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DE DOCTEUR EN MÉDECINE

Impact de la sarcopénie, des marqueurs inflammatoires et des facteurs anthropométriques sur la survie des patients opérés d'un adénocarcinome pancréatique résécable d'emblée.

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Abstract:

Introduction. Pancreatic adenocarcinoma (PDAC) is becoming a public health issue with a 5-years survival rate around 5%. Patients with PDAC are often sarcopenic, which impacts postoperative outcome. At the same time, overweight population is increasing and adipose tissue promotes tumor related-inflammation. With several studies supporting independently these data, we aimed to assess if they held an impact on survival when combined.

Methods. We included 232 patients from two university hospitals (CHU de Lille, Institut Paoli Calmette), from January 2011 to December 2018, who underwent Pancreaticoduodenectomy (PD) for resectable PDAC. Preoperative CT scan was used to measure sarcopenia and visceral fat according to international cut-offs. Neutrophil to lymphocyte (NLR) and platelet to lymphocyte ratios (PLR) were used to measure inflammation. For univariate and multivariate analyses, the Cox proportional-hazard model was used. P-values below 0.05 were considered significant.

Results. Sarcopenic patients with visceral obesity were less likely to survive than the others in multivariate analysis (OS, HR 1.65, p= 0.043). Cutaneous obesity did not influence survival. We also observed an influence on survival when we studied sarcopenia with visceral obesity (OS, p= 0.056; PFS, p = 0.014), sarcopenia with cutaneous obesity (PFS, p= 0.005) and sarcopenia with PLR (PFS, p= 0.043). This poor prognosis was also found in sarcopenic obese patients with high PLR (OS, p= 0.05; PFS, p= 0.01).

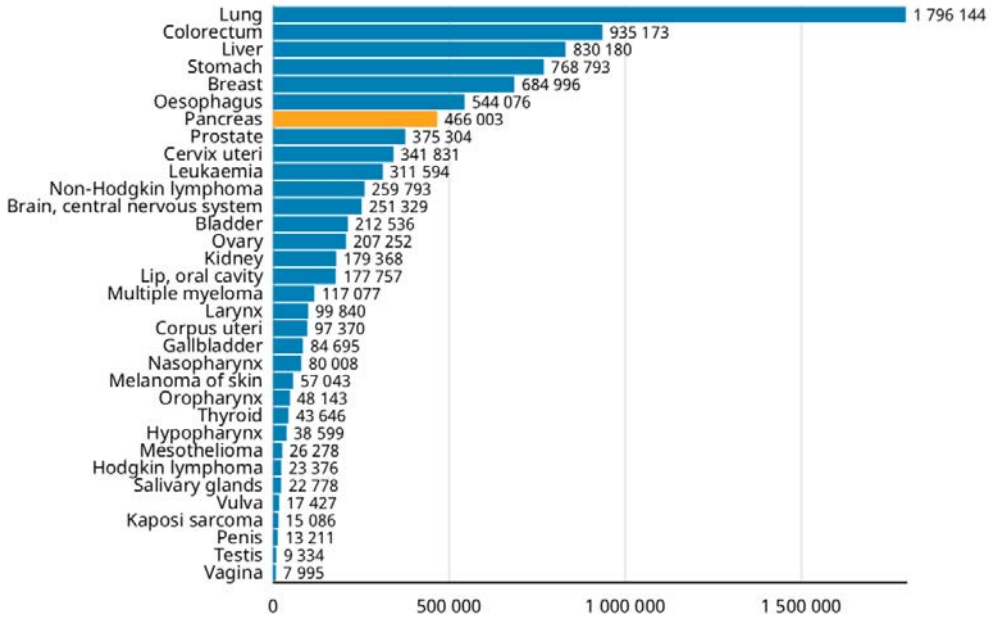
Conclusion. Sarcopenic obesity was associated with poor prognosis after PD for PDAC, especially in patients with systemic inflammation. Prehabilitation program and neoadjuvant chemotherapy should be preferred in these patients.

Introduction:

Pancreatic adenocarcinoma (PDAC) represents the majority of all pancreatic cancers and is becoming a public health issue. Its incidence is growing year by year and the 5-year survival rate stays around 5% (1)(2). Despite the evolution of chemotherapy and radiotherapy, it may become the second cause of mortality by cancer in 2030 (3).

Pancreatic cancer is divided into two groups: adenocarcinoma, which represents about 90% of the cases, and other histology like endocrine tumors. Based on GLOBOSCAN 2020 (Figure 1), PDAC is the twelfth most frequent cancer in the world and the seventh leading cause of death from cancer with 466,003 deaths in 2020 (4).

A



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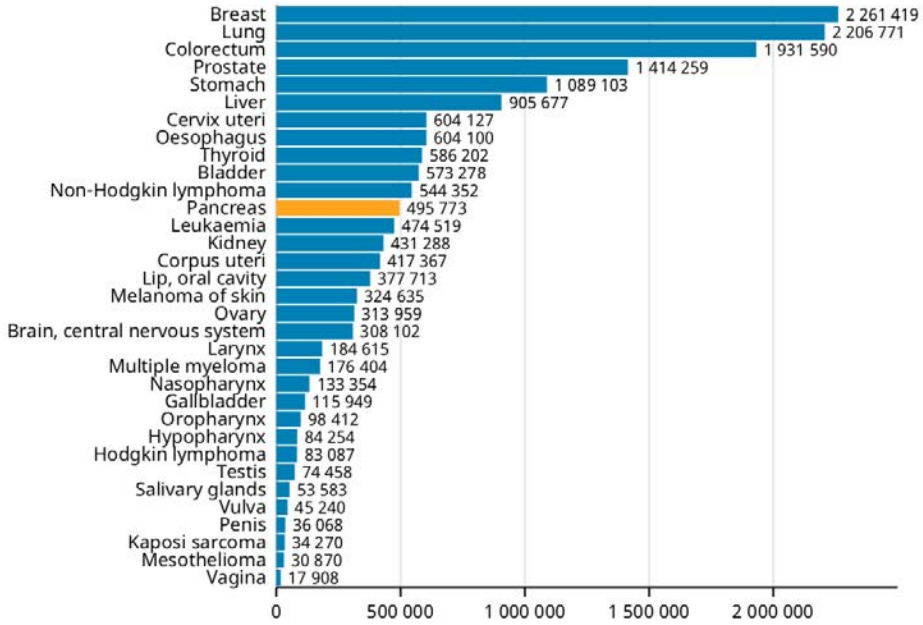


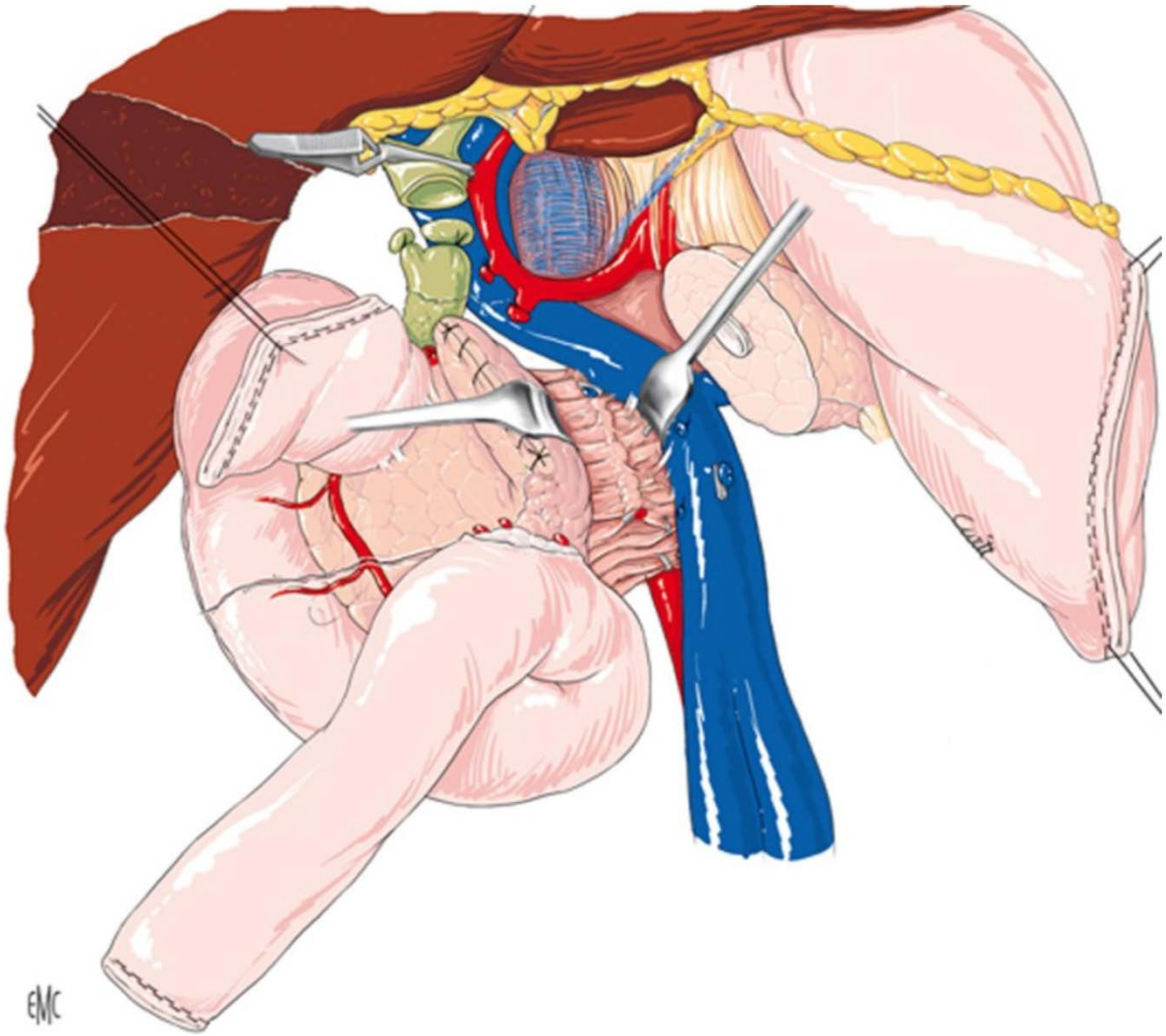
Figure 1: Number of new cancer cases (A) and death (B) in 2020, both sexes, all ages, according to GLOBOSCAN.

