UNIVESIDADE FEDERAL DO RIO GRANDE DO SUL
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PROGRAMA DE PÓS-GRADUAÇÃO:
CIÊNCIAS EM GASTROENTEROLOGIA E HEPATOLOGIA

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EQUAÇÃO DE PREDIÇÃO DE PESO SECO E MORTALIDADE EM PACIENTES COM CIRROSE E ASCITE REFRATÁRIA SUBMETIDOS A PARACENTESE DE GRANDE VOLUME: ASSOCIAÇÃO COM INGESTÃO DE SÓDIO E DESNUTRIÇÃO

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Esta Tese de Doutorado segue o formato proposto pelo Programa de Pós-graduação: Ciências em Gastroenterologia e Hepatologia da Universidade Federal do Rio Grande do Sul, apresentada na forma de revisão de literatura, seguido dos dois manuscritos confeccionados sobre o tema da tese, constituindo-se dos seguintes elementos textuais:

1. Revisão da literatura
2. Justificativa
3. Questões de pesquisa e Hipóteses
4. Objetivos
5. Artigos:

Artigo 1: Predicting dry weight in patients with cirrhotic ascites undergoing large-volume paracentesis.

Artigo 2: Nutritional and dietary sodium assessment, ascites formation, and mortality in patients with decompensated cirrhosis submitted to large-volume paracentesis.

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RESUMO

A ascite, definida como o acúmulo patológico de líquido livre na cavidade peritoneal, indica o desenvolvimento de descompensação hepática na cirrose, e está associada à desnutrição e mortalidade. Sua presença prejudica o correto diagnóstico e conduta nutricional, pois comumente o peso, medida necessária para avaliação nutricional e cálculo das necessidades nutricionais, está superestimado. A restrição de sódio dietético é indicada no manejo da ascite, no entanto, ela pode levar a redução da ingestão alimentar e piora do estado nutricional do paciente. Sendo assim, este trabalho teve como objetivo desenvolver uma equação preditiva para estimar com mais confiabilidade e menos subjetividade o peso seco, definido como o peso corporal do paciente na ausência de ascite, e também avaliar o sódio dietético e sua relação com formação de ascite, desnutrição e mortalidade em pacientes com cirrose descompensada e ascite refratária.

Este estudo incluiu pacientes com cirrose descompensada submetidos à paracentese de grande volume. Os pacientes passaram por avaliação clínica e laboratorial, triagem de risco nutricional pela *Royal Free Hospital–Nutritional Prioritizing Tool (RFH-NPT), e* avaliação nutricional, que incluiu a *Royal Free Hospital-Global Assessment* (RFH-GA)*,* avaliação nutricional subjetiva global (ASG), ângulo de fase (PhA) pela impedância bioelétrica, e medidas antropométricas. Foram aferidos peso corporal, circunferência abdominal (antes e após a paracentese), altura, circunferência do braço (CB) e dobra cutânea tricipital para cálculo da circunferência muscular do braço (CMB).

Equações preditivas para peso seco foram desenvolvidas a partir de modelos de regressão linear, cujas variáveis preditoras foram altura, peso pré-paracentese,

circunferência abdominal ou circunferência do braço, e a variável resposta o peso pós-paracentese. A confiabilidade das equações preditivas foi avaliada pelo coeficiente de correlação intraclasse (CCI) e pelo erro quadrático médio (EQM) que foram comparados com os ajustes de peso atualmente utilizados, com os quais se reduz de 2,2 a 14 kg ou 5 a 15% do peso pré-paracentese de acordo com o grau de ascite.

A ingestão alimentar e a de sódio foram avaliados por registro alimentar de 3 dias e questionário de frequência alimentar de sódio (QFA-Só). Durante 6 meses os pacientes foram acompanhados por prontuário eletrônico, e o número de paracentese, volumes de ascite drenados e ocorrência de óbito foram verificados.

O estudo incluiu 19 pacientes, com mediana de idade de 64 (47 – 71) anos, 15 homens, 11 classificados como Child-Pugh C, 18 com alto risco nutricional, 18 com algum grau de desnutrição pela ASG e 9 pela RFH-GA. A diferença de peso pós-paracentese e peso pré-paracentese foi de -5,0 (-3,6 – -9,9) kg, correlacionado ao volume de ascite drenado.

Duas equações foram desenvolvidas para predizer o peso pós-paracentese. Os valores de CCI mostraram que ambas as equações de predição estavam fortemente correlacionadas (r > 0,94) com o peso pós-paracentese. Os modelos também demostraram menores EQMs (< 17,97), em comparação com os ajustes de peso atualmente utilizados (EQMs > 33,24), indicando uma previsão mais precisa.

A mediana de ingestão de sódio foi de 3,42 (2,22 – 6,05) g/d e de sal foi de 6,67 (3,70 – 11,1) g/d e não foram associadas a ingestão calórica. A ingestão de sódio menor que 2,5 g/d e de sal menor que 5 g/d foram associadas a menor formação de ascite (p < 0.035 para ambos). A formação de ascite correlacionou-se positivamente com sal (p = 0,048; r = 0,459) e negativamente com PhA (p = 0,033; r = -0,552). A mortalidade em 6 meses foi de 47% e foi associada à desnutrição por CB, CMB, RFH-

GA e PhA (p < 0,03 para todos). Nem a ingestão de sódio e nem a de sal foram associados à mortalidade, porém, a sobrevida dos pacientes com PhA menor que 4,0° e daqueles com menos de 10 dias de intervalo entre paracenteses foi menor (p < 0,03 para ambos).

Em conclusão, as equações preditivas desenvolvidas neste estudo demonstraram maior confiabilidade que os ajustes de peso atualmente utilizados, e poderão ser melhores opções para estimativa de peso seco em pacientes com cirrose e ascite refratária. Sódio dietético maior que 2,5 g/d foi associado à formação de ascite, mas não à desnutrição e nem à mortalidade. Além disso, a maioria dos pacientes apresentou um consumo elevado de sódio, bem como de sal. Sendo assim, orientar escolhas alimentares mais saudáveis e uma dieta livre de alimentos processados que contém alto teor de sódio, substituindo-os por alimentos *in natura* ou minimamente processados parece ser melhor que as dietas muito restritivas em sódio e livres de sal.

Palavras-chave: cirrose hepática; ascite; peso corporal; cloreto de sódio na dieta; avaliação nutricional, desnutrição.

ABSTRACT

Ascites, defined as the pathological accumulation of fluid within the peritoneal cavity, indicates the development of liver decompensation in cirrhosis and is associated with malnutrition and mortality. Its presence impairs the correct diagnosis and nutritional management, as the body weight, an important measure for nutritional assessment and calculation of nutritional needs, is overestimated. Dietary sodium restriction is indicated in the management of ascites, however, it can lead to reduced food intake and worsening nutritional status. Therefore, this study aimed to develop a predictive equation to estimate with more reliability and less subjectivity the dry weight, defined as the patient's body weight in the absence of ascites, and to evaluate dietary sodium and its relationship with ascites formation, malnutrition, and mortality in patients with decompensated cirrhosis and refractory ascites.

This study included patients with decompensated cirrhosis undergoing large-volume paracentesis. Patients underwent nutritional risk screening by the Royal Free Hospital–Nutritional Prioritizing Tool, and nutritional assessment, which included the Royal Free Hospital-Global Assessment (RFH-GA), subjective global nutritional assessment (ASG), phase angle (PhA) by bioelectrical impedance, and anthropometric measurements, which included height, body weight, waist circumference (both measured before and after paracentesis), mid-upper arm circumference (MUAC) and triceps skinfold thickness to calculate mid-arm muscle circumference (MAMC).

Predictive equations for dry weight were developed by linear regression models, whose predictor variables were height, pre-paracentesis weight, abdominal circumference, or arm circumference, and the response variable was post-

paracentesis weight. The reliability of the predictive equations was evaluated by the intraclass correlation coefficient (CCI) and by the mean square error (MSE) that were compared with the weight adjustments currently used when the weight is reduced from 2.2 to 14 kg or 5 to 15% of pre-paracentesis weight according to the degree of ascites.

Food and sodium intake was evaluated by a 3-day food record and a sodium food frequency questionnaire (FFQ-Na). During 6 months, patients were followed up using electronic medical records, and the number of paracentesis, volumes of ascites drained, and the occurrence of death was verified.

The study included 19 patients, with a median age of 64 (47 – 71) years, 15 men, 11 classified as Child-Pugh C, 18 at high nutritional risk, 18 with some degree of malnutrition by SGA, and 9 by RFH-GA. The difference in post-paracentesis weight and pre-paracentesis weight was -5.0 (-3.6 – -9.9) kg, correlated with the volume of drained ascites.

Two equations were developed to predict post-paracentesis weight. The ICC values showed that both prediction equations were strongly correlated ($r > 0.94$) with post-paracentesis weight. The models also showed lower MSEs (< 17.97) compared to currently used weight adjustments (NDEs > 33.24), indicating a more accurate prediction.

Median sodium intake was 3.42 (2.22 – 6.05) g/d and median salt intake was 6.67 (3.70 – 11.1) g/d and both were not associated with caloric intake. Sodium intake less than 2.5 g/d and salt intake less than 5 g/d were associated with less ascites formation ($p < 0.035$ for both). Ascites formation correlated positively with salt ($p = 0.048$; $r = 0.459$) and negatively with PhA ($p = 0.033$; $r = -0.552$). The six-month mortality rate was 47% and it was associated with malnutrition from CB, CMB, RFH-GA, and PhA ($p < 0.03$ for all). Neither sodium nor salt intake was associated with

mortality, however, the survival of patients with a PhA lower than 4.0° and those with less than 10 days of interval between paracentesis was lower ($p < 0.03$ for both).

In conclution, the predictive equations developed in this study demonstrated greater reliability than the currently used weight adjustments and may be better options for estimating dry weight in patients with cirrhosis and refractory ascites. Dietary sodium greater than 2.5 g/d was associated with ascites formation, but not with malnutrition or mortality. In addition, most patients had a high consumption of sodium as well as salt. Therefore, guiding healthier food choices and a diet free of processed foods that contain high sodium content, replacing them with natural or minimally processed foods seems to be better than very restricted sodium and salt-free diets.

Keywords: liver cirrhosis; ascites; body weight; dietary sodium, nutritional assessment, malnutrition.

LISTA DE ABREVIATURAS

3dFR – *3-day Food Record*

AASLD – *American Association for the Study of Liver Diseases*

AC – *Abdominal circumference*

BIA – *Bioelectrical impedance analysis*

BMI – *Body mass index*

CAAE – Certificado de Apresentação para Apreciação Ética

CB – Circunferência do braço

CMB – Circunferência muscular do braço

CT – *Computed tomography*

EASL – *European Association for the Study of the Liver*

FFQ-Na – *Food Frequency Questionnaire for Sodium*

HCPA – Hospital de Clínicas de Porto Alegre

HCV – *Hepatitis C Virus*

ICC – *Intraclass Correlation Coefficient*

INR – *International Normalized Ratio*

MAMC – Mid-arm muscle circumference

MAFLD – *Metabolic associated fatty liver disease*

MELD-Na – *Model for End-Stage Liver Disease-Sodium*

MSE – *Mean squared error*

MUAC – *Mid-upper arm circumference*

NAFLD – *Non-alcoholic Fatty Liver Disease*

PBE – Peritonite bacteriana espontânea (PBE)

PhA – *Phase angle*

R – *Resistance*

RFH-GA – *Royal Free Hospital-Global Assessment*

RFH-NPT – *Royal Free Hospital–Nutritional Prioritizing Tool*

SGA – *Subjective Global Assessment*

TSF – *Triceps skinfold thickness*

Xc – *Reactance*

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1. INTRODUÇÃO

A cirrose é uma das principais causas de mortalidade, responsável por mais de 1 milhão de mortes ao ano no mundo (1). É caracterizada pela formação de septos e nódulos fibrosos, colapso das estruturas hepáticas e distorção do parênquima e da arquitetura vascular hepática em consequência da inflamação hepática crônica, sendo o estágio final comum a diversas patologias do fígado, independente da etiologia, como etilismo, hepatites virais, autoimunes e de origem metabólica, biliar e vascular (1–3).

A presença de complicações da hipertensão portal e da insuficiência hepática, como ascite, encefalopatia hepática, hemorragia digestiva alta, icterícia e infecções, marcam o curso da doença à cirrose descompensada (4–6). Dentre essas complicações, a ascite é uma das mais frequentes e tem sido associada ao aumento da morbimortalidade nos pacientes com doença hepática crônica (7).

As causas da ascite são multifatoriais e envolvem principalmente o mecanismo patogênico de hipertensão portal e disfunção hepatocelular. O aumento da resistência intra-hepática contribui para o aumento da pressão venosa portal que leva a disfunção endotelial na circulação esplâncnica e sistêmica. Isso causa hipovolemia central e hipotensão arterial, com posterior ativação de sistemas vasoconstritores, como renina-angiotensina-aldosterona. Assim, ocasiona o aumento renal de reabsorção de sódio, contribuindo para a retenção de fluidos e sódio, com consequente desenvolvimento da ascite e/ou edema (8,9).

O manejo desses pacientes com ascite requer uma abordagem gradual, iniciando com restrição dietética de sódio e terapia diurética (10,11). Porém, a restrição de sódio ainda é controversa, pois a restrição excessiva de cloreto de sódio

(sal) pode contribuir para menor ingestão alimentar e, consequentemente, piora do estado nutricional (12).

A sobrecarga hídrica, em função da ascite e do edema, pode prejudicar o diagnóstico e monitoramento nutricional, por superestimar o peso aferido, subdiagnosticando a desnutrição (13). Além disso, tais fatores podem comprometer a prescrição adequada das necessidades proteico-calóricas dos pacientes com cirrose, uma vez que as recomendações dietéticas de energia e proteína são baseadas considerando o peso seco obtido por meio de ajustes relacionados com o nível de gravidade de edema e ascite.

