMI was not associated with overall survival.

As known, the malnourished phenotypes (cachexia, sarcopenia and sarcopenic obesity) are all associated with a higher risk of developing postoperative complications and increasing mortality in pancreatic surgery [23].

For this reason, a new parameter that is not based on BMI is needed to stratify preoperative risk, especially in pancreatic surgery.

Frailty, expressed objectively by sarcopenia, has recently been proposed among the main prognostic factors in surgical patients, however it has not yet been standardized [10,11].

Our study showed that preoperative sarcopenia was related with the development of postoperative infectious and surgical complications. In particular, it is really interesting the relation between sarcopenia and the presence of a pancreatic fistula Grade C. Probably this relation is due to the scarce metabolic condition of these patients that is manifested by a sarcopenic status.

However, survival analyses didn't showed significant differences in OS and DFS between sarcopenic and non-sarcopenic patients.

These results are partially unexpected. In fact, as known from previous studies, sarcopenia should relate with both short-term and long-term outcomes in pancreatic surgery [24-26].

The reason for this discrepancy is not completely clear, although at least partially attributable to the small sample size of the study that did not allow the multivariate analysis to be performed.

There are also different definitions of sarcopenia that can influence the results. It is necessary to unify criteria, not only in the definition but also in the cut-off values [16,27].

Prospective studies and consensus on the diagnosis of sarcopenia should be achieved by combining radiological criteria with functional criteria expressing the patient's frailty.

Conclusions

Our results showed that sarcopenia was widespread in early stage pancreatic cancer patients and was not related with BMI. In our study, sarcopenia was associated with the development of infectious and surgical postoperative complications, particularly with grade C pancreatic fistula. However, no statistically significant differences were found in short-term outcomes between sarcopenic and non-sarcopenic patients.

Based on our experience, sarcopenia defined on the basis of radiological criteria is not sufficient alone to predict the survival of these patients and became a contraindication to surgery.

Further prospective large-scale studies on this topic will be useful to accurately assessing the real role of preoperative sarcopenia on short and long-term outcomes, integrating the functional aspect with the radiological one.

Riassunto

La sarcopenia nei pazienti oncologici, intesa in termini di atrofia del muscolo scheletrico, potrebbe rappresentare un valido parametro per oggettivare la fragilità e predire i risultati a breve e lungo termine indipendentemente da fattori tumore-specifici. La sarcopenia è stata recentemente riconosciuta come la componente principale della cachessia neoplastica, molto diffusa nei pazienti affetti da adenocarcinoma duttale del pancreas: fino all'80% di essi presenta un grave stato cachettico al momento del decesso. Tuttavia, il suo reale impatto prognostico non è stato chiaramente definito.

Questo studio retrospettivo monocentrico si propone di investigare la correlazione tra lo stato sarcopenico, le complicanze postoperatorie e la sopravvivenza nei pazienti sottoposti a duodenocefalopancreasectomia per adenocarcinoma duttale della testa del pancreas.

In accordo con la letteratura, si è osservato come la maggior parte dei pazienti che hanno sviluppato almeno una complicanza postoperatoria, infettiva e/o chirurgica, presentasse un quadro radiologico di sarcopenia. Tuttavia, non è stata documentata una correlazione statisticamente significativa tra la sarcopenia e le complicanze postoperatorie, né con gli outcomes di sopravvivenza.

I nostri risultati hanno mostrato che la sarcopenia preoperatoria non sia un fattore in grado di condizionare né l'indicazione all'intervento chirurgico né gli outcomes a breve e lungo termine in questi pazienti. D'altra parte, la sarcopenia non può essere studiata unicamente mediante parametri radiologici, siano essi quantitativi e/o qualitativi. Infatti, la sua determinazione non può prescindere da caratteristiche cliniche e funzionali, soprattutto in pazienti oncologici.

In futuro studi prospettici su larga casistica potranno definire più accuratamente l'effettivo ruolo della sarcopenia preoperatoria sugli outcomes a breve e lungo ter-

mine integrando allo studio radiologico la valutazione dell'aspetto funzionale.

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