To date, there is no single cause that has been identified to induce PDAC, but several risk factors such as smoking, obesity with a body mass index (BMI) superior to 30 kg/m², sedentary lifestyle, type1 and type 2 diabetes, the intake of red or processed meat, chronic pancreatitis and genetics (Lynch Syndrome, Li Fraumeni, Familial adenomatous polyposis, mutations of K-RAS, PRSS1, p16, p53 and BRCA2) (5). Older patients are more likely to develop a PDAC. Finally, patients from Western and Asian countries are at risk to develop one (4). Due to the numerous PDAC risk factors, there are no current recommendation to prevent it, nor reliable screening test to detect it earlier.

Nowadays, we aim at offering patients with PDAC the best survival chances with surgery. Actually, surgical treatment is the only curative option. It is associated with chemotherapy for better results (6). However, this treatment is linked with a high morbidity and mortality. The intervention consists in a pancreatectomy. Depending on

the adenocarcinoma localization, either a Whipple procedure (duodenopancreatectomy – PD) or a distal pancreatectomy is done (Figure 2) (7).

A



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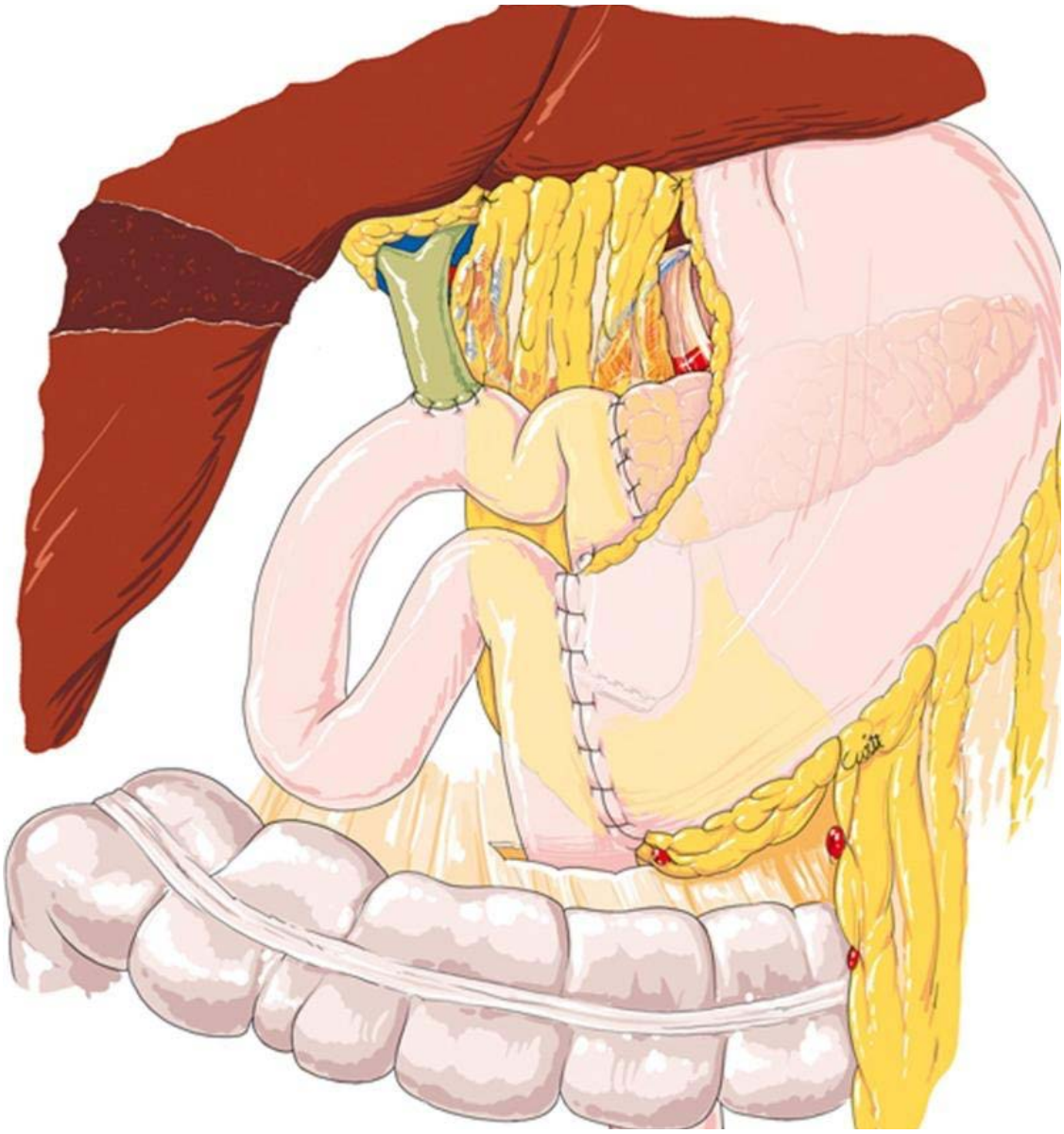


Figure 2: A: Whipple procedure including resection of the head of the pancreas, the duodenum, the gallbladder and the bile duct. B: Child reconstruction consisting of successive drainage of the pancreas, bile duct and stomach in the first jejunal loop.

PD is associated with a high morbidity rate, mostly because of the pancreatic fistula. However, the mortality rate after PD is less than 4% in expert centers (8). These results can also be explained by the preoperative patient's assessment. It is becoming more specific in order to get the best post-operative aftermath. Moreover, some patients who are diagnosed at an early stage of the disease are not fit enough to endure heavy surgery and its complications.

Several studies showed that anthropometric factors such as sarcopenia or visceral obesity influenced postoperative survival in gastric cancer, lung cancer and colorectal cancer (9)(10)(11)(12)(13). Some have shown that sarcopenic patients with PDAC have a worse survival rate than non-sarcopenic patients (14). Besides, survival is more impacted when patients are sarcopenic and obese (15).

Sarcopenia is defined as the presence of low muscle mass and low muscle strength. It is divided in two categories: primary and secondary sarcopenia. Primary sarcopenia occurs in older patients, it is the age-related decline of skeletal muscle mass. Secondary sarcopenia occurs in younger patients and is associated with sickness (16). The European working group on sarcopenia in older people (EWGSOP) defines sarcopenia as the association of low muscle mass and impaired muscle function (strength or performance).

Muscle strength or performance can be assessed clinically, but muscle mass requires the measure of skeletal muscle index (SMI). It can be determined with a single CT Scan slice (17)(18) at the third lumbar vertebra level (L3), adjusted with height (cm^2/m^2). Different cut-offs are used for men, women and obese patients (BMI ≥ 30 kg/m^2) and permit to know if a patient is sarcopenic or not before surgery (19). Every

patient benefits from an abdominal CT Scan before surgery. Thus, it is possible to easily measure SMI prior to surgery.

The World Health Organization (WHO), define obesity by a BMI superior to 30 kg/m² and a wide waist circumference (superior to 102 cm for men and 88 cm for women). It is a huge public health concern across the globe. Over the past two decades, obesity has increased worldwide (20). In addition to being associated with poor health behavior, it is associated with poor health outcomes such as cancer (21). Sarcopenic obesity (15) is not quite surprising. In fact, it can be explained with ageing. Fat mass is increasing while physical activity and basal metabolism are decreasing (22). With CT Scan, visceral fat area (VFA) and subcutaneous fat area (SFA) can be measured. They enable us to assess visceral obesity, which is depicted as being a poor prognostic factor in different cancers. (23)

Lately, sarcopenia as well as inflammation received attention in several malignancies. Previous reports have shown that they affect each other and predict a poor prognosis when they are both present in cancer patients (24).

The entanglement of these two factors is well explained. Malignant state causes inflammation, as a systemic reaction. This inflammatory response, mediated by cytokine release, induces the loss of muscle mass (25). Currently, PLR and NLR seem to be useful markers to identify systemic inflammatory response (SIR) (10).

