

BMJ Open Is sarcopenia a risk factor for reduced diaphragm function following hepatic resection? A study protocol for a prospective observational study

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ABSTRACT

Introduction Sarcopenia is associated with reduced pulmonary function in healthy adults, as well as with increased risk of pneumonia following abdominal surgery. Consequentially, postoperative pneumonia prolongs hospital admission, and increases in-hospital mortality following a range of surgical interventions. Little is known about the function of the diaphragm in the context of sarcopenia and wasting disorders or how its function is influenced by abdominal surgery. Liver surgery induces reactive pleural effusion in most patients, compromising postoperative pulmonary function. We hypothesise that both major hepatic resection and sarcopenia have a measurable impact on diaphragm function. Furthermore, we hypothesise that sarcopenia is associated with reduced preoperative diaphragm function, and that patients with reduced preoperative diaphragm function show a greater decline and reduced recovery of diaphragm function following major hepatic resection. The primary goal of this study is to evaluate whether sarcopenic patients have a reduced diaphragm function prior to major liver resection compared with non-sarcopenic patients, and to evaluate whether sarcopenic patients show a greater reduction in respiratory muscle function following major liver resection when compared with non-sarcopenic patients.

Methods and analysis Transcostal B-mode, M-mode ultrasound and speckle tracking imaging will be used to assess diaphragm function perioperatively in 33 sarcopenic and 33 non-sarcopenic patients undergoing right-sided hemihepatectomy starting 1 day prior to surgery and up to 30 days after surgery. In addition, rectus abdominis and quadriceps femoris muscles thickness will be measured using ultrasound to measure sarcopenia, and pulmonary function will be measured using a hand-held bedside spirometer. Muscle mass will be determined preoperatively using CT-muscle volumetry of abdominal muscle and adipose tissue at the third lumbar vertebra level (L3). Muscle function will be assessed using handgrip strength and physical condition will be measured with a short physical performance battery. A rectus abdominis muscle biopsy will be taken intraoperatively to measure proteolytic and mitochondrial activity as well as inflammation and redox status. Systemic inflammation and sarcopenia biomarkers will be assessed in serum acquired perioperatively.

Strengths and limitations of this study

- This study prospectively investigates the impact of sarcopenia on diaphragm function of patients undergoing right-sided hemihepatectomy in a homogenous surgical cohort.
- Patient physical condition and pulmonary function is extensively and objectively recorded.
- This study uses novel non-invasive speckle ultrasound to measure diaphragmatic strain as a measure of diaphragm effort.

Ethics and dissemination This trial is open for recruitment. The protocol was approved by the official Independent Medical Ethical Committee at Uniklinik (Rheinisch Westphälische Technische Hochschule (RWTH) Aachen (reference EK309-18) in July 2019. Results will be published via international peer-reviewed journals and the findings of the study will be communicated using a comprehensive dissemination strategy aimed at healthcare professionals and patients.

Trial registration number ClinicalTrials.gov (EK309-18); Pre-results.

INTRODUCTION

Sarcopenia and muscle wasting are known risk factors for outcome following hepatic resection.^{1–5} Sarcopenia has also been shown to be associated with reduced pulmonary function and increased risk of pneumonia following abdominal surgery.^{6–10} Postoperative pneumonia has been shown to prolong hospital admission and increase in-hospital mortality following a range of surgical interventions, including major abdominal and upper gastrointestinal surgery.^{11–15} In addition, patients undergoing partial hepatectomy frequently develop reactive pleural effusion and postoperative pneumonia incidences above 10%.^{11 13–18} Besides medical implications, pulmonary complications

constitute a significant burden to healthcare systems by increasing healthcare costs.^{13 16}

Cachexia and sarcopenia are interrelated wasting disorders, the pathogenesis of which is complex due to its multifactorial nature and is characterised by a negative protein and energy balance that is driven by a variable combination of reduced food intake and abnormal metabolism.¹⁹ The known associations between sarcopenia and pulmonary outcome are based on appendicular muscle mass measurements, or measurements at the third lumbar vertebra (L3). Interestingly, very little is known about the function of the diaphragm in the context of sarcopenia and wasting disorders or how its function is influenced by abdominal surgery.^{20 21} Some preclinical animal studies have shown that sarcopenia is associated with atrophy of diaphragmatic muscle fibres, and that ageing is related to a decline in diaphragmatic function.^{22–24} Clinical studies in the context of prolonged mechanical ventilation of acutely ill patients have focused on diaphragm function using ultrasound technology and have shown that prolonged ventilation can lead to diaphragm atrophy which is associated with worse clinical outcome.^{25–27}

