Adipose Tissue Imaging as Nutritional Predictors in Patients Undergoing Enterocutaneous Fistula Repair

Konstantinos C. Fragkos,[1*] Debbie Thong,[1*] Kenneth Cheung,[2] Helen J. Thomson,[3] Alastair C. J. Windsor,[1] Alec Engledow,[3] Jonathan McCullough,[1] Shameer J. Mehta,[1] Farooq Rahman,[1] Andrew A. Plumb,[2] Simona Di Caro[1]

[1] *Intestinal Failure Service, Department of Gastroenterology, University College London Hospitals NHS Foundation Trust, United Kingdom*

[2] *Imaging Department, University College London Hospitals NHS Foundation Trust, United Kingdom*

[3] *Colorectal Surgery Department, The Mid Yorkshire Hospitals NHS Trust, United Kingdom*

[*] These authors contributed equally to the present paper.

Correspondence to:

Simona Di Caro

Intestinal Failure Service, Department of Gastroenterology

University College London Hospitals NHS Foundation Trust

250 Euston Road, London NW1 2PG, United Kingdom

e-mail: simona.dicaro@nhs.net

Tel. +44 (0) 20344 79311, Fax: +44 (0) 20344 79217

Running head: Nutritional status based on abdominal fat tissue imaging in ECF repair

Abbreviations: BMI Body Mass Index; CI Confidence Intervals; CT Computed Tomography; ECF Enterocutaneous fistula/fistulae; EN Enteral Nutrition; HR Hazard Ratio; IQR Interquartile Range; L3 third lumbar vertebra; MRI Magnetic Resonance Imaging; NG Nasogastric Feeding; ONS Oral Nutritional Supplements; PN Parenteral Nutrition; ROC Receiver Operating Characteristic; SD Standard Deviations; TFA Total Fat Area; UCLH University College London Hospital

ABSTRACT

BACKGROUND: The management of enterocutaneous fistulae (ECF) is complex, challenging and often associated with metabolic, septic and nutritional complications. Radiographic quantification of body composition such as fat or lean body mass distribution is a potentially valuable pre-operative assessment tool to optimise nutritional status.

AIM: To investigate the correlation between total adipose tissue (fat) area (TFA), assessed by CT and MRI radiological tests, with body weight, body mass index, various biochemical parameters, need for nutritional support and survival in patients undergoing ECF repair.

METHOD: Biochemical and anthropometric parameters at the time of ECF surgery were retrospectively collected for adult patients undergoing ECF repair at University College London Hospital, UK. Visceral and subcutaneous adiposity was measured at the level of the third lumbar vertebra (Image J) at CT or MRI. Statistical analysis included descriptives, univariate and multivariate analysis between TFA and various parameters and their influence on post-operative survival.

RESULTS: A complete set of data was available for 85 patients (51 females, age 56.9±14.5 years) who underwent ECF repair. ECF originated mainly as a surgical complication (86%) while 14% of patients had previously had attempted ECF repair. Median BMI was 22.8kg/m^2 while mean TFA was 361±174.9cm^2, with a higher visceral fat content in males compared to females (183.8±99.2 vs 99.0±59.7cm^2, p<0.001). BMI, body weight and creatinine were significantly positively correlated with TFA (rho= 0.77, rho=0.73, rho=0.50, respectively, p<0.001); no correlation was noted between TFA and pre-operative albumin levels. Patients in the low TFA group had a higher use of parenteral nutrition (p=0.049). Length of stay in hospital was longer in patients receiving artificial nutrition support (70 vs 22 days, p<0.001). A TFA cut-off point of 290.0cm^2 discriminated patients who required artificial nutrition vs no nutritional support with moderate sensitivity (75%) but poor specificity (45%). At multivariate analysis, only age over 60 years (hazard ratio=2.69, p<0.02) and use of parenteral nutrition (hazard ratio=3.90, p<0.02) were associated with worse overall survival.

CONCLUSION: Abdominal adiposity was strongly correlated with anthropometric parameters at the time of surgery. Earlier identification of patients requiring artificial nutrition at standard pre-operative imaging might allow integration of nutritional optimisation into initial clinical management plans reducing length of stay and improving clinical outcomes.

Keywords: abdominal total adipose tissue area, enterocutaneous fistula, third lumbar vertebra, nutrition

INTRODUCTION

Enterocutaneous fistulae (ECF) are pathological connections that develop between the gastrointestinal (GI) tract and the skin [1]. The management of ECF is complex and challenging, particularly when it is associated with metabolic, septic and nutritional complications. To address this challenge, the 'Sepsis-Nutrition-Anatomy-Plan' (SNAP) approach has been widely adopted in the UK. It focuses on the control of sepsis (S), the optimization of nutritional status (N), understanding the anatomy of the fistula (A), and planning a surgical procedure to repair the fistula (P) [2, 3]. ECF most commonly develop from the small bowel, colon, stomach and duodenum, in descending order of prevalence [1] and are classified according to a number of characteristics including anatomical location, etiological or physiological characteristics and degree of complexities [4]. Most enteric fistulas (85%) arise from iatrogenic causes such as bowel injuries during surgery, disruption of repaired enterotomies, or anastomotic leak. The remaining 15% form secondary to underlying pathology, such as Crohn's disease, radiation enteropathy, appendicitis, malignancies, ischemic bowel, intra-abdominal sepsis or abdominal trauma [4, 5]. Fistula closure can occur with conservative treatment in up to 75% of patients, usually within four to six weeks of nutrition support. Surgical intervention is indicated in the remaining cases [6]. ECF have been associated with substantial morbidity and mortality, predominantly from its complications [7]. Sepsis with malnutrition is the leading cause of death [8, 9]. Mortality is heavily dependent on the severity of surgical complications, fistula output, nutritional deficiencies and electrolyte abnormalities [10, 11], with a previously reported mortality rate of 62% in patients with gastric and duodenal fistulas [12].

Excessive output volume consisting of protein-rich nutrients, digestive fluids, water and electrolyte can cause a wide array of consequences such as dehydration, metabolic disorders, malnutrition and hypovolemia with consequent development of intestinal failure and necessity for parenteral support.

Following improvements in infection control, nutritional care and surgical advances, the overall mortality rate has declined to around 10% [13]. Nevertheless, the success rate of ECF closure following definitive surgical repair has shown little improvement during the past few decades. In general, a failure of ECF closure occurs 15% to 30% of the time [14].

A detailed nutritional assessment is multifaceted; it relies on anthropometry data, biochemical and metabolic parameters, clinical assessment of nutritional requirements, and evaluation of dietary intake. Routine anthropometric measurements, including height, weight, mid-upper circumference, skinfold thickness and body mass index (BMI), are credible indicators for nutritional assessment in a healthy population, and can be obtained conveniently and easily [15]. However, the reliability of these measurements is undermined in patients with ECF, mainly by alterations in fluid status owing to fluctuating volume of fistula output, especially in the early phases [16]. Furthermore, many of these data are based on assumptions; for example, BMI assumes a standard distribution of adipose and muscular tissues for all individuals.