A partir destas considerações, avaliar o impacto do sódio dietético em pacientes com cirrose e ascite bem como estabelecer uma forma confiável de obtenção do peso seco desses pacientes é fundamental para auxiliar no delineamento de uma terapia nutricional específica e no adequado diagnóstico nutricional. O presente estudo teve como objetivo desenvolver uma equação preditiva para estimar peso seco e avaliar o sódio dietético e sua relação com formação de ascite, desnutrição e mortalidade em pacientes com cirrose descompensada e ascite refratária.

2. REVISÃO BIBLIOGRÁFICA

2.1. Cirrose

A cirrose representa a fase final e irreversível da doença hepática crônica, resultante de diferentes mecanismos de lesão hepática, que causam morte celular dos hepatócitos, e, que levam a inflamação e fibrogênese (14,15). Apesar das diferentes etiologias, histologicamente, a cirrose é caracterizada pela regeneração nodular difusa cercada de septos fibrosos densos com subsequente extinção parenquimatosa e colapso de estruturas hepáticas, que leva a distorção pronunciada da arquitetura vascular hepática (1,2,14). Esse processo de cicatrização anormal é estimulado por citocinas inflamatórias e espécies reativas de oxigênio (16). A cirrose representa o desfecho de décadas de doença hepática crônica, e, à medida que progride, a distorção vascular resulta em congestão hepática, fluxo venoso deficiente e aumento da pressão portal (16,17).

Clinicamente, a cirrose cursa da sua forma compensada para descompensada, de acordo com a presença de complicações da hipertensão portal e insuficiência hepática. Na fase compensada, os pacientes são frequentemente assintomáticos e podem se manter estáveis durante anos. Já a fase descompensada é marcada pelo aparecimento de complicações como ascite, hemorragia digestiva alta, encefalopatia hepática, icterícia e infecções como peritonite bacteriana espontânea (PBE) (18–20). A taxa de descompensação da cirrose é de 5% ao ano, e, em consequência dessas complicações, ela é um marco no prognóstico do paciente, cuja sobrevida reduz de uma média de 12 anos, na fase compensada, para 2 anos (16,21,22).

Em relação as etiologias da cirrose, historicamente, as hepatites virais são as principais etiologias, embora as estratégias de vacinação da hepatite B e de tratamento da hepatite C já contribuam na redução dessas prevalências (23,24). Em

contrapartida, atualmente observa-se o aumento dos casos de doença hepática gordurosa não alcoólica (NAFLD) também, mais recentemente identificada como doença hepática gordurosa associada à disfunção metabólica (MAFLD) (25), que já tem se tornado a doença hepática crônica mais comum, com uma prevalência de 25% da população adulta (26,27). A Figura 1 apresenta o espectro da NAFLD, nítido reflexo da epidemia global de obesidade e diabetes mellitus tipo 2, afetando o fígado (27,28).

Não menos importante, a doença hepática alcoólica (ALD) também continua sendo uma das principais causas de cirrose, e é comum coexistir com outra etiologia de cirrose, o que pode exacerbar ainda mais a disfunção hepatocelular (29). As causas de cirrose mais frequentes variam nas diferentes regiões do mundo. Enquanto na China e em países asiáticos, a hepatite B continua sendo a principal causa de cirrose, no Ocidente e em países industrializados, NAFLD e ALD ultrapassaram as hepatites virais como principais causas de cirrose (29,30). O estudo de coorte de Fleming et al., projetando a incidência da cirrose, demonstrou que para 2040, no Canadá, é esperado que 90% dos novos diagnósticos de cirrose serão por NAFLD e ALD (31). Outras etiologias comuns de cirrose são: hemocromatose, deficiência de alfa-1 antitripsina, hepatite autoimune, colangite biliar primária e colangite esclerosante primária (1).

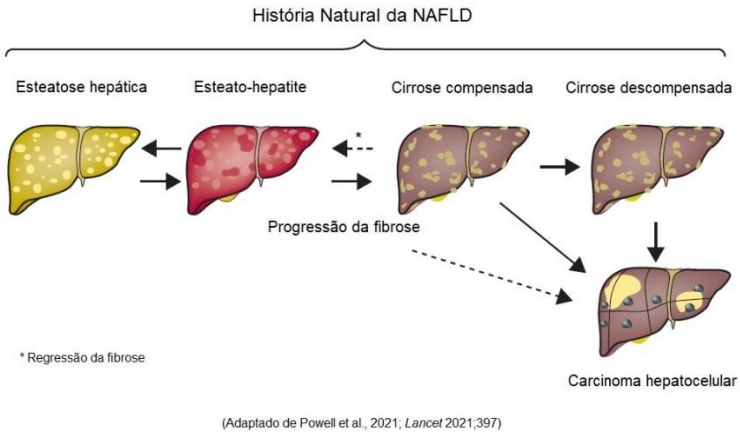

Figura 1. História natural da Doença Hepática Gordurosa Não Alcoólica

A cirrose é uma das principais causas de morbimortalidade no mundo, sendo a 11ª causa de morte, responsável por 2,2% dos óbitos, e, a 15ª entre as principais causa de morbidade (29). É descrito que mais de 1 milhão de mortes ao redor do mundo são causadas devido à cirrose (1,29), e este número vem aumentando consideravelmente (24). Apesar de ser um grave problema de saúde pública global, em muitas regiões os dados de morbimortalidade por cirrose são pouco disponíveis (24). Além disso, acredita-se que a prevalência verdadeira de cirrose seja muito mais alta que as descritas, já que é muito comum a fase compensada da doença ser assintomática, colaborando para o subdiagnóstico (14,24). No Brasil, 853 mil internações hospitalares foram atribuídas à doença hepática nos anos de 2001 a 2010, correspondendo a 0,72% de todas as admissões (32).

Como forma de classificar a gravidade da disfunção hepática e avaliar o prognóstico dos pacientes com cirrose são utilizados os escores de Child-Pugh e o *Model for end-stage liver disease* (MELD) (33–35). O escore de Child-Pugh classifica os pacientes de acordo com os níveis séricos de bilirrubina e albumina, a presença de ascite e distúrbio neurológico e o tempo de protrombina, enquanto que o escore MELD utiliza na sua predição, apenas os níveis de bilirrubina, de creatinina e o tempo de protrombina. Posteriormente, foi proposta a inclusão dos níveis de sódio sérico ao escore MELD, melhorando seu desempenho, por predizer com mais acurácia a sobrevivência dos pacientes (36). O escore MELD é amplamente utilizado como critério de alocação dos pacientes em lista de transplante hepático, como forma de priorizar os pacientes mais graves (37).

2.2. Ascite na Cirrose

A ascite é definida como o acúmulo fisiopatológico de fluido no espaço peritoneal da cavidade abdominal (9). Aproximadamente, 80% dos casos de ascite são devido a cirrose (38), sendo considerada uma das complicações mais frequentes em paciente com cirrose, já indicando o desenvolvimento de descompensação hepática(5,7).

A formação de ascite está associada a um pior prognóstico, com o aumento da morbimortalidade (7). Dados apontam que 50-70% dos indivíduos com diagnóstico recente de cirrose desenvolvem ascite dentro de 10 anos e aproximadamente 20% dos pacientes com cirrose já apresentam ascite no diagnóstico (38,39). A expectativa de vida é de aproximadamente 2 anos para 50% dos pacientes com doença hepática crônica e de 6 meses para aqueles com excreção urinária de sódio inferior a 10 mEq/L (39). As taxas de mortalidade variam de 15-20% em 1 ano a aproximadamente 50-60% em 5 anos desde o primeiro sintoma (22,40). A redução da taxa de sobrevida desses pacientes se deve em parte pela propensão a complicações adicionais, como infecções bacterianas, distúrbios eletrolíticos, síndrome hepatorrenal, desequilíbrios nutricionais e consequente declínio clínico (41). Além da redução da taxa de sobrevida, é importante ressaltar que a ascite reduz significativamente a qualidade de vida dos pacientes (42).

As causas da ascite são multifatoriais, mas envolvem principalmente o mecanismo patogênico de hipertensão portal. O aumento da resistência intra-hepática contribui para hipertensão portal ocasionando disfunção endotelial na circulação esplâncnica, bem como anormalidades renais que favorecem a retenção de sódio e água, com consequente formação da ascite e edema (8,9,43). Acima do limiar da hipertensão portal clinicamente significativa (≥10mmHg), varizes esofágicas e sinais

evidentes de descompensação hepática, incluindo ascite, sangramento, encefalopatia e icterícia podem ocorrer (43). A partir da análise do fluido ascítico pode-se confirmar a hipertensão portal como etiologia da cirrose. O gradiente de albumina soro-ascite deve ser superior a 1,1 g/dL, ademais quando a proteína total for inferior a 2,5 g/dL exclui-se também a etiologia cardíaca (41,44).

De acordo com a *American Association for the Study of Liver Disease* (AASLD), a ascite pode ser classificada de acordo com a quantidade de fluido acumulado na cavidade abdominal e a resposta ao tratamento conforme a Tabela 1 (41). A partir da classificação da ascite, pode-se definir a melhor terapêutica.

Tabela 1. Classificação da Ascite

De acordo com a quantidade de fluido acumulado		De acordo com a resposta ao tratamento	
Grau 1. Leve	Somente detectado por ultrassom	Responsiva	Pode ser completamente mobilizada ou limitada ao grau 1 com terapia diurética associada ou não a restrição moderada de sódio
Grau 2. Moderada	Moderada e simétrica distensão do abdome	Recorrente	Recorre em ao menos 3 ocasiões em 12 meses apesar da restrição de sódio e adequada terapia diurética
Grau 3. Grande	Marcada distensão do abdome	Refratária	Não pode ser mobilizada ou a recorrência precoce não pode ser satisfatoriamente prevenida pela terapia médica.

[adaptado de Biggins et al., *Hepatology* 2021;74(2)]

A menos que o paciente seja candidato a *shunt* portossistêmico intra-hepático transjugular ou transplante hepático, o tratamento para ascite refratária consiste em

paracenteses de grande volume (com infusão de albumina se o fluido drenado for maior que 5 litros), uso contínuo de diuréticos e restrição de sódio da dieta (e restrição hídrica se hiponatremia). Paracentese é o procedimento de drenagem do fluido ascítico da cavidade peritoneal através de punção abdominal com agulha, e é realizado para reduzir a pressão intra-abdominal e aliviar os sintomas da ascite, como a distensão abdominal severa, dor e dispneia (45,46). Considerando que a ascite refratária é aquela que não pode ser mobilizada ou recorre após a paracentese de grande volume apesar da restrição de sódio da dieta e da terapia diurética, ela pode ser também definida como resistente a diuréticos, quando persiste apesar das doses máximas de diuréticos, e intratável a diuréticos, quando os efeitos colaterais dos diuréticos impedem o uso de doses máximas (41).

2.3. Restrição de Sódio na Ascite

Pacientes com cirrose descompensada e ascite apresentam excesso de sódio corporal total, sendo assim, a redução de sódio da dieta, incluindo restrição de sal, pode ajudar no balanço negativo de sódio (42,47). Atualmente, a maioria das diretrizes orientam a restrição moderada de sódio da dieta. A quantidade recomendada geralmente varia entre 1,8 a 2,8 gramas ao dia de sódio, que corresponde ao uso de 4,6 a 7,0 gramas ao dia de sal (21,36,48–50). E, ainda, para pacientes com ascite refratária encontra-se recomendações de dieta mais restritiva em sódio, constituída de menos de 2 gramas de sódio ao dia (41,51). No entanto, dietas muito restritas em sódio e até mesmo isentas de cloreto de sódio (sal) também têm sido contraindicadas, pois podem induzir à redução da ingestão alimentar pela piora da palatabilidade dos alimentos, favorecendo a desnutrição, e também contribuir para a hiponatremia e complicações da doença hepática crônica (21,52,53).

A revisão sistemática de Baki et al (54). que incluiu ensaios clínicos randomizados de intervenções nutricionais para ascite demonstrou que até o momento as conclusões sobre a restrição de sódio são contraditórias e que estratégias nutricionais específicas neste contexto ainda são limitadas pela heterogeneidade dos estudos. Dos poucos estudos que avaliaram o efeito da restrição de sódio, a maioria mostra um efeito positivo na redução da ascite, no entanto, a relevância clínica desta conduta ainda é discutida (12,55). Sendo assim, ainda há muito questionamento sobre o quão restritiva em sódio pode ser a dieta desses pacientes, com vistas a reduzir a ascite, melhorar o estado nutricional e aumentar a sobrevida.

2.4. Desnutrição na Cirrose

Conforme a *European Association for the Study of the Liver* (EASL), a desnutrição é definida como a desordem relacionada à nutrição resultante da falta de ingestão ou absorção de nutrientes que leva à alteração da composição corporal (diminuição da massa livre de gordura) e da massa celular corporal. Essa condição leva à diminuição da função física e mental e ao resultado clínico prejudicado da doença (48).

Na cirrose a desnutrição é uma complicação bastante prevalente, que se agrava conforme a severidade da doença. Estima-se que a desnutrição afeta mais de 80% dos pacientes com cirrose descompensada, sendo a complicação mais comum dentre as reconhecidas disfunções relacionadas a cirrose, como encefalopatia, ascite refratária, sangramento de varizes esofágicas, entre outros (56–58). Os dados de prevalência de desnutrição na cirrose variam substancialmente, devido a diferentes

ferramentas, metodologias e valores de referências utilizados na avalição nutricional (58,59).

A etiologia da desnutrição na cirrose é complexa e multifatorial. Diminuição da ingestão alimentar, má absorção, metabolismo alterado de nutrientes, hipermetabolismo, distúrbios hormonais, inflamação e alteração da microbiota intestinal são aspectos da cirrose que contribuem para a desnutrição (60). Além disso, a presença de ascite pode agravar ainda mais a desnutrição, por dificultar a ingestão alimentar, já que leva à saciedade precoce e à dispneia em decorrência dos efeitos da pressão intra-abdominal secundária ao fluido peritoneal (60).

