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Atrophie diaphragmatique séquellaire du sepsis : étude tomодensitométrique rétrospective

Simon Légère

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UNIVERSITÉ DE MONTPELLIER
FACULTÉ DE MÉDECINE MONTPELLIER-NÎMES

THÈSE D'EXERCICE

Pour l'obtention du titre de

DOCTEUR EN MÉDECINE

Présentée et soutenue publiquement par

SIMON LÉGÈRE

Le 19 Octobre 2021, à Montpellier

**ATROPHIE DIAPHRAGMATIQUE SÉQUELLAIRE DU
SEPSIS :
ÉTUDE TOMODENSITOMÉTRIQUE RÉTROSPECTIVE.**

Sous la Direction de Monsieur le Professeur Boris JUNG

JURY

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Second Assesseur : **Docteur Stéphanie NOUGARET**

DIAPHRAGMATIC ATROPHIC

SEQUELAE OF SEPSIS :

A RETROSPECTIVE COMPUTED

TOMOGRAPHY STUDY.

*« Le travail éloigne de nous trois grands maux :
l'ennui, le vice et le besoin. »*

– Voltaire

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette École, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure au nom de l'Être Suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses. Que je sois couvert d'opprobre et méprisé par mes confrères si j'y manque.

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1. INTRODUCTION

I. Background

Severe infectious conditions represent a great challenge for modern intensive care medicine and public health. According to the World Health Organisation [1],[2], it is more than 11 millions worldwide deaths by sepsis, that is 20% of global mortality. Almost 85 % of the cases of sepsis occur in low-income regions, where it represents a heavy burden on emergent countries, in first instance because of materno-fetal and neonatal infections. Even in modern health systems, sepsis remains a major source of fatalities (up to 50 % for the most severe form, septic shock) and a frequent complication of all causes hospitalisation, especially in ICU : 18% at admission and up to 40 % of overall occurrence during the stay [3]. The medical research participated in a clear improvement in sepsis incidence and mortality, respectively decreased by 37 % and 52 % in the last two decades [4].

These past years, intensive care medicine has made great advance in understanding the pathophysiology and improving the management of the sepsis. Yet, progress remains to be made in secondary and more insidious consequences, such as muscular sepsis-related atrophy, that is known to be part of critical illness acquired neuromyopathy, and which is associated with an important morbidity, difficulties to wean from ventilator, and delayed resumption to a normal life. Many authors [5],[6] warn the practicing clinicians about the dramatic underestimation of diaphragmatic impairment in septic patients, a fortiori if mechanically ventilated.

Beyond the excess of mortality cause byf prolonged mechanical ventilation (MV), leading to infectious and static complications, the diaphragmatic sepsis-related

sequelae could represent a major morbidity factor for survivors and a heavy burden upon the medical system.

II. Knowledge

Prolonged stay in the ICU, involving critical condition and aggressive therapeutics, leads to systematic neuromuscular loss of strength by skeletal muscle atrophy and neuronal lesion, which is now commonly considered in patients invasive ventilation withdrawal. It has long been known [7] that critical illness polyneuropathy and myopathy are classic causes of ventilator dependency, due to a multifactorial diaphragmatic and accessories muscles weakness. These factors are very frequently present at some point of the ICU stay, and are even more common with sepsis or multi-organ failure : hyperglycemia, MV, paralysing agents, protein deprivation, hypophosphatemia, hypokalemia, hypoguesemia, hypocalcemia, thyroid disturbance, and any process diminishing the pulmonary compliance : pneumonia, atelectasis, bronchospasm, pneumothorax, or pulmonary oedema. Inadequate energy supply, direct pathogen damage and therapeutic side effects, all of these are components of a complex pathophysiology, involving increased oxidative stress and exaggerated proteolysis [8],[9].

Diaphragm dysfunction can also be part of a multi-organ failure, more specifically in the sepsis, and is associated with a poor prognosis, even early in the onset of a critical illness, as it has been demonstrated by invasive phrenic stimulation to assess the inspiratory pressure capacity [10]. Beyond the global aftereffects of a critical illness and its invasive management in ICU, patients undergoing sepsis are specifically prone to diaphragmatic weakness, as Supinski and colleagues studied in depth [11],[12]. It has been significantly linked to sepsis as a major risk factor of diaphragmatic dysfunction ; it is also correlated to poor outcomes of MV, which is the most frequently used supportive therapy in ICU.

Diaphragmatic injury is known to occur very rapidly after mechanical ventilation initiation, as of the very first hours, and is characterised by both loss of strength (decrease of the inspiratory pressure under phrenic electrostimulation) and ultrastructural injury (fiber atrophy and overexpression of proteolytic proteins in postmortem biopsy) [13]. The reverse process is on the contrary poorly known. The diaphragmatic injuries recovery has been more described in the case of acute phrenic atrophy. For example, post-traumatic or infectious paralysis, recovery occurs in most of patients but may take up to several years, less because of the myofibers cicatrisation, than the phrenic nerve regeneration. Even in an 11 years follow-up, some patients can show an incomplete recovery, and full recuperation would take a minimum of 2 years in prospective studies [14].

III. Objectives

A previous prospective single-center study, by Jung et al. (Anesthesiology, 2014) [15], provided the basis of this present study. By comparing the diaphragm muscle with the psoas as a control skeletal muscle, among 14 patients with sepsis and 9 critically ill non-septic patients, it demonstrated a preferential loss of diaphragm volume and contractile force (evaluated by magnetic stimulation of the phrenic nerve). Before that, pilot studies [16] had already shown that critical illness polyneuromyopathy is highly prevalent among septic patients (especially with prolonged weaning from ventilator) and that peripheral muscles inabilities explored by electrophysiology are significantly associated with diaphragmatic impairment. Despite a small sample size, Jung et al. were the first to show in human model the greater susceptibility of the diaphragm to septic aggression, above any other muscle group.

We tried to complete the results of this previous study by recruiting a larger and more homogenous group of patients, and use them as their own comparator, to demonstrate the importance of muscular atrophy after an ICU stay due to a sepsis or a septic shock. We used again the psoas to illustrate the atrophy of the systemic muscular tissue.

After several studies comparing muscle atrophy between critically and non critically ill patients, or septic and non septic patients, the aim of ours was therefore to highlight the difference of diaphragm and psoas volume during a critical infectious illness. We compared the patients with themselves, before and after their ICU stay, and described the hypothetical link between muscle atrophy and various individual fragility and gravity criteria.

2. METHODS

I. Design

This study was retrospectively conducted in a single french teaching hospital ICU (*Réanimation Médicale, CHRU Lapeyronie, Montpellier, France*), with the support of the emergencies department of the same hospital, and in strong collaboration with an oncology institute which is a non-profit private clinic (*Institut du Cancer de Montpellier, France*),

All included subjects are drawn from a retrospective cohorte of patients, undergoing an oncological treatment or follow-up for at the ICM, between January 2015 and December 2018. It was a deliberate choice to study a group of patients with a history of cancer, knowing they are the most likely to have a reliable and easily available diaphragmatic imaging. Therefore, both CT-scan were performed at the ICM as the routine course of the cancer medical follow-up. The study design is represented in [Figure 1](#).

We preferred a retrospective design over prospective inclusion, that would have require a very long term study to obtain 41 subjects as we did, given the need for patients surviving severals months after cancer evolution and critical infection.

Considering that this *post-hoc* analysis does not impact upon the diagnosis, prognosis, or therapeutics strategies, there was no legal requirement for any written consent according to the French Biomedical Research Legislation (Law 88-1138 of 20/12/1988 modified on 9/08/2004).

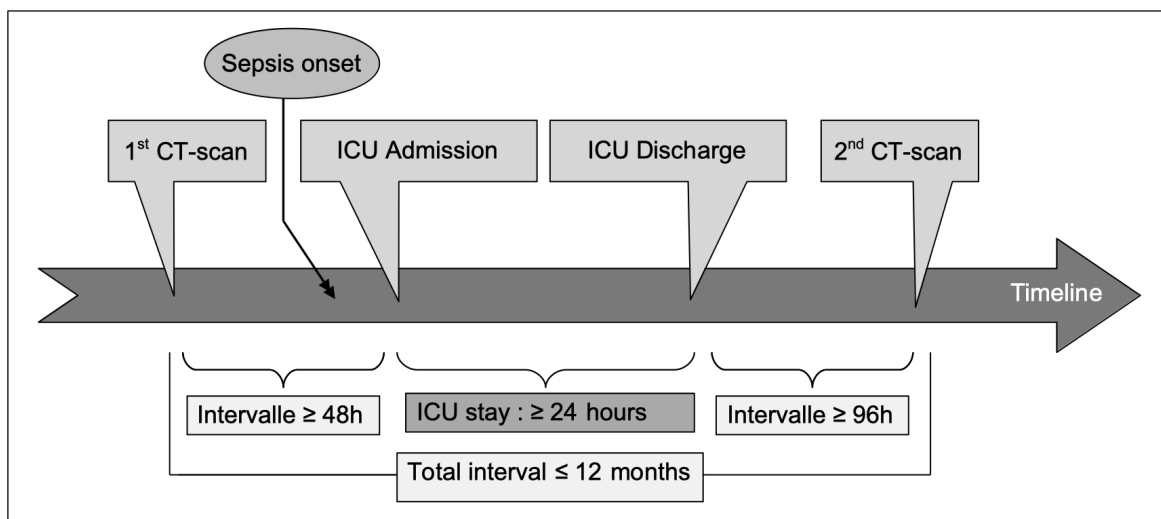


Fig. 1 Design of the study.

II. Population

We delineated the inclusion criteria of our study population as patients being hospitalised at least one day in ICU for a severe infection (with or without state of shock). Patients suffering infection in the course of the ICU stay were not included if they were admitted for an other medical issue. Severe infection was defined according to the Third International Consensus (*Society of Critical Care Medicine and European Society of Intensive Care Medicine, JAMA, 2016 [17]*) :

- Sepsis : life-threatening organ dysfunction caused by a dysregulated host response to infection, which can be represented as an increase of at least 2 points in the Sequential Organ Failure Assessment score (SOFA), associated with an in-hospital mortality greater than 10%.
- Septic Shock : infection complicated by hemodynamic instability and profound cellular abnormalities, that is a serum lactate greater than 2 mmol/L (in the absence of hypovolemia) and a vasopressor requirement to reach a mean arterial pressure of at least 65 mmHg. The in-hospital mortality is then greater than 40%.

A flow chart of our study is represented in [Figure 2](#). The initial study cohort counted 1039 patients known for a history of neoplasia, active or past, diagnosed or suspected, all of them having been admitted in our ICU at some point, during the date range from January 2015 to December 2018 (4 years). We spot out 211 cases of sepsis or septic shock at admission, and that were hospitalised at least 24 hours in ICU ; this particular criterion was to prevent errors of orientation (simple infection or any overestimated condition mistaken for complicated sepsis) and to ensure a sufficient quantity of clinical and biological data.

We specifically choose the patients followed at the ICM (n = 175) for logistic reasons, the radiology imaging being of easier access ; the other patients (n = 36) were followed in other clinics or even other regions. Among them, 121 did not survive the ICU stay (or died some time after because of the cancer evolution), resulting in the absence of a post-ICU CT for comparison. Moreover, 13 could not be included because they presented some exclusion criterion :

- Recent control thoracic CT unavailable in the ICM archives, that is in the year before or after the ICU admission (for example, some had completed the scheduled cancer follow-up, or others had a cancer that did not require an imaging with diaphragmatic views).
- Juvenile subjects (under the age of 18 years old) or pregnant women, for ethical issues and extrapolation limits.
- Comorbidity known before the ICU admission, affecting the diaphragmatic muscle physiology or mechanic : phrenic paralysis, diaphragmatic hernia, spinal injury or severe plegia, amyotrophic lateral sclerosis, medulla tumor or malformation, thoracic scoliosis... It should be noted that no eligible patient presented such confounding factor.

In total, 41 patients matched all inclusion criteria and had the right imaging data enabling the analyses, meaning one CT-scan before the ICU admission, and a second CT after the ICU discharge.