Transcostal B-mode and M-mode ultrasound is a non-invasive technique which has been used to measure diaphragm function.^{27–31} Diaphragm inspirational amplitude (DIA) has been shown to decrease significantly following open cholecystectomy.²⁸ Fractional thickening (FT) of the diaphragm has been used in previous studies to quantify effort of the diaphragm.^{31 32} Recently, Deniz *et al*²¹ demonstrated that sarcopenic elderly patients have significantly reduced diaphragm thickness and pulmonary function than non-sarcopenic elderly. Two-dimensional deformation ultrasound or speckle tracking (ST) has emerged as a tool which can be used to evaluate diaphragm function in a way that is highly correlated to the gold standard trans diaphragmatic pressure measurements.^{33 34} ST finds its origins in myocardial function ultrasound and enables distinct assessment of cardiac muscle function.³⁴ The grey value pattern in ultrasound images remains relatively constant for any small region in muscle tissue, this is called a speckle. In the ST technique, a defined cluster of speckles is tracked from one frame to another during a contractile cycle. This enables the two-dimensional quantification of diaphragm deformation (strain).

We hypothesise that both major hepatic resection and sarcopenia have a measurable impact on diaphragm function. Furthermore, we hypothesise that sarcopenia is associated with reduced preoperative diaphragm function, and that patients with reduced preoperative diaphragm function show a greater decline and reduced recovery of diaphragm function following right-sided hemihepatectomy.

The primary goal of this study is to evaluate whether sarcopenic patients have a reduced diaphragm function prior to major liver resection compared with non-sarcopenic patients, and to evaluate whether sarcopenic

patients show a greater reduction in respiratory muscle function following right-sided hemihepatectomy when compared with non-sarcopenic patients. The secondary objective of this study is to investigate proteolytic activation and markers of mitochondrial activity in muscle tissue, as well as systemic inflammation markers of sarcopenic and non-sarcopenic patients.

METHODS AND ANALYSIS

Inclusion and exclusion criteria

This study will entail a prospective observational single-centre study, analysing consecutive patients undergoing open right-sided hemihepatectomy with biliary reconstruction between the ages of 18 years and 80 years. Surgery is performed as part of standard care. Only patients undergoing open right-sided hemihepatectomy with biliary reconstruction will be included in the study to achieve a homogeneous study cohort. Exclusion will be on the basis of American Anesthesiology Association classification IV or higher, liver cirrhosis child grade B or higher, end-stage renal disease requiring dialysis, severe heart disease New York Heart Association class IV, pre-existing pulmonary conditions including, chronic obstructive pulmonary disease, asthma, history of pulmonary surgery, history of pulmonary embolism, smoking, pleural effusion occupying more than 1/3 of the pleural space, neurological disorders leading to paraparesis of the upper or lower limbs or known muscular dystrophic disorders. Patients will consecutively be assigned to a sarcopenic and non-sarcopenic group based on CT-muscle quantification and hand grip strength (definitions will be detailed below). Sarcopenia stratification will be performed by an investigator blinded for the diaphragm ultrasound and pulmonary function testing and vice versa.

Patients will receive postoperative analgesia in the form of standard postoperative analgesia protocols. Administration of analgesia and pain scoring (Visual Analogue Scales) will be recorded by the primary investigator to correct for pain-associated restriction of pulmonary function.

Blinding of results

To ensure unbiased ultrasound evaluation and pulmonary function testing, the investigator performing diaphragm ultrasound and pulmonary function testing will be blinded for the sarcopenia stratification. Thus, investigator 1 will perform stratification of patients into sarcopenic and non-sarcopenic groups based on L3 CT and handgrip strength measurements. Investigator 2 will perform ultrasound and pulmonary function testing as well as physical condition testing and blood sampling.