Furthermore, a large number of studies directly linked systemic inflammation in cancer patients to the tumor and its progression. Several inflammatory biomarkers had been investigated to predict cancer prognosis, such as C-reactive protein (CRP), NLR and PLR. Among them, NLR and PLR seem to be efficient in predicting post-operative survival in patients with PDAC. (26)

In this study, we aimed to demonstrate the impact of sarcopenia, visceral obesity, sarcopenic obesity and inflammation status (NLR and PLR) (27)(28)(29) on oncological outcomes after PD for PDAC. Preoperatively, all of these parameters can be checked and for some be corrected before surgery using a pre-habilitation program.

Patients and methods:

Study population:

We included all consecutive patients who underwent PD for PDAC in the department of digestive surgery and transplantation (Lille University Hospital) and the department of surgical oncology (Institut Paoli-Calmette, Marseille). The period of inclusion was from the 1st of January 2011 to the 31st of December 2018. Only patients with PDAC whose tumors were considered as resectable were included. The exclusion criteria were underage patients, patients treated with neoadjuvant chemo and/or radiotherapy, patients who underwent palliative procedures and those with low quality CT Scans.

Data collection:

Clinical data including demographics, ASA score, Charlson comorbidity score, preoperative body weight, height, BMI, laboratory data, tumor characteristics were collected via review of medical records. Intraoperative (operative time, blood loss, type of pancreatic anastomosis, vascular reconstruction), histological (histologic classification, degree of differentiation, and the status of the resection

margins), postoperative (length of stay, post-operative complications defined according to the Clavien-Dindo classification, specific pancreatic surgery complications were defined using guidelines of International Study Group of pancreatic

surgery (30)), and follow-up data (the adjuvant therapy rate, the recurrence rate, overall survival and disease-free survival) were also recorded.

Muscle mass, subcutaneous and visceral adipose tissue measurements:

Preoperative CT images were analyzed with the MYRIAN software. The preoperative CT Scans were done at least one month before surgery. Total abdominal muscle area (TAMA) (transversus abdominis, external and internal obliques, rectus abdominis, psoas muscles and para spinal muscles) was measured on one slice at vertebral level L3 (Figure 3). The same measurement method was used for SFA (Figure 4) and VFA (Figure 5). The skeletal muscle index (SMI) was defined as follows: TAMA measured at L3 in cm^2 divided by height in m^2. Sarcopenia was defined according to BMI. We used different cut-offs to define sarcopenia according to the BMI: obese (BMI> 30 kg/m^2) women are sarcopenic if their SMI <38.5 cm^2/m^2 and non-obese (BMI <30 kg/m^2) women are sarcopenic if their SMI <32 cm^2/m^2. Obese men are sarcopenic if their SMI <52.4 cm^2/m^2 and non-obese men are sarcopenic if their SMI <42 cm^2/m^2 (19).

Visceral obesity was defined by VFA> 130 cm^2 when measured at L3 level. (31) Subcutaneous obesity was high when patients had SFA> 177 cm^2. Because there was no gold standard cut-off, we used our median measure, as in other studies (32).

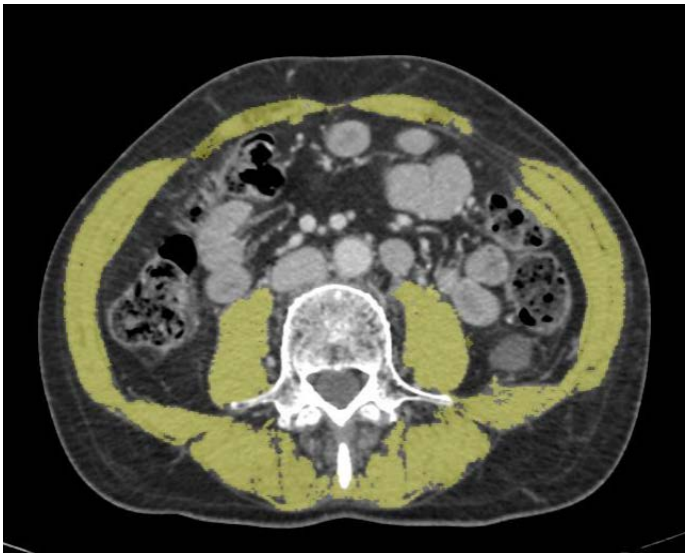


Figure 3: Total abdominal muscle area measurement in CT Scan.

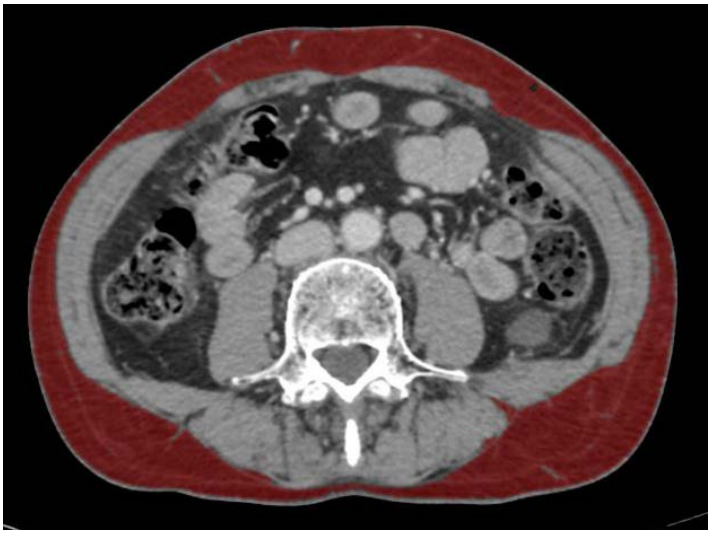


Figure 4: Subcutaneous Fat area measurement in CT scans.

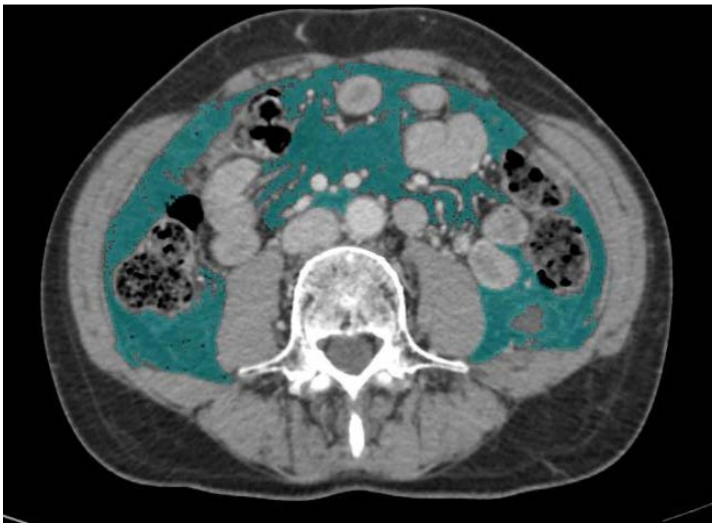


Figure 5: Visceral fat area measurement in CT scans.

Inflammatory markers:

Biological data were retrospectively collected. We used laboratory data that were at most six months old. As previously reported, we defined NLR as high if it was higher than 3 (32). Besides, the PLR cut-off used in our study was 156, as elsewhere. (33)

Statistical analysis:

We used R software to do all of our computation, p-values below 0.05 were considered significant. Student t-test was used to compare continuous variables, and Fisher's test was used for categorical ones. Survival curves were calculated using the Kaplan-Meier method, differences between them were assessed with the log-rank test. For univariate and multivariate analyses, the Cox proportional-hazard model was used.

Results:

A total of 364 patients underwent PD during the study period. In 88 of them, preoperative CT scans were not available. Of the 276 remaining patients, 20 were excluded because they received neoadjuvant treatment. Finally, 24 more were excluded since they received other procedures than PD (Figure 6). Of the 232 patients included in our study, 49% were sarcopenic and 10% suffered from sarcopenic obesity.