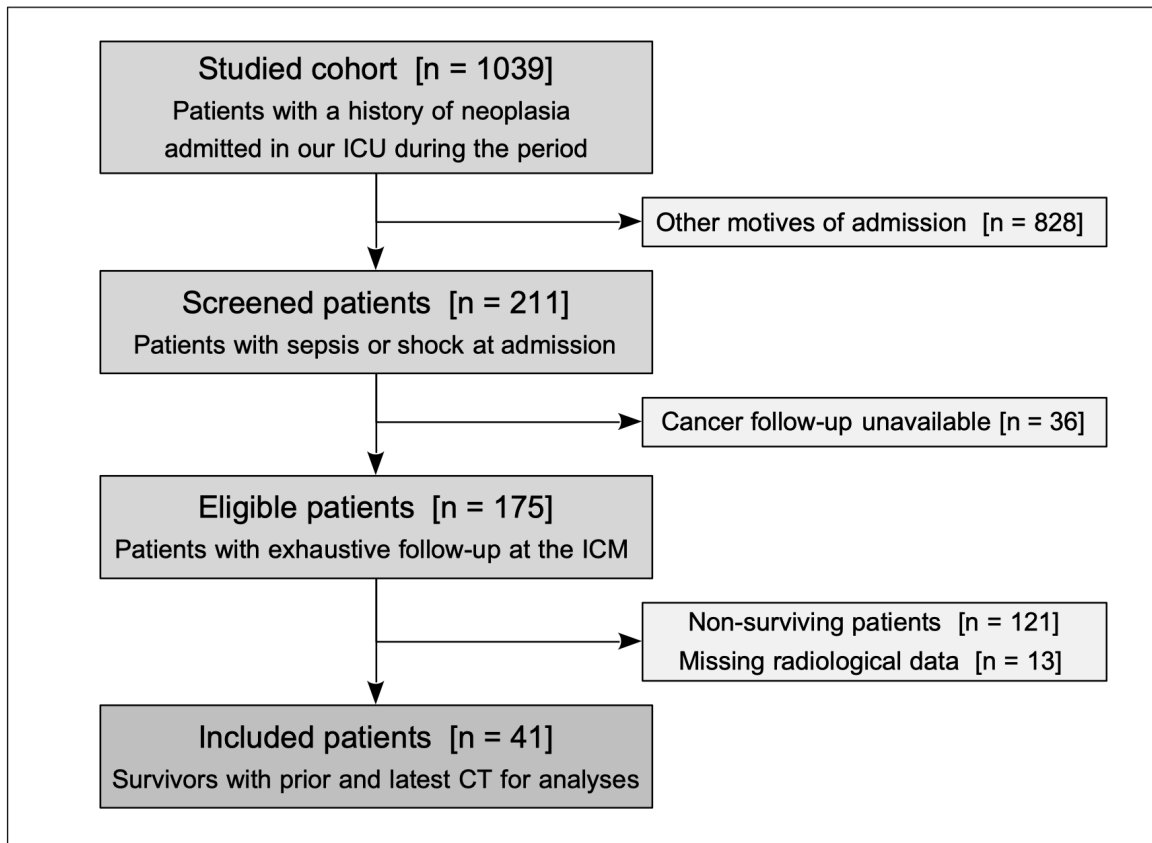


Fig. 2 Flow Chart of the study.

III. Measurements

We collected general data for sex, age at ICU admission, height, body mass index (BMI), date of ICU admission, and time in days between both CT and between CT and ICU admission. We also collected medical history of interest, in regard of respiratory and micro-circulatory morbidity that could affect the diaphragmatic function or response to sepsis : metastatic cancer, arteriopathy disease, chronic obstructive pulmonary disease (COPD), restrictive lung disease, diabetes mellitus, and state of immunosuppression. See Table 1 for specific de criteria taken into account. Finally, we collected informations about the ICU stay in terms of baseline severity and global medical care : state of septic shock, SOFA score at admission, duration of MV, duration of neuromuscular blockade agents (curares), duration of

sedation, duration of Norepinephrine, use of hydrocortisone, values of procalcitonin (PCT), lactates, and creatin kinase (CPK). We chose these last biological elements as rapidly responsive markers of severe infection, cellular hypoxia, and muscular lesion respectively, assuming they could be indirectly representative of diaphragmatic damage.

Then we collected the computed tomography (CT) images, one performed before the sepsis onset and another one after the sepsis resolution. If several CT-scans including a proper view of the interesting anatomical area were available, we systematically selected the nearest CT from the date of admission, but never during the ICU stay, or 48 hours preceding or following it. The aim was to prevent other factors than sepsis to modify the phrenic muscle in case of a long delay between the two compared CT, but not to underestimate the impact of sepsis by interpreting on or both CT during the active phase of the infection (after its onset, or before its resolution). The duration between the first and the second CT has to be a maximum of 1 year, to avoid a potential recovery of the diaphragm injury.

We carried out manual computer-assisted segmentation with *Slicer 3D* version 4.11.2021.0226, available on <https://www.slicer.org> [18]. The segmentation was proceeded by a single investigator to ensure a reproductibility from a patient to another one. A experimented senior radiologist (NOUGARET S, MD) vouched for the methodolgy of the segmentation. We selected CT scan showing the entirety of the diaphragm from the cupulas to the base of the pillars, and of the psoas from an insertion to the other. It has hence to be at least an abdominal CT with low thoracic sections. We preferentially selected portal phase if available. The diaphragm and both psoas muscles were entirely and precisely segmented on one slice out of three, and use an extrapolation tool of the software filling the empty spaces from a segmented slice to another. After several test, this method presented the most efficient balance between time, reproducibility, and precision in volumetric assessment. The volume was the automatically measured in voxels and converted in cubic centimetre (cm³). See [Annex 3](#) for an example of Slicer usage an preview.

IV. Endpoints

This study represents a straight continuation of the precedent publication of Jung et al. [15]. Our goal was to describe the epidemiology, in terms of incidence and severity, of diaphragmatic atrophy linked to sepsis and septic shock, via a reference and easily available exam which is computed tomography. The primary endpoint is to observe the sepsis-associated atrophy of the diaphragm and psoas between a reference CT (before ICU admission) and an imaging after a variable period of evolution.

The secondary endpoints were on one hand, to compare the difference of diaphragm versus psoas variation ; and on the other hand, to try to highlight some baseline characteristics or initial sepsis-linked variables, associated with diaphragmatic atrophy, that could possibly be predictive factors of an aftereffect risk. We incidentally wanted to evaluate a radiological volumetric software tool to measure the potential diaphragmatic loss of volume, for future studies.

V. Statistics

The results are, as most adapted, expressed as mean with standard deviation and median. All Durations are expressed as days, and volumes as cube centimeter (cm^3). Statistical analyses were performed using the software *Medistica – pvalue.io 2020* (Graphic User Interface to the R statistical analyses software for scientific medical publications), available on <https://www.pvalue.io/fr>. The statistical significance was considered for a p-value of less than 0,05, with 80% statistical β power and one-sided α value of 5%.

The main variables “variation of diaphragm” and “variation of psoas” were expressed in percentage of the initial volume (%), a positive value corresponding to a loss of muscle mass volume between the two CT. These variables had a normal-like distribution (according to the law of Laplace-Gauss), see Annex 4, enabling a

comparison by a paired Student T-test between before and after volumetric measures. Univariate analyses of quantitative variables were done with Pearson product-moment Correlation test. Univariate analyses of qualitative binary variable (presence or absence of characteristic) were done with Wilcoxon-Mann-Whitney rank sum test with continuity correction or with a Spearman correlation test when more adapted.

We operated multivariate analyses on the characteristics that demonstrated a significant link ($p < 0,05$) or at least a statistical trend ($p < 0,2$) with a variation of muscle volume (marked by \diamond). We use a linear logistic regression model with a bootstrap method, with adjustment on 1 to 3 pertinent confounding variables, according to the effective of 41 subjects. The coefficients Beta are expressed in percentage of volume and correspond directly to the proportional factor of the loss of volume, for a difference of 1 unit in the multivariate analysed variable (i.e an interval coefficient Beta comprising 0 is not significative of volume modification).

3. RESULTS

I. Characteristics

A total of 41 patients were analysed (that is 82 CT-scan). Table 1 shows their main characteristics at baseline or admission. They were mostly women (59%) and on average 59 years old (extreme ages 31 and 82, median 63), with a mean BMI of 23,3 (\pm 3,8 SD). In their medical history, 14% had COPD, 10% had diabetes mellitus, and 34% had arteriopathy. Concerning this last characteristic, we took into account clinically relevant with several cardiovascular risk factors (as defined by the European Cardiology Society) or with a significant arterial lesion (heart attack, aortic aneurysm or dissection, lower limbs claudication, renal arteries occlusion, ischemic stroke...). 66% of the studied population was to be considered in state of immunosuppression, wether with a neutropenia, a recent chemotherapy or corticotherapy, or suffering from any pathology known to be immunosuppressive. No patient had any condition of restrictive lung disease or restrictive respiratory mechanics (see criteria in Table 1).

At admission in ICU, the average SOFA score was 6/24 (mean and median, with extreme values of 2 and 13), while 23 of the 41 patients (56%) were in septic shock. The majority of them had biological markers of septic severity such as augmented lactates (mean 2,2 \pm 1,8 mmol/L considering a normal value $<$ 1,2 mmol/L), and augmented PCT (mean 13,2 \pm 24,2 ng/mL considering a normal value \leq 0,8 ng/mL). During the ICU stay, 68% of them required a vasopressive support (continuous infusion of Norepinephrine for at least 24 hours ; we reported no case of use of epinephrine or dobutamine), and 19% were supplemented with Hydrocortisone, not mattering if it had to be prolonged or discontinued. Respectively 15 and 14 patients had to be mechanically ventilated and sedated with anaesthetic drugs, 10% (4) underwent ARDS complication (as defined by the SRLF guidelines).

It has to be noticed that we searched for occurrence of some other conditions during the ICU stay, or in the last days before admission. These complication could have affected the respiratory physiology or the general state of inflammation, but too few cases were found to be relevantly analysed : there was no case of pulmonary embolism, only two non-programmed major surgery with supposed systemic inflammatory state (1 cholecystectomy, 1 peritoneal lavage), and a unique case of cardiorespiratory arrest (at day 3 of the ICU stay).

Table 1. Baseline characteristics of the studied patients (n= 41)

Studied characteristics	Percentage of positiveness	Mean \pm standard deviation	Median
Female sex	59 % (24)	–	–
Age (year)	–	59 \pm 15	63
Height (cm)	–	166 \pm 9	165
Body Mass Index (kg/m ²)	–	23,3 \pm 3,8	23,1
Metastasis	71 % (29)	–	–
Arteriopathy disease *	34 % (14)	–	–
COPD	14 % (6)	–	–
Restrictive Lung Disease History **	0 % (0)	–	–
Diabetes Mellitus	10 % (4)	–	–
State of Immunosuppression ***	66 % (27)	–	–
Septic shock	56 % (23)	–	–
SOFA score upon admission	–	6 \pm 3	6
CPK (UI/mL) upon admission	29,2% (13)	306 \pm 682	70
PCT (ng/mL) upon admission	73,4% (30)	13,2 \pm 24,2	2,8
Lactates (mmol/L) upon admission	53,4% (22)	2,2 \pm 1,8	1,6
Hydrocortison use	19 % (8)	–	–
Norepinephrine (days)	68 % (28)	2 \pm 2	2
Curare agents (days)	19 % (8)	1 \pm 1	0
Sedative drugs (days)	34 % (14)	2 \pm 4	0
Mechanical Ventilation (days)	37 % (15)	2 \pm 5	0
Acute Respiratory Distress Syndrome	10 % (4)	–	–

* Arteriopathy History :

coronary artery disease / lower limb artery disease / aortic anevrysm / stroke / carotid stenosis / diabetes mellitus with artery disease / vascular sexual impotence / or \geq 3 cardiovascular risk factors (hypertension, dyslipidemia, smoking, age >70...)

** Restrictive Lung Disease History :

severe obesity (BMI > 35) / thoraco-lumbar scoliosis / diaphragmatic hernia / pleural effusion or pneumothorax / recent ribs or vertebra fracture / pulmonary fibrosis / major ascites / ALS or Guillain-Barre Syndrome or other proximal neuromyopathy

*** Immunosuppression :

chemotherapy in the last 2 weeks / ongoing corticotherapy / neutropenia < 1000/mm³ / nephrotic syndrome / monoclonal gammopathy / known immune congenital deficiency

Figures 3A & 3B highlight among the studied population, the diversity of infections and primitive cancers respectively. The majority of the patients presented with pleuropneumopathy (17), and the others had pyelonephritis (6), peritonitis or intraabdominal infection (6), bacteriemia (6, 4 of which began with a central veinous line or implantable port), endocarditis (1), osteoarthritis (1) ; for 4 cases, no microbiology exploration could have objectified any germ (“unknown” infectious site) ; there was no meningitis or skin and soft tissues infection. We also identify as primitive cancer origins : 6 bronchopulmonary (lung), 6 colorectal (colon / rectum / anus), 6 gynecological (uterus / ovaries), 6 otorhinolaryngology (pharynx / larynx), 5 gastroesophageal (stomach / esophagus), 4 urological (bladder / kidney), 3 mammary (breasts), 2 skeletal (bones), 1 pancreatic (pancreas), 1 hematological (lymphoma), 1 dermatological (skin). Other cancer localisation such as cerebral or hepatic or thyroid primitives were not represented in the cohort. In total, 71% of the patients had at least one metastatic lesion, not including regional malignant adenopathy.

