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The intervention of acupuncture on the clinical status of dialysis patients.

Marta Correia de Carvalho

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Marta Raquel Custódio Correia de Carvalho

Instituto de Ciências Biomédicas Abel Salazar

MARTA RAQUEL CUSTÓDIO CORREIA DE CARVALHO

The intervention of acupuncture on the clinical status of dialysis patients

Tese de Candidatura ao grau de Doutor em Ciências Biomédicas submetida ao Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto.

Orientador – Professor Doutor Manuel Laranjeira
Categoria – Professor Auxiliar Convidado Aposentado
Afiliação – Instituto de Ciências Biomédicas Abel Salazar - Universidade do Porto.

Coorientador – Dr. José Nunes de Azevedo
Categoria – Nefrologista, Diretor Clínico.
Afiliação – TECSAM Tecnologia e Serviços Médicos

Coorientador – Professor Doutor Jorge P. Machado
Categoria – Professor Associado
Afiliação – Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto.

MARTA RAQUEL CUSTÓDIO CORREIA DE CARVALHO

The intervention of acupuncture on the clinical status of dialysis patients

Dissertation in fulfillment of the requirements for the Ph.D. degree in Biomedical Sciences, submitted to IBAS School of Medicine and Biomedical Sciences of the University of Porto

Supervisor – Ph.D. Manuel Laranjeira
Category – Retired Visiting Assistant Professor
Affiliation – IBAS School of Medicine and Biomedical Sciences, University of Porto

Co-Supervisor – Dr. José Nunes de Azevedo
Category – Nephrologist, Clinical Director
Affiliation – TECSAM Tecnologia e Serviços Médicos

Co-Supervisor – Ph.D. Jorge P. Machado
Category – Associated Professor
Affiliation – IBAS School of Medicine and Biomedical Sciences, University of Porto

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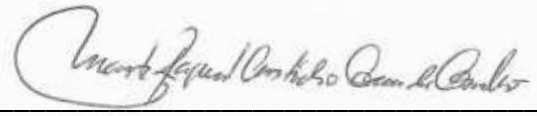

(Marta Raquel Custódio Correia de Carvalho)

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Scientific Contribution

Regarding the scientific contribution, I affirm my active involvement in the conception and execution of the experimental research, as well as in the analysis of the findings and the drafting of the manuscripts for the published works, including those presently under submission for publication, which constitute integral components of this Thesis.

Papers published in peer-review journals and indexed in Pubmed:

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Author contribution: Marta Correia de Carvalho was responsible for the conception and design of the experimental work, figure and table preparation, initial drafting, and revision of the final manuscript for publication.

2. Correia de Carvalho, M.; Nunes de Azevedo, J.; Azevedo, P.; Pires, C.; Laranjeira, M.; Machado, J.P. Effect of Acupuncture on Functional Capacity in Patients Undergoing Hemodialysis: A Patient-Assessor Blinded Randomized Controlled Trial. *Healthcare (Basel)* 2022, *10*, doi:10.3390/healthcare10101947.

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3. Correia de Carvalho, M.; Nunes de Azevedo, J.; Azevedo, P.; Pires, C.; Machado, J.P.; Laranjeira, M. Effectiveness of Acupuncture on Health-Related Quality of Life in Patients Receiving Maintenance Hemodialysis. *Healthcare (Basel)* 2023**,** *11,* doi:10.3390/healthcare11091355.

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Paper accepted in a specialty congress:

5. Correia de Carvalho, M.; Nunes de Azevedo, J.; Azevedo, P.; Pires, C.; Machado, J.P.; Laranjeira, M. Effect of frequency of acupuncture treatment on hemodialysis patients: subgroup analysis from a randomized controlled trial. European Congress of Integrative Medicine (Porto) Sept 30 Oct 1, 2022.

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Resumo

Caraterizada pelo seu perfil degenerativo, a doença renal crónica (DRC) tem contribuído substancialmente para o aumento das taxas de mortalidade das doenças não transmissíveis a nível mundial. A crescente prevalência e incidência da DRC e o notável impacto económico associado constitui um importante problema de saúde pública. Estima-se que em Portugal, cerca de 20% da população portuguesa sofra de DRC. A perda progressiva e irreversível da função renal conduz à terapia de substituição renal, pelo que a hemodiálise (HD) é a modalidade terapêutica mais frequente.

A HD introduz alterações significativas na vida do doente, com elevado impacto físico, emocional, social e no bem-estar, interferindo negativamente na capacidade funcional (CF) e qualidade de vida relacionada com a saúde (QVrS), aumentando o risco de morbilidade e mortalidade.

A Medicina Tradicional Chinesa (MTC) é alicerçada em conceitos etiológicos, fisiopatológicos e terapêuticos distintos e tem sido amplamente aceite pela medicina ocidental. Atualmente, verifica-se uma crescente utilização de terapias complementares e integrativas como intervenções adjuvantes para gerir os sintomas decorrentes de doença. A aplicação da acupunctura no campo da nefrologia tem também sido cada vez mais descrita em investigações recentes. Contudo, mais estudos randomizados controlados sobre a aplicação clínica da acupunctura em doentes em terapia de substituição renal são necessários.

O presente trabalho de investigação foi concebido para avaliar o efeito da acupunctura na CF e QVrS em doentes com doença renal crónica estádio 5 (DRC-5) em tratamento de HD. Pretendeu-se ainda, analisar as diferenças na frequência do tratamento (três vezes por semana ou uma vez por semana), comparar o efeito especifico com um placebo, avaliar os efeitos a curto e longo prazo e analisar a aceitação e viabilidade de integrar a acupuntura num centro de diálise.

Os resultados da nossa investigação são apresentados como um conjunto articulado de quatro artigos que procuram responder aos objetivos previamente delineados.

No primeiro artigo, apresenta-se o protocolo do nosso ensaio clínico randomizado controlado e cego para o paciente, concebido para sistematizar a nossa intervenção e criar um protocolo de acupunctura padronizado e repetível.

No segundo artigo de investigação, verifica-se o efeito da acupunctura na CF em pacientes com DRC-5 em HD e exploram-se as diferenças na frequência do tratamento (três vezes por semana ou uma vez por semana). A acupunctura comparada com os grupos de acupunctura *sham* ou sem acupunctura, melhorou a CF e a força muscular periférica e, em alguns parâmetros, os resultados persistiram no período de acompanhamento de doze semanas. No que diz respeito aos resultados da frequência do tratamento, a acupunctura uma vez por semana produziu efeitos semelhantes em comparação com três vezes por semana.

No terceiro artigo de investigação, descreve-se a avaliação da eficácia da acupunctura na QVrS, o efeito específico da acupunctura em comparação com o placebo e os efeitos a curto prazo. Em comparação com os grupos de acupunctura *sham* ou sem acupunctura, a acupunctura aumentou a pontuação da QVrS das componentes física e mental, a saúde geral e as áreas específicas da doença renal (lista de sintomas/problemas, efeitos da doença renal, função cognitiva, sono). Estes efeitos positivos foram observados a curto prazo, mas não persistiram três meses após o tratamento.

No quarto artigo de investigação, analisa-se a aceitabilidade e viabilidade da integração da acupunctura num centro de diálise, aferindo a perspetiva e atitudes dos doentes e dos profissionais de saúde face à possibilidade de incluir a acupuntura como terapia integrativa no cuidado ao doente em HD. Os resultados obtidos sugerem que esta pode ser uma opção de tratamento complementar viável e altamente benéfica na gestão dos sintomas da doença renal crónica e da qualidade de vida dos doentes em HD.

A acupuntura pode constituir-se como uma terapia complementar para a população clínica em estudo, mostrando-se eficaz e segura, em virtude da não ocorrência de eventos adversos. Contudo, salienta-se a necessidade de futuros ensaios clínicos randomizados controlados com amostras em número mais significativo com vista a validar a efetividade do protocolo de acupuntura administrado.

Por fim, almeja-se que o modesto e inovador contributo da nossa investigação possa servir de base à reflexão e implementação de políticas de saúde integradoras, abordagens centradas no paciente e práticas clínicas baseadas na evidência científica, de forma a proporcionar tratamentos integrativos seguros e viáveis a doentes renais crónicos em HD.

Palavras-chave: Doença Renal Crónica; Hemodiálise; Medicina Tradicional Chinesa; Acupuntura; Capacidade Funcional; Qualidade de Vida relacionada com a Saúde; Medicina Integrativa.

Abstract

Characterized by its degenerative profile, chronic kidney disease (CKD) has contributed substantially to the increase in mortality rates of non-communicable diseases worldwide. Therefore, the increasing prevalence and incidence of CKD and the notable associated economic impact constitute a major public health problem. It is estimated that in Portugal, about 20% of the Portuguese population suffers from CKD. The progressive and irreversible loss of kidney function leads to kidney replacement therapy, whereby hemodialysis (HD) is the most frequent therapeutic modality.

HD introduces significant changes in the patient's life, with high physical, emotional, social, and well-being impact, interfering negatively with functional capacity (FC) and health-related quality of life (HRQOL), increasing the risk of morbidity and mortality.

Traditional Chinese Medicine (TCM) is based on distinct etiological, pathophysiological, and therapeutic concepts and has been widely accepted by Western medicine. Currently, complementary and integrative therapies are increasingly used as adjunctive interventions to manage symptoms arising from disease. The application of acupuncture concepts in nephrology has also been increasingly described in recent research. However, more randomized controlled studies on the clinical application of acupuncture in patients with kidney replacement therapy are needed.

The present research work was designed to evaluate the effect of acupuncture on FC and HRQOL in patients with stage 5 chronic kidney disease (CKD-5) undergoing HD treatment to analyze the differences in frequency of treatment (three times a week or once a week), to compare the specific effect with a placebo, to evaluate the short- and long-term effects, and to analyze the acceptance and feasibility of integrating acupuncture in a dialysis center.

The results of our research are presented as an articulated set of four articles that seek to answer the previously outlined objectives.

The first research paper presents the protocol of our randomized controlled, patient-blinded clinical trial, designed to systematize our intervention and create a standardized and repeatable acupuncture protocol.

In the second research paper, the effect of acupuncture on FC in patients with CKD-5 on HD is verified and explores the differences in the frequency of treatment (three times a week or once a week). Acupuncture, compared with the *sham* or no acupuncture groups, improved FC and peripheral muscle strength, and in some parameters, the results persisted into the 12-week follow-up period. Concerning the results of treatment frequency, acupuncture once a week produced similar effects compared to three times a week.

In the third research article, the evaluation of the effectiveness of acupuncture on HRQOL, the specific effect of acupuncture compared to placebo, and the short-term effects are described. Compared to the *sham* or non-acupuncture groups, acupuncture increased HRQOL physical and mental component scores, overall health, and kidney disease-specific areas (symptom/problem list, effects of kidney disease, cognitive function, sleep). These positive effects were observed in the short term but did not persist three months after treatment.

In the fourth research paper, the acceptance and feasibility of integrating acupuncture in a dialysis center are analyzed, assessing the perspective and attitudes of patients and health professionals towards the possibility of including acupuncture as an integrative therapy in the care of HD patients. The results obtained suggest that this may be a viable and highly beneficial complementary treatment option in managing the symptoms of CKD and the quality of life of HD patients.

Acupuncture may constitute a complementary therapy for the clinical population under study since it was effective and safe since no adverse events were reported. However, future randomized controlled trials with larger sample sizes are required to validate the effectiveness of the acupuncture protocol.

Finally, it is hoped that our research's modest and innovative contribution can serve as a basis for reflection and implementation of integrative health policies, patient-centered approaches, and clinical practices based on scientific evidence, providing safe and feasible integrative treatments for chronic kidney patients in HD.

Keywords: Chronic Kidney Disease; Hemodialysis; Traditional Chinese Medicine; Acupuncture; Functional Capacity; Health-Related Quality of Life; Integrative Medicine.

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Acronyms and Abbreviations

CKD	Chronic Kidney Disease
UACR	Urine Albumin-Creatinine Ratio
eGFR	Estimated Glomerular Filtration Rate
KDIGO	Kidney Disease: Improving Global Outcomes
DM	Diabetes Mellitus
GFR	Glomerular Filtration Rate
AER	Albuminuria
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
ACR	Albumin to Creatinine Ratio
RAAS	Renin-Angiotensin-Aldosterone System
AKI	Acute Kidney Injury
KRT	Kidney Replacement Therapy
SLE	Systemic Lupus Erythematosus
NSAIDs	Nonsteroidal Anti-Inflammatory Agents
KF	Kidney Failure
HD	Hemodialysis
PD	Peritoneal Dialysis
IgA	Immunoglobulin A
ANCA	Anti-Neutrophil Cytoplasmic Antibody
CCC	Comprehensive Conservative Care
KT	Kidney Transplantation
AVF	Arteriovenous Fistula
AVGs	Arteriovenous Grafts
KDOQI	Kidney Disease Outcomes Quality Initiative
6MWT	Six-Minute Walk Test
STS-30	Thirty-Second Sit-to-Stand Test
HGS	Handgrip Strength Test
HRQOL	Health-Related Quality of Life
PCS	Physical Component Summary
KDQOL-SF™ 1.3	Kidney Disease Quality of Life Short Form ™ 1.3
SF-36	36-Item Short Form Survey
TCM	Traditional Chinese Medicine
ICD-11	International Statistical Classification of Diseases and Related Health Problems
WM	Western Medicine
HM-TCM	Heidelberg Model of Traditional Chinese Medicine
GC	Guiding Criteria
CMM	Chinese Materia Medica
WHO	World Health Organization

CNS	Central Nervous System
CAIP	Cholinergic Anti-Inflammatory Pathway
HPA	Hypothalamic–Pituitary–Adrenal
ACh	Acetylcholine
ChAT	Choline Acetyltransferase
AChE	Acetylcholinesterase
JAK2/STAT3	Janus Kinase 2/Signal Transducer and Activator of Transcription 3
NF-κB	Nuclear Factor kappa-B
MAPK	Mitogen-Activated Protein Kinase
NPY+	Neuropeptide Y+
CCs	Chromaffin Cells
DA	Dopamine
NE	Norepinephrine
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
STRICTA	Standards for Reporting Interventions in Clinical Trials of Acupuncture
CKD G5	Glomerular Filtration Rate category 5
FC	Functional Capacity
KGF	Kilograms-Force
VA	Verum Acupuncture
SA	Sham Acupuncture
WL	Waiting-List
RCT	Randomized Clinical Trial
MCS	Mental Component Summary
T&CM	Traditional and Complementary Medicine
NCT	Non-Conventional Therapies
CM	Conventional Medicine

Chapter I Introduction

1. Introductory Remarks

The present Thesis embodies the research work carried out within the scope of the Doctoral Program in Biomedical Sciences, with the general objective of transferring results to clinical practice, thus contributing to reinforcing the implementation of an integrative approach in the care delivery to chronic renal disease patients receiving maintenance hemodialysis, and with the specific objective of assessing the effect of acupuncture on the functional capacity, quality of life, and its acceptance in this clinical population.

For this purpose, a critical analysis of the available scientific evidence was performed, a standard and repeatable acupuncture intervention protocol was developed according to the international guidelines, the therapeutic intervention was performed in clinical settings, and the results were published in scientific articles in indexed journals.

This Thesis is structured into seven chapters, each dedicated to specific aspects of the research work.

The first chapter contains the theoretical contextualization through the literature review, a description of the concepts and theories used, the study's relevance, and the aims. Specifically, we describe the general concepts regarding chronic kidney disease, from its prevalence, definition and classification, prognosis, etiology and pathophysiology, and renal replacement therapies. Here, we describe hemodialysis and its relationship to functional capacity and quality of life of patients in more detail. We describe the general foundations of contemporary Traditional Chinese Medicine, from its etiology to its therapeutic approaches. We focus, in particular, on the description of acupuncture, alluding to its mechanisms of action and specifying its choice as a therapeutic and complementary option for patients undergoing hemodialysis.

An articulated set of three articles presents the results of our research. Each article was prepared according to the criteria required by the scientific journals in which they were published, with a systematic literature review, rigorous methodologies, and critical analysis of the results. It is presented from the second to the fourth chapter.

In chapter five, an integrated discussion of the results and directions for future research is conducted. Finally, in chapter six, the main conclusions of the research work are presented.

By conducting a parallel group patient-assessor-blinded randomized controlled trial we found the effectiveness of an acupuncture intervention protocol. Compared to the control groups, the effect of acupuncture was reflected in improved functional capacity and

peripheral muscle strength, increased physical composite summary score, mental composite summary score, overall health, and specific kidney disease targeted areas such as symptom/problem list, effects of kidney disease, cognitive function, and sleep. Furthermore, these positive effects were observed in most variables after treatment and on the 12-week follow-up, except for health-related quality of life scores, which did not persist three months after treatment. The acceptability and feasibility evaluation findings suggest that acupuncture may serve as a viable adjunctive therapeutic option for managing the symptom burden of chronic kidney disease and improving the quality of life in patients undergoing maintenance hemodialysis.

2. Chronic Kidney Disease
2.1 Prevalence

Chronic kidney disease (CKD) is a highly prevalent condition and has become a significant contributor to non-communicable mortality globally [1]. The escalating incidence and prevalence of CKD and its substantial economic burden have made it a significant public health concern. It negatively impacts the patient's quality of life and significantly burdens the healthcare system [2]. CKD was ranked as the 16th leading cause of mortality in 2016, and as per the latest statistics, it is projected to become one of the primary causes of death, ranking fifth by 2040 [3,4].

Currently, it is estimated that 9% to 13% of the worldwide population is affected by CKD [5,6]. However, according to the most recent data from the CaReMe (CArdioRenal and MEtabolic) study [7], designed to determine the prevalence of CKD through the collection of data from the national health systems of 11 countries (Portugal included), counting a total of 2.4 million potential patients, the prevalence of CKD was estimated to be around 10%. As far as Portugal is concerned, the prevalence of “Possible CKD”, defined as patients with a CKD diagnosis or one pathological urine albumin-creatinine ratio (UACR) or estimated glomerular filtration rate (eGFR) value, was 11.1% (n=11,802); the prevalence of “Measured CKD”, defined by patients with eGFR and UACR categories established by Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [8] was 9.8% (n=10,455).

The most recent cross-sectional study conducted in Portugal to assess the prevalence of CKD and to characterize CKD patients at a national level, called the RENA study [9] showed a prevalence of CKD of 20.9% (95% CI: 6.5-35.3%), a value well above the one previously presented as well as the European and world average. According to the study mentioned above, CKD was more prevalent in older individuals (74.4%; 95% CI: 68.4-80.5%), females (21.7%; 95% CI: 12.3-31.0%) from the central region of Portugal (24.9%; 95% CI: 16.8-33.1%) and among individuals with diabetes mellitus (DM) (31.4%; 95% CI: 16.8-46.0%) compared with patients without DM. The prevalence of CKD stages 3 to 5 was 10.62%. Also, the prevalence of hypertension was 61.5%, dyslipidemia was 42.2%, DM was 32%, and obesity was 34.8%.

Beyond estimated global prevalence rates, CKD maintains an upward trend, primarily due to the aging population and increased metabolic and cardiovascular diseases worldwide. Furthermore, this trend significantly burdens healthcare systems with substantial economic costs [5].

2.2 Definition, classification and prognosis

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, defines CKD as abnormalities of kidney structure or function, present for more than 3 months, with implications on health and classified based on cause, on glomerular filtration rate (GFR<60 ml/min/1.73 m2) and albuminuria (AER≥30 mg/24 hours; ACR≥30 mg/g [≥3 mg/mmol]) categories [8].

Attending to the definition as mentioned above, eGFR is calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [10]. Individuals with an eGFR below 60 mL/min per 1.73m2 are classified as having diminished kidney function. The urinary albumin level is evaluated by measuring the albumin to creatinine ratio (ACR), which is categorized into four levels: <10 mg/g, 10 to <30 mg/g (normal to slightly elevated), 30 to 300 mg/g (moderately increased), and >300 mg/g (severely increased) [8]. Patients who meet the previously described criteria for diagnosis of CKD should be staged according to Figure 1, considering the cause of the disease, six categories of eGFR (G stages), and three levels of albuminuria (A stages). eGFR is clinically used to assess the degree of kidney impairment, monitor the progression of the disease, and evaluate the efficacy of treatment [8]

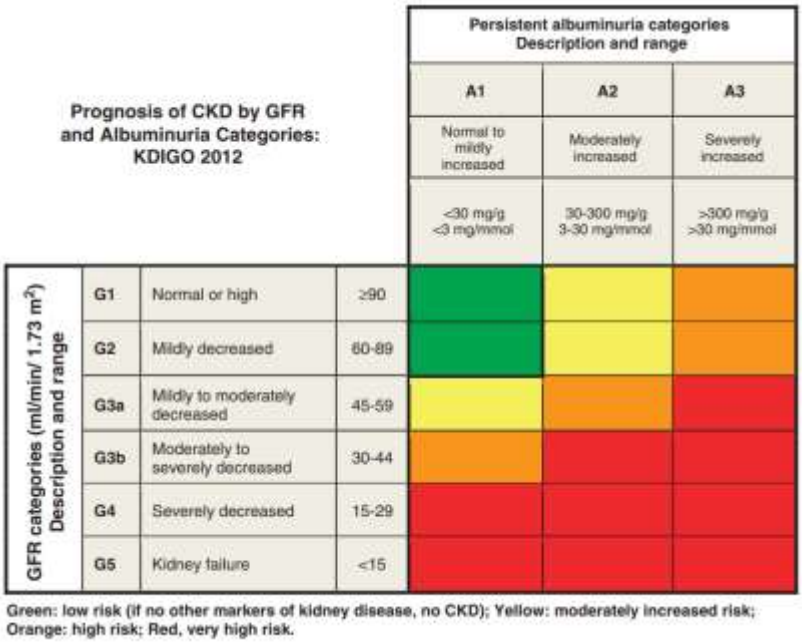

Figure 1. Prognosis of chronic kidney disease (CKD) by glomerular filtration rate (GFR) and albuminuria categories: KDIGO 2012. The colors represent different risks [8].

Reprinted from Kidney International Supplement, 3 (1), Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease, page 6, Copyright (2013), with permission from KDIGO.

As illustrated in Figure 1, an increase in albuminuria is associated with a higher risk of adverse events regardless of the eGFR level, including kidney outcomes and mortality. Risk stratification enables determining suitable treatments and the required monitoring level and facilitates patient education. Moreover, CKD's definition and staging have proven helpful in providing a standard language for CKD, making it easier to study its epidemiology, natural history, and prognosis [8].

Identifying CKD at an early stage is important to define a specific kidney diagnosis and to instruct treatment to prevent its progression, such as inhibition of the renin-angiotensin-aldosterone system (RAAS) [11]; to manage the complications of CKD, such as hypertension [12,13], cardiovascular risk [14-16], anemia [17], CKD-related bone mineral disease [18,19], metabolic acidosis [20], electrolytes disorders [21,22], uremic symptoms [23], secondary hyperparathyroidism [24], and malnutrition [25] and to improve measures to prevent and detect acute kidney injury (AKI) [26]. Moreover, to plan kidney replacement therapy (KRT), to initiate transplant evaluation and to plan for vascular or peritoneal access to initiate dialysis. Failure to an early diagnose of CKD promptly results in patients who already have advanced or end-stage disease, often requiring the initiation of emergency dialysis, which is associated with worse outcomes [27].

The occurrence of late referral to a nephrologist is common, leading to unfavorable outcomes such as risen morbidity and mortality risk, severe uremia, higher usage of catheters for vascular access, which has associated morbidity, reduced utilization of the preferred arteriovenous fistula for vascular access, limited patient options for treatment modality, longer and more expensive hospitalization during the initial stages of dialysis, heightened levels of emotional and socioeconomic [28,29]. When a patient is referred early, a productive partnership can be established with a multidisciplinary team of healthcare professionals. This collaboration enables patients to make more informed decisions about renal replacement options, such as transplantation, and to receive timely KRT to maintain their optimal health. Furthermore, patients can receive advice regarding dietary adjustments, immediate placement of dialysis access, and to support services to address any unfulfilled psychological, social, or financial requirements [27,30,31].

The most recent findings from the KDIGO Controversies Conference (2021) point to a consensus that CKD screening coupled with risk stratification and treatment should be

prioritized in people at high risk, namely with hypertension, DM or cardiovascular disease. For optimal outcomes, screening programs should be implemented within primary or community healthcare facilities and customized to fit the specific needs of the local environment [32].

CKD progression varies depending on the underlying cause, eGFR and UACR values, as well as the presence of risk factors and the existence of other comorbidities. Several risk factors may contribute to the development of CKD, including DM; hypertension; cardiovascular disease; multisystem diseases with potential kidney involvement, such as systemic lupus erythematosus (SLE); family history of kidney failure; history of and recovery from AKI; obesity; metabolic syndrome; frequent urinary tract infections; lower urinary tract obstruction; kidney stones; reduction in kidney mass; low birth weight; exposure to nephrotoxic drugs, such as nonsteroidal anti-inflammatory agents (NSAIDs) or aminoglycoside antibiotics [33]. CKD also correlates with socioeconomic risk factors such as advanced age, race/ethnicity [34,35], and exposure to specific chemicals or environmental circumstances [36].

CKD is often associated with comorbidities such as cardiovascular diseases, hypertension, and DM [6]. These comorbidities can exacerbate its progression, increasing morbidity and mortality rates and significantly challenging healthcare systems. According to the latest data from CaReMe (CArdioRenal and MEtabolic) study conducted by Sundstrom et al. (2022), the estimated frequencies of comorbidities with CKD in Portugal were as follows: DM at 47% (n=4885), heart failure at 13% (n=1403), stroke at 13% (n=1340), atrial fibrillation/flutter at 12% (n=1272), cancer at 11% (n=1110), coronary artery disease at 10% (n=1075), and peripheral artery disease at 3% (n=344) [7] . It is, therefore, essential to managing these comorbidities effectively to improve patient outcomes and reduce the burden of CKD on healthcare resources.

The correlation between CKD and DM is well established and is recognized as a growing global concern, with DM constituting a major cause of CKD [37]. The progression of CKD may further interfering with the management of DM and increase the risk of cardiovascular disease. Also, the growing prevalence of other risk factors, such as hypertension or metabolic syndrome, considerably increases the risk of cardiovascular disease in CKD patients [15]. Moreover, CKD itself constitutes an independent risk factor for cardiovascular disease. Notably, the risk of death among CKD patients, especially from cardiovascular disease, surpasses the risk of eventually needing dialysis. Furthermore, CKD patients exhibit poorer outcomes from cardiovascular disease, such as higher mortality following acute myocardial infarction [14,16].

2.3 Etiology and pathophysiology

Several pathologies or etiological factors can lead to kidney failure (KF), including immunological reactions triggered by immune system complexes or cellular damage, tissue hypoxia and ischemia, drug use or exposure to endogenous substances such as glucose or paraproteins, and genetic defects. Structural and functional kidney damage can be detected by signs such as increased urine protein excretion (microalbuminuria or macro proteinuria), imaging findings (such as polycystic kidneys), or decreased eGFR (< 60 ml/min/1.73m^2) [38].

DM, hypertension, glomerulonephritis, and cystic kidney disease are the primary causes of CKD [39]. The increasing incidence of DM in the industrialized world has primarily contributed to diabetic nephropathy being the leading cause of CKD. Globally, a consistent pattern emerges, indicating that countries with the highest proportion of diabetic nephropathy as a primary cause of CKD also have the highest rate of new patients initiating KRT [5]. Regarding Portugal, in patients on hemodialysis and peritoneal dialysis, the percentage of DM as a primary cause of CKD is around 30%, higher than the European average [40].

Diabetic nephropathy presents clinically as albuminuria and a gradual decline in renal function. Structural manifestations of this condition include thickening of the glomerular and tubular basement membranes, expansion of the mesangium, which may form nodules known as Kimmelstiel-Wilson lesions, arteriolar hyalinosis, and tubulointerstitial fibrosis [38,41].

Regarding non-diabetic nephropathy, CKD can be categorized into including glomerular, tubulointerstitial, vascular, cystic and congenital diseases (Table 1).

Table 1. Chronic kidney disease categories and examples(1).

Glomerular Diseases	Focal and segmental glomerulosclerosis
	Immunoglobulin A (IgA) nephropathy
	Membranous nephropathy
	Diffuse proliferative glomerulonephritis
Tubulointerstitial Diseases	Urinary tract infection
	Tubulo-interstitial nephropathy
	Stones
	Obstruction
	Gouty nephropathy

Vascular Diseases	Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis Hypertensive nephroangiosclerosis Atherosclerotic ischemic renal disease
Cystic and Congenital Diseases	Autosomal dominant polycystic kidney disease Medullary cystic disease Kidney dysplasia

(1) Adapted from Edgar V. Lerma, M.A.S.; Topf, J.M. *Nephrology secrets*. Fourth ed.; Elsevier: Philadelphia, PA, 2019, page 124.

Notably, CKD does not represent a single diagnosis but rather an umbrella term for several diseases, each with its specific pathophysiology and treatment [33].

The decline of renal function is gradual and may initially present asymptomatically. Although the course of kidney failure (KF) depends on the etiology of CKD, it ultimately entails the activation of early homeostatic mechanisms, which lead to hyperfiltration of the nephrons [42]. Each nephron contributes to the total GFR in a normal kidney. Despite progressive destruction of the nephrons, the kidney can maintain the GFR as the remaining normal nephrons develop compensatory hyperfiltration and hypertrophy. Consequently, individuals with mild renal failure may exhibit normal creatinine levels, and the condition could remain undetected. Only when the glomerular filtration rate is reduced by 50% do the plasma urea and creatinine levels start to show measurable increases [42,43].

Although the adaptive mechanism of nephron function allows the average clearance of plasma solutes to continue, the limit of adjustment is reached at some point. As more nephrons are lost, the GFR decreases, with hyperfiltration and hypertrophy of the remaining nephrons contributing as significant factors in the gradual deterioration of renal function. In addition, the elevated pressure within the glomerular capillaries can guide to their damage, ultimately leading to the development of focal and segmental glomerulosclerosis and eventual global glomerulosclerosis [44,45].

A combination of glomerulosclerosis, tubular atrophy, leukocyte infiltration, and tubulointerstitial fibrosis characterizes the progression of CKD. These processes affect the glomeruli and the tubulointerstitial tissue, contributing to the severity of kidney disease.

The glomerular sclerosis may be associated with inflammatory and proliferative components. Progressive fibrosis in tubulointerstitial tissue is always associated with persistent sterile inflammation initiated by generating soluble mediators in response to stress and tissue injury. The respective inflammation leads to leukocyte infiltration and the

secretion of various mediators by resident bone marrow-derived cells, tubular epithelial cells, and interstitial fibroblasts as illustrated in Figure 2 [45,46].

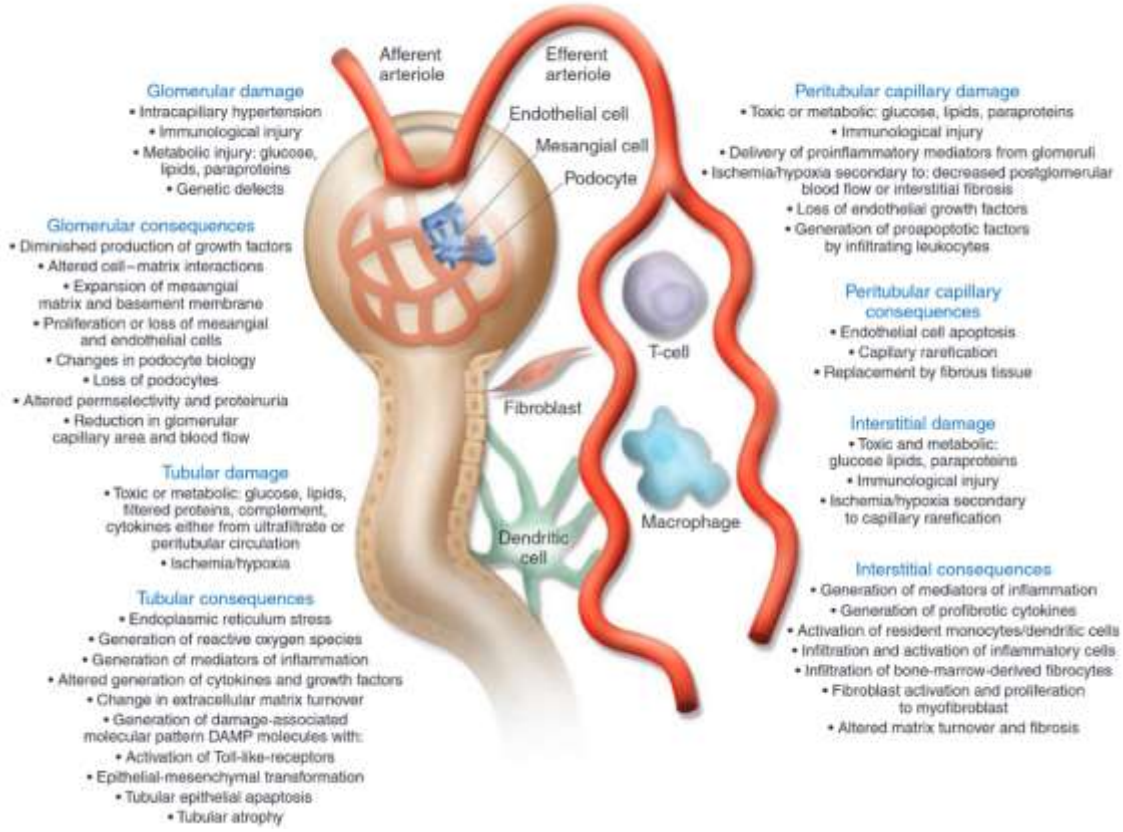

Figure 2. Overall scheme of factors and pathways contributing to the progression of renal disease [45]. Reprinted from Kidney International, 74, Schlondorff, D.O., Overview of factors contributing to the pathophysiology of progressive renal disease, page 861, Copyright (2008), with permission from Elsevier.

The arrangement of these actions aims to rectify and restore local tissue damage. However, they also trigger the activation of profibrotic cells, primarily myofibroblasts, leading to localized scar tissue or fibrosis development. This fibrosis disrupts the delicate cellular structure of the nephron, setting off a detrimental cycle that poses new threats to cellular homeostasis [47]. The repair process may come to a relative standstill, or the damage may progress relentlessly toward KF, depending on the extent of tissue distortion caused by fibrosis and ongoing cellular stress [45,46,48].

2.4 Kidney replacement therapy

The loss of GFR over time defines kidney disease progression. Individuals without proteinuria or comorbidity exhibit a decline in kidney function ranging from 0.3 to 1.0 mL/min per 1.73 m^2 per year. In contrast, patients with established CKD display varying progression rates, typically between 2.5 and 4.5 mL/min per 1.73 m^2 per year, with rapid progression identified as rates exceeding 5 mL/min per 1.73 m^2 per year [33]. Complications of decreased kidney function can lead KF (GFR<15 ml/min/1.73 m^2) and may require the initiation of KRT [49]. KRT refers to the medical interventions used to replace kidney function and sustain life, such as particular comprehensive conservative care (CCC), peritoneal dialysis (PD), hemodialysis (HD), or kidney transplantation (KT).

While unable to fully replicate the complex functions of a healthy kidney, maintenance dialysis seeks to remove toxins usually filtered by the kidneys and maintain proper fluid balance in the patient. The dialysis's ultimate goal is to alleviate uremia's signs and symptoms and enable patients to regain a functional status [33,38].

Two primary forms of dialysis are currently used: HD, which can be carried out in a specialized dialysis unit or at home, and PD, which is predominantly performed at home. In-center HD is the most common treatment option, involving visits to a dialysis center about three times a week, lasting three to four hours. The selection of the appropriate dialysis modality is contingent upon factors such as patient preferences, accessibility of treatment options, and potential contraindications to either method [50].

The initiation of dialysis concerns significant adjustments to the patient's lifestyle and may involve medical complications. Therefore, a comprehensive assessment of the potential benefits of initiating dialysis is crucial [51]. Urgent initiation of dialysis may be necessary for life-threatening conditions and ideally should be initiated before the requirement emerges. Potential symptoms for starting dialysis may include refractory volume overload despite diuretic therapy, hyperkalemia, pleuritis or pericarditis, peripheral neuropathy, encephalopathy, malnutrition, nausea/vomiting, uremic bleeding, metabolic acidosis, resistant hypertension, severe hyperphosphatemia, and severe hypocalcemia [33].

According to the KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, dialysis initiation may be warranted when symptoms or signs of kidney disease manifest, blood pressure or volume status cannot be effectively controlled, nutritional status deteriorates, or cognitive dysfunction is evident [8].

2.5 Hemodialysis

In Portugal, dialysis treatments show a high prevalence and incidence. According to the annual report from the CKD Registry Office of the Portuguese Society of Nephrology, over the last 20 years, there has been an increasing trend of new patients starting KRT, as is generally the case in Europe. The Portuguese Registry of Kidney Replacement Therapy 2022 points to a high incidence of new patients starting KRT (> 240 per million population), with an increase of 2% compared to 2021 [40].

Despite the option of PD, most patients worldwide still elect HD as their initial modality [52], and Portugal is no exception. On December 31, 2022, 12878 patients were treated by HD, 881 by PD, and 159 by comprehensive conservative care [40].

The National Health System (NHS) is the primary funder of HD treatments through direct convention agreements with private operators or providing healthcare services in public hospitals.

According to the latest report of monitoring information on the HD convention sector of the Entidade Reguladora de Saúde, based on data from the Platform for Integrated Disease Management in June 2022, 12,426 patients were undergoing HD treatment. Of the total enrolled patients, 11,539 (92.86%) were treated in 101 dialysis units of the private and social sectors, and only 887 (7.14%) received treatments in hospital units of the NHS. These numbers represent an expenditure of 116 457 675.36 euros, equivalent to 19.1% of the total charges of the health convention sector, and highlight the substantial financial burden of HD treatment on the Portuguese public health system [53].

HD is a complex procedure that requires specialized training and expertise to function safely and effectively. In dialysis centers, patients are accompanied by healthcare professionals trained to perform and monitor HD treatment. The evolution and technological innovation of dialysis machines, also called dialyzers, allow for the rapid and effective removal of small molecular weight solutes during a treatment that can range from 3 to 5 hours, three times per week [50].

Regarding the HD procedure, blood is rapidly circulated through an extracorporeal circuit. A needle or catheter port is used to withdraw blood, entering the dialysis filter. The dialysis filter comprises numerous hollow tubes that contain a semipermeable membrane. The dialysate, on the outside of the tubes, moves in a countercurrent manner. Through diffusion, solutes in the blood (high concentration) move into the dialysate (low concentration). The blood is subsequently returned via a separate venous needle or port. Additionally, ultrafiltration removes fluid, which involves modifying the hydrostatic pressure

across the dialysis membrane. For either high or low-flux, the use of biocompatible membranes is recommended [50,54].

A specialized access point is required to allow for efficient blood flow in patients who undergo HD on a regular basis [55]. The preferred dialysis access is an arteriovenous fistula (AVF), created by surgical anastomoses of an artery to a vein, usually in the arm. AVFs have the lowest rate of complications, both infectious and non-infectious, and tend to be more durable compared to other types of vascular access. However, AVFs require time to mature, usually taking six to eight weeks, but sometimes up to six to nine months, and there is a chance they may not become suitable for dialysis. Before creating an AVF, ultrasound imaging is typically used to map the veins in the upper extremities, allowing for the detection of central stenosis and measurement of vein diameter [56,57].

In addition to AVFs, there are other options for dialysis access, such as arteriovenous grafts (AVGs) and double-lumen catheters. AVGs are synthetic grafts attached to the artery and vein, and they can be used for dialysis more quickly than AVFs, sometimes as early as two-three weeks after placement. AVGs also have a higher initial success rate compared to AVFs. However, AVGs tend to fail earlier due to a condition called neointimal hyperplasia, and they require frequent interventions to maintain patency. Moreover, AVGs have a higher risk of infection compared to AVFs. Ideally, AVGs should be placed in the arms, but in cases where suitable veins are not available in the arms, they can be placed in the thigh [33,50,57].

On the other hand, double-lumen catheters are another type of dialysis access that can be used immediately for dialysis. These catheters are often placed in the internal jugular vein, recommended instead of the subclavian. Subclavian catheters are associated with a high risk of subclavian stenosis, which can cause complications and may prevent future dialysis access in the same arm. Catheters intended to be used over a few days are usually tunneled under the skin to decrease the risk of infection. However, it is essential to note that catheters have a much higher infection rate than AVFs or AVGs and a higher dysfunction rate [33,58].

Regarding the type and location of vascular access, the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Vascular Access: 2019 Update recommends a patient-centered approach to attending to patient needs and dialysis access eligibility [56].

Despite its advantages and critical role in managing kidney failure and maintaining the chronic renal patient's overall health and well-being, HD also has some limitations and burden with treatment-related symptoms [59]. Since it is not an ongoing treatment, fluid

removal is not physiological and often requires the removal of large volumes of fluid during treatment. Furthermore, HD is ineffective at removing larger molecules or solutes bound to proteins [33,50].

HD can be accompanied by various complications, both infectious and noninfectious, related to vascular access. Infections are relatively common in hemodialysis patients and can result in significant morbidity [60].

Another complication associated with vascular access is stenosis, which can occur near the venous anastomoses or in central veins in AVFs and AVGs. Venous stenosis can lead to arm swelling, difficulty with cannulation, and prolonged bleeding after dialysis. Therefore, percutaneous angioplasty is often used to treat it [61,62].

During the initial dialysis treatments, patients may experience the disequilibrium syndrome, characterized by symptoms such as headache, somnolence, and rarely seizures or coma. This syndrome is thought to be caused by cerebral edema resulting from a rapid decrease in plasma osmolality, and it is less common if the initial dialysis treatments are short and performed with low blood flow [63].

Hypotension is a common complication of the dialysis procedure and is associated with fast ultrafiltration rates and/or autonomic dysfunction [64,65]. Another recently recognized complication of dialysis is the development of silent myocardial ischemia during treatment [66,67]. In addition, the dialysis procedure has rare but potentially fatal complications, such as air emboli and anaphylaxis. These complications require prompt recognition and appropriate management to prevent serious consequences [68].

2.6 Hemodialysis and Functional Capacity

HD is the most commonly used form of dialysis and is known for its complex and demanding treatment regimen. Patients undergoing HD must cope with physical and emotional challenges associated with the chronicity of the disease, which compromise their overall health and well-being [69,70].

As previously mentioned, CKD has a high comorbidity with cardiovascular disease which may impair patients' physical performance. In addition, the catabolic state inherent in CKD involves oxidative damage, a propensity for inflammation, and malnutrition, leading to skeletal muscle mass loss and decreased function [71]. Sarcopenia, the loss of skeletal muscle, may lead to skeletal muscle dysfunction, negatively impacting mobility and functional capacity [72-74].

Numerous research has unequivocally demonstrated that poor physical activity is related to poorer quality of life and higher mortality in the general population. In addition, patients undergoing HD often experience a decline in their physical condition due to reduced dietary intake, a sedentary lifestyle, and HD-associated catabolism [75-77]. Compared to healthy individuals, HD patients typically have reduced exercise capacity, which is associated with impaired daily activities, lower quality of life, and reduced survival rates [78-80].

Chen *et al.* (2023) showed that muscle strength and physical performance were associated with lower survival and a higher risk of death in patients receiving maintenance HD. Their findings support the idea that physical performance is a better predictor of mortality and an effective and cost-efficient approach to prognosis, based on the possible explanation of the function of the muscles in the lower extremities, could be more critical than those in the upper extremities in terms of predicting adverse outcomes in patients [81].

Brief physical performance tests assessing physical function, peripheral muscle strength or gait speed are particularly helpful in identifying clinical and subclinical CKD burden and as prognostic markers of mortality and disability [82,83].

The Six-Minute Walk Test (6MWT) is a simple and suitable walking test that measures an individual's submaximal functional exercise capacity. It is used to evaluate the effectiveness of therapeutic interventions by tracking changes in the distance walked during the six-minute test [84]. The 6MWT distance is considered an independent predictor of mortality, and for every additional 100 meters walked, the survival rate of patients undergoing HD increased by approximately 5% [85]. The Thirty-Second Sit-to-Stand (STS-30) test is a dependable test for functional evaluation in HD patients and is used to assess functional lower extremity strength [86,87]. The Handgrip Strength (HGS) test is a reliable and often-used measure of overall muscle strength [88]. The study conducted by Lopes et al. (2022) examined the associations HGS, body composition, FC, muscle quality, and inflammatory markers among individuals receiving maintenance HD. The findings indicated a significant correlation between reduced HGS values, higher inflammation levels, and lower FC [89]. Additionally, prior research studies have revealed that handgrip strength can predict all-cause mortality in both men and women undergoing HD [90-92].

2.7 Hemodialysis and Health-related Quality of Life

Health-related quality of life (HRQOL) encompasses the multi-dimensional assessment of how an individual's health status impacts different aspects of their life over time. It includes various conceptual dimensions, such as physical, mental, emotional, and social well-being, collectively contributing to an individual's holistic evaluation of their overall quality of life [93,94].

Assessing treatment outcomes and monitoring the quality of care for patients on maintenance dialysis has led to a growing recognition of the importance of measuring HRQOL. Additionally, KDOQI recommendations highlight the significance of evaluating HRQOL to assess patients' overall well-being and determine the efficacy of new therapeutic interventions [95].

Compared to clinical and non-clinical groups, patients receiving HD exhibit a substantial decline in HRQOL measures [94,96-99]. Moreover, there is compelling evidence that associates reduced HRQOL scores with increased risks of adverse outcomes, including hospitalization and mortality [96,100,101]. Data from recent research indicate a significant correlation between decreased Physical Component Summary (PCS) scores three months after starting hemodialysis (HD) and overall mortality among patients undergoing HD [102]. Furthermore, comorbidities such as depression and DM have been recognized as predictors of reduced PCS scores [103].

Low HRQOL scores are frequently reported in patients receiving maintenance HD and a higher probability of suffering from various health problems, including deteriorating mental health [104], declining nutritional status [105], fatigue [106], chronic pain [107], and depressive and anxiety symptoms occurs [108-110]. Enhancing HRQOL has emerged as a required objective in KRT as it is associated with improved subjective satisfaction and overall prognosis in patients undergoing HD [95].

Accurate evaluation and enhancement of patients' self-reported physical and mental well-being are crucial in effective disease management and delivering high-quality patient care. To evaluate the dimensions of HRQOL, the validated Portuguese version of the Kidney Disease Quality of Life Short Form ™ 1.3 (KDQOL-SF™ 1.3) was selected due to its established validity among individuals with CKD. Additionally, this instrument encompasses a generic core that has been extensively utilized to measure the overall quality of life [111-113].

The KDQOL-SF™ 1.3 is a self-reported HRQOL instrument comprising a generic scale, a 36-item health survey, and a specific scale that addresses the unique concerns of individuals with kidney failure undergoing KRT, such as PD or HD [113].

The 36-Item Short Form Survey (SF-36) evaluates overall health status based on eight domains: "*physical functioning, role-physical, pain, general health, emotional well-being, role-emotional, social function and energy/fatigue"*. Each question is rated on a scale that ranges from 0 (representing the poorest health) to 100 (indicating the best health). Moreover, the SF-36 offers standardized scores that calculate physical and mental functioning, referred to as physical component summary (PCS) and mental component summary (MCS) scores [112,113].

The KDQOL-SFTTM 1.3 is a disease-specific tool that evaluates the quality of life of individuals with kidney disease. *It comprises forty-three items that measure eleven specific components of HRQOL, including "symptom/problem list, effects of kidney disease, work status, the burden of kidney disease, cognitive function, quality of social interaction, sexual function, sleep, social support, dialysis staff encouragement, patient satisfaction, and a single-item overall rating of health"* [112,113].

Considering the HRQOL of patients with end-stage renal disease has become crucial to making treatment-related decisions. The symptoms of advanced CKD and the burden of HD treatment significantly impact HRQOL [110]. The relevance of the clinical prognosis of advanced CKD highlights and reinforces the need to make specialized support available to manage patients appropriately.

HRQOL is one of the most representative components of patient-reported outcomes, and its assessment provides relevant information about patients' subjective satisfaction and overall health status. It is beneficial in clinical practice or research and helps ensure that support to the patient is provided [97].

3.Traditional Chinese Medicine

Traditional Chinese Medicine (TCM) is a system of medicine developed in China over thousands of years. However, the origin of TCM remains uncertain, with the earliest records dating back more than two thousand years to the Han dynasty (206 BCE–220 CE) The classic of Chinese medical literature, the "Yellow Emperor's Classic on Internal Medicine," is often cited as the official starting point of Chinese medicine. This book presents the fundamental concepts of TCM, which have been further clarified and improved over the years [114,115].

TCM has been practiced in China for centuries and has attained international recognition and respect as a medical practice. While remaining loyal to its traditional heritage, TCM continues to progress and adapt to the demands of the modern era. Furthermore, including Traditional Chinese Medicine (TCM) in the 11th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-11) marks a significant achievement for TCM and the ICD. This initiative by the World Health Organization (WHO) serves as an important recognition of the value of TCM and is a response to the demands of member states. Moreover, it aims to promote the integration of TCM with Western medicine (WM), thus improving the overall quality of healthcare. As a result, this initiative is expected to increase research, education, adoption, and recognition of TCM globally [116].

3.1 Physiology and pathology

TCM has established a systematic health model through extensive clinical background grounded in a scientific regulatory model. As one of the most significant domains of complementary and integrative medicine, TCM relies on unique theories and practices to treat disease and enhance overall health [117].

Two fundamental ideological concepts have permeated the entire process of formation and development of TCM. The first concept is the idea of homeostasis, which emphasizes the importance of maintaining the integrity of the human body and recognizes the close relationship between the human body and its social and natural environment (i.e., the integrity between humans and the cosmos). The second concept is the idea of dynamic balance, which emphasizes the importance of movement in the context of the overall

integrity of the body. TCM also recognizes the human body through a cybernetic and systematic discrimination approach, in which external information is analyzed to reveal the intrinsic activities of the body [114,115,118].

The concept of Yin-Yang is considered the most essential and distinctive theory of Chinese medicine. All Chinese medical physiology, pathology, and treatment can be reduced to Yin-Yang. Despite its simplicity, the concept is profoundly complex and continues to reveal new expressions in clinical practice and life in general. In contrast to the Aristotelian premise of the opposition of opposites, the concept of Yin-Yang and Qi has been a fundamental part of Chinese philosophy for centuries. Yin and Yang are opposing but complementary qualities. Each thing or phenomenon can be both itself, and it is opposite. Additionally, Yin contains the seed of Yang, making it possible for Yin to transform into Yang and vice versa [114,119-121].[1]

The essential theory of Yin and Yang is central to understanding all of Chinese medicine, including its physiology, pathology, diagnosis, and treatment. All physiological processes and symptoms can be interpreted and analyzed in light of this theory. In other words, Yin and Yang are the basis for explaining most concepts and practices of Chinese medicine [114,115]. From a cybernetic regulation point of view, yin is described by descending values below the target value and lack of substrate, which results in unstable regulation. On the other hand, yang is characterized by rising values above the target value, with a high action potential and function, which can lead to problems in primordial regulation [117,118].

Alongside the Yin-Yang theory, the Five Elements theory forms the foundation of Chinese medical theory. The human body is divided into five systems: wood, fire, earth, metal, and water. By analyzing these natural materials, specific characteristics of each system can be inferred. In addition, the movement and interchange between these elements explain the physiology of the human body [114].

According to the Heidelberg model of TCM (HM-TCM), the metaphoric meaning of each phase (designated as the element in the classical literature of TCM) [122] can be associated with a specific functional activity as follows: *Wood* represents the generation of potential; *Fire* symbolizes the conversion of potential into function; *Metal* is characterized

[1] According to WHO (2022) international standard terminologies on traditional Chinese medicine *"Yin is the opposite of yang. The qualities of Yin include cold/cool, dimness, descending, stillness, introversion, and heaviness, among others. Yang is the opposite of Yin. The qualities of yang include warm/hot, bright, ascending, movement, extroversion, light, and clearness, among others*" [121].

by a rhythmic distribution of energy and a relatively low level of activity, *Water* represents regeneration and renewal, and *Earth* stimulates transformation and growth [117].

Another absolute and fundamental concept at the basis of Chinese medical thought is the concept of Qi [2]. Characterized by its changing nature between a tangible material form and an intangible, delicate force, this concept is central to the TCM view of body and mind as an integrated unit. According to the classical literature on TCM, the interaction of certain vital substances is responsible for body-mind functioning. These substances vary in their materiality, some being very subtle and others being immaterial, and jointly, they form the traditional Chinese view of body and mind. Qi is the basis of all these vital substances, with the others being manifestations of Qi in varying degrees of materiality, from entirely material, such as physiological body fluids (*Jin ye*), to the immaterial such as the mind (*Shen*) [114,115,122].

TCM features a unique perspective of the human body's physiology, enabling it to take a specific approach to disorders in the body. From a pathological point of view, TCM focuses on the pathogenicity of social and natural factors closely linked to humans and their integrity. Rather than looking for the specific pathogen or the pathological changes in a specific organ, TCM looks at all symptoms and signs to identify disturbances in the autonomic systems. TCM emphasizes the dynamic changes in all parts and connections of a system with self-regulatory capacity [114,118].

In the cybernetic approach, TCM considers the human body a complex network of closely related systems that work together to maintain its integrity reflecting its regulatory capacity. This network is connected by meridians, also called conduits or channels, and collaterals which are found in the interstitial connective tissue. According to the theoretical assumptions of TCM, in addition to serving as conduits for the flow of Qi and Xue (Blood),

[2] According to the HM-TCM and to Greten (2013), Qi refers to *"the vegetative capacity to function of a tissue or an organ which may cause the sensation of pressure, tearing or flow."* From a Western perspective, it can be compared to the clinical effects of the vegetative system, where a lack of activation is called depletion, and excess activation is called repletion. Xue or "Blood" refers to the "*form of functional capacity bound to body fluids with functions such as warming, moisturizing, creating qi and nutrifying a tissue*". From a Western medical view, the clinical effects of Xue can be comparable to the effects of microcirculation, including the functional relations of microcirculation, blood cells, plasma factors, endothelium, and parenchyma. *Shen* refers to the *"functional capacity to put order into mental associativity and emotions, thus creating "mental presence."* The functional state of Shen is evaluated by signs such as the coherence of speech, the gloss of eyes, and fluent fine motoric (control of motor functions) and is comparable to the capacity to exert certain higher brain functions in Western medicine. Jing is equivalent *"to innate/pre-natal essence as it is the primordial substance responsible for constructing and maintaining the body's structure, function, and ability to reproduce, especially the reproductive essence stored in the Kidney*." From a Western point of view, it is comparable to DNA. It exhibits similar clinical effects as those caused by the cell nucleus and is susceptible to damage from radiation, chemotherapy, age, and genetic alterations [117].

allowing them to reach all parts of the body through a cyclical circulation, they also connect the internal organs to the external body, establishing the link between the specific clinical manifestations reflected by the acupuncture points, and ensuring balance and homeostasis [118].

The primary meridians are categorized as bilateral, regular, or cardinal. These meridians are linked to the Zan-fu organs, with six classified as yin and the other six as yang. The meridians are subdivided into three hand-yin meridians, three hand-yang meridians, three foot-yin meridians, and three foot-yang meridians. Apart from the twelve regular meridians, eight extraordinary meridians are not directly connected to them. Two of these, the Du meridian (or Governor Vessel) and the Ren meridian, also called the Conception vessel, are located in the anterior region and have no point in common with any other conduit. Nevertheless, it is essential to note that the twelve regular meridians are the main ones used in contemporary TCM clinical practice [115,117,121].

According to TCM fundamentals, the designation Zang-fu refers to the anatomical structures of the internal organs and the human body's integrated physiological processes. Usually coupled in pairs and by phase or element, the Zang-fu includes five Zang organs, six fu organs, and extraordinary organs [115,121].[3]

3.2 Diagnosis and therapeutic approaches

As previously described, the physiology of TCM is based on identifying self-regulating systems, and pathology is characterized by dynamic changes in these systems, whether direct or indirect, specific or non-specific.

Regarding the diagnostic approach, TCM differs from Western Medicine as TCM does not focus on analyzing microscopic pathological changes or the chemical and tissue changes occurring in the body. Instead, TCM pathology considers disease processes and changes attending to general factors like pathogenic factors, the body's Qi, and the balance of Yin and Yang. The diagnosis is based on the complete characterization of the clinical manifestations and the functional deviation from the target value for each individual, seeking

[3] According to WHO (2022), the five *Zang* organs are a collective term for the five internal organs: the heart, liver, spleen/pancreas, lung, and kidney. Six *fu* organs refer to the six internal organs: gallbladder, stomach, large intestine, small intestine, urinary bladder, and sanjiao (literally translated into “triple energizer”). Extraordinary fu organs are a collective term for brain, marrow, bone, vessels, gallbladder, and uterus. These organs are extraordinary because they store like Zang organs.
The Zang–fu organs mutually correspond with one another, with a (yin) interior–(yang) exterior connection between the *Zang* and *fu* organs [121].

a precise therapeutic plan for each specific patterns. Its refer to signs and symptoms of imbalance due to pathogenic factors and are the basis for defining and differentiating clinical diagnosis in TCM [114,117,119].

Concerning HM-TCM principles, it preconizes that the clinical diagnosis of the functional state should be based on the individual's constitution *("What is the patient "inner nature"?")*, the pathogens that invade him *("What affected the patient?")*, and the vegetative tendency of an organ, also called *orb ("Which signs and symptoms appear now?")* [117].

The constitution concerns the individual's vegetative reaction, inner self, phenotype, behavioral and emotional characteristics, how expresses himself, posture, expression, and body corporal language [117].

An agent or pathogenic factor elicits specific signs and symptoms. These may resemble and therefore promote orb patterns. Agents may be divided up into external, internal, and neutral agents. The external pathogenic factors correspond to the vegetative defense reaction of the individual to the aggressions of elements of nature such as cold (*algor*), heat (*calor*), humidity (*humor*), wind (*ventus*), the blushing (*ardor*) and the dryness (*ariditas*). The internal agents, are the emotions such as joy (*voluptas*), anger (*ira*), sadness (*maeror*), fear (*timor*) and shock (*pavor*). Neutral pathogenic factors are related to overwork, stress, poor eating habits, inappropriate lifestyle, accidents/trauma, and hereditable aspects [117].

The orbs denote an absence of balance and encompass a collection of standardized signs that are clinically pertinent in ascertaining an individual's functional state. This set of signs and symptoms manifests the regulation of the body and is referred to as organ regions or body islands [117].

The current symptoms are interpreted in the context of the global regulation of the organism through guiding criteria (GC). In this context, a GC can be defined as an evaluation of clinical signs according to a regulatory model of the underlying physiology. MH-TCM establishes four GC based on four regulatory physiology models as follows: the neurovegetative system (repletion/depletion), the humoro-vegetative system (calor/algor), the neuroimmune system (extima/intima), and the correlation between structure and the regulation processes (yin-yang), a shown in Table 2 [117,118].

Table 2. Four Components of the Functional Diagnosis in TCM according to the MH-TCM [117].

Guiding Criteria	Description
GC1: repletio/depletion ("fullness"/"emptiness")	It evaluates clinical signs that in TCM are believed to originate from Qi and orbs primarily. In Western medical terms, these signs of Qi and orbs are of primary neuro vegetative origin. In general, signs of *repletion* indicate too much qi in the organism as the origin of symptoms. Signs of *depletion* indicate a lack of Qi. In a comprehensive approach, *repletion* is analogous to the relative over-excitation of neuro-vegetative activating mechanisms. *Depletion* is a lack of respective activation or excess de-activation.
GC2: calor/algor. ("heat"/"cold")	It evaluates signs that in TCM are believed to originate from the effects of Xue ("blood"). In Western terms, these signs are due to over-activation of mechanisms involving microcirculation and the local interdependent mechanisms of the plasma, blood cells, endothelium, and functional tissue of the organ and activation of body fluids, at least in some parts of the body. In addition, it may evoke vegetative and systemic responses in the fluid distribution supply and circulation (e.g., changes in thirst, urine production, and heart rate). Signs of this kind can be called humorous-vegetative in origin. Signs of over-activation of Xue (effects of microcirculation) are generally called c*alor.* Signs of a lack of functional microcirculation are called a*lgor.*
GC3: extima/intima ("exterior"/"interior")	It evaluates signs that in TCM are believed to originate from the effects of a pathogenic factor (agent) invading the body from the exterior. From the point of view of Western understanding, external agents like algor produce unbalanced reflex patterns, and the organism answers these patterns by counter-mechanisms. In TCM, this counter-reaction is called reactive calor, which may, according to Western medicine, even comprise inflammation, increased microcirculation, fever, and sepsis. It also refers to the location/depth of the disease and is related to the neuro-immunological status, allowing the identification of exogenous etiology and the development of the disease.
GC4: yin/vang	It evaluates signs which, according to TCM, distinguish between primary dysregulation (*yang*) and secondary dysregulation due to structural deficiency (*yin*), correlating body structure and symptoms. If functional tissue is deficient, it will be excessively up-regulated to achieve appropriate function. As this augmentation of tissue function cannot be kept up, functional deficiency follows this excessive up-regulation. It represents the condition of structural deficiency versus regulatory deficiency.

The collection of clinical information considers the overall clinical manifestations, assesses the relative strength of pathogenic factors versus the body's Qi, the interactions between organs, and pathological changes, and is done by questioning, observing, palpating, and assessing the pulse and tongue. This assessment determines the appropriate treatment principle, method, and prognosis [114,115,118].

Therefore, the therapeutic approach of TCM aims to increase the human body's resistance to disease and prevent problems by improving the interconnectedness of the

autonomic systems. To achieve these goals, TCM uses different therapeutic methods, such as acupuncture, moxibustion, Chinese manual massage therapy (Tuina), *Qigong*, herbal medicine and dietetics.

The acupuncture procedure refers to inserting and manipulating needles of various sizes, thicknesses, and materials into mapped acupuncture points on the body surface, defined as a system of anatomical landmarks at specific locations, also called acupoints. Moxibustion involves burning Chinese mugworts, such as *Artemisia argyi* or *Artemisia vulgaris*, either on or near a specific body location. The standard moxibustion technique involves shaping the tinder into a cone and applying it to acupuncture points on the skin. As a manual therapy, Tuina uses the hands as an intervention tool for manipulating acupuncture points and skin structures. It combines a wide range of techniques designed to stimulate specific points, muscles, and connective tissue and to trigger reflexes. *Qigong* is recognized as a conventional form of vegetative biofeedback therapy that employs postures, movements, breathing exercises, and meditation. These techniques work together to promote the stabilization and self-regulation of the body's biological systems. Chinese herbal medicine and dietetics, also known as *Chinese Materia medica (*CMM), follow the same diagnostic principles as the other therapeutical methods and are focused on the restorative effects of herbs and foods on the body. Furthermore, they are categorized based on their thermal nature, flavor, organ network, and direction of functional effect [117,119,123].

3.3 Chronic kidney disease according to Traditional Chinese Medicine

Despite being founded on distinct principles of etiopathogenesis, semiology, physiology, and therapeutics, TCM has gained significant acceptance within WM.

According to the *Yellow Emperor's Canon of Internal Medicine* the kidney represents the location of authentic Yin and Yang. It is a foundation for storing and concealing the essence, transforming qi, and producing blood [122]. [4]

From the point of view of Western medicine, the Chinese medical concept of essence, resembles an essential substance that constitutes the human body and is responsible for building and maintaining the body's structure, function, and ability to

[4] According to WHO (2022), qi refers to *the intangible, high-mobility nutritive substance that maintains vital activities.* Blood refers to *the red liquid that circulates within the blood vessels to moisten and nourish the body. It is an essential substance to maintain life activities* [121].
Blood is itself a form of Qi, a very dense and material one, but Qi nevertheless. Moreover, Blood is inseparable from Qi itself as Qi infuses life into Blood; without Qi, Blood would be an inert fluid. [115].

reproduce. Therefore, this essence, stored in the kidney, must not be released and should be kept within the human body. Kidney injury can cause a depletion of essential substances, resulting in a deficiency of qi and yang. According to the clinical foundations of TCM, proteinuria is the pathological product of the outflow and leakage of substances from the human essence, primarily affecting the spleen and kidneys [114,124].

Besides storing vital essences, the kidney is responsible for body fluid, and in case of water stagnation, dampness and heat will occur. Furthermore, damage to the kidney's essence will not allow qi to consolidate blood, resulting in unfavorable blood circulation and the formation of blood stasis[5]. In addition, it is worth noting that the maintenance of vital substances stored in the kidneys relies on the spleen's efficient transportation and distribution functions. Restricting the spleen's transport function can result from an inappropriate diet, endowment deficiency, or excessive fatigue, ultimately causing spleen qi deficiency. As this condition progresses, it can lead to disease development, culminating in spleen yang deficiency pattern. Consequently, the spleen's inability disrupts the regular transportation of fluids and water, ultimately leading to internal retention of water dampness [114,124,125].

In the TCM perspective, the etiology of CKD is primarily characterized by blood stasis (anticoagulation), dampness heat (hyperpyrexia), and turbid toxin (entangled dangerous substances). Blood stasis syndrome is one of the most frequently observed TCM patterns among primary glomerular diseases. Therefore, blood stasis encompasses glomerulosclerosis, increased extraglomerular matrix, thickening of the basement membrane, balloon adhesion, micro thrombosis in the glomerulus, collapse or stenosis of the capillary lumen, compression, and occlusion of the vascular loops, and tubulointerstitial fibrosis and atrophy [114,126,127].

As regard the differentiation of syndromes at the microscopic level, renal pathology is characterized by excess heat and dampness that often manifests through endothelial cell edema, microthrombus formation, capillary lumen narrowing, and the release of inflammatory mediators [128]. If left untreated, this will affect the function of the spleen and stomach, leading to the accumulation of metabolites in the body and the clinical uremic syndrome. These metabolites are called uremic toxins, equivalent to the turbid toxins in TCM. The turbid toxin causes turbidity in cells, tissues, and organs, resulting in pathological

[5] Blood stasis refers to a pathological state of slow, coagulated or stagnant circulation of blood [121].

conditions and changes in inflammation, degeneration, apoptosis, and necrosis in the human body [114,126].

According to Wang et al. (2022), "*in the early stage of CKD, although the spleen and kidneys are insufficient, the vital Qi can still resist exogenous pathogens, and the pathogenesis is characterized by pathogenic excess (such as dampness heat and blood stasis). However, as the disease progresses to the middle stage, the vital Qi cannot overcome the pathogenic factors, various pathological products are formed, and its pathogenesis characteristics change into a mixture of deficiency and excess. When the disease progresses to the terminal stage, the vital Qi is exhausted, and the pathogenesis is characterized by a deficiency of vital Qi (leading to the accumulation of liquid and turbid toxin). In different stages of nephropathy, the priority of the deficiency and the excess are different. Deficiency and excess are cause and effect of each other, which leads to the continuous progress of CKD"* [125].

Recent clinical and animal research highlight the potential of Chinese Materia medica (CMM) in delaying CKD [129,130]. The efficacy of CMM is the result of long-term clinical practice under the guidance of TCM theory, which looks through the synergistic effect of multiple targets and pathways. CMM shows potential for inhibiting myofibroblast activation, inflammatory cell infiltration, trans differentiation of epithelial cells into mesenchymal cells, and improving renal fibrosis through various mechanisms [131,132]. In addition, it has been shown to improve blood flow, inhibit the proliferation of glomerular cells, accumulate solutes, and improve water retention [133-135].

According to Xiong et al. (2018), the data gathered from their review delineates the prospective mechanism of acupuncture as applied to patients with CKD. The findings revealed that acupuncture showed improvements in various clinical symptoms of CKD, such as improving renal function (through the improvement of renal microcirculation and alleviating glomerulosclerosis and tubulointerstitial fibrosis); reducing proteinuria (decreasing podocin, nephrin, and depressing sympathetic nerve); regulating hypertension (depressing sympathetic nervous system, inhibiting renin-angiotensin-aldosterone system, inhibiting oxidative stress and promoting nitric oxide production, downregulating endothelin-1); correcting of anemia (improving recombinant human erythropoietin); ameliorating of pain (regulating bioactive chemicals) and muscle atrophy (upregulating insulin-like growth factor 1) [136].

3.4 Acupuncture

As a therapeutic practice of TCM, acupuncture is a simple, minimally invasive procedure with minimal side effects. From ancient times to nowadays, acupuncture has progress into a complete treatment system that generally includes manual acupuncture, electroacupuncture and other techniques. Additionally, specialized approaches are called microsystems, such as hand-foot, auricular, and scalp acupuncture [119].

The existence of hundreds of acupuncture points along the entire surface of the human body, which can be activated through acupuncture, is one of the basic assumptions of TCM. The World Health Organization (WHO) Standard Acupoint Location in the Western Pacific Region (2008) identified 361 acupuncture points and stipulated the methodology for their location [137]. For millennia, acupuncture has been employed as a therapeutic modality for various diseases, with the selection of specific acupoints along relevant meridians serving as a fundamental principle in its practice, widely acknowledged and accepted [114].

Primarily localized in the interspace between muscles and bones, the acupuncture points are characterized by a higher density of nerves than the surrounding nonacupoint areas. The type, quantity, and arrangement of nerves within acupoints vary depending on the specific acupoint. Some of them are located near regions where nerve endings are densely distributed, while others are near the convergence point of superficial nerves or the nerve plexus. Studies suggest that the basis of the needling sensation, referred to in classical literature of TCM as the *Deqi* sensation, is due to the neuroreceptors abundant in the nerve terminals of the acupoints, such as the free nerve terminal muscle spindle, the annular corpuscles, the Kirschner terminal ball, and others [138-140].

Deqi is well recognized as the sign of effectiveness during acupuncture and is characterized by patients' local or conductive sensations integrating soreness, numbness, heaviness, swelling, and tenderness felt around the needle. When experienced by the practitioner, it pertains to a sensation of tightness or pressure underneath the needle. It is worth noting that the activation of the nervous system is strongly linked with *Deqi* [121,141].

Acupoints are classified according to different dominant neural structures under the skin. In addition, most acupoints are characterized by thinner skin, higher density, and regular arrangement of blood vessels. They also contain densely distributed connective tissue, including elastic fibers, collagen fibers, muscles, and fascia. The majority of acupoints share a similar three-dimensional structure: the epidermis, dermis, subcutaneous tissue, muscles, and various related structures, including nerves, blood vessels, lymphatics,

tendons, and more. Due to their distinctive composition of blood vessels, mast cells, and nerve fibers that optimize the transmission of acupuncture signals, acupoints are more readily activated than non-acupoints [138,142].

As a minimally invasive stimulation, the insertion and manipulation of the needles on acupoints inducing changes in local connective tissue is the universal mechanism underlying the therapeutic action of acupuncture. The physiological effects of acupuncture stimulation encompass both peripheral and central responses. Peripheral effects involve the formation of needle-induced lesions, mechanical signal transduction via cutaneous microcurrents in connective tissues, local alleviation of muscle shortening and contracture, and other neuro-endocrine immune reactions at the local level, as shown in Figure 3 [138].

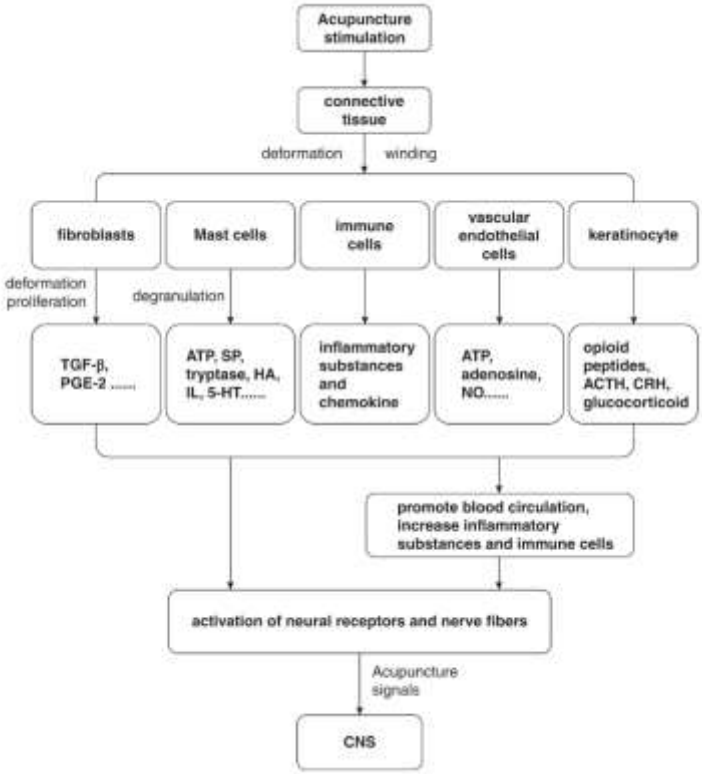

Figure 3. The microenvironment of acupoints that mediate acupuncture effect [138]. Reprinted from Journal of Leukocyte Biology, 108, Gong, Y.; Li, N.; Lv, Z.; Zhang, K.; Zhang, Y.; Yang, T.; Wang, H.; Zhao, X.; Chen, Z.; Dou, B.; et al. The neuro-immune microenvironment of acupoints-initiation of acupuncture effectiveness, page 193, Copyright (2020), with permission from Oxford University Press.

Citing Gong et al. (2020), "*Acupuncture would cause deformation and winding of connective tissue, thus initiating various cellular responses. The insertion of needle on acupoints would induce the deformation, proliferation of fibroblasts, as well as their*

secretion of transforming growth factor beta (TGF-β) and prostaglandin E2 (PGE-2). Besides, the degranulation of mast cells would be promoted, which would cause the release of adenosine triphosphate (ATP), substance P (SP), tryptase, histamine (HA), interleukin (IL), and 5-hydroxytryptamine (5-HT), among others. Additionally, a large number of immune cells, especially macrophages, would secret inflammatory substances such as high mobility group box 1 (HMGB1), toll-like receptor 4 (TLR4), tumor necrosis factor α (TNF- α) , interleukin-6 (IL-6), interleuin-1β (IL-1β), and chemokine such as C-X-C motif chemokine ligand 1 (CXCL1), stem cell factor (SCF), monocyte chemotactic protein 1 (MCP-1), and intercellular cell adhesion molecule-1 (ICAM-1). Besides, vascular endothelial cells would secret ATP, adenosine, and nitric oxide (NO). The last but not the least, keratinocytes would release opioid, peptides, adreno-cortico-tropic hormone (ACTH), corticotrophin releasing hormone (CRH), and glucocorticoid (GC). Some of the active substances would promote blood circulation and accelerate the production of immune cells and inflammatory substances. Finally, substances mentioned earlier would activate the receptors on nerve endings so that acupuncture signals would be transferred to the central nervous system (CNS)" [138].

As regard the central effects, after dynamic changes occur in the microenvironment of the acupuncture points, acupuncture signals are transmitted to the central nervous system (CNS), which results in the modulation of organ functions. For instance, in the case of pain relief, acupuncture signals are transmitted from acupoints to the spinal cord and to the relevant areas of the brain, resulting in the secretion of neurotransmitters and neuromodulin, such as opioid peptide, serotonin, norepinephrine, and dopamine, from the spinal cord and brain. The descending pain modulation system, including the anterior cingulated cortex, the periaqueductal gray, and the rostral ventromedial medulla, are ultimately activated to relieve pain [142,143].

The latest evidence-based and basic research has assessed acupuncture's safety and effectiveness and uncovered acupuncture's anti-inflammatory mechanism from diverse perspectives and levels of analysis. Its clinical anti-inflammatory effect has been widely recognized [140,143,144].

Acupuncture has been found to activate several neuro-immune pathways upon information integration within the brain. These include the cholinergic anti-inflammatory pathway (CAIP), vagus-adrenal medulla-dopamine, sympathetic pathways, and the hypothalamic–pituitary–adrenal (HPA) axis. The resulting release of neurotransmitters and hormones modulates the activity of immune cells [143,144].

Following the activation of the CAIP, which involves the neurotransmitter acetylcholine (ACh) and its corresponding receptors, as well as the enzymes choline acetyltransferase (ChAT) and acetylcholinesterase (AChE), the cellular pathways of janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3), nuclear factor kappa-B (NF-κB), and mitogen-activated protein kinase (MAPK) are regulated in a manner that results in an anti-inflammatory response (Figure 4).

In addition to its effects on the CAIP pathway, acupuncture has been shown to stimulate the vagus-adrenal medulla-dopamine pathway. Precisely, this pathway activates the neuropeptide Y+ (NPY+) chromaffin cells (CCs) of the adrenal gland, segregating dopamine (DA), which adheres to D1 receptors to inhibit cytokine production. Additionally, efferent fibers of the vagus nerve regulate the α7nAChR receptors of celiac ganglion neurons by releasing ACh, which activates the splenic sympathetic nerve. Finally, due to norepinephrine (NE) release, ChAT plus T-cells are stimulated, leading to the release of ACh and inhibiting cytokine production from macrophages [140,143,144].

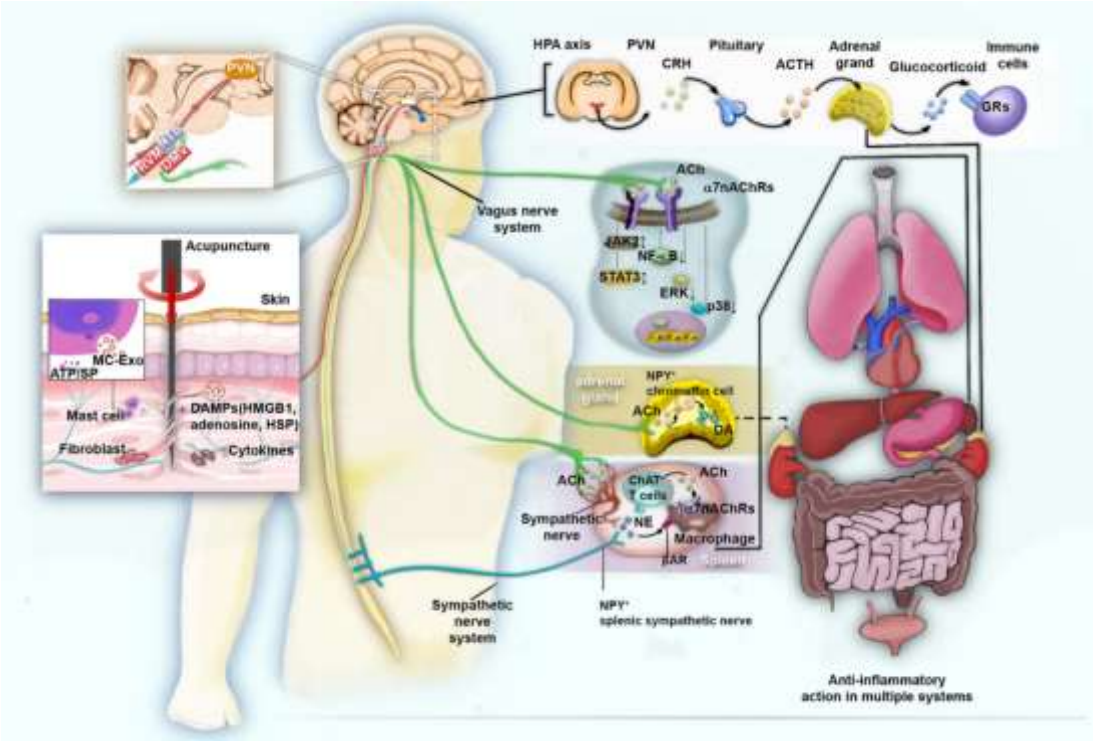

Figure 4. The anti-inflammatory mechanisms of acupuncture from acupoint to target organs.[6] Reprinted from Journal of Inflammation Research 2021:14, 7191-7224, originally published by Li, N.; Guo, Y.;

[6] *Abbreviations: ATP, adenosine triphosphate; SP, substance P; MC-Exo, mast cell-derived exosome; DAMPs, damage associated molecular patterns; HSP, heat shock protein; NTS, nucleus tractus solitarius; RVM, rostral ventrolateral medulla; DMV, dorsal motor nucleus of vagus; PVN, paraventricular nucleus; CRH, corticotropin-releasing hormone; ATCH, adrenocorticotropic hormone; GRs, glucocorticoid receptors; ACh, acetylcholine;*

Gong, Y.; Zhang, Y.; Fan, W.; Yao, K.; Chen, Z.; Dou, B.; Lin, X.; Chen, B.; et al. The Anti-Inflammatory Actions and Mechanisms of Acupuncture from Acupoint to Target Organs via Neuro-Immune Regulation, page 721, Copyright (2021), with permission from Dove Medical Press Ltd.

The signal transduction mechanism and integration between the microenvironment of acupuncture points and target organs vary depending on the pathology being treated. Additionally, the effectiveness of acupuncture in reducing inflammation is associated with several factors, including the selection of acupuncture points, the type of acupuncture utilized (manual or electroacupuncture), the intensity of stimulation employed, and the current physiological state of the individual [138,140].

As one of the most widely used complementary therapies, the World Health Organization (WHO) endorsed acupuncture as a treatment option and approved its usage for over one hundred indications, divided into groups covering a wide range of health conditions, such as musculoskeletal, nervous, respiratory, and digestive systems, among others [145]. Furthermore, acupuncture has been shown to alleviate symptoms, promote the recovery of body function, and enhance patients' overall quality of life.

3.5 Acupuncture in Hemodialysis

In the last decade, research has increasingly documented the application of Traditional Chinese Medicine (TCM) and acupuncture concepts in nephrology [125,126].

The potential impact of acupuncture on renal function in patients with CKD was evaluated, and results suggested reduced creatinine levels and increased GFR [146].

Regarding patients undergoing HD, acupuncture was found to be a feasible and secure approach for symptom management [147]. Moreover, data from a review has demonstrated that acupuncture can effectively manage complications related to hemodialysis, such as uremic pruritus (by activating the endogenous opioid system and reducing histamine and mast cells), insomnia (by regulating neurotransmitters involved in sleep-wake regulation and suppressing sympathetic activity), and fatigue [136].

To the best o authors' knowledge and based on their literature review, no study was studies were found assessing the effectiveness of acupuncture in FC capacity and muscle

α7nAChR, nicotinic acetylcholine receptor α7; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; NF-κB, NF-kappaB; ERK, extracellular signal-regulated kinase; NE, noradrenaline; NPY, neuropeptide Y; DA, dopamine [140].

strength in patients undergoing HD. However, it was found that unilateral manual acupuncture and electroacupuncture at selected acupoints on ankle dorsiflexion could improve muscle strength in both limbs, while electroacupuncture at non-acupoints induced similar strength gains [148]. Additionally, it was demonstrated that acupuncture with low-frequency electrical stimulation improved KD-induced skeletal muscle atrophy in 5/6 nephrectomy rats by increasing protein metabolism and myogenesis [149]. Nevertheless, contradictory results were found besides no statistically significant difference between acupuncture and non-acupuncture groups in muscle mass, muscle strength, functionality, and inflammatory markers in older people with sarcopenia [150]. Therefore, the effectiveness of acupuncture in improving functional capacity and muscle strength in hemodialysis patients remains to be determined.

Concerning HRQOL, research has demonstrated that the administration of acupuncture during hemodialysis has the potential to result in a positive effect on it [151] Additionally, comparing the efficacy of zolpidem 10 mg and acupressure therapy on foot acupoints in patients with CKD-associated pruritus undergoing HD revealed improvements in sleep quality and overall quality of life [152].

Acupressure elicited increased salivary flow and reduced thirst severity, as evaluated by the visual analog scale. Besides, the physical component sub-dimension of HRQOL was observed to have improved in patients undergoing hemodialysis [153].

The choice of acupuncture points and the manipulation techniques to be used vary according to the condition of the acupoints and the disease to be treated, which results in distinct therapeutic effects [138,140].

Individuals undergoing HD face the challenging and disruptive burden of chronic illness, leading to physical performance impairment and emotional distress, adversely affecting their overall well-being [69,154]. Given this premise, the selection of acupuncture points for our research was based on a literature review of the general guidelines of acupuncture and TCM meridian theory, clinical experience, and consensus method by experts in nephrology, TCM, and acupuncture [114,115,119,124]. Furthermore, the acupuncture points were chosen considering the anatomical location and attending to the position of the participants during HD treatment (supine). Therefore, the set of points to be part of the intervention protocol should be adequate in number, and, if possible, its synergy should be enhanced.

The *Taixi* (KI3) acupoint is a significant point in TCM for tonifying the Kidneys. It directly connects with the Original Qi and has the potential to tonify the bones and marrow

since the Kidneys store Essence. *Taixi* (KI3), in combination with *Guanyuan* (CV4), is one of the primary points for tonifying the Kidneys.

The *Sanyinjao* (SP6) acupoint was selected due to its multifaceted benefits. It is primarily utilized for tonifying the Spleen and can treat various spleen deficiencies that lead to symptoms such as lack of appetite and fatigue. Combined with the *Zusanli* (ST36) acupoint, it is particularly effective in replenishing both Qi and Blood, alleviating chronic fatigue. Finally, as a crucial intersection point of the Kidney channel, SP6 also tonifies the Kidneys.

The *Zunsali* (ST36) acupoint is one of the most studied and its choice use due to its one of the major point to tonify Qi, Blood, Yang, Yin and the Original Qi. The *Shenmen (*HT7) acupoint was selected based on its capacity to calm and regulate the spirit. On the other hand, the *Guanyuan* (CV4) acupoint is renowned for significantly strengthening the body and mind. Furthermore, due to its ability to tonify the kidney and original Qi, it is acknowledged as an effective acupoint for treating chronic illnesses [114,115,124].

4. Relevance of the study and Aims

CKD is a widespread health problem affecting millions worldwide. Its prevalence has been increasing in recent years, and an average of 10% of the world's population is estimated to suffer from CKD [7].

Commonly referred to as a "silent disease," the gradual loss of kidney function characterizes CKD, which can lead to kidney failure, demanding KRT to maintain adequate kidney function. Furthermore, CKD increases the risk of heart disease, stroke, and other serious health complications and can significantly impact mortality rates [14].

Hemodialysis is the most commonly used KRT, and although it is considered an effective treatment, it can also be associated with a significant burden of symptoms. The symptoms experienced by hemodialysis patients can range from mild to severe and can profoundly impact their quality of life [155].

Reduced HRQOL has been identified as an independent predictor of disease progression, cardiovascular events, and all-cause mortality [106,156]. Effective symptom management based on a centered-person approach is essential to maintain patients' independence and lead fulfilling lives. Therefore, it is imperative to consider the impact of HD treatment on patients' HRQOL and subjective well-being [157]. While the ultimate goal of HD is to improve survival, the decline in HRQOL may cause some patients to refuse treatment altogether. Regrettably, the issues of impaired physical function, mental health problems (such as depression and anxiety), and reduced HRQOL in kidney failure patients receiving KRT, particularly in the elderly group, have received inadequate attention. It is, therefore, essential to prioritize the management of these factors in order to provide comprehensive care for patients receiving maintenance HD.

The extensive history of TCM spanning several centuries has fostered a comprehensive approach to preventing diseases, preserving health, and enhancing overall well-being. As exemplified by acupuncture treatment, TCM principles and methodologies are designed to promote physical and mental strength and support health maintenance [158].

Integrative medicine, which combines conventional Western medicine with complementary therapies such as acupuncture, is becoming increasingly popular in disease management [159]. In the particular instance of kidney failure, adopting a holistic treatment approach may facilitate the more effective management of HD-related symptoms while concurrently improving their overall quality of life.

Despite the growing body of literature regarding randomized controlled trials (RCTs) and meta-analyses investigating the therapeutic effects of acupuncture, additional scientific research is required to substantiate its clinical efficacy. According to a current systematic review, it is essential to conduct future high-quality RCTs to establish the safety and efficacy of acupuncture in patients with CKD, including those undergoing dialysis and pre-dialysis patients. Likewise, it is crucial to investigate whether intensive short-term or ongoing but less frequent acupuncture interventions are more favorable for patients. Finally, comparing the effects of acupuncture with a placebo should be considered in future studies to determine its superiority [160].

So far, and to our best knowledge, there are no clinical studies in Portugal evaluating the effect of TCM therapeutic strategies in advanced CKD patients undergoing HD. Furthermore, during our research timeline, no prior research has been identified on the impact of acupuncture on FC and HRQOL in this clinical population.

The present research work intends to be one of the first contributions to fill the existing gap. To this end, the multidisciplinary research team has defined the following set of fundamental questions: What is the effect of Traditional Chinese Medicine strategies in improving symptoms in chronic kidney disease patients with glomerular filtration rate category 5 undergoing hemodialysis? Does acupuncture positively affect their functional capacity and health-related quality of life? If so, are the results maintained over the long term? Furthermore, what is the effectiveness of short-term intensive interventions over time compared to less frequent and prolonged interventions? Finally, is it possible to integrate acupuncture into the dialysis care routine?

Given the complexity of chronic kidney disease and based on previous research questions, the objectives of our study were to:

1) Investigate the effect of acupuncture on the functional capacity in patients undergoing hemodialysis.
2) Verify the difference in the acupuncture frequency of treatment.
3) Assess the effectiveness of acupuncture in health-related quality of life improvement.
4) Compare the specific effects of acupuncture with placebo.
5) Assess the short-term and long-term effects of acupuncture.
6) Analyze the acceptability and feasibility of integrating acupuncture into a dialysis center.

To pursue the investigation project's aims, an integral part of this dissertation, the multidisciplinary research team designed a study protocol reported in agreement with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [161] and already published [162]. The purpose of the study protocol was to provide a standardized and repeatable acupuncture intervention. It was designed following the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) 2010 Checklist [163], presented as research paper 1.

The results of our work are presented as an articulated set of three papers (two published articles and one submitted article under in international journals with peer review and impact factor) that seek to respond to the primary and specific objectives outlined.

Research paper 2, “Effect of Acupuncture on Functional Capacity in Patients Undergoing Hemodialysis: a patient-assessor blinded randomized controlled trial” [164] evaluates the effect of acupuncture on FC in patients with CKD G5 undergoing HD and explores the differences in the frequency of treatment (three times a week or once a week).

Research paper 3, “Effectiveness of Acupuncture on Health-Related Quality of Life in Patients Receiving Maintenance Hemodialysis”, verifies the effectiveness of acupuncture in the HRQOL improvement, the specific effect of acupuncture compared to placebo, and the short-term effects.

Research paper 4, “Integrating Acupuncture into a Dialysis Center”, stems from the need to evaluate the attitude of patients and health professionals towards the possibility of including an integrative and complementary therapy, such as acupuncture, in a private service providing health care to patients receiving maintenance HD.

These papers are presented as full-length articles and reproduced under Creative Commons licenses for open-access publishing. The articles relevant to this Thesis were never included in other theses or dissertations.

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Chapter II Research Paper 1

Effect of Acupuncture on Functional Capacity and Health-Related Quality of Life of Hemodialysis Patients: Study Protocol for a Randomized Controlled Trial

Marta Correia de Carvalho [1], Jorge Pereira Machado [1,2], Manuel Laranjeira [1,3], José Nunes de Azevedo [4] and Pedro Azevedo [4]

[1] ICBAS–School of Medicine and Biomedical Sciences, University of Porto, 4050-313 Porto, Portugal.
[2] CBSin—Center of BioSciences in Integrative Health, 4000-105 Porto, Portugal.
[3] INC–Instituto de Neurociências, 4100-141 Porto, Portugal.
[4] TECSAM-Tecnologia e Serviços Médicos SA, 5370-530 Mirandela, Portugal.

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Abstract: The proposed randomized controlled trial protocol will evaluate the effect of acupuncture treatment on the functional capacity (FC) and health-related quality of life (HRQOL) in chronic kidney disease (CKD) with glomerular filtration rate (GFR) category 5 (CKG G5) patients receiving maintenance dialysis. Patients undergoing hemodialysis (HD) from a dialysis center will be randomly assigned to experimental, placebo and control groups. In order to determine the difference between the same number of treatments performed three times or one treatment a week, experimental (verum acupuncture) and placebo (sham acupuncture) groups will receive a total of nine acupuncture treatments; however, both groups will be divided into subgroups A and B. The same selection of acupuncture points will be applied to both experimental subgroups and the placebo subgroups will receive acupuncture on non-acupuncture points. The results will be assessed by the 6-min Walk Test, Handgrip Test, 30-sec Sit-to-Stand and Kidney Disease Quality of Life-Short Form and will be held at baseline, after treatment and 12 weeks post-treatment follow up. This paper describes the rationale and design for a randomized, patient-assessor blinded con-trolled trial, which may provide evidence for the clinical application of acupuncture in CKG G5 patients undergoing HD.

Keywords: chronic kidney disease; hemodialysis; acupuncture; functional capacity; health-related quality of life; integrative medicine; randomized controlled trial.

1. Introduction

Over the last few decades, chronic diseases have become increasingly relevant and, according to the statistics, this type of disease is the leading cause of death worldwide and considered by the World Health Organization (WHO) to be the greatest threat to the health of the population in the 21st century [1].

Chronic kidney disease (CKD) is considered a public health problem due to the increasing incidence and prevalence, as well as to high associated economic costs, substantially affecting the life of the patient and implying a significant burden on the health system [2,3]. Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease defines CKD as abnormalities of kidney structure or function, present for more than 3 months, with implications for health and classified based on cause, glomerular filtration rate (GFR < 60 mL/min/1.73 m2 and albuminuria (AER ≥ 30 mg/24 h; ACR ≥ 30 mg/g (≥3 mg/mmol))categories. Glomerular filtration rate (GFR) is generally accepted as the best overall index of kidney function and decreased GFR is associated with a higher risk of complications of CKD [4,5].

Although CKD etiology is diverse and due to diseases, such as glomerulopathies, polycystic kidney disease, autoimmune diseases, systemic infections, recurrent urinary tract infections, obstructive uropathies and neoplasms, CKD is most commonly associated with diabetes and hypertension, which are determining factors in the increase and prevalence of the disease [6]. Complications of decreased kidney function can lead to kidney failure (GFR < 15 mL/min/1.73 m2), the most advanced stage of CKD. Patients who have CKD with GFR category 5 (CKG G5) can only be treated by kidney replacement therapy (KRT), in particular peritoneal dialysis (PD), hemodialysis (HD), kidney transplantation (KT) and conservative kidney management [4].

The improvement in technologies and innovation around hemodialysis (HD) treatment has contributed to the increase in kidney failure prevalence due to the fact that patients survive longer on dialysis [7,8]. Patients undergoing HD suffer from several physical and emotional problems, have a complex and demanding treatment regimen, face a stressful and disruptive chronic illness with high impact on their quality of life [4,9,10] and have a significant decrease in functional capacity (FC) [11].

Traditional Chinese Medicine (TCM), recognized by the WHO and increasingly accepted in Western medicine as a therapeutic approach to the treatment of various diseases, is based on different concepts of etiopathogenesis, semiology, physiology and therapeutics. Scientific advances, especially in the field of neurosciences, have decisively

contributed to the clarification and understanding of the neurobiological basis inherent in the acupuncture mechanisms of action [12,13].

Recent studies report early research for the application of TCM concepts and acupuncture in the field of nephrology. Examples include a study conducted by Paterno et al. (2008) suggested that there can be beneficial effects of electroacupuncture and moxibustion on CKD [14]; Kim et al. (2011) studied patients undergoing hemodialysis and receiving acupuncture treatment for their symptoms, and acupuncture seemed to be feasible and safe for symptom management [15]; Bullen et al. (2018) concluded that acupuncture during HD may contribute toward improvements in health-related quality of life [16]; Yu et al. (2017) evaluated the feasibility effect of acupuncture on renal function in patients with CKD and results suggested reduced creatinine levels and in-creased GFR [17].

Despite encouraging results, more scientific research will be required to expand understanding of the mechanisms responsible for positive action and of the therapeutic effects of acupuncture [18]. According to Kim et al. (2016), future high-quality randomized controlled trials are required to verify the safety and effectiveness in pre-dialysis patients with CKD and in those undergoing dialysis, to compare acupuncture with placebos and to verify whether intensive short-term acupuncture interventions or ongoing but less frequent treatments are advantageous for patients [19].

The fundamental questions guiding our entire research project are: What is the effect of TCM therapeutic strategies in the improvement of symptoms resulting from renal replacement therapy in CKG G5 patients undergoing HD? Does acupuncture have a positive effect on FC and health-related quality of life (HRQOL) in hemodialysis patients? If it does, are the results maintained over the long term? In addition, what is the effectiveness of short-term intensive interventions when compared to less frequent and prolonged interventions? Is it possible to integrate acupuncture into the dialysis care routine? Given our research project and the complexity of CKD, the objectives of this study are: (1) to assess the effect of acupuncture on FC and HRQOL in patients undergoing hemodialysis; (2) to evaluate the specific effects of acupuncture as compared to a placebo; (3) to evaluate short- and long-term effects of acupuncture; (4) to determine the difference between short-term intensive and ongoing but less frequent acupuncture treatments; (5) to assess the feasibility of integrating acupuncture in dialysis care.

2. Materials and Methods

2.1. Study Setting

A parallel-group patient-assessor blinded randomized controlled trial will be conducted in a single center and according to the trial flow chart procedure presented in

Figure 1. The recruitment and the whole treatment process will be carried out at the Hemodialysis Center of TECSAM—Tecnologia e Serviços Médicos, SA, in Mirandela, Portugal. The research protocol and informed consent procedure were approved by the Ethics Committee of Centro Hospitalar Universitário do Porto/Instituto Ciências Biomédicas Abel Salazar (registered number 2019/CE/P026_P304/2019/CETI), and is an integral part of the research project of the Doctoral Program in Biomedical Sciences of ICBAS School of Medicine and Biomedical Sciences, Oporto University, Portugal. This trial was registered at ClinicalTrials.gov (NCT05362643). The study protocol will be reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [20].

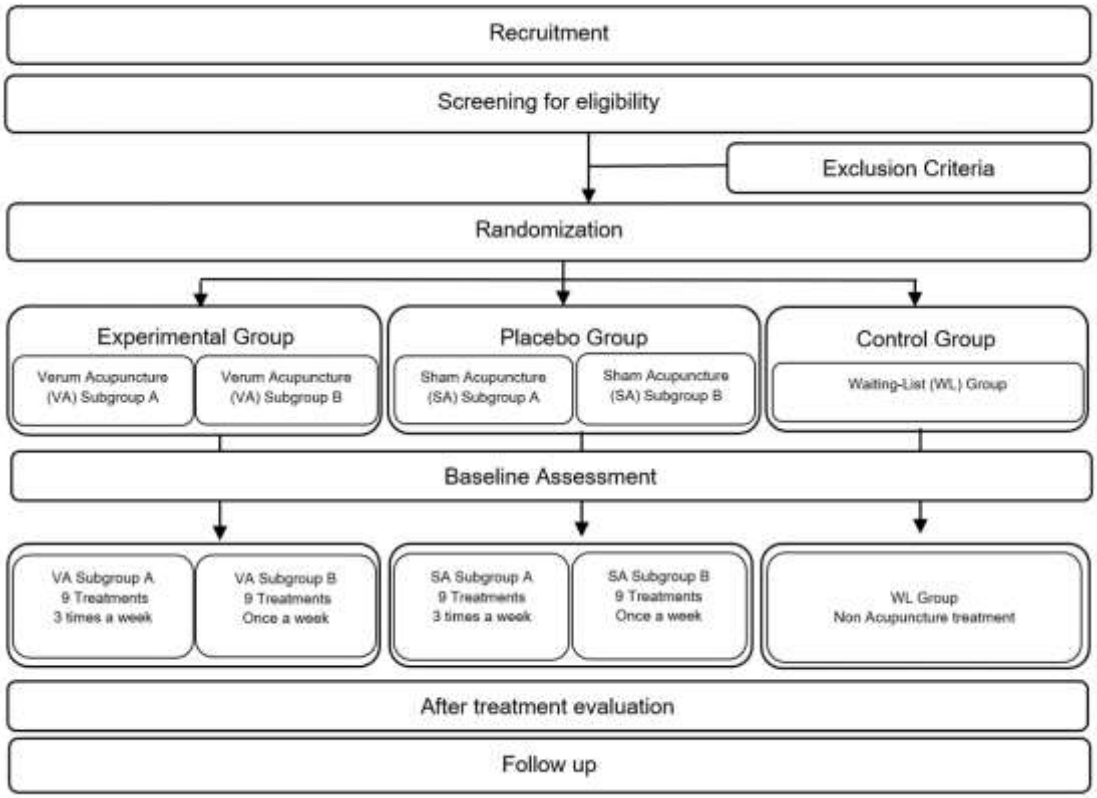

Figure 1. Trial Flow Chart.

2.2. Recruitment

An advertisement will be posted on the clinic notice board and if all study criteria are met, volunteer patients who are receiving treatment at TECSAM Hemodialysis Center will be invited to participate.

2.3. Eligibility Criteria

Inclusion and exclusion criteria will be applied during the participant selection process and potentially eligible participants will be identified by a nephrologist and through screening of their TECSAM Hemodialysis Center patient medical records.

This trial will include male and female patients, age 18 years or older, who have been receiving regular hemodialysis treatment for more than 3 months, undergoing sessions 3 times a week, at 4 h per session, and who are in a medically stable condition.

Patients who refuse to participate in the study or who have a clinical indication that prevents their participation in the study, and patients with other comorbidities, such as poorly controlled malignant hypertension, unstable angina, uncontrolled diabetes mellitus, cerebrovascular failure with recurrent syncope, uncontrolled heart failure, severe mental illness or cognitive impairment, will be excluded. Those with other relevant circumstances, including the inability to practice physical exercise, having undergone acupuncture treatment in the past two weeks, having experienced a known hypersensitivity reaction and/or other side effects after acupuncture treatment, and displaying an inability to cooperate with the procedures inherent to the application of the procedure, will be also excluded from the study.

2.4. Randomization and Allocation

After screening for eligibility, a written informed consent form containing an explanation of the objectives and procedures for the research project's implementation will be obtained from each individual who agrees to participate, in compliance with the revised version of the Declaration of Helsinki and the Oviedo Convention. The procedure will be performed by an independent assessor, with each one assigned an anonymous code. Participants will be randomly allocated in a 1:1:1 ratio and assigned to the experimental group (verum acupuncture), the placebo group (sham acupuncture) or the control group (non-acupuncture) following simple randomization procedures employing a computerized random number list. The randomization sequence will be created using Microsoft® Excel® for Microsoft 365 MSO Microsoft, Washington, USA by an independent researcher who will prepare the assignments in opaque envelopes and take charge of concealing the allocation sequence.

After the random assignment of the participants into the three groups and regarding the frequency of treatment, the first 12 randomized patients in the verum acupuncture (VA) and sham acupuncture (SA) groups will receive treatment 3 times a week, and the

remaining 12 will receive treatment once a week, with a total of 9 treatments for each subgroup.

2.5. Blinding

The participants, the outcome assessor, the statistician and the Traditional Chinese Medicine practitioner will be blind to the allocation. Regarding the intervention itself, due to its specific nature, only the Traditional Chinese Medicine practitioner will not be blind to the verum acupuncture, sham and non-acupuncture groups.

To assess the effectiveness of the blinding, after the treatment, a questionnaire will be administered to ask the participants in the VA and SA groups what sort of acupuncture treatment (verum or sham) they believe they received. This question will allow the calculation of the James Blinding Index (BI) [21,22].

2.6. Intervention

The experimental (verum acupuncture) and placebo (sham acupuncture) groups will receive 9 acupuncture treatments. Both groups will be divided into two subgroups with a different treatment frequency: subgroup A will receive 3 acupuncture sessions per week over 3 weeks; and subgroup B will receive 1 acupuncture session per week over 9 weeks. The same selection of acupuncture points, identified according to the method of point location issued by the WHO [23], will be applied to both experimental subgroups A and B. Placebo subgroups A and B will receive acupuncture at the same non-specific acupuncture points. Details of the acupuncture intervention will be described according to the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) 2010 Checklist [24], as listed in Table 1.

Table 1. Details of acupuncture treatment.

Item	Detail	
1. Acupuncture Rationale	(1a) Style of acupuncture	Manual acupuncture.
	(1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate.	The protocol treatment provided is based on traditional meridian theory, literature sources, clinical experience and consensus method of experts in Traditional Chinese Medicine, Acupuncture and Nephrology [1-3], members of research team.
	(1c) Extent to which treatment was varied	Experimental (verum acupuncture) group will receive a total of 9 acupuncture treatments, however, will be divided into subgroups A and B. Experimental subgroup A will receive three acupuncture sessions per week over

		3 weeks and subgroup B will receive one a week for 9 weeks. The same choice of acupuncture points will be applied to both experimental subgroups A and B.
2. Details of Needling	(2a) Number of needle insertions per subject per session	A total of 5 fixed acupoints and a total of 8 needle insertions per subject and per session.
	(2b) Names of points used	*Taixi* (KI3), bilateral; *Sanyinjiao* (SP6), bilateral; *Zusanli* (ST36), bilateral; *Shenmen* (HT7) unilateral, in the arm without arteriovenous fistula; *Guanyuan* (CV4), unilateral. Acupuncture points will be found according to the WHO points location method.
	(2c) Depth of insertion, based on a specified unit of measurement, or on a particular tissue level	After local area disinfection with alcohol wipes, acupoints CV4, ST36, KI3 and SP6 will be inserted perpendicularly (15 to 20 mm depth) and HT7 inserted slightly obliquely (10 mm depth).
	(2d) Response sought	*De qi* sensation (described as a compositional sensation including numbness, soreness, distention, heaviness) will be achieved through lifting, thrusting and twirling manipulations.
	(2e) Needle stimulation	Manual stimulation. After generating a needling sensation, needles will be manipulated for one minute every ten minutes during needle retention.
	(2f) Needle retention time	25 min.
	(2g) Needle type	Sterilized stainless-steel needle (0.25 × 25 mm) Tewa, asia-med GmbH, Kirchplatz 1, 82049 Pullach, Germany.
3. Treatment Regimen	(3a) Number of treatment sessions	A total of 9 treatment sessions for both groups.
	(3b) Frequency and duration of treatment sessions	Verum Acupuncture Subgroup A: three times a week for 3 weeks. Verum Acupuncture Subgroup B: once a week for 9 weeks.
4. Other Components of Treatment	(4a) Details of other interventions administered to the acupuncture group	Apart from the usual care routine for hemodialysis sessions, during the study period, no further intervention will be allowed.
	(4b) Setting and context of treatment, including instructions to practitioners, and information and explanations to patients	Treatment sessions will take place at the Hemodialysis Center of TECSAM Tecnologia e Serviços Médicos, SA, in Mirandela, during hemodialysis sessions. Participants will be informed about the entire procedure and a clarification meeting will also be held with the hemodialysis clinical team before treatments starts.
5. Practitioner Background	(5) Description of participating acupuncturists	M.C.d.C is a licensed specialist in Traditional Chinese Medicine with professional card number C-006513 issued by the Regulator of Health System Central Administration in Portugal, ACSS (Administração Central do Sistema de Saúde, I.P.); five years of professional experience; a Traditional Chinese Medicine Master's degree from Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Portugal; completion of Advanced Chinese Medicine Course from Guangzhou University of Chinese Medicine, Guangzhou, P.R. China.
6. Control or Comparator Interventions	(6a) Rationale for the control or comparator in the context of the research question,	Participants will randomly be assigned to experimental group (verum acupuncture), placebo group (sham acupuncture) or control group (waiting list).

	with sources that justify this choice	
		The placebo group (sham acupuncture) will receive a total of 9 acupuncture treatments, however, will be divided into subgroups A and B. Placebo subgroup A will receive three acupuncture sessions per week over 3 weeks and subgroup B will receive one a week for 9 weeks. Manual acupuncture will be performed as superficial needling (5 mm depth) at non-acupuncture points without an attempt to achieve a *De qi* sensation and without stimulation, lasting 25 min, using a sterilized stainless-steel needle (0.25 × 25 mm; Tewa, asia-med GmbH, Kirchplatz 1, 82049 Pullach, Germany). The control group (waiting list) will not receive any acupuncture treatment during the study period.
	(6b) Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, provide details as for Items 1 to 3 above.	**List of Non-Acupuncture points used and their location** In the present study, the non-acupuncture points selected will be the points located on the non-meridian but near the acupuncture points described above. • Non-Acupuncture point 1 (NA1) Located near KI3 (*Taixi*). On the posteromedial aspect of the ankle, at the midpoint of KI3 (*Taixi*) and (*Fuliu*). KI7 (*Fuliu*) is located on the posteromedial aspect of the leg, anterior to the calcaneal tendon, 2 *cun* superior to the prominence of the medial malleolus. • Non-Acupuncture point 2 (NA2) Located near SP6 (*Sanyinjiao*). On the leg, at the midpoint of the medial side of the tibia, 1 *cun* distal from SP6 (*Sanyinjiao*). • Non-Acupuncture point 3 (NA3) Located near ST36 (*Zusanli*). On the anterior aspect of the leg, at midpoint of ST37 (*Shangjuxu*) and the Gallbladder Meridian. ST37 (*Shangjuxu*) is located on the anterior aspect of the leg, on the line connecting ST35 (*Dubi*) with ST41 (*Jiexi*), 6 *cun* inferior to ST35 (*Dubi*), on the tibialis anterior muscle. • Non-Acupuncture point 4 (NA4) Located near HT7 (*Shenmen*). On the wrist, at the transverse crease of the wrist, at the midpoint of HT7 (*Shenmen*) and PC7 (*Daling*), between the Pericardium Meridian and the Heart Meridian. • Non-Acupuncture point 5 (NA5) Located near CV4 (*Guanyuan*). On the lower abdomen, 1 *cun* lateral from CV6 (*Qihai*). CV6 (*Qihai*) is located 1.5 *cun* inferior to the center of the umbilicus, on the anterior median line.

3. Outcome Measurement

3.1. Primary Outcome

The primary outcome measure will be the change in the parameters of FC and HRQOL. FC will be measured by a 6-Minute Walk Test (6MWT) [28]. The 6MWT assesses the submaximal level of functional exercise capacity and is simple and convenient to carry out. Changes in the distance walked in 6 minutes will be used to evaluate the efficacy of therapeutic interventions. Quality of Life will be assessed by Kidney Disease Quality of Life-Short Form (KDQOL-SFTM 1. 3) [29]. The KDQOL-SF contains eight generic subscales that assess various aspects of HRQOL and has been widely used in CKD.

3.2. Secondary Outcomes

Secondary outcome measures will be changes in handgrip and lower-limb strength. Handgrip strength will be measured by a Hand Grip Strength (HGS) test [30,31], using a digital dynamometer. The HGS test is an indicator of overall muscle strength and is commonly used.

Lower-limb strength will be measured by a 30 s Sit-to-Stand (30STS) test [32]. Demographic, clinical variables and blood analytical data will be collected using a Sociodemographic and Clinical Data Collection Form in the baseline period. Pre- and post-intervention questionnaires will be applied before and after the treatment period. The outcome measurement time points are detailed in Figure 2.

3.3. Participant Timeline

The timeline for the study visits, enrolment process, interventions, assessments, and follow-ups carried out on the participants will be reported based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [20], as shown in Figure 2.

		Screening	Baseline	Treatment Period			Follow-up Period
			0-Week	1-Week	3-Week	9-Week	After treatment 12-Week
Patient	Eligibility	X					
	Informed Consent		X				
	Demographics and clinical data		X				
	Physical examination		X				
	Randomization		X				
							X
Intervention	Verum Acupuncture (VA) Subgroup A			9 Acupuncture treatments (3 sessions per week for 3 week			X
	Verum Acupuncture (VA) Subgroup B			9 Acupuncture treatments (1 session per week for 9 weeks)			
Comparison	Sham Acupuncture (SA) Subgroup A			9 Acupuncture treatments in non-acupuncture points (3 sessions per week for 3 weeks)			X
	Sham Acupuncture (SA) Subgroup B			9 Acupuncture treatments in non-acupuncture points (1 session per week for 9 weeks)			X
	Waiting-List (WL) Group			Non-acupuncture Treatment			X
Outcomes	Functional Capacity		X		X	X	X
	Quality of Life		X		X	X	X
	Lower Limbs Strength		X		X	X	X
	Handgrip Strength		X		X	X	X
	Blood Tests		X		X	X	X
	Pre-intervention Questionnaire		X				
	Post-intervention Questionnaire				X	X	
Participant Safety	Adverse effects		X		X	X	X

Figure 2. Timing of visits and data collection according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [20].

3.4. Statistical Analysis and Sample size

Demographic and clinical data for each group at baseline will be compared using Fishers' Exact Test (categorical variables) and one-way ANOVA (continuous variables). Two-way repeated-measures ANOVA with interaction between time (baseline, 3 weeks, 9 weeks and follow-up period 12 weeks after treatment) and group will be used to assess the effect of the treatment. Differences over time within each group and sub-group will be assessed with repeated-measures ANOVA, and differences among groups at each moment will be evaluated with one-way ANOVA. A significance level of 5% will be used; differences will be considered statistically significant for p-value < 0.05. Statistical analysis will be performed with IBM SPSS Statistics software, version 27.0, IBM, New York, NY, USA [33].

For the sample size, a minimum of 20 patients in each group (experimental, placebo and control groups) was estimated to achieve a small to medium effect size (f = 0.19) [34] in the two-way repeated-measures ANOVA, with a statistical power of 80% and a significance level of 5%. Sample-size calculations were carried out using G*Power V.3.1

[35]. Assuming a possible dropout rate of 15%, a minimum of 24 patients will be randomly selected for each group. In the experimental and placebo groups, half of the patients (n = 12) will be placed in subgroup A, with three acupuncture sessions per week over 3 weeks, and half (n = 12) will be placed in subgroup B, with one acupuncture session per week over 9 weeks.

3.5. Adverse Events Assessment

Regarding patient safety, any adverse event related to the acupuncture treatment will be observed and reported by patients, practitioners or care providers during each patient visit. Although the participants in the study will not need medical assistance in the acupuncture treatments, which will occur during hemodialysis sessions, they will be under permanent medical surveillance. If any adverse reaction occurs during the intervention, emergency measures will be taken as appropriate.

3.6. Quality Control and Data Collection

Before the clinical trial begins, the research team will receive specialized training to ensure the quality of the study is maintained. Topics concerning the research process, eligibility criteria, data collection and management and assessment of adverse events will be covered.

Screening for eligibility, demographic and clinical-data collection and physical examinations will be performed by the TECSAM clinical team, acting as an independent assessor. The main researcher, the practitioner who will provide the acupuncture treatments, will not have access to patient data until anonymization, randomization and allocation procedures are complete. Baseline, after-treatment and follow-up outcome variables will be assessed by the TECSAM head nurse, who will not know to which group each subject is assigned. Moreover, the statistician will be unaware of the allocation details during the research period, to ensure that the objectivity and impartiality of the data are guaranteed.

The clinical trial will be stopped in case of serious adverse events. Participants will be withdrawn from the study if they are reluctant to continue or if they ask to be excluded.

4. Discussion

The protocol described above refers to a parallel-group patient-assessor blinded randomized clinical trial planned to assess the effect of acupuncture compared with

placebo-sham acupuncture and non-acupuncture groups. Therefore, it was designed following the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [24] and reported with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [20].

CKD is a debilitating disease, and standards of medical care involve aggressive monitoring for signs of disease progression and early referral to specialists for dialysis or possible renal transplant [36]. As kidney disease progresses, patients often experience a variety of symptoms. The initiation of dialysis can have a variable effect on quality-of-life measures and on the alleviation of uremic signs and symptoms, such as anorexia, fatigue, cognitive impairment, depressive symptoms, pruritus and sleep disturbance [37].

HRQOL has been widely accepted as a valid marker of treatment outcomes and mortality for patients with chronic diseases [38]. Hemodialysis negatively impacts the HRQOL of patients, affecting their physical, functional, metabolic, social and mental conditions, with a high impact on functional capacity when compared to healthy individuals [39–41].

Many pharmacological interventions for people with CKD have known risks of adverse events and, according to the literature, acupuncture is commonly used in symptom management for chronic diseases as well as in palliative care [42]. However, the safety and efficacy of acupuncture for people with CKD remains largely unknown. Considering the aims of our study, we expect that verum acupuncture compared to sham acupuncture and non-acupuncture will improve the functional capacity of hemodialysis patients, as evidenced by an increase in the distance walked on the 6MWT and an increase in scores for quality of life. In addition, we expect an increase in handgrip strength and an improvement in peripheral muscle strength. According to Kim et al. (2016), there was low-quality evidence of the short-term effects of manual acupressure as an adjuvant intervention for fatigue, depression, sleep disturbance and uremic pruritus in patients undergoing regular hemodialysis [19]. Under this assumption, this study protocol was designed to check the effect of acupuncture after treatment and at 12 weeks post-treatment. In this way, we expect that the effect of acupuncture will be maintained in the follow-up period.

Some studies, especially in the pain field, suggest that three treatments per week obtain better results than one treatment per week [43,44]. We also expect to see better results with more intensive interventions compared to less frequent and prolonged interventions.

Following review of the literature and to the best of the authors' knowledge, there are currently no comparable studies. Therefore, our trial seems to be an innovative study for exploring the effect of acupuncture and the frequency of treatment on improving FC and HRQOL in patients undergoing HD. Furthermore, supported by only a few clinical cases

reported (personal data) prior to the design and development of the research project, it is possible to predict efficacy and the advantages of integrating acupuncture treatments into routine hemodialysis as a complementary therapy to conventional treatments.

Despite fulfilling strict methodological criteria, it is possible to identify limitations in our study protocol. First, the sample size; second, the TCM practitioner performing the acupuncture treatment will not be blinded due to the nature of the intervention; third, comorbidities inherent to chronic kidney disease may lead to a high dropout rate during the follow-up period.

5. Conclusions

In conclusion, this study protocol provides a standardized procedure for conducting our randomized clinical trial. Despite its limitations, we expect the results to provide evidence for the efficacy of acupuncture on FC and HRQOL, as well as for further research to validate the therapeutic effects of acupuncture in patients under-going HD.

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Chapter III Research Paper 2

Effect of Acupuncture on Functional Capacity in Patients Undergoing Hemodialysis: A Patient-Assessor Blinded Randomized Controlled Trial

Marta Correia de Carvalho [1], José Nunes de Azevedo [2], Pedro Azevedo [2], Carlos Pires [3], Manuel Laranjeira [1,4] and Jorge Pereira Machado [1,5]

[1] ICBAS–School of Medicine and Biomedical Sciences, University of Porto, 4050-313 Porto, Portugal.
[2] TECSAM-Tecnologia e Serviços Médicos SA, 5370-530 Mirandela, Portugal.
[3] Center for Research in Neuropsychology and Cognitive and Behavioral Intervention (CINEICC), Faculty of Psychology and Educational Sciences, University of Coimbra, 3000-115 Coimbra, Portugal.
[4] INC–Instituto de Neurociências, 4100-141 Porto, Portugal.
[5] CBSin—Center of BioSciences in Integrative Health, 4000-105 Porto, Portugal.

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Abstract: Decreased functional capacity (FC) in patients undergoing hemodialysis (HD) is associated with adverse health events and poor survival. Acupuncture is recognized as a safe and effective integrative treatment. The aim of this study is to evaluate the effect of acupuncture treatment on the FC in chronic kidney disease with GFR category 5 (CKG G5) patients undergoing HD. In this patient-assessor blinded randomized controlled trial, seventy-two kidney failure (KF) patients were randomly assigned to experimental (n = 24), placebo (n = 24) and control groups (n = 24). The primary outcome was the improvement in FC assessed by the 6-Minute Walk Test (6-MWT). Secondary outcomes included assessment of peripheral muscle strength by the Handgrip Strength Test (HGS) and the 30-Second Sit-to-Stand Test (STS-30) at baseline, after treatment and at 12-week follow up. A mixed ANOVA with interaction time*group was used. The experimental group increased walk distance ($p < 0.001$), lower limbs strength ($p < 0.001$) and handgrip strength ($p = 0.012$) after nine acupuncture sessions and stabilized in the follow-up ($p > 0.05$). In the placebo and control groups the 6-MWT and 30STS results decreased ($p < 0.001$) and the HGS scores did not change through time ($p > 0.05$). Acupuncture treatment improved FC and muscle strength in patients undergoing HD.

Keywords: chronic kidney disease; hemodialysis; acupuncture; functional capacity; integrative medicine.

1. Introduction

The growing incidence and prevalence of chronic kidney disease (CKD) are associated with increased morbidity, mortality and additional burden and economic cost to the healthcare system and social assistance [1,2]. According to the most recent data, in 2016, CKD was ranked as the 16th leading cause of death worldwide, and by 2040 it is expected to be the fifth leading cause of death [3].

The etiology of CKD is diverse, with diabetes and hypertension mainly contributing to the increased prevalence of the disease [4]. Patients who have CKD with glomerular filtration rate (GFR) category 5 (CKG G5) can only be treated by kidney replacement therapy (KRT), in particular peritoneal dialysis (PD), hemodialysis (HD), kidney transplantation (KT) and conservative kidney management [4]. Technological innovation and optimization of medical therapy applied to hemodialysis treatments contributed to patients surviving longer on dialysis and after kidney transplantation, helping to increase worldwide the prevalence of kidney failure [5–7].

HD is the most predominant dialysis modality and is characterized as a complex and demanding treatment regimen. One of the significant problems in patients on maintenance HD and a substantial predictor of morbidity and mortality is skeletal muscle atrophy, which contributes significantly to reduced functional capacity [8,9].

Even though traditional Chinese medicine (TCM) is based on different concepts of etiopathogenesis, semiology, physiology and therapeutics, it is being widely accepted by Western medicine. Currently, there is increasing use of complementary and integrative therapies with adjunctive interventions to manage symptoms arising from CKD [10,11]. The application of TCM and acupuncture concepts in the field of nephrology has been increasingly described in recent research [12]. Kim et al. (2011) studied patients undergoing hemodialysis receiving acupuncture treatment for some of their symptoms, and acupuncture seemed to be feasible and safe for symptom management [13]; Bullen et al. (2018) have concluded that acupuncture during HD may contribute toward the improvement of health-related QoL [14]; Yu et al. (2017) evaluated the feasibility effect of acupuncture on renal function in patients with CKD and results suggest reduced creatinine levels and increased GFR [15].

Despite the increasing number of RCT and meta-analysis articles, more scientific research is needed to validate the therapeutic effects of acupuncture. A systematic review suggests that future high-quality randomized controlled trials are required to verify the safety

and effectiveness in pre-dialysis patients with CKD and those undergoing dialysis, to compare acupuncture with placebo and verify whether intensive short-term acupuncture interventions or ongoing but less frequent treatments are advantageous for patients [16].

According to the literature review and the best of the authors' knowledge, no similar study was found assessing the effect of acupuncture or treatment frequency on improving FC and muscle strength in HD patients. Several studies have focused on the symptomatic treatment of other functional state. Damasceno et al. (2019) analyzed the effect of manual acupuncture on muscle mass and inflammation markers in older adults with sarcopenia [17]; Zhou et al. (2012) conducted a pilot study to determine the effect of unilateral manual acupuncture on selected acupoints on ankle dorsiflexion strength of both limbs on young men [18]; Wang et al. (2020) evaluated whether three weekly acupuncture treatment sessions were superior to one weekly session for symptomatic outcomes in postprandial distress syndrome [19]; Lin et al.(2020) assessed the symptomatic improvement in patients with knee osteoarthritis on three sessions per week of acupuncture compared to one session per week [20]. The evidence for the role of acupuncture treatment frequency is unclear, and there are currently no defined and accepted consensus criteria for treatment frequency [21].

Given the paucity of scientific research on the clinical application of acupuncture in patients on kidney replacement therapy, the present study was designed to evaluate the effect of acupuncture on FC in patients with CKD G5 undergoing HD and to analyze the differences in the frequency of treatment (three times a week or once a week).

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2. Materials and Methods

2.1. Design and Settings

This parallel group patient-assessor blinded randomized controlled trial (RCT) was conducted at the Hemodialysis Center of TECSAM—Tecnologia e Serviços Médicos, SA, in Mirandela, Portugal, from August 2021 to February 2022. The study protocol and informed consent were approved by the Ethics Committee of Centro Hospitalar Universitário do Porto/Instituto Ciências Biomédicas Abel Salazar (registered number 2019/CE/P026_P304/2019/CETI) and are an integral part of the research project of the

Doctoral Program in Biomedical Sciences of ICBAS School of Medicine and Biomedical Sciences, University of Porto, Portugal. This trial was registered at ClinicalTrials.gov (NCT05362643).

2.2. Participants

Potentially eligible participants were identified by TECSAM's nephrologist, and an advertisement was posted on the hemodialysis center notice board inviting patients to participate.

Inclusion and exclusion criteria were applied in the participant selection process. Male and female patients, age 18 years or older, who had been receiving regular HD treatment for more than 3 months, 3 sessions per week, 4 h per session, with the medically stable condition were included. Excluded were patients who refused to participate in the study, those with a clinical indication that prevented their participation in the research, and patients having other comorbidities such as poorly controlled malignant hypertension, unstable angina, uncontrolled diabetes mellitus, cerebrovascular failure with recurrent syncope, uncontrolled heart failure, severe mental illness or cognitive impairment, or inability to practice physical exercise. Patients that have had acupuncture treatment in the past two weeks, have known hypersensitivity reaction and/or other side effects after acupuncture treatment, inability to cooperate with the procedures inherent to the application of the procedure were also excluded.

After screening for eligibility, a written informed consent explaining the objectives and procedures for the research project implementation was obtained from everyone who agreed to participate in compliance with the revised version of the Declaration of Helsinki and the Oviedo Convention. This procedure was performed by an independent evaluator who assigned each an anonymous code.

2.3. Intervention

Our research team developed a standardized and repeatable protocol. The selection of acupuncture points was based on a literature review, on the general principles of acupuncture and traditional Chinese medicine (TCM) meridian theory, clinical experience, and consensus method by experts in TCM, acupuncture and nephrology [22–25].

Experimental (verum acupuncture) and placebo (sham acupuncture) groups received 9 acupuncture treatments. Both groups were divided into two subgroups with a different treatment frequency: subgroup A received 3 acupuncture sessions per week over

3 weeks; subgroup B received 1 acupuncture session per week over 9 weeks. The same selection of acupuncture points was applied to both experimental subgroups A and B. Both placebo subgroups A and B received acupuncture on the same non-acupuncture points.

Details of needling and treatment regimen according to the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)—2010 Checklist [26] are listed in Table 1.

Table 1. Details of needling and treatment regimen.

		EXPERIMENTAL GROUP		**PLACEBO GROUP**		**CONTROL GROUP**
		Verum Acupuncture (VA)		Sham Acupuncture (SA)		Waiting-list (WL)
DETAILS OF NEEDLING	***Number of needles***	5 fixed acupoints and a total of 8 needle insertions per subject and session.		5 fixed acupoints and a total of 8 needle insertions per subject and session.		No acupuncture treatment will be performed from the time of randomization until the end of the follow-up period.
	Names of points used	*Taixi* (KI3), bilateral. *Sanyinjiao* (SP6), bilateral. *Zusanli* (ST36), bilateral. *Shenmen* (HT7) unilateral, in the arm without arteriovenous fistula. *Guan Yuan* (CV4), unilateral.		Non-acupuncture points near the acupuncture points selected as described in Appendix Table 2.		
	Depth of insertion	CV4, ST36, KI3 and SP6 were inserted perpendicularly (15 to 20mm depth) and HT7 was inserted slightly oblique (10mm depth).		Superficial needling (5mm depth) at non-acupuncture points abovementioned.		
	Response sought	*De qi* sensation (described as a compositional sensation including numbness, soreness, distention, heaviness) was achieved through lifting, thrusting, and twirling manipulations.		No *De qi* sensation.		
	Needle stimulation	Manual stimulation. After generating needling sensation, needles were manipulated for one minute every ten minutes during needle retention.		No stimulation.		
	Needle retention time	25 minutes.		25 minutes.		
	Needle type	Sterilized stainless-steel needle (0,25x25mm) Tewa, asia-med GmbH, Kirchplatz 1, 82049 Pullach, Germany.		Sterilized stainless-steel needle (0,25x25mm) Tewa, asia-med GmbH, Kirchplatz 1, 82049 Pullach, Germany.		
TREATMENT REGIMEN	***Number of treatment sessions***	9 treatment sessions.		9 treatment sessions.		Not applicable.
	Frequency of treatment sessions	VA subgroup A (VA.A) Tree times a week for 3 weeks. (3*3)	VA subgroup B (VA.B) Once a week for 9 weeks. (1*9)	SA subgroup A (SA.A) Tree times a week for 3 weeks.(3*3)	SA subgroup B (SA.B) Once a week for 9 weeks.(1*9)	

Locations of the selected acupuncture and non-acupuncture points for this study are described in Appendix A, Tables A1 and A2.

The acupuncture treatment was provided by a licensed specialist in TCM with professional card number C-006513 issued by the regulator of health system central administration in Portugal, ACSS-Administração Central do Sistema de Saúde, I.P., with five years of professional experience.

Apart from the usual care routine for hemodialysis sessions, no further interventions were allowed during the study period. The acupuncture treatment took place at the Hemodialysis Center of TECSAM Tecnologia e Serviços Médicos, SA, in Mirandela, during the hemodialysis session.

2.4. Outcome Measurement

The primary outcomes were the change in functional capacity measured by the distance walked (meters) obtained by the 6-Minute Walk Test (6MWT) and whether there were differences in the frequency of treatment (three times a week or once a week).

Secondary outcomes included changes in peripheral muscle strength. Lower limb strength was measured by 30-Second Sit-to-Stand (STS-30) Test, and handgrip strength was measured by Handgrip Strength (HGS) Test.

All assessments were performed at baseline, after treatment and at a 12-week follow-up. Demographic, clinical and laboratory data were collected at baseline as described in the participant timeline in Appendix A, Table A3.

Regarding safety, and since the acupuncture treatment was performed during the period of the hemodialysis session, patients were under permanent medical surveillance, and any adverse event would be immediately communicated.

2.4.1. Six-Minute Walk Test (6MWT)

The 6MWT assesses the submaximal level of functional exercise capacity and is a simple and convenient to use walking test. Changes in the six-minute walk distance are used to evaluate the efficacy of therapeutic interventions [27].

According to the “ATS Statement: Guidelines for the Six-Minute Walk Test” [27], patients were instructed to walk as fast as possible during 6 min on a 30 m straight, enclosed corridor. The corridor length was marked every 3 m, and the turnaround points were marked with an orange traffic cone. A colored tape was used to mark the starting line on the ground,

indicating the beginning and end of each 60 m turn. The distance walked was registered in meters. Patients were allowed to stop and rest during the test. However, they were encouraged to resume walking as soon as possible.

2.4.2. Thirty-Second Sit-to-Stand (STS-30) Test

The STS-30 test is a reliable test for functional evaluation in hemodialysis patients and is used to assess functional lower extremity strength [28,29].

Patients were asked to stand up and sit down again in a chair without the help of their arms, and to perform the most significant number of repetitions in 30 seconds, in a single attempt. For this, they adopted a posture with the trunk erect, arms crossed in front of the chest, and feet flat on the ground.

2.4.3. Handgrip Strength (HGS) Test

Handgrip strength was measured, in kilograms-force (KGF), by the HGS Test [30,31], using an electronic hand dynamometer (CAMRY, EH101). The HGS test is reliable, simple to use and an indicator of overall muscle strength [32].

Patients were asked to sit in a chair, with their backs supported on the backrest, feet fully supported on the floor, with the extremity of the upper limb forming a 90° angle with the trunk, elbow fully extended, pressing as hard as possible on the dynamometer with finger flexion.

This test was repeated twice with each hand, with a one-minute interval between each repetition, and the best attempt of each hand was considered.

2.5. Randomization and Blinding

Patients were randomly allocated in a 1:1:1 ratio and assigned to an experimental group (verum acupuncture), placebo group (sham acupuncture), or control group (waiting list) following simple randomization procedures through a computerized random number list. Randomization sequences were created using Microsoft® Excel® for Microsoft 365 MSO, Microsoft, Washington, USA, by an independent researcher who prepared the assignments in opaque envelopes and took charge of the allocation sequence concealment.

After the random assignment of the participants to the three groups and regarding the frequency of treatment, it was defined that the first 12 randomized patients in the VA

and SA groups would receive treatment 3 times a week, and the remaining 12 would receive treatment once a week.

Participants, outcome assessor and statistician were blind to the allocation. Regarding the intervention and its specific nature, only the traditional Chinese medicine practitioner was not blind to the verum acupuncture, sham or non-acupuncture groups.

2.6. Quality Control and Data Collection

Before the clinical trial began, the research team received specialized training to maintain the study quality. Topics such as research process, eligibility criteria, data collection and management, and adverse events assessment were covered.

Screening for eligibility, demographic and clinical data collection, and physical examination were performed by the TECSAM clinical team as an independent assessor. The leading researcher, who provided the acupuncture treatments, had no access to patient data until anonymization, randomization and allocation procedures were complete. Baseline, after-treatment and follow-up outcome variables were assessed by the TECSAM head nurse, who did not know which group each subject was assigned to. Additionally, the statistician was unaware of the allocation during the research period to guarantee the objectivity and impartiality of the data.

2.7. Statistical Analysis and Sample Size

Statistical analysis was performed with IBM SPSS Statistics software, version 27.0, IBM, New York, USA [33].

Demographic, clinical and laboratorial data at baseline were described by group through the mean, standard deviation and frequencies. Groups were compared with Fishers' Exact Test (categorical variables) and the one-way ANOVA (continuous variables). A mixed ANOVA with interaction time*group and time*regimen was used to assess the acupuncture's effect and the frequency of treatment, respectively. As the interaction time*treatment frequency was not significant, a new mixed ANOVA was performed without the factor treatment frequency. Differences through time within each group were assessed with the repeated-measures ANOVA. The Bonferroni correction was used for multiple comparisons. Partial Eta squared (η2p) was used to assess the effect size of the interaction, considering the thresholds: η2p = 0.01 small effect, η2p = 0.06 medium effect, η2p = 0.14 large effect [34]. The assumptions for the mixed ANOVA were assessed and validated through Shapiro–Wilk's Test (normality), Levene's Test (homogeneity of variances), and

Box's M Test (sphericity of the covariance matrix). A significance level of 5% was considered for the statistical tests.

To assess the effectiveness of blinding, participants of verum acupuncture (VA) and sham acupuncture (SA) groups were asked, after treatment, to guess what type of acupuncture treatment they believe they had received ("Verum", "Sham", "I do not know"). The answers were used to calculate the James Blinding Index (BI). This index ranges from 0 (lack of blinding) to 1 (complete blinding); values above 0.50 indicate that the subjects have been blinded [35,36]. To calculate the BI, the package "BI" available in the statistical software R was used [37].

Owing to the lack of previous data, the sample size was estimated to achieve a small to medium effect size (f = 0.19) [34] in the mixed ANOVA (3 groups × 3 repeated measures) with statistical power of 80% and a significant level of 5%. The calculations, carried out with G*Power V.3.1, Heinrich Heine University Dusseldorf, Dusseldorf, Germany [38], led to estimate a minimum of 20 patients in each group (Acupuncture Group, Sham Acupuncture Group and Waiting-List Group). Computational formulas for sample size estimation can be found in the paper that describes the software G*Power [38].

3. Results

From December 2020 to May 2021, 88 HD patients from the TECSAM Hemodialysis center were assessed for eligibility; 10 were excluded because they did not meet the inclusion criteria, and 6 declined to participate. A total of 72 patients were included and randomly assigned to the study groups: 24 in the verum acupuncture (VA) group, 24 in the sham acupuncture (SA) group, and 24 in the waiting-list (WL) group.

During the study period, between the post-treatment assessment and before the follow-up assessment, 1 patient in the VA group, 2 in the SA group and 2 in the WL group dropped with the causes identified in Figure 1. Therefore, 67 HD patients were included in the complete analysis set, as shown in the study flow diagram (Figure 1).

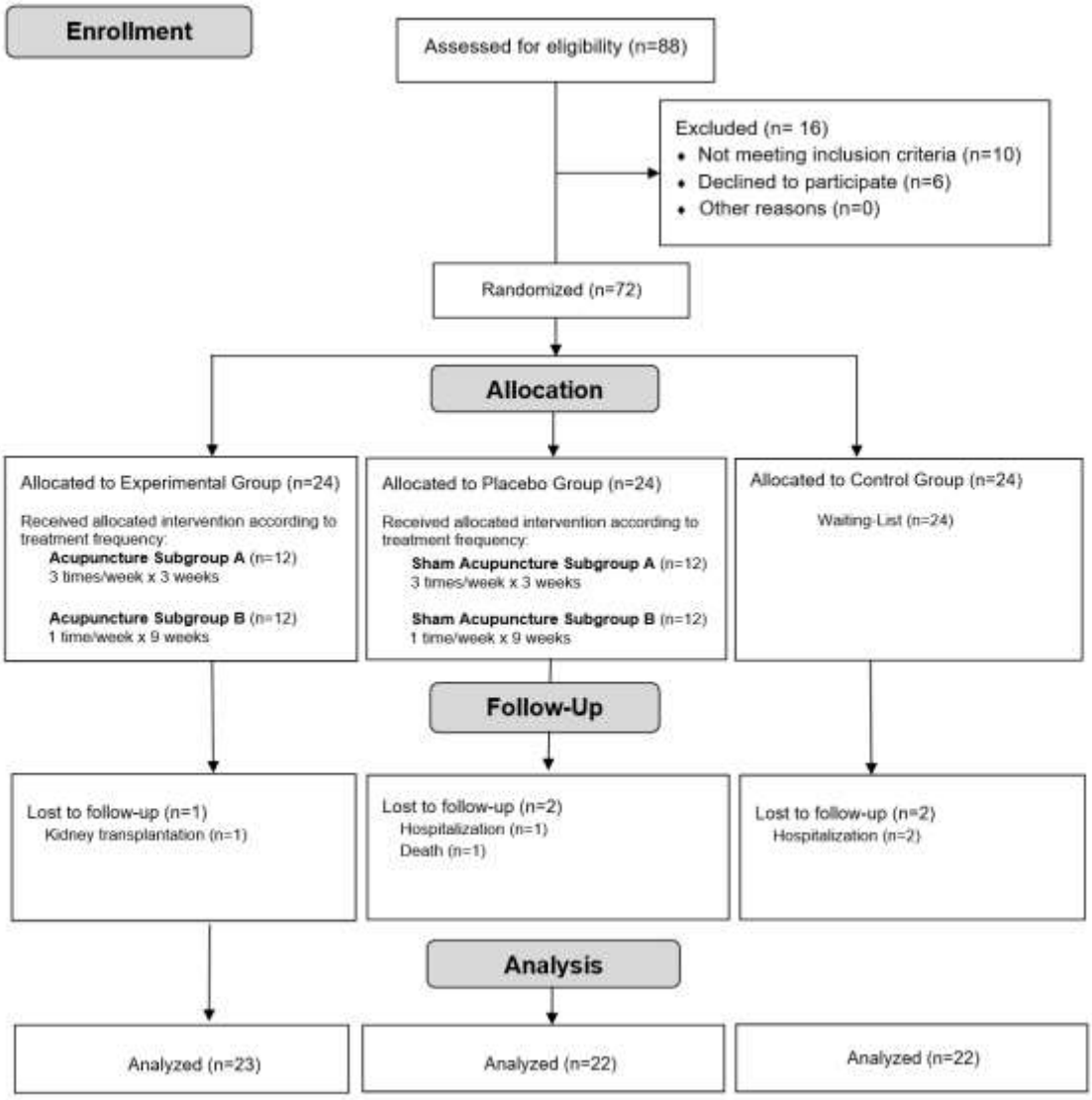

Figure 1. Study flow diagram.

The sample included 67 hemodialysis patients aged between 56 and 91, with a mean age of 71.6 (SD = 7.7). Most were men (61.2%), lived in rural areas (64.2%), were retired (85.1%), and had low education levels (73.1% with the 1° Cycle and 7.5% without any education level). No statistical differences were found between the groups in any of these variables ($p > 0.05$). As for the clinical characteristics, the most prevalent cause of CKD was diabetes mellitus (43.3%). Most of the patients were undergoing HD treatment for over a year and less than 10 years (83.6%) and used arteriovenous fistula (91.0%). No statistical differences were found between the groups regarding the clinical and laboratory variables ($p > 0.05$).

The baseline demographic, clinical and laboratorial characteristics are shown in Table 2.

Table 2. Sociodemographic, clinical, and laboratorial characteristics of the sample, overall and by group (baseline).

Variables	Total (N = 67)	Verum Acupuncture Group (n = 23)	Sham Acupuncture Group (n = 22)	Non-Acupuncture Group (n = 22)	*p*
SOCIODEMOGRAPHIC					
Sex					
Female	26 (38.8%)	9 (39.1%)	8 (36.4%)	9 (40.9%)	*1.000* [1]
Male	41 (61.2%)	14 (60.9%)	14 (63.6%)	13 (59.1%)	
Age					
Minimum - Maximum	56 - 91	60 - 84	57 - 91	56 - 87	
Mean (SD)	71.6 (7.7)	71.2 (5.1)	72.6 (8.3)	71.0 (9.4)	*0.764* [2]
Residence					
Urban	24 (35.8%)	9 (39.1%)	8 (36.4%)	7 (31.8%)	*0.948* [1]
Rural	43 (64.2%)	14 (60.9%)	14 (63.6%)	15 (68.2%)	
Education level					
No literacy	5 (7.5%)	0 (0.0%)	2 (9.1%)	3 (13.6%)	*0.279* [1]
1º Cycle (4 years)	49 (73.1%)	20 (87.0%)	17 (77.3%)	12 (54.5%)	
2º Cycle (6 years)	7 (10.4%)	2 (8.7%)	1 (4.5%)	4 (18.2%)	
3º Cycle (9 years)	1 (1.5%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	
High school (12 years)	5 (7.5%)	1 (4.3%)	2 (9.1%)	2 (9.1%)	
Professional status					
Employed	4 (6.0%)	0 (0.0%)	2 (9.1%)	2 (9.1%)	*0.481* [1]
Self-employed	4 (6.0%)	2 (8.7%)	0 (0.0%)	2 (9.1%)	
Unemployed	2 (3.0%)	1 (4.3%)	1 (4.5%)	0 (0.0%)	
Retired	57 (85.1%)	20 (87.0%)	19 (86.4%)	18 (81.8%)	
CLINICAL					
CKD causes					
Diabetes mellitus	29 (43.3%)	10 (43.5%)	10 (45.5%)	9 (40.9%)	*0.537* [1]
Chronic Rejection	7 (10.4%)	1 (4.3%)	4 (18.2%)	2 (9.1%)	
Hypertensive nephropathy	4 (6.0%)	3 (13.0%)	0 (0.0%)	1 (4.5%)	
High Blood Pressure	2 (3.0%)	0 (0.0%)	1 (4.5%)	1 (4.5%)	
Glomerulonephritis	2 (3.0%)	1 (4.3%)	0 (0.0%)	1 (4.5%)	
Polycystic disease	2 (3.0%)	0 (0.0%)	0 (0.0%)	2 (9.1%)	
Interstitial tubular necrosis	2 (3.0%)	0 (0.0%)	2 (9.1%)	0 (0.0%)	
Other	5 (7.5%)	3 (13.0%)	1 (4.5%)	1 (4.5%)	
Unknown	14 (20.9%)	5 (21.7%)	4 (18.2%)	5 (22.7%)	
Hemodialysis time					
< 12 months	2 (3.0%)	2 (8.7%)	0 (0.0%)	0 (0.0%)	*0.240* [1
12 to 120 months	56 (83.6%)	19 (82.6%)	20 (90.9%)	17 (77.3%)	
> 120 meses	9 (13.4%)	2 (8.7%)	2 (9.1%)	5 (22.7%)	
Vascular access					
Arteriovenous fistula	61 (91.0%)	22 (95.7%)	18 (81.8%)	21 (95.5%)	*0.306* [1
Central venous catheter	6 (9.0%)	1 (4.3%)	4 (18.2%)	1 (4.5%)	
LABORATORIAL	Mean (SD)				
Hemoglobin (g/dL)	10.93 (1.03)	10.88 (0.94)	10.86 (1.05)	11.05 (1.12)	*0.797* [2]
Potassium (mEq/L)	5.44 (0.81)	5.52 (0.89)	5.35 (0.81)	5.45 (0.74)	*0.799* [2]
Calcium (mg/dL)	9.11 (0.51)	9.13 (0.55)	9.10 (0.49)	9.10 (0.51)	*0.970* [2]
Phosphor (mg/dL)	4.74 (1.13)	4.71 (1.17)	4.70 (1.25)	4.80 (1.00)	*0.944* [2]
Sodium (mg/dL)	138.1 (3.0)	138.5 (2.9)	138.6 (3.8)	137.3 (2.0)	*0.296* [2]

Albumin (g/dL)	3.91 (0.28)	3.98 (0.27)	3.81 (0.27)	3.95 (0.29)	*0.101* [(2)]
Urea (before HD) (mg/dL)	152.6 (37.5)	161.0 (37.9)	145.3 (36.2)	151.0 (38.3)	*0.369* [(2)]
Creatinine (mg/dL)	9.94 (2.12)	10.15 (2.26)	9.51 (1.94)	10.16 (2.16)	*0.514* [(2)]
Parathyroid hormone (pg/dL)	418.0 (243.2)	454.2 (256.9)	358.2 (193.3)	439.9 (271.5)	*0.370* [(2)]
Cholesterol (mg/dL)	162.8 (37.1)	166.0 (47.2)	155.5 (35.8)	166.6 (25.0)	*0.536* [(2)]

[(1)] significance value of value Fisher's Exact Test; [(2)] significance value of ANOVA.

Table 3 shows the results of the ANOVA with interaction time*group*treatment frequency for 6MWT, STS-30 Test and HGS Test. The interaction time*group was statistically significant for total walked distance measured by the 6MW Test ($p < 0.001$, $\eta 2p = 0.521$), for lower limb strength measured by the STS-30 Test ($p < 0.001$, $\eta 2p = 0.600$), and for handgrip strength measured by the HGS Test ($p = 0.032$, $\eta 2p = 0.083$). These results lead to conclude that the evolution through time differed significantly amongst the groups (Table 3).

Table 3. Results of the ANOVA (time*group*treatment frequency) for 6MWT, STS-30 Test, and HGS Test.

Effects	**6MWT**	**STS-30 Test**	**HGS Test**
Time	$p = 0.001$, $\eta^2_p = 0.114$	$p < 0.001$, $\eta^2_p = 0.240$	$p = 0.004$, $\eta^2_p = 0.168$
Interaction time*group	$p < 0.001$, $\eta^2_p = 0.521$	$p < 0.001$, $\eta^2_p = 0.600$	$p = 0.032$, $\eta^2_p = 0.083$
Interaction time* treatment frequency	$p = 0.172$, $\eta^2_p = 0.028$	$p = 0.438$, $\eta^2_p = 0.027$	$p = 0.843$, $\eta^2_p = 0.002$

p - p-value of the terms of the mixed ANOVA; η^2_p - partial Eta squared.

As for the interaction time*treatment frequency, no statistically significant effects were found for the results of 6MWT ($p = 0.172$, $\eta 2p = 0.028$), STS-30 Test ($p = 0.438$, $\eta 2p = 0.027$) or HGS Test ($p = 0.843$, $\eta 2p = 0.002$), showing that the evolution through time did not differ significantly between acupuncture treatment frequency (3 times/week × 3 weeks vs. 1 time/week × 9 weeks) (Table 3).

Owing to the absence of significant differences between treatment frequencies, a new ANOVA was performed without the factor treatment frequency. Results of the new ANOVA with interaction time*group for each variable are presented in Table 4 and Figure 2.

Table 4. Descriptive statistics and comparison of 6-Minute Walk Test (6MWT), 30-second Sit-to-Stand (STS-30) Test and Hand Grip Strength (HGS) Test by group and over time.

	Verum Acupuncture (VA) Group (n = 23) Mean ± SD	**Sham Acupuncture (SA) Group** (n = 22) Mean ± SD	**Waiting-List (WL) Group** (n = 22) Mean ± SD
6MWT			
Walked distance (m)			
Baseline	307.2 ± 80.1 [a]	296.2 ± 97.8 [a]	304.1 ± 119.3 [a]
After treatment	383.2 ± 70.7 [b]	283.4 ± 95.2 [a]	268.8 ± 113.8 [b]
Follow-up	368.9 ± 68.2 [b]	262.5 ± 101.8 [b]	241.7 ± 118.1 [c]
ANOVA [(1)]	*p < 0.001*	*p < 0.001*	*p < 0.001*
*Interaction time*group*		*p < 0.001, η^2_p = 0.509*	
STS-30Test			
Nº of Repetition sit-to-stand in 30s			
Baseline	9.7 ± 2.8 [a]	9.1 ± 3.8 [a]	9.1 ± 3.7 [a]
After treatment	11.5 ± 2.8 [b]	7.9 ± 3.8 [b]	7.9 ± 3.1 [b]
Follow-up	11.2 ± 3.0 [b]	7.4 ± 3.6 [b]	7.0 ± 3.7 [c]
ANOVA [(1)]	*p < 0.001*	*p < 0.001*	*p < 0.001*
*Interaction time*group*		*p < 0.001, η^2_p = 0.565*	
HGS Test			
Isometric handgrip force (kgf)			
Baseline	21.4 ± 5.5 [a]	20.4 ± 4.7 [a]	20.9 ± 6.5 [a]
After treatment	22.8 ± 5.7 [b]	20.6 ± 5.1 [a]	20.5 ± 6.1 [a]
Follow-up	21.7 ± 5.1 [ab]	20.2 ± 5.6 [a]	19.8 ± 5.9 [a]
ANOVA [(1)]	*p = 0.012*	*p = 0.601*	*p = 0.112*
*Interaction time*group*		*p = 0.043, η^2_p = 0.083*	

[(1)] p-value of repeated measures ANOVA for comparison over time within each group; [a,b,c] moments (baseline, after treatment, follow-up) with a superscript letter in common do not differ significantly: p > 0.05 in the multiple comparison tests with Bonferroni correction; η^2_p – Partial Eta squared.

Results show that the evolution through time of the three variables differed significantly among the groups (p < 0.05 for the interaction time*group). The effects were large for 6MWT (p < 0.001, η2p = 0.509) and the STS-30 Test (p < 0.001, η2p = 0.565), and medium for the HGS Test (p = 0.043, η2p = 0.083) (Table 4).

The analysis of the evolution within each group shows that, in the VA group, walked distance increased significantly (p < 0.05) from 307.2 ± 80.1 in the baseline assessment to 383.2 ± 70.7 after treatment, but did not change in the follow-up (368.9 ± 68.2) (p > 0.05). The mean in the follow-up was still significantly higher than the mean in the baseline assessment (p < 0.05). On the other hand, in the SA group and in the WL group, a trend of decrease in the walked distance was observed, with the mean in the follow-up moment significantly lower than the mean in the baseline assessment (p < 0.05) (Table 4 and Figure 2).

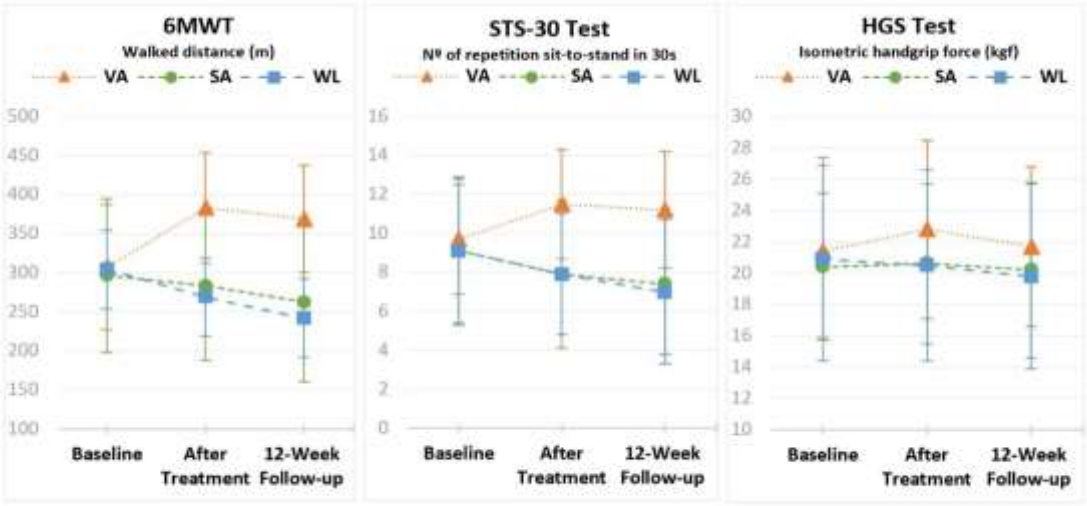

Figure 2. Means (±SD) of 6MWT, STS-30 Test and HGS Test in the baseline assessment, after treatment and follow-up assessment, within each group (VA—Verum Acupuncture Group, SA—Sham Acupuncture Group, WL—Waiting-List Group).

Similar results were found in the lower limb strength — the mean of the VA group increased from 9.7 ± 2.8 in the baseline assessment to 11.5 ± 2.8 after treatment ($p < 0.05$) but did not change in the follow-up (11.2 ± 3.0) ($p > 0.05$). The mean in the follow-up was significantly higher than the mean in the baseline assessment ($p < 0.05$). The means in the SA group and in the WL group decreased significantly through time ($p < 0.05$) (Table 4 and Figure 2).

As for the isometric handgrip force, in the VA group, the mean increased from 21.4 ± 5.5 in the baseline assessment to 22.8 ± 5.7 after treatment ($p < 0.05$) but did not change significantly in the follow-up (21.7 ± 5.1) ($p > 0.05$). There were no significant differences between the means in the baseline assessment and the follow-up in this group ($p > 0.05$). No significant differences through time were found in the SA group ($p = 0.601$) or in the WL group ($p = 0.112$) (Table 4 and Figure 2).

Results of the blinding success assessment (Table 5) show that 31.1% of the participants believe that they received verum acupuncture (30.4% in VA and 31.8% in SA) and 68.9% answered “I do not know” (69.6% in VA and 68.2% in SA)—none of the patients answered “sham acupuncture”. The value of the Blinding Index of 0.84 (95% confidence interval: 0.78–0.91) allows for concluding that the participant blinding was successful.

Table 5. Assessment of blinding success.

Groups	Participants' Guess, *n* (%)		
	Verum Acupuncture	**Sham Acupuncture**	**Do Not Know**
Verum Acupuncture (*n* = 23)	7 (30.4%)	0 (0.0%)	16 (69.6%)
Sham Acupuncture (*n* = 22)	7 (31.8%)	0 (0.0%)	15 (68.2%)
Total (*n* = 45)	14 (31.1%)	0 (0.0%)	31 (68.9%)
Blinding Index: 0.84 (95% Confidence Interval: 0.78–0.91)			

Throughout the trial period, no adverse events related to treatment were observed or reported by patients, practitioner or care providers, suggesting the safety of using acupuncture during hemodialysis sessions.

4. Discussion

CKD is a debilitating disease and as it progresses to kidney replacement therapy, patients often experience numerous symptoms that negatively impact their quality of life, affecting their physical, functional, metabolic, social and mental conditions with high impact on functional capacity when compared to healthy individuals [8,39]. Although there are only a few clinical trials comparing the effect of different acupuncture treatment frequencies, an appropriate dose of acupuncture must be considered in order to improve outcomes [21].

In this study, a parallel patient-assessor blinded RCT was conducted to evaluate the effect of acupuncture in patients with kidney failure undergoing HD and also to establish the differences in the frequency of treatment (three times a week or once a week). The outcomes showed that nine sessions of manual acupuncture improved functional capacity and increased peripheral muscle strength in the experimental group (VA group) compared to the placebo (SA) and control (WL) groups.

The primary and secondary outcomes did not depend on the frequency of acupuncture treatment since no significant differences were observed, indicating that three treatments per week do not provide better results than one treatment per week on functional capacity and muscle strength in patients undergoing HD.

To the authors' knowledge, no RCT was performed to assess the effect of different acupuncture treatment frequencies on FC parameters and in the clinical sample of the

present study. The impact of the frequency of acupuncture has been investigated in other medical conditions, and the reflections found are not consensual. The pilot study conducted by Yuan et al. (2009), designed to compare the effectiveness of two different frequencies, two versus five times per week of acupuncture treatment for chronic low back pain, showed no significant differences among groups in any outcome, and at each time point [40]. Lin et al. (2020) reported that three sessions per week of acupuncture produced superior and persisting improvement (≥16 weeks) in knee osteoarthritis treatment compared with one session per week of acupuncture [20]. Wang et al. (2020) conducted a pilot study to establish if three sessions per week of acupuncture treatment were superior to one session per week for symptomatic outcomes in postprandial distress syndrome. After four weeks of treatment, three sessions per week tended to improve symptoms and quality of life compared to once a week [19]. Given the results of the present study, it cannot be said that more frequent weekly acupuncture treatments provided greater therapeutic effects. Only studies in chronic pain seem to support this concept, which needs further research with more robust results.

Acupuncture treatment increased walked distance after treatment and lasted beyond a 12-week follow-up. The results of sham acupuncture (SA group) or no-acupuncture treatment (WL group) did not improve walked distance after treatment, followed by a decreasing tendency from baseline to 12-week follow-up. The longer lasting results of acupuncture treatment may offer the advantage to the patient to keep a greater functional capacity through time. Similar results were obtained for muscle strength after treatment. Verum acupuncture increased muscle strength, but it did not last beyond the 12-week follow-up period. A decrease in muscle strength was observed from baseline to 12-week follow-up in the SA and WL groups. Acupuncture also increased handgrip strength, at the end of treatment. Given the high percentage of elderly hemodialysis patients, many of whom need to walk with the help of a cane or a walker, the greater handgrip strength achieved with acupuncture treatment may offer the advantage of stronger support for their ambulation. At the 12-week follow-up, no significant differences were observed compared to baseline and post-treatment. No increase was found in grip strength in either the SA group or the WL group at different assessment time points.

No studies were found assessing the effectiveness of acupuncture in improving functional capacity and muscle strength in hemodialysis patients. Zhou et al. (2012) concluded that unilateral manual acupuncture and electroacupuncture at selected acupoints on ankle dorsiflexion could improve muscle strength in both limbs, and electroacupuncture at the non-acupoints as used in this study can also induce similar strength gains [18]. Hu et al. (2015) demonstrated the improvement of muscle atrophy in

5/6 nephrectomy rats by low-frequency electrical stimulation of an acupuncture point, due to increased protein metabolism and myogenesis [41]. Although these reports point to a positive effect of acupuncture, the study conducted by Soares Mendes Damasceno et al. (2019) showed no statistically significant difference between acupuncture and non-acupuncture groups on muscle mass, muscle strength, functionality, and inflammatory markers in older people with sarcopenia [17]. Perhaps these discrepancies are due to the fact that each of the studies had a specific acupuncture treatment protocol for the clinical conditions under investigation with different types of acupuncture, duration, treatment frequency and control interventions, so it is not possible to compare the results.

Regarding the results of the present study, it can be speculated that the improvement in functional capacity and muscle strength was due to the effect of acupuncture needle stimulation on increased blood flow, cytokines and growth factors that may result in modulation of sensory input afferents through changes in the connective tissue milieu [42].

In kidney failure patients undergoing HD, the 6MWT distance is considered an independent predictor of mortality. According to Kohl et al. (2012), the survival rate of patients undergoing HD increased by approximately 5% for every 100 m walked in the 6MWT [43]. Additionally, different studies have shown that handgrip strength predicts all-cause mortality in men and women on maintenance HD [44–46].

The results of this study are encouraging and may contribute to the integration of acupuncture as an integrative therapy for symptom management in HD patients. The progression of CKD and the initiation of dialysis are associated with adverse outcomes or increased mortality. An increase in functional capacity and muscle strength means that HD patients will be able to perform activities of daily living more autonomously and with a higher level of functioning.

Strengths of the present study include comparing the experimental group with two groups (sham and non-acupuncture groups); the participants, the outcome evaluator and the statistician were blinded to allocation; and the number of dropouts during follow-up was as low as possible.

Patients undergoing HD have to cope with a stressful and disruptive chronic illness and suffer from emotional problems that negatively impact on their overall health [7,47]. Given this assumption and the fundamentals of TCM, the acupuncture points *Shenmen* (HT7) and *Guanyuan* (CV4) were included in the study protocol. The *Shenmen* (HT7) acupoint was chosen since it is an important acupuncture point for calming and regulating the spirit. The *Guanyuan* (CV4) acupuncture point is described as a crucial point for

strengthening the body and mind. Moreover, as it tonifies the kidney and the original Qi, it is recognized as an effective point in the case of chronic diseases [22].

Despite the methodological rigor considered in the design of this study, a few limitations can be found: first, the sample size used to compare different frequencies of acupuncture treatment, which resulted from the subdivision of the participants from experimental and placebo groups; second, the TCM practitioner who provided acupuncture treatment cannot be blinded due to the type of intervention; finally, although the effect of acupuncture treatment had been observed 12 weeks after the end of treatment, this time interval was not long enough to evaluate the long-term effect of acupuncture.

Further research is required to verify the tested acupuncture treatment protocol and validate its clinical efficacy in a significant sample of patients with CKD without kidney replacement therapy or in a healthy population. Complete data regarding nutritional status might be valuable to correlate with the effect of acupuncture on the parameters evaluated by this RCT. In addition, an active control group should be considered in the design of a future study, such as a comparison with an intradialytic exercise or physical therapy group.

5. Conclusions

In conclusion, verum acupuncture, compared to sham or no-acupuncture groups, improved FC and peripheral muscle strength in patients with maintenance HD, and in some parameters, the results persist into the 12-week follow-up period. Although acupuncture treatment once a week appeared to produce similar effects compared to three times a week, more solid prospective research will be needed to validate the impact of the frequency of acupuncture treatment.

Appendix A

Table A1. Acupuncture points selected for this study*.

Acupuncture Points	Location
KI3 (*Taixi*; 太谿(溪))	On the posteromedial aspect of the ankle, in the depression between the prominence of the medial malleolus and the calcaneal tendon.
SP6 (*Sanyinjiao*; 三陰(阴)交)	On the tibial aspect of the leg, posterior to the medial border of the tibia, 3 *cun* superior to the prominence of the medial malleolus.
ST36 (*Zusanli*; 足三里)	On the anterior aspect of the leg, on the line connecting ST35 with ST41, 3 *cun* inferior to ST35, on the tibialis anterior muscle.
HT7 (*Shenmen*; 神(神)門(门))	On the wrist, at the ulnar end of the transverse crease of the wrist, in the depression on the redial side of the tendon of m. flexor carpi ulnaris.
CV4 (Guanyuan; 關(关,関)元)	On the lower abdomen, 3 *cun* inferior to the center of the umbilicus, on the anterior median line.

* The description of acupoints were made according to international standard terminology of WHO (2008).
Reference: WHO Regional Office for the Western Pacific. WHO Standard Acupuncture Point Locations in the Western Pacific Region. Manila: World Health Organization; 2008.

Table A2. Non-Acupuncture points* selected for this study.

Non-Acupuncture Points	Location
Non-Acupuncture point 1 (NA1)	Located near KI3 (*Taixi).* On the posteromedial aspect of the ankle, at the midpoint of KI3 (*Taixi)* and KI7*(Fuliu).* KI7*(Fuliu)* is located on the posteromedial aspect of the leg, anterior to the calcaneal tendon, 2 *cun* superior to the prominence of the medial malleolus.
Non-Acupuncture point 2 (NA2)	Located near SP6 (*Sanyinjiao).* On the leg, at the midpoint of the medial side of the tibia, 1 *cun* distal from SP6 (*Sanyinjiao*).
Non-Acupuncture point 3 (NA3)	Located near ST36 (*Zusanli*). On the anterior aspect of the leg, at midpoint of ST37 (*Shangjuxu*) and the Gallbladder Meridian. ST37 (*Shangjuxu*) is located on the anterior aspect of the leg, on the line connecting ST35 (*Dubi*) with ST41(*Jiexi*), 6 *cun* inferior to ST35 (*Dubi*), on the tibialis anterior muscle.

Non-Acupuncture point 4 (NA4)	Located near HT7 (*Shenmen*). On the wrist, at the transverse crease of the wrist, at the midpoint of HT7 (*Shenmen*) and PC7 (*Daling*), between the Pericardium Meridian and Heart Meridian.
Non-Acupuncture point 5 (NA5)	Located near CV4 (*Guanyuan*). On the lower abdomen, 1 *cun* lateral from CV6 (*Qihai*). CV6 (*Qihai*) is located 1.5 *cun* inferior to the center of the umbilicus, on the anterior median line.

*In the present study, the non-acupuncture points selected were the points located on the non-meridian but near the acupuncture points described above.

Table A3. Timing of visits and data collection according to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)*.

		Screening	Baseline	Treatment Period			Follow-up Period
			0-Week	1-Week	3-Week	9-Week	After treatment 12-Week
Patient	Eligibility	X					
	Informed Consent		X				
	Demographics and clinical data		X				
	Physical examination		X				
	Randomization		X				
	Laboratorial data		X				
							X
Intervention	Verum Acupuncture Subgroup A			9 Acupuncture treatments (3 sessions per week for 3 weeks)			X
	Verum Acupuncture Subgroup B			9 Acupuncture treatments (1 session per week for 9 weeks)			
Comparison	Sham Acupuncture Subgroup A			9 Acupuncture treatments in non-acupuncture points (3 sessions per week for 3 weeks)			X
	Sham Acupuncture Subgroup B			9 Acupuncture treatments in non-acupuncture points (1 session per week for 9 weeks)			X
	Non-Acupuncture Group 0			Non-Acupuncture Treatment			X
Outcomes	6MWT walked distance		X		X	X	X
	Lower Limbs Strength		X		X	X	X
	Handgrip Strength		X		X	X	X
	Assessment of blinding success				X	X	
Participant Safety	Adverse events		X		X	X	X

***Reference**: Chan, A.W.; Tetzlaff, J.M.; Gøtzsche, P.C.; Altman, D.G.; Mann, H.; Berlin, J.A.; Dickersin, K.; Hróbjartsson, A.; Schulz, K.F.; Parulekar, W.R.; et al. SPIRIT 2013 explanation and elaboration: Guidance for protocols of clinical trials. BMJ 2013, 346, e7586. https://doi.org/10.1136/bmj.e7586.

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Chapter IV Research Paper 3

Effectiveness of Acupuncture on Health-Related Quality of Life in Patients Receiving Maintenance Hemodialysis

Marta Correia de Carvalho [1], José Nunes de Azevedo [2], Pedro Azevedo [2], Carlos Pires [3], Jorge Pereira Machado [1,4] and Manuel Laranjeira [1,5]

[1] ICBAS–School of Medicine and Biomedical Sciences, University of Porto, 4050-313 Porto, Portugal.
[2] TECSAM-Tecnologia e Serviços Médicos SA, 5370-530 Mirandela, Portugal.
[3] Center for Research in Neuropsychology and Cognitive and Behavioral Intervention (CINEICC), Faculty of Psychology and Educational Sciences, University of Coimbra, 3000-115 Coimbra, Portugal.
[4] CBSin—Center of BioSciences in Integrative Health, 4000-105 Porto, Portugal.
[5] INC–Instituto de Neurociências, 4100-141 Porto, Portugal.

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Abstract: Patients with kidney failure (KF) receiving maintenance hemodialysis (HD) experience numerous symptoms that impair health-related quality of life (HRQOL) and contribute to high mortality. Acupuncture is often used for symptom enhancement and HRQOL. This patient-assessor blinded randomized controlled trial evaluated the effectiveness of acupuncture compared with sham acupuncture on the HRQOL, as a secondary analysis, in patients receiving maintenance HD. Seventy-two participants were randomly assigned to verum acupuncture (VA), sham acupuncture (SA) or waiting-list (WL) groups. The outcome was the improvement in HRQOL assessed by the Kidney Disease Quality of Life-Short Form, version 1.3 (KDQOL-SF™ v1.3) at baseline, after treatment and at 12-week follow up. Non-parametric tests were used for statistical analysis. Of the 72 randomized patients, 67 were included in the complete analysis set. As for the changes between baseline and after treatment, the VA group showed significantly increased scores on most of the KDQOL-SF™ v1.3 scales compared to SA or WL groups ($p < 0.05$). No statistically significant differences between groups were observed in the changes from baseline to the follow-up ($p > 0.05$). Compared to sham, acupuncture improved HRQOL in patients receiving maintenance HD after treatment but not at the follow-up.

Keywords: chronic kidney disease; hemodialysis; acupuncture; health-related quality of life; integrative medicine; randomized controlled trial.

1. Introduction

The increasing number of chronic kidney disease (CKD) patients with glomerular filtration rate category 5 (CKG G5) is considered a public health concern [1]. The latest data from the CaReMe CKD study indicates that the prevalence of CKD is around 10% in the adult population, usually underestimated in most studies, with substantial mortality and high health costs [2]. In Portugal, the prevalence of CKD is high compared to other countries and its diagnostic and therapeutic approach is more expensive than other very prevalent chronic diseases, such as heart failure, acute myocardial infarction, or peripheral arterial disease [2,3].

CKD is a debilitating disease, and its progression often requires kidney replacement therapy (KRT), such as hemodialysis (HD) treatment.

Patients in maintenance HD have a complex treatment and experience numerous physical and emotional limitations that severely impact daily living activities and clinical outcomes[4-6]. While innovation and improvements in technologies associated with HD treatment have contributed to increased life expectancy, patients often experience physical and mental disabilities and poor health-related quality of life (HRQOL) [5,7,8].

Although difficult to define, given the multiple variables inherent to its meaning, HRQOL is considered an individual's subjective assessment of the impact of health status on various aspects of their life over time. It includes physical, mental, emotional, and social conceptual dimensions [8,9].

Previous studies have consistently reported a significant reduction in HRQOL measures in the patients undergoing HD compared to the clinical and non-clinical populations [9-13]. An association between reduced HRQOL scores and adverse events, such as hospitalization and mortality, has been demonstrated [10,14,15]. Regarding the HRQOL component summary scores, recent research reported that lower physical component summary (PCS) at 3 months after initiation of dialysis significantly correlates with overall mortality in patients undergoing HD [16]. Comorbid conditions of depression and diabetes also predicted a decreased PCS [17].

The importance of the HRQOL concept has increased as a measure to assess treatment outcomes and monitor the quality of care delivered to maintenance dialysis patients. The KDOQI recommendations emphasize the relevance of measuring HRQOL in assessing patients' well-being and the adequacy of new therapeutic approaches [18].

Complementary and integrative medicine interventions have been reported to positively impact HRQOL and well-being in different clinical populations and medical conditions [19,20]. Acupuncture, as a Traditional Chinese Medicine (TCM) practice, has

been progressively more accepted and often used for pain management, supportive care for oncological disease [21] and chronic illness for symptom enhancement [22-25] and HRQOL [26,27].

Literature reports that acupuncture may be a feasible and safe add-on treatment option for managing symptoms and improving HRQOL in patients undergoing regular HD [28-30]. The study conducted by Jung et al. (2022) shows promising results by demonstrating the action of acupuncture in potentially preserving residual renal function in HD patients by increasing residual urine volume and glomerular filtration rate after eight sessions of interdialytic acupuncture [31]. Also, the effect of acupuncture on improving functional capacity and peripheral muscle strength in patients undergoing HD was reported [32]. Furthermore, a current systematic review and meta-analysis assessed the effectiveness and safety of acupuncture in treating uremic pruritus among patients undergoing HD. The analysis concluded that combining acupuncture with HD was more effective than hemodialysis alone in alleviating symptoms of uremic pruritus [33].

To overcome the lack of randomized clinical trials (RCT) evaluating the effectiveness of acupuncture on HRQOL of patients receiving maintenance HD, this study presents new data not described in the primary analysis of a previously conducted RCT [32,34]. A new analysis was performed to verify the effectiveness of acupuncture in the HRQOL improvement, the specific effect of acupuncture compared to placebo and the short-term effects.

2. Materials and Methods

2.1. Study Design and Participants

The present study is a new and secondary analysis of a randomized controlled trial [32,34] conducted at a Portuguese hemodialysis center. The study began in August 2021 and ended in February 2022, and was designed to assess the effectiveness of acupuncture on health-related quality of life in advanced CKD patients with kidney replacement therapy (KRT). The study received ethical approval from the University Hospital Center of Porto/ICBAS – School of Medicine and Biomedical Sciences ethics commission and registered on ClinicalTrials.gov platform.

Male and female participants were enrolled, aged over eighteen years old, with kidney failure on KRT for more than three months, with a regular three-weekly HD program lasting four hours and stable clinical status.

Exclusion criteria were applied to participants with contraindicated medical conditions, unstable angina pectoris, malignant hypertension, poorly controlled diabetes mellitus, cerebrovascular events and syncope, decompensated heart disease, severe

mental disorder, or cognitive disability. Additionally, those who declined to participate, with incapable of performing physical activity, recently received acupuncture treatment (< 2 weeks), encountered established allergic responses or other adverse effects resulting from prior acupuncture treatment, or were incapable of complying with the necessary actions involved to the procedure were also considered ineligible for the clinical trial.

Before enrollment, every eligible participant who agreed to participate provided written informed consent following the revised version of the Declaration of Helsinki and the Oviedo Convention.

2.2. Random assignment and masking

Eligible participants were assigned in an equal allocation ratio, either the verum acupuncture (VA) group, sham acupuncture (SA) group, or waiting-list (WL) group using simple randomization procedures. An independent researcher created the randomization sequences using Microsoft® Excel® for Microsoft 365 MSO. The assignments were then placed in indistinct envelopes to ensure allocation series blinding. Regarding the random allocation of participants in the subgroups created according to the frequency of acupuncture treatment, it was determined that the first twelve participants from both the VA and the SA groups would be allocated to subgroup A (three treatments three times a week). The remaining twelve would be allocated to subgroup B (one treatment once a week) [34].

In order to ensure blinding, the group allocation was kept concealed from participants, outcome assessors, and the statistician. Additionally, only the TCM practitioner responsible for administering the acupuncture treatments was aware of each group's specific intervention**.**

2.3. Intervention

The acupuncture intervention was based on a standardized and repeatable protocol developed by the research team. Details of acupuncture treatment were described according to the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)* 2010 Checklist [35], as presented in a prior study [34].

Regarding the acupuncture rationale, acupoints were chosen through a consensus method, which involved reviewing relevant literature, considering the general principles of acupuncture and traditional Chinese medicine (TCM) meridian theory, and drawing upon clinical expertise from specialists in TCM, acupuncture, and nephrology [36-38].

Subgroups were defined to assess the impact of acupuncture frequency on HRQOL in both the verum acupuncture (VA) and sham acupuncture (SA) group. Subgroup A

underwent acupuncture treatments three times a week for three weeks (3x3), while subgroup B received treatments only once weekly for nine weeks (1x9). In total, both subgroups received a total of nine acupuncture sessions. These treatment frequencies (3x3 or 1x9) were chosen based on the participants' hemodialysis (HD) routine. Patients at the TECSAM hemodialysis center undergo HD three times a week, making 3x3 and 1x9 treatment frequencies appropriate for this study. Considering the physical and emotional burden of HD treatments on patients, a balanced number of acupuncture sessions for the participants was determined.

2.3.1. Verum Acupuncture Group

The experimental group (verum acupuncture) was divided into verum acupuncture subgroups A(3x3) and B (1x9). A total of 9 acupuncture treatments were performed and the same choice of acupuncture points were applied to each subgroup.

For each session and subject, a total of 8 needle insertions were made at five acupoints, namely *Taixi* (KI3), *Sanyinjiao* (SP6), *Zusanli* (ST36), *Shenmen* (HT7), and Guan-yuan (CV4). *Taixi* (KI3), *Sanyinjiao* (SP6), and *Zusanli* (ST36) were punctured bilaterally, and *Guanyuan* (CV4) unilaterally. Also, *Shenmen* (HT7) was used unilaterally in the arm without the arterial-venous fistula (AVF) or in the right arm in those participants with a central venous catheter (CVC).

Sterilized and disposable stainless-steel needles (0,25x25mm) were inserted and, after *De qi* sensation, were manually manipulated one minute every ten minutes during needle retention (25 minutes). Interaction between patient and TCM practitioner has been kept to the minimum necessary to avoid non-specific treatment effects.

2.3.2. Sham Acupuncture Group

The placebo group, which received sham acupuncture, was also divided into subgroups and received a total of nine acupuncture treatments. Manual acupuncture was performed using the same type of needles as described above, but with superficial needling (5mm depth) at non-acupuncture points without attempting to achieve *De qi* sensation or stimulation.

The locations of the acupuncture and non-acupuncture points referred above are detailed in appendix A (Tables A1 and A2) of our published paper [32].

2.3.3. Waiting List Group

Regarding the waiting-list group, no acupuncture treatment was performed from the time of randomization until the end of the follow-up period.

While the HD weekly session was underway, a licensed TCM specialist with five years of professional experience administered acupuncture treatment. The study timeline followed the standard care routine for HD sessions, and no other interventions were allowed.

2.4. Outcome measurement

The primary outcome was the specific effect of acupuncture compared to sham acupuncture. This was observed through the change in HRQOL assessed using the validated Portuguese version of Kidney Disease Quality of Life-Short Form, Version 1.3 (KDQOL-SFTM 1.3), physical component summary score (PCS) [39]. Secondary outcomes included selected multi-item and burden of kidney disease scales scores from KDQOL-SFTM 1.3.

The assessments were performed at baseline, after treatment, and at 12-week follow-up.

2.4.1. Kidney Disease Quality of Life- Short Form, Version 1.3 (KDQOL-SFTM 1.3)

KDQOL-SFTM 1.3 is a self-report disease-specific HRQOL measure composed of a generic scale including a 36-item health survey and a specific scale targeting the particular concerns of individuals with kidney failure with KRT (peritoneal dialysis or hemodialysis) [40].

The 36-Item Short Form Survey (SF-36) evaluates general health across eight different domains: physical functioning (10 items); role-physical (4 items); pain (2 items); general health (5 items); emotional well-being (5 items); role-emotional (3 items); social function (2 items) and energy/fatigue (4 items). Each question is scored ranging from 0 (representing the poorest health) to 100 (indicating the best health). Physical and mental functioning are assessed by calculating normalized scores from the individual scales, referred to as physical component summary (PCS) and mental component summary (MCS) scores [41].

As a kidney disease-specific instrument, the KDQOL-SFTTM 1.3 comprises 43 kidney items targeting kidney disease and assesses 11 kidney disease-specific components of HRQOL. These components include a symptom/problem list (12 items); effects of kidney disease (8 items); work status (2 items); burden of kidney disease (4 items); cognitive function (3 items); quality of social interaction (3 items); sexual function (2

items); sleep (4 items); social support (2 items); dialysis staff encouragement (2 items) and patient satisfaction (1 item). It also includes a single-item overall rating of health [40,41].

2.4.2. Sociodemographic and Clinical Data Collection Form

This document was designed to collect patients' sociodemographic information such as gender, age, level of education, and employment status, as well as medical variables including time on hemodialysis and laboratory data at baseline. The participant time-line is outlined in Table 1.

Table 1. Timing of visits and data collection

		Screening	Baseline	Treatment			Follow-up
			0-Week	1-Week	3-Week	9-Week	After treatment 12-Week
Patient	Eligibility	X					
	Informed consent		X				
	Demographics and clinical data		X				
	Physical examination		X				
	Randomization		X				
	Laboratorial data		X				X
Intervention	Verum Acupuncture Subgroup A (VA SgA)			9 Acupuncture treatments (3 sessions per week for 3 weeks)			X
	Verum Acupuncture Subgroup B (VA SgB)			9 Acupuncture treatments (1 session per week for 9 weeks)			
Comparison	Sham Acupuncture Subgroup A (SA SgA)			9 Acupuncture treatments in non-acupuncture points (3 sessions per week for 3 weeks)			X
	Sham Acupuncture Subgroup B (SA SgB)			9 Acupuncture treatments in non-acupuncture points (1 session per week for 9 weeks)			X
	Waiting-List Group (WL)			Non-Acupuncture Treatment			X
Outcomes	Health-related Quality of Life (Kidney Disease Quality of Life-Short Form, Version 1.3 - KDQOL-SF™ 1.3)		X		X	X	X
	Assessment of blinding success				X	X	
Participant Safety	Adverse effects			X	X	X	X

2.5. Statistical analysis and sample size

At baseline, demographic, clinical, and laboratorial data were presented by group through the mean, the standard deviation and frequencies