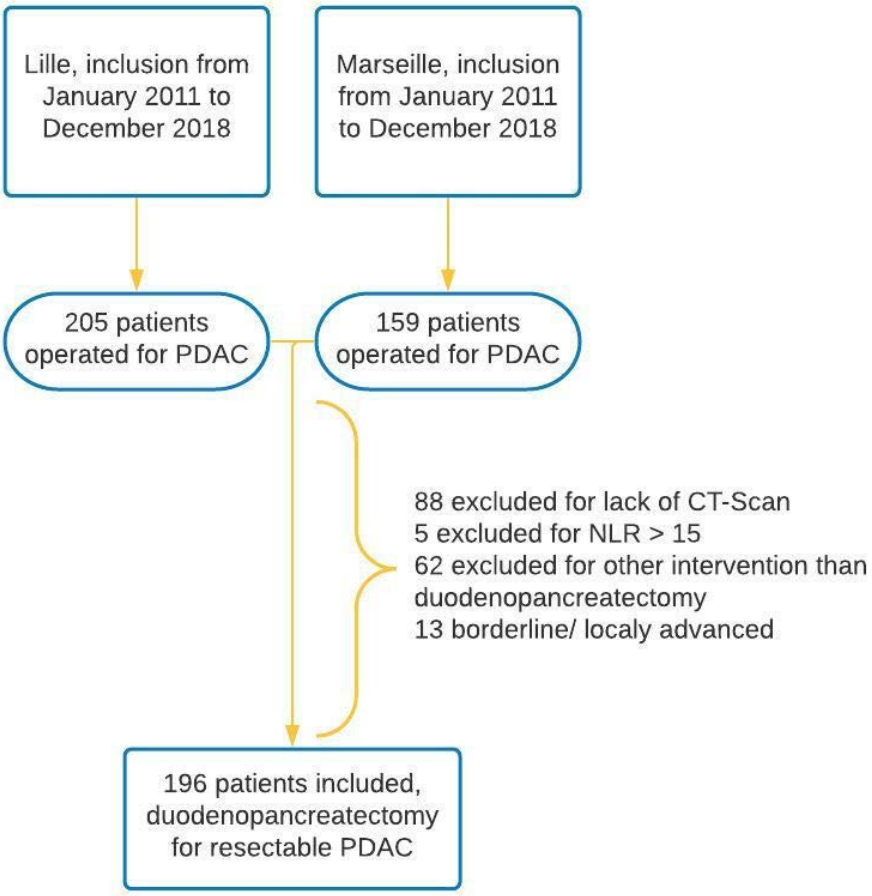


Figure 6: Flow Chart of our data, inclusion and exclusion criteria.

Sarcopenic patients were more likely to have low BMI, SMI and cutaneous adipose tissue (Table 1).

Table 1: Patients Characteristics, overall and by sarcopenia

				Sarcopenia				
		All patients		No		Yes		p-value
Characteristics	N	(n=196)		(n=98)		(n=94)		
Age (mean (SD))	196	67.47	(9.82)	67.73	(8.69)	67.63	(10.36)	0.945
Sex (n male(%))	195	108	(55.4)	37	(37.8)	68	(72.3)	< 0.001
ASA Score (mean (SD))	196	2.11	(0.64)	2.08	(0.65)	2.15	(0.62)	0.465
ASA 0 – 2 (n(%))		149	(76)	76	(77.6)	69	(73.4)	
ASA 3 – 4 (n(%))		47	(24)	22	(22.4)	25	(26.6)	
Charlson (mean (SD))	115	2.96	(1.55)	3.24	(1.49)	2.73	(1.59)	0.087
Score 0 – 2 (n(%))		45	(39.13)	18	(30.5)	24	(46.15)	
Score 3 – 4 (n(%))		52	(45.22)	28	(47.5)	23	(44.23)	
Score > 4 (n(%))		18	(15.65)	13	(22.0)	5	(9.62)	
Medical History: (n(%))								
High blood pressure	133	63	(47.4)	37	(54.4)	23	(37.7)	0.058
Ischemic heart disease	114	12	(10.5)	8	(13.8)	4	(7.7)	0.303
Heart failure	114	1	(0.9)	0	(0)	1	(1.9)	0.322
Kidney failure	114	1	(0.9)	1	(1.7)	0	(0)	0.322
COPD	115	4	(3.5)	4	(6.8)	0	(0)	0.045
Respiratory failure	114	0	(0)	0	(0)	0	(0)	-
chronic pancreatitis	113	6	(5.3)	3	(5.3)	3	(5.8)	0.909
Diabetes	133	31	(23.3)	18	(26.5)	12	(19.7)	0.363
Cirrhosis	103	1	(1.0)	1	(2.0)	0	(0)	0.322
Discovery circumstances: (n(%))								
Abdominal pain	112	57	(50.9)	31	(54.4)	25	(49.0)	0.582
Jaundice	114	80	(70.2)	41	(70.7)	36	(69.2)	0.869
Acute cholitis	110	8	(7.3)	3	(5.5)	4	(7.8)	0.627
Worsening diabetes	111	10	(9.0)	7	(12.5)	3	(5.9)	0.237
Pancratitis	113	19	(17.1)	8	(14.3)	11	(21.6)	0.333
Malnutrition: (n(%))	115							0.424
Moderate		51	(44.35)	23	(39.0)	26	(50)	
Severe		29	(25.22)	15	(25.4)	13	(25)	
BMI (mean(SD))	192	24.54	(4.13)	26.10	(4.34)	22.82	(3.19)	< 0.001
SMI (mean(SD))	193	46.46	(13.08)	52.77	(12.48)	39.87	(10.23)	< 0.001
Sarcopenia (n(%))	192	94	(49.0)	0	(0)	1	(100)	
Cutaneous fat (cm^2/m^2) (mean(SD))	196	197	(99)	240.46	(102.96)	148.73	(68.36)	< 0.001
Visceral fat (cm^2/m^2) (mean(SD))	193	146	(94)	159.67	(95.22)	129.45	(88.03)	0.024
Ca19-9 (mean(SD))	81	495.79	(851)	430.37	(874.58)	562.04	(853.97)	0.506
Albumin (mean(SD))	115	37.03	(6.24)	37.70	(5.86)	36.81	(6.00)	0.432
Pre-albumin (mean(SD))	114	0.19	(0.07)	0.19	(0.07)	0.20	(0.08)	0.564
CRP (mean(SD))	85	17.90	(29.90)	16.77	(25.6)	19.10	(34.26)	0.725
NLR (mean(SD))	161	3.50	(2.35)	3.17	(2.26)	3.78	(2.40)	0.099
PLR (mean(SD))	160	181.09	(98.22)	171.4	(84.85)	191.3	(109.08)	0.199
Post operative complications:								
Clavien Dindo ≥ 3a (n(%))	130	28	(21.5)	17	(24.6)	11	(18.6)	0.414
Anatomopathology:								
pT: (n(%))	192							0.194
pT1-pT2		51	(26.6)	30	(31.2)	21	(22.6)	
pT3-pT4		141	(73.4)	66	(68.8)	72	(77.4)	
Vascular embolus (n(%))	154	65	(42.2)	28	(36.4)	36	(48.6)	0.129
Lymphatic embolus (n(%))	108	20	(18.5)	9	(16.7)	9	(17.6)	0.895
Resection: (n(%))	194							0.664
R0		169	(87.1)	86	(87.8)	80	(86.0)	
R1		24	(12.4)	11	(11.2)	13	(14.0)	
R2		1	(0.5)	1	(1.0)	0	(0)	
N+ (mean(SD))	189	2.47	(2.64)	2.37	(2.75)	2.54	(2.50)	0.660
N+/N (mean(SD))	189	0.19	(0.43)	0.20	(0.58)	0.17	(0.18)	0.611
Adjuvant chemotherapy (n(%))	112		(83.9)	46	(80.7)	44	(86.3)	0.439
Mortality at 90 days (n(%))	196	8	(4.1)	5	(5.1)	3	(3.2)	0.508
Dead (n(%))	196	135	(69)	64	(65.3)	69	(73.4)	0.226

ASA: American society of anesthesiologists, COPD: chronic obstructive pulmonary disease, BMI: body mass index, SMI: squeletal muscle index.

We then studied correlation between sarcopenia and inflammatory markers. As it can be seen on the plots (figure 7 and figure 8), no correlation was observed between sarcopenia and NLR as well as between sarcopenia and PLR. However, sarcopenic patients tended to have high NLR and PLR compared to non-sarcopenic patients.

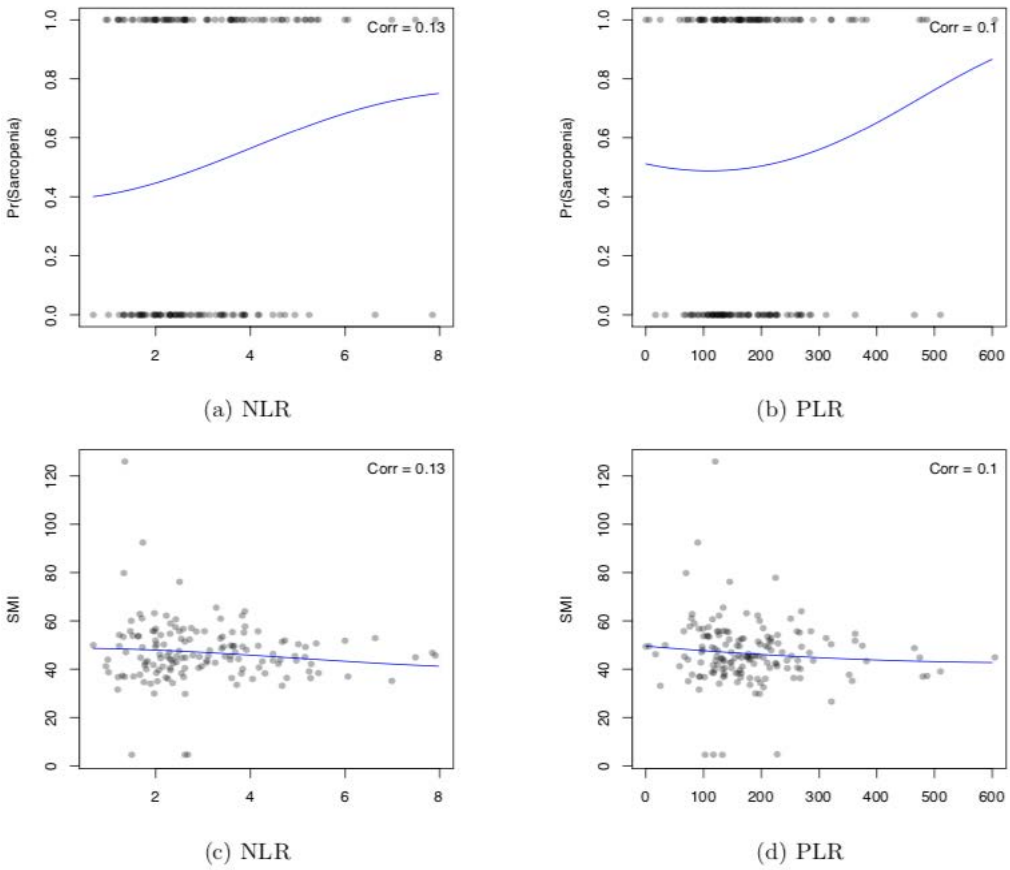


Figure 7: Sarcopenia and SMI relation with NLR and PLR, correlation factor included.