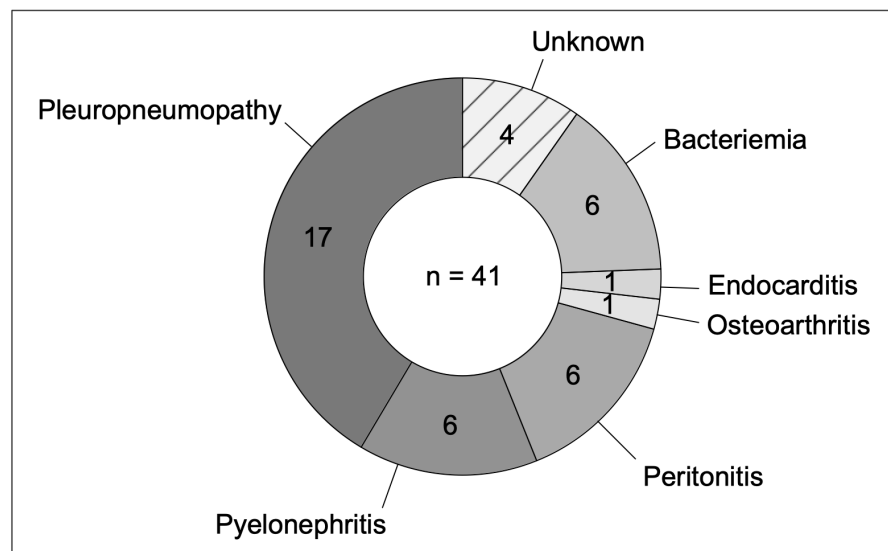


Fig. 3a Repartition of infection sites in the study population

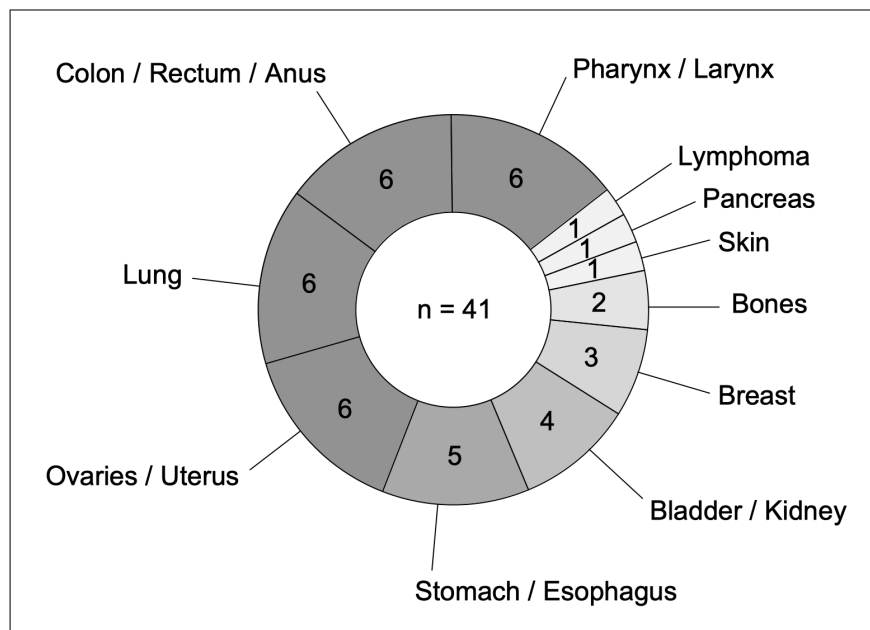


Fig. 3b Repartition of primitive cancer origins in the study population

II. Segmentation

Over a total of 41 included patients, 82 CT (2 for each subject) have been segmented. As reported in [Table 2](#). The firsts CTs have been performed on average 49 ± 42 days before the admission in ICU (extreme from 2 to 144 days), and seconds CTs have been performed 52 ± 51 days after (extreme from 7 to 230 days), with a mean time interval of 102 ± 62 days (extreme from 15 to 317 days).

We measured a pre-ICU psoas volume of 208 ± 61 cm³ (minimal 65 and maximal 382 cm³) and a post-ICU psoas volume of 181 ± 54 cm³ (minimal 60 and maximal 334 cm³). The mean variation was 26 ± 25 cm³ (minimal loss 1 cm³ and maximal 126 cm³), that is a 12,1% variation of psoas volume. We recorded one case of gain of volume (1,1%). Concerning the diaphragm, we measured a pre-ICU volume of 176 ± 45 cm³ (minimal 103 and maximal 305 cm³) and a post-ICU volume of 155 ± 35 cm³ (minimal 99 and maximal 292 cm³). The mean variation of diaphragm volume was 21 ± 25 cm³ (minimal loss 1 cm³ and maximal 107 cm³), that is a 10,7% variation of diaphragm volume. We recorded 4 cases of gain of volume, respectively 1,6%, 10,8%, 6,4% and 4,2% (this last values corresponding to the same patient

whom psoas gained 1,1% previously mentioned). It should be noted that the gains of muscle volume are considered as inverse variations of expected loss of volume, and therefore are noted as negative values in the tables Annex 5.

Figure 4 shows the repartition of diaphragm and psoas volumetric variation of each 41 analysed patient. We attempted to organise the values in three groups, according to the pattern of the variation of muscle volume. A first ensemble (green) shows the patients with a variation of psoas volume at least double of their variation of diaphragm volume ; a second ensemble (red) shows on the contrary the patients with a variation of diaphragm volume at least double of the psoas ; a last ensemble (purple) gathers the patients which did not fit the two other groups, and which appear to have a more homogenous ratio between variation of diaphragm and psoas volumes (i.e : variation of diaphragm (%) = / [0,5 ; 2] x variation of psoas (%)).

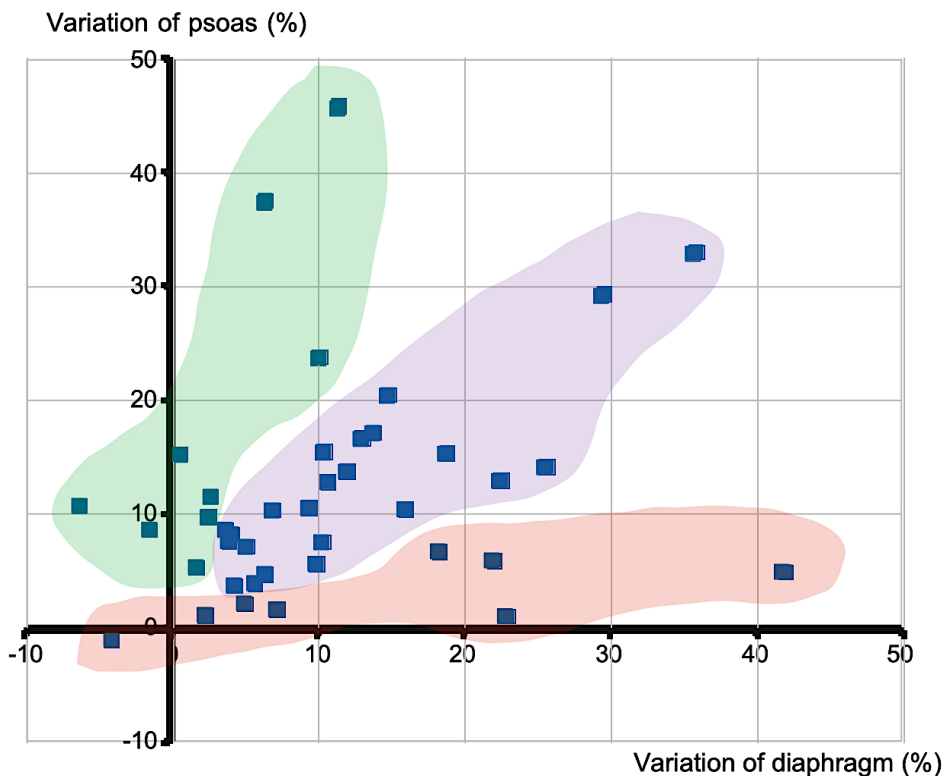


Fig. 4 Individual variation of psoas volume over diaphragm volume Arbitrarily separated in 3 groups : green = predominant variation of psoas volume (n=10) ; red = predominant variation of diaphragm volume (n=8) ; purple = relatively homogenous variation of psoas and diaphragm (n=23)

Table 2. Radiological data of the studied patients.

Studied characteristics	Mean ± standard deviation (n = 41)	Median	Percentage	P-value
Durations (days)				
from 1 st CT to ICU admission	49 ± 42	28	–	–
from ICU admission to 2 nd CT	52 ± 51	35	–	–
between 1 st and 2 nd CTs	102 ± 62	88	–	–
Volumes (cm ³)				
Psoas on pre-ICU CT	208 ± 61	197	–	–
Psoas on post-ICU CT	181 ± 53	170	–	–
Psoas variation between both CTs	26 ± 25	18	12,10%	p < 0,001
Diaphragm on pre-ICU CT	176 ± 45	162	–	–
Diaphragm on post-ICU CT	155 ± 36	152	–	–
Diaphragm variation between both CTs	21 ± 25	14	10,70%	p < 0,001

III. Analyses

We found a significant loss of diaphragm and psoas muscle volume between pre-ICU CT and post-ICU CT (see [Figure 5A & 5B](#)), both at $p < 0,001$, as expected following a sepsis or septic shock. But these loss of diaphragm and psoas volume were not found to be correlated with each other ($p = 0,098$).

[Table 3](#) show the univariate analyses of the variation of diaphragm and psoas volume, with the different studied characteristics. No correlation was found between variation of diaphragm or psoas volume and the time between the two CTs, or the time between ICU stay and the second CT, that can represents the period of hypothetical muscular recovery.

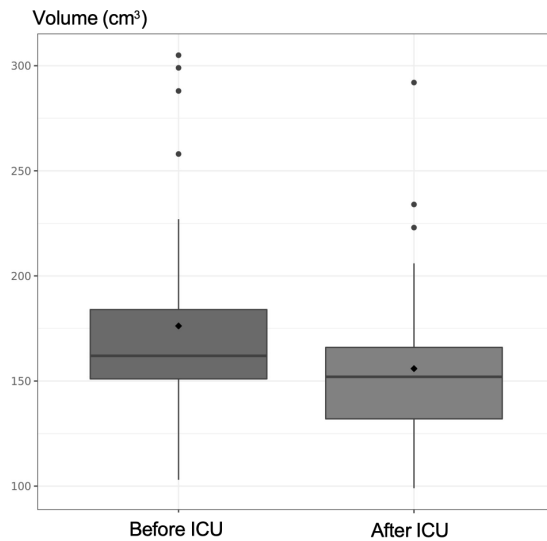


Figure 5A. Comparison of the diaphragm volume before ($176 \pm 45 \text{ cm}^3$) and after ($155 \pm 36 \text{ cm}^3$) the ICU stay ($p < 0,001$)

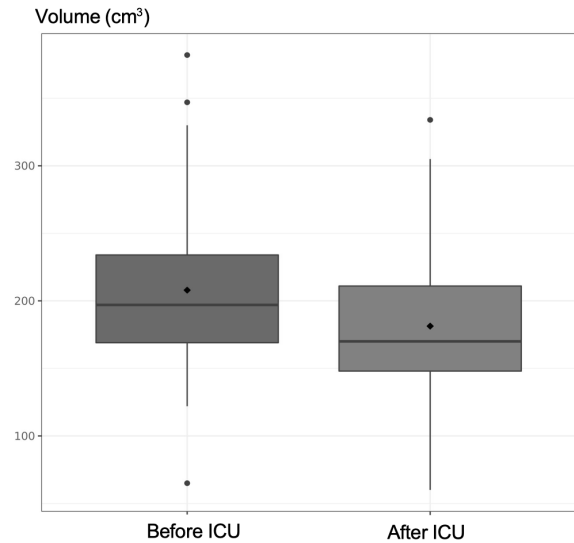


Figure 5B. Comparison of the psoas volume before ($208 \pm 61 \text{ cm}^3$) and after ($181 \pm 53 \text{ cm}^3$) the ICU stay ($p < 0,001$)

No correlation was found between variation of psoas volume and sex, height, BMI, COPD or diabetes mellitus anteriority, immunosuppression, metastasis, lactates, PCT or CPK at admission, SOFA score, curares agents, hydrocortisone use, ARDS occurrence, duration of mechanical ventilation or sedation drugs. Variation of psoas volume was significantly correlated with **age** ($p=0,033$, all patients less than 50 years old had a loss of psoas $< 20\%$), **arteriopathy history** (mean loss of $18 \pm 13\%$ in arteriopathic population versus $8 \pm 6\%$, $p=0,014$), **duration of norepinephrine infusion** ($p=0,029$, all patients with 1 day or less of norepinephrine having a loss of psoas $< 20\%$), **state of septic shock** (mean loss of $14 \pm 10\%$ if in shock versus $9 \pm 9\%$ $p=0,044$).