A desnutrição é bastante preocupante, pois além de aumentar a incidência e gravidade das complicações decorrentes da descompensação da cirrose, reduz massa muscular, piora estado funcional, reduz a qualidade de vida, compromete a função imune, o que pode aumentar risco de infecções e dificultando a cicatrização (56). O comprometimento do estado nutricional é considerado um importante preditor de morbimortalidade e inclusive pode implicar na seleção de pacientes ao transplante hepático, já que a desnutrição se correlaciona com mais complicações pós-operatórias (58,61). Ademais, já é bem descrito que a sarcopenia e a fragilidade, disfunções relacionadas à desnutrição, são comuns na cirrose e também impactam negativamente o curso da doença, pioram o prognóstico e estão associados a maior mortalidade (62–66). Sendo assim, é de fundamental importância avaliar o estado nutricional e iniciar as devidas intervenções precocemente para minimizar a descompensação hepática e o óbito.

2.5. Triagem e Avaliação Nutricional na Cirrose

Considerando a alta prevalência de desnutrição na cirrose e o seu impacto na sobrevida, idealmente esses pacientes devem passar pela triagem nutricional, que determina o risco de desnutrição. Assim, aqueles pacientes em risco, devem ser priorizados à completa avaliação nutricional (67,68). Entende-se que a triagem nutricional deva ser realizada através de ferramenta simples, que possa ser aplicada por qualquer profissional não treinado e até mesmo pelo próprio paciente, e que tenha uma aceitável sensibilidade e especificidade (68). Sendo assim, ferramentas validadas para pacientes com cirrose, como a *Royal Free Hospital – Nutritional Prioritizing Tool* (RFH-NPT) (69) são indicadas. O uso da RFH-NPT (anexo 1) tem sido recomendado pelas principais diretrizes clínicas de nutrição na doença hepática (48,66,70). Essa ferramenta contempla a presença de hepatite alcoólica aguda, uso de nutrição enteral, sobrecarga hídrica, redução da ingestão alimentar e perda de peso.

Todos os pacientes em risco nutricional devem passar por uma avaliação nutricional detalhada, fundamental para realização do diagnóstico nutricional e para determinação da conduta dietética mais assertiva (58). A avaliação nutricional apresenta como objetivo identificar os distúrbios nutricionais para possibilitar uma intervenção nutricional adequada de forma a auxiliar na recuperação e manutenção do estado de saúde do paciente (71).

Na prática clínica, a avaliação nutricional deve envolver um processo sistemático de obtenção e interpretação de informações clínicas, incluindo anamnese nutricional, história clínica, exames físico e laboratorial dos pacientes, a fim de também investigar sinais de deficiências nutricionais (72,73).

A avaliação nutricional objetiva é baseada em parâmetros antropométricos, como peso, altura, índice de massa corporal (IMC), dobras cutâneas, circunferência do braço, circunferência muscular do braço (CMB), circunferência da cintura, entre outros. Métodos de avaliação funcional também podem integrar a avaliação nutricional, como força do aperto de mão e espessura do músculo adutor do polegar (57,74). Sobretudo na cirrose, tem-se preconizado pela avaliação da massa muscular para rastreio de sarcopenia e fragilidade (66). Na ausência de métodos de imagem, que são padrão-ouro para avaliação de composição corporal, a CMB, medida derivada da circunferência do braço e da dobra cutânea tricipital, parece ser uma boa alternativa, por apresentar valor prognóstico em estudos nessa população (48).

A avaliação nutricional de pacientes com cirrose ainda é um desafio até mesmo para profissionais treinados, devido às diversas complicações, incluindo a presença de edema e ascite que interferem e prejudicam a confiabilidade dos métodos antropométricos, por superestimar o peso e as circunferências da cintura, da panturrilha e com menos intensidade, do braço. Assim, o uso de diferentes ferramentas, incluindo métodos não antropométricos, é recomendado como forma de avaliação nutricional até que se valide um padrão ouro de diagnóstico nutricional nessa população (67).

Atualmente, uma ferramenta validada para avaliação nutricional nessa população é a *Royal Free Hospital – Global Assessment* (RFH-GA), que determina o estado nutricional com base no IMC, CMB e ingestão alimentar (anexo 2) (75). No entanto, a RFH-GA apresenta algumas limitações, uma vez que requer o peso corporal sem sobrecarga hídrica (peso seco) para cálculo do IMC e além disso não estabelece de forma objetiva como classificar a ingestão alimentar.

Muito tem se tratado a respeito do ângulo de fase (AF) como um promissor marcador de estado nutricional na doença hepática (76–78). O AF é o arco-tangente da reactância/resistência obtido através da bioimpedância elétrica, que é uma corrente elétrica imperceptível, de baixa amplitude e alta frequência capaz de gerar resistência e reactância aos tecidos não condutores de energia. Assim, o AF é uma conhecida medida que reflete a vitalidade e integridade celular (67). Além de estar associado ao estado nutricional, os estudos apontam o papel prognóstico do AF, que também demonstra ser um preditor independente de mortalidade em paciente com cirrose (76,77,79) .

Ainda neste cenário, é clinicamente relevante ter uma estimativa previsível do peso seco, ou seja, do peso corporal na ausência de ascite, de pacientes com retenção hídrica, inclusive para se calcular as necessidades nutricionais dos pacientes. Existem algumas recomendações de ajustes de peso (Tabela 2 e Tabela 3) que costumam ser bastante utilizadas como referência na estimativa de peso seco dos pacientes com edema e ascite (80,81). No entanto há pouca evidência científica que baseie esses valores de descontos de peso para estabelecer o peso seco. Essas tabelas não são atuais e não se tem certeza de como elas foram desenvolvidas. Já existem algumas equações para predição de peso, no entanto, não são validadas para pacientes com cirrose, e, utilizam medidas antropométricas que normalmente sofrem influência de edema e ascite (82,83).

Tabela 2. Guia de desconto de peso conforme grau de ascite (68,80,81).

Grau de ascite	Desconto de peso (kg)	Desconto de peso (%)
Leve	-2,2	-5%
Moderada	-6,0	-10%
Severa	-14,0	-15%

Adaptado de Mendenhall, 1992 e Tandon et al., 2017

Tabela 3. Guia de desconto de peso conforme grau de edema(80,81).

Grau de edema	Desconto de peso (kg)
Leve	-1,0
Moderado	-5,0
Severo	-10,0

Adaptado de Mendenhall, 1992 e James, 1989.

Até o presente momento, observa-se pouca disponibilidade de estudos clínicos que buscaram avaliar e estimar peso seco de pacientes com cirrose a ascite. As tentativas de estimar o peso seco dos pacientes com cirrose variam entre estudos. Ney et al., consideraram como peso seco de pacientes cirróticos candidatos a transplante hepático, aquele obtido após a paracentese. Quando isso não fosse possível, o peso do paciente foi corrigido, pela subtração de 5% do peso na presença de ascite leve, 10% ascite moderada e 15% ascite grave a fim de estimar o peso seco (84). Esta correção do peso foi criada por um consenso de profissionais (68) e é uma estimativa subjetiva, o que pode comprometer o delineamento de uma terapia nutricional adequada, que possa retardar futuras deficiências nutricionais advindas da história natural da doença.

Já no estudo de McHugh et al.,(85) os pesquisadores desenvolveram uma fórmula por regressão linear multivariada para estimar o peso seco de pacientes com cirrose candidatos a transplante hepático, baseada nas medidas de gordura linear e

volumétrica, obtidas por tomografia computadorizada abdominal, peso e altura no pré-transplante e do líquido ascítico drenado no transplante. No entanto, este método apresenta limitações importantes para a utilização na prática clínica, uma vez que nem todos os pacientes têm indicação para realizar tomografia computadorizada, além de ser um procedimento caro. Em outro estudo, que teve como objetivo avaliar o impacto da obesidade pré-transplante na mortalidade, o cálculo do peso seco foi realizado com o peso medido antes do transplante, subtraído do líquido ascítico drenado durante o transplante, considerando 1L igual a 1 kg (86).

3. JUSTIFICATIVA

Apesar do peso corporal ser um parâmetro importante para o diagnóstico e conduta nutricional, sabe-se que a obtenção dessa medida em pacientes com ascite não apresenta boa acurácia. Além disso, sabe-se que existe relação entre a ingestão excessiva de sódio dietético com a formação de ascite, o que estimula a manutenção de estratégias nutricionais para redução da ingestão de sódio pelos pacientes com doença hepática crônica. Considerando essas informações, torna-se necessário estabelecer uma estimativa segura de predição de peso seco, verificando a adequação dos valores sugeridos na literatura de descontos de peso corporal, e avaliar a relação da ingestão de sódio com desnutrição e mortalidade em pacientes com cirrose e ascite.

4. QUESTÕES DE PESQUISA E HIPÓTESES:

1) A equação preditiva para estimativa de peso seco utilizando volume drenado na paracentese apresenta confiabilidade superior às propostas utilizadas na prática clínica?

H0: A equação preditiva para estimativa de peso seco utilizando volume drenado na paracentese não apresenta confiabilidade superior às propostas utilizadas na prática clínica.

H1: A equação preditiva para estimativa de peso seco utilizando volume drenado na paracentese apresenta confiabilidade superior às propostas utilizadas na prática clínica.

2) Maior consumo de sal está associado com formação de ascite, desnutrição e mortalidade?

H0: Maior consumo de sal não está associado com formação de ascite, desnutrição e mortalidade.

H1: Maior consumo de sal está associado com formação de ascite, desnutrição e mortalidade.

5. OBJETIVOS

5.1 Objetivo Geral:

Desenvolver uma equação preditiva com elevada confiabilidade para estimar peso seco, e, avaliar o sódio dietético para identificar a relação com a formação de ascite, desnutrição e mortalidade em pacientes com cirrose descompensada e ascite refratária.

5.2 Objetivos Específicos:

- Avaliar a confiabilidade dos métodos de ajustes de peso corporal atualmente utilizados na prática clínica em pacientes com cirrose descompensada.
- Acompanhar a frequência de paracenteses e os volumes de ascite drenados durante 6 meses, calculando a quantidade de formação de ascite diária.
- Avaliar a relação entre o sódio dietético com a ingestão calórica, formação de ascite, estado nutricional e mortalidade;

6. ARTIGOS ORIGINAIS EM INGLÊS

Título: Predicting dry weight in patients with cirrhotic ascites undergoing large-volume paracentesis.

Título: Nutritional and dietary sodium assessment, ascites formation, and mortality in patients with decompensated cirrhosis submitted to large-volume paracentesis.

TITLE: Predicting dry weight in patients with cirrhotic ascites undergoing large-volume paracentesis.

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ABSTRACT

Background & Aims: Ascites is the most common complication in patients with cirrhosis, associated with malnutrition and higher mortality. The presence of ascites impairs the nutritional assessment, by overestimating body weight and, consequently, underdiagnosing malnutrition. These factors, including the incorrect body weight measure, compromise the adequate establishment of the dietary needs. To adjust the weight in patients with ascites, dietetic guidances indicate substracting 2.2-14kg or 5-15% of the measured body weight according to the degree of ascites, however, there is a lack of evidence to substantiate these values. This study aims to explore the measure of body weight in patients who underwent paracentesis, for developing new predictions equations to estimate the dry weight, comparing them with the currently used weight adjustments in patients with refractory cirrhotic ascites.

Methods: Cross-sectional study, that included patients with decompensated cirrhosis undergoing large-volume paracentesis. Patients were submitted to nutritional risk screening, nutritional assessment, and anthropometric measurements that included body weight, abdominal circumference (both measured before and after paracentesis) height, and upper mid-arm circumference. The volume of ascitic fluid drained was also registered. For the predictions of dry weight, linear regression models were performed using as predictor variables: height, pre-paracentesis weight, pre-paracentesis abdominal circumference, or mid-upper arm circumference, and as response variable: post-paracentesis weight. The capacity of these models to predict

the post-paracentesis weight was evaluated comparing it with the currently used predictions through the intraclass correlation coefficient (ICC) and the mean square error (MSE).

Results: Nineteen patients were included, 15 male, and 18 with high nutritional risk and malnutrition. The difference of post-paracentesis weight and pre-paracentesis weight was -5.0 (-3.6 – -9.9) kg, similar to ascitic fluid volume drained. Two equations were developed to predict post-paracentesis weight. ICC values showed that both prediction equations were strongly correlated (r >0.94) with post-paracentesis weight. Our models also showed lower MSEs (<17.97), compared with the current predictions (MSEs <64.19, when the pre-paracentesis weight is adjusted from absolute values and MSEs <33.24 when adjusted from percentage values), indicating more accurate prediction.

Conclusion: The predictive equations from this study may be better options for dry weight estimation in patients with refractory cirrhotic ascites, since they showed higher reliability compared to the currently used weight adjustment. External validation in a larger sample is still needed to confirm the clinical applicability of these equations.

Keywords: ascites; liver cirrhosis; body weight; nutritional assessment; malnutrition.

Abbreviation: AC: abdominal circumference; MUAC: mid-upper arm circumference; ICC: intraclass correlation coefficient; MSE: mean squared error; CT: computed tomography

INTRODUCTION

Ascites is the most frequent complication in cirrhosis, indicating the decompensation of liver disease, when life prognosis is significantly reduced (1–4) This stage is also marked by malnutrition, estimated between 50% to 90% of these patients, and associated with disease aggravation, higher morbidity, and mortality (5,6).

Multiple factors and pathophysiological mechanisms can compromise the nutritional status of patients with decompensated cirrhosis (7,8). Nutritional assessment, especially in the presence of fluid overload (ascites and peripheral edema) can be quite difficult even for trained professionals (5,9). Patients with ascites often report that they are unable to eat properly due to discomfort, early satiety, and shortness of breath, caused by the intra-abdominal pressure secondary to the peritoneal fluid that compresses the gastrointestinal tract (5,10). Thus, they have a greater nutritional risk compared to those without ascites (9). Evaluating the nutritional status of these patients is extremely important for nutritional diagnosis, definition of the most accurate diet therapy approach, and monitoring.