We assessed the impact of sarcopenia, NLR and PLR on oncological outcomes after PD for PDAC (Figure 8). As mentioned in Figure 8A, sarcopenic patients tended to have a low progression-free survival (PFS) compared to non-sarcopenic patients ($p=0.09$). However, sarcopenic patients did not show any difference in overall survival when compared with non-sarcopenic patients ($p=0.2$). Regarding inflammatory status, there are no significant differences in PFS and OS between patients with high NLR and those with low NLR. Similar results were observed for PLR status.

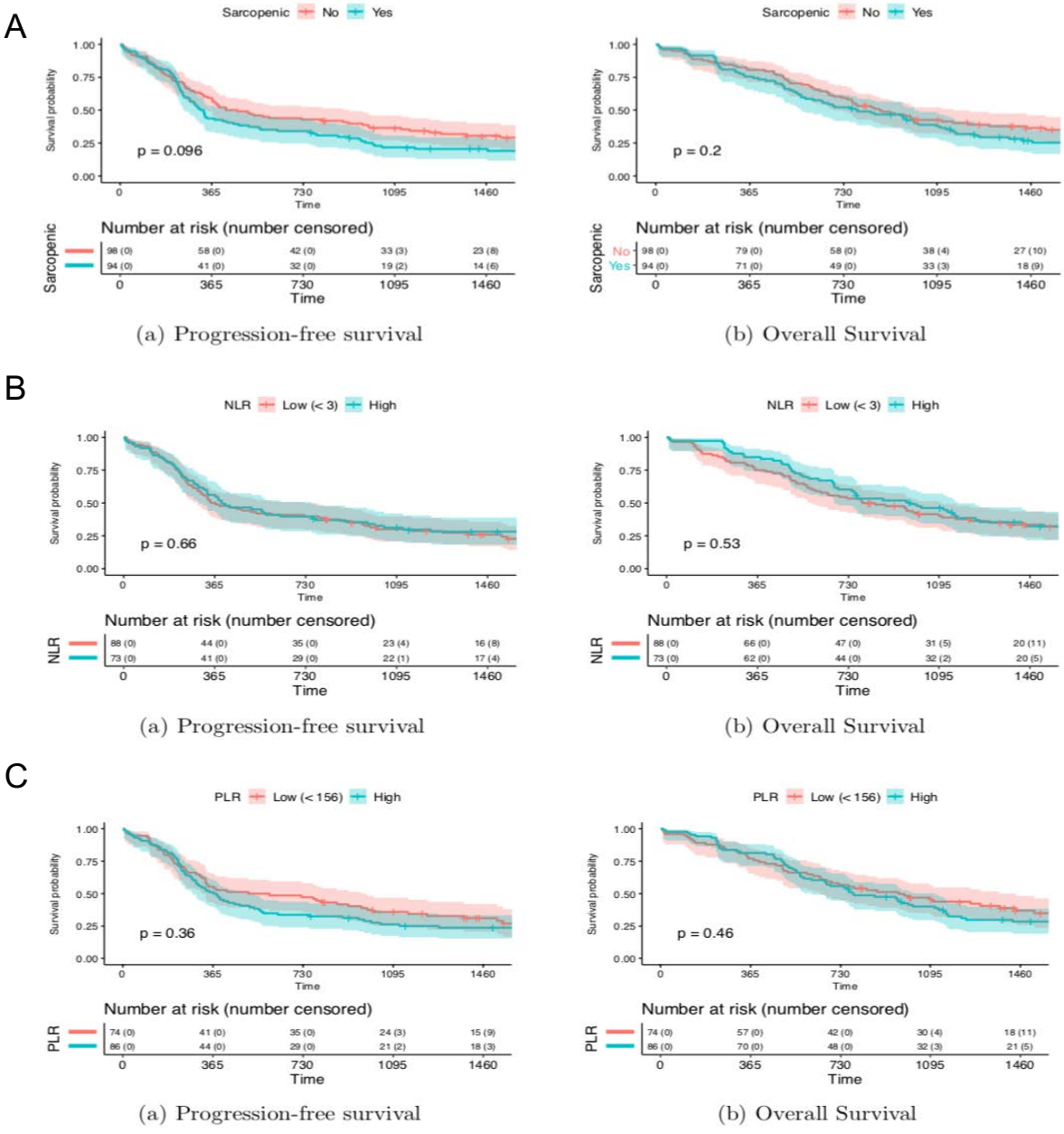
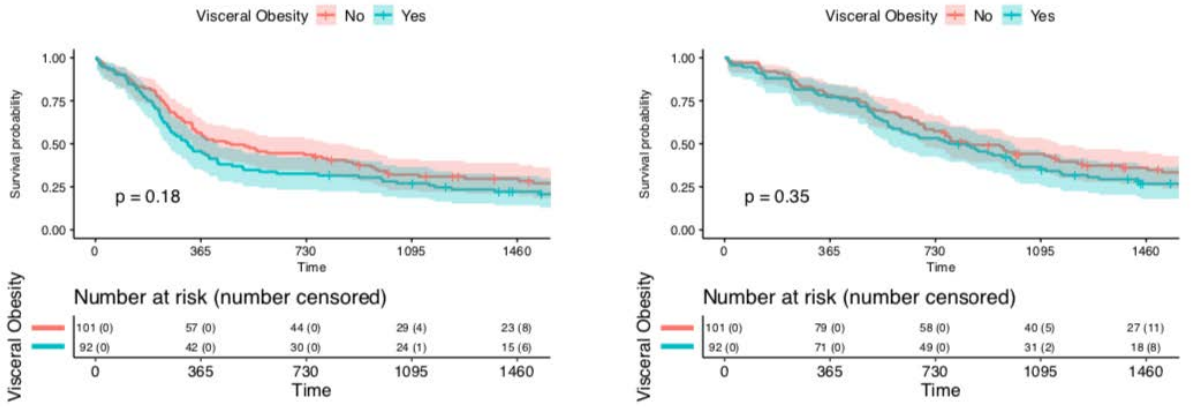


Figure 8: Overall and progression free survival by sarcopenia (A), NLR (B) and PLR (C).

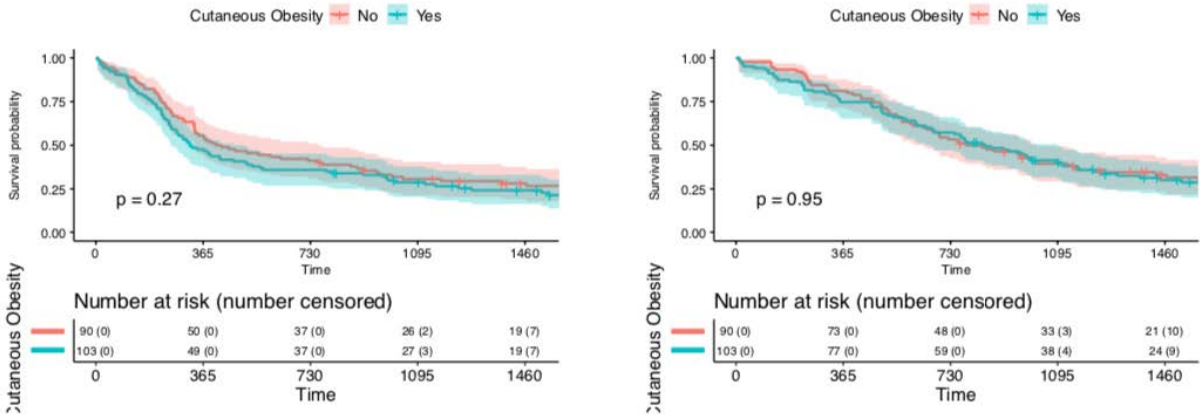
Regarding obesity status, VFA and SFA impacted nether OS nor PFS after PD for PDAC (Figure 9).