No correlation was found between variation of diaphragm volume and age, sex, height, BMI, arteriopathy history, COPD or diabetes mellitus anteriority, immunosuppression, metastasis, lactates, PCT or CPK at admission, SOFA score, septic shock, norepinephrine use, curares agents or hydrocortisone use, ARDS occurrence, duration of mechanical ventilation or sedation drugs. The variation of diaphragm volume was significantly correlated with **initial diaphragm volume** ($p < 0,01$), whereas the variation of psoas volume did not significantly depend on the pre-ICU psoas measure ($p=0,22$).

Table 3. Univariate analyses of volume variation with baseline characteristics.
Correlation coefficient [Confidence Interval] – p-value

Studied characteristics (n=41)	Variation of psoas volume (%)	Variation of diaphragm volume (%)
Sex	p = 0,19 \diamond	p = 0,27
Age (year)	0,333 [0,0249;0,545] p = 0,033 \diamond	0,125 [-0,19;0,41] p = 0,44
Height (cm)	0,131 [-0,184;0,422] p = 0,41	0,249 [-0,064;0,517] p = 0,12 \diamond
Body Mass Index (kg/m ²)	0,157 [-0,158;0,443] p = 0,66	-0,30 [-0,55;0,008] p = 0,057 \diamond
Metastasis	p = 0,17 \diamond	p = 0,19 \diamond
Arteriopathy disease *	p = 0,014 \diamond	p = 0,38
COPD	p = 0,53	p = 0,94
Diabetes Mellitus	p = 0,24	p = 0,14 \diamond
State of Immunosuppression ***	p = 0,52	p = 0,32
Septic shock	p = 0,044 \diamond	p = 0,75
SOFA score upon admission	0,221 [-0,0925;0,495] p = 0,16 \diamond	0,280 [-0,0302;0,541] p = 0,076 \diamond
CPK (UI/mL)	0,0167 [-0,300;0,330] p = 0,92	-0,072 ; IC [-0,38;0,24] p = 0,66
PCT (ng/mL)	0,0460 [-0,273;0,356] p = 0,78	-0,227 [-0,507;0,0950] p = 0,16 \diamond
Lactates (mmol/L)	-0,167 [-0,452;0,148] p = 0,3	-0,0668 [-0,367;0,246] p = 0,68
Hydrocortisone use	p = 0,081 \diamond	p = 0,073 \diamond
Norepinephrine	0,114 [0,201;0,407] p = 0,029 \diamond	0,273 [-0,0383;0,535] p = 0,085 \diamond
Curare agents (days)	0,061 [-0,251;0,362] p = 0,7	-0,196 ; IC [-0,118;0,475] p = 0,22
Sedative drugs (days)	p = 0,17 \diamond	0,0554 [-0,257;0,357] p = 0,73
Mechanical Ventilation (days)	-0,0141 [-0,320;0,295] p = 0,93	0,134 [-0,181;0,424] p = 0,4
ARDS	p = 0,96	p = 0,26
Psoas volume before ICU	0,196 [-0,118;0,475] p = 0,22	–
Diaphragm volume before ICU	–	0,438 (0,151;0,657) p < 0,01
Variation of psoas volume (%)	–	0,262 [-0,0498;0,527] p = 0,098 \diamond

Variation of diaphragm volume (%)	0,262 [-0,0498;0,527] p = 0,098 \diamond	–
Duration between ICU and 2 nd CT	0,074 [-0,239;0,373] p = 0,65	0,034 [-0,267;0,338] p = 0,83
Duration between 1 st and 2 nd CT	-0,0073 [-0,314;0,301] p = 0,96	0,0125 [-0,296;0,319] p = 0,94

\diamond = results concerned by multivariate analyses

In both case of diaphragm and psoas, the loss of volume was not correlated with the initial site of sepsis, especially not with pleuropneumopathy, which could have been hypothesised considering a direct local inflammation (Figure 6A & 6B).

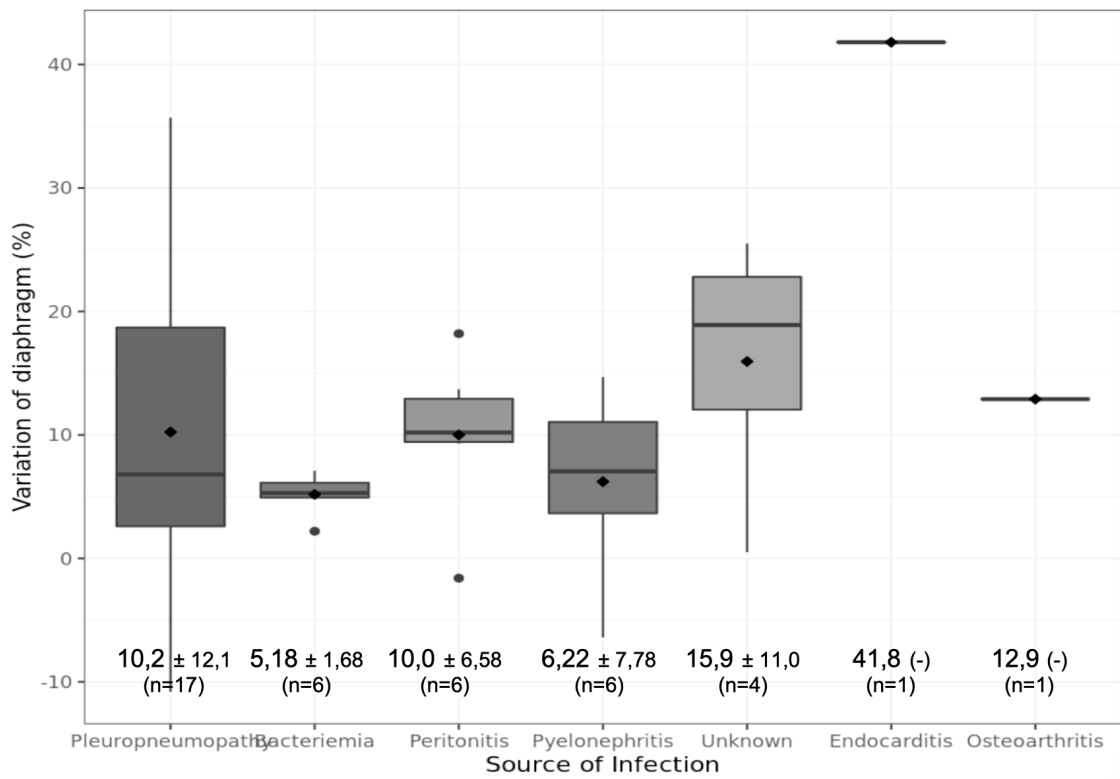


Fig 6A. variation of diaphragm volume (%) in source of infection subgroups (p = 0,36)

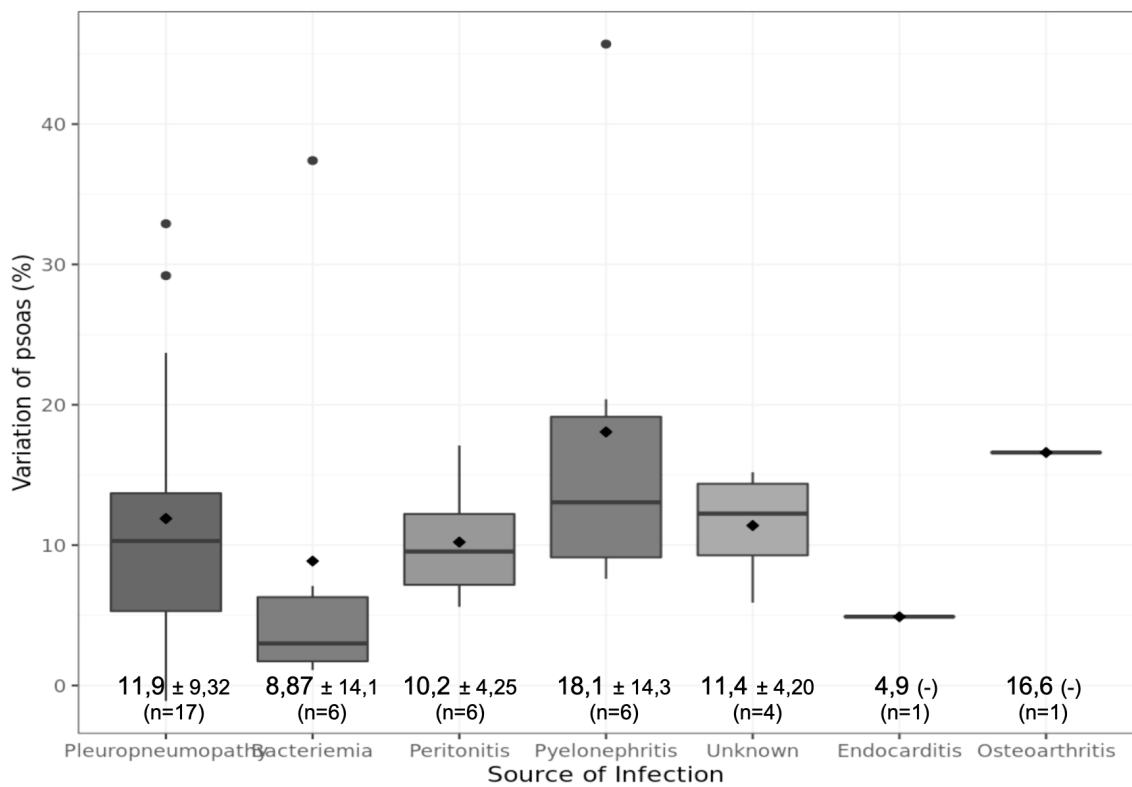


Fig 6B. variation of psoas volume (%) in source of infection subgroups (p = 0,26)

In multivariate analyses, the variation of psoas volume was still strongly associated with a comorbidity of **arteriopathy**, even when adjusted on age, sex, diabetes mellitus, MV, state of shock, metastasis and immunosuppression status, (coefficient 9.40 [3.40;15.40] at **p<0,01**). A significant association have been unmasked when adjusted on sex, arteriopathy, diabetes mellitus, MV, shock, metastasis and immunosuppression status, with the **age** (coefficient 6.98 [2.45;13.3] at **p=0.025**) for a threshold >59 years old. There was no more significant association with septic shock (p=0.087) and norepinephrine use (p=0.77) when adjusted on other confusing factors, and the statistical trend were not confirmed for metastasis (p=0.2), sedative drugs (p=0.39), hydrocortisone (p=0.073) and SOFA score (p=0.21).

Multivariate analyses in logistic regression have revealed a significant association between the variation of diaphragm volume and the **metastatic** status, confirming the trend of greater diaphragm atrophy in absence of metastasis (coefficient -7.98 [-15.2;-0.761] at **p=0.031**). It is also associated to **heights** for a threshold >166 cm (coefficient 7.64 [1.11;14.2] at **p=0.023**) when adjusted on age, arteriopathy, diabetes, mellitus, MV, shock, immunosuppression. BMI, diabetes, PCT, state of shock, mechanical ventilation, were not statistically linked with atrophy of the diaphragm. On the contrary of the psoas, diaphragmatic atrophy was not associated with arteriopathy and age. A strong statistical trend remained between diaphragmatic atrophy and hydrocortisone use and norepinephrine duration after adjustment (see [Annex 6](#)).

There was no statistically proven link between the respective variation of diaphragmatic and psoas volume when adjusted on the diverse influence factors (statistical trend at p=0.075). But even after adjustment, the loss of diaphragm volume remained associated with its initial volume, that is the baseline measurement on the pre-ICU CT : diaphragm atrophy was greater at a threshold of 176 cm³ (coefficient 10.5 [4.18;16.8], **p<0.01**). That was not the case for the psoas, which has no statistical link between initial volume and importance of variation.