The presence of ascites interferes with nutritional assessment by overestimating body weight and, consequently, underdiagnosing malnutrition (11,12). Other methods for nutritional assessment such as arm circumference or phase angle have already been proved to be adequate and not influenced by fluid accumulation (13,14). Even though in cirrhosis, the body weight, as well as its related parameters, such as body mass index (BMI) should be used with caution to assess nutritional status(15,16), the weight is still one of the most used and required measurements, either for estimating energy and protein recommendations or to establish doses of many drugs.

Due to the importance of this anthropometric measure, in clinical nutrition practice, the dry weight uses to be estimated based on post-paracentesis weight or

weight adjustments (9). That is, subtracting an amount (-2.2, -6.0, or -14.0 kg) (17) or a percentual (-5%, 10% or -15%) (10) of measured body weight according to the degree of ascites, in order to discount the weight related to the abdominal fluid retention. However, there is a lack of evidence to substantiate the reliability of these weight adjustments.

Thus, considering the importance of body weight for nutrition management, this study aims to explore the measure of body weight in patients who underwent paracentesis, in order to develop new predictions equations to estimate the dry weight, comparing them with the currently used weight adjustments in patients with cirrhosis and refractory ascites.

MATERIAL AND METHODS

This cross-sectional study included adult outpatients with decompensated cirrhosis (18) with refractory ascites undergoing large-volume paracentesis at the Outpatient Surgical Center of Hospital de Clínicas de Porto Alegre (HCPA), in Brazil from October 2018 to June 2020. Patients unable to measure weight, with anasarca, or who did not undergo large-volume paracentesis were not included. The Ethics and Research Committee at HCPA approved the protocol (CAAE 90618218.0.0000.5327), and patients were included only after reading, understanding, and signing an Informed Consent Form.

All evaluations were performed on the same day in the morning. Demographic data, including gender, ethnic origin, age, etiology, and duration of the liver disease since diagnosis, medication, and the frequency of paracentesis were obtained.

Nutritional risk screening and nutritional assessment

Nutritional risk screening and nutritional assessment were performed using the Royal Free Hospital-Nutritional Prioritizing Tool and the Subjective Global Nutritional Assessment respectively (9).

Classification of Ascites

As in clinical routine, for each patient, ascites were graded by a single gastroenterologist before paracentesis, according to the amount of fluid accumulated in the abdominal cavity and classified according to response of treatment (19).

Paracentesis procedure

Large-volume paracenteses were performed by a single gastroenterologist under point-of-care ultrasound with patients in supine position (20). The fluid was drained through a 14-gauge catheter into a 3-liter bottle that was emptied into dosage cups. During the paracentesis all patients were placed in lateral decubitus position to reduce the amount of residual ascitis. The volume of drained fluid was checked throughout paracentesis until the end of the procedure. All patients had 50ml of ascitic fluid sent to laboratory analysis. As recommended for all patients who removed >5L of ascites, albumin infusion was administrated at 6 – 8 grams per litter of ascites drained (21).

Anthropometric measurements

Height was verified with the patient barefoot, with his back to the stadiometer, heels together, in an upright position, looking straight ahead, and with arms extended along the body, using a stadiometer fixed on the wall. Weight was measured with the

patient barefoot and wearing light clothing through an electronic anthropometric scale (22).

Abdominal circumference (AC) was measured at the largest circumference, and the mid-upper arm circumference (MUAC) was measured at the midpoint between the acromion and the olecranon of the non-dominant arm with the forearm flexed at 45° (23). Both circumference measurements were performed with an inextensible measuring tape and the patient in an orthostatic position. The weight was measured immediately before paracentesis (pre-paracentesis weight) and right after the procedure (post-paracentesis weight). The AC was also measured before and after paracentesis.

Statistical analysis

The statistical analysis was performed using PASW Statistics for Windows, Version 18.0. Variables with a normal distribution were expressed as mean±SD, and asymmetrically distributed data were presented as median and interquartile range. For the development of the equations to predict dry weight, linear regression models were performed. The predictive and response variables of each model are demonstrated in Box 1. Post-paracentesis weight was considered the main response variable since we judge it to be the closest to the dry and real weight. The reliability of the prediction equations to estimate post-paracentesis weight was evaluated comparing them with the currently used weight adjustments (Box 2) through the intraclass correlation coefficient (ICC) to assess the agreement between the estimated weight and the post-paracentesis weight, and the mean squared error (MSE), which estimates the forecast error. Bland-Altman plots were also used to compare the agreement between the prediction equations.

RESULTS

The flow of patients with details is shown in Figure 1. Patients were previously invited to participate in the study whose data collection would be performed in the next paracentesis. Patients with no need to undergo another paracentesis could not participate in this study protocol.

The main causes of liver disease in these patients were alcoholic liver disease (37%) and hepatitis C vírus (37%). Most patients were male (79%), caucasian (65%), with a median age of 64 (47 – 71) years old. Most patients were Caucasian (65%). The main causes of liver disease in these patients were alcoholic liver disease (37%), hepatitis C virus (37%). Nine patients (47%) received oral diuretic therapy. The clinical and nutritional profiles of the decompensated cirrhosis patients are shown in Table 1. Table 2 shows the volume of ascitic fluid drained and the differences in weight and waist circumference after paracentesis.

The prediction equations and the parameters of reliability are presented in Box 3. Figure 2 presents the differences (errors) in relation to the post-paracentesis weight for the developed prediction equations and the usual weight adjustments for ascites, where a solid line marks the inexistence of error (difference = 0). Clearly, the performance of the equation 1 for estimating dry weight were better than the other parameters, followed by the equation 2. Both weight adjustments tended to underestimate the dry weight.

DISCUSSION

The present study explored the difference in body weight in patients with refractory cirrhotic ascites who underwent large-volume paracentesis. Through anthropometric assessments, we also developed prediction equations to estimate the

dry weight of these patients. In addition, we notice that the currently used weight adjustments seem not to be adequate for estimating dry weight in these patients.

Nowadays, the weight adjustments are based on the degree of ascites (24), which defines the number of kilograms that should be subtracted from the overestimated weight. However, these weight adjustments are not free of criticism. The weight adjustment by Mendenhall (17) was established in the 1980s, whose sample was American military from the Veterans Health Administration Cooperative Studies Program, who had alcoholic liver disease and were receiving nutritional therapy. Based on the calculated approximation of initial body weight and final body weight (weight gain) and considering the time between, the average contribution of ascites for each degree was established (Box 2). The other possibility of weight adjustment (25) in which a percentage of weight is subtracted according to the degree of ascites was established by consensus among professionals, and there is still no study that has indeed tested this option.

In our sample, we only included patients with grade 3 ascites, considered large or gross. However, even to the same degree, the volumes of ascites varied considerably. So, we judge that this degree classification of ascites may not be helpful for dry weight estimation. Even because this classification may be subjective and influenced by overall patient size and time with ascites, that can influence the muscle distension and tolerability of larger volumes of ascites.

There are few other equations for estimating body weight used for the elderly or patients with mobility restrictions (24,26,27), however, none of them seems to be appropriate for patients with cirrhosis. The equation developed by Chumlea et al. (28) includes the measurement of calf circumference. As it is known that commonly patients with decompensated cirrhosis present lower limb edema, this equation is probably not

accurate for these patients. Another equation is from Rabito et al. (26), which contains also the measure of abdominal circumference in predicting weight. However, the authors did not include patients with ascites in the study, so this equation is also potentially flawed for our patients. There is still a very simple equation to predict body weight that includes knee height and mid-upper arm circumference, however, this seems to overestimate body weight measure (27).

Furthermore, it would be more interesting and could estimate dry weight more accurately if we used more anthropometric data, considering that height can influence weight, waist circumference could be a good predictor of ascitic fluid volume, for instance. In fact, the idea of developing new estimates for dry weight has always been on the ease of applying the formulas in clinical practice. And, knowing that it is often not possible to weigh the patient at the bedside, we also developed a dry weight estimate without the need for this measure. We wanted to present different formulas so the health professionals, especially the nutrition therapy team, can choose the most viable one for their clinical practice.

The post-paracentesis weight was considered the dry weight in this study, even knowing that the presence of some remaining ascitic fluid is possible. However, the therapeutic paracenteses have drained as much fluid as possible, so, we believe that the volume of fluid remaining after was minimal. Some patients did present edema, mostly in the heel, but we decided not to consider it as our objective was to predict the contribution of ascites to weight. Therefore, the terminology "dry weight" may not be the most suitable for this type of weight estimation or adjustment, considering that the weight adjustment for edema is still needed.

Few studies have tried to estimate the dry weight or the ascites volume from patients with cirrhosis. Stepanian and Tayek (29), in a case report, obtained the volume

of ascites calculating the volume of a sphere [4/3 * Pi * (radius)^3], whose radius was calculated through the abdominal circumference measurement. The authors assumed the specific gravity of 1.0, so the 11.8 litters that were found as a volume of ascites, were considered 11.8 kilograms. We believe that abdominal circumference is a keypoint for the estimation of ascites, however, in our study, the inclusion of another anthropometric measurement, such as height, improved the reliability of the estimation.

Also concerned with nutritional assessment in patients with cirrhosis due to the presence of ascites, Lamarti and Hickson (30) also assessed the amount of ascitic fluid (ascites weight) in 18 patients undergoing paracentesis and its influence on BMI. A slightly larger volume of ascites was found in this British study compared to ours. They also formulated an equation to estimate the amount of ascitic fluid from pre-paracentesis waist circumference, however, the authors described that they did not get a precise estimate.

Using abdominal computed tomography (CT) imaging, Mc-Hugh et al (31). also estimated dry weight of cirrhotic transplant candidates with ascites. Even though the precision of the CT imaging, which is the gold-standard method for assessing body composition (32), the applicability of the equations in most health centers is mostly unworkable, considering the difficult access to CT imaging and the exposure of patients to radiation.

Our study has relevant strengths. This study assesses the volume of ascites as well as the weight and waist circumference with and without ascites in patients with decompensated cirrhosis, data rarely found in the scientific literature. With this information, we instigate a reflection about the real influence of ascites on body weight, and propose new equations to estimate dry weight. All patients were measured in the same day-shift (morning), that could contribute to less variation on weight. However,

a few important considerations in respect to our study must be commented on. The small sample size is the most concern. Because of the methodology required due to other aims of the study protocol, it was difficult to include a larger number of patients, since the data collection was pre-scheduled depending on the day of paracentesis, besides, many patients had aggravation and have needed to undergo paracentesis another date without communicating the researchers. We also did not include patients with mild ascites, who do not have an indication of therapeutic paracentesis. Additional research, with a larger sample, would be convenient to test our formula.

CONCLUSION

We developed prediction equations to adjust body weight in cirrhotic patients with ascites. The predictive equations developed in this study may be better options for dry weight estimation than those currently used. We understand that it is predictable that our model had better results than the current weight adjustments, so an external validation in a larger sample is still needed to confirm the applicability of these equations.

Conflict of Interest: None to declare.

Author Contribution: BCA: study concept and design, acquisition of data, statistical analysis, analysis and interpretation of data, drafting of the manuscript; MLC: acquisition of data; CS: technical support; ABL: acquisition of data, critical revision of the manuscript for important intellectual content, VD: study concept and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, study supervision.

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FIGURE LEGENDS:

Figure 1. Participants' inclusion process

Figure 2. Difference of the equations in relation to the post-paracentesis weight. Each point represents a patient, and the solid line marks the inexistence of error (difference = 0) where points should be concentrated.

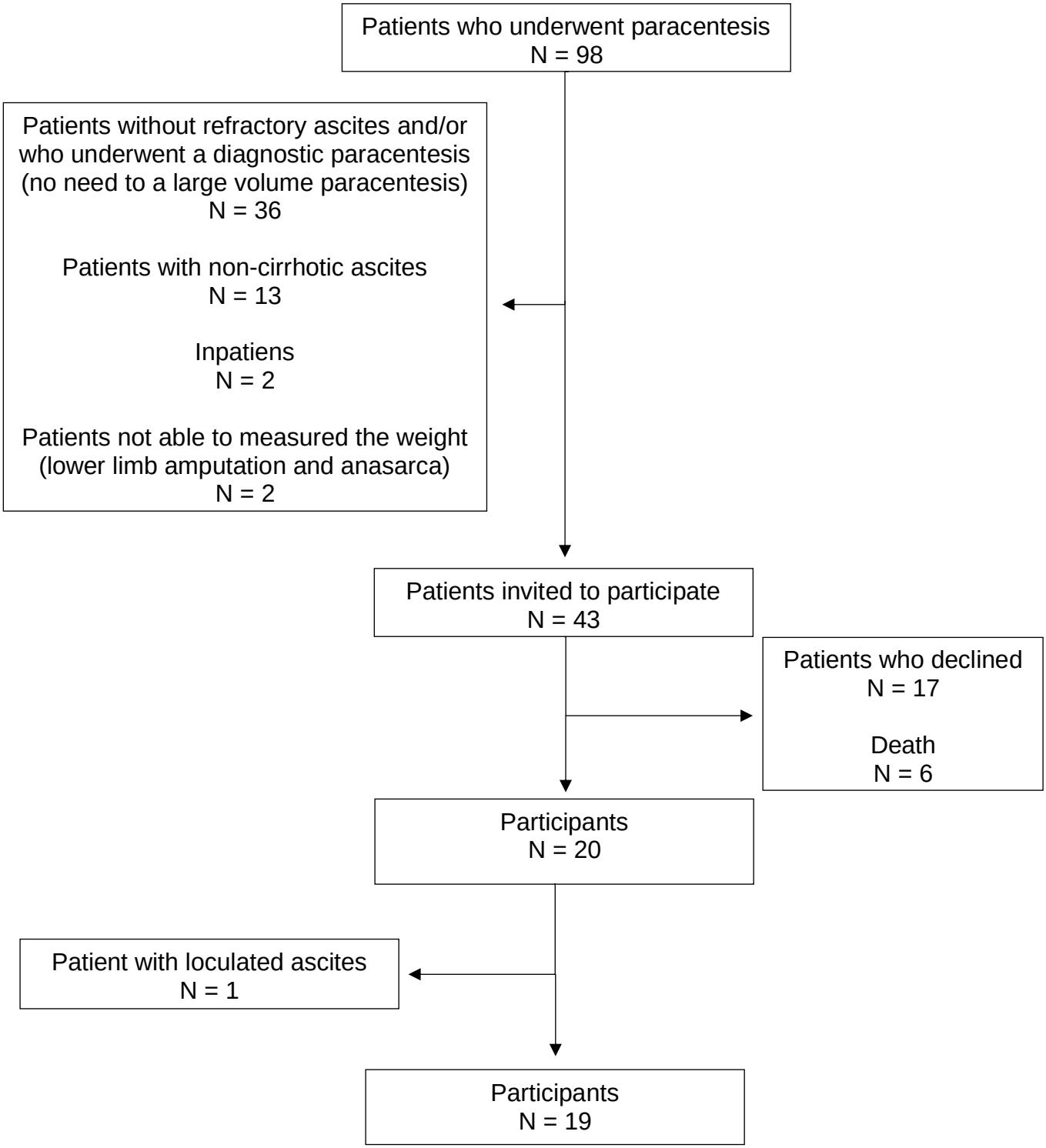

Figure 1. Participants' inclusion process

Box 1. Linear regression model data

Prediction equation name	Predictive variables*	Response variable
Equation 1	Height (cm) Weight (kg) Abdominal circumference (cm)	Postparacentesis weight
Equation 2	Height (cm) Abdominal circumference (cm) Mid-upper arm circumference (cm)	Postparacentesis weight

*pre-paracentesis measurements.

