UNIVERSIDADE CATÓLICA DE PELOTAS

PROGRAMA DE PÓS-GRADUAÇÃO EM SAÚDE E COMPORTAMENTO

KAIANE FUHRMANN STIGGER

COMPARAÇÃO DA BIOIMPEDÂNCIA POR ESPECTROSCOPIA COM O EXAME CLÍNICO NA DETERMINAÇÃO DE PESO SECO DE PACIENTES PORTADORES DE DOENÇA RENAL CRÔNICA EM TRATAMENTO POR HEMODIÁLISE

Pelotas

2022

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Orientador: Profª Dra. Maristela Bohlke

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RESUMO

Esta tese está composta basicamente por três componentes, o primeiro componente é o projeto de pesquisa que foi utilizado para a qualificação pela universidade católica de pelotas, este projeto de pesquisa mostra como foi realizado o decorrer da pesquisa, quais seriam os procedimentos utilizados e como seria feito a coleta de dados para criação dos três artigos para completar a tese. segundo componente da tese é o artigo intitulado *"**Lower Incidence of Hospital Admissions in Bioimpedance-guided Fluid Management in Maintenance Hemodialysis Patients – Results of a Randomized Controlled Trial"*** que teve como intuito avaliar o impacto em desfechos clínicos do uso da (BIS) na estimativa do peso alvo para a hemodiálise. Este estudo obteve como resultado que houve menor taxa de internação hospitalar nos pacientes que tiveram o peso alvo avaliado pela BIS juntamente com o exame clinico médico. O terceiro componente da tese é o artigo intitulado ***"BIS-guided versus clinical exam alone to guide target weight estimation in hemodialysis recipients - A Systematic Review and Meta-Analysis",*** onde foi realizado uma revisão sistemática e meta-análise como objetivo de avaliar a evidência científica atualmente disponível acerca do impacto da estimativa do peso alvo guiada por BIS em desfechos substitutos e clínicos em pacientes tratados por hemodiálise de manutenção. Este estudo que a utilização da BIS não é ampara suficientemente por evidência científica, devido a pouca literatura existentes, com artigos com alto risco de viés e baixa certeza de evidência. Sobre o artigo terceiro mencionado no projeto de pesquisa sobre a avaliação da qualidade de vida através do KDQOL, não foi realizado devido a coleta do instrumento não poder ser realizada devido ao período da pandemia. Esta tese conclui sugerindo a necessidade de mais estudos sobre o tema, com adequado rigor cientifico, maiores amostras e tempos de seguimento mais longos.

Palavras-chave: Hemodiálise, super-hidratação, estado de fluidos, bioimpedância de espectroscopia.

ABSTRACT

This thesis is basically composed of three components, the first component is the research project that was used for the qualification by the Catholic University of Pelotas, this research project shows how the research was carried out, what would be the procedures used and how it would be Data collection was carried out to create the three articles to complete the thesis. The second component of the thesis is the article entitled "Lower Incidence of Hospital Admissions in Bioimpedance-guided Fluid Management in Maintenance Hemodialysis Patients – Results of a Randomized Controlled Trial" which aimed to assess the impact on clinical outcomes of the use of bioimpedance (BIS) by spectroscopy in estimating the target weight for hemodialysis. The result of this study was that there was a lower rate of hospital admission in patients who had their target weight assessed by the BIS together with the clinical medical examination The third component of the thesis is the article entitled "BIS-guided versus clinical exam alone to guide target weight estimation in hemodialysis recipients - A Systematic Review and Meta-Analysis", where a systematic review and meta-analysis was performed to assess the currently available scientific evidence on the impact of BIS-guided target weight estimation on surrogate and clinical outcomes in patients treated by maintenance hemodialysis. This study that the use of the BIS is not sufficiently supported by scientific evidence, due to the little existing literature, with articles with high risk of bias and low certainty of evidence. Regarding the third article mentioned in the research project on the assessment of quality of life through kdcol, it was not carried out because the collection of the instrument could not be carried out due to the perilous of the pandemic. This thesis concludes by suggesting the need for more studies on the subject, with adequate scientific rigor, larger samples and longer follow-up times.

Keywords: Hemodialysis, overhydration, fluid status, bioimpedance spectroscopy.

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LISTA DE ABREVIATURAS E SIGLAS

BIA	Bioimpedância elétrica
BIS	Bioimpedância elétrica por espectroscopia
HD	Hemodiálise
PA	Pressão arterial
PS	Peso seco
DRC	Doença renal crônica

SUMÁRIO

APRESENTAÇÃO

A estimativa do peso seco (PS), principal guia na determinação do volume de ultra filtração a ser obtida em cada sessão de hemodiálise, geralmente é realizada com base no exame clínico, método que tem demonstrado baixa acurácia na avaliação do estado de hidratação. A bioimpedância por espectroscopia, por ser um método não invasivo, prático e rápido tem sido estudado como ferramenta adicional que visa aumentar a precisão na estimativa do PS. No entanto, poucos estudos têm avaliado o impacto clínico desta prática entre os pacientes tratados por hemodiálise de manutenção.

Em função dos motivos expostos acima, a presente tese foi formulada para revisar a literatura existente no tema e avançar no conhecimento através da condução de um ensaio clínico randomizado comparando os efeitos clínicos entre pacientes com PS estimado exclusivamente através de exame clínico com pacientes cujo PS foi estimado pelo exame clinico e guiado por dados obtidos do exame dos líquidos corporais pela bioimpedância por espectroscopia.

PROJETO DE PESQUISA

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Pelotas

2019

1.IDENTIFICAÇÃO

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1.2 Designação da titulação pretendida pelo autor: Doutorado

1.2 Orientador: Profª Dra Maristela Bohlke

1.4 Instituição: Universidade Católica de Pelotas (UCPel)

1.5 Curso: Doutorado em Saúde e Comportamento

1.6 Linha de pesquisa: Pesquisa clínica

1.7 Data: Abril de 2019

2. INTRODUÇÃO

A doença renal crônica (DRC) é caracterizada como uma doença que ocasiona uma perda leve, severa ou progressiva da função dos rins, sendo considerada como um importante problema saúde pública. Quando o indivíduo é acometido por essa enfermidade ele deve ter um tratamento mais precoce possível, devido as possíveis complicações que a doença pode gerar. Quando a doença atinge seu estágio mais avançado, a intervenção mais utilizada é a hemodiálise, podendo também ser empregada a diálise peritoneal ou o transplante renal. [1]

A hemodiálise foi desenvolvida a partir da década de 1940, com o intuito de encontrar um tratamento para os portadores de insuficiência renal aguda. No final de 1962 e início de 1963, foram implantadas as dialises peritoneal e a hemodiálise como forma de intervenção terapêutica para os indivíduos com DRC,[2] fatos de grande importância por aumentar a sobrevida de pacientes acometidos por essa enfermidade. Apesar dos avanços da medicina em relação ao tratamento da DRC, a mortalidade permanece elevada. [1]

A hemodiálise consiste em filtrar do sangue sustâncias como a ureia e a creatinina, que precisam ser eliminadas da corrente sanguínea, o que seria atribuição dos rins em falência. [3] A complicação mais frequente durante a hemodiálise é a hipotensão, devido ao grande volume de fluidos que é retirado durante a sessão.[3] Durante uma média de 4 horas, o método da hemodiálise pode remover 4 ou mais litros de líquido corporal. Se a quantidade correta de líquido não for retirada, o paciente pode sofrer de edema e congestão pulmonar ou hipotensão e desidratação. Cada sessão de HD tem por objetivo atingir o peso seco estimado. [4] O peso seco nada mais é do que o menor peso alcançado pós-diálise, em que o paciente não obtenha sintomas de hipotensão.

A determinação correta do peso seco em pacientes tratados por hemodiálise continua a ser um imenso problema para os nefrologistas. [4] O acréscimo de liquido no volume corporal total é um obstáculo frequente em pacientes com doença renal terminal tratados por hemodiálise, e está associado ao aumento da pressão arterial, hipertrofia ventricular esquerda e morte destes indivíduos [3] Controlar o estado volêmico dentro de um intervalo ideal e manter os pacientes com a quantidade de volume de líquido corporal adequada é, portanto, indispensável para diminuir o risco de doenças cardíacas e melhorar a qualidade de vida dos pacientes tratados por hemodiálise. O peso seco costuma ser

estimado na grande maioria dos centros de diálise através do exame clínico, conforme os sinais e sintomas dos pacientes. Novos métodos que busquem a padronização da avaliação do peso seco estão sendo buscados, sendo recentemente a bioimpedância por espectroscopia o procedimento mais promissor e resolutivo. [5] A bioimpedância é um dispositivo não invasivo que avalia a resistência elétrica e a reactância no tecido humano em resposta a passagem elétrica de baixa voltagem.[6] Existem três tipos de bioimpedância, sendo eles a de frequência única, a de multifrequência e a bioimpedância por espectroscopia. [7] Quando os resultados da bioimpedância são alcançados através de uma frequência de 50 Hz, este dispositivo é chamado de frequência única, que avalia o somatório da água intra e extracelular. O dispositivo de multifrequência estima o volume de água corporal, através de várias frequências (5 a100 Hz), as frequências baixas refletem somente a água extracelular, já as altas frequências refletem a água intra e extra celular. O recurso da bioimpedância de espectroscopia (BIS) é determinado em frequências de zero e a infinitas, que são utilizadas para diferenciar com maior precisão os componentes de água intra- e extracelular, elemento de máxima importância na determinação do peso seco, tendo em vista que o acúmulo de líquido inter dialítico se dá quase que inteiramente no ambiente extracelular (medido como hiperidratação através da BIS). [7]

A avalição pela bioimpedância tem a habilidade de aprimorar o controle do volume de líquido corporal, aumentando a precisão na determinação do peso seco. No entanto, essa tecnologia ainda é subutilizada em centros de hemodiálise. Um dos motivos para a inserção fragmentaria do método seria a lacuna existente na literatura em relação ao impacto da determinação do peso seco por BIS em desfechos clínicos significativos. [6]

Com o objetivo de acrescentar dados ao conhecimento atual acerca do tema, o atual estudo pretende comparar qualidade de vida, taxa de hospitalização e sobrevida cardiovascular e por todas as causas em pacientes portadores de doença renal crônica em tratamento por hemodiálise cujo peso seco foi estimado usando bioimpedância por espectroscopia e exame clínico com pacientes cujo peso seco foi estimado exclusivamente pelo exame clínico.

3. OBJETIVOS

3.1 Artigo 1

O Impacto da determinação do peso seco por bioimpedância na sobrevida de pacientes portadores de doença renal crônica tratados por hemodiálise.

3.1.1 Objetivo Geral

Comparar a sobrevida dos pacientes portadores de doença renal crônica tratados por hemodiálise, utilizando dois métodos dois métodos, um com a determinação do peso seco pela bioimpedância por espectroscopia junto com a avaliação clínica médica, e outro só pelo exame clínico isolado.

3.1.2 Objetivos Específicos

Comparar as taxas de internação e sobrevida em 2 anos de pacientes cujo peso seco foi estimado por BIS ou exame clínico isolado.

3.2Artigo 2

Impacto da determinação do peso seco por bioimpedância na qualidade de vida e taxa de hospitalização de pacientes portadores de doença renal crônica tratados por hemodiálise.

3.2.1 Objetivo Geral

Comparar a qualidade de vida dos pacientes portadores de doença renal crônica tratados por hemodiálise, utilizando dois métodos, um com a determinação do peso seco pela bioimpedância por espectroscopia junto com a avaliação clínica médica, e outro só pelo exame clínico isolado.

3.2.2 Objetivos Específicos

Comparar a qualidade de vida em 2 anos de pacientes cujo peso seco foi estimado por BIS ou exame clínico isolado.

3.2Artigo 3

Impacto da determinação do peso seco por bioimpedância na pressão arterial de pacientes portadores de doença renal crônica tratados por hemodiálise.

3.3.1 Objetivo Geral

Comparar a pressão arterial dos pacientes portadores de doença renal crônica tratados por hemodiálise, utilizando dois métodos, um com a determinação do peso seco pela

bioimpedância por espectroscopia junto com a avaliação clínica médica, e outro só pelo exame clínico isolado.

3.3.2 Objetivos Específicos

1). Comparar o número de classes e doses de medicamentos anti-hipertensivos usados por pacientes cujo peso seco foi estimado por cada um dos métodos;

2). Comparar as pressões arteriais sistólica e diastólica antes e após a sessão de HD entre pacientes cujo peso seco foi estimado por BIS ou exame clínico isolado.

4. HIPÓTESES

4.1 Hipóteses do Artigo 1

As taxas de internação e mortalidade em 2 anos dos pacientes cujo peso seco foi estimado pela BIS + exame clínico serão menores em relação a pacientes cujo peso seco foi estimado por exame clínico isolado;

4.2 Hipóteses do Artigo 2

A qualidade de vida dos pacientes cujo peso seco foi estimado com BIS + exame clínico será superior quando comparada àquela de pacientes que tiverem o peso seco avaliado somente por exame clínico;

4.3 Hipóteses do Artigo 3

O número de classes e doses de medicamentos anti-hipertensivos utilizados por pacientes cujo peso seco foi estimado por BIS + exame clínico serão menores em relação aos pacientes cujo peso seco foi estimado por exame clínico isolado.

5. REVISÃO DE LITERATURA

5.1 Bases de dados

A base de dado utilizada foram: PubMed e Scielo

5.2 Descritores

O descritor utilizado, para base de dados da PUBMED em língua inglesa, na busca de artigos, combinados conforme observados no Quadro 1, foi o seguinte: ((dry weight) AND ((("hemodialysis") OR "haemodialysis") OR "dialysis")) AND ((("bioimpedance") OR "electrical bioimpedance") OR "bioimpedance spectroscopy")

O descritor utilizado, para base de dados da Scielo em língua portuguesa, conforme no quadro 2, foi o seguinte: Hemodiálise

5.3 Limites

Os limites, utilizados com o intuito de focar a busca nos artigos mais específicos e recentes sobre os assuntos de interesse, foram os seguintes:

- Artigos escritos em língua inglesa, espanhola ou portuguesa.
- Estudos realizados em humanos

5.4 Achados da revisão

A revisão de literatura teve início em dezembro de 2017. Estão apresentados no Quadro 1 (busca no PUBMED) e no Quadro 2 (busca no Scielo)

Quadro 1. Combinação de descritores e número de títulos encontrados e selecionado na base de dados PUBMED.

Descritores	Encontrados	Selecionados
((dry weight) AND ((("hemodialysis") OR "haemodialysis") OR "dialysis")) AND ((("bioimpedance") OR "electrical bioimpedance") OR "bioimpedance spectroscopy")	136	17

Quadro 1. Combinação de descritores e número de títulos encontrados e selecionado na base de dados Scielo.

Descritores	Encontrados	Selecionados
Hemodiálise	159	6

5.5 Corpo da revisão

Na Alemanha, uma pesquisa realizada no Hospital do Sarre, Homburg, com o objetivo de avaliar a bioimpedância por espectroscopia em 15 pacientes, mostrou que o uso da mesma na determinação do peso seco em HD está associado a diminuição da pressão arterial e da massa ventricular esquerda. Concluiu que esse método para determinar o peso seco em pacientes em hemodiálise foi considerado seguro, podendo levar a desfechos clínicos favoráveis. [8]

Com o objetivo de avaliar a eficácia da bioimpedância na determinação do peso seco, um estudo realizado em Israel avaliando 21 pacientes, obteve como resultado que um novo modelo de BIS de corpo inteiro é um meio seguro para prognosticar peso alvo quando este está próximo da hidratação normal. [9]

Em 2011 foi realizado um estudo em Taiwan que teve como objetivo analisar a viabilidade da bioimpedância na avaliação do peso seco em 194 pessoas. Esta pesquisa concluiu que o dispositivo é promissor e que pode prontamente ser adotado na prática clínica a beira do leito. [10]

Um estudo realizado em 2012 com 41 pacientes do centro de diálise da Universidade de Pequim, teve como objetivo comparar três equações inseridas na bioimpedância e a exame clínico para avaliação do peso seco. Este estudo demonstrou que o peso seco calculado pela equação de Carlos Basile, que leva em consideração gênero, peso, altura, idade e pós-diálise, foi a que obteve o resultado mais correlacionado ao exame clínico. Além disso relata que a bioimpedância de frequência única combinada com a avalição clínica rigorosa por parte dos profissionais da medicina pode melhorar a estimativa do peso seco nos pacientes em hemodiálise de manutenção. [5]

Um artigo de revisão publicado em 2014, conduzido por Davies e Davenport, obteve como resultado que bioimpedância não apenas auxilia na detecção de desidratação como ajuda no ajuste do peso alvo, além de auxiliar na avalição nutricional. [11]

Em uma revisão sistemática realizada em 2017, foi avaliada a bioimpedância na determinação do peso seco e da sobrecarga de líquido em pacientes tratados por hemodiálise, com diagnóstico de doença renal crônica terminal. Essa revisão incluiu 7 artigos, e conclui que ações por intermédio do resultado da bioimpedância para correção da sobrecarga do volume de líquido têm pouca ou nenhuma influência em relação a mortalidade, entretanto melhorou o ajuste da pressão arterial sistólica. [12]

Estudo conduzido por Stemberg et al, publicado em 2018, avaliou 25 profissionais da área da saúde em13 unidades de hemodiálise de 4 regiões suecas com meta de verificar barreiras e facilitadores percebidos pelos profissionais da área da nefrologia no uso da bioimpedância na estimativa do peso seco. Os autores citam estudos transversais que mostram que este dispositivo está presente em vários locais que oferecem hemodiálise, porém somente 25% deles utilizam o método. As barreiras identificadas foram a credibilidade insuficiente, conhecimento insuficiente, eficácia limitada, falta de estrutura e regulamentos contraditórios e os facilitadores foram a inovação, o contexto organizacional e a característica não invasiva. [6]

Outro estudo realizado em 2018, teve como objetivo analisar os vários tipos de bioimpedância elétrica para avaliação do peso seco, e obteve que este método é conveniente para controlar o volume em pacientes tratados por hemodiálise, e refere que estudos que busquem um método de padronização na avaliação do peso seco são indispensáveis. [7]

Um estudo realizado em 2019, incluindo pacientes em hemodiálise crônica no Hospital universitário de La Paz, e com intuito de avaliar a bioimpedância elétrica como meio de atingir o peso seco dos pacientes em hemodiálise, obteve como resultado que o peso seco foi atingido em 84% dos pacientes no final da pesquisa com uma redução expressiva da pressão arterial. Concluiu que a bioimpedância elétrica é um método útil para estipular o peso seco de pessoas tratadas por hemodiálise. [13]

6. METODOLOGIA

6.1. Delineamento

Este estudo será delineado como um ensaio clínico randomizado e controlado.