ENDPOINTS

Primary endpoints

Differences in diaphragm kinetics as measured by ST ultrasound (eg, deformation% (strain), deformation

velocity (strain rate), and dimensional measures which are FT and range of DIA) and abdominal muscle kinetics (eg, deformation%, deformation velocity, FT and DIA, see above) between sarcopenic and non-sarcopenic study groups prior to elective right-sided hemihepatectomy.

Secondary endpoints

Longitudinal changes from baseline values in diaphragm and abdominal muscle (rectus abdominis muscle) kinetics (eg, deformation%, deformation velocity, FT and DIA), and the occurrence and quantification of pleural effusion in the postoperative phase across sarcopenic and non-sarcopenic groups following elective right-sided hemihepatectomy as measured by ST ultrasound compared with each other and preoperative values.

Tertiary endpoints

Perioperative quantitative and qualitative evaluation of a panel of biomarkers associated with inflammation, mitochondrial function and the pathogenesis of sarcopenia (see online supplemental appendix 1) in the sarcopenic and non-sarcopenic groups.

DEFINING SARCOPENIA AND PHYSICAL CONDITION

Sarcopenia will be defined as either low estimated muscle mass measured by CT-muscle volumetry or reduced muscle function measured by handgrip strength, or reduced physical condition as defined by the European Working Group on Sarcopenia in Older People (EWGSOP).³⁵

CT-muscle quantification

CT-muscle volumetry of abdominal muscle and adipose tissue at L3 will be performed on abdominal CT scans. This method provides an accurate estimation of whole-body muscle mass as well as the detection of sarcopenia.³⁶ These scans will be taken for routine diagnostic purposes and will not lead to additional radiation exposure of patients for the purpose of this study. Muscle volumetry at the L3 level will be corrected for patient stature. Using gender and body mass index specific cut offs as described by Martin *et al* (L3-skeletal muscle index of $<55 \text{ cm}^2/\text{m}^2$ for men or $<39 \text{ cm}^2/\text{m}^2$ for women), patients will be categorised as sarcopenic or non-sarcopenic.^{36 37} In addition, other body composition parameters, such as muscle radiation attenuation, visceral fat mass and subcutaneous fat mass will be evaluated for association with our primary outcome variable.

Functional muscle measurement (handgrip strength)

In addition to muscle mass, a measurement of muscle function will be performed. A handgrip strength test will be performed to ascertain muscle strength on both hands with the elbow flexed at 90°. Three repeats will be performed and the highest value will be used for analysis. The value of the dominant hand will be used for stratification into sarcopenic and non-sarcopenic groups. This method has been validated for the detection of

sarcopenic patients and cut-off points for detection have been defined by the EWGSOP.³⁵

Physical condition test

To assess physical performance, a short physical performance battery (SPPB) test will be performed. The SPPB has been recently recommended by an international working group for use as a functional outcome measure in clinical trials in frail older persons and is recommended as part of the detection algorithm for sarcopenia by the EWGSOP.³⁸ Furthermore, cut-off points have been defined by the EWGSOP.

ULTRASOUND

Patients will undergo a transcostal ultrasound in the supine position 1 day prior to surgery, as well as on the first, third, fifth and seventh postoperative day. The ultrasound transducer will be positioned longitudinally to the anterior axillary line between the 9th and 11th intercostal space. In this location, the diaphragm is identified as a three-layered structure just superficial to the liver, consisting of a relatively non-echogenic muscular layer bounded by the echogenic membranes of the diaphragmatic pleura and peritoneum. A 10 s recording will be made at maximum frame rate for analysis. In addition, pleural effusion will be observed, and if present, quantified.