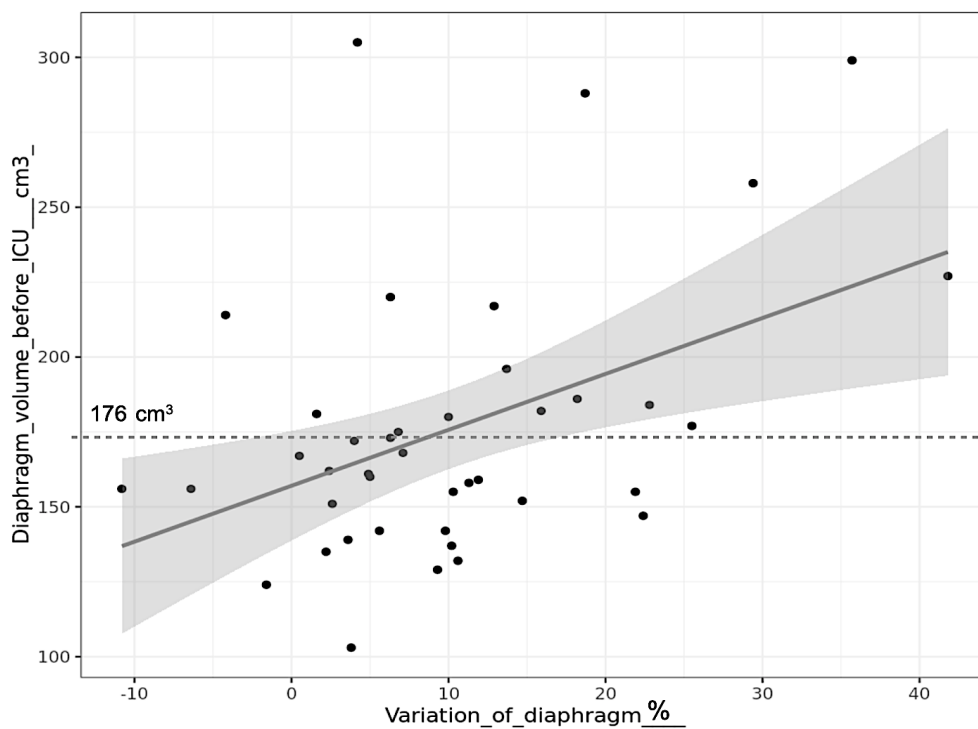


Fig 7A. variation of diaphragm volume (%) with initial pre-ICU volume of diaphragm (cm³), $p < 0.01$

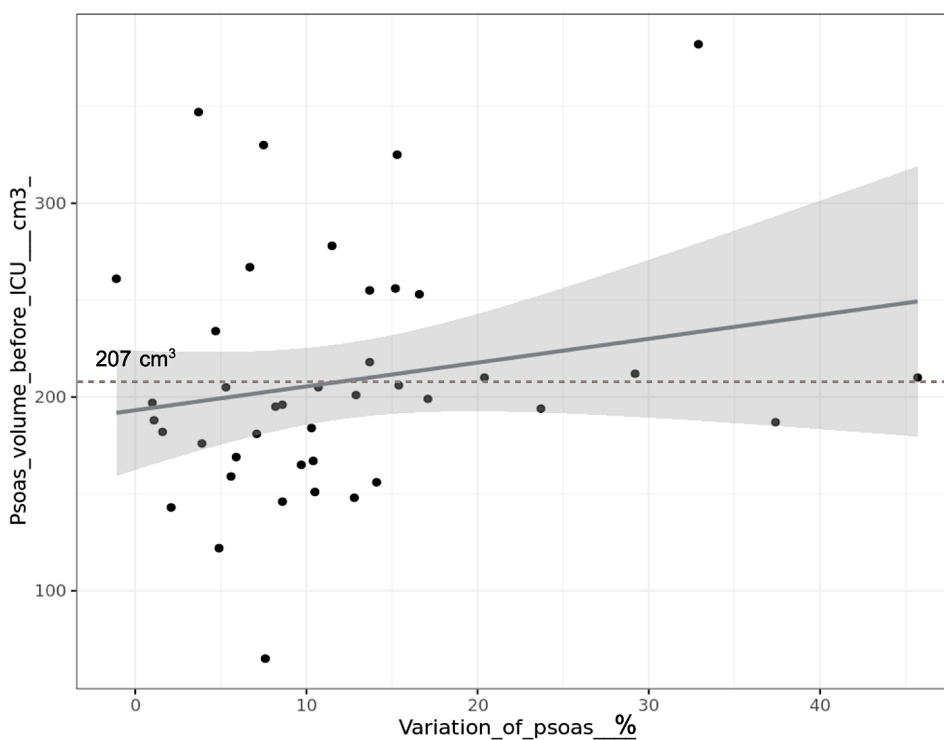


Fig 7B. variation of psoas volume (%) with initial pre-ICU volume of psoas (cm³), $p = 0.029$

It is interesting to note some different results in the subgroup of homogenous atrophic diaphragm and psoas ratio (comprised from 0,5 to 2 ratio), to eventually consider “ideal” profile patients with no discordant radiological data. We included 23 patients (purple zone of [Figure 4](#)) over the 41 initially analysed [patients n°7,12,13,15,19,20,22,23,24,25,26,27,29,30,31,34,35,36,37,38,40,41,42], which had a mean loss of diaphragm of $10 \pm 8\%$, and psoas of $10 \pm 7\%$. In this subgroup analyse, a correlation was revealed between the variation of diaphragm volume and **height** ($p=0,033$), duration of **curare agents** (all cases of curare use had at least 15% of diaphragm loss, $p=0,037$), absence of **diabetes mellitus** ($6 \pm 3\%$ with diabetes versus $13 \pm 9\%$ without, $p=0,046$), absence of **metastasis** ($9 \pm 5\%$ with metastasis versus $21 \pm 11\%$ without, $p=0,036$), **PCT** upon admission ($p=0,028$), duration of **sedative drugs** and **mechanical ventilation** (all patients losing more than 18% of the diaphragm volume being mechanically ventilated, both $p<0,01$). See [Figure 8](#).

After adjustment on confounding factors, height, curare duration, PCT and diabetes were not associated any more with variation of diaphragm volume, but **metastasis**, **sedative drugs** and **mechanical ventilation** remained statistically correlated with diaphragmatic atrophy (all at $p<0,01$).

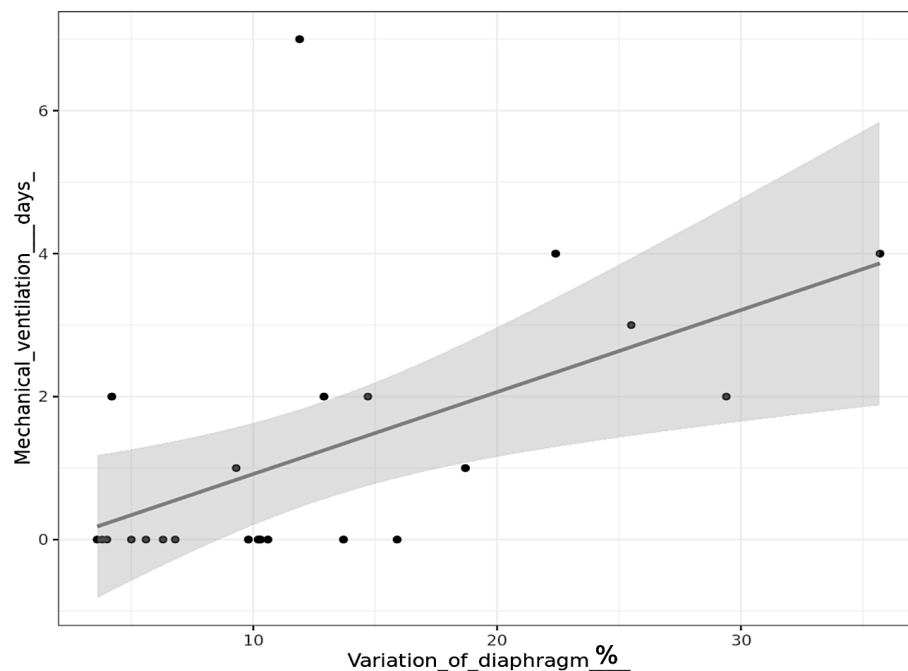


Fig 8. variation of diaphragm volume (%) with duration of mechanical ventilation (days), $p<0.01$ (subgroup $n = 23$)

4. DISCUSSION

I. Strength

Our sample of patients was relatively representative of the general population, being very diversified as to sources of infection and primitive origins of cancer, and considering the intra-study prevalence of comorbidities such as diabetes mellitus, arteriopathy or COPD. The baseline characteristics were also congruent with the usual epidemiological profile of patients admitted in ICU for severe infection in developed countries. The mainly represented sepsis were pleuropneumopathy and intra-abdominal infections. Our patients were rather grave at admission with a mean SOFA score of 6, more than half of them presenting a complicated stage of shock, and augmented lactatemia (mean 3,5 for a normal threshold of 1,2 mmol/L), and more than two-thirds of them needing hemodynamic support by Norepinephrine in the first days.

Some other characteristics or less consistent with “classic” ICU patients. Our population evolved with a rather good prognosis and few complication, which is quite foreseeable since all our patients survived (at least until their second CT) : there was no reported pulmonary embolism and only 1 cardiac arrest and 4 cases of ARDS. About one-third were mechanically ventilated, and above all, the mean duration of mechanical ventilation was very modest (about 2 days, only 2 patients being under ventilator more than a week). On the other hand, our population was affected more frequently than usual from by immunosuppression (about two-thirds), most likely due to specific oncological risk factors (chemotherapy, aplasia, corticotherapy...).

One of the strength of our study is that very little clinical information were missing in pre-analytic data collect. There was no radiological or segmentation missing data, and only a few results of PCT could not have been found, due to a non systematic dosage at the time of the oldest ICU admission (2015 to 2017).

II. Limitation

Our study has some limitations that should be taken into account. It is a single-center retrospective study, with few included subjects compared to the initial cohort, and thereby weakly designed. But it is to our knowledge the first study of this type, observing the volume of diaphragm in a before / after sepsis-associated atrophy design, and must be considered as a preliminary study for research trail.

Another major limitation to extrapolation from these results is the origin of our population sample. All of our subjects were suffering from a cancer, most of them advanced (ie metastatic for 2/3 of them), which is not representative of the global ICU population, and could even be a confounding bias : it is predictable that the cancer natural evolution lead to a deterioration of the general status, frequently resulting in a loss of weight and amyotrophy, or a minima a fragility to ICU and sepsis-associated muscle atrophy, and a dysfunction in the long term recovery capacity. The time between the two CTs, especially the time between the ICU admission and the second CT being very heterogenous (in the a range of a week to a half year), it is likely that the more this time is long, the more muscles should theoretically recover from atrophy, and thus the more this effect might be attenuated in our oncological population. However, no statistical interaction could have been found between the dates of the CTs and the variation of muscle volume.

It also as to be noted that no gold standard method was used to measure muscle volumes, and even if the segmentation was made as accurately as possible by a unique person and with always the same anatomical markers, a certain margin of error has to be considered in measurements. That is why we decided to analyse a subgroup of patients considered as "ideal" with a relatively homogenous loss of psoas and diaphragm volume (see [Figure 4](#)), considering that a big disparity between both muscle or a hypertrophy could be the result of a lack of precision during segmentation, more than a relevant physiological phenomena.

III. Hypothesis

Several of our results were statistically significant but discordant between the diaphragm and the psoas. If exact, these results might be the reflect of profound difference of physiological mechanism and response to aggression. It is supported by some works proving that locomotor muscles (including psoas) are more prone to histological lesion than respiratory muscles (diaphragm...), for example in a mouse model by a sepsis-induced mitochondrial injury mediated by NFκB transcription factor [20]. Skeletal musculature could undergo a sustained activation of the autophagolysosomal pathways in acute phase [21],[22], resulting in a loss of effective mass, but also probably preventing the accumulation of dysfunctional and toxic inflammatory proteins. Autophagy has been shown to decrease drastically in late phase permitting the recovery [23]. It make sense to see the diaphragm as a partially protected muscle against autophagy, since the proteolysis and impaired proteosynthesis of skeletal muscle is to provide substrate for vital organs. But it has also been clearly shown that the diaphragm is not totally unharmed in sepsis condition, and the mechanism of likely specific micro-injury of the diaphragm remains unsolved.

We brought to light a significant, but at first sight contradictory, link between the absence of metastasis and a greater atrophy of the diaphragm. Indeed, a positive metastatic status is generally accompanied by a fragility and susceptibility to severe infections and delayed cicatrisation. Unless this result is fortuitous, a consistent explanation can be that metastatic patient are associated with the most advanced cancer, and consequently the most altered general condition with pre-existant amyotrophy ; this group of patient would be less susceptible to loose greater muscular volume when critically ill.

Other factors clearly appeared with a statistical trend but were not considered to significantly impact the diaphragmatic atrophy because of heterogenous results in multivariate analyses (see Annex 6). It is the case of hydrocortisone use and norepinephrine duration, which could be the reflect of a susceptibility of the respiratory muscle to hemodynamic instability.

Unlike the commonly accepted idea of dependence to severity, we found no association between a greater amyotrophy and an initial state of shock. Our study also failed to establish a link between amyotrophy (especially diaphragmatic one) and MV, but it is probably because of a lack of statistical power ; too few included patient needed respiratory support more than one or two days was certainly too weak to show a statistical association between diaphragmatic and MV, which would be deleterious via the accompanying positive expiratory pressure [24], sedative drugs or curares.