6.2. Ambiente

O estudo será conduzido no setor de hemodiálise do Hospital Universitário São Francisco de Paula da Universidade Católica de Pelotas.

6.3. Amostra

A amostra será composta por pacientes portadores de doença renal crônica tratados por hemodiálise no hospital sede do estudo.

6.3.1. Critérios de inclusão

Todos os pacientes adultos (igual ou maior a 18 anos de idade) portadores de doença renal crônica tratados no referido setor há um período de tempo igual ou superior a três meses.

6.3.2. Critérios de exclusão

Pacientes em uso de marcapasso cardíaco ou com amputação de membros inferiores.

6.3.3. Cálculo do tamanho da amostra

O desfecho principal do presente estudo é a comparação da sobrevida em 2 anos entre pacientes cujo peso seco foi estimado por exame clínico isolado ou BIS + exame clínico. Considerando que a taxa de mortalidade anual aproximada conforme a literatura para pacientes portadores de DRC e tratados por HD é de 15%, e considerando que esperamos obter um acréscimo de sobrevida de 20% para pacientes cujo peso seco foi estimado pelo método combinado, estimamos a necessidade mínima de 134 pacientes (67 em cada braço do estudo)

Figura 1: Resultado de cálculo de tamanho de amostra gerado por Stata 15.1

. power logrank 0.70 0.90, power (0.8 0.85 0.9)

Estimated sample sizes for two-sample comparison of survivor functions

Log-rank test, Freedman method

Ho: HR = 1 versus Ha: HR!= 1

alpha	power	N	N1	N2	E	delta	ratio	s1	s2	Pr_E
.05	.8	134	67	67	27	.2954	.2954	.7	.9	.2
.05	.85	152	76	76	31	.2954	.2954	.7	.9	.2
.05	.9	178	89	89	36	.2954	.2954	.7	.9	.2

6.3.4. Randomização e Cegamento

O processo de randomização será realizado através da criação de uma tabela de números aleatórios no pacote estatístico Stata versão 15.1. Os pacientes serão randomizados em blocos por turnos de diálise (manhã, tarde e noite). Somente os avaliadores dos desfechos e responsáveis pela análise estatística estarão cegados, tendo em vista a característica de avaliação impedir o cegamento dos demais envolvidos.

6.4. Desfechos

6.4.1. Desfecho Primário:

Sobrevida em 2 anos.

6.4.2. Desfechos Secundários:

Mortalidade cardiovascular em 2 anos; taxa de hospitalização e tempo de internação em 2 anos; qualidade de vida ao final de 2 anos; taxas de controle de pressão

arterial sistólica e diastólica (conforme diretrizes vigentes); número de classes e doses de anti-hipertensivos utilizados para o controle da pressão arterial.

6.5. Logística:

Depois da obtenção da assinatura do termo de consentimento livre e esclarecido (TCLE) (APÊNDICE I), o paciente será alocado em um dos dois grupos pelo método randomização.

Grupo 1: O paciente receberá o instrumento KDQOL (APÊNDICE I) para avaliação da qualidade de vida e terá o peso seco avaliado através do exame clínico (ausculta pulmonar, verificação da pressão arterial, e investigação de edema) realizado por um médico nefrologista. Enquanto o participante do estudo realiza a hemodiálise será coletado em seu prontuário dados como: Tempo de hemodiálise; medicamentos utilizados; taxa de internação. Após um mês o participante passará novamente pelo mesmo processo. O seguimento será estendido até um total de 24 meses.

Grupo 2: O paciente receberá o instrumento KDQOL (APÊNDICE I) para avaliação da qualidade de vida. Depois do preenchimento do questionário ele terá peso seco avaliado através do exame clínico (ausculta pulmonar, verificação da pressão arterial, e investigação de edema) realizado por um médico nefrologista juntamente com bioimpedância por espectroscopia. Enquanto o participante do estudo realiza a hemodiálise será coletado em seu prontuário dados como: Tempo de hemodiálise; medicamentos utilizados; taxa de internação. Após um mês o participante passará novamente pelo mesmo processo. O seguimento será estendido até um total de 24 meses.

A Intervenção proposta pelo estudo será adicionar a Bioimpedância por espectroscopia ao exame clínico médico para determinação do peso seco.

6.5. Procedimentos e Instrumentos

6.5.1. Bioimpedância por Espectroscopia

O modelo de bioimpedância utilizado será o da BIS (Modelo multifrequêncial; Monitor de Composição Corporal - BCM) da marca Fresenius®. Este modelo de

avaliação mede o conteúdo de água corporal, através de sinais elétricos de alta frequência que refletem a água intracelular e extracelular, juntamente com os sinais de baixa frequência, que refletem a água extracelular. [14]

A avaliação da composição corporal realizada pela BIS associada pelo exame clínico médico serão realizados mensalmente antes e após uma sessão de hemodiálise de meio de semana. A medida será realizada por pessoal previamente treinado antes de uma sessão de HD no meio da semana, após cinco minutos de repouso em decúbito dorsal, utilizando eletrodos colocados nos membros superiores e inferiores ipsilaterais. O paciente foi orientado a evitar café ou qualquer refeição 30 minutos antes da avaliação.

6.5.2 Exame clínico médico:

O exame clínico básico atualmente preconizado para a estimativa do peso seco envolve a medida da pressão arterial, a ausculta pulmonar e a avaliação de membros inferiores (ou região sacral em pacientes acamados) em busca de edema. O exame clínico será realizado mensalmente por um nefrologista antes e após uma sessão de hemodiálise de meio de semana.

A pressão arterial será aferida conforme a International Society of Hypertension Global Hypertension Practice Guidelines utilizando um esfigmomanômetro aneroide da marca Tycos, Welch Allyn, USA.O paciente será colocado sentado em uma cadeira, com o braço esticado, a seguir o manguito do aparelho será colocado superiormente de 2 a 3 cm da sua fossa cubital, o estetoscópico será colocado na artéria braquial e o manguito será inflado a fim de obter o resultado da pressão arterial. A ausculta pulmonar será realizada através de um estetoscópico da marca Litmann, (3M, USA) o qual será posicionado na região torácica posterior do paciente para ausculta de murmúrio vesicular e eventuais ruídos adventícios. A verificação do edema será realizada através da digitopressão da área alvo (membros inferiores ou região sacral e posterior constatação da formação de cacifo e de sua extensão.

6.5.3. Qualidade de vida:

Através do instrumento Kidney Disease Quality of Life Short Form (KDQOL-SF) (APÊNDICE II) que avalia a qualidade de vida em pacientes com doença renal em tratamento por hemodiálise, através de 24 questões relacionadas a saúde, atividades físicas, dor, estado emocional, efeitos da doença renal e satisfação com o tratamento. O

referido instrumento foi validado no ano de 2003 em São Paulo para língua portuguesa pela autora Priscila Duarte Silveira na Faculdade de Medicina de são José de Rio Preto.

O questionário auto aplicado será entregue para o preenchimento pelo paciente após a assinatura do TCLE

6.5.4. Sobrevida e Medicamentos Anti-hipertensivos:

Estas variáveis serão coletadas através do prontuário hospitalar dos pacientes enquanto os participantes da pesquisa estiverem realizando a hemodiálise.

6.4. Análise de dados

Os dados serão codificados e digitados no programa Excel. A análise estatística será feita através do programa Stata 15.1. Para a descrição das características da amostra será utilizada estatística descritiva. As variáveis serão testadas para o padrão de distribuição (paramétrico ou não paramétrico) pelo teste de Shapiro-Wilk. As curvas de sobrevida construídas através de Kaplan Meier serão comparadas entre pacientes cujo peso seco foi avaliado pelos diferentes métodos com análise de Log Rank. As taxas de internação entre os diferentes grupos serão avaliadas através de teste t e as taxas de controle adequado da pressão arterial e número de medicamentos anti-hipertensivos por qui-quadrado.

6.5. Aspectos éticos

Os pacientes tratados por hemodiálise no setor em estudo, e que adequados ao estudo conforme os critérios de inclusão e exclusão serão informados a respeito da pesquisa e de seus objetivos. Os indivíduos que aceitarem participar irão receber o Termo de Consentimento Livre e Esclarecido (APENDICE II) que deve ser lido e assinado. O projeto está de acordo com a resolução 466, foi submetido e aprovado pelo Comitê de Ética em Pesquisa da Universidade Católica de Pelotas pelo número do parecer 3.484.130. O projeto foi aceito pelo NIEPAS (Núcleo de Integração Ensino e Pesquisa) que aprovou a realização do estudo no Hospital Universitário São Francisco de Paula da Universidade Católica de Pelotas

6. 6Cronograma

	2019													2020												2021				
Atividades	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	***17***	***18***	***19***	***20***	***21***	***22***	***23***	***24***	***25***	***26***	***27***	***28***	***29***	***30***
Revisão de Literatura	**X**	**x**	**x**	**x**	**x**	**x**	**x**	**X**	**x**	**x**	**x**	**X**	**X**	**x**	**x**	**X**														
Elaboração do Projeto		**x**	**x**	**x**																										
Qualificação						**x**																								
Trabalho de campo						**x**	**x**	**X**	**x**	**x**	**x**	**x**	**X**	**x**	**x**	**X**	**x**	**x**	**x**	**X**	**x**	**x**	**X**	**x**	**x**	**x**	**x**	**x**	**x**	
Digitação dos dados															**x**	**X**	**x**	**x**	**x**	**X**	**x**	**x**	**X**	**x**	**x**	**x**	**x**	**x**	**x**	
Análise dos resultados																													**x**	
Redação do artigo																											**x**	**x**	**x**	
Defesa da tese																														**x**

7. Orçamento

Item	**Quantidade**	**Valor Total**
Lápis	20	15,40
Caneta	20	15,60
Borracha	20	50,00
Folha de ofício	1.500	71,70
Cartucho impressora	2	67,80
Eletrodos para bioimpedância	600	450,0
	Total:	**670,50**

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QUESTIONÁRIO

Estamos entrevistando pacientes que utilizam a hemodiálise para um trabalho sobre comparação entre bioimpedância elétrica e a análise clínica médica para avaliação do peso seco. Para isso, precisamos de sua colaboração e compreensão. Sua participação é muito importante! As informações deste questionário serão mantidas em sigilo (segredo). Desde já agradecemos sua disponibilidade.

Quest __ __ __ __ **Prontuário** __ __ __ __ __ __ **Data de aplicação:** ____ **/**____ **/** _____

Nome: _____

Telefone:_____ - _____

1. Em geral, você diria que sua saúde é:

( ) Excelente ( ) Muito boa ( ) Boa

( ) Regular ( ) Ruim

2. <u>Comparada há um ano atrás</u>, como você avaliaria sua saúde em geral <u>agora</u>?

( ) Muito melhor ( ) Um pouco melhor ( ) aproximadamente igual

( ) Um pouco pior ( ) Muito pior

3. Os itens seguintes são sobre atividades que você pode realizar durante um dia normal. <u>Seu estado de saúde atual o dificulta</u> a realizar estas atividades? atualmente?

Pergunta	Dificulta Muito	Dificulta um pouco	Não Dificulta
Atividades que requerem muito esforço, como corrida, levantar objetos pesados participar de esportes que requerem muito esforço			
Atividades moderadas, tais como mover uma mesa, varrer o chão, jogar boliche, ou caminhar mais de uma hora			
Levantar ou carregar compras de supermercado			
Subir vários lances de escada			
Subir um lance de escada			
Inclinar-se, ajoelhar-se, ou curvar-se			
Caminhar mais do que um quilômetro			
Caminhar vários quarteirões			
Caminhar um quarteirão			
Tomar banho ou vestir-se			

4. Durante as 4 últimas semanas, você tem tido algum dos problemas seguintes com seu trabalho ou outras atividades habituais, devido a sua saúde física?

Você reduziu a quantidade de tempo que passa trabalhando ou em outras atividades ( ) sim ( ) não
Fez menos coisas do que gostaria ( ) sim ( ) não
Sentiu dificuldade no tipo de trabalho que realiza ou outras atividades ( ) sim ( ) não
Teve dificuldade para trabalhar ou para realizar outras atividades ( ) sim ( ) não

5. Durante as 4 últimas semanas, você tem tido algum dos problemas abaixo com seu trabalho ou outras atividades de vida diária devido a alguns problemas emocionais (tais como sentir-se deprimido ou ansioso)?

Reduziu a quantidade de tempo que passa trabalhando ou em outras atividades ( ) sim ( ) não
Fez menos coisas do que gostaria ( ) sim ( ) não
Trabalhou ou realizou outras atividades com menos atenção do que de costume ( ) sim ( ) não

6. Durante as 4 últimas semanas, até que ponto os problemas com sua saúde física ou emocional interferiram com atividades sociais normais com família, amigos, vizinhos, ou grupos?

( ) Nada ( ) Moderadamente ( ) Extremamente
( ) Um pouco ( ) Bastante

7. Quanta dor no corpo você sentiu durante as 4 últimas semanas?

( ) Nada ( ) Leve ( ) Intensa
( ) Um pouco ( ) Moderada ( ) Muito intensa

8. Durante as 4 últimas semanas, quanto a dor interferiu com seu trabalho habitual (incluindo o trabalho fora de casa e o trabalho em casa)?

( ) Nada ( ) Moderadamente ( ) Extremamente
( ) Um pouco ( ) Bastante

9. Estas questões são sobre como você se sente e como as coisas tem acontecido com você durante as 4 últimas semanas. Para cada questão, por favor dê uma resposta que mais se aproxime da forma como você tem se sentido. Durante as 4 últimas semanas, quanto tempo...

10. Durante as 4 últimas semanas, por quanto tempo os problemas de sua saúde física ou emocional

Pergunta	Todo o tempo	A maior parte do tempo	Uma boa parte do tempo	Alguma parte do tempo	Uma pequena parte do tempo	Nenhum momento
Você se sentiu cheio de vida?						
Você se sentiu uma pessoa muito nervosa?						
Você se sentiu tão "para baixo" que nada conseguia animá-lo?						
Você se sentiu calmo e tranquilo?						
Você teve muita energia?						
Você se sentiu desanimado e deprimido?						
Você se sentiu esgotado (muito cansado)?						
Você se sentiu uma pessoa feliz?						
Você se sentiu						

interferiram com suas atividades sociais (como visitar seus amigos, parentes, etc.)?

( ) Todo tempo ( ) Alguma parte do tempo ( ) Nenhum momento
( ) A maior parte do tempo ( ) Uma pequena parte do tempo

11. Por favor, escolha a resposta que melhor descreve até que ponto cada uma das seguintes declarações é verdade ou falso para você.

12. Até que ponto cada uma das seguintes declarações é verdadeira ou falsa para você?

Pergunta	Sem Dúvida Verdade	Geralmente Verdade	Não Sei	Geralmente Falso	Sem dúvida Falso
Parece que eu fico doente com mais facilidade do que outras pessoas cheias de vida?					
Eu me sinto tão saudável quanto qualquer pessoa que Conheço					
Eu me sinto tão saudável quanto qualquer pessoa que conheço					
Acredito que minha saúde vai piorar					
Minha saúde está excelente					

13. Estas questões são sobre como você se sente e como tem sido sua vida nas 4 últimas semanas.

Pergunta	Sem Dúvida Verdade	Geralmente Verdade	Não Sei	Geralmente Falso	Sem dúvida Falso
Minha doença renal interfere demais com a minha vida					
Muito do meu tempo é gasto com minha doença renal					
Eu me sinto decepcionado ao lidar com minha doença Renal					
Eu me sinto um peso para minha família					

Para cada questão, por favor assinale a resposta que mais se aproxima de como você tem se sentido.

14. Durante as 4 últimas semanas, quanto você se incomodou com cada um dos seguintes problemas?

Pergunta	Nenhum momento	Uma pequena parte do tempo	Uma boa parte do tempo	Alguma parte do tempo	A maior parte do tempo	Todo o tempo
Você se isolou (se afastou) da pessoas ao seu redor?						
Você demorou para reagir às coisas que foram ditas ou aconteceram?						
Você se irritou com as pessoas próximas?						
Você teve dificuldade para concentrar-se ou pensar?						
Você se relacionou bem com as outras pessoas						
Você se sentiu confuso?						

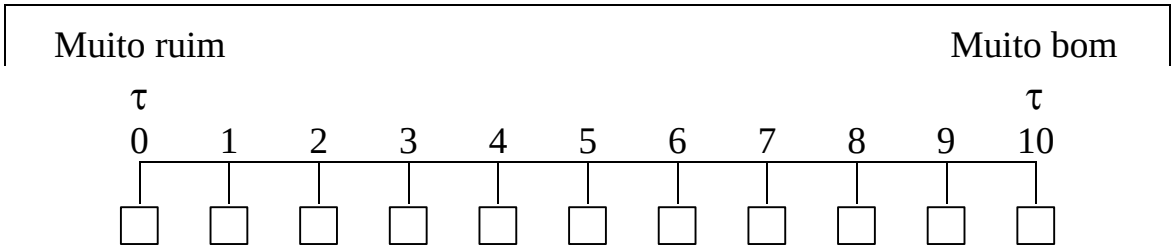
Pergunta	Não me Incomodou De forma alguma	Fiquei um Pouco incomodado	Incomodou de forma moderada	Muito incomodada	Extremamente incomodada
Dores musculares?					
Dor no peito					
Câimbra					
Coceira na pele					
Pele seca					
Falta de ar					
Fraqueza ou tontura					
Falta de apetite					
Esgotamento (cansaço)					
Formigamento					
Vômito / indisposição					
Problemas com acesso					

15. Algumas pessoas ficam incomodadas com os efeitos da doença renal em suas vidas diárias, enquanto outras não. Até que ponto a doença renal lhe incomoda em cada uma das seguintes áreas?