A



(a) Progression-free survival (b) Overall Survival

B



(a) Progression-free survival (b) Overall Survival

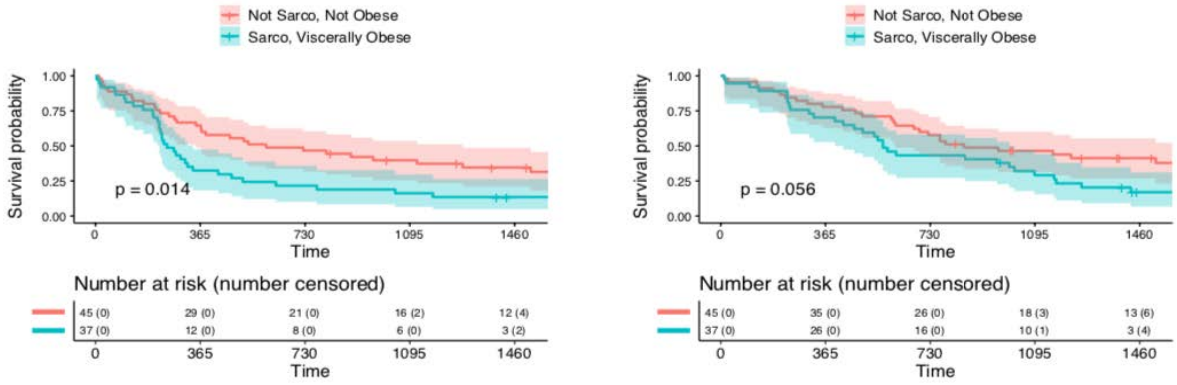
Figure 9: Overall and progression free survival by visceral obesity (A) and cutaneous obesity (B).

We then investigated the survival outcome according to sarcopenia and inflammatory status (Figure 10). Whereas sarcopenic patients with high NLR tended to have worse prognosis, no significant difference was observed between these subgroups. However, there was a significant difference in PFS between sarcopenic patients with high PLR versus non sarcopenic patients with low PLR (p=0.043) (figure 10, D). Although not significant (p=0.096), we observed this subgroup tended to have less OS compared to non-sarcopenic patients with low PLR.

Similarly, we performed the survival analysis according to the obesity and sarcopenia status. As shown in the figure 9, patients with visceral obesity and cutaneous obesity had the same prognosis compared to non-obese patients.

We also tried to identify the impact of sarcopenia and obesity on survival (Figure 10). Patients considered as sarcopenic and viscerally obese had lower survival probabilities (OS, p= 0.014; PFS, p=0.05) (Figure 10A). Furthermore, sarcopenic patients with cutaneous obesity had a lower PFS (p = 0.0059) compared to non-sarcopenic and non-cutaneous obese patients (Figure 10B).

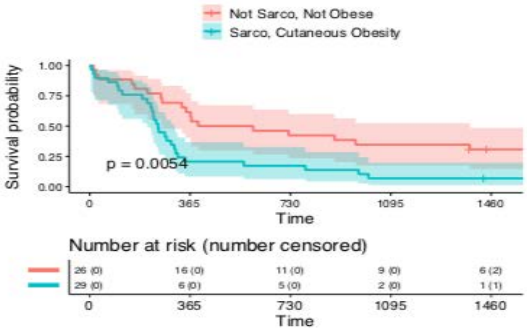
A



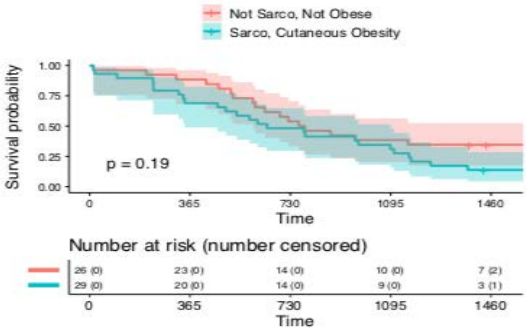
(a) Progression-free survival

(b) Overall Survival

B

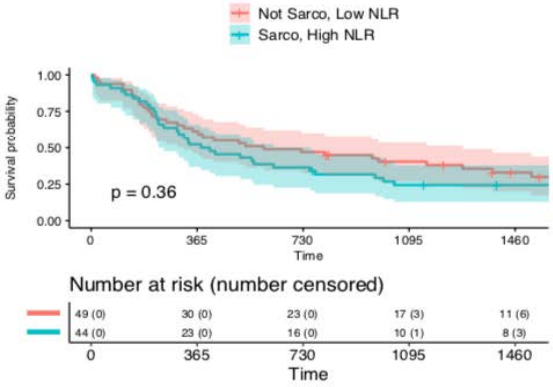


(a) Progression-free survival

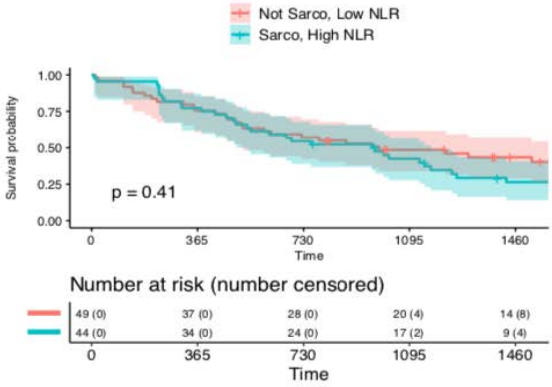


(b) Overall Survival

C

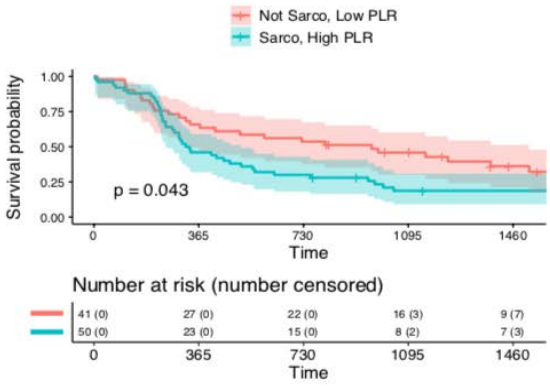


(a) Progression-free survival

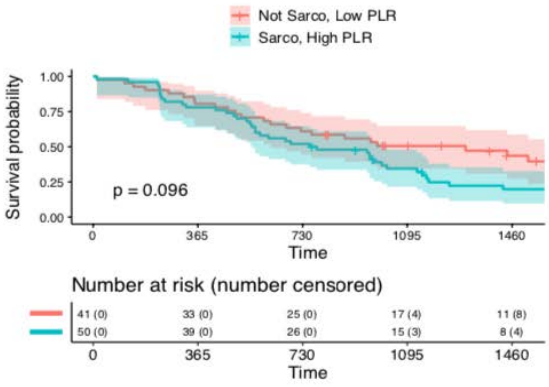


(b) Overall Survival

D



(a) Progression-free survival

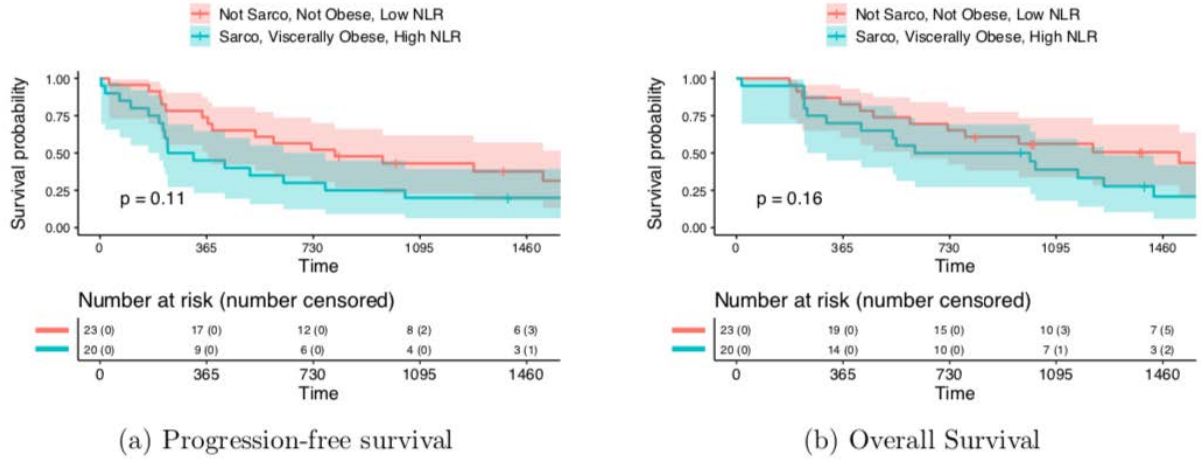


(b) Overall Survival

Figure 10: Survival analysis by sarcopenia associated to different variables: visceral obesity (A), cutaneous obesity (B), NLR (C) and PLR (D).