Box 2. Usual weight adjustments* according to the degree of ascites

	Mendenhall, 1992 (17)	Tandon, 2017 (10)
Mild	-2,2 kg	- 5,0 %
Moderate	-6,0 kg	-10,0 %
Severe	-14,0 kg	-15,0 %

*Subtraction from pre-paracentesis weight according to the degree of ascites

Table 1. Clinical and nutritional characteristics of patients with decompensated cirrhosis (n=19)

Male, n (%)	15 (79%)
Age in Years, median (p25 – p75)	64 (47 – 71)
Child-Pugh	
B, n (%)	8 (42%)
C, n (%)	11 (58%)
MELD-Na score, mean ± SD	17,4 ± 5,6
Grade 3 ascites, n (%)	19 (100%)
Number of days between paracentesis, median (p25 – p75)	14 (7 – 21)
High nutritional risk, n (%)	18 (95%)
Malnutrition*	
Moderately, n (%)	10 (53%)
Severely, n (%)	7 (37%)

Results presented as %, median (p25 – p75), mean±SD. * Subjective Global Nutritional Assessment

Table 2. Volume of ascitic fluid drained, and differences in weight and abdominal circumference before and after paracentesis (n=19)

Ascitic fluid drained (L)	5.0 (3.6 – 10.0)
ΔpreW-postW (kg)	5.0 (3.6 – 9.9)
ΔpreAC-postAC (cm)	8.0 (6.0 – 12.7)

Results showed in median (p25 – 75). preW: pre-paracentesis weight; postW: post-paracentesis weight. preAC: pre-paracenesis abdominal circumference; postAC: post-paracentesis abdominal circumference.

Box 3. Prediction equations to estimate dry weight, and its mean square error and intraclass correlation coefficient in patients with cirrhotic ascites			
		MSE	ICC
Equation 1	DW: = 44.966 - 0.127 * H + 1.015 * W - 0.289 * AC	3.95	0.987
Equation 2	DW = -116.618 + 0.536 * H + 0.462 * AC + 1.875 * MAC	17.97	0.937
WAkg (Mendenhall, 1992)	Table 2	64.19	0.849
WA% (Tandon, 2017)	Table 2	33.24	0.902
MSE: mean squared error; ICC: intraclass correlation coeficiente; DW: dry weight; H: height in centimeters; AC: abdominal circumference in centimeters; MUAC: mid-upper arm circumference in centimeters; W: weight in kilograms; WA: weight adjustment.			

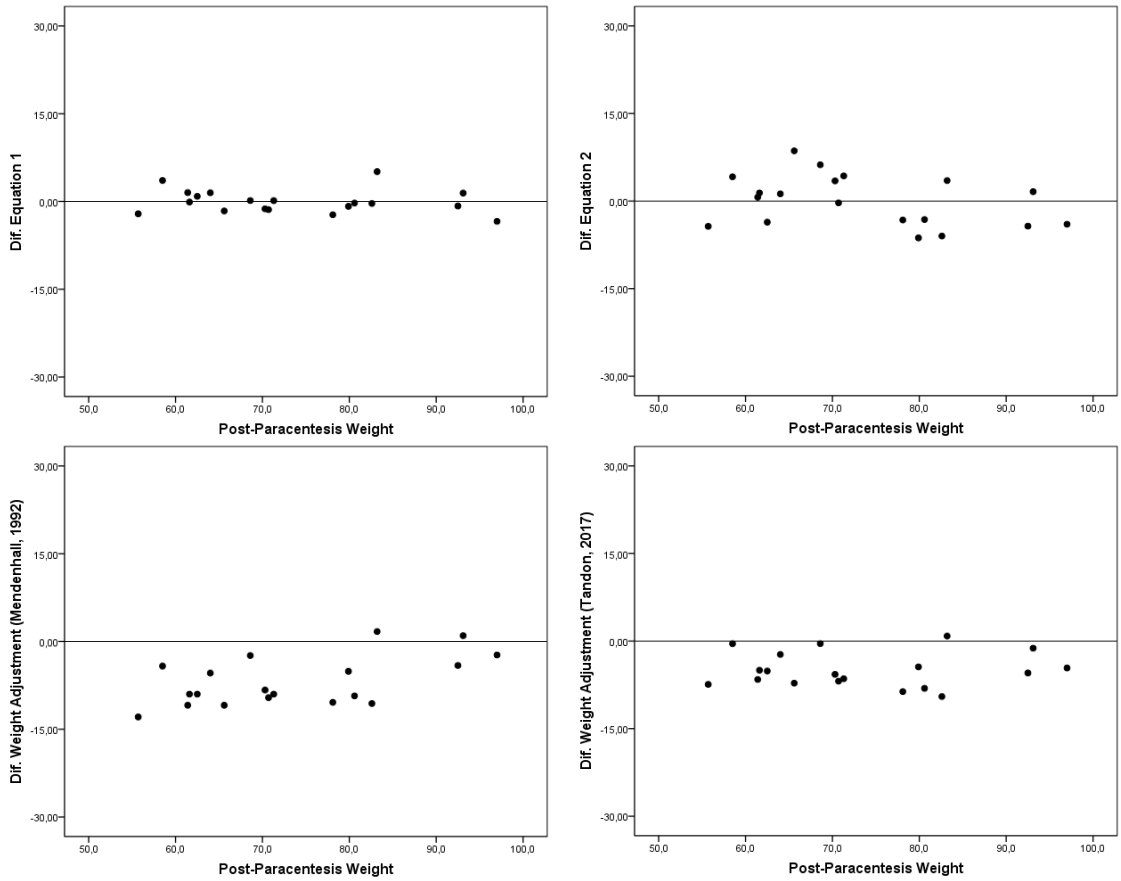

Figure 2. Difference of the equations in relation to the post-paracentesis weight. Each point represents a patient, and the solid line marks the inexistence of error (difference = 0) where points should be concentrated.

TITLE: **Nutritional and dietary sodium assessment, ascites formation, and mortality in patients with decompensated cirrhosis submitted to large-volume paracentesis.**

RUNNING HEAD: **Dietary sodium, ascites, and mortality**

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ABSTRACT

Objectives: To evaluate cirrhotic patients with refractory ascites in relation to dietary sodium (DNa), ascites formation, nutritional status, and their associations with 6-month mortality.

Methods: Pilot study that included 19 outpatients with decompensated cirrhosis undergoing large-volume paracentesis (LVP) who were followed-up for 6 months. Patients were submitted to laboratorial, clinical and nutritional assessment, that included Royal Free Hospital-Global Assessment (RFH-GA), mid-upper arm circumference (MUAC), mid-arm muscle circumference (MAMC), and phase angle (PhA) by bioimpedanciometry. Dietary, DNa, and salt intake were evaluated by 3-day Food Record and Food Frequency Questionnaire for Sodium. Number of LVP and volume of ascites were accessed by electronic medical record.

Results: Nineteen patients were included, 15 were male, 11 Child-Pugh C score, 17 had new episodes of LVP. The median of DNa was 3.42 (2.22–6.05)g/d and salt was 6.67 (3.70–11.1)g/d, both were not correlated with dietary calories. DNa <2.5g/d and salt <5g/d were associated with lower ascites formation (p=0.020 and p=0.035 respectively). Ascites formation was correlated positively with salt (p=0.048; r=0.459) and negatively with PhA (p=0.033; r=-0.552). Overall 6-month mortality was 47% and was associated with malnutrition by MUAC, MAMC, PhA and RFH-GA (p<0.03 for all). Neither DNa nor salt was associated with mortality, however, the survival rate of patients with PhA <4.0 and <10-day interval between LVP were shorter (p<0.03 for both).

Conclusions: DNa > 2.5g was associated with less ascites formation and malnutrition with 6-month mortality. DNa was not associated with calories or malnutrition, however, education for DNa adequacy must care for sufficient dietary intake.

KEYWORDS: liver cirrhosis; refractory ascites; dietary sodium; nutritional assessment, malnutrition.

INTRODUCTION

Decompensated cirrhosis is marked by complications of portal hypertension, such as ascites, variceal bleeding, and hepatic encephalopathy (1,2). Ascites is the major complication of decompensated cirrhosis, impairing the patient's working and social life, besides, it is associated with a poor prognosis, impacting a 5-year survival reduction from 80% to 30% (3,4). Patients with refractory ascites, defined when ascites can not be mobilized or its early recurrence is not prevented by diuretic therapy, need to come into the hospital every few weeks to have the ascitic fluid drained through paracentesis (4,5).

Intensified by ascites, malnutrition is an important complication in chronic liver disease, and, as well as malnutrition-related disorders, such as sarcopenia and frailty, are commonly found in these patients (6,7). The severity of liver disease aggravates malnutrition, which is caused by multiple factors, such as inadequate food intake, malabsorption, hypermetabolism, and anabolic resistance (6,8,9). It is well described that malnutrition aggravates the liver disease, including the development of ascites, as well as patient's prognosis, being considered an independent predictor of lower survival in cirrhosis and also a risk factor for mortality even in patients with a MELD-Na score ≤ 15 (10–12).

For ascites management, a low sodium diet (≈2 grams per day), including salt restriction, is one of the main orientations by clinical guidelines(3,13), assuming a role as an important preventive approach (14). However, a low sodium diet can also contribute to an inadequate food intake due to compromising the palatability of the diet (15,16). This fact is alarming since it is extremely needed to favor food intake to prevent malnutrition. For this reason, the low sodium diet with salt restriction for ascites management in cirrhotic patients is under debate.

Therefore, further evidence on this issue, including the relation with dietary sodium, nutritional status, ascites formation, and mortality, is still needed. Considering that, the present study aimed to evaluate patients with refractory cirrhotic ascites in relation to dietary sodium, ascites formation, nutritional status, and their associations with 6-month mortality.

METHODS

This pilot study included adult outpatients with decompensated cirrhosis (17) and refractory ascites who were undergoing large-volume paracentesis at the Outpatient Surgical Center of Hospital de Clínicas de Porto Alegre (HCPA), in Brazil from October 2018 to June 2020. These patients were followed up for 6 months by electronic medical records to access paracentesis and mortality data. Patients unable to measure weight, with anasarca, or who did not undergo large-volume paracentesis were not included. The Ethics and Research Committee at HCPA approved the protocol (CAAE 90618218.0.0000.5327), and patients were included only after reading, understanding, and signing an Informed Consent Form.

Demographic and Clinical Assessment

Demographic and clinical data (including gender, ethnic origin, age, etiology, and, duration of the liver disease since diagnosis and medication) were assessed. Ascites were graded before paracentesis according to the amount of fluid accumulated in the abdominal cavity and classified according to the response to treatment by a single gastroenterologist (4). A serum albumin ascites gradient ≥1.1 g/dL and ascites protein <2.5 g/dL were used to confirm the etiology of ascites due to portal hypertension (4,13).

Laboratory Assessment

Blood samples for laboratory analysis (serum albumin, creatinine, total bilirubin, and prothrombin time test/INR) were assessed on the same day in the morning (before paracentesis). Patients were classified according to the Child-Pugh-Turcotte score (18,19), and MELD-Na score to predict the short-term prognosis of these decompensated patients (13,20,21).

Dietary and Sodium Intake

Dietary intake was assessed by a 3-day Food Record (3dFR). The patient or the person responsible for the patient was instructed to write down all the food intake at the time of consumption on two non-consecutive weekdays and one weekend day. The three records were converted into daily consumption, and the calculation of calories, dietary macronutrients, and also sodium was performed with the support of the NutriBase 2007 software (Clinical Nutrition Manager v.7.14; Cybersoft).

A semi-quantitative food frequency questionnaire (FFQ-Na) developed and validated to evaluate dietary patterns of sodium consumption among low-income Brazilian hypertensive subjects was applied to all patients (22). This instrument assessed the frequency of intake of foods that are rich in sodium, and also the amount of salt they use per month at home when preparing meals. Dietary sodium from salt was calculated considering that 40% of salt is sodium. For daily amounts, all sodium variables were divided by 30 (22).

Anthropometric measurements

Body weight was measured after paracentesis on a Urano® digital upright scale after large-volume paracentesis, and height on a Sanny® wall-mounted stadiometer.