Therefore, the study of body composition is particularly relevant in patients with ECF undergoing operative repair to ensure correct timing of surgery and to offer the best chances for wound healing and sepsis-free recovery. Understanding the clinical implications of malnutrition is critical for pre-operative risk stratification so that appropriate intervention such as provision of early nutrition support can be provided in patients with ECF, before embarking on surgical treatments [17]. Body composition can be measured by various techniques such as dual energy X-ray absorptiometry, densitometry or bioelectrical impedance analysis. However, in practice, some methods are limited by their availability, complexity, cost and accuracy. Non-invasive computerized tomography (CT) and magnetic resonance imaging (MRI) specific software have been developed in the last decade to allow quantification of skeletal muscle or subcutaneous and visceral adiposity mass as indicators of nutritional status. A recent European consensus statement identified CT and MRI as the current gold standard in body composition evaluation in research studies [15]. Translation of the use of these tools routinely in clinical practice for assessment of body composition might allow timely referrals for nutritional support, comprehensive assessments and earlier treatment plan optimisation in patients with ECF. Since radiological scans are performed as standard for the investigation of ECF aetiology, to exclude sepsis and to define anatomy, body composition can be evaluated at no additional cost or patient inconvenience. Axial cross-sectional radiological images at the third lumbar vertebra (L3) level provide accurate estimates of body composition and correspond linearly to whole-body tissue measurements [18, 19].

Several studies have also explored the impact of sarcopenia (i.e. low muscle mass), assessed by CT, as a predictor for surgical complications and outcome particularly in oncology [20-25] including endometrial cancer, abdominal malignancies, gastrointestinal and hepato-pancreatobiliary malignancies [20-29]. These studies have consistently demonstrated that CT is an accurate tool to measure body composition, and that excessive abdominal fat or low muscle mass adversely influences treatment outcome. Other research has examined the negative role of visceral obesity, the excessive build-up of visceral fat distribution in the abdominal cavity, in the prediction of colorectal surgical outcomes [30, 31].

To date, the correlation between body composition analysis by imaging with anthropometric and laboratory parameters, need for nutritional support and postoperative outcomes has not been explored in patients with ECF undergoing surgical repair, offering a potential for future research in this area to improve the trajectory of clinical outcomes. Hence, the aim of this retrospective study was to examine the correlation among imaging-based total adipose tissue (fat) area (TFA) and anthropometric characteristics, biochemistry parameters with need for artificial nutritional support, hospital length of stay and postoperative survival.

METHODS

Study Settings

This is a retrospective study and adherence to the principles of the Declaration of Helsinki was followed during design and analysis. It was approved by the Institutional Review Board and patient written consent was waived. University College London Hospital (UCLH) is a tertiary referral centre for intestinal failure and operative repair of ECF in the UK, where patients are thoroughly assessed by a multidisciplinary team to decide a comprehensive management plan.

Inclusion and Exclusion Criteria

Adult patients (18 years or older) who underwent ECF repair at UCLH until 31 May 2016 identified through the surgical intestinal failure database, were considered eligible when all the data necessary for analysis were available. Patients who had no CT or MRI scans performed within three months of surgery or within one month after surgery were excluded. To best represent patients' nutritional status prior surgery, the nearest radiology scan to surgery date was chosen for body composition analysis. All types (internal, external or a combination) of enteric fistulas were included in the study.

Data Collection

The following data were collected:

Demographics and Surgical History. Gender, age at time of ECF repair, ECF aetiology and type, and number of previous ECF repair attempts were recorded.

Anthropometric Characteristics. Admission height and weight during the perioperative period. BMI was then calculated. The perioperative period was considered the period of time extending from when the patient goes into the hospital until the time the patient is discharged home.

Nutritional Requirements. Types of artificial nutrition during the perioperative period were recorded (oral nutritional supplements, enteral nutrition, parenteral nutrition).

Serum Biochemistry. Alkaline phosphatase, albumin, calcium, phosphate, International normalised ratio (INR), C-reactive protein, sodium, potassium, urea, creatinine, white cell count, haemoglobin, platelets, neutrophils, total bilirubin, alanine transaminase, magnesium were collected. Values were extracted within the two weeks leading to day of surgery, and when data were not available, to the date of radiological scan selected for body composition evaluation.

Radiological Studies and Body Composition Analysis. Diagnostic radiological scans were used to calculate TFA (visceral and subcutaneous adipose tissue) of the abdominal area. CT abdomen and MRI small bowel scans were evaluated without the knowledge of surgical outcomes, at the time of quantification. Axial CT images were retrieved from the local Picture Archiving and Communication System (PACS) and anonymised using OsiriX DICOM Viewer (OsiriX, Switzerland). Image analysis was performed using Fiji, an image-processing package based on ImageJ [32]. An in-house macro was developed to enable a semi-automated workflow. The image slice representing the level of the centre of the L3 lumbar vertebra was selected by an experienced radiologist. A region of interest was manually drawn to include approximately 50% fat and 50% muscle. The selected pixels were displayed as a histogram of Hounsfield values (for CT) or pixel intensity (for MRI) within the region of interest, which resulted in two peaks - one representing fat and the other muscle. Thresholding was then applied based on these Hounsfield or pixel intensity values to select fat-only areas to create a binary image. Free-hand selection was then performed to refine the boundaries of the fat and to remove any external artefacts such as the CT/MRI table and oxygen tubing. The total fat area was selected by thresholding and measured using the software's electronic area measurement tool. A region of interest was then drawn along the inner margin of the abdominal wall to separate the visceral (intra-abdominal) and subcutaneous (extra-abdominal) compartments. The areas of abdominal subcutaneous and visceral fat were then measured and recorded (Supplementary Figures 1 and 2).

Postoperative variables. Length of hospital stay (defined as the time from the date of admission to either date of discharge, in-patient death, or transfer to other institution) and overall survival (reported in weeks), from the date of surgery as the starting time to date of death or post-surgery censoring date as the end point (30 May 2017).

Statistical Analysis

Descriptive statistics were computed for the study cohort. Normally distributed continuous data were presented as mean and standard deviations (SD); non-parametric data were shown as medians with interquartile range (IQR). Categorical data were shown as absolute frequency and percentages. For univariate analyses, independent *t*-tests and Kruskal-Wallis or Mann-Whitney U tests were used for parametric and non-parametric variables respectively, while Chi-square test was used for dichotomous variables. A median value was used to establish a cut-off value for low and high TFA to evaluate its impact on other variables. Spearman's rank correlation coefficient (rho) was used to identify the correlation between TFA and various biochemical or anthropometric parameters, illustrated in a heatmap, arranged using a hierarchical clustering algorithm, using the function `heatmap.2` in the gplots package for R. The larger the correlation between a pair of variables, the closer in proximity they appear in the heatmap. Overall survival was presented using the nonparametric Kaplan-Meier method, after which the log-rank test was used for the comparison of survival between patient's groups. Univariate and multivariate Cox proportional hazard models were conducted to identify variables that affected survival. Finally, empirical receiver operating characteristic plots were constructed to establish cut-off values for TFA above which artificial nutrition was used. Two-tailed tests of significance were used, a p-value ≤ 0.05 was considered significant. For data analysis, IBM SPSS Statistics (Release 22.0.0. 2010, Chicago (IL), USA: SPSS, Inc., an IBM Company) and R 3.3.1 [33] were used.