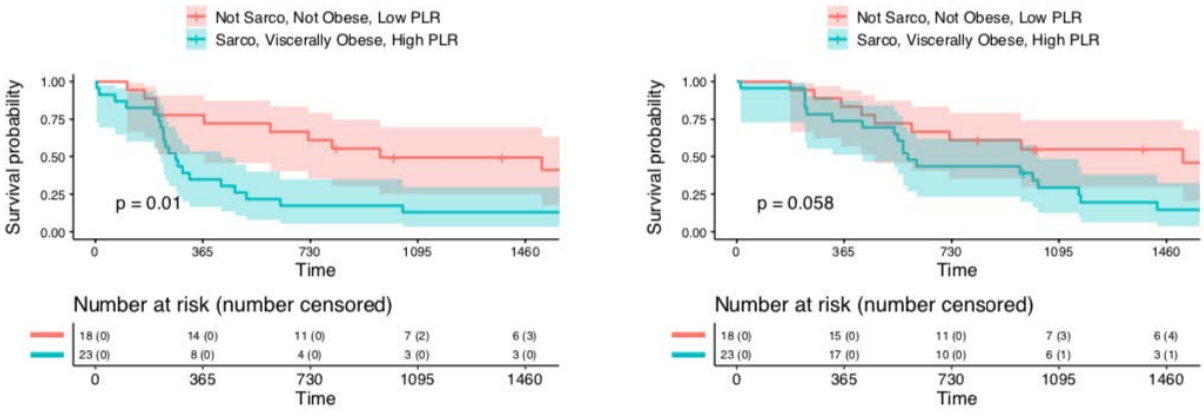
Among patients included in our study, 20 were considered as sarcopenic, viscerally obese and with high NLR. Although the difference was not significant, these patients had lower rates of OS and PFS (Figure 11A). As expected in the figure 11B, sarcopenic obesity in patients with high PLR survived for shorter periods without progression (p=0.01) and overall (p=0.05) than did the others.

A



(a) Progression-free survival (b) Overall Survival

B



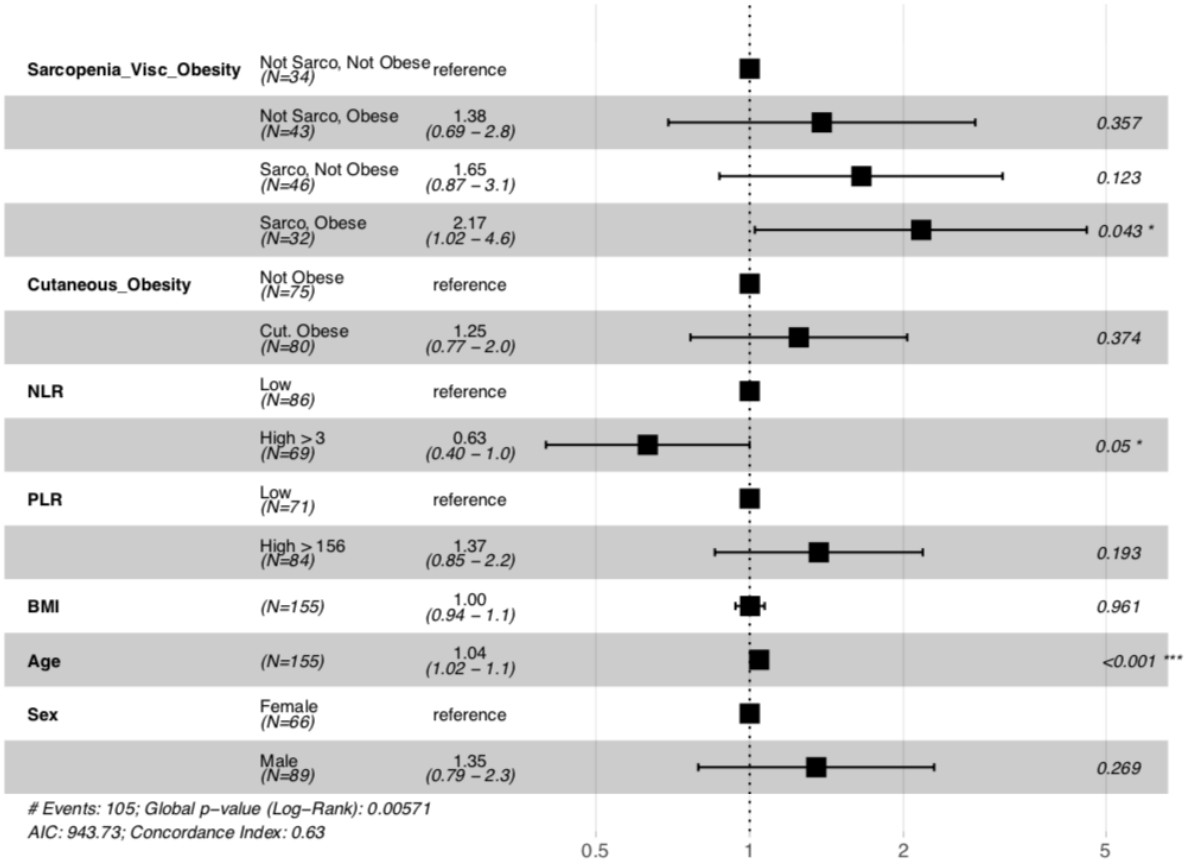
(a) Progression-free survival (b) Overall Survival

Figure 11: Survival analysis by sarcopenia and visceral obesity associated to NLR (A) and PLR (B).

Finally, we did a multivariate analysis with Cox proportional-hazard ratio to identify risk factors of worse prognosis after PD for PDAC. On multivariate analysis, the sarcopenic viscerally obese variable was independent from poor prognostic factors. The result was significant for OS (HR, 2.17; 95% CI,1.2–4.6, p=0.04) (Figure 12A) and PFS (HR, 2.34; 95% CI,1.16–4.7, p=0.018) (Figure 12B).

Regarding inflammatory markers, high PLR was associated with a tendency to have a poor PFS (p= 0.08). Similarly, we found that patients with cutaneous obesity had likelihood to relapse more often (PFS, p = 0.064) (figure 12B)

A



B

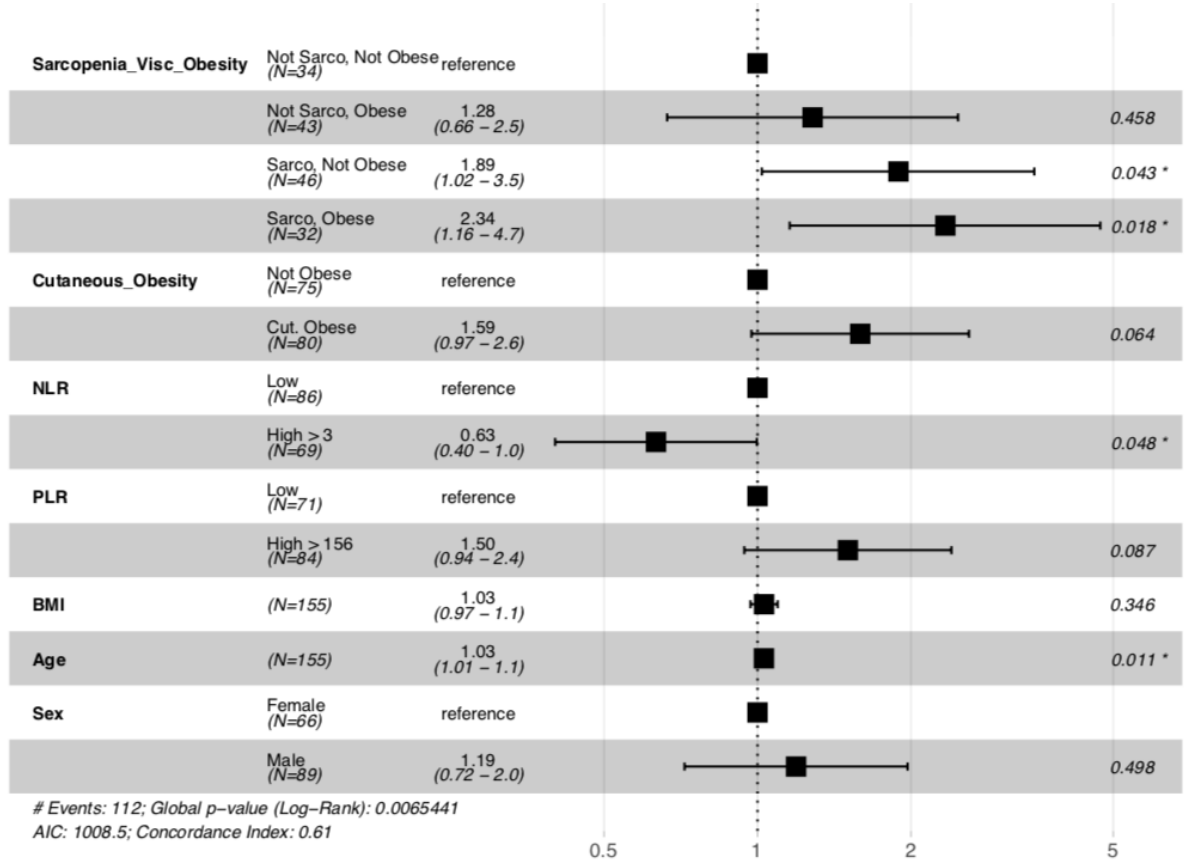


Figure 12: multivariate analysis, A) overall survival, B) progression-free survival

Discussion:

This represents the first study analyzing the relationship between SIR, sarcopenia and visceral obesity in PDAC. Herein, we demonstrated the link between inflammation and sarcopenia and their impact on survival after resection of PDAC. Interestingly, we found that sarcopenic patients with visceral obesity were more likely to relapse and had a reduced post-operative survival. We also observed that sarcopenic and obese patients with high PLR had a shorten OS and PFS after PD for PDAC. These data suggest that preoperative determination of sarcopenic, inflammatory and visceral obesity status could help to identify the better candidate for surgery.