B-mode and M-mode Ultrasound FT will be measured using a 13 MHz linear array transducer. Diaphragmatic thickness will be measured at end-expiration (Tdi,ee) and peak inspiration (Tdi,pi; that is, peak thickness value during inspiration) as the distance between the diaphragmatic pleura and the peritoneum using M-mode. Measurements of Tdi,ee and Tdi,pi will always be made on two respiratory cycles visualised in a single M-mode. Diaphragm thickening during inspiration (DTdi) will be taken as the difference between Tdi,pi and Tdi,ee. Diaphragm thickening fraction will be defined as the percentage change in diaphragm thickness during inspiration (computed from the quotient of DTdi and Tdi,ee).^{31 32} DIA will be determined using M-mode ultrasound.²⁷

ST analysis

Following the ultrasound recording of diaphragm kinetics, images will be analysed using software to ascertain strain rate, FT and range of motion.

Strain describes the relative change in length between an initial reference state (L0) and compressed/shortened state (L). The conventional strain is defined as: $\epsilon = (L-L0)/L0$. Positive strain means stretching, whereas negative strain means shortening. To investigate strain, a region of interest will be placed between the echogenic line of the peritoneum and pleural line. Strain rate indicates the rate of deformation as follows: $\epsilon' = d\epsilon/dt$. Strain rate is an instantaneous measurement not requiring a relation to a reference state. The strain will be measured

as longitudinal strain using commercially available software (EchoPac, GE Healthcare).

Lung function testing

Following ultrasound, diaphragm kinetics will be recorded during normal breathing on both sides, and once at pi-max (peak inspiratory pressure). Pi-max will be measured with a portable hand-held spirometer (Micro Respiratory Pressure Meter (RPM) handheld spirometer) which patients must breath through at maximum capacity. This will provide broad insight into the general respiratory capacity, as well as at maximum effort.

STUDY TIME PLAN

Patients will be asked to participate in the study at the time of first contact in the outpatient clinic, in the weeks prior to surgery. Data collection will commence 1 day prior to surgery and will end 6 months after discharge from the hospital. Data will be collected at eight time points (T1 though T8) during this period, namely 1 day prior to surgery, during surgery, and at day 1, 3, 5 and 7 postoperatively. Thirty days after surgery, data collection will be performed during a routine postoperative check-up. Six-months after surgery, a telephone questionnaire focused on physical activity and quality of life (36-Item Short Form Health Survey Questionnaire, SF-36) will be performed (see study flowchart [figure 1](#)). Drop-outs from the study as well as loss to follow-up and missing data will be recorded and stated in the final draft of the manuscript.

► T1 (1 day preoperative)

First data collection. Patients will be stratified as being sarcopenic or non-sarcopenic. An additional blood sample will be taken and frozen (5 mL EDTA) from the antecubital vein. The handgrip strength test will be performed to assess muscle strength. The SPPB test will be performed to determine physical condition. CT-muscle volumetry will be performed on existing preoperative CT scans to distinguish sarcopenic and non-sarcopenic patients and assignment to sarcopenic and non-sarcopenic groups. Diaphragm, quadriceps femoris and rectus abdominis ultrasound will be performed as previously described. Lung function testing will be performed at the bedside as described. A Health-related Quality of Life questionnaire will be filled out (HRQoL) (SF-36).

► T2 (intraoperative sampling)

Intraoperative tissue sampling of the m. rectus abdominis, samples will be snap frozen in liquid nitrogen in the operating theatre and stored at -80°C . Sample size will be approximately 1 cm^3 and will be resected using non-electric scissors.

► T3 (day 1 postoperative)

Diaphragm, quadriceps femoris and rectus abdominis ultrasound will be performed. Handgrip strength test will be performed, and blood samples will be taken

from the antecubital vein; serum or plasma will be processed and frozen.

► T4 (day 3 postoperative)

Diaphragm, quadriceps and rectus abdominis ultrasound will be performed. Handgrip strength test will be performed, and blood samples will be taken; serum or plasma will be processed and frozen.

► T5 (day 5 postoperative)

Diaphragm, quadriceps and rectus abdominis ultrasound will be performed. Handgrip strength test will be performed, and blood samples will be taken; serum or plasma will be processed and frozen.

► T6 (day 7 postoperative)

Diaphragm, quadriceps and rectus abdominis ultrasound will be performed. Handgrip strength test will be performed and blood samples will be taken; serum or plasma will be processed and frozen. HRQoL questionnaire will be filled out. The SPPB test will be performed.