RESULTS

Descriptive Characteristics, Nutritional Support and Survival

A complete data set was available for 85 patients [34 males (40%), mean age of 56.9 ± 14.5 years]. The mean follow-up duration of the study was 205 (±136) weeks. Patients' demographic profile, ECF aetiology, requirement for nutritional support, TFA, length of stay, anthropometric and biochemical characteristics and type of surgery are summarised in Table 1. ECF formed as a surgical complication in 86% (n=73), while 14% (n=12) formed spontaneously (Figure 2). Overall, Crohn's disease represented the main etiological group in the formation of ECFs (n=24, 28%). Other causes of ECFs were related to procedures performed for ischemic bowel, adhesiolysis, appendectomy and colonoscopy or laparoscopy. Eleven patients had previous attempt(s) at ECF repair. The types of surgery were classified into three categories: ECF repair was the most common surgery performed (59%), followed by ECF repair with abdominal wall reconstruction (21%), and for the remaining patients (20%) the surgery involved other procedures such as small bowel resection, hemicolectomy and refashioning of ileostomy.

The median BMI for the study cohort resulted within the normal range at 22.8 kg/m^2 [IQR 19.4-28.4], with no significant differences between gender (p=0.29). Respectively, 16%, 43% and 41% of patients were classified as underweight, normal weight or overweight/obese. None of the patients had a BMI ≥40 kg/m^2. Mean pre-operative serum albumin levels for the cohort was 32 ± 8 g/L with 31% of patients having values < 30 g/L.

The median overall hospital length of stay was 53 days [IQR 24-100], with significant difference (p<0.001) between patients under or over 60 years [medians: 29 (n=46) vs 78 days (n=39)] (p<0.001). Two patients died within thirty days of surgery contributing to an early mortality of 2% (95% CI 1%-8%). There were no intra-operative deaths.

During the perioperative period, 73% (n=62) of patients were given nutrition support in various forms (Figure 3). Parenteral nutrition and oral nutritional supplements were the most frequently used nutritional intervention (35%). A total of 49 patients (58%) received total or supplementary parenteral nutrition during the peri-operative period. Approximately a quarter (27%) of patients did not receive any artificial nutrition, while 16% of patients (n=14) received total parenteral support. The median length of stay in patients receiving parenteral nutrition was 63 days (IQR 33-117) versus 24 days (IQR 14-58) for patients who did not receive parenteral nutrition ($p<0.0001$). 21 patients (25%) could not be weaned off parenteral nutrition and were discharged on home parenteral nutrition. Patients who received artificial nutrition had significantly longer length of stay (median=70 days, n=62) compared to those who did not receive artificial nutrition support (median=22 days, n=23) ($p<0.001$). Serum albumin levels did not differ between patients who received parenteral nutrition and those who did not ($p=0.29$) confirming that albumin is a poor marker of nutrition status.

Kaplan-Meier survival analysis revealed that advanced age (>60 years), low albumin (<30g/L) and the use of parenteral nutrition support were significant predictors of mortality ($p<0.05$) (Figure 3). Univariate Cox proportional hazard analysis revealed that patients in the low albumin groups had a two-fold increased risk of death ($p=0.04$) and overall survival was shorter in females compared to males ($p=0.03$). Patients who received parenteral nutrition had a three-fold increased risk of mortality ($p<0.01$) (Table 2). Of note, BMI failed to show an association with overall survival. In the multivariate model, only advanced age [hazard ratio (HR) = 2.69, $p<0.02$] and use of parenteral nutrition (HR = 0.90, $p<0.02$) were confirmed as independent predictors of overall survival while the effect of low albumin levels on survival disappeared. Survival was shorter for older patients [median: 184 weeks (IQR 164-274)] than those of younger age [median: 194 weeks (IQR 41-272)]; while patients with parenteral nutrition support has a shorter survival [median: 180 weeks (IQR 61-362)] compared to patients who did not require parenteral nutrition support [median: 200 weeks (IQR 161-286)].

---Table 1 and Figure 1, Figure 2 and Figure 3 here---

Total Adipose Tissue Area: Correlation Analysis

CT and MRI scans were performed in 70 and 15 patients, respectively. Data on L3 single-slice cross sectional area representing TFA were available for 52 patients (61%). In some patients, TFA could not be analysed due to poor quality of scan images, discrepancies or outliers due to various reasons such as whole abdomen not covered by scan, presence of gross ascites and anasarca. A wide range of TFA was observed, ranging from 65 to 718 cm^2. The mean TFA for males was significantly higher at 433.4 ±

172.8 cm^2 compared to females (319.7 ± 164.6 cm^2) ($p<0.05$). However, no significant differences were found after TFA was normalized by height. Males had significantly higher visceral fat (183.8±99.2 vs 99.0±59.7 cm2, $p<0.001$) than females, while no difference was found in subcutaneous fat.

A median cut-off point of 339 cm^2 was calculated to categorise the study population in low (<339 cm^2) or high (≥339cm^2) TFA groups. Although serum albumin levels were higher in the high-TFA group, the differences did not achieve statistical significance (p=0.71). No correlation was observed between TFA groups and age or type of surgery. Patients with low-TFA had a higher use of parenteral nutrition support (p=0.049). Moreover, patients requiring parenteral nutrition support had lower subcutaneous adipose tissue compared to those without (194 ± 105 cm^2 versus 274 ± 116 cm^2, p=0.0033); this trend was not confirmed for visceral adipose tissue values.

Length of stay was not correlated with TFA (p=0.19). There was a significant positive correlation between TFA and BMI (rho=0.77, n=50, $p<0.001$), but a wide range of TFA was observed within each BMI category (Supplementary Figure 3). When stratified according to gender, TFA correlated better to BMI for males (rho=0.92, n=18, $p<0.001$) than females (rho=0.66, n=32, $p<0.001$). The hierarchical clustering of dendrogram reflected the correlations among TFA, anthropometric and laboratory parameters taken pre-surgery. Three clusters were identified whose components were correlated: inflammation profile, anthropometrics/Fat Area, and renal/liver/ bone profile (Figure 4). The measurements for TFA and BMI were shown to be closely correlated and clustered together (Figure 4). Among the collected laboratory parameters, albumin levels were not significantly correlated, while creatinine levels were significantly associated with TFA measurements (rho=0.50, $p<0.001$); some haematological parameters were correlated with radiological indices but did not achieve statistical significance. Supplementary Table 1 provides a summary of Spearman's correlation between TFA at the L3 region and various parameters taken pre-surgery.

The ROC analyses estimated an optimal cut-off point of 290.0 cm^2 for TFA to discriminate patients who did or did not require artificial nutrition support; this point yielded moderate sensitivity (75%) and poor specificity (45%) and the area under the curve was 0.59 (95% CI 0.39-0.80). As patients who were prescribed artificial nutrition had longer LOS, early nutritional optimisation using the TFA cut-off may be used prospectively to improve overall outcome. None of the body fat compartment measurements were associated with overall survival.

---Figure 4 and Table 2 here---

DISCUSSION

ECFs are one of the most feared sequelae of abdominal surgery. In this retrospective study of 85 patients who underwent surgery for ECF, fistula had developed mainly as a result of bowel injury or extensive laparotomies with high prevalence of patients affected by Crohn's disease, which confirm previous data published from groups in the UK and North America [34-36]. More than half of the study population were females as reported a North American study [37], although two recent studies have reported a higher prevalence of ECF in males (up to 93% of study participants) [38, 39].

Patients with ECF are often nutritionally compromised which affects overall clinical outcomes and risk of mortality. It is well documented that malnutrition results in delayed wound healing and increased risk of post-operative complications and mortality [40].