Body mass index (BMI) was calculated as weight divided by height in square meters (kg/m^2). Mid-upper arm circumference (MUAC) was measured at the midpoint between the acromion and olecranon of the non-dominant arm with an inextensible tape measure and the patient in an orthostatic position with the forearm flexed at 45°. Triceps skinfold thickness (TSF) was also measured at the midpoint between the acromion and olecranon of the non-dominant arm with the adipometer placed 01 cm below the fingers that pinch the fold. Mid-arm muscle circumference (MAMC) was determined from the following formulas (23,24): MAMC = MUAC - π(TSF).

Bioelectrical impedance analysis

The Bioelectrical impedance analysis (BIA) was performed in duplicate after paracentesis, with portable tetrapolar equipment (Biodynamics model 450) with a current intensity of 800 μA and a single frequency of 50 kHz, enabling the measurement of the resistance (R) and the reactance (Xc). Phase angle (PhA), which is a reliable tool for nutritional assessment, and also reflects the cellular vitality and integrity, was calculated through the arctangent formula (Xc/R). The mean values PhA used in statistical analysis (25,26).A PhA value that was associated with mortality was also identified (4.0°).

Nutrition Risk Screening

The nutritional risk was assessed by the Royal Free Hospital–Nutritional Prioritizing Tool (RFH-NPT), which is a validated tool for nutrition risk assessment in cirrhotic patients (27), and recommended by the main practical guidelines on nutrition in liver disease (11,15).

Subjective Global Assessment.

Subjective Global Assessment for nutritional assessment combines the clinical and physical parameters such as weight changes, dietary intake, gastrointestinal symptoms, functional capacity, and physical examination, and classifies the individuals as well-nourished, suspected malnutrition, or moderately malnourished, or severely malnourished(28).

Royal Free Hospital-Global Assessment

Royal Free Hospital-Global Assessment (RFH-GA) (27) determines nutritional status in patients with cirrhosis, stratifying them into one of three categories: adequately nourished, moderately malnourished, or suspected of easlbeing, and severely malnourished. The RFH-GA scheme is based on dry weight-based BMI, MAMC, and dietary intake, which was considered adequate if dietary intake was greater than 60% of dietary requirements (35 kcal/kg), inadequate if less than 60%, or negligible if below 25% (29–32).

Ascites and Paracentesis data

Patient evaluations were performed on the day of a paracentesis. Large-volume paracentesis was performed by a gastroenterologist under point-of-care ultrasound with patients in the supine position (33). The fluid was drained through a 14-gauge catheter into a 3-liter bottle that was emptied into dosage cups. During the paracentesis, when drainage started to slow down, all patients were placed in lateral decubitus position to reduce the volume of residual ascites. The volume of drained fluid was checked throughout paracentesis until the end of the procedure. All patients had

50ml of ascitic fluid sent to laboratory analysis. Albumin infusion (6 - 8g/L of ascites removed) was administered in those patients who removed >5L (3).

The number of paracentesis in which the patients were submitted and the volume of fluid drained in each one during the 6 months of follow-up were accessed in the electronic medical record. For analysis, the volume of ascites was considered as the average volume drained in each paracentesis, and, the interval between paracentesis was the average of days between the first and the last paracentesis accessed in the study divided by the number of paracentesis. Ascites formation, which is the volume of fluid accumulated as ascites per day, was calculated as the volume of ascites divided by the interval between paracentesis.

Survival

Mortality data and its causes were collected from electronic medical records or by telephone contact at the end of the study.

Statistical Analysis

Shapiro-Wilk test was performed to check the normality of each quantitative variable that was described by the mean and standard deviation for normal distribution or median and interquartile ranges for non-normal distribution. Categorical variables were described by absolute and relative frequencies. Bivariate correlations were performed by the Pearson or Spearman correlation coefficient depending on the nature of the distribution. Comparisons of independent samples were analyzed by Student's t-test or Mann-Whitney's U-test for continuous variables, and by Chi^2 test for categorical variables. Survival over time was estimated using Kaplan-Meier curves and compared using the log-rank test. The level of statistical significance considered will

be 5% (p <0.05) and the analyzes will be performed using the Statistical Package for the Social Sciences (SPSS) 18.0 program.

RESULTS

This pilot study included 19 patients. Patients' inclusion is detailed in Figure 1. Patients were previously invited to participate in the study whose data collection would be performed in the next paracentesis. Patients with no need to undergo another paracentesis could not participate in this study protocol.

Fifteen patients (74%) had cirrhosis caused by HCV infeccion, alcohol, or both, with or without hepatocellular carcinoma. All patients presented grade 3 ascites due to portal hypertension, and nine patients (47%) received oral diuretic therapy. The clinical and nutritional profiles of the decompensated cirrhotic patients according to 6-month mortality are described in Table 1.

Dietary and sodium intake

Dietary intake assessed by the 3dFR and dietary sodium assessed by FFQ-Na is presented in Table 2. The median salt intake was 6.67 (3.70 – 11.1) g/day, and corresponds to 78% of dietary sodium, while a smaller part comes from high sodium foods, artificial seasonings, and broth tablets, described in Table 3. Of the thirteen patients with a low food intake (<25 kcal/kg), eleven presented dietary sodium >2g. There was no correlation between dietary sodium and calorie intake.

Ascites formation

Of the 19 patients included, 17 had new episodes of paracentesis in six months of follow-up. Data related to ascites formation compared to sodium intake is presented in Table 4.

Correlations related to ascites parameters and dietary and nutritional aspects are presented in Figure 1. Salt intake higher than 5g (that corresponds to 2g of sodium) was associated with greater ascites formation (p = 0.035). However, higher ascites formation was not associated with mortality.

Seric and urinary sodium concentration

Fifteen patients had 24-hour urinary samples collected for sodium excretion test, and 7 of those presented concentrations below 30 mEq/L, which was associated with 6-month mortality (p=0.041). Urinary sodium was correlated with both salt intake (p=0.04; rho=0.534) and dietary sodium from the 3-day food registry (p=0.007; r=0.663), demonstrating that a higher intake of sodium is associated with higher sodium excretion. Serum sodium also correlated with 24-hour urinary sodium (p=0.025; rho = 0.575), however, neither serum sodium nor 24-hour urinary sodium correlated with the volume of ascites, the interval between paracentesis, or ascites formation.

Mortality

Overall mortality was 47% (n=9 of 19) in 6 months. All deaths were related to liver disease complications. The median time from the beginning of the follow-up to death was 3.11 months (1.89 – 5.46 months). Nutritional assessments of patients compared according to death in 6 months are presented in Table 5. By survival analysis, neither the dietary sodium nor the salt intake had an association with

mortality, however, the survival rate of patients that were submitted to paracentesis more frequently was shorter (Figures 3).

DISCUSSION

The present study evaluated dietary sodium, ascites formation, nutritional status, and their associations with 6-month mortality in a sample of outpatients with refractory ascites due to decompensated cirrhosis. Few patients had low sodium intake (<2.5 g/d), which was associated with lower ascites formation, but it was not associated with malnutrition and mortality. Malnutrition, demonstrated by lower PhA, MUAC, and MAMC was associated with 6-month mortality.

In this study, we found a high sodium intake and salt use, even in patients with low dietary intake. The greatest amount of dietary sodium comes from salt use, consistent with an epidemiological study of the Brazilian population that described high dietary sodium (a mean of 4.7g per 2000 kcal), and the contribution of 74.4% of dietary sodium from salt use (34). This fact leads us to believe that the control of salt use, instead of foods containing sodium, has probably more impact on the disease condition. However, reducing the intake of high sodium foods, condiments, and seasonings, usually added sodium-containing preservatives, helps to further reduce dietary sodium, making it possible to compensate with controlled use of salt (35). In other words, it is not necessary to cook free-salt meals, as long as the quantities of salt are controlled. As an example, for a family of 4, a 1-kilo pack of salt should last at least 50 days. Besides, choosing freshly cooked dishes, instead of canned and pre-prepared foods, and also adding herbs and spices, instead of salt for seasoning are the best choices (16).

Although dietary sodium has not been associated with caloric intake in this study, it is believed that by restricting salt and reducing food palatability, it becomes even more difficult for patients to reach dietary requirements (8,11,36). Morando et al. (36), evaluating the adherence to a moderate sodium restriction in outpatients with cirrhosis and ascites, found a reducing daily calorie intake of 20% in those who follow the moderate sodium restriction compared to those who did not restrict sodium, which is quite worrying, given that food intake in patients with cirrhosis and ascites is already inadequate due to the several reasons inherent to the chronic liver disease, such as early satiety, dysgeusia, anorexia, nausea, vomiting, impaired level of consciousness, etc. that contribute to increasing nutritional risk and malnutrition (6,8,9).

In this regard, it is questionable how strict the low sodium diet should be to prevent ascites formation. Daily dietary sodium recommendations by hepatology societies range from 1.8 to 2.8 grams (equivalent to 4.6 – 6.9 g of salt) for ascites management, which are similar to the WHO recommendation for healthy individuals (5g of salt) (3–5,11,13). In this sample, the benefit of reduced dietary sodium in ascites formation was observed in patients that had dietary sodium below 2.5 g/d, who also presented a mean salt intake of 3.7± 1.1 g/d. The rigid sodium restriction (less than 2 g) and even a sodium free-diet are far from being risk-free. Besides all the preoccupations related to nutritional aspects, a very low sodium diet can favor diuretic-induced complications, renal failure, and sodium depletion, which itself is of great concern and is highly associated with mortality (3,37,38). A study with a larger population could be useful to better identify the effect and differences of moderate and more restricted dietary sodium restriction in refractory cirrhotic patients. Thus, like any nutritional intervention, it would be preferable to assess the dietary pattern of sodium

intake by each patient individually and from there on, educate on moderate sodium restriction (no more than 2.5 g), taking care that an adequate food intake is guaranteed.

Mortality was associated with malnutrition demonstrated in different parameters. Considering global assessments, only the RFH-GA, which was designed and validated for liver disease patients, demonstrated that a higher proportion of malnourished patients died in 6 months. In this sample, no patient had eaten less than 25% of dietary requirements and only one had a BMI < 20 kg/m^2, thus, a meaningful part of the sample was classified as adequately nourished. It is worth mentioning that the patients included were not hospitalized, and the post-paracentesis weight was used for BMI calculation. We confirm the importance of having validated tools for patients with cirrhosis to categorize and differentiate patients more accurately. With respect to the high prevalence of malnutrition and protein depletion in cirrhotic patients, nutrition guidelines point out the importance of muscle mass evaluation (11,15), also for the identification of sarcopenia. Previously, all patients in this sample presented low handgrip strength by dynamometry, so we know that sarcopenia is quite relevant. Therefore, anthropometric measurements could be useful and appropriate. MUAC and MAMC are simple low-cost tools that are not influenced by fluid overload (39,40). Growing evidence suggests that both mid-arm measurements correlate with muscle mass and are good predictors of malnutrition, sarcopenia, and frailty, besides, may improve prognostic information in cirrhosis (39,41–44).

PhA has been well described as an indicator of nutritional status and severity of the liver disease (41,45–48). Despite being quantified by BIA, the PhA is not influenced by the presence of ascites (49), which increases its applicability in these patients. Saueressig et al. (25), in a larger sample of patients with decompensated cirrhosis from the same hospital of this study, found that a PhA ≤5.52° was an independent

predictor of 6-month mortality. We observed a lower mean PhA in our sample, probably reflected by the malnutrition and severity of the patients, and also it was clearly associated with mortality.

Although we found a correlation between serum and urinary sodium concentrations with dietary sodium, we could not find any relationship between these concentrations and ascites formation. A higher proportion of patients with low urinary sodium excretion died, which was expected since low urinary sodium excretion is associated with poor survival, probably related to progressive decline in renal function (50,51).

Treating ascites is important even though its treatment alone has no improvement in survival, however, it improves the quality of life and prevents the occurrence of spontaneous bacterial peritonitis, which is associated with mortality (16,52,53). The fact that patients who died underwent paracentesis more frequently, may be due to the fact that some patients, as they get with their cirrhosis even more decompensated, were unable to follow medical treatment with diuretics, were more frequently hospitalized, and perhaps with greater abdominal discomfort, regardless of the volume of ascites.

Our study has relevant strengths. This study assesses dietary sodium, and ascites formation and mortality during 6 months, which is little demonstrated in recent studies. Besides, we evaluate dietary sodium by two different tools and also serum and urinary sodium. However, a few important considerations with respect to our study must be commented on. The limited sample size is the main concern. Also, dietary sodium and laboratory evaluation were evaluated only at the beginning of the study, although we have evaluated the sodium intake by a food frequency questionnaire that particularly identifies consumption patterns.

In conclusion, the present study adds to evidence that moderate sodium intake was associated with less ascites formation, and malnutrition was associated with 6-month mortality. Although this study did not find any association between dietary sodium with caloric intake or malnutrition, we emphasize that education for dietary sodium adequacy must be accompanied by emphasized orientation for adequate dietary intake.