► T7 (30 days after hospital discharge)

Diaphragm, quadriceps and rectus abdominis ultrasound will be performed. Handgrip strength test will be performed, and blood samples will be taken; serum or plasma will be processed and frozen. HRQoL questionnaire will be filled out. The SPPB test will be performed.

► T8 (6 months after surgery)

A telephone questionnaire will be performed containing a physical activity questionnaire, return to baseline work/activity questionnaire and a HRQoL questionnaire (SF36).

Setting

Recruitment of patients and subsequent sampling will be performed tertiary university hospital in Germany, Uniklinik Rheinisch Westphälische Technische Hochschule (RWTH) Aachen.

STATISTICAL ANALYSIS

Power analyses

No data regarding speckle imaging variables (strain or strain rate) among different patient groups are available. However, Deniz *et al* recently investigated differences in lung function between older sarcopenic and non-sarcopenic patients by measuring diaphragm thickness.²¹ We calculated the expected effect size based on mean diaphragm thickness values and SD after forced expiration of the aforementioned study. Based on a mean FT in the non-sarcopenic group ($n=30$) of 1.5 mm (SD 0.7) and 1.1 mm (SD 0.4) in the sarcopenic group ($n=30$), we calculated an effect size of 0.70. Considering an alpha of 0.05 and a beta of 0.80, a total sample size of 66 patients (33 patients per group) will be needed.

Analysis of primary and secondary outcome parameters

SPSS will be used for statistical analysis (IBM, Released 2013, IBM SPSS Statistics for Macintosh, V.22.0.). A