Nevertheless, data on body composition analysis using diagnostic imaging in patients undergoing ECF repair, are not available. In this study, the abdominal fat (both visceral and subcutaneous adipose tissue) was correlated with biochemical, anthropometric parameters and clinical outcomes. In particular, previous studies have shown that visceral fat, the adipose tissue surrounding the organs, is reported to be associated with unfavourable surgical outcomes related to metabolic disturbances including insulin resistance and altered lipid homeostasis [41-43] while a decline in subcutaneous fat has been reported to be an indicator of malnutrition [44]. Interestingly, in our study TFA measurements strongly correlated with anthropometric measurements, particularly in males. Although TFA measurements are still a new parameters that we are not familiar to use in everyday clinical practice and may require rescaling into more meaningful values, the distinction could be related to gender differences in body fat distribution, where males generally store more fat in the abdominal depot, and women in the gluteal-femoral area [45]. Consequently, early nutrition interventions can be provided accordingly to body composition assessment from initial diagnostic radiological scan with benefits demonstrated in several studies of detecting patients who are at high-risk of malnutrition [46, 47].

A previous study by Visschers et al. [38] showed that mortality rate was significantly higher in patients with sepsis, low pre-operative albumin level (below 25 g/L), of male sex and aged over 60 years old. Our retrospective study, also demonstrated a lower mortality rate in younger patients. Likewise, multivariate analysis identified younger age as a favourable prognostic variable for shorter length of stay. Although the provision of perioperative parenteral nutrition was a poor prognostic predictor for overall survival, careful interpretation of this finding needs to be exercised, as a marker of a more severe disease/malnutrition. The choice of best route for nutritional administration is still contentious. Although enteral nutrition remains the first-line of choice for patients who require artificial nutrition in most clinical settings [36], parenteral nutrition can be considered when enteral nutrition or fistuloclysis is not feasible or tolerated.

In our cohort, a cut-off of 290 cm^2 for TFA showed some ability to discriminate patients requiring artificial nutrition versus patients who did not. Since patients that required artificial nutrition support had a longer length of stay, it is possible that early identification of these patients at initial imaging will allow prompt nutritional intervention to reduce length of stay (costs) and improve surgical outcomes. At multivariate analysis only age and need for parenteral nutrition was associated with overall survival, demonstrating that the need for parenteral nutrition correlates with disease/malnutrition severity while, interestingly, the effect of albumin of univariate analysis disappeared.

In our study, 73% of patients required artificial nutrition, of which 16% received only parenteral nutrition for a median of 39 days. While several studies have supported the link between body composition and clinical outcome, our results did not find a significant correlation between TFA and inflammatory markers, nor any significant difference in the prediction of survival post ECF repair. Nevertheless, this retrospective study was undertaken after all patients had completed their surgeries, hence, the body composition features from radiological images were not in any way used as prognostic factors to predict or improve surgical outcomes of patients, prior to surgery. In addition, TFA measurements were not normalized according to patients' comorbidities which inevitably contributed to survival [48, 49] nor ethnicity or environment factors that affect body fat distribution, which could hinder the study of clinical outcomes. TFA measurements obtained could not be compared with a healthy population. Likewise, as the study of body composition from radiological images is a relatively new technique for pre-operative risk assessment, especially within the field of ECF repair, limited research is available to provide a risk score to distinguish and compare the clinical outcomes between patients with and without normal TFA or different visceral-to-subcutaneous fat area ratio. Secondly, the TFA data in this study represented body fat area form a single-slice image; it may be more valuable to obtain three-dimensional segmentation (such as volumetric analysis), to allow a more accurate representation of the whole-body fat area in the selected region rather than information from a single slice. Thirdly, the rates of missing data in this study were relatively high (up to 39%), in relation to the measurements of TFA. In addition, the nearest radiology scan to surgery date (including immediately post-surgery) was chosen for body composition analysis which might have not been representative of initial assessment.

One aspect of the present study was the measurement of adipose tissue instead of skeletal muscle mass, which is now considered a strong predictor of outcome and a method for classifying into sarcopenic status, and it can be assessed and measured simultaneously with adipose tissue. The reason for selecting adipose tissue in this study was the ECF and its impact on abdominal skeletal muscle. Usually in this condition, patients have undergone quite a few surgeries and there has been loss of muscle mass in the abdominal area. This would not necessarily reflect a sarcopenic status since the patient might be on artificial nutrition thus maintaining a satisfactory nutritional status. One limitation of this choice was the fact that the predictive value of adipose tissue against muscle mass has not been captured.

A second limitation of the present study is that adipose tissue measurements was not compared between CT and MRI. This was chosen since MRI was performed in 15 patients only compared to 70 patients who had a CT and hence wouldn’t represent comparable groups.

The authors also used MRI to assess adipose tissue. It would be important to disclose whetehr any difference in the predictive value of adipose tissue exists when it is measured by CT or by MMRI

Conversely, the strengths of this study are the relatively large sample size of patients that were all treated in a major centre by a multidisciplinary team with an expertise in managing ECF thus minimising any protocol-related confounding factors.

Various studies have showed that nutritional support leads to improved clinical outcomes in nutritionally depleted patients and malnutrition is an adverse prognostic factor for surgical outcomes [50]. Similarly, optimising patients' nutritional status is a fundamental aspect of ECF management.

In conclusion, objective and accurate body composition assessment is crucial in the management of patients with ECF providing information which may not be identified by BMI or other serum markers alone. TFA results significantly correlated with anthropometric measures and was able to discriminate patients who required artificial nutrition support. Nevertheless, considerable challenges remain in defining cut-offs for TFA, variation in the pre-surgical risk assessment methods and institution's protocol design, which make the study of body composition in ECF patients complicated.

Despite the emerging interest in the clinical implications of body composition study as prognostic markers of surgical outcomes, the scope of available data is limited for patients undergoing ECF repair. Imaging is routinely performed in this cohort of patients to guide clinical management. Moreover, radiological scans can be relatively easily transferred from local Hospitals to tertiary referral centres with expertise in managing these patients for assessment and if body composition is incorporated in such evaluation, nutrition plans can be integrated and implemented in the early stages. Body composition evaluation could complement malnutrition screening allowing accurate quantification of disease-specific changes in lean body mass and adipose tissue at interval scans which are usually performed during the patient journey for other clinical indications. Understanding the pathophysiology prior to surgery and implementing the necessary interventions can reduce complications related to ECF surgery, and thereby decrease duration of hospitalization and improve patients' quality of life. Further prospective research is warranted to examine the changes in body composition over time to determine if early nutrition intervention can reduce post-operative complications in patients undergoing ECF repair and improve the trajectory of the current unsatisfactory surgical outcomes and mortality rates.

FUNDING SOURCES

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICTS OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

KCF and DT contributed to data collection, data analysis, and manuscript writing and editing. KC performed the radiological image analysis and contributed to manuscript writing and editing. HJT, ACJW, AE, JM, SJM, and FR contributed to study design, supervision, data analysis and manuscript writing and editing. AAP assisted in the construction of the radiological analysis pathway and contributed to study design, study supervision, and manuscript writing and editing. SDC conceived the study, and contributed to study design, study supervision, data analysis, and manuscript writing and editing.

REFERENCES

[1] Orangio GR. Enterocutaneous fistula: medical and surgical management including patients with Crohn's disease. Clin Colon Rectal Surg. 2010;23:169-75, doi:10.1055/s-0030-1262984.