16. Você teve alguma atividade sexual nas 4 últimas semanas?

( ) sim
( ) não

17. Em uma escala de 0 a 10, como você avaliaria seu sono em geral? [Marque um X abaixo do número.]



18. Com que frequência, durante as 4 últimas semanas você...

Pergunta	Não me Incomodou De forma alguma	Fiquei um Pouco incomodado	Incomodou de forma moderada	Muito Incomodo	Extremamente Incomodo
Diminuição de líquido					
Diminuição alimentar?					
Sua capacidade de trabalhar em casa?					
Sua capacidade de viajar?					
Depender dos médicos e outros profissionais da saúde?					
Estresse ou preocupações causadas pela doença renal?					
Sua vida sexual?					
Sua aparência?					

19. Em relação à sua família e amigos, até que ponto você está satisfeito com...

A quantidade de tempo que você passa com sua família e amigos?

( ) Muito insatisfeito ( ) Um pouco insatisfeito ( ) Um pouco satisfeito
( ) Muito satisfeito

O apoio que você recebe de sua família e amigos?

( ) Muito insatisfeito ( ) Um pouco insatisfeito ( ) Um pouco satisfeito
( ) Muito satisfeito

20. Durante as 4 últimas semanas, você recebeu dinheiro para trabalhar?

( ) sim
( ) não

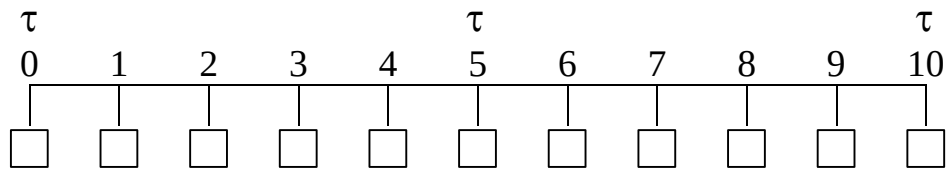
Pergunta	Nenhum momento	Uma pequena parte do tempo	Uma boa parte do tempo	Alguma parte do tempo	A maior parte do tempo	Todo o tempo
Acordou durante a noite e teve dificuldade para voltar a dormir?						
Dormiu pelo tempo necessário?						
Teve dificuldade para ficar acordado durante o dia?						

21. Sua saúde o impossibilitou de ter um trabalho pago?

( ) sim
( ) não

22. No geral, como você avaliaria sua saúde?

A pior possível (tão ruim ou pior do que estar morto)	Meio termo entre pior e melhor	A melhor possível



23. Pense a respeito dos cuidados que você recebe na diálise. Em termos de satisfação, como você classificaria a amizade e o interesse deles demonstrado em você como pessoa?

( ) Muito ruim ( ) Regular ( ) Bom ( ) Muito bom
( ) Ruim ( ) Excelente ( ) O melhor

24. Quanto cada uma das afirmações a seguir é verdade ou falso?

Pergunta	Sem Dúvida Verdade	Geralmente Verdade	Não Sei	Geralmente Falso	Sem dúvida Falso
O pessoal da diálise me encorajou a ser o mais independente possível					
O pessoal da diálise ajudou-me a lidar com minha doença renal					

Prontuário __ __ __ __ __ __ **Data:** ____ **/**____ **/** _____

Nome:

Medicamentos:

Taxa de internação:

Pressão arterial (antes HD): **Pressão arterial (pós HD):**

Ausculta pulmonar (antes HD) **Ausculta pulmonar (pós HD)**

Teste de edema (antes HD) **Teste de edema (pós HD)**

Bioimpedância:

APÊNDICE I

UNIVERSIDADE CATÓLICA DE PELOTAS
DOUTORADO EM SAÚDE E COMPORTAMENTO
TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Gostaríamos de convidá-la para participar do estudo "A Comparação da bioimpedância elétrica e a análise clínica médica para avalição do peso seco dos usuários da hemodiálise. Antes de sua participação neste estudo, é preciso esclarecer alguns detalhes importantes, para que possíveis dúvidas sejam resolvidas. Em caso de qualquer dúvida você poderá contatar a enfermeira Kaiane Stigger, pelo telefone (53) 98129-7291.

Qual é o objetivo da pesquisa?

Comparar a bioimpedância elétrica e o exame clinico para avaliação do peso seco dos pacientes portadores de Doença Renal Crônica tratados por Hemodiálise.

Como será realizada a pesquisa?

Aos usuários da hemodiálise que aceitarem participar do estudo terão o peso seco avaliado. Após um mês o peso seco do participante será avaliado novamente e será aplicado um questionário, com perguntas referentes a qualidade de vida. A sua identidade será mantida em sigilo.

Quais os riscos em participar?

Não há qualquer risco em participar deste projeto.

O que a paciente ganha com este estudo?

Ser acompanhado pelos profissionais que estão realizando o estudo

Quais são os direitos das participantes?

Os seus dados e registros médicos serão sempre tratados confidencialmente. Os resultados deste estudo poderão ser usados para fins científicos, mas você não será identificada.
Sua participação no estudo é voluntária. Caso você decida não participar, ou desistir a qualquer momento, isto não afetará no tratamento normal que tem direito.

Declaração da entrevistada:

Eu, _____,
declaro que após receber informações, aceito participar desta pesquisa. Além disso, declaro ter recebido uma cópia deste consentimento e que uma cópia assinada por mim será mantida pela equipe da pesquisa.
Assinatura da entrevistada:_____

Declaração de responsabilidade do entrevistador:

Eu, _____,
declaro ter explicado sobre a natureza deste estudo e me coloquei à disposição para esclarecer as suas dúvidas.
Assinatura do entrevistador: _____

Pelotas, _____ de _____ de 20 ___.

APROVAÇÃO COMITÊ DE ÉTICA UCPEL

UNIVERSIDADE CATÓLICA DE PELOTAS - UCPEL

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: COMPARAÇÃO DA BIOIMPEDÂNCIA POR ESPECTROSCOPIA COM O EXAME CLÍNICO NA DETERMINAÇÃO DE PESO SECO DE PACIENTES PORTADORES DE DOENÇA RENAL CRÔNICA EM TRATAMENTO POR HEMODIÁLISE

Pesquisador: KAIANE FUHRMANN STIGGER

Área Temática:

Versão: 2

CAAE: 14907019.2.0000.5339

Instituição Proponente: Universidade Católica de Pelotas - UCPel

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.484.130

Apresentação do Projeto:

Trata-se de um projeto de tese de doutorado do Programa de Pós-Graduação em Saúde e Comportamento da Universidade Católica de Pelotas. O projeto busca avaliar o uso da bioimpedância por espectroscopia associado ao exame clínico para determinação do peso seco de pacientes portadores de doença renal crônica em tratamento por hemodiálise.

Objetivo da Pesquisa:

Objetivo geral:

Comparar a bioimpedância por espectroscopia e exame clínico com exame clínico isolado para a determinação do peso seco dos pacientes portadores de doença renal crônica tratados por hemodiálise.

Objetivos específicos:

1) Comparar as taxas de internação e mortalidade em 2 anos de pacientes cujo peso seco foi estimado por bioimpedância por espectroscopia ou por exame clínico isolado;

2) Comparar a qualidade de vida em 2 anos de pacientes cujo peso seco foi estimado por bioimpedância por espectroscopia ou exame clínico isolado;

3) Comparar o número de classes e doses de medicamentos anti-hipertensivos usados por pacientes cujo peso seco foi estimado por cada um dos métodos;

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UF: RS **Município:** PELOTAS
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UNIVERSIDADE CATÓLICA DE PELOTAS - UCPEL

Continuação do Parecer: 3.484.130

Avaliação dos Riscos e Benefícios:
Refeita

Comentários e Considerações sobre a Pesquisa:
Atendidos

Considerações sobre os Termos de apresentação obrigatória:
Apresentados

Recomendações:
Atendidas

Conclusões ou Pendências e Lista de Inadequações:
Atendidas

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1352843.pdf	17/07/2019 13:49:55		Aceito
Outros	cartadependencia.pdf	17/07/2019 13:48:40	KAIANE FUHRMANN STIGGER	Aceito
Outros	cartacep.docx	03/07/2019 14:12:04	KAIANE FUHRMANN STIGGER	Aceito
Outros	instrumentodapesquisa.pdf	03/07/2019 14:04:10	KAIANE FUHRMANN STIGGER	Aceito
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Outros	CURRICULO.pdf	30/05/2019 17:18:13	KAIANE FUHRMANN STIGGER	Aceito
Outros	termohu.pdf	23/05/2019 15:00:58	KAIANE FUHRMANN STIGGER	Aceito
Projeto Detalhado / Brochura Investigador	projfinalpdf.pdf	23/05/2019 14:29:17	KAIANE FUHRMANN STIGGER	Aceito
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Cronograma	cronogramapdf.pdf	23/05/2019 14:27:54	KAIANE FUHRMANN STIGGER	Aceito
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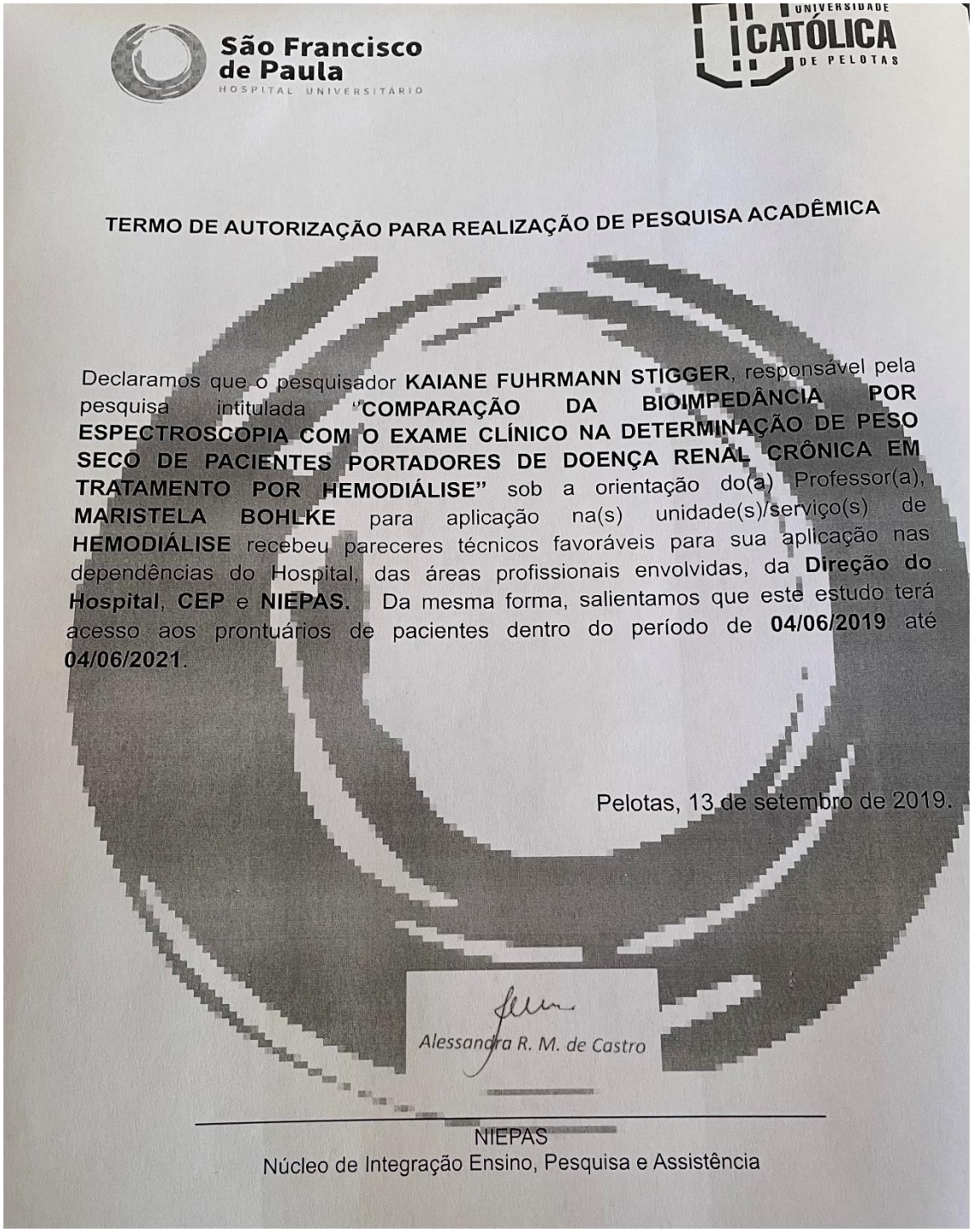
Não

PELOTAS, 04 de Agosto de 2019

Assinado por:
RICARDO AZEVEDO DA SILVA
(Coordenador(a))

APROVAÇÃO NIEPAS (HUSFP)



São Francisco de Paula
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TERMO DE AUTORIZAÇÃO PARA REALIZAÇÃO DE PESQUISA ACADÊMICA

Declaramos que o pesquisador **KAIANE FUHRMANN STIGGER**, responsável pela pesquisa intitulada **"COMPARAÇÃO DA BIOIMPEDÂNCIA POR ESPECTROSCOPIA COM O EXAME CLÍNICO NA DETERMINAÇÃO DE PESO SECO DE PACIENTES PORTADORES DE DOENÇA RENAL CRÔNICA EM TRATAMENTO POR HEMODIÁLISE"** sob a orientação do(a) Professor(a), **MARISTELA BOHLKE** para aplicação na(s) unidade(s)/serviço(s) de **HEMODIÁLISE** recebeu pareceres técnicos favoráveis para sua aplicação nas dependências do Hospital, das áreas profissionais envolvidas, da **Direção do Hospital**, **CEP** e **NIEPAS.** Da mesma forma, salientamos que este estudo terá acesso aos prontuários de pacientes dentro do período de **04/06/2019** até **04/06/2021**.

Pelotas, 13 de setembro de 2019.

Alessandra R. M. de Castro

NIEPAS
Núcleo de Integração Ensino, Pesquisa e Assistência

ARTIGO 1

Bioimpedance spectroscopy-guided versus clinical exam alone to guide target weight estimation in hemodialysis recipients - A Systematic Review and Meta-Analysis

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Abstract

Background: Hemodialysis (HD), despite sustaining life in kidney failure, often did not provide adequate fluid balance. Bioimpedance spectroscopy (BIS) is a tool that may contribute to the estimation of target weight (TW), the basis for HD fluid removal. **Objectives:** This systematic review and meta-analysis integrated randomized controlled trials (RCTs) that compared clinical outcomes between BIS-guided evaluation and clinical assessment alone to estimate TW in patients on maintenance HD. **Search methods:** The MEDLINE, Web of Science, Embase and Cochrane CENTRAL databases were searched using PICOT-based strategies. **Data collection and analysis:** Two authors independently extracted data, assessed the study's risk of bias (Cochrane risk of bias tool) and analyzed the certainty of the evidence (GRADE). Treatment effect was expressed as mean difference for continuous outcomes, risk ratio for dichotomous outcomes and hazard ratio (HR) or rate ratio for time-related endpoints. **Main results:** Eleven studies (1,923 participants) with a mean follow-up of 12.3 months were included. There was no difference between intervention and control groups in all-cause mortality (3 studies, 679 participants; HR 1.07, 95%CI 0.77-1.48), incidence of hospital admissions (2 studies, 548 participants; HR 1.07, 95%CI 0.80-1.43), acute overload (2 studies, 548 participants; HR 0.87, 95%CI 0.59-1.23), composite outcome of death or CV events (2 studies, 695 participants, HR 0.83 95%CI 0.59-1.17), intra-dialytic complications, fluid overload, blood pressure, left ventricular mass index, pulse wave velocity or serum levels of NT-proBNP. Most studies presented a high risk of bias. **Authors' conclusions:** Currently, there is insufficient evidence of clinical benefit of BIS-guided target weight estimation in HD recipients to justify the widespread use of this technological adjunct.

Background

Description of the condition: Chronic kidney disease (CKD) is an emerging public health problem around the world[1]. In the most advanced stage of CKD, kidney failure, patients require renal replacement therapy (RRT) to survive. Worldwide, the most used RRT method is hemodialysis (HD)[2]. Despite being a life-sustaining therapy, HD is intermittent and lacks the sophisticated kidney apparatus for regulating body fluids. The often-resulting fluid overload or depletion is associated with shorter survival among patients on maintenance hemodialysis[3,4].

Description of the intervention: The amount of fluid to be removed for each HD session is usually estimated with base on the target weight (TW). TW, often estimated by clinical examination, is considered the weight at which patients present no sign of volume overload (edema, lung crackles or hypertension) or volume depletion (hypotension, cramps). However, this method of TW estimation is known to present low accuracy[4]. Bioimpedance spectroscopy (BIS) has been proposed as an ancillary technology for TW estimation[5,6], but studies about its impact on clinical endpoints, such as survival or hospital admissions rate, are scarce and present heterogenous results[7–11].

How the intervention might work: BIS is a multi-frequency bioelectrical impedance analysis (BIA) modality. This equipment uses the electrical properties of tissues to estimate their different components. BIS uses a wider range of frequencies, which is useful to better differentiate intra- and extra-cellular water (where fluid usually accumulates between HD sessions), allowing the determination of a parameter known as over-hydration (OH)[12]. OH is the difference between the expected extra-cellular water according to sex, age, weight and height, and the volume of extra-cellular water actually found. The OH measured before an HD session could be an adjunct guide to determine the volume of fluid to be removed by HD.

Why it is important to do this review: Current evidence on the benefits of using BIS as an adjunct to clinical evaluation to determine target weight is heterogeneous. This review intends to evaluate these findings together through a meta-analysis, trying to clarify the issue.