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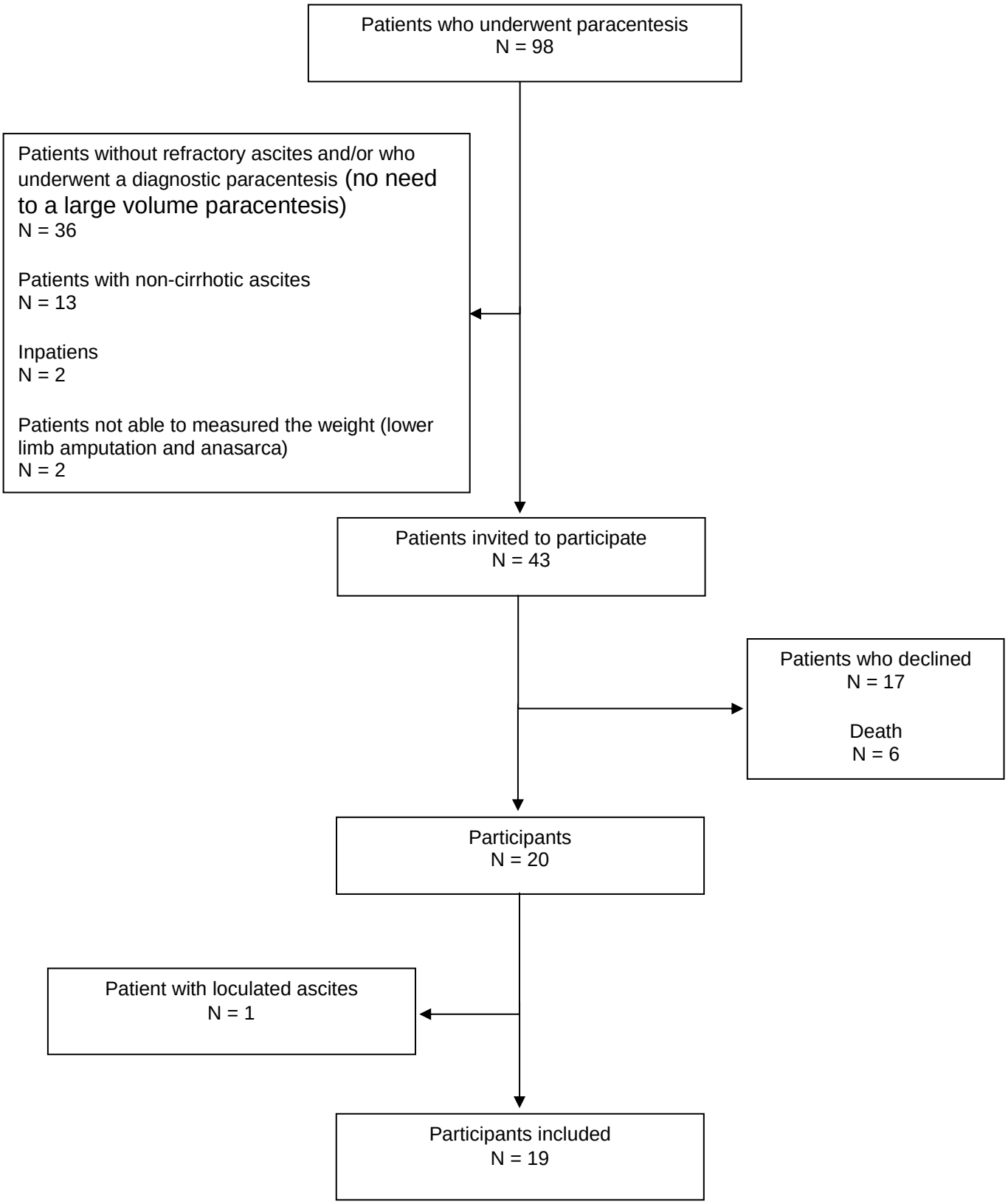


Figure 1. Participants' inclusion process

Table 1. Clinical and nutritional characteristics of patients with decompensated cirrhosis according to death in 6 months.

Mortality	**Yes (n=9)**	**No (n=10)**	***p*-valor**
Caucasian, n (%)	7 (%)	6 (%)	0.582
Male, n (%)	7 (%)	2 (%)	1.000
Age in years	67 (52 – 72)[a]	55 (45 – 69)[a]	0.219
Albumin (g/dL)	2.7 ± 0.3[b]	3.0 ± 0.3[b]	0.130
Creatinine (mg/dL)	1.21 (0.79 – 1.87)[a]	1.13 (0.98 – 2.06)[a]	0.806
Total bilirubin (mg/dL)	2.6 (1.7 – 3.9)[a]	0.95 (0.48 – 1.95)[a]	**0.009**
Prothrombin time test (INR)	1.34 (1.21 – 1.73)[a]	1.33 (1.24 – 1.65)[a]	0.806
Serum sodium (mEq/L)	137 (131 – 138)[a]	139 (137 – 141)[a]	**0.021**
24-h urinary sodium (mEq/L)*	19 (6 – 32)[a]	43.2 (31.7 – 76.8)[a]	**0.018**
Child-Pugh			0.650
B, n(%)	3 (%)	5 ()	
C, n(%)	6 (%)	5 ()	
MELD-Na score	20.0 ± 5.8[b]	15.1 ± 4.6[b]	0.055

[a]Results expressed as median (p25 – p75); [b]Results expressed as mean±SD; *n=15.

Table 2. Dietary intake assessed by 3-day food record and sodium-food frequency questionnaire

Kcal	1651.3 (1274.9 – 1953.8)[a]
Kcal/kg	23.2 (15.0 – 29.0)[a]
Carbohydrates (%)	50.8 (40.0 – 56.3)[a]
Lipid (%)	33.7 (28.1 – 40.0)[a]
Protein (%)	14.8 (12.8 – 16.5)[a]
Protein (g/kg)	0.85 (0.62 – 1.14)[a]
Sodium from 3dFR(g/d)	2.49 (1.64 – 3.34)[a]
Total * (g/d)	3.42 (2.22 – 6.05)[a]
From salt * (g/d)	2.67 (1.48 – 4.44)[a]
From high sodium foods * (g/d)	0.20 (0.04 – 0.37)[a]
From artificial seasonings and broth tablets * (g/d)	0.35 (0.00 – 12.6)[a]

[a]Results expressed in median (p25 – p75); *from NA-FFQ; 3dRF: 3-day food record.

Table 3. Sodium intake from each high sodium food included on Na-FFQ

	N	Sodium (mg/d)
Artifitial Seasoning	4	1311.7 (293.0 – 6419.0)[a]
Broth tablet	8	175.6 (32.8 – 827.5)[a]
Brazilian bean stew	4	133.8 (33.5 – 1017.1)[a]
Noodles	3	91.0 – 181.9[b]
Weiner/hot dog	10	78.8 (17.2 – 78.8)[a]
Chicken sausage	2	40.5 – 10.1[b]
Ham	8	40.0 (3.3 – 190.1)[a]
Pizza	11	36.2 (9.1 – 54.4)[a]
Pork sausage	6	32.8 (9.6 – 147.4)[a]
Hamburguer	4	27.3 (10.9 – 76.5)[a]
Snacks/chips	4	18.7 (6.3 – 94.1)[a]
Mortadella	8	12.5 (6.2 – 37.4)[a]
FastFood	2	4.2 – 33.3[b]
Bacon	2	4.0 – 2.0[b]
Canned sardine	5	3.8 (3.8 – 52.8)[a]

[a]Results expressed as median (p25 – p75); [b]Results expressed in min-max.

Table 4. Characteristics of ascites and paracentesis in patients with decompensated cirrhosis in 6 months of follow-up according to sodium intake[#] assessed by FFQ-Na.

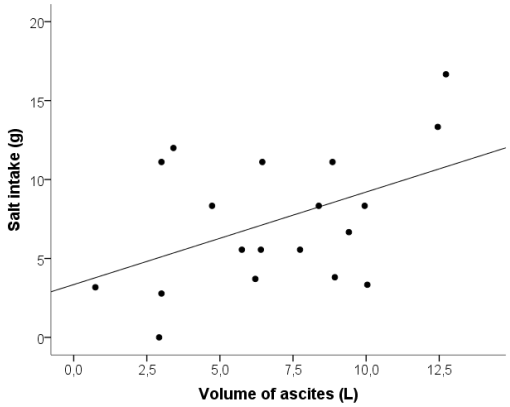
	< 2.5g (n = 5)	**> 2.5g (n = 14)**	***p*-value**
Number of paracentesis	7.0 (2.5 – 7.0)	7 (4.8 – 11.3)	0.447 [a]
Interval between paracentesis*	17.4 ± 7.9	13.9 ± 7.3	0.410 [b]
Drained fluid*	5.2 ± 3.5	7.5 ± 3.2	0.183 [b]
Ascites formation* (ml/d)	275,0 ± 120,6	629.2 ± 258.8	**0.020** [b]

FFQ-Na: Food Frequency Questionnaire for Sodium; [#]2.5g of sodium= 5g of salt *mean of 6 months; n =3 in <2g group [a]Mann-Whitney U test; [b]T-test

Table 5. Nutritional status of patients with decompensated cirrhosis according to death in 6 months.

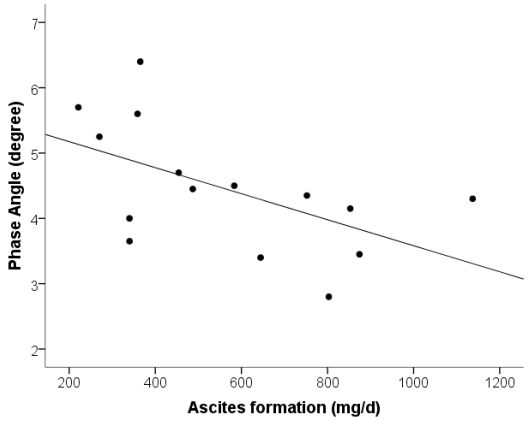
Mortality	**Yes (n = 9)**	**No (n = 10)**	***p*-value**
High nutritional risk*, n (%)	9 (90%)	9 (100%)	1.000 [b]
*Malnutrition - SGA***			0.221 [b]
Moderately malnourished, n (%)	4 (40%)	2 (22%)	
Severely malnourished, n (%	4 (40%)	7 (78%)	
*Malnutrition - RFH-GA****			**0.023** [b]
Moderately malnourished	7(78%)	2 (20%)	
Adequately nourished	2 (22%)	8 (80%)	
MUAC	23.4 ± 3.7	29.2 ± 2.8	**0.001** [a]
MAMC	20.0 ± 3.1	24.1 ± 1.7	**0.002** [a]
Phase Angle [#]	3.74 ± 0.65	4.83 ± 0.90	**0.016** [a]

Results expressed as mean±SD; [a]T-test; [b]Chi^2 Test [#]n=18; *Royal Free Hospital - Nutritional Prioritizing Tool; **Subjective Global Assessment; ***Royal Free Hospital Global – Assessment; MUAC: Mid-upper arm circumference; MAMC: Mid-arm mescle circumference;



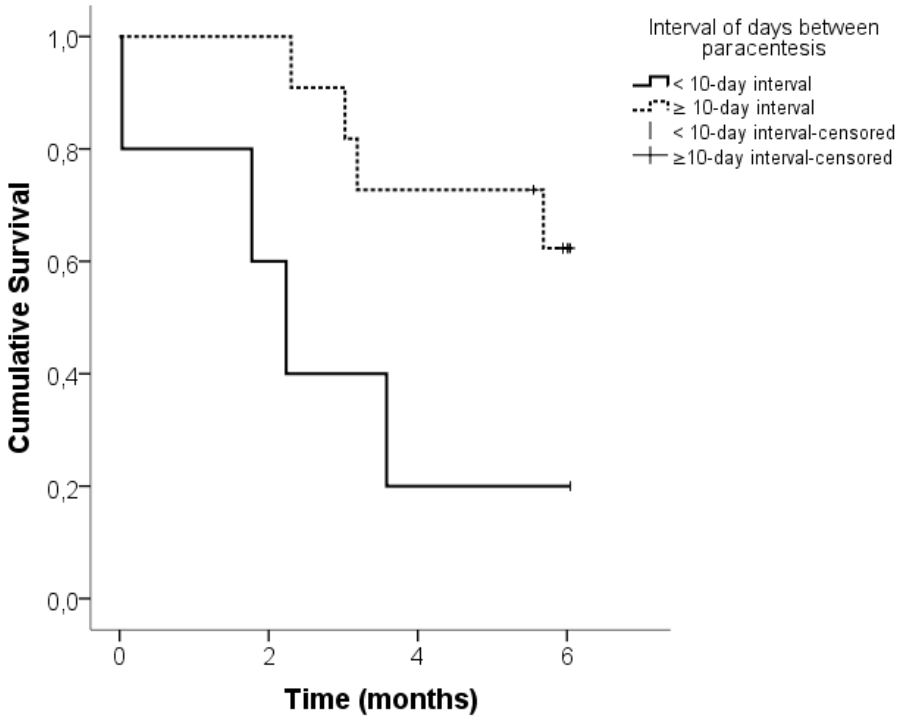
A $p = 0.048$; r = 0.459

B

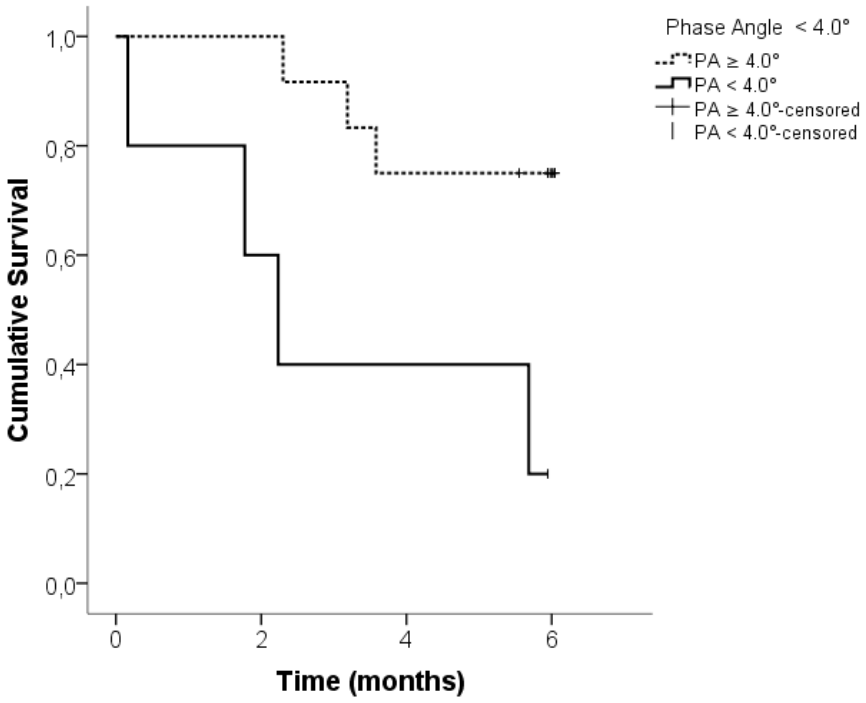


C $p = 0.033$; r = -0.552.