[2] Klek S, Forbes A, Gabe S, Holst M, Wanten G, Irtun O, et al. Management of acute intestinal failure: A position paper from the European Society for Clinical Nutrition and Metabolism (ESPEN) Special Interest Group. Clin Nutr. 2016;35:1209-18, doi:10.1016/j.clnu.2016.04.009.

[3] Lal S, Teubner A, Shaffer JL. Review article: intestinal failure. Aliment Pharmacol Ther. 2006;24:19-31, doi:10.1111/j.1365-2036.2006.02941.x.

[4] Pironi L, Arends J, Baxter J, Bozzetti F, Pelaez RB, Cuerda C, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr. 2015;34:171-80, doi:10.1016/j.clnu.2014.08.017.

[5] Makhdoom ZA, Komar MJ, Still CD. Nutrition and enterocutaneous fistulas. J Clin Gastroenterol. 2000;31:195-204

[6] Haffejee AA. Surgical management of high output enterocutaneous fistulae: a 24-year experience. Curr Opin Clin Nutr Metab Care. 2004;7:309-16

[7] Datta V, Engledow A, Chan S, Forbes A, Cohen CR, Windsor A. The management of enterocutaneous fistula in a regional unit in the United kingdom: a prospective study. Dis Colon Rectum. 2010;53:192-9, doi:10.1007/DCR.0b013e3181b4c34a.

[8] Galie KL, Whitlow CB. Postoperative enterocutaneous fistula: when to reoperate and how to succeed. Clin Colon Rectal Surg. 2006;19:237-46, doi:10.1055/s-2006-956446.

[9] Polk TM, Schwab CW. Metabolic and nutritional support of the enterocutaneous fistula patient: a three-phase approach. World J Surg. 2012;36:524-33, doi:10.1007/s00268-011-1315-0.

[10] Martinez JL, Luque-de-Leon E, Mier J, Blanco-Benavides R, Robledo F. Systematic management of postoperative enterocutaneous fistulas: factors related to outcomes. World J Surg. 2008;32:436-43; discussion 44, doi:10.1007/s00268-007-9304-z.

[11] Mawdsley JE, Hollington P, Bassett P, Windsor AJ, Forbes A, Gabe SM. An analysis of predictive factors for healing and mortality in patients with enterocutaneous fistulas. Aliment Pharmacol Ther. 2008;28:1111-21, doi:10.1111/j.1365-2036.2008.03819.x.

[12] Edmunds LH, Jr., Williams GM, Welch CE. External fistulas arising from the gastro-intestinal tract. Ann Surg. 1960;152:445-71

[13] Murphy J, Hotouras A, Koers L, Bhan C, Glynn M, Chan CL. Establishing a regional enterocutaneous fistula service: the Royal London hospital experience. Int J Surg. 2013;11:952-6, doi:10.1016/j.ijsu.2013.06.011.

[14] Owen RM, Love TP, Perez SD, Srinivasan JK, Sharma J, Pollock JD, et al. Definitive surgical treatment of enterocutaneous fistula: outcomes of a 23-year experience. JAMA Surg. 2013;148:118-26, doi:10.1001/2013.jamasurg.153.

[15] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412-23, doi:10.1093/ageing/afq034.

[16] Lloyd DA, Gabe SM, Windsor AC. Nutrition and management of enterocutaneous fistula. Br J Surg. 2006;93:1045-55, doi:10.1002/bjs.5396.

[17] Chamberlain M, Dwyer R. Reducing pre-operative length of stay for enterocutaneous fistula repair with a multi-disciplinary approach. BMJ Qual Improv Rep. 2015;4, doi:10.1136/bmjquality.u204075.w1773.

[18] Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33:997-1006, doi:10.1139/H08-075.

[19] Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol (1985). 2004;97:2333-8, doi:10.1152/japplphysiol.00744.2004.

[20] Reisinger KW, van Vugt JL, Tegels JJ, Snijders C, Hulsewe KW, Hoofwijk AG, et al. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. Ann Surg. 2015;261:345-52, doi:10.1097/SLA.0000000000000628.

[21] Peng P, Hyder O, Firoozmand A, Kneuertz P, Schulick RD, Huang D, et al. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. J Gastrointest Surg. 2012;16:1478-86, doi:10.1007/s11605-012-1923-5.

[22] Joglekar S, Nau PN, Mezhir JJ. The impact of sarcopenia on survival and complications in surgical oncology: A review of the current literature. J Surg Oncol. 2015;112:503-9, doi:10.1002/jso.24025.

[23] Harimoto N, Shirabe K, Yamashita YI, Ikegami T, Yoshizumi T, Soejima Y, et al. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. Br J Surg. 2013;100:1523-30, doi:10.1002/bjs.9258.
[24] Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31:1539-47, doi:10.1200/JCO.2012.45.2722.
[25] Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. Am J Clin Nutr. 2010;91:1133S-7S, doi:10.3945/ajcn.2010.28608C.
[26] Gibson DJ, Burden ST, Strauss BJ, Todd C, Lal S. The role of computed tomography in evaluating body composition and the influence of reduced muscle mass on clinical outcome in abdominal malignancy: a systematic review. Eur J Clin Nutr. 2015;69:1079-86, doi:10.1038/ejcn.2015.32.
[27] Levolger S, van Vugt JL, de Bruin RW, JN IJ. Systematic review of sarcopenia in patients operated on for gastrointestinal and hepatopancreatobiliary malignancies. Br J Surg. 2015;102:1448-58, doi:10.1002/bjs.9893.
[28] van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN. Body composition and outcome in patients undergoing resection of colorectal liver metastases. Br J Surg. 2012;99:550-7, doi:10.1002/bjs.7823.
[29] Keane N, Fragkos KC, Patel PS, Bertsch F, Mehta SJ, Di Caro S, et al. Performance Status, Prognostic Scoring, and Parenteral Nutrition Requirements Predict Survival in Patients with Advanced Cancer Receiving Home Parenteral Nutrition. Nutr Cancer. 2018;70:73-82, doi:10.1080/01635581.2018.1380206.
[30] Seki Y, Ohue M, Sekimoto M, Takiguchi S, Takemasa I, Ikeda M, et al. Evaluation of the technical difficulty performing laparoscopic resection of a rectosigmoid carcinoma: visceral fat reflects technical difficulty more accurately than body mass index. Surg Endosc. 2007;21:929-34, doi:10.1007/s00464-006-9084-9.
[31] Tsujinaka S, Konishi F, Kawamura YJ, Saito M, Tajima N, Tanaka O, et al. Visceral obesity predicts surgical outcomes after laparoscopic colectomy for sigmoid colon cancer. Dis Colon Rectum. 2008;51:1757-65; discussion 65-7, doi:10.1007/s10350-008-9395-0.
[32] Schindelin J, Arganda-Carreras I, Frise E, Kaynig V, Longair M, Pietzsch T, et al. Fiji: an open-source platform for biological-image analysis. Nat Methods. 2012;9:676-82, doi:10.1038/nmeth.2019.
[33] Team RC. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2016.

[34] Berry SM, Fischer JE. Classification and pathophysiology of enterocutaneous fistulas. Surg Clin North Am. 1996;76:1009-18

[35] Evenson AR, Fischer JE. Current management of enterocutaneous fistula. J Gastrointest Surg. 2006;10:455-64, doi:10.1016/j.gassur.2005.08.001.