Objectives: The present review intends to assess the current evidence on the clinical impact of the use of BIS added to clinical evaluation compared to clinical evaluation alone in estimating target weight in maintenance HD recipients.

Methods

Criteria for considering studies for this review

Types of studies: Randomized controlled trials (RCT), quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods), and cluster RCTs that evaluated the benefits and harms of BIS-guided dry weight estimation in adults on maintenance HD.

Types of participants

Inclusion Criteria: Studies enrolling adults with CKD on maintenance HD for three months or longer, undergoing HD sessions of at least four hours, thrice weekly were included. **Exclusion Criteria:** Studies with participants without kidney failure or with kidney failure but treated with other modalities of renal replacement therapy (peritoneal dialysis or kidney transplantation), or participants younger than 18 years of age were excluded.

Types of interventions: We included studies that compared BIS-guided TW estimation (alone or in combination with clinical data or another tool, with a pragmatic or structured decision flow including a pre-designed algorithm) with target weight estimation based on clinical examination alone.

Types of outcome measures: There was no restriction on outcomes in the search for RCTs. However, clinical endpoints were considered of highest interest.

Primary outcomes: Survival, mortality, quality of life and rate of hospital admissions.

Secondary outcomes: All other outcomes described, including harms, were included in the review.

Search methods for identification of studies

Electronic searches: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (PubMed), Science Citation Indexes (Web of Science), EMBASE,

the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov. The strategies included only the population and intervention domains of the acronym PICOT, opting for a comprehensive approach. The strategy in MEDLINE (adapted with the same terms for the other databases) was:

1. dry weight/
2. exp hemodialysis/
3. haemodialysis/
4. dialysis/
5. or/2-4
6. bioimpedance spectroscopy/
7. BIS/
8. exp bioimpedance/
9. electrical bioimpedance/
10. or/6-9
11. and/1,5,10

Searching other resources Reference lists of review articles and relevant studies and clinical practice guidelines were also searched, as were gray literature sources (e.g. abstracts, dissertations and theses).

Data collection and analysis

Selection of studies: The title and abstract of the studies retrieved by the search were independently screened by two authors (MB and KS) in search of studies eligible for the review. Relevant studies were retained for full text review. In case of disagreement between the authors, the issue was discussed until a consensus was achieved, sometimes consulting a third author (NF).

Data extraction and management: Data extraction was carried out independently by two authors (MB and KS), with supplementary confirmation using Robot Reviewer software (https://www.robotreviewer.net/) (Suppl 1). Studies reported in non-English language

journals were translated before assessment. Studies with more than one publication, each reporting different outcomes, were included separately. Continuous parametric outcomes were extracted as mean and standard deviation for each group, and mean differences were calculated. For continuous non-parametric outcomes, medians and inter-quartile ranges were converted to mean and standard deviation by validated techniques. Treatment effects were expressed as risk ratio (RR) with 95% confidence intervals (CI) for dichotomous outcomes. For time-related outcomes, hazard ratio (HR) or incidence rate ratio (IRR) with 95% CI were used. In cases of insufficient information available for the necessary estimates, the authors were contacted to provide further details.

Assessment of risk of bias in included studies: Risk of bias was independently assessed by three authors (MB, GP and RN) using the Cochrane risk of bias tool[13] and certainty of the evidence was evaluated using Grading of Recommendations Assessment, Development and Evaluation (GRADE)[14,15] (NF). The estimated risk of bias was critically compared with the results from the Robot Reviewer tool.

Measures of treatment effect: Results were expressed as mean difference (MD) and 95% confidence interval (CI) for continuous outcomes (pre-HD and post-HD fluid overload, pre-HD systolic and diastolic blood pressure, post-HD systolic and diastolic blood pressure, left ventricular mass index, pulse wave velocity and NT-proBNP). For time-related outcomes (survival, hospital admissions and AFO or CV-related events), the hazard ratio with 95% CI was used. The treatment effect on intra-dialytic complications was expressed as an incidence rate ratio with a 95% CI.

Unit of analysis issues: The unit of analysis was preferably the individual studied. However, cluster randomized controlled trials were included in the meta-analysis.

Dealing with missing data: Any necessary additional information was requested from the original author and relevant data was included in the review. Important numerical data were

evaluated, such as screened and randomized number of patients and results of analyzes by intention-to-treat, as-treated, and per-protocol. Attrition rates, such as drop-outs, losses to follow-up, and withdrawals, were investigated, including balance between treatment groups.

Assessment of heterogeneity: Heterogeneity was assessed by visual inspection of the forest plot and quantified using the I^2 statistic, which describes the percentage of total variation across studies that is likely due to statistical heterogeneity rather than sampling error (Higgins 2003). A guide to the interpretation of I^2 values was as follows: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity

Meta-regression was not performed in analysis with substantial heterogeneity due to the relatively small number of studies for each outcome.

Assessment of reporting biases: To assess potential biases from small-study effects, we constructed funnel plots for outcomes with six or more individual studies.

Data synthesis: We summarized the relative treatment effects for each outcome along with certainty of the evidence using the GRADE guidelines[15] for each outcome evaluated.

Subgroup analysis and investigation of heterogeneity: It was not possible to perform subgroup analyzes to explore potential sources of heterogeneity due to the small number of studies for each outcome. We had planned subgroup analyses according to the characteristics of the participants and the studies, when subgroups could contain four or more independent studies.

Sensitivity analysis: Sensitivity analyses had been planned to explore the influence of risk of bias, sample size and follow-up time of the studies on the meta-analysis results. However, a small number of studies for each outcome precluded this analysis.

Results

Description of studies

Results of the search: The search was broadly comprehensive and retrieved 166 articles from MEDLINE, 323 from Web of Science, 711 from Embase and 49 from CENTRAL Cochrane. Of this total, 163 duplicates were removed, leaving 43 articles for full text reading, from which 11 studies[6–10,16–21] were included in the systematic review and meta-analysis (Figure 1).

Included studies: Details of included studies are provided in the Characteristics of Included Studies Table. (Table 1) ***Characteristics of studies:*** The studies presented a median of 135 participants, with an interquartile range (IQR) of 50 to 445 participants. Three studies included more than 200 participants[7,8,17]. Most studies included adult patients on maintenance HD with no other exclusion factors except contraindications for BIS application, and one study included only patients with fluid overload on online hemodiafiltration[10]. All studies were carried out in European or Asian populations. One was reported in a Chinese journal in the local language and was translated into English before data extraction[21]. Most studies used the BIS to reevaluate the target weight once a month, but this interval ranged from two weeks to three months. Most of them used BIS data to estimate the target weight as a complement to clinical evaluation without describing a structured flow of decision making. Two described a structured algorithm for decision making[7,17]. The median follow-up was 12 months (range 3 to 30 months).

Outcomes: Three studies reported survival[7,9,17], with follow-up ranging from 12 to 30 months. Two of these trials also reported rate of hospital admissions and AFO or CV-related events[7,17]. Six studies reported the effect of using BIS information to estimate target weight on intra-dialytic complications (intra-dialytic hypotension, dizziness, or cramps episodes)[7,10,17-19,21] . Six studies evaluated fluid overload[6,7,9,10,18,19], two of them presented

data before and after HD[6,7], three only after HD[9,10,19] e one only before HD[18]. Seven studies evaluated the effect of BIS-guided target weight estimation on blood pressure[6,9,10,16,18,19,21], three of them evaluated systolic and diastolic BP before and after HD[6,10,19], two studies evaluated systolic and diastolic BP before HD[16,21], one only systolic BP before HD[9] and one of them only post-dialysis systolic and diastolic BP[18]. Four studies evaluated pulse-wave velocity as an outcome[6,9,16,17]. Two studies evaluated left ventricular mass index[6,20] or the composite outcome of death and CV events[8,17]. Finally, three studies evaluated the outcome serum levels of NT-proBNP[16,17,19]. Outcomes left atrial volume[6], left ventricular ejection fraction (LVEF)[20], fractional shortening (FS)[20], radial LV mechanics[20], inferior vena cava diameter[19], breathing variability[19], troponin T[19] and C-reactive protein levels[21], residual renal function and 24-hour urinary volume[21] were evaluated in only one study each, which precluded the inclusion of these endpoints in the meta-analysis.

Excluded studies

A total of 400 studies were excluded due to: different study design (not an RCT), different population of interest (most with peritoneal dialysis patients or children) or different intervention (other bioimpedance devices). (Suppl. Table 1)

Risk of bias in included studies (Fig. 2; Suppl. Fig.17 and Table 2)

Allocation (selection bias): There was low risk of bias in random sequence generation in 5 of the included studies, unclear in 3 studies (no details reported)[9,16,18] and high in 2 studies, one randomized by dialysis center and no method described[10], and another randomized by consecutive participant[19]. There was high risk of bias in allocation concealment in 2 studies[10,19], and unclear in the remaining 9 studies (no mention of concealment in the report).

Blinding (performance bias and detection bias): Participants and personnel were not blinded in 10 studies, considered to be at high risk of bias in this regard, and blinding is not reported in another study, with unclear risk of bias[7]. Five studies blinded the outcome

assessors (low risk of bias)[6,8,17,19,20], five did not report whether the outcome assessors were blinded or not (unclear risk of bias) and one describes the open label outcome assessment (high risk of bias)[16].

Incomplete outcome data (attrition bias): The risk of attrition bias seems to be low in five of the included studies, high in five studies due to high number of participants who dropped out[6,7,9,10] or no report of dropouts[18]. The remaining study did not provide sufficient information to allow judgement and therefore considered as presenting unclear risk of bias[16].

Selective reporting (reporting bias): Eight included studies presented an unclear risk of reporting bias due to no previous protocol publication or registration. Three studies presented a low risk of selective reporting[7,17,19].

Other potential sources of bias: Four studies were at high risk of another potential source of bias due to poor study reporting[9,10,16,18]. One study was at high risk of potential bias, as it describes unusual survival and dropout rates for the HD population[16]. Another study was considered to have an unclear risk of potential bias due to not stating clearly that it is reporting other outcomes from the same participants from another publication of the same author[9]. The authors of four studies[6,9,10,16] presented links to Fresenius Medical Care (BIS manufacturer), which led to the consideration of these studies as being at high risk of other bias.

Effects of interventions

Survival: Three studies reported survival[7,9,17], with low heterogeneity and two of the studies with low risk of bias[7,9]. No significant effect of BIS-guided target weight estimation on survival was detected (3 studies, 679 participants): HR 1.009, 95% CI 0.498 to 2.043; I^2 = 0%; moderate certainty of evidence. (Table 2, Suppl. Table 2, Suppl. Fig. 1)

Hospital Admissions: Two trials reported rate of hospital admissions[7,17], with low heterogeneity and both with low risk of bias. There was no significant effect of BIS-guided target weight estimation on hospital admissions (2 studies, 548 participants): HR 1.07, 95% CI 0.80 to 1.43; $I^2 = 0\%$; low certainty of evidence. (Table 2, Suppl. Table 2, Suppl. Fig. 2)

Cardiovascular Events: Two trials reported rate of AFO or CV-related events[7,17], with low heterogeneity and both with low risk of bias. There is no significant effect of BIS-guided target weight estimation on AFO or CV-related events (2 studies, 548 participants): HR 0.86, 95% CI 0.59 to 1.23; $I^2 = 0\%$; moderate certainty of evidence. (Table 2, Suppl. Table 2, Suppl. Fig. 3)

Intra-dialytic Complications: Six studies reported the effect of using of BIS information to estimate target weight on intra-dialytic complications (intra-dialytic hypotension, dizziness, or cramps episodes)[7,10,17-19,21]. Most of these studies presented high risk of bias and the meta-analysis results presented moderate heterogeneity. No effect of BIS data was found on this outcome (6 studies, 956 participants): HR 1.02, 95% CI 0.90 to 1.15; $I^2 = 33\%$; moderate certainty of evidence. (Table 2, Suppl. Table 2, Suppl. Fig. 4)

Fluid Overload: Six studies evaluated fluid overload[6,7,9,10,18,19], five of them presented data before[6,7,9,10,19] ([5 studies, 855 participants]: mean difference -0.16, 95% CI -0.52 to 0.19; $I^2 = 69\%$; very low certainty of evidence) (Table 2, Suppl. Table 2, Suppl. Fig.5) and three after HD[6,7,18] ([3 studies, 574 participants]: mean difference 0.04, 95% CI -0.57 to 0.65; $I^2 = 82\%$; very low certainty of evidence) (Table 2, Suppl. Table 2, Suppl. Fig. 6). Most of these studies presented a high risk of bias and their meta-analysis presented high heterogeneity. No difference was found in fluid overload before or after HD between the BIS-guided and the control groups.

Blood Pressure: Seven studies evaluated the effect of BIS-guided target weight estimation on blood pressure[6,9,10,16,18,19,21], six of them evaluated systolic BP[6,9,10,19,16,21] ([6 studies, 750

participants]: mean difference -2.39, 95% CI -5.58 to 0.81; I^2 = 38%; very low certainty of evidence) (Table 2, Suppl. Table 2, Suppl. Fig. 7) and five diastolic BP[6,10,19,16,21] ([5 studies, 619 participants]: mean difference -1.70, 95% CI -4.12 to 0.72; I^2 = 39%; low certainty of evidence)(Table 2, Suppl. Table 2, Suppl. Fig. 8) before HD, and four of them assessed post-dialysis systolic BP[6,10,18,19] ([4 studies, 572 participants]: mean difference -2.64, 95% CI -7.60 to 2.32; I^2 = 37%; very low certainty of evidence)(Table 2, Suppl. Table 2, Suppl. Fig. 9) and diastolic BP[6,10,18,19] ([4 studies, 572 participants]: mean difference -1.50, 95% CI -4.27 to 1.27; I^2 = 60%; very low certainty of evidence) (Table 2, Suppl. Table 2, Suppl. Fig. 10). The BP analysis included studies with an overall high risk of bias and the meta-analysis presented moderate to high heterogeneity. No effect of the BIS data could be found on blood pressure control.

Pulse-wave Velocity: Four studies evaluated pulse-wave velocity[6,9,16,17] as an outcome ([4 studies, 642 participants]: mean difference -1.04, 95% CI -2.34 to 0.27; I^2 = 94%; very low certainty of evidence) (Table 2, Suppl. Table 2, Suppl. Fig. 11), most of them with a high risk of bias, resulting in very high heterogeneity in the meta-analysis. No effect of the BIS data could be found on pulse-wave velocity.

Left Ventricular Mass Index: Two studies[6,20] evaluated left ventricular mass index ([2 studies, 199 participants]: mean difference -4.62, 95% CI -13.27 to 4.04; I^2 = 0%; very low certainty of evidence) (Table 2, Suppl. Table 2, Suppl. Fig. 12), all at low risk of bias, resulting in a meta-analysis with low heterogeneity. No effect of BIS data could be found on left ventricular mass index.

Composite CV Events and Survival: Two studies evaluated the composite outcome of survival and CV events[8,17] ([2 studies, 695 participants]: HR 0.83, 95% CI 0.59 to 1.17; I^2 =0%; moderate certainty of evidence) (Table 2, Suppl. Table 2, Suppl. Fig. 13), all with a

low risk of bias, resulting in a meta-analysis with low heterogeneity. No effect of the BIS data could be found on composite outcome of death and CV events.

Serum NT-proBNP: Three studies evaluated the NT-proBNP outcome[16,17,19] ([2 studies, 510 participants]: mean difference -500.86, 95% CI -2,196.37 to 1,194.66; I^2 =46%; very low certainty of evidence) (Table 2, Suppl. Table 2, Suppl. Fig. 14), most at low risk of bias, resulting in moderate heterogeneity in the meta-analysis. No effect of BIS-guided target weight estimation was also found on serum NT-proBNP levels.

Discussion

Summary of main results: This review found no significant difference in clinical or surrogate outcomes between HD recipients whose target weight was estimated based on clinical assessment alone and those whose target weight was estimated with adjunct bioimpedance spectroscopy data. However, few randomized controlled trials have been conducted so far evaluating the application of BIS to guide ultrafiltration during HD. In addition, most RCTs on the issue present a high risk of bias and a relatively small sample size.

Although few, most studies that have analyzed the clinically meaningful outcome survival (alone or within a composite outcome) have a low risk of bias and low heterogeneity, favoring the idea that within this short follow-up time (around two years) there is no effect of BIS-guided target weight estimation on these endpoints in maintenance HD patients, with a moderate certainty of evidence. Regarding intra-dialytic complications, most studies present a high risk of bias, the meta-analysis showed moderate heterogeneity, however it leads to a moderate certainty of evidence that there is no difference in adverse events between intervention and control groups. The studies evaluating over-hydration, blood pressure, pulse wave velocity and serum NT-proBNP levels presented high risk of bias, resulting in a meta-analysis with moderate to high heterogeneity and providing a very low certainty of evidence. No significant impact of using BIS data for target weight estimation was found regarding these outcomes.

Only two small studies, with a relatively low risk of bias, reported the outcome left ventricular mass index. The heterogeneity of the analysis is low. Despite both studies showed a central tendency value favoring the BIS-guided approach, no significant difference between groups and a very low certainty of evidence were achieved.

Overall completeness and applicability of evidence: Current data on the effects of BIS-guided target weight estimation are based on eleven small studies with short follow-up and most at high risk of bias. All studies were carried out in populations from Europe (mostly in Eastern Europe) or Asia (China, Taiwan, or India). The meta-analysis for most of the outcomes presented high heterogeneity, but sensitivity or meta-regression analyses were precluded by the small number of studies.

Almost half of the included studies did not systematically evaluate and report adverse events such as intra-dialytic hypotension, dizziness, or cramps. There were no reports of patient-important outcomes, such as health-related quality of life. Most studies evaluated over-hydration as the continuous variable OH derived from the BIS software, finding no difference in OH between the intervention and control groups. However, this construct cannot distinguish a set of patients whose OH remained unchanged from a set of patients with some of them underhydrated and others overhydrated, both improving hydration status towards normality.

Quality of the evidence: The wide confidence interval around the reported effect suggests that the current evidence included in this meta-analysis is still insufficient to detect the true impact of BIS-guided target weight estimation on risk of death and other meaningful outcomes. The certainty of evidence was moderate for survival, cardiovascular events, a composite of both, and intra-dialytic complications. Regarding all other outcomes, the certainty of evidence was low or very low. The analysis was limited by the low number of trials, with small sample size, short follow-up, and substantial risk of bias. These trials also varied widely in the methodology used to adjust the target weight, potentially contributing to heterogeneity. It is important to note that subgroup analyses could not be performed due to the insufficient number of studies evaluating the main outcomes.

Potential biases in the review process: This review is reported using Cochrane standardized methods and the PRISMA checklist[22]. It includes a highly comprehensive electronic search of the most important databases. Despite the application of these best practice approaches, there may be biases in the review process. Despite the highly inclusive search, without restriction of outcomes or language, a small number of studies were retrieved, most of them at high risk of bias and reporting a wide range of different outcomes. The small number of studies including each outcome limited the power to detect differences between the intervention and control groups. For example, data on the effects of BIS use on LVMI suggest a potential benefit, but the small total sample results in imprecision in estimating the effect. For the most important outcomes survival and hospital admissions, the small total sample may also limit the statistical power to detect heterogeneity. Some reported outcomes could not even be submitted to meta-analysis, due to the uniqueness of the report. Paunic at al.[20] results about FO (presented as %) and BP (presented as mean arterial pressure) could not be included in the meta-analysis. In Ponce et al[10], hospitalizations were not used in the meta-analysis due to lack of rate of incidence data and survival was not used due to the lack of HR report. In Siriopol et al[17], fluid overload is described as an outcome, but the data were not reported in the publication.

Agreements and disagreements with other studies or reviews: A systematic review with meta-analysis (twelve trials, seven using BIS in HD recipients) published in 2019[23] found that the use of technology adjuncts (not exclusively bioimpedance) for fluid management in dialysis patients (hemodialysis and peritoneal dialysis) was not different from standard care regarding mortality, cardiovascular events, hospitalizations, intra-dialytic complications and left ventricular mass index. They found a 3mmHg greater reduction in systolic blood pressure in the intervention group, a difference probably not clinically meaningful. In addition, the meta-analysis did not specify whether systolic BP was evaluated before or after

the dialysis session. They also found, in a subgroup analysis, that the hospitalization rate was lower in the intervention group, especially among those treated by peritoneal dialysis.

Two other meta-analyses[24,25] that focused on the impact of bioimpedance (not exclusively BIS) use on dialysis recipients also found no reduction of all-cause mortality or other clinical outcomes. One of them, which also provided cost-effectiveness analysis[24] included five RCTs (four in HD recipients) and eight non-randomized studies assessing BIS-guided target weight estimation. They found less overhydration in the intervention group and no difference in systolic BP, arterial stiffness, or mortality between groups. Covic et al.[25] reviewed seven RCTs (five in HD recipients, four of which using BIS) and found that bioimpedance-guided target weight estimation had no effect on mortality but decreased systolic BP 3mmHg below that obtained in the control group.

To the best of our knowledge, this is the first meta-analysis to focus exclusively on BIS as an adjunct to volume assessment in hemodialysis recipients. All previous meta-analyses have evaluated various modalities of bioimpedance to guide volume management in hemodialysis and peritoneal dialysis, including a smaller number of randomized controlled trials using BIS. Therefore, previous analyzes have less statistical power to detect any effect of BIS-guided target weight estimation on clinical and surrogate outcomes. The present systematic review updated the evidence with a broad and comprehensive strategy, including multiple databases.

Authors' conclusions

Implications for practice: Currently, there is not enough evidence of clinical benefits from BIS-guided target weight estimation among HD patients to justify the widespread use of this technological adjunct.

Implications for research: Further studies evaluating BIS-guided target weight estimation in HD recipients are needed. These studies should pursue a more structured flow of decision based on BIS data, to allow greater comparability between different studies results. In the search for some relevant clinical outcomes such as survival, a longer follow-up would be recommended. Furthermore, looking for surrogate intermediate outcomes may help to explain the mechanisms linking better hydration control with longer survival or fewer hospital admissions, should these associations be established in future clinical trials.

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Tables

Table 1 Characteristics of included studies

Author, year, country	Groups (n)	Sample	Follow-up	Outcomes	Results
Huan-Sheng et al. (2016), China.	**Intervention** (n=148): BIS-based algorithm for DW estimation **Control** (n=150): DW estimation based in clinical examination	62±12 ys. old, male 49%, DM 37.6%.	12 months	Hospitalization rate, acute fluid overload (FO) or CV- related events, survival, hypertensive, and intradialytic complications	No difference in hospital admission rate; lower incidence of acute and intra-dialytic complications in the intervention group.
Hur et al. (2013), Turkey.	**Intervention** (n=78): BIS-guided DW estimation. **Control** (n=78): DW estimation based in clinical examination	52±12 ys. old, male 69%, DM 17.0%, high BP 12%	12 months	Left ventricular mass index (LVMI), blood pressure (BP), left atrial volume, pulse wave velocity (PWV)	Greater decrease in LVMI, BP, left atrial volume and PWV in the intervention group.
Liu et al. (2020), China**.**	**Intervention** (n=236): BIS-guided DW estimation. **Control** (n=209): DW estimation based in clinical examination	55±13 ys. old, male 54%, DM 11.8%, high BP 11.4%.	12 months	Survival and composite endpoint (death, myocardial infarction, stroke, peripheral vascular disease.	No significant difference in survival or composite endpoint.
Onofriescu et al. (2014), Romania.	**Intervention** (n=62): BIS-guided DW estimation. **Control** (n=69): DW estimation based in clinical examination.	53±13 ys. old, male 53%, DM 10%.	2.5 years	Survival, PWV, overhydration (OH), BP	Increase in survival and decrease in OH in intervention group. No difference in BP
Onofriescu et al. (2012), Romania.	**Intervention** (n=71): BIS-guided DW estimation. **Control** (n=64): DW estimation based in clinical examination.	55±13 ys. old, DM 10.3%, High BP	12 months	BP, PWV, body mass index (BMI), OH, serum N-terminal fragment of B-type natriuretic peptide (NT-proBNP).	Decrease in BP and PWV only in intervention group, maybe greater NT-proBNP decrease in intervention group (no proper statistics).
Patel et al. (2019), India.	**Intervention** (n=25): BIS-guided DW estimation. **Control** (n=25): DW estimation based in clinical examination.	56±12 ys. old, male 70%.	6 months	BP, OH, intradialytic complications and antihypertensive drug burden	Decrease in BP, antihypertensive drugs, and intradialytic complication in intervention group.
Paunic et al. (2020), Serbia.	**Intervention** (n=38): BIS-guided DW estimation. **Control** (n=35): DW estimation based in clinical examination	57±12 ys. old, male 58.0 %, DM 9.0 %. High BP 74%.	9 months	LVMI, left ventricular (LV) ejection fraction (EF), fractional shortening (FS), radial LV mechanics, OH, NT- proBNP	Decrease in LVMI and increase in LVFE, FS and radial LV mechanics in intervention group

Ponce et al. (2014), Portugal.	**Intervention** (n=101): BIS-guided DW estimation. **Control** (n=88): DW estimation based in clinical examination.	Overhydrated, 66±15 ys. old, male 75% DM 39,0%.	12 months	OH, BP, weight gain, hospitalization, and survival rate.	Greater decrease in OH in intervention group. No difference in hospitalization or survival.
Siriopol et al. (2017), Romania.	**Intervention** (n=123): lung US and BIS-guided DW estimation. **Control** (n=127): DW estimation based in clinical examination	59±14 ys. old, male 46%, DM 19.2%, High BP 76%.	21 months	Survival and incidence of first CV event, hospitalization, intra-dialytic events, NT - proBNP, troponin T, OH, PWV	No difference in outcomes.
Sommerer et al. (2021), Germany.	**Intervention** (n=65): BIS-guided DW estimation. **Control** (n=67): DW estimation based in clinical examination	71±10 ys. old, male 57%,DM High BP 24%	4 months	NT-proBNP, intradialytic complications, BP, OH, troponin T, inferior vena cava diameter, breathing variability	No difference in NT-proBNP, BP and troponin T. OH and intradialytic complications in intervention group.
Wang et al. (2017), China.	**Intervention** (n=31): BIS-guided DW estimation. **Control** (n=31): DW estimation based in clinical examination.	62±10 ys. old, male 52,8%, High BP 6,4%	3 months	Residual renal function (RRF), 24 hours urine volume, BP, biochemical variables, and intra-dialytic complications.	Lower decrease in RRF and urine volume in intervention group. No difference in other outcomes.

Table 2 Data and analyses, all studies

Outcomes	Studies	N	Statistical Method	Effect Estimate
1.1 All-cause Hospital Admissions	2	548	Hazard Ratio (IV, Random, 95% CI)	1.07 [0.80, 1.43]
1.2 All-cause Mortality	3	679	Hazard Ratio (IV, Random, 95% CI)	0.83 [0.48, 1.43]
1.3 AFO or CV-related events	2	548	Hazard Ratio (IV, Random, 95% CI)	0.86 [0.59, 1.23]
1.4 Intra-dialytic Complications	6	956	Rate Ratio (IV, Random, 95% CI)	1.02 [0.90, 1.15]
1.5 Pre-HD Fluid Overload	5	855	Mean Difference (IV, Random, 95% CI)	-0.16 [-0.52, 0.19]
1.6 Post-HD Fluid Overload	3	474	Mean Difference (IV, Random, 95% CI)	0.04 [-0.57, 0.65]
1.7 Left ventricular mass index	2	199	Mean Difference (IV, Fixed, 95% CI)	-4.62 [-13.27, 4.04]
1.8 Post-HD Systolic Blood Pressure	4	472	Mean Difference (IV, Random, 95% CI)	-2.64 [-7.60, 2.32]
1.9 Post-HD Diastolic Blood Pressure	4	472	Mean Difference (IV, Random, 95% CI)	-1.50 [-4.27, 1.27]
1.10 Pre-HD Systolic Blood Pressure	6	750	Mean Difference (IV, Random, 95% CI)	-2.39 [-5.58, 0.81]
1.11 Pre-HD Diastolic Blood Pressure	5	619	Mean Difference (IV, Random, 95% CI)	-1.70 [-4.12, 0.72]
1.12 Pulse Wave Velocity	4	642	Mean Difference (IV, Random, 95% CI)	-1.04 [-2.34, 0.27]
1.13 Composite of death and CV events	2	695	Hazard Ratio (IV, Random, 95% CI)	0.83 [0.59, 1.17]
1.14 NT-proBNP	3	510	Mean Difference (IV, Random, 95% CI)	-500.86 [-2196.37, 1194.66]

Figure Captions

Figure 1: Flow diagram of databases search

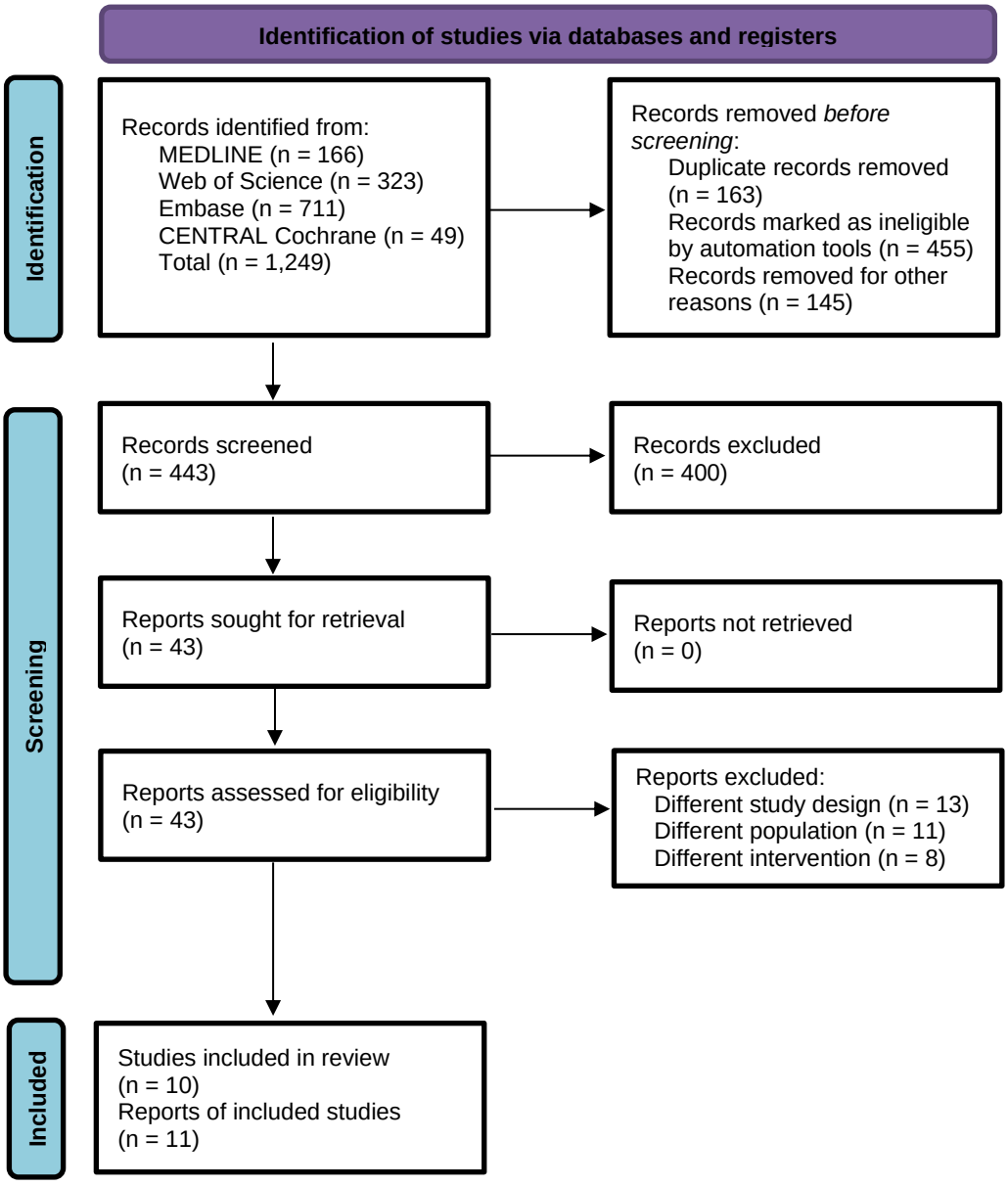
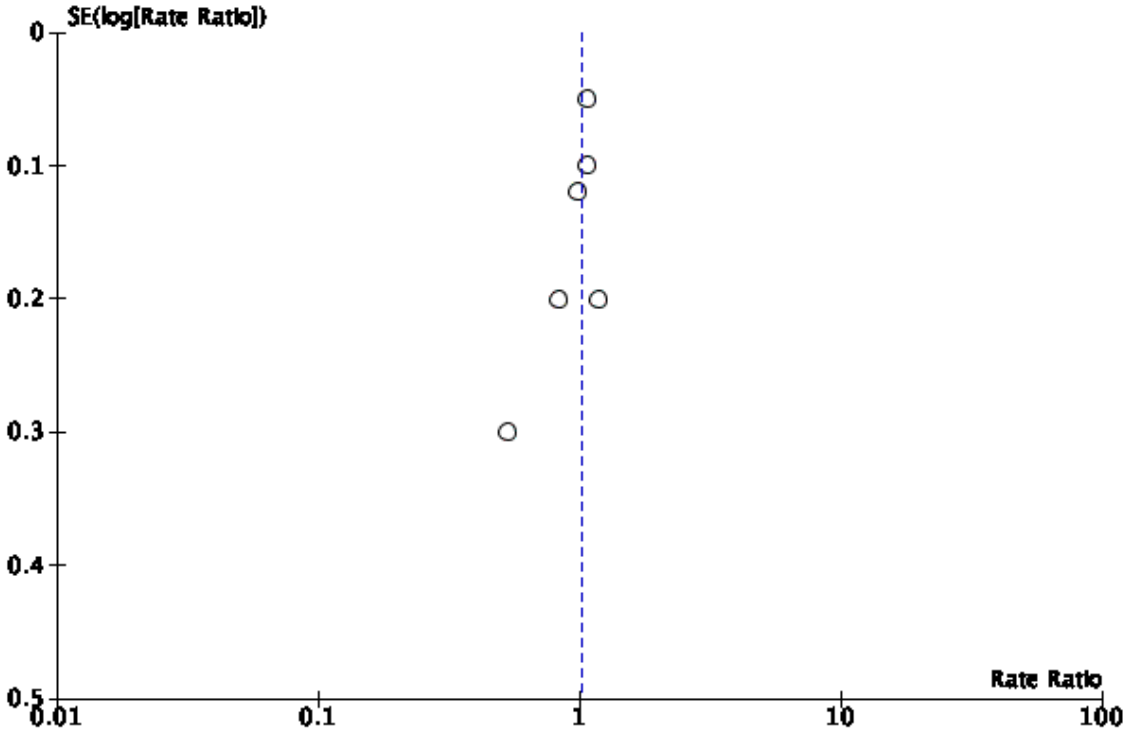
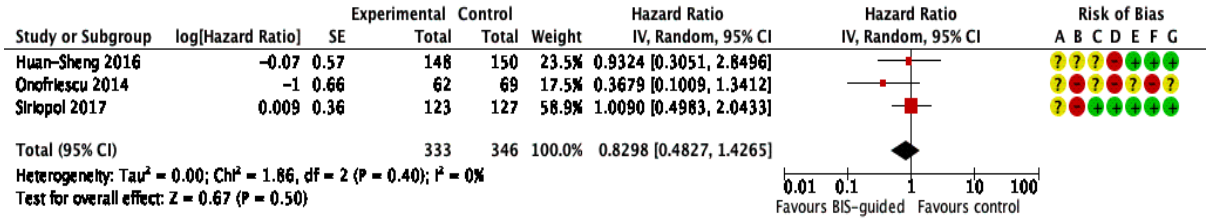


Figure 2 Risk of bias graph



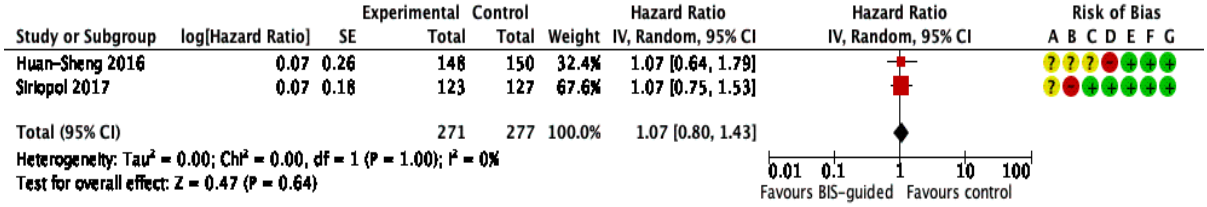
Supplementary Material

Figure 1 Forest plot of comparison: Survival.



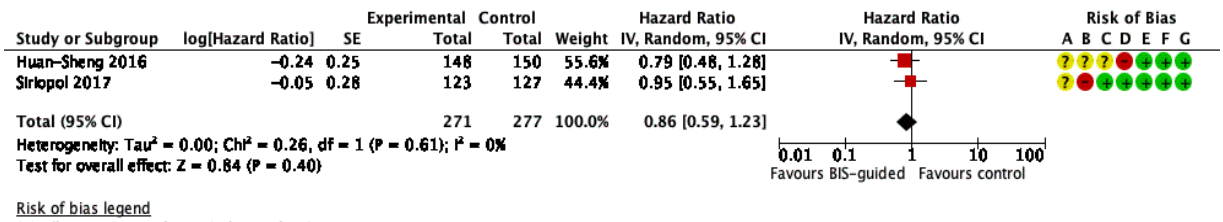
Risk of bias legend
(A) Allocation concealment (selection bias)
(B) Blinding of participants and personnel (performance bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias
(G) Random sequence generation (selection bias)

Figure 2 Forest plot of comparison: All-cause Hospital Admissions.



Risk of bias legend
(A) Allocation concealment (selection bias)
(B) Blinding of participants and personnel (performance bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias
(G) Random sequence generation (selection bias)

Figure 3 Forest plot of comparison: AFO or CV-related events.



Risk of bias legend
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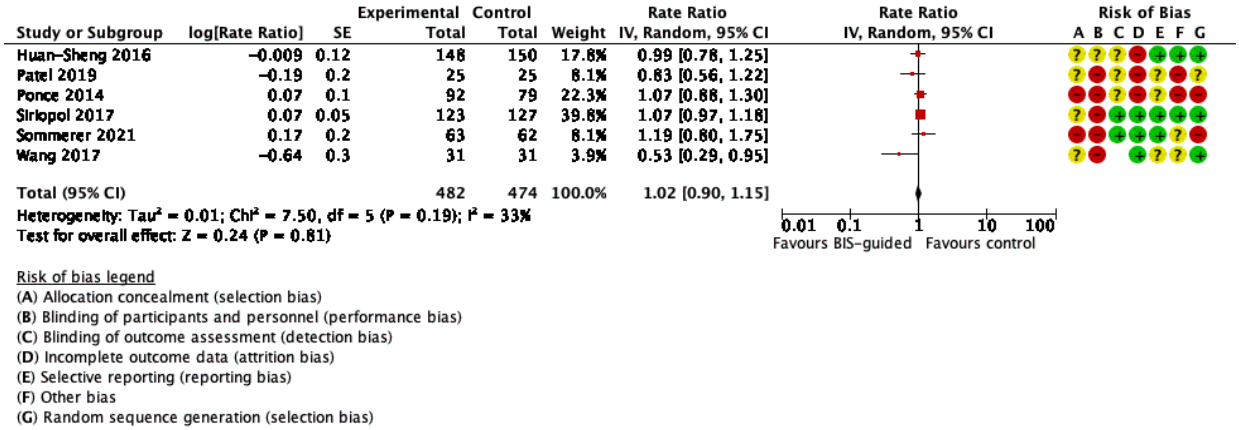
(B) Blinding of participants and personnel (performance bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias
(G) Random sequence generation (selection bias)

Figure 4 Forest plot of comparison: Intra-dialytic Complications.



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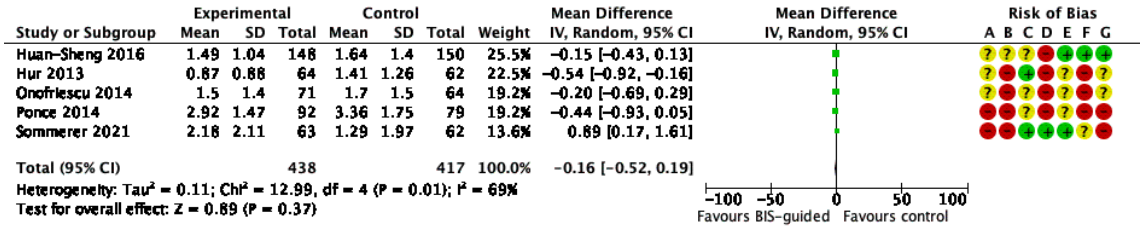
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias
(G) Random sequence generation (selection bias)

Figure 5 Forest plot of comparison: Pre-HD Fluid Overload



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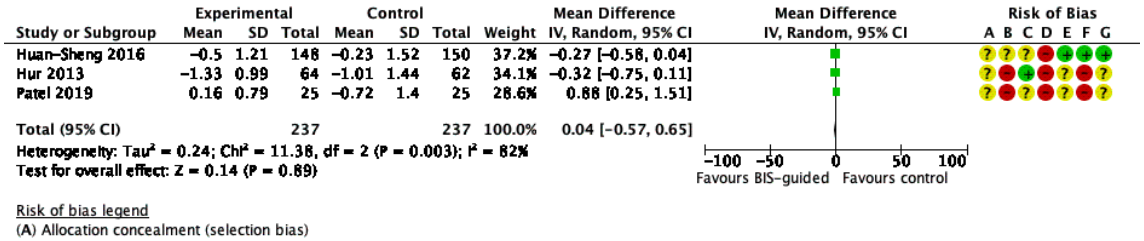
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias
(G) Random sequence generation (selection bias)

Figure 6 Forest plot of comparison: Post-HD Fluid Overload.



Risk of bias legend
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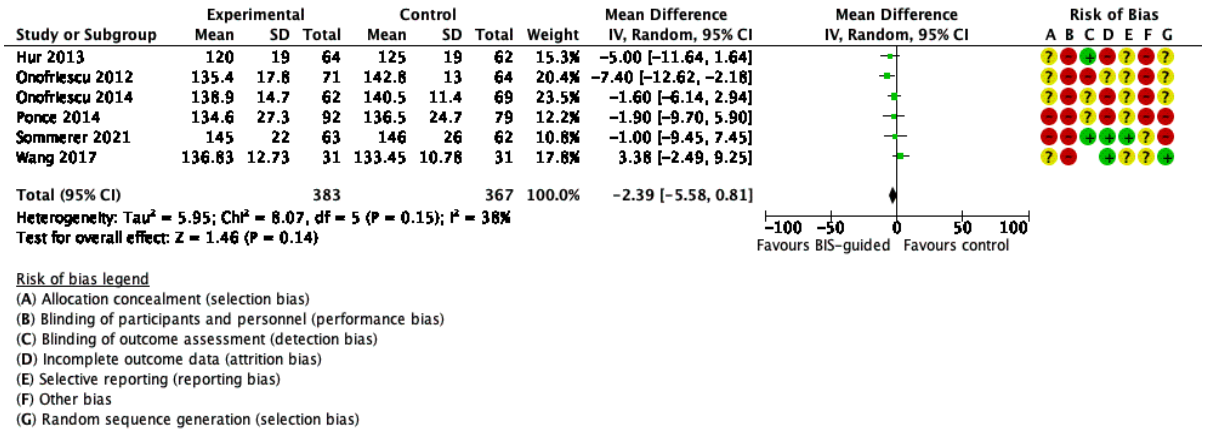
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias
(G) Random sequence generation (selection bias)

Figure 7 Forest plot of comparison: Pre-HD Systolic Blood Pressure.



Risk of bias legend
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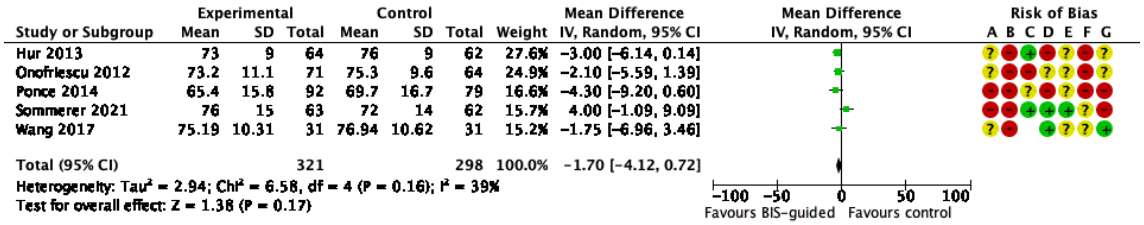
(B) Blinding of participants and personnel (performance bias)
(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias
(G) Random sequence generation (selection bias)

Figure 8 Forest plot of comparison: Pre-HD Diastolic Blood Pressure.



Risk of bias legend
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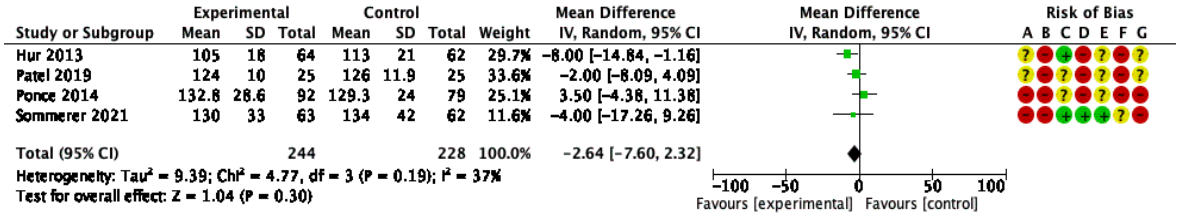
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias
(G) Random sequence generation (selection bias)

Figure 9 Forest plot of comparison: Post-HD Systolic Blood Pressure.



Risk of bias legend
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(C) Blinding of outcome assessment (detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias
(G) Random sequence generation (selection bias)

Figure 10 Forest plot of comparison: Post-HD Diastolic Blood Pressure.

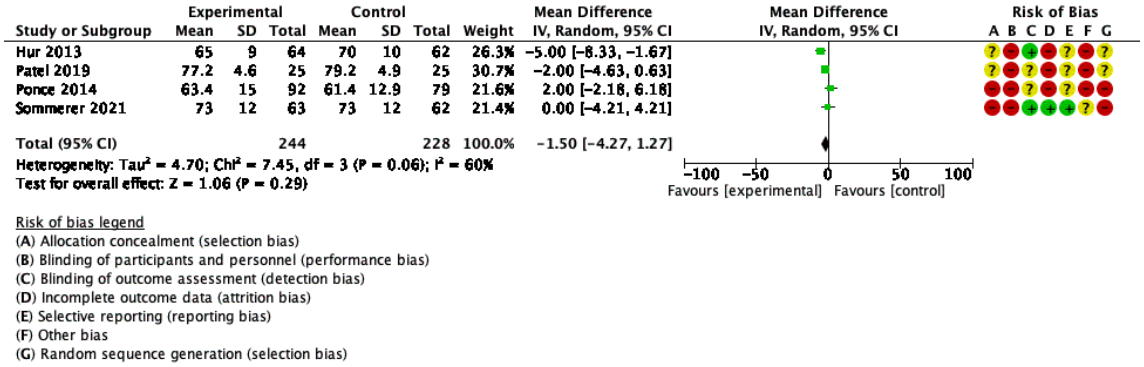

Figure 11 Forest plot of comparison: Left ventricular mass index.

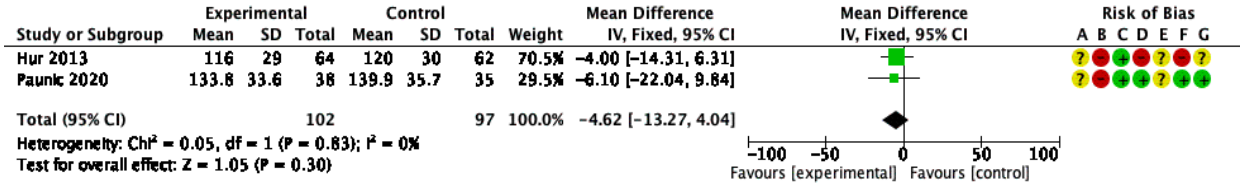

Figure 12 Forest plot of comparison: Pulse Wave Velocity.

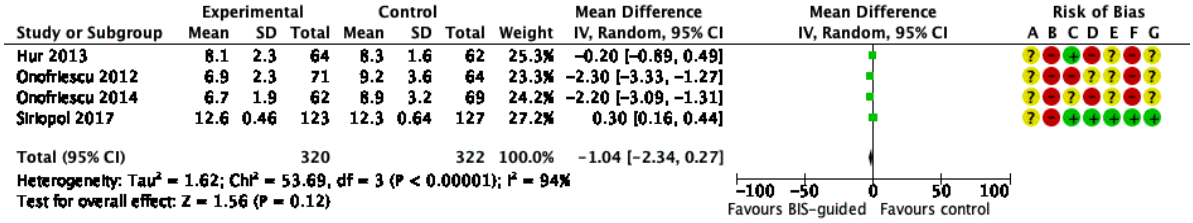

Figure 13 Forest plot of comparison: Composite of death and CV events.

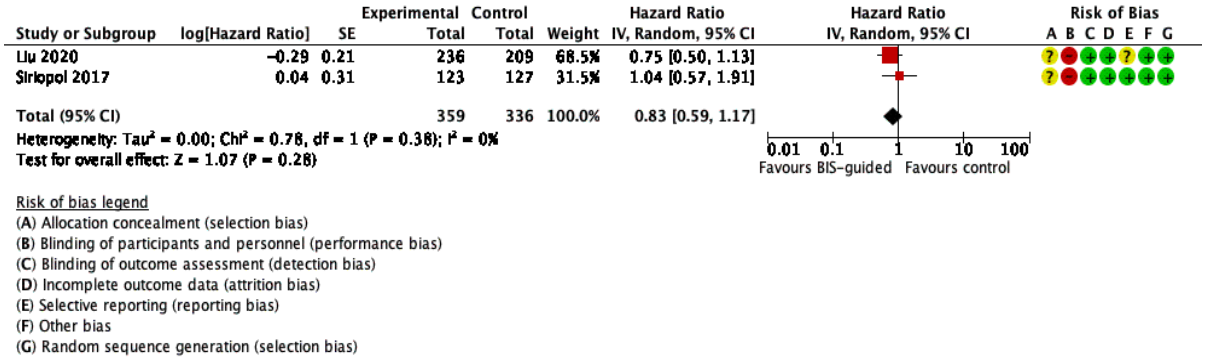

Figure 14 Forest plot of comparison: NT-proBNP.

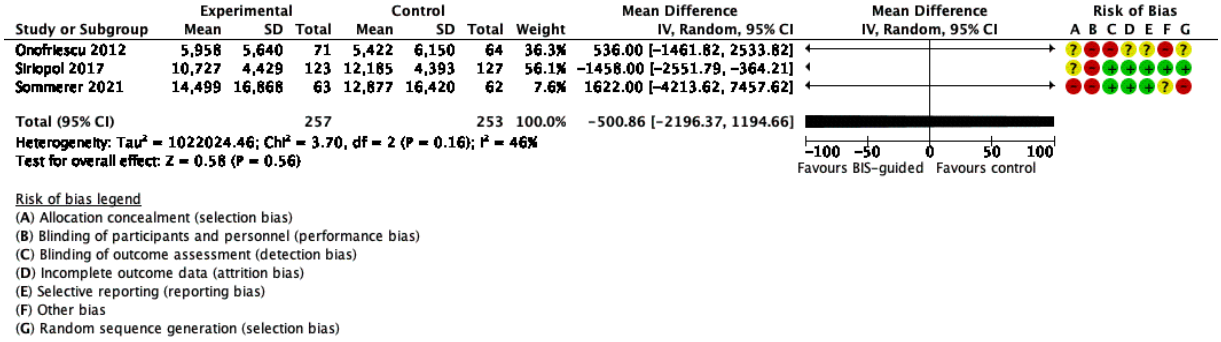

Figure 15 Funnel plot of comparison: Pre-HD Systolic Blood Pressure.

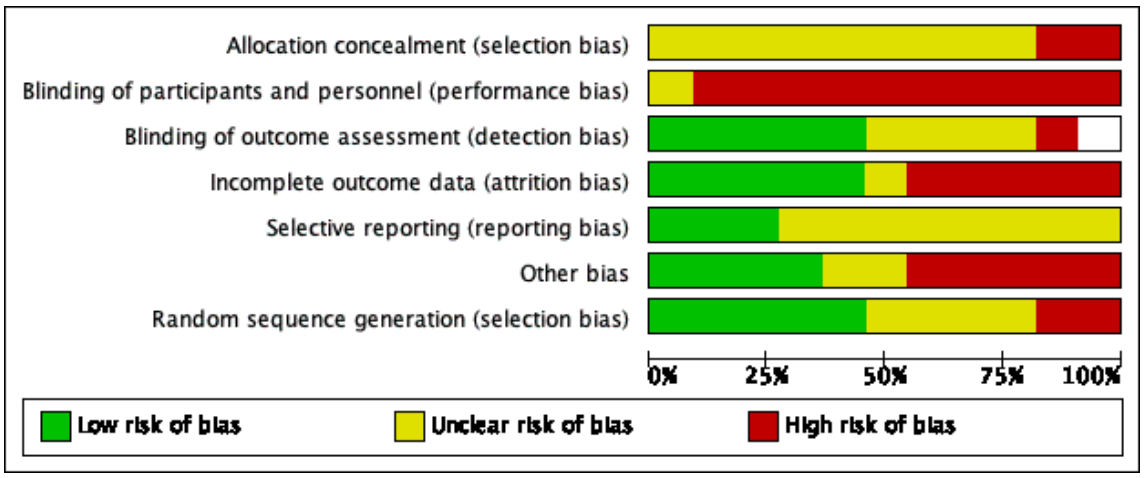

Figure 16 Funnel plot of comparison: Intra-dialytic Complications.

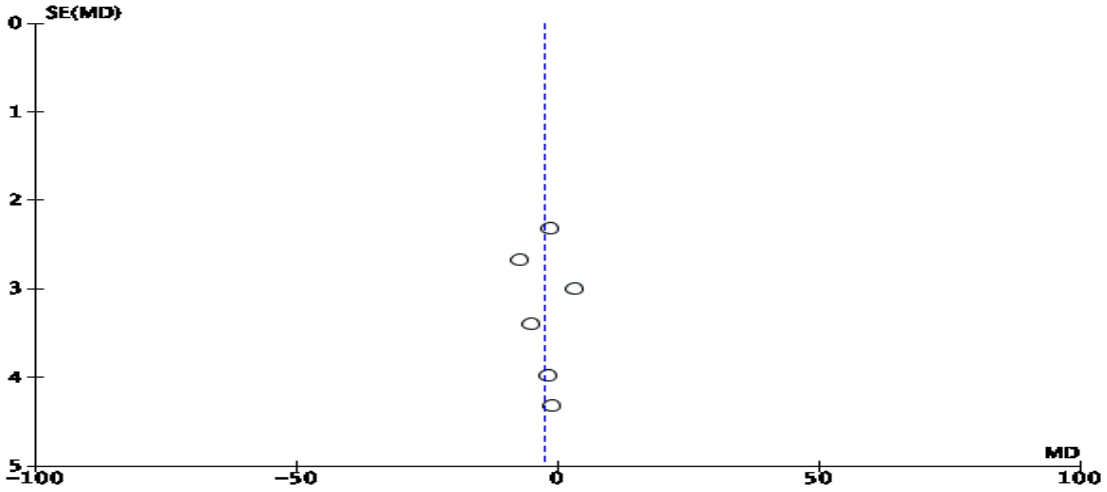

Figure 17 Risk of bias by RobotReviewer.

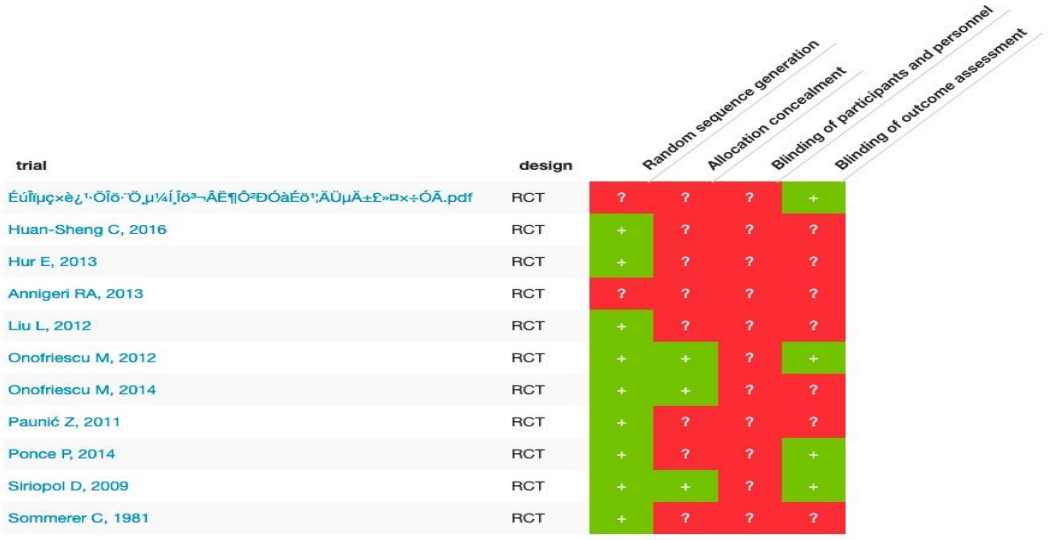

Table 2 Certainty of the evidence by Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BIS	clinical evaluation alone	Relative (95% CI)	Absolute (95% CI)		
Survival (follow-up: mean 12 months)												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	271 participants	277 participants	**HR 1.07** (0.80 to 1.43) [Survival]	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁◯ Moderate	
							-	0.0%		**0 fewer per 1,000** (from 0 fewer to 0 fewer)		
Hospital admission (follow-up: mean 12 months)												
3	randomised trials	serious[b]	not serious	not serious	serious[a]	none	333 participants	346 participants	**HR 0.83** (0.48 to 1.43) [Hospital admission]	**-- per 1,000** (from -- to --)	⨁⨁◯◯ Low	
							-	0.0%		**-- per 1,000** (from -- to --)		
AFO or CV-related events												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	271 participants	277 participants	**HR 0.86** (0.59 to 1.23) [AFO or CV-related events]	**-- per 1,000** (from -- to --)	⨁⨁⨁◯ Moderate	
							-	0.0%		**-- per 1,000** (from -- to --)		
Intra-dialytic Complications (follow-up: mean 12 months)												
6	randomised trials	serious[c]	not serious	not serious	not serious	none	0/482 (0.0%)	0/474 (0.0%)	**RR 1.02** (0.90 to 1.15)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁◯ Moderate	
Pre-HD Fluid Overload (Scale from: -100 to 100)												
5	randomised trials	serious[c]	serious[d]	not serious	serious[a]	none	438	417	-	MD **0.16 lower** (0.52 lower to 0.19 higher)	⨁◯◯◯ Very low	
Post-HD Fluid Overload												
3	randomised trials	serious[c]	serious[d]	not serious	serious[d]	none	237	237	-	MD **0.04 higher** (0.57 lower to 0.65 higher)	⨁◯◯◯ Very low	
Pre-HD Systolic Blood Pressure												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BIS	clinical evaluation alone	Relative (95% CI)	Absolute (95% CI)		
6	randomised trials	serious[c]	serious[d]	not serious	serious[a]	none	383	367	-	MD **2.39 lower** (5.58 lower to 0.81 higher)	⊕◯◯◯ Very low	
Pre-HD Diastolic Blood Pressure												
5	randomised trials	serious[c]	not serious	not serious	serious[a]	none	321	298	-	MD **1.7 lower** (4.12 lower to 0.72 higher)	⊕⊕◯◯ Low	
Post-HD Systolic Blood Pressure												
4	randomised trials	serious[c]	serious[d]	not serious	serious[a]	none	244	228	-	MD **2.64 lower** (7.6 lower to 2.32 higher)	⊕◯◯◯ Very low	
Post-HD Diastolic Blood Pressure												
4	randomised trials	serious[c]	serious[d]	not serious	serious[a]	none	244	228	-	MD **1.5 lower** (4.27 lower to 1.27 higher)	⊕◯◯◯ Very low	
Left ventricular mass index												
2	randomised trials	serious[c]	serious[d]	not serious	serious[a]	none	102	97	-	MD **4.62 lower** (13.27 lower to 4.04 higher)	⊕◯◯◯ Very low	
Pulse Wave Velocity												
4	randomised trials	serious[c]	serious[d]	not serious	serious[a]	none	320	322	-	MD **1.04 lower** (2.34 lower to 0.27 higher)	⊕◯◯◯ Very low	
Composite of death and CV events												
2	randomised trials	not serious	not serious	not serious	serious[a]	none	359	336	-	MD **0.83 higher** (0.59 higher to 1.17 higher)	⊕⊕⊕◯ Moderate	
NT-proBNP												
3	randomised trials	serious[e]	very serious[d]	not serious	extremely serious[a]	none	257	253	-	MD **500.86 lower** (2196.37 lower to 1194.66 higher)	⊕◯◯◯ Very low	

CI: confidence interval; **HR:** hazard Ratio; **MD:** mean difference; **RR:** risk ratio

Explanations a. Large 95%CI - low precision b. Articles showed high risk of bias related to blinding of participants and incomplete outcome data. c. Articles showed high risk of bias related, blinding of participants and incomplete outcome data, and other bias. d. Findings diverged. e. Articles showed a high risk of bias related to selection and performance bias.

Table 2 Risk of Bias Table.

Risk of Bias Tables

Huan-Sheng 2016

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Unknown blinding of participants, no blinding of personnel
Blinding of outcome assessment (detection bias)	Unclear risk	Unknown blinding of assessors
Incomplete outcome data (attrition bias)	High risk	high number of participants who dropped out.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	
Random sequence generation (selection bias)	Low risk	

Hur 2013

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias)	High risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	High risk	high number of participants who dropped out.
Selective reporting (reporting bias)	Unclear risk	No protocol publication or trial registration
Other bias	High risk	Links with Fresenius Medical Care (BIS manufacturer)
Random sequence generation (selection bias)	Unclear risk	Not described.

Liu 2020

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias)	High risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Unclear risk	No previous protocol publication or trial registration
Other bias	Low risk	
Random sequence generation (selection bias)	Low risk	

Onofriescu 2012

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	
Blinding of outcome assessment (detection bias)	High risk	
Incomplete outcome data (attrition bias)	Unclear risk	No deaths or dropouts for 12 months follow-up
Selective reporting (reporting bias)	Unclear risk	No previous publication
Other bias	High risk	No deaths or dropouts for 12 months follow-up. Links with Fresenius Medical Care (BIS manufacturer).
Random sequence generation (selection bias)	Unclear risk	No baseline table

Onofriescu 2014

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Personnel not blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data (attrition bias)	High risk	high number of participants who dropped out.
Selective reporting (reporting bias)	Unclear risk	No protocol registration or publication
Other bias	High risk	Seems to be the same sample of previous study but it is not clarified. Links with Fresenius Medical Care (BIS manufacturer).
Random sequence generation (selection bias)	Unclear risk	No described method

Patel 2019

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	No described
Blinding of participants and personnel (performance bias)	High risk	No described
Blinding of outcome assessment (detection bias)	Unclear risk	No described
Incomplete outcome data (attrition bias)	High risk	No description of dropouts
Selective reporting (reporting bias)	Unclear risk	No protocol publication
Other bias	High risk	Poor description in general
Random sequence generation (selection bias)	Unclear risk	No technique description

Paunic 2020

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Unclear risk	No protocol publication
Other bias	Low risk	
Random sequence generation (selection bias)	Low risk	

Ponce 2014

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Randomization by center
Blinding of participants and personnel (performance bias)	High risk	No blinding
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	High risk	29 out of 101 (28.7%) and 42 out of 88 (47.7%) discontinuations were observed in the intervention and control groups, respectively.
Selective reporting (reporting bias)	Unclear risk	No protocol publication
Other bias	High risk	Poor report. Links with Fresenius Medical Care (BIS manufacturer).
Random sequence generation (selection bias)	High risk	Randomization by center, no method described

Siriopol 2017

Bias	Authors' judgement	Support for judgement

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	Not blinded
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	
Random sequence generation (selection bias)	Low risk	

Sommerer 2021

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	
Blinding of participants and personnel (performance bias)	High risk	
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Poor report
Random sequence generation (selection bias)	High risk	Randomization by consecutive patient

Wang 2017

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	High risk	
Blinding of outcome assessment (detection bias)	Unclear risk	
Incomplete outcome data (attrition bias)	Low risk	
Selective reporting (reporting bias)	Unclear risk	No previous protocol publication
Other bias	Unclear risk	Poor report
Random sequence generation (selection bias)	Low risk	

ARTIGO 2

Lower Incidence of Hospital Admissions in Bioimpedance-guided Fluid Management in Maintenance Hemodialysis Patients – Results of a Randomized Controlled Trial

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Abstract

Background Hemodialysis (HD) is life-sustaining in kidney failure. However, proper body fluids regulation depends on an accurate targe weight (TW) estimation. This trial aims to compare clinical endpoints between bioimpedance spectroscopy (BIS) - guided and usual care to estimate TW in HD patients. **Methods** This is an open label, parallel groups, controlled trial that randomized, through a table of random numbers, adult patients on maintenance HD to monthly clinical evaluation (CE) alone or added to BIS-guided TW estimation twice a year. The primary outcome was survival, and the secondary outcomes were rate of hospital admissions, blood pressure (BP) and the antihypertensive drugs burden. The participants were followed-up for two years. Adjusted survival analysis was performed by Cox proportional hazards regression and hospital admissions were analyzed by incidence-rate ratio. **Results** One hundred and ten patients were randomized for CE (52) or BIS group (58), with a mean age of 57.4 (15.4) years, 64 (58%) males. There was no difference between the groups at baseline. The survival time was not significantly different between the groups (HR 0.53 95% CI 0.21-1.29, p=0.16). There was also no difference between the groups in systolic or diastolic BP change or in the number of antihypertensive drugs in use. The incidence rate of hospital admissions was 3.1 and 2.1 per person-year in the CE and BIS groups, respectively, with a time-adjusted incidence rate ratio of 1.48 (95% CI 1.20-1.82, p=0.0001) and attributable fraction of risk among the exposed of 0.32 (95% CI 0.17-0.45). **Conclusion** The inclusion of BIS data to guide TW estimation in HD patients did not present a detectable impact on survival or BP control, but significantly reduced the incidence rate of hospital admissions. **ClinicalTrials.gov Identifier: NCT05272800**

Key Words: hemodialysis, overhydration, fluid status, bioimpedance spectroscopy, BIS

Introduction

Chronic kidney disease (CKD) affects between 8% and 16% of the world population and is estimated to become the fifth most frequent cause of death by 2040. About 5.9 million patients receive kidney replacement therapy (KRT), mostly hemodialysis (HD).[1,2] Despite being a life-sustaining therapy, dialysis is associated with high mortality rates, especially due to cardiovascular disease (CVD).[1] Fluid overload (FO) is a non-traditional cardiovascular (CV) risk factor well-stablished among kidney failure patients.[3-7] Kidney failure precludes the physiological body fluids regulation, which becomes dependent on dialysis. In the specific case of HD, ultrafiltration (UF) is the main driving force for fluid removal. UF is prescribed taking into account estimated target weight (TW), which is defined as the lowest post-dialysis weight that a patient can tolerate without hypotension or intradialytic symptoms and without evidence of FO.[8] The physical examination including blood pressure (BP) measurement, lungs auscultation and edema screening is the mostly used method to evaluate FO. This detection workup may include devices or equipment, such as lung or inferior vena cava evaluation by ultrasound (US). Physical examination, with or without ancillary US, presents low accuracy in FO detection.[9]

About 30% of the prevalent HD patients in Europe present FO.[9] Several studies have reported an association between FO and hypertension, left ventricular hypertrophy, shorter survival, and higher hospitalization rates.[4] Due to this worrisome scenario, there has been an ongoing search for more accurate ways to measure the FO, allowing a better estimation of the TW. The measurement, theoretically more accurate than the indirect assessment of body fluids, can be performed using dilution techniques (gold standard) or bioimpedance analysis (BIA).[9]

Dilution techniques are too cumbersome and time-consuming to be employed in the clinical practice. BIA uses the electrical resistance of body fluids and tissue to an alternate

current flow, to estimate fluids volume and distribution. The bioimpedance spectroscopy bioimpedance (BIS) is a multifrequency (5 to 1,000 kHz) modality of BIA, which extrapolates resistance at measured frequencies from zero to infinite, creating a spectrum. This spectrum of frequencies allows the construction of a three-dimensional model of intra- and extracellular water, and overhydration (OH).[10,11] Previous studies of HD patients using BIS-guided UF have shown benefits for surrogate outcomes such as blood pressure control, left ventricular hypertrophy and arterial stiffness, but no consistent improvement in clinical endpoints such as survival or hospitalizations. [12–16]

This randomized controlled trial (RCT) aims to compare survival, blood pressure changes, and hospitalization rates between HD patients with BIS-guided TW estimation and patients with TW estimated by clinical examination alone.

Methods

Study Design: The study was designed as an open-label, parallel, randomized controlled trial.

Inclusion and Exclusion Criteria: The RCT included adult CKD patients (over 18 years of age) on in-center HD for longer than three months in the Dialysis and Transplantation unit of a University Hospital in southern Brazil. Exclusion criteria were HD sessions less than thrice a week, lower limbs amputation, pregnancy and use of a pacemaker, implantable cardioverter-defibrillator, or use of orthopedic protheses.

Ethical Aspects: All eligible patients or their relatives were asked to sign an informed consent form before inclusion in the trial. Enrollment was from September 2019 to September 2021. The trial was registered at ClinicalTrials.gov Identifier: NCT05272800. The research protocol was approved by the Ethics Committee of the Catholic University of Pelotas.

Randomization and Blinding: Randomization was performed in blocs according to dialysis shifts, using random number table created in the statistical software Stata 15.1 (StataCorp, College Station, TX). The patients were randomized to one of two groups: 1) BIS, whose target weight was assessed monthly by clinical examination and twice a year guided by the BIS; 2) CE, whose dry weight was evaluated monthly by clinical examination alone. Participants and researchers were not blinded due to the nature of the intervention. Statistical analysis was performed by a blinded evaluator.

Outcomes: The main outcome was two-year survival. Secondary outcomes included all-cause and cause-specific hospitalization rate (vascular access-related, infection-related, other medical admissions), change in systolic and diastolic BP (mean of the last three post-dialysis BP measurement - mean of three baseline post-dialysis BP measurement), number of anti-hypertensive drug classes used after intervention time. Participant's data

included as dependent variables for adjusted analysis (sex, age, and target weigh) were recorded from electronic clinical records at inception in the study. Follow-up time for primary and secondary outcomes was up to two years. Data on hospitalizations, deaths, cause of death, blood pressure and antihypertensive drugs in use were collected from the electronic medical registry.

Procedures and Equipment

Bioimpedance spectroscopy: Patients randomized to the BIS group were submitted to an initial evaluation using Body Composition Monitor (BCM) (Fresenius Medical Care, Bad Homburg, Germany). The BCM provides information on extracellular (ECW), intracellular (ICW) and total body water through a range of electric frequencies from 5 to 1,000 kHz. Based on these measurements, the equipment calculates parameters such as overhydration (OH), derived from the difference between the measured and expected extracellular water for an individual of the same weight and stature in euvolemia. The BCM also calculates the extra-intracellular water ratio (E/I). The measurement was performed by previously trained personal before a mid-week HD session, after five minutes of rest in the supine position, using electrodes placed on the ipsilateral upper and lower limbs. The patient was advised to avoid coffee or any meal 30 minutes before the evaluation. The data obtained was stored on a memory card to be discharged and analyzed using an accompanying software (Fluid Management Tool, Fresenius Medical Care). BIS has been previously validated as an accurate estimator of extracellular volume against dilution techniques in HD patients.[17]

Clinical Examination: The clinical evaluation was performed by a nephrologist with hemodialysis expertise and includes blood pressure measurements before and after a dialysis session, lung examination searching for rales and lower limbs (or sacral region for bedridden patients) for edema. The aim of the examination is to estimate and/or

reassess the estimated dry weight. Blood pressure was measured using a sphygmomanometer (Tycos, Welch Allyn, USA) by the auscultatory technique, with the patient seated in the dialysis chair and the upper limb extended. The cuff was placed two to three centimeters from the cubital fossa, and a stethoscope (Litmann, 3M, USA) placed over the brachial artery to detect Korotkoff sounds during inflation and deflation of the sphygmomanometer cuff. Lung examination was performed using the same stethoscope placed on posterior and anterior chest during an entire inspiration and expiration periods. The lower limbs were examined by pressing the index finger over the ankle and pretibial area searching for pitting edema.

Data Analysis: The minimum sample size required was calculated based on the expected difference in the main outcome (two-year survival) between intervention (BIS) and control (CE) groups. According to previous publications on chronic HD mortality, we intended to find a 20% survival difference between the groups, resulting in a minimum sample of 134 patients (67 in each group), to obtain an alpha error below 5% and a power of 80%.

The distribution of the variables was tested by Shapiro-Wilk. Parametric variables were described as mean and standard deviation and nonparametric variables as median and interquartile range. Survival analysis was performed using Cox Proportional Hazard Regression. Crude incidence rates of hospitalization were expressed as hospital admissions per patient-year. The incidence-rate ratio (IRR) and confidence interval (CI) between groups and the fraction of attributable risk among the exposed were also calculated. The number of antihypertensive classes (0, 1, ≥2) was compared between groups by Person's chi-square. The difference between baseline and final systolic and diastolic blood pressure was tested by Student's t test. The statistical package Stata 15.1 (StataCorp, College Station, TX) was used in the analysis.

Results

Sample Characteristics: One hundred and ten patients were enrolled, 52 for the clinical examination group and 58 for the bioimpedance spectroscopy group. The mean age of participants was 57.4 (15.4) years, 55.8 (13.9) years in CE and 58.8 (16.7) years in BIS, p=0.19. There were 58% male (56% in the CE and 65% in the BIS group, p=0.33).

Follow-up: There were dropouts due to kidney transplantation, change of dialysis center or withdrawal for other reasons. Some BIS measurements were lost due to technical problems. (Figure 1) The BIS evaluation scheduled for the 18º month of study was suspended due to the peak of the Covid-19 pandemic within the dialysis center. Follow-up time was 1.3 (0.3-2.2) years for the CE group and 1.9 (1.1-2.2) years for the BIS group.

Survival Analysis: There were 10 deaths in the CE group and 12 deaths in the BIS group. There was no significant difference in survival between the groups in the crude analysis (HR 0.84 95% CI 0.36-1.94, p=0.67) (Figure 2) or in the age-adjusted analysis (HR 0.53 95% CI 0.21-1.29, p=0.16).

Hospital Admissions: The incidence rate (IR) for all-cause hospital admissions, out of a total of 188 and 191 admissions, or 59.6 and 89.6 persons-time (years), was 3.1 and 2.1 hospitalizations per person-year in CE and BIS groups, respectively. The time-adjusted IRR was 1.48 (95% CI 1.20-1.82, p=0.0001) and the fraction of attributable risk among exposed was 0.32 (95% CI 0.17-0.45). (Figure 3) Regarding clinical admissions (excluding vascular access and infectious complications), there were 127 and 126 admissions, 61.8 and 89.6 persons-time (years), and IR of 2.1 and 1.4 per person-year in CE and BIS groups, respectively. The time-adjusted IRR time-adjusted was 1.46 (95% CI 1.13-1.88, p=0.003) and the fraction of attributable risk among exposed was 0.31 (95% CI 0.12-0.47). The IR of hospital admissions due to vascular access and infectious complications were not different between the groups. (Table 1)

Blood Pressure: There was no difference between the groups in the change in systolic or diastolic blood pressure or in the number of anti-hypertensive drugs classes required at the trial closure. (Table 1)

Discussion

This trial randomized CKD patients on HD to receive periodic target weight assessment based on BIS data and clinical evaluation or clinical evaluation alone and compared clinical endpoints between the groups after a up to two years follow-up. There was a significantly lower incidence rate of all-cause and medical hospital admissions in patients evaluated by bioimpedance. There was no difference in vascular access-related or infection-related hospitalizations, survival or blood pressure between control and intervention groups.

Fluid overload has been consistently associated with poorer survival among HD patients[3-7,18]. However, BIS-guided target weight estimation has not consistently been found to increase survival.[12–16,19–21] There are a number of potential explanations for these divergent findings. a) Fluid overload may be a confounding factor. Fluid overload is often combined with malnutrition and/or inflammation, and the clustering of these risk factors has been associated with the lowest survival.[22] b) BIS-guided target weight estimation may not be effective in reducing fluid overload. Previous studies have shown no effect of BIS-guided TW estimation on the median of the OH parameter before[20] and after HD[16]. This seemingly negative finding has been attributed to the sum of patients decreasing both overhydration and underhydration, which maintain the median of OH unchanged, despite the improvement in the individual hydration status of the patients. This explanatory hypothesis, however, has never been clearly demonstrated. c) The increase in UF in patients with clinically not apparent, but BIS-detected overhydration, may not reduce cardiovascular overload. There is a non-linear relationship between change in body weight and blood volume during HD[23] probably due to the wide variability in the percentage of weight loss that comes from the intravascular fluid (54 to 99%).[24] There have been described cases in which blood volume and body weight change even in

opposite directions.[24] d) Adverse events due to higher ultrafiltration rate may also limit the benefits obtained from BIS-guided TW estimation.[25] Fluid overload correction should include a strict restriction of sodium and water intake or/and an increase in time/frequency of HD sessions. e) In addition, most studies performed to date, including the present one, have been relatively small and underpowered for survival analysis.[15,21,26] We also found no differences in blood pressure control or in the need for antihypertensive drugs between the groups. Some authors have found benefits of BIS-guided TW estimation on outcomes such as hypertension, left ventricular hypertrophy and arterial stiffness,[16-18,27] but there is significant heterogeneity between studies. The present trial evaluated the difference between the mean of three blood pressure measurements at trial inception and the last three blood pressure measurements at the end of the trial. These measurements restricted to a few time points may have failed to detect variations and burden of blood pressure over time.

The participants who had BIS-guided TW estimation presented, however, a significantly lower incidence rate of all-cause and clinical hospital admissions, with no difference for vascular access-related or infection-related admissions. Large cohort studies have described that most hospital admissions among HD patients are due to fluid overload and its complications.[28,29] In a prospective study of more than 100,000 patients on maintenance HD, with a follow-up of 2.5 years, 14% of patients required hospitalizations for FO, heart failure or pulmonary edema.[30] Among 350,000 HD patients in the United States, about 280,000 episodes of FO, 80% of which require hospitalization, are reported by the USRDS.[31] In addition to economic costs, hospital admissions are associated with an increase in the mortality rate after discharge. Among Medicare beneficiaries in 2018, there were 1.58 admissions per person-year. More than 30% of these patients required

readmission (rates were even higher if initial admission was due to FO or hyperkalemia) and 10% died within 30 days of the hospital discharge.[31,29]

The weak points of the present RCT are the relatively small sample size, which did not reach the minimum size calculated for survival analysis. The smaller than expected sample size is largely due to the Covid-19 pandemic, which also precluded the latest BIS-guided TW estimation. Another weakness was the restriction of the BIS assessment to the intervention group, which made it impossible to blind the participants and the staff and prevented the comparison of the change in the FO between the groups.

However, the association between the BIS-guided TW estimation and a lower incidence rate of hospital admission, mainly due to clinical complications other than infections, is a noteworthy finding.

Conclusions

The analysis of one hundred and ten patients on maintenance hemodialysis randomized for target weight estimation based on clinical and BIS data or clinical data alone found no difference in survival or blood pressure control between the groups, but found a significantly lower incidence rate of hospital admissions in the BIS-guided TW estimation group. Larger and longer RCTs should be conducted to reassess and better explain these findings.

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Legend of Figures

Figure 1: Flow Diagram of the study

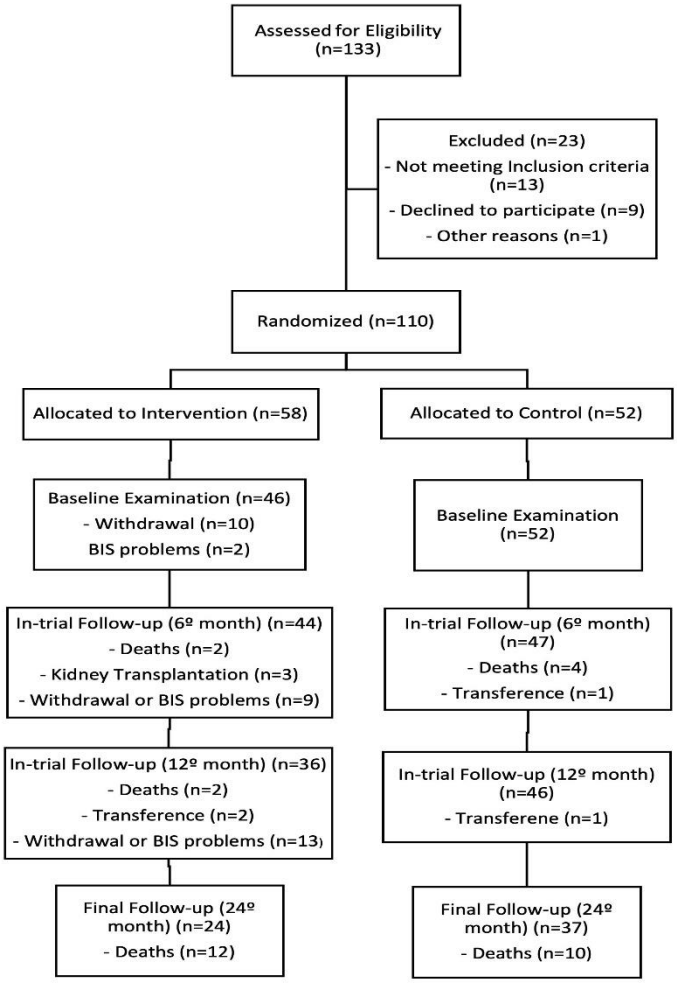

Figure 2: Survival Analysis by study groups

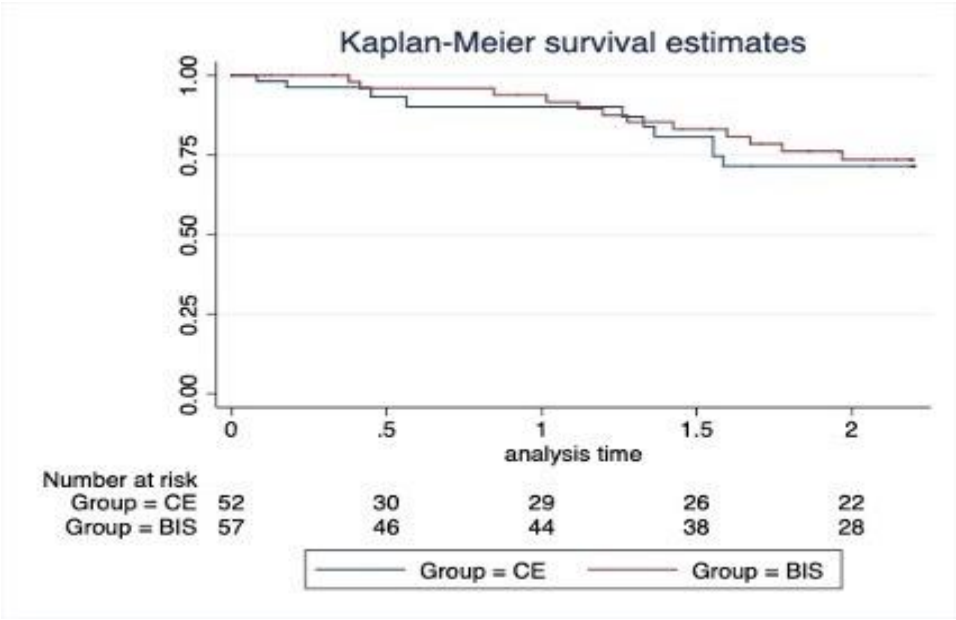

Figure 3: Cumulative Hazards estimates for hospital admissions by groups

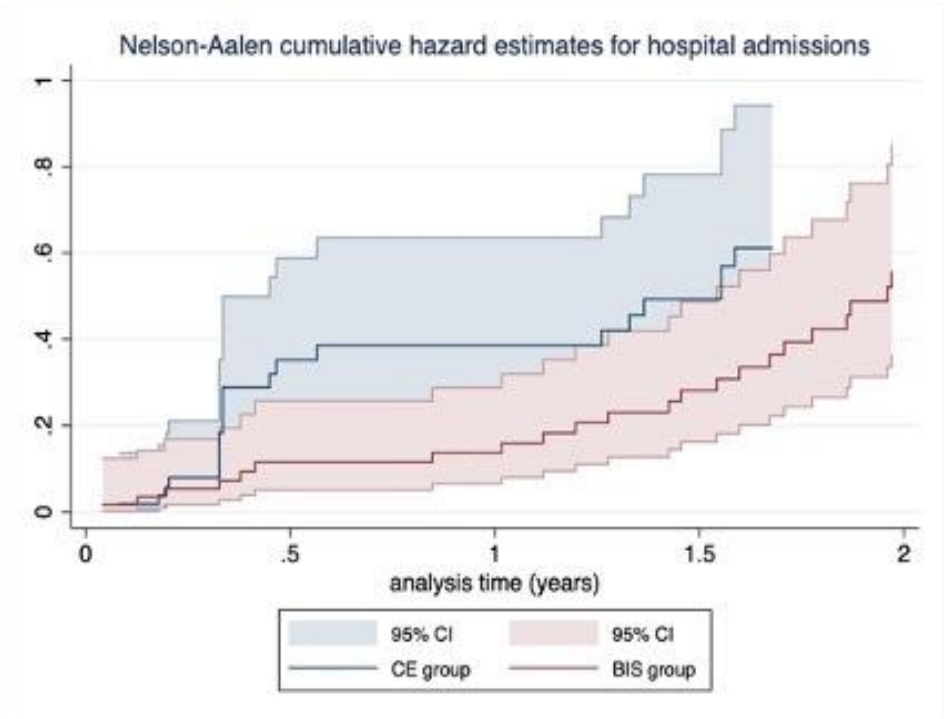

Table 1 Differences between CE and BIS groups regarding clinical outcomes after up to two years of follow-up

	CE group	BIS group	IRR (95%CI)	p-value
SBP baseline	142.2 (2.7)	143.3 (2.5)		0.76
DBP baseline	84.4 (1.8)	81.9 (1.5)		0.28
SBP final	138.9 (2.7)	142.3 (3.1)		0.42
DBP final	82.8 (1.6)	83.6 (1.8)		0.74
Delta SBP	-3.3 (3.7)	-1.1 (2.5)		0.61
Delta DBP	-1.6 (2.4)	1.7 (1.5)		0.23
Antihypertensive drugs (0/1/≥2)	13/19/20	17/14/27		0.37
OH baseline		1.8 (0.3-2.8)		
OH 6 months		2.2 (1.5-3.4)		
OH 12 months		1.2 (0.8-2.4)		
All-cause hospital admissions (IR)	3.1	2.1	1.5 (1.2-1.8)	0.0001
Medical hospital admissions (IR)	2.1	1.4	1.4 (1.1-1.9)	0.003
Vascular hospital admissions (IR)	0.7	0.5	1.5 (0.9-2.3)	0.06
Infectious hospital admissions (IR)	0.19	0.17	1.09 (0.47-2.45	0.82

SBP: systolic blood pressure; DBP: diastolic blood pressure; OH: overhydration; IR: incidence rate

CONSIDERAÇÕES FINAIS

Apesar da pandemia comprometer parcialmente a coleta de dados na área da pesquisa e não ter sido possível a avaliação da qualidade de vida dos pacientes pelo instrumento proposto, alguns objetivos foram realizados

Sobre objetivo de analisar as taxas de internação e sobrevida em pacientes usuários do serviço de HD, cujo peso seco foi estimado por BIS ou exame clínico isolado, mostrou o artigo 1 que a sobrevida dos pacientes não foi diferente entre os dois grupos, não confirmando a hipótese gerada no projeto de pesquisa. No entanto, o grupo que teve o PS avaliado pela BIS teve menor taxa de internação hospitalar, o que confirmou uma das hipóteses geradas no projeto de pesquisa.

A respeito do objetivo de comparar o número de classes e doses de medicamentos anti-hipertensivos usados por pacientes e avaliar as pressões arteriais sistólica e diastólica entre pacientes cujo peso seco foi estimado por BIS ou exame clínico isolado, o artigo 1 mostrou que não houve diferença significativa entre os dois grupos, não confirmando a hipótese gerada no projeto de pesquisa

Conforme mostrado nos dois artigos, a utilização da BIS para avalição do peso seco, no presente momento, não é amparada por suficiente evidência cientifica.

Concluímos sugerindo a necessidade de mais estudos sobre o tema, com adequado rigor cientifico, maiores amostras e tempos de seguimento mais longos.