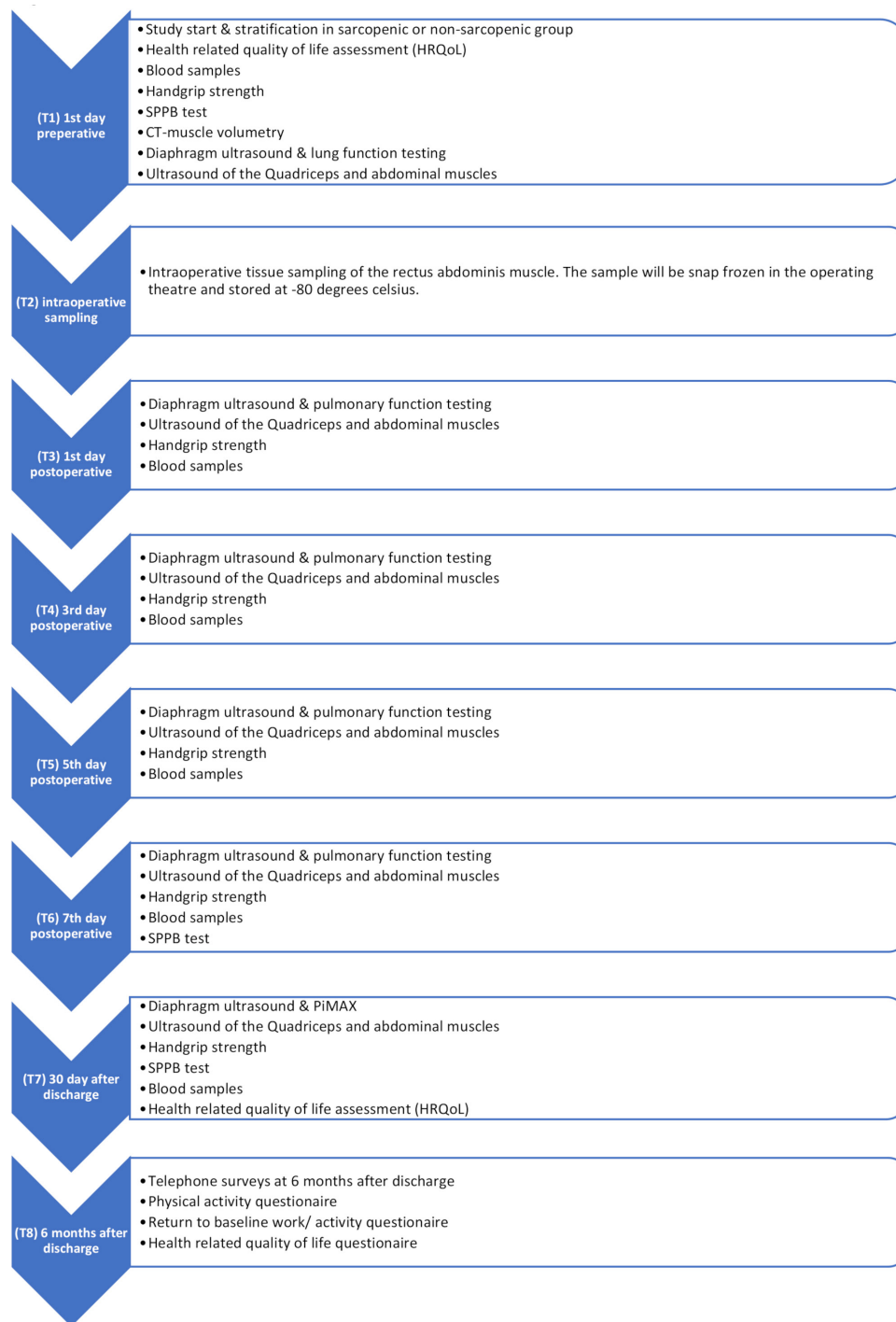


Figure 1 Flow chart showing study time plan from T1 1-day preoperative to T8 6 months after discharge. SPPB, short physical performance battery.

two-tailed $p < 0.05$ will be considered statistically significant. To allow comparisons between groups, data will be tested for normal distribution, and appropriate statistical tests will be applied, potentially including Student's t-test, Mann-Whitney U test, analysis of variance, Kruskal-Wallis test, χ^2 test or Fisher's exact test. Normally distributed continuous variables will be evaluated as mean values and SD. Non-normally distributed continuous variables will be evaluated as median and range.

PATIENT AND PUBLIC INVOLVEMENT

No patients involved

ETHICS AND DISSEMINATION

The protocol was ethically approved by the official Independent Medical Ethical Committee of the Uniklinik (RWTH) Aachen (reference EK309-18) in July 2019. Written informed consent will be obtained from all participants. The study will be performed in accordance

with the principles of the Declaration of Helsinki, as well as the guidelines of Good Clinical Practice. Recruitment started in the first quarter of 2020, and recruitment is currently ongoing. Patients deemed eligible for enrolment are initially recruited by their surgeon at the time of approval for surgery. If interested in participation, the patient will be contacted by the researcher and given detailed information about the study, in both oral and written form. After a 2-week period, the subjects are contacted to obtain informed consent, and then they will be officially enrolled in the study.

DISCUSSION

Sarcopenia is characterised by concurrent hypermetabolism, hypercatabolism and hypoanabolism which aggravate weight loss and are provoked by tumour induced systemic inflammation and catabolic factors partly mediated by the central nervous system.³⁹ Irrespective of the cause, sarcopenia has been shown to have a significant negative impact on short-term and long-term outcome following a range of oncological treatments.^{1 3 37 40–45} Not only long-term outcome has been shown to be impacted by sarcopenia. Postoperative complications (morbidity) have profound impact on the burden of disease and suffering following surgical treatment.^{4 41 42 46–48} Pulmonary morbidity, especially postoperative pneumonia, is of particular importance and has been shown to prolong hospital admission and increase in-hospital mortality following a range of surgical interventions, most notably after major abdominal and upper gastrointestinal surgery.^{11–15}

The results of this study will contribute to the understanding of the role of the diaphragm in pulmonary morbidity following liver resection and will provide insight into the role of sarcopenia in pulmonary morbidity. To our knowledge, this approach has not previously been implemented for the investigation of the impact of abdominal surgery or sarcopenia and wasting disorders on diaphragm function.

We hypothesise that the results of this study will contribute to identifying patients at risk of pulmonary complications following liver resection. Identification of these at-risk patients is of great importance for the implementation of improved preconditioning of patients, thus potentially contributing to the reduction of postoperative pulmonary morbidity in the future.

‘Is Sarcopenia a Risk Factor for Reduced Diaphragm Function Following Hepatic Resection, a Study Protocol for a Prospective Observational Study’, is a study currently recruiting patients.

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