Figure 2. Correlation of volume of ascites, salt intake, lean body mass and phase angle in patients with refractory cirrhotic ascites.



p=0.034



p=0.014

Figure 3. Keplan-Meier survival plots of patients with refractory cirrhosis ascites by interval between paracentesis and phase angle.

7. CONCLUSÕES

O presente estudo desenvolveu novas equações preditivas que apresentaram maior confiabilidade e, portanto, podem ser melhores opções para estimar o peso seco dos pacientes com cirrose e ascite refratária do que os descontos de peso atualmente utilizados. O sódio dietético foi associado à menor formação de ascite, mas não foi associado à desnutrição e nem à mortalidade em 6 meses. Considerando que grande parte dos pacientes apresentaram uso de sal em quantidade elevada bem como uma alta ingestão de sódio dietético, orientar escolhas alimentares mais saudáveis e uma dieta livre de alimentos processados que contém alto teor de sódio, substituindo-os por alimentos *in natura* ou minimamente processados pode ser uma melhor opção às dietas muito restritivas em sódio e livres de sal.

8. PERSPECTIVAS FUTURAS

Ainda existem dados a serem analisados deste projeto. Pretendemos validar as equações preditivas de peso seco em uma amostra maior de pacientes. Iremos avaliar os dados de bioimpedância, especialmente analisar e comparar os dados pré e pós-paracentese. Também pretendemos analisar as amostras de líquido ascítico que estão armazenas a -80°C quanto às vesículas extracelulares.

9. OUTRAS PRODUÇÕES

Além dos artigos apresentados ao longo desta tese, outras produções científicas, citadas abaixo, foram elaboradas, desenvolvidas e divulgadas a partir dos dados deste projeto.

- Malnutrition in patients with refractory ascites: is sodium restriction associated with ascites and mortality? Trabalho de Conclusão do curso de nutrição de Moiséli Luchi da Cruz, 2021.

- A New Predictive Equation for Estimating Body Weight in Cirrhotic Patients With Refractory Ascites, apresentação oral no Nutrition 2021 (Congresso da American Society of Nutrition), e publicado nos anais em *Current Developments in Nutrition 2021;5(Suppl 2):868.* Também apresentado no EASL Interational Liver Congress. Trabalho classificado entre os “Best of ILC” na *categoria Nurses and allied health professionals*, 2021.

- Equação de predição para estimar peso seco em pacientes cirróticos com ascite”, apresentado no apresentado como Tema Livre concorrendo a premiação, no Congresso Ganepão 2021.

- Desnutrição em pacientes com ascite refratária: a restrição de sódio está associada à ascite? 40ª Semana Científica Científica do HCPA. Publicado em *Clin Biomed Res* 2020; 40 (Supl.).

- Marcadores de desnutrição e suas associações com gravidade da cirrose, ingestão de sódio e frequência de paracentese, poster apresentado no XXV Congresso Brasileiro de Hepatologia, 2019.

- Associação do ângulo de fase com marcadores de estado nutricional, funcional e prognóstico da doença em pacientes com cirrose descompensada:

resultados preliminares, Trabalho apresentado a 39ª Semana Científica do HCPA, 2019. Publicado em *Clin Biomed Res* 2019; 39 (Supl.).

Outras produções científicas foram realizadas na área de nutrição e hepatologia:

- Lesão hepática induzida por ervas e suplementos alimentares: uma análise agrupada de estudos de caso, Co-orientadora do Trabalho de Conclusão do curso de nutrição de Michelle Hoff de Assis.

- Efeitos da suplementação de probióticos na estrutura e enzimas hepáticas e perfis lipídico, glicêmico e inflamatório na doença hepática gordurosa não alcoólica: uma revisão sistemática, Co-orientadora do Trabalho de Conclusão do curso de nutrição de Cláudia Belchior Cervi

- Effect of probiotic supplementation in nonalcoholic steatohepatitis patients: PROBILIVER TRIAL protocol, publicado em *Trials*, 2019;20(1):580.

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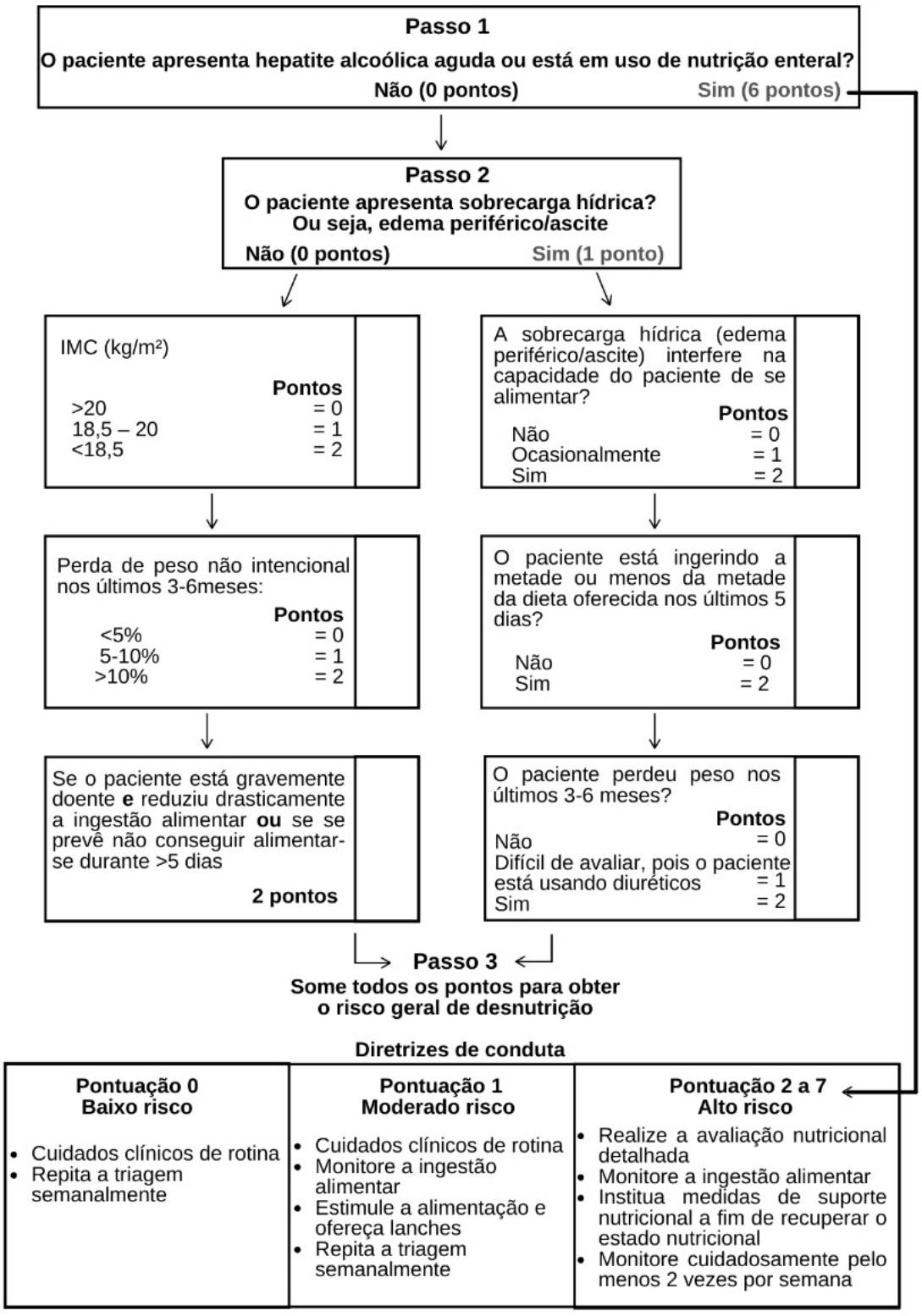
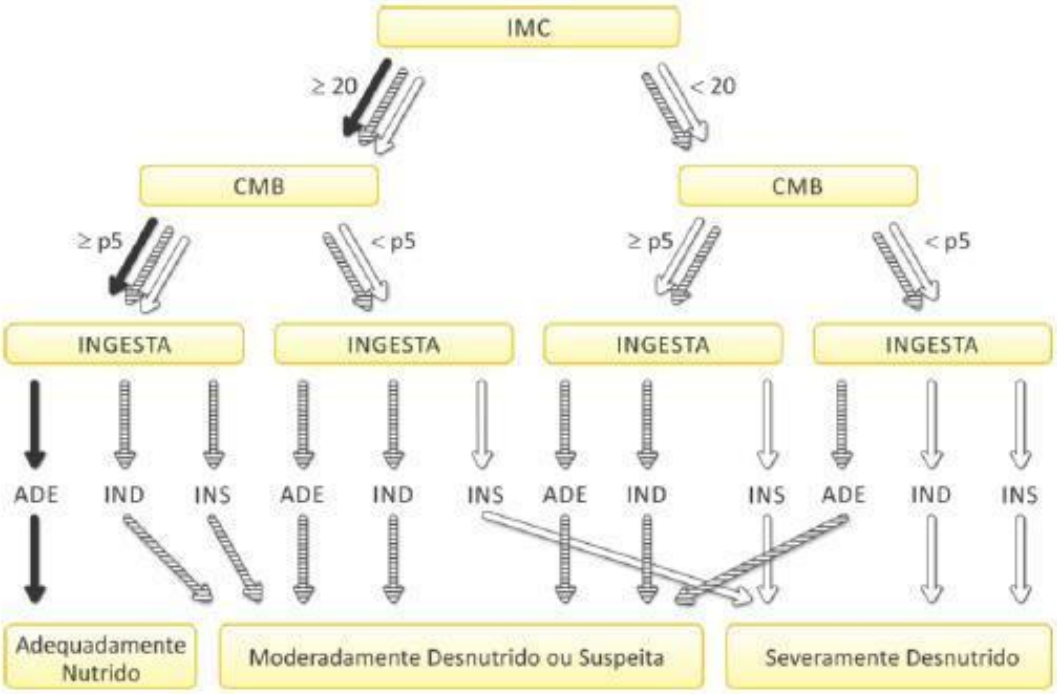
ANEXO I – Royal Free Hospital – Nutrition Prioritizing Tool (RFH-NPT)



ANEXO II – Royal Free Hospital – Global Assessment (RFH-GA)



Adaptada de Morgan et al. *Hepatology*. 2006;44(4):823–35.

ANEXO III – Questionário de Frequência Alimentar de Sódio (QFA-Só)

QFASÓ-Questionário de Freqüência Alimentar de Alimentos com alto Teor de Sódio

Paciente nº:_____

Este instrumento avalia a freqüência com que você consome alimentos que são ricos em sal (sódio) e também a quantidade de sal que você usa por mês em sua casa, no preparo de suas refeições.

A quantidade dos alimentos se refere ao que você costuma consumir habitualmente. Hoje vamos registrar a freqüência e a quantidade usual que você consumiu desses alimentos **NOS ÚLTIMOS SEIS MESES.**

Vamos lá:

1ª Parte: Consumo de sódio (sal) in natura

1. Quantos pacotes de sal são gastos na sua casa por mês?_____
2. Quantas pessoas moram com você em sua casa?_____
3. Quantas pessoas fazem as principais refeições (almoço e jantar) em sua casa pelo menos cinco vezes por semana?_____

2ª Parte: Consumo de alimentos com alto teor de sódio (sal)

Agora, vou apresentar para você uma lista de alimentos. Para cada um deles você deve responder a freqüência e a quantidade que costuma consumir.

Para a freqüência vamos usar essa classificação:

1	Nunca como
2	Como menos de uma vez por mês
3	Como uma a três vezes por mês
4	Como uma vez por semana
5	Como duas a quatro vezes por semana
6	Como uma vez ao dia
7	Como duas vezes ou mais ao dia

Para descrever a quantidade, você pode escolher entre uma porção pequena, média ou grande, conforme descrito nas colunas abaixo. Escolha a coluna que mais se adequar ao seu consumo habitual.

Ferreira-Sae MC, Gallani MC, Nadruz W, Rodrigues RC, Franchini KG, Cabral PC, Sales ML. Reliability and validity of a semi-quantitative FFQ for sodium intake in low-income and low-literacy Brazilian hypertensive subjects Public Health Nutr. 2009 Nov;12(11):2168-73. Epub 2009 May 28.

Alimento	Porção			Sua porção	1	2	3	4	5	6	7
	P	M	G								
Presunto magro	1 fatia	2 fatias	3 fatias								
Mortadela	1 fatia	2 fatias	3 fatias								
Lingüiça de porco	½ unidade	1 unidade média	2 unid								
Lingüiça de frango	½ unidade	1 unidade média	2 unid								
Salsicha	½ unidade	1 unidade média	2 unid								
Hambúrguer bovino	½ unidade	1 unidade média	2 unid								
Bacon	½ colher de sopa	1 colher de sopa	2 colheres de sopa								
Feijoada	1 concha média	2 conchas médias	3 conchas médias								
Sardinha enlatada	1 unidade	2 unidades	3 unidades								
Tempero pronto tipo alho e sal (Tipo Arisco)	½ colher de chá	1 colher de chá	2 colheres de chá								
Caldo em tablete	½ tablete	1 tablete	2 tabletes								
Salgadinhos de pacote industrializado	½ unidade	1 unidade	2 unidades								
Macarrão instantâneo (tipo Miojo)	½ unidade	1 unidade	2 unidades								
Lanche/Hambúrguer (tipo Fast Food)	½ unidade	1 unidade	2 unidades								
Pizza	1 fatia	2 fatias	3 fatias								

Ferreira-Sae MC, Gallani MC, Nadruz W, Rodrigues RC, Franchini KG, Cabral PC, Sales ML. Reliability and validity of a semi-quantitative FFQ for sodium intake in low-income and low-literacy Brazilian hypertensive subjects Public Health Nutr. 2009 Nov;12(11):2168-73. Epub 2009 May 28.