[36] Hollington P, Mawdsley J, Lim W, Gabe SM, Forbes A, Windsor AJ. An 11-year experience of enterocutaneous fistula. Br J Surg. 2004;91:1646-51, doi:10.1002/bjs.4788.

[37] Betteridge JD, Armbruster SP, Maydonovitch C, Veerappan GR. Inflammatory bowel disease prevalence by age, gender, race, and geographic location in the U.S. military health care population. Inflamm Bowel Dis. 2013;19:1421-7, doi:10.1097/MIB.0b013e318281334d.

[38] Visschers RG, Olde Damink SW, Winkens B, Soeters PB, van Gemert WG. Treatment strategies in 135 consecutive patients with enterocutaneous fistulas. World J Surg. 2008;32:445-53, doi:10.1007/s00268-007-9371-1.

[39] Fischer PE, Fabian TC, Magnotti LJ, Schroeppel TJ, Bee TK, Maish GO, 3rd, et al. A ten-year review of enterocutaneous fistulas after laparotomy for trauma. J Trauma. 2009;67:924-8, doi:10.1097/TA.0b013e3181ad5463.

[40] Kudsk KA, Tolley EA, DeWitt RC, Janu PG, Blackwell AP, Yeary S, et al. Preoperative albumin and surgical site identify surgical risk for major postoperative complications. JPEN J Parenter Enteral Nutr. 2003;27:1-9, doi:10.1177/014860710302700101.

[41] Moon HG, Ju YT, Jeong CY, Jung EJ, Lee YJ, Hong SC, et al. Visceral obesity may affect oncologic outcome in patients with colorectal cancer. Ann Surg Oncol. 2008;15:1918-22, doi:10.1245/s10434-008-9891-4.

[42] Tokunaga M, Hiki N, Fukunaga T, Ogura T, Miyata S, Yamaguchi T. Effect of individual fat areas on early surgical outcomes after open gastrectomy for gastric cancer. Br J Surg. 2009;96:496-500, doi:10.1002/bjs.6586.

[43] Ritchie SA, Connell JM. The link between abdominal obesity, metabolic syndrome and cardiovascular disease. Nutr Metab Cardiovasc Dis. 2007;17:319-26, doi:10.1016/j.numecd.2006.07.005.

[44] Bharadwaj S, Ginoya S, Tandon P, Gohel TD, Guirguis J, Vallabh H, et al. Malnutrition: laboratory markers vs nutritional assessment. Gastroenterol Rep (Oxf). 2016;4:272-80, doi:10.1093/gastro/gow013.

[45] Blaak E. Gender differences in fat metabolism. Curr Opin Clin Nutr Metab Care. 2001;4:499-502

[46] Jagoe RT, Goodship TH, Gibson GJ. The influence of nutritional status on complications after operations for lung cancer. Ann Thorac Surg. 2001;71:936-43

[47] Di Sebastiano KM, Yang L, Zbuk K, Wong RK, Chow T, Koff D, et al. Accelerated muscle and adipose tissue loss may predict survival in pancreatic cancer patients: the relationship with diabetes and anaemia. Br J Nutr. 2013;109:302-12, doi:10.1017/S0007114512001067.

[48] Jensen MD. Role of body fat distribution and the metabolic complications of obesity. J Clin Endocrinol Metab. 2008;93:S57-63, doi:10.1210/jc.2008-1585.

[49] Gomez-Ambrosi J, Silva C, Galofre JC, Escalada J, Santos S, Gil MJ, et al. Body adiposity and type 2 diabetes: increased risk with a high body fat percentage even having a normal BMI. Obesity (Silver Spring). 2011;19:1439-44, doi:10.1038/oby.2011.36.

[50] Johansen N, Kondrup J, Plum LM, Bak L, Norregaard P, Bunch E, et al. Effect of nutritional support on clinical outcome in patients at nutritional risk. Clin Nutr. 2004;23:539-50, doi:10.1016/j.clnu.2003.10.008.

FIGURE LEGENDS

Figure 1. ECF Aetiology.

Figure 2. Nutritional Management and Types of Artificial Nutrition Support during the Perioperative Period.

Figure 3. Kaplan-Meier curves of continued survivals according to various variables: (a) Age groups; (b) parenteral nutrition support; (c) Albumin Groups; (d) BMI category.

Figure 4. Spearman correlation heatmap based on TFA and biochemical parameters taken prior ECF surgery. Dendrogram is displayed at the top and left of the heatmap. Spearman correlation was mapped to a colour scale ranging from red to blue. ** $p<0.01$ * $p<0.05$.

FIGURES

Figure 1. ECF Aetiology.

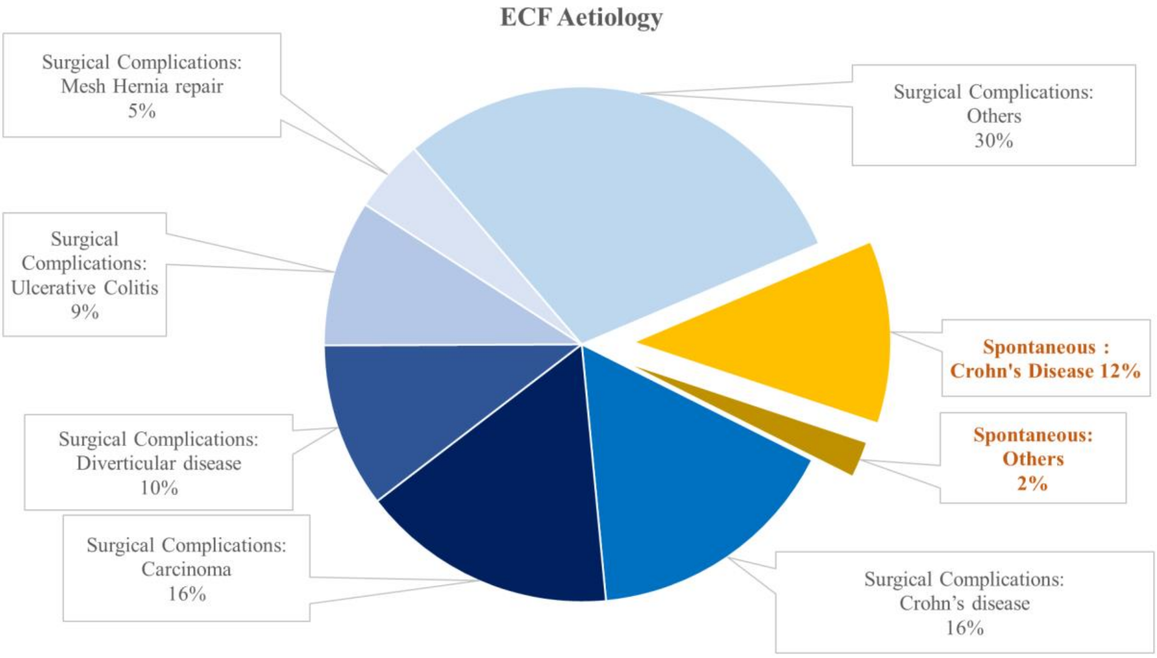


Figure 2. Nutritional Management and Types of Artificial Nutrition Support during the Perioperative Period.