In the current study, sarcopenia alone did not influence oncological outcome after PD for PDAC (OS, p= 0.2; PFS, P= 0.09). Still, we observed a downward trend of survival rates in sarcopenic patients compared to non-sarcopenic patients. Several papers reported that sarcopenia was associated with poor prognosis in many cancers including PDAC (13). Furthermore, some authors suggested that the tumour aggressiveness was correlated to sarcopenic status (34). Leads on how to reverse sarcopenic state exist, but data are lacking for patients undergoing PD. Physical training against resistance and improved nutrition (nutritional supplements or drugs) up to three months before surgery seemed to enhance post-operative survival (35). Other studies suggested that preoperative exercise, for six weeks, induced a lower hospital stay for at least two days and was highly recommended before surgery with a heightened recovery after surgery strategy (36). Currently, several randomized controlled studies are in progress to identify the best preoperative program for sarcopenic patients before highly complex procedures such as PD.

Sarcopenia in cancer patients is frequently associated with an inflammatory state. Indeed, tumors create an inflammatory environment by producing diverse cytokines, altering local balance and attracting leukocytes like neutrophils. Moreover, chronic inflammation generates neoplastic process by inducing DNA damage (37). Thus, tumor creates inflammation, which breaks protein balance and enhances tumoral growth leading to sarcopenia (38). Generally, NLR and PLR are used to evaluate the inflammatory status of patients (39). Numerous data suggested that PLR was useful as a prognostic factor in some cancers (33). Indeed, platelets stimulate tumor development by improving angiogenesis via the cytokine vascular endothelial growth factor (VEGF). Then, they induce angiogenesis with proliferation of new blood vessels, leading to tumor growth (43).

NLR is usually used because of the implication of lymphocytes and neutrophils in PDAC and the tumoral microenvironment. In general, lymphocytes have an anti-tumoral role, but are absent in PDAC. Neutrophils have both pro and anti-tumoral properties; they promote an inflammatory environment and display cytotoxic effects (44). NLR is also used as a prognostic factor in different cancers (head and neck cancer, small cell lung cancer, hepatocellular cancer, urinary cancer, gastrointestinal tract cancer and biliary tract cancer) (45)(46)(39) including PDAC (45). Thus, when the NLR is really high, upfront surgery should be avoided for the benefit of neoadjuvant treatment. In fact, neoadjuvant chemotherapy lowers NLR and improves postoperative prognosis in patients with breast cancer (46). Moreover, the normalisation of PLR and NLR after the first cure of FOLFOX in patients with gastric cancer was associated with better overall survival (47). In our study, we interestingly found that SMI was lower in patients with high PLR and NLR. Also, survival analysis demonstrated that sarcopenic patients with high PLR had high rates of recurrence after surgery. As previously

reported, these findings indicate that the association of sarcopenia and inflammation reflect aggressive tumor process (28)(48)(49).

We also focused our investigation on the impact of VFA and SFA on the prognosis of PDAC. It is interesting to note that taking alone, visceral obesity and subcutaneous obesity had no influence on survival after pancreatic surgery for PD. However, sarcopenic and viscerally obese patients had a poor OS and PFS whatever the BMI. In line with the current result, Okumura et al reported that sarcopenic visceral obesity was closely associated with mortality and recurrence even for patients with BMI <30 kg/m2 (50) (51)(50)(52). These findings suggested that beyond BMI, the redistribution of muscle mass and adipose tissue is more relevant to take into account (50).

The originality of our study is to highlight the prognostic role of sarcopenic visceral obesity associated with inflammation in patients with PDAC. Our results revealed that patients within these 3 categories had a lower survival than all other patients. It is interesting to note that both myocytes and myokines produce cytokines (myokines for myocytes and adipokines for adipocytes) (53)(54). Moreover, visceral fat is functionally different from subcutaneous fat in terms of the cytokine production profile. Visceral fat increases the levels of proinflammatory cytokines leading to chronic inflammation and carcinogenesis (55)(56). Also, adipokines and myokines affect the immune system and promote inflammation (57). Thus, visceral adiposity, loss of muscle mass, and inflammation are linked processes which the association is considered to predict poor survival (58).

Various adjustments are needed to improve the prognosis of pancreatic cancer patients. Because, sarcopenia, visceral obesity and inflammatory status are poor

prognosis factors, it is probably reasonable to consider these patients as borderline resectable PDAC requiring neoadjuvant chemotherapy. The recent international consensus on the definition of borderline resectable PDAC distinguished 3 categories: anatomical, biological and conditional borderline PDAC (59). Therefore, it would be relevant to consider sarcopenia, inflammation and visceral obesity as parameters included in the definition of borderline PDAC.

After screening patients for sarcopenia in daily practice, nutritional care and exercising should be proposed. Progressive resistance training (PRT) seemed to have a positive effect on muscle mass and strength (60). It consists of exercising muscle against any type of resistance (elastic bands, weights or machines), then regularly increasing it depending on muscle strength. Nutrition revolves around adequate protein intake with 1.2 g/kg/day. Supplementation by vitamin D, ß-methylbutyrate and creatine could also be an effective way to help rebuild muscle mass, muscle strength and physical performance (17)(61)(62).

Our study had some limitations. First, the retrospective design of our work could induce bias. As such, a prospective study may be warranted in the future. Second, we used non-validate cut-offs to define sarcopenia, visceral obesity and inflammation in patients with PDAC. However, consensual definition is currently lacking. Third, we focused our analysis only on patients undergoing PD, which does not allow generalising our results for all patients. Finally, the assessment of sarcopenia was only made on preoperative CT Scan by measuring the TAMA. Other methods exist to detect sarcopenic state such as dual X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA). They are proven to be more effective than a single slice measurement (17). Despite these limitations, our analysis suggests considering other preoperative parameters to determine the strategy of choice in the management of resectable PDAC.

Conclusion:

Sarcopenic obesity and SIR are associated with lower survival rate. Several designs can be fulfilled to improve survival such as exercise, nutrition modification or neoadjuvant chemotherapy. Further studies should be done to assess the efficiency of these measures in PDAC.

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Date de soutenance : 18/10/2021

Titre de la thèse**: Impact on survival of sarcopenia, systemic inflammatory response and anthropometric factors after pancreatectomy for resectable pancreatic adenocarcinoma.**

Thèse - Médecine - Lille 2021

Cadre de classement **: Médecine**

DES + spécialité **: Chirurgie viscérale et digestive**

Mots-clés**: Pancreatic adenocarcinoma, sarcopenia, visceral obesity, cutaneous obesity, inflammation, Neutrophil to lymphocyte ratio, Platelet to lymphocyte ratio.**

Introduction: Pancreatic adenocarcinoma (PDAC) is becoming a public health issue with a 5-years survival rate around 5%. Patients with PDAC are often sarcopenic, which impacts post-operative outcome. At the same time, overweight population is increasing and adipose tissue promotes tumor related-inflammation. With several studies supporting these data, we aimed to assess if they held an impact on survival when combined.

Methods: We included 232 patients from two university hospitals (CHU de Lille, Institut Paoli Calmette), from January 2011 to December 2018, who underwent Pancreaticoduodenectomy (PD) for resectable PDAC. Preoperative CT scan was used to measure sarcopenia and visceral fat according to international cut-offs. Neutrophil to lymphocyte (NLR) and platelet to lymphocyte ratios (PLR) were used to measure inflammation. For univariate and multivariate analyses, the Cox proportional-hazard model was used. p-values below 0,05 were considered significant.

Results: Sarcopenic patients with visceral obesity were less likely to survive than the others in multivariate analysis (OS, HR 1.65, p= 0.043). Cutaneous obesity did not influence survival. We also observed an influence on survival when we studied sarcopenia with visceral obesity (OS, p= 0.056; PFS, p = 0.014), sarcopenia with cutaneous obesity (PFS, p= 0.005) and sarcopenia with PLR (PFS, p= 0.043). This poor prognosis was also found in sarcopenic obese patients with high PLR (OS, p= 0.05; PFS, p= 0.01).

Conclusion: Sarcopenic obesity was associated with poor prognosis after PD for PDAC, especially in patients with systemic inflammation. Prehabilitation program and neoadjuvant chemotherapy should be preferred in these patients.

<u>Composition du Jury</u> :

Président : Pr Stéphanie TRUANT

Assesseurs : Pr Olivier TURRINI, Dr Anthony TURPIN

Directeur de thèse : Dr, MCU-PH, Mehdi EL AMRANI