IV. Prospect

Several techniques for assessing diaphragm force and activity already exist on critically ill patients bedside [25], such as electromyography, pressure measurement, and ultrasonography of the diaphragm, but none are relevant for a long-term follow-up of the critical illness-associated diaphragm weakness.

The real physiological impact of the long-term diaphragmatic dysfunction could be explored with non-invasive pulmonary-function tests, showing a restrictive profile in vital capacity. Some authors [5] suggest that clinically significant diaphragmatic weakness is unlikely, if the vital capacity is reduced by less than 10 % of the theoretical value. Inspiratory pressure measurement could also be useful, whereas the expiratory phase is typically preserved in case of diaphragmatic damage, because it is largely dependent on active accessory muscles contraction and passive diaphragm relaxation.

Diaphragmatic ultrasonography is now commonly used in ICU in patients with ventilator weaning difficulties [26],[27],[28]. The probe is apposed at the insertion zone of the diaphragm with the ribs cage, to measure modification of thickness during the inspiration, that reflects active diaphragmatic shortening. Diaphragmatic ultrasonography could even be performed upon the emergency room to diagnose early sepsis-associated diaphragmatic dysfunction, considering it is a simple quick tool that already equip most of modern emergency ward. It might even be used to

monitor recovery of diaphragmatic dysfunction in long term follow-up, to avoid irradiations.

However, the ICU require an other precise and reproductive tool, to complete the non-invasive ultrasonography and the physiological neuromyostimulation. It can be a tomodesitometric volumetric assessment of the diaphragm, considering it is not rare that a critically ill patient would benefit from iterative CT scans for any reason. Yet, very few ICUs conduct routine monitoring of respiratory muscle function, and even fewer radiology units deliver volumetric information. The limitation is of course the long and complex manual segmentation we have performed (1 hour on average per CT scan after a training of 10 CTs), which can't be routinely applied by clinicians. For now, radiological automated tool are not precise and reliable enough to be used in clinical practice. In contrast, a semi-automated segmentation software is far more realistic : calculating a relatively precise anatomical volume from a quick and simple manipulation to delimit approximatively a targeted organ (diaphragm, adrenals, myocardium, kidney, skeletal muscles, tumours...) can be helpful for the follow-up of many conditions, including the sepsis-related diaphragmatic atrophy. Such tool, for example by boxing method, remains to be evaluated in comparison of a traditional segmentation software.

IV. Conclusion

The acquired critical illness-induced myopathy results in prolonged MV with all of its potential complications, heavy physical rehabilitation, and eventually poor health-related quality of life. Last studies, including ours, suggest two new important theories : firstly, among critical illness, the sepsis is specifically linked to a global amyotrophy ; secondly, among the musculature, the diaphragm reacts peculiarly to sepsis aggression and could even be more prone to amyotrophy. The diaphragmatic atrophy in the course of an ICU stay has already been largely studied [29],[30],[31] with a bedside ultrasonographic monitoring, showing a strong association between

ultrasound thickness and clinical outcomes in ICU and between mechanical ventilation and diaphragmatic atrophy.

But to our knowledge, our small retrospective cohort is the first of this kind, comparing patients with each themselves and observing amyotrophy sometimes several months after the ICU stay. Despite some weakness, we managed to show a significant loss of diaphragm and psoas volume even long after a severe infection treated in ICU. We bring to light some clinical factors that seem to be associated with diaphragmatic injury susceptibility or difficulties to long term recovery from atrophy. These factors were discordant with those supposed to affect the psoas, suggesting a diaphragmatic pathophysiological specificity, if our results are to be confirmed. It might be quite interesting to integrate a 3rd CT and homogenise the time for performing the CTs, in order to obtain a more accurate view of the evolution the diaphragmatic atrophy, from a baseline volume to a late CT showing recovery, through a volumetric measure at the discharge of ICU.

The ultimate goal will be to understand, to prevent and eventually to treat the diaphragmatic atrophy to improve outcomes in patients with acute respiratory insufficiency, especially sepsis-induced.

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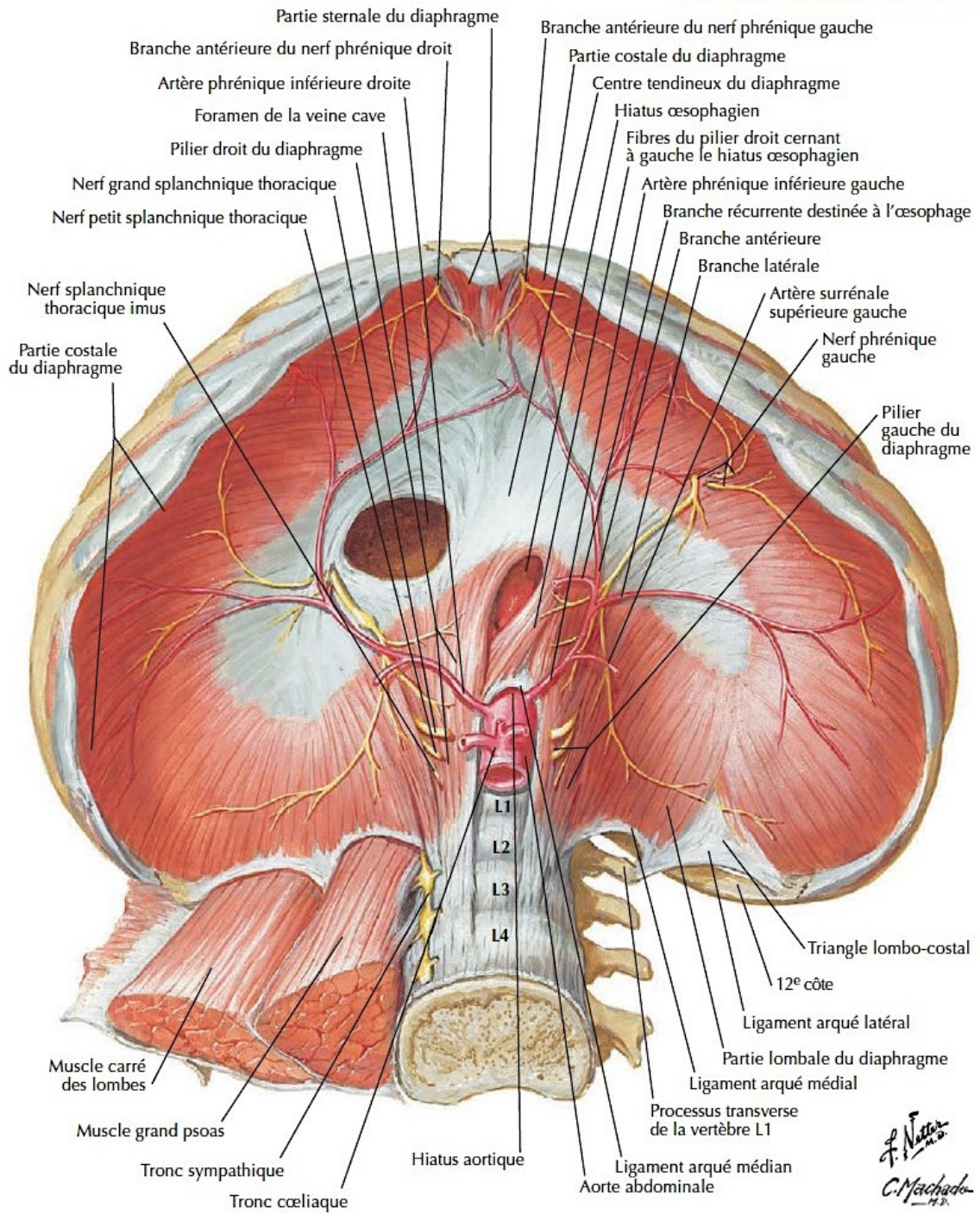
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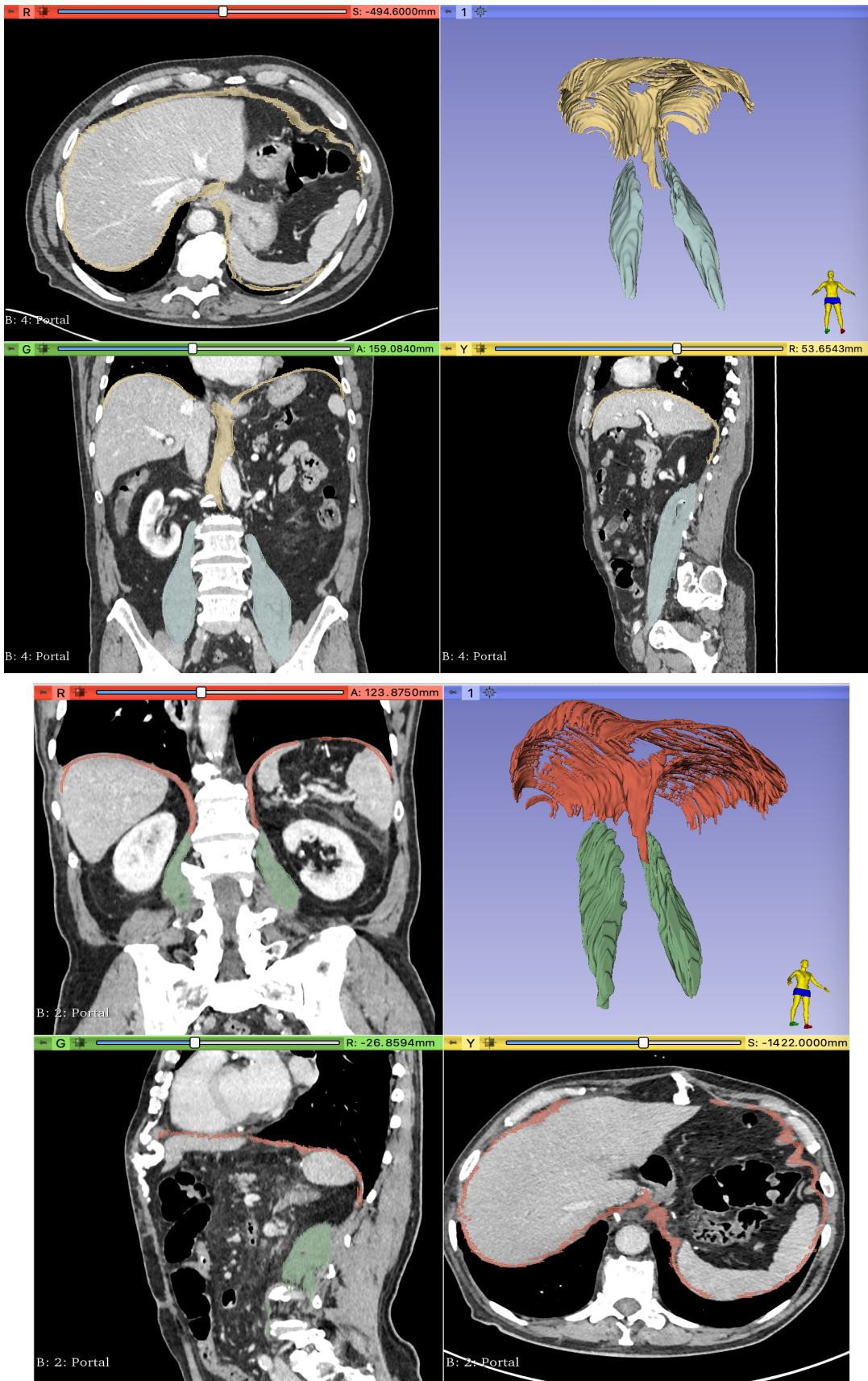
ANNEXES

	0 points	1 point	2 points	3 points	4 points
<u>Respiration</u> PaO ₂ /FiO ₂ (mmHg)	≥400	399–300	299–200	199–100 + ventilation	<100 + ventilation
<u>Coagulation</u> Platelets (G/L)	≥150	149–100	99–50	49–20	<20
<u>Hepatic function</u> Bilirubin (μmol/L)	<20	20–32	33–101	102–204	>204
<u>Circulation</u> MAP (mmHg) or amine use (μg/kg/min)	MAP ≥70	MAP <70	Dopa ≤5 or Dobu	Dopa >5 or Norad ≤0,1 or Adre ≤0,1	Dopa >15 or Norad >0,1 or Adre >0,1
<u>Renal function</u> Creatinine (μmol/L)	<110	110–170	171–299	300–440 + oliguria	>440 + anuria
<u>Consciousness</u> Glasgow scale	15	13–14	10–12	6–9	<6

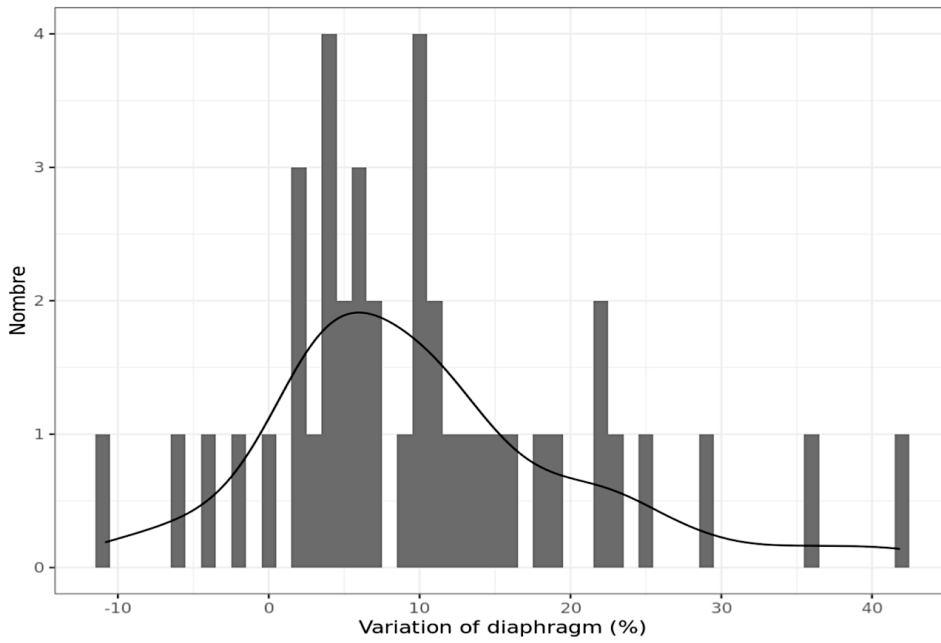
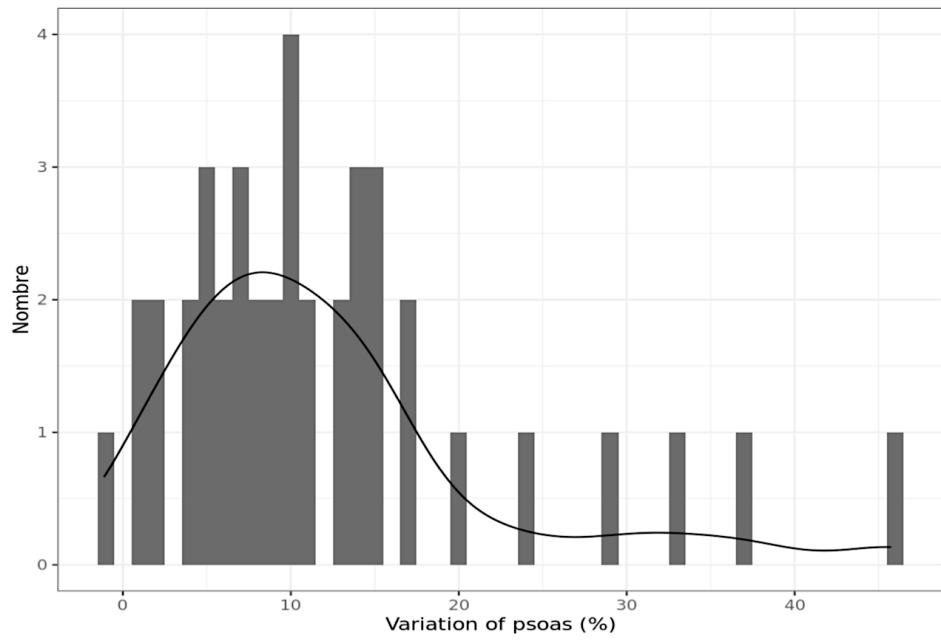
Annex 1. Sequential Organ Failure Assessment score.



Annex 2. Anatomy of the diaphragm (shape, insertions, vascularisation, thoracic wall relation, and psoas relation) as described by F.H NETTER in Atlas of Human Anatomy, 5th ed. Elsevier Masson.



Annex 3. Illustrative case (patient 41) of muscular atrophy in 3-dimensions segmented CT : psoas before (blue) and after (green), and diaphragm before (yellow) and after (red) the sepsis-linked ICU stay.



Annex. 4 Normal distribution of the included subjects (n=41) as variation of psoas and diaphragm volume

Annex 5.A. Table of baseline characteristics of all included patients.

Patient	Sex	Age	Height (cm)	BMI	Primitive Cancer	Metastasis	COPD	Diabetes	Arteriopathy	Restrictive Lung	Immunosuppression
2	H	57	178	17,6	Gastro-œsophagien	0	0	0	0	0	0
3	F	63	168	19,1	Entéro-colique	1	0	0	0	0	0
4	F	64	160	25,2	urologique	1	0	0	1	0	1
5	F	53	158	21,1	gynécologique	1	0	0	0	0	0
6	F	28	156	26,3	osseux	1	0	0	0	0	1
7	H	69	178	17,6	ORL	0	1	0	1	0	1
8	F	78	161	24,2	Entéro-colique	0	0	0	0	0	1
9	F	66	160	21,4	pancreas	1	0	0	0	0	1
10	H	67	171	26,6	Broncho-pulmonaire	1	0	1	1	0	1
11	F	61	163	18,4	mammaire	1	0	0	0	0	0
12	H	62	180	24,1	Broncho-pulmonaire	1	0	0	0	0	1
13	F	64	160	31,5	mammaire	1	0	0	0	0	1
14	F	45	178	29,3	Entéro-colique	1	0	0	0	0	1
15	F	48	163	28,9	tissus mous	1	0	0	0	0	0
16	H	60	164	19,6	ORL	0	0	0	1	0	0
17	F	57	163	27,5	mammaire	1	1	0	0	0	1
18	F	60	160	27,7	gynécologique	0	0	0	0	0	1
19	H	41	173	21,7	ORL	1	0	0	0	0	1
20	F	38	159	21,7	osseux	1	0	0	0	0	1
21	H	73	177	29,3	urologique	0	0	0	1	0	0
22	H	69	163	20,1	Broncho-pulmonaire	1	1	0	0	0	1
23	F	75	153	20,2	Entéro-colique	1	0	0	1	0	1
24	F	70	156	21,7	Gastro-œsophagien	0	0	0	0	0	0
25	F	70	156	23,1	Broncho-pulmonaire	1	1	0	1	0	1
26	F	57	155	24,1	ORL	0	0	0	0	0	1
27	F	69	150	25,3	gynécologique	1	0	1	1	0	1
28	F	82	166	24,6	Hémato-ganglionnaire	0	0	0	0	0	1
29	H	59	180	23,4	Entéro-colique	1	0	0	0	0	0
30	H	75	161	28,9	Gastro-œsophagien	1	1	1	1	0	1
31	F	68	165	18,1	urologique	1	0	0	0	0	1
32	H	21	178	22,1	Broncho-pulmonaire	1	0	0	0	0	1
33	H	54	171	27,6	Entéro-colique	1	0	0	0	0	1
34	H	68	176	17,1	Gastro-œsophagien	0	0	0	1	0	0
35	F	71	150	25,7	gynécologique	1	0	1	1	0	1
36	H	64	172	21,4	Broncho-pulmonaire	1	0	0	0	0	1
37	F	18	169	17,1	ORL	0	0	0	0	0	0
38	F	23	170	21,8	gynécologique	1	0	0	0	0	1
39	F	57	175	25,4	gynécologique	1	0	0	0	0	0
40	H	62	188	22,1	ORL	1	1	0	1	0	0
41	H	70	172	27,7	Gastro-œsophagien	0	0	0	1	0	0
42	H	70	168	19,7	urologique	1	0	0	1	0	1

Annex 5.B. Table of clinical and biological data from CU of all included patients.

Patient	Septic shock	SOFA	Source of Infection	Mechanical ventilation (days)	Sedation drugs (days)	Curares agents (days)	Norepinephrine (days)	Hydrocortisone use	CPK (UJ/mL)	Lactates (mmol/L)	PCT (ng/mL)
2	1	8	Endocarditis	0	0	0	13	1	106	1,6	5,7
3	0	13	Pleuropneumopathy	4	3	1	3	0	51	2	6,2
4	1	6	Pyelonephritis	0	0	0	3	1	37	2,8	40,3
5	0	2	Bacteriemia	0	0	0	0	0	66	0,9	0,3
6	0	1	Unknown	18	5	3	1	0	36	1,5	0,4
7	1	6	Unknown	3	2	0	2	0	70	3,5	0,8
8	0	4	Peritonitis	2	1	0	0	0	206	0,6	2,4
9	1	3	Peritonitis	0	0	0	3	0	81	1,6	14
10	0	2	Pleuropneumopathy	0	0	0	0	0	22	2,8	0,3
11	0	12	Pleuropneumopathy	28	25	4	10	0	2417	1,2	
12	1	10	Pleuropneumopathy	1	1	0	1	1	54	3,2	11,2
13	0	4	Peritonitis	0	0	0	0	0	27	1,2	1,1
14	0	4	Bacteriemia	0	0	0	0	0	32	58,2	1,4
15	0	2	Bacteriemia	0	0	0	1	0	400	3,9	97
16	0	2	Pleuropneumopathy	0	0	0	0	0	17	1,1	1,2
17	1	6	Pleuropneumopathy	0	0	0	3	0	60	0,6	0,5
18	1	9	Pyelonephritis	1	1	1	2	0	115	6,3	100,6
19	1	9	Pleuropneumopathy	7	6	5	7	1	342	5,7	38,3
20	1	7	Pyelonephritis	0	0	0	0	0	127	1,6	3,1
21	1	5	Bacteriemia	0	0	0	3	0	155	1,6	9,9
22	0	5	Pleuropneumopathy	0	0	0	0	0	36	3	2,5
23	1	6	Peritonitis	1	1	0	1	0	131	1,5	67,1
24	0	10	Pleuropneumopathy	4	3	3	2	0	57	0,5	0,6
25	1	7	Peritonitis	0	0	0	1	0	211	0,9	8,1
26	1	8	Bacteriemia	0	0	0	2	0	32	1,6	1,8
27	1	6	Pyelonephritis	0	0	0	3	0	3220	8,8	
28	1	10	Unknown	0	0	0	6	0	136	1,1	2,8
29	0	4	Pleuropneumopathy	2	2	0	0	0		1,2	12,8
30	0	5	Pleuropneumopathy	0	0	0	0	0	84	2,4	17
31	1	8	Unknown	0	0	0	3	0	318	4,8	3,8
32	0	2	Pleuropneumopathy	0	0	0	0	0	90	1,1	0,1
33	1	6	Pleuropneumopathy	0	0	0	3	1	144	3,6	21
34	0	6	Pleuropneumopathy	2	2	0	0	0	28	1,1	0,2
35	1	7	Peritonitis	0	0	0	3	0	16	1	8,2
36	1	2	Pleuropneumopathy	0	0	0	0	0	1825	0,8	1,8
37	1	5	Pleuropneumopathy	0	0	0	2	0	45	2,2	21,5
38	1	5	Pyelonephritis	0	0	0	2	1	42	0,6	0,5
39	1	5	Bacteriemia	0	0	0	2	1	13	1,8	1,4
40	0	9	Osteoarthritis	2	2	0	2	0		1	7,8
41	0	8	Pleuropneumopathy	4	3	2	3	0	1075	1,4	2,2
42	1	12	Pyelonephritis	2	2	1	2	1	22	1,2	1,6

Annex 5.C. Table of radiological and volumetry data of all included patients.

Patient	1 st CT to ICU (days)	Diaphragm volume before ICU (cm ³)	Psoas volume before ICU (cm ³)	ICU to 2 nd CT (days)	Diaphragm volume after ICU (cm ³)	Psoas volume after ICU (cm ³)	Duration between 1 st and 2 nd CT	Variation of diaphragm volume (cm ³)	Variation of diaphragm (%)	Variation of psoas volume (cm ³)	Variation of psoas (%)
2	94	227	122	22	132	116	116	95	41,8	6	4,9
3	24	184	197	14	142	195	38	42	22,8	2	1
4	81	158	210	10	148	114	91	18	11,3	96	45,7
5	20	135	188	62	133	186	82	3	2,2	2	1,1
6	15	155	169	27	121	159	42	34	21,9	10	5,9
7	36	177	156	52	132	134	88	45	25,5	22	14,1
8	130	186	267	7	152	249	137	34	18,2	18	6,7
9	87	124	196	230	126	179	317	-2	-1,6	17	8,6
10	116	181	205	15	178	194	131	3	1,6	11	5,3
11	50	151	278	76	147	246	126	4	2,6	32	11,5
12	12	288	325	84	234	275	96	54	18,7	50	15,3
13	28	196	199	13	169	165	41	27	13,7	34	17,1
14	47	168	182	28	155	179	75	12	7,1	3	1,6
15	4	142	176	35	134	169	39	8	5,6	7	3,9
16	112	162	165	19	158	149	131	4	2,4	16	9,7
17	14	156	218	12	173	188	26	-17	-10,8	30	13,7
18	12	156	205	18	166	183	30	-10	-6,4	22	10,7
19	134	159	255	24	140	220	158	19	11,9	35	13,7
20	26	103	65	54	99	60	80	4	3,8	5	7,6
21	16	220	187	93	206	117	109	14	6,3	70	37,4
22	4	173	234	62	162	223	63	11	6,3	11	4,7
23	23	129	151	9	117	135	32	12	9,3	16	10,5
24	3	147	201	172	114	175	175	33	22,4	26	12,9
25	59	132	148	10	118	131	69	14	10,6	17	12,8
26	22	160	181	14	152	168	36	8	5	13	7,1
27	144	139	146	52	134	124	196	5	3,6	12	8,6
28	11	167	256	57	166	217	69	1	0,5	39	15,2
29	55	305	347	13	292	334	88	13	4,2	13	3,7
30	10	172	195	58	165	170	68	7	4	16	8,2
31	124	182	167	23	153	148	148	29	15,9	19	10,4
32	35	214	261	53	223	258	88	-9	-4,2	-3	-1,1
33	21	180	194	45	162	148	66	18	10	46	23,7
34	2	258	212	13	182	150	15	76	29,4	62	29,2
35	97	142	159	66	128	151	163	14	9,8	8	5,6
36	57	175	184	71	163	163	128	12	6,8	19	10,3
37	18	137	330	214	123	305	232	14	10,2	25	7,5
38	9	155	206	67	139	182	76	16	10,3	24	15,4
39	99	161	143	15	153	140	114	8	4,9	3	2,1
40	11	217	253	34	188	211	45	28	12,9	42	16,6
41	49	299	382	111	192	256	160	107	35,7	126	32,9
42	100	152	210	113	121	167	213	31	14,7	43	20,4

Annex 6. Table of multivariate analyses.

Green = psoas data ; red = diaphragm data ; Ø = not applicable

Studied characteristics	Adjustment factors	Factors of fragility age + diabetes + arteriopathy	Factors of susceptibility Immunosuppression + metastasis	Factors of severity septic shock + mechanical ventilation	multiple adjustment
Sex	Ø Ø	4.16 [-2.18; 10.5] p=0.19 4.27 [-2.25; 10.8] p=0.19	5.64 [-0.316; 11.4] p=0.078 5.13 [-1.78; 12.0] p=0.14	3.37 [-3.13; 9.28] p=0.28 3.78 [-3.36; 10.9] p=0.29	
Age >59 years old	Ø Ø	6.69 [1.65; 12.8] p=0.04 2.35 [-4.46; 9.16] p=0.49	7.58 [2.70; 12.9] p=0.019 3.01 [-4.18; 10.2] p=0.4	8.79 [2.91; 15.3] p<0.01 0.0921 [-8.15; 8.34] p=0.98	
Height > 166 cm	0.0357 [-0.262; 0.334] p=0.81 7.41 [0.624; 14.2] p=0.033	2.75 [-3.84; 7.59] p=0.41 6.48 [0.0819; 12.9] p=0.047	2.52 [-4.19; 8.64] p=0.42 7.78 [2.62; 15.5] p=0.017	0.147 [-0.164; 0.458] p=0.34 7.64 [1.11; 14.2] p=0.023	
BMI	7.20 [2.31; 12.1] p<0.01 -0.657 [-1.57; 0.253] p=0.15	0.511 [-0.327; 1.35] p=0.22 -0.615 [-1.47; 0.240] p=0.15	0.523 [-0.565; 1.35] p=0.23 -0.850 [-1.75; 0.0449] p=0.062	2.91 [-2.73; 8.56] p=0.3 -0.823 [-1.73; 0.0819] p=0.073	
Metastasis	-1.32 [-7.18; 4.53] p=0.65 -7.61 [-14.9; -0.296] p=0.042	Ø Ø	Ø Ø	-4.03 [-11.2; 2.47] p=0.2 -7.98 [-15.2; -0.761] p=0.031	
Arteriopathy	Ø Ø	14.1 [7.96; 20.2] p<0.001 2.91 [-3.91; 9.74] p=0.39	9.92 [3.60; 18.5] p<0.001 4.07 [-1.69; 11.6] p=0.27	9.40 [3.40; 15.4] p<0.01 3.35 [-5.03; 11.7] p=0.42	
Diabetes mellitus	Ø Ø	-4.57 [-11.2; -0.849] p=0.42 Ø	-5.18 [-11.5; -0.672] p=0.32 -5.85 [-17.6; 5.88] p=0.32	-8.88 [-16.1; -3.77] p=0.082 -10.9 [-21.0; -3.38] p=0.084	
Septic shock	4.12 [-0.410; 8.85] p=0.093 -2.65 [-9.46; 4.15] p=0.43	5.16 [-1.97; 11.9] p=0.15 -2.59 [-9.13; 3.95] p=0.43	Ø Ø	5.17 [-0.0436; 10.9] p=0.087 -4.03 [-11.7; 3.68] p=0.3	
SOFA score >6	0.426 [-0.474; 1.33] p=0.34 6.23 [-0.870; 13.3] p=0.084	0.640 [-0.436; 1.28] p=0.23 4.98 [-1.55; 11.5] p=0.13	0.583 [-0.540; 1.68] p=0.31 1.17 [-0.0548; 2.40] p=0.061	0.605 [-0.365; 1.23] p=0.21 5.39 [-1.52; 12.3] p=0.12	
Hydrocortisone use	7.95 [-0.111; 20.2] p=0.023 6.96 [-0.135; 18.9] p=0.12	8.34 [-0.724; 21.0] p=0.025 8.59 [0.744; 16.4] p=0.033	5.57 [-2.98; 18.6] p=0.17 5.39 [-1.52; 12.3] p=0.048	7.30 [-1.88; 20.4] p=0.073 9.27 [1.41; 17.1] p=0.012	
Norepinephrine > 1 day	0.638 [-0.293; 1.57] p=0.17 1.20 [-0.927; 2.83] p=0.078	0.303 [-1.03; 1.67] p=0.64 0.767 [-0.462; 1.99] p=0.21	0.0860 [-0.731; 2.47] p=0.9 1.57 [0.0216; 3.11] p=0.047	-0.217 [-1.48; 2.08] p=0.77 1.13 [-2.04; 2.82] p=0.11	
Mechanical ventilation > 1 day	0.0512 [-0.466; 0.568] p=0.84 0.290 [-0.260; 2.44] p=0.34	0.0330 [-0.525; 1.24] p=0.91 Ø	Ø Ø	0.135 [-0.418; 1.17] p=0.64 0.274 [-0.180; 3.05] p=0.098	
Psoas volume pre-ICU >207 cm³	3.86 [-1.43; 9.14] p=0.15 Ø	5.65 [0.0255; 14.9] p=0.095 Ø	6.65 [0.982; 15.5] p=0.042 Ø	5.70 [0.935; 13.7] p=0.058 Ø	
Diaphragm volume pre-ICU >176 cm³	9.42 [2.97; 15.9] p<0.01 Ø	8.87 [2.59; 15.2] p<0.01 Ø	8.87 [1.63; 16.1] p=0.018 Ø	10.5 [4.18; 16.8] p<0.01 Ø	
Variation of psoas volume	3.28 [-6.25; 9.49] p=0.39 Ø	6.82 [-1.47; 14.0] p=0.051 Ø	5.54 [-0.974; 12.1] p=0.093 Ø	4.73 [-2.10; 11.6] p=0.17 Ø	
Variation of diaphragm volume	2.83 [-2.79; 8.45] p=0.31 Ø	5.92 [0.0180; 13.4] p=0.056 Ø	7.38 [1.17; 14.8] p=0.015 Ø	5.08 [-1.54; 13.4] p=0.12 Ø	

TABLE DES ABBRÉVIATIONS

• ARDS	Acute Respiratory Distress Syndrome
• BMI	Body Mass Index
• CHRU	Centre Hospitalier Régional Uiversitaire
• CPK	Creatin-Phospho-Kinase
• COPD	Chronic Obstructive Pulmonary Disease
• CRP	C-Reactive Protein
• CT	Computed Tomography
• ICM	Institut du Cancer de Montpellier
• ICU	Intensive Care Unit
• MAP	Mean Arterial Pressure
• MV	Mechanical Ventilation
• ND	No Data
• ORL	Oto-rhino-laryngology
• PCT	Procalcitonin
• SOFA	Sequential Organ Failure Assessment

ABSTRACT

Introduction : In addition of the aftereffects associated with a critical illness and the aggressive intensive care management, diaphragm is affected by sepsis as well as other muscles such as psoas. Its mechanism and duration remain unclear but atrophic sequelae is a major factor of difficulties to ventilator withdrawal in ICU and long term physical rehabilitation. We tried to observe the importance of the diaphragm and psoas atrophy after ICU discharge comparing to anterior data.

Methodes : We retrospectively included 41 patients admitted in our ICU for a sepsis or a septic shock, and for whom CT-scans have been performed in the course of an oncological follow-up. We used a segmentation software to compare volumetric measurements of the diaphragmatic and the psoas before, and after the ICU stay. The primary endpoint was to the observable atrophy in this period.

Results : Between 2 CTs, 102 ± 62 days apart, we found a significant loss of volume of 12,1% (that is $26 \pm 25 \text{ cm}^3$, $p < 0.01$) for the psoas and 10,70% (that is $21 \pm 25 \text{ cm}^3$, $p < 0.01$) for the diaphragm, with no correlation between each other, but a significantly link between initial volume of the diaphragm ant its loss of volume after ICU ($p < 0.01$). Atrophy of psoas was associated with an history of arteriopathy ($p < 0.01$) and age > 59 ans ($p = 0.01$), whereas the atrophy of diaphragm was associated with height $> 166 \text{ cm}$ ($p = 0.023$) and absence of metastasis ($p = 0.031$).

Conclusion : The diaphragm and psoas are concurrently but independently affected by a loss of muscular mass, in case of severe infection admitted in ICU. We were able to be bring to light differential associated factors, giving reasons to believe that the pathophysiology behind the sepsis-linked atrophy of the diaphragm and psoas is not equivalent and comparable in all points.

Key-words : diaphragmatic atrophy – amyotrophiy – diaphragm – sepsis –, septic shock – intensive care unit – mechanical ventilation – computed tomography – volumetry – segmentation

DIAPHRAGMATIC ATROPHIC SEQUELAE OF SEPSIS :

A RETROSPECTIVE COMPUTED STUDY.

Doctoral Thesis presented by Simon Legere.



RÉSUMÉ

Introduction : En plus des effets néfastes de toute pathologie aiguë grave, et ceux secondaires à la prise en charge agressive de réanimation, le sepsis affecte tout spécifiquement le diaphragme ainsi que les autres muscles tels que le psoas. Mécanismes et évolution de cette agression demeurent obscurs, mais l'atrophie séquellaire est un facteur majeur de retard au sevrage de la ventilation mécanique puis à la rééducation et reprise d'une vie normale. Nous avons voulu observer la survenue de cette atrophie au décours d'un sepsis, en comparaison à des données antérieures au séjour en réanimation.

Méthode : Chez 41 patients admis réanimation (CHU Lapeyronie, 2015-2019) pour sepsis ou choc septique, nous avons calculé par méthode de segmentation informatique, le volume des psoas et du diaphragme sur des TDM antérieures et postérieures à l'hospitalisation, réalisées dans le cadre du suivi d'un cancer. Le critère principal était l'atrophie observable dans cet intervalle.

Résultats : Entre 2 TDM espacées de 102 ± 62 jours, nous avons confirmé une atrophie musculaire moyenne après séjour en réanimation pour sepsis, de 12.1% (soit 26 ± 25 cm³, $p < 0.01$) pour le psoas et 10,7% (soit 21 ± 25 cm³, $p < 0.01$) pour le diaphragme, sans corrélation statistique entre ces deux variations, mais la variation de diaphragme dépendant significativement du volume musculaire de base ($p < 0.01$). L'atrophie du psoas était associée à un antécédent artériopathique ($p < 0.01$) et l'âge > 59 ans ($p < 0.01$) ; alors que celle du diaphragme était associée à la taille > 166 cm ($p = 0.023$) et l'absence de métastases ($p = 0.031$).

Conclusion : Le diaphragme et le psoas semblent souffrir de manière concomitante mais indépendante d'une infection sévère en réanimation. Les facteurs qui s'y associent ne sont pas les mêmes, peut être du fait d'une réponse physiologique différente entre diaphragme et muscles périphériques.

Mots-clefs : atrophie, amyotrophie, diaphragme, sepsis, choc septique, réanimation, ventilation mécanique, tomодensitométrie, volumétrie, segmentation