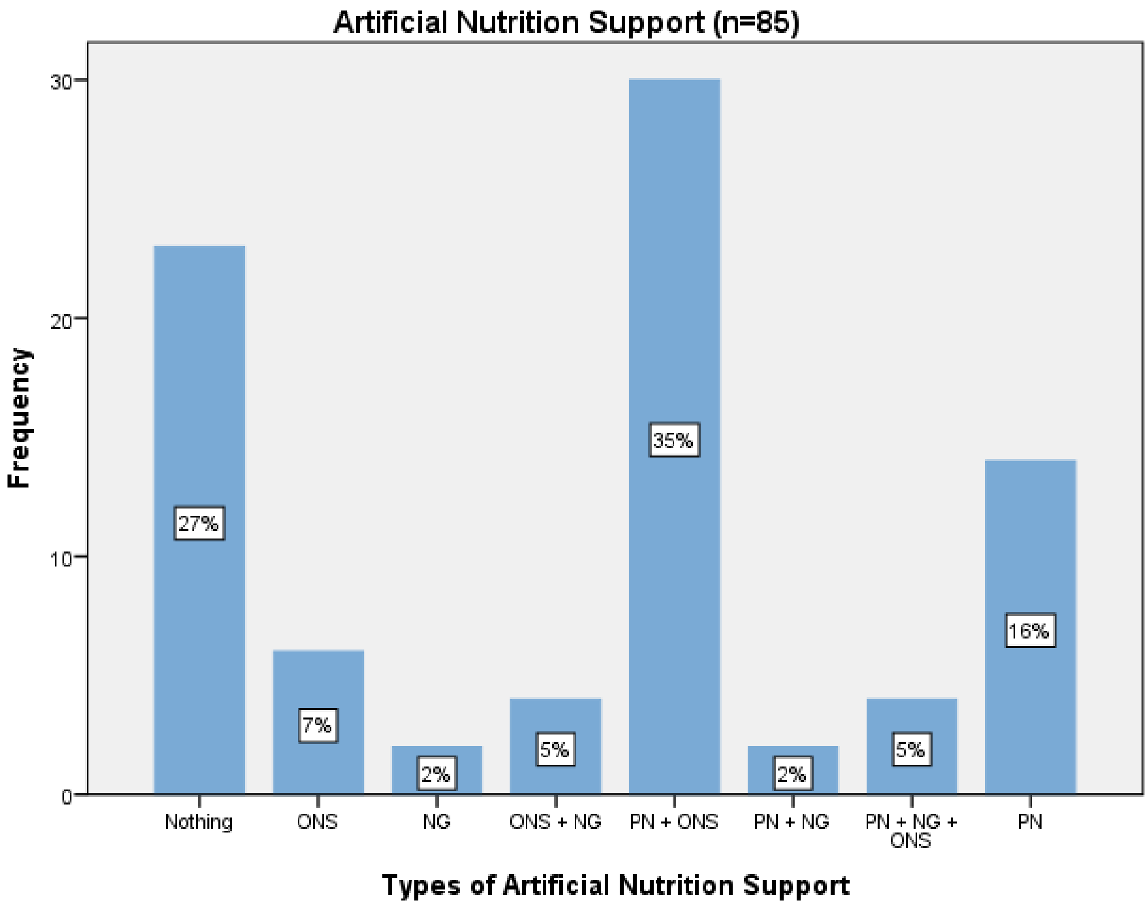


Figure 3. Kaplan-Meier curves of continued survivals according to various variables: (a) Age groups; (b) parenteral nutrition support; (c) Albumin Groups; (d) BMI category.

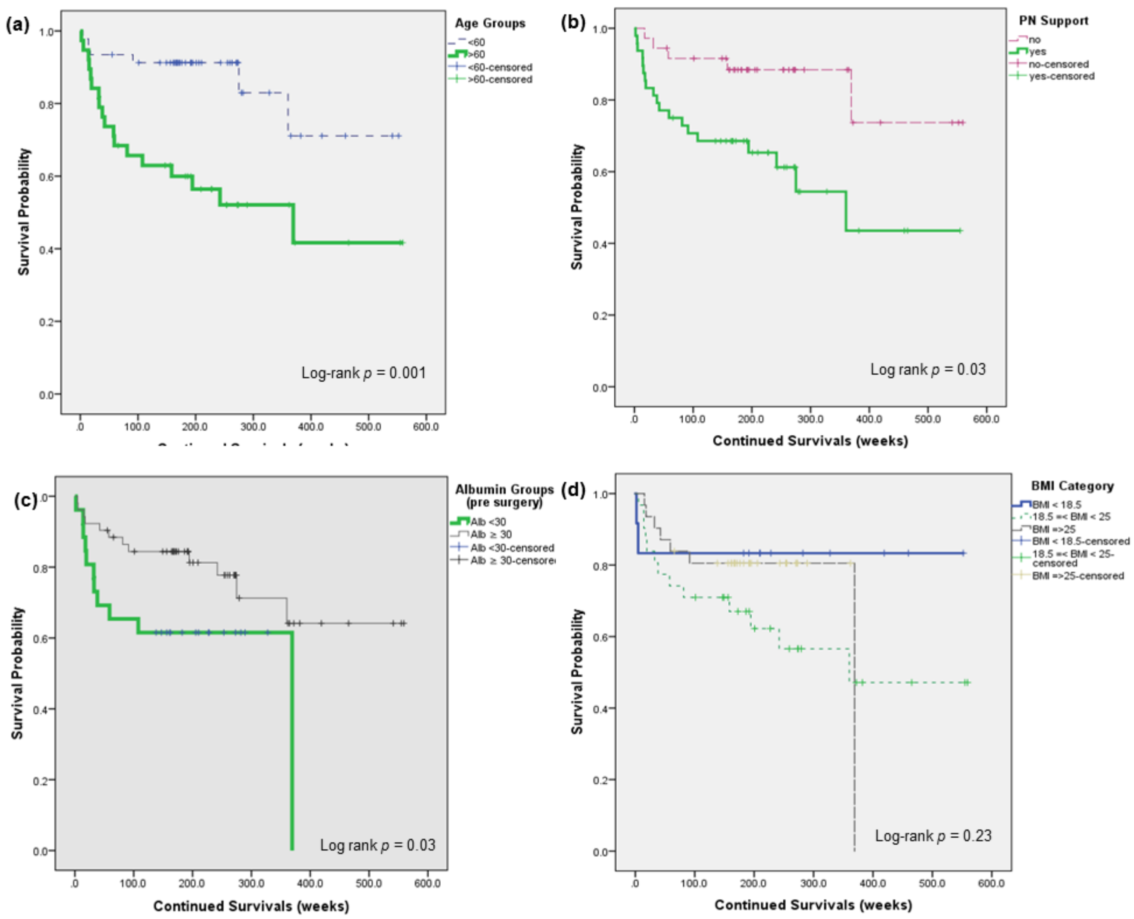
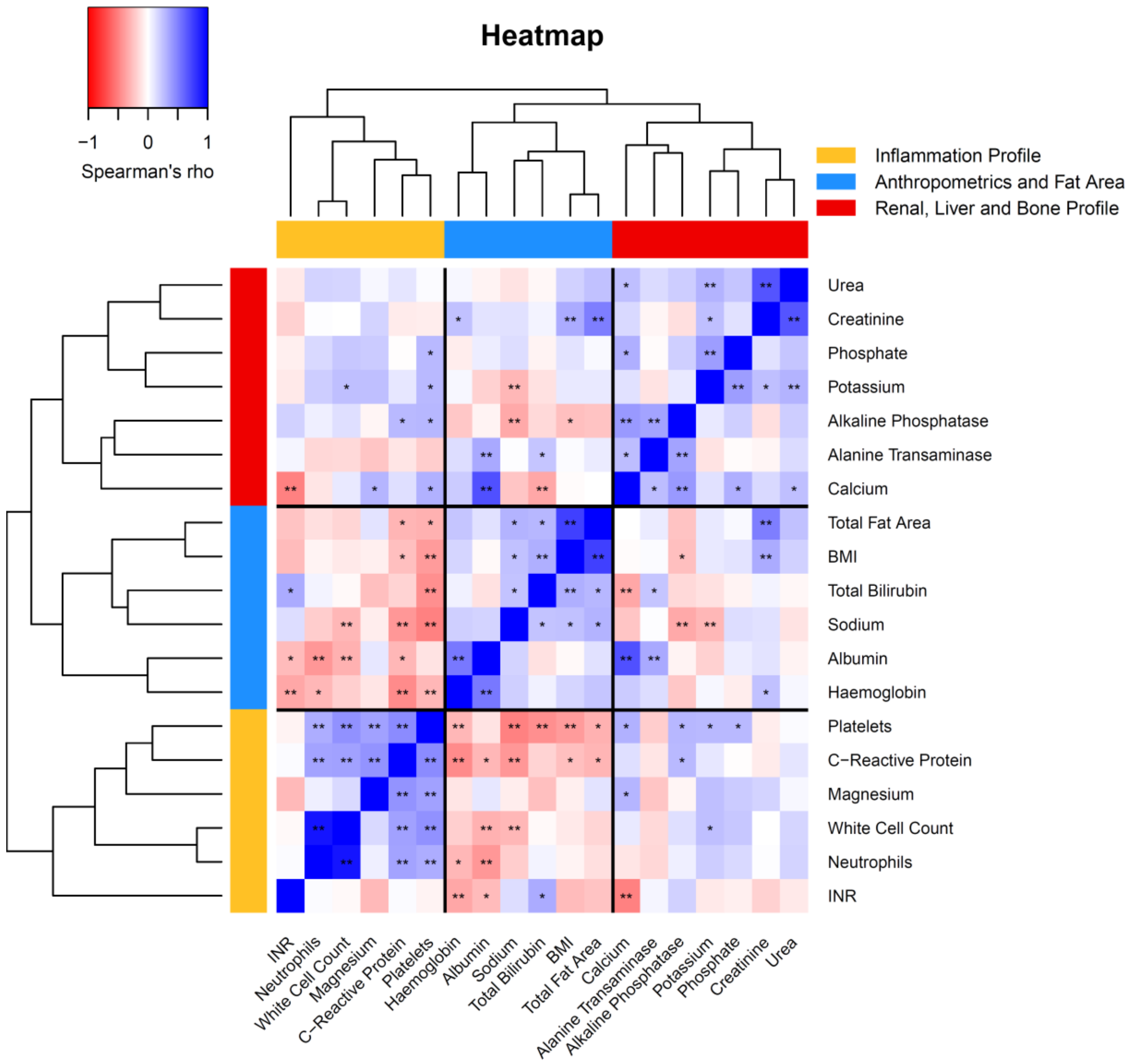


Figure 4. Spearman correlation heatmap based on TFA and biochemical parameters taken prior ECF surgery. Dendrogram is displayed at the top and left of the heatmap. Spearman correlation was mapped to a colour scale ranging from red to blue. ** p<0.01 * p<0.05



TABLES

Table 1. Patient Characteristics.

Patient characteristics	Males (n=34)	Females (n=51)	Total (n=85)
Age at surgery (years)[¶]	56.0 ± 15.5	57.5 ± 13.8	56.9 ± 14.5
Weight (kg)[*,¶]	72.0 ± 17.9	63.8 ±20.0	66.9 ± 19.5
Height (m)[*,¶]	1.74 ± 0.06 [c]	1.64 ± 0.08 [c]	1.68 ± 0.09
BMI (kg/m^2)[*,†]	22.8 [19.8 to 31.1]	22.9 [19.2 to 27.1]	22.8 [19.4 to 28.4]
BMI (kg/m^2) (n=75)[‡]			
Underweight (<18.5)	4 (12%)	8 (16%)	12 (14%)
Normal weight (18.5-24.9)	12 (35%)	20 (39%)	32 (38%)
Overweight and obese (≥ 25)	15 (44%)	16 (31%)	31 (36%)
Fistula classification[‡]			
Digestive system	51 (100%)	47 (92%)	81 (95%)
Urogenital system	0 (0%)	3 (6%)	3 (4%)
Others	0 (0%)	1 (2%)	1 (1%)
Surgery type[‡]			
ECF	22 (65%)	28 (55%)	50 (59%)
ECF and Abdominal wall	7 (21%)	11 (22%)	18 (21%)
ECF and Others	5 (14%)	12 (23%)	17 (20%)
Hospital length of stay (days)[†]	37 [18 to 110]	55 [28 to 91]	53 [24 to 102]
Other Parameters			
Total Fat Area (cm^2) [*,¶]	433.4 ± 172.8 [a]	319.7 ± 164.6 [a]	361.3 ± 174.9
Visceral Fat (cm^2) [*,¶]	183.8 ± 99.2 [c]	99.0 ± 59.7 [c]	130.0 ± 86.1
Subcutaneous Fat (cm^2) [*,¶]	243.1 ± 105.7	219.6 ± 122.3	228.1 ± 116.0
Albumin (g/L) [*,¶]	34 ± 9	31 ± 7	32 ± 8
Creatinine (mg/dL) [*,¶]	92 ± 34 [a]	69 ± 31 [a]	79 ± 34
Albumin (g/L)[*,‡]			
< 30	24 (71%)	18 (35%)	26 (31%)
≥ 30	8 (24%)	29 (57%)	53 (62%)
Use of artificial nutrition[‡]			
Yes	23 (68%)	39 (77%)	62 (73%)
No	11 (32%)	12 (23%)	23 (27%)
Use of parenteral nutrition[‡]			
Yes	18 (53%)	31 (61%)	49 (58%)
No	16 (47%)	20 (39%)	36 (42%)

Percentages were calculated from column totals. Differences between gender, significant at ^{a}p <0.05, ^{b}p < 0.01, and ^{c}p <0.001. [*]missing data, [¶] mean ± SD, [†] median [IQR], [‡] N(%).

Table 2. Univariate and multivariate Cox regression models assessing the effect of variables associated with overall survival.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Age (years)				
< 60	Reference		Reference	
≥ 60	4.15 (1.65-10.48)	<0.001	2.69 (1.03-7.01)	0.040
Gender				
Female	Reference		Reference	
Male	0.34 (0.13-0.92)	0.030	0.60 (0.21-1.74)	0.350
BMI (kg/m^2)				
< 18.5	Reference		---	---
18.5-24.9	2.74 (0.62-12.2)	0.190	---	---
≥ 25	1.51 (0.31-7.34)	0.610	---	---
Total Fat Area (cm^2)				
Low	Reference		---	---
High	0.35 (0.09-1.31)	0.120	---	---
Albumin (g/L)				
< 30	Reference		Reference	
≥ 30	0.42 (0.18-0.95)	0.040	0.52 (0.21-1.28)	0.160
Parenteral nutrition				
No	Reference		Reference	
Yes	3.51 (1.31-9.42)	<0.010	3.90 (1.27-11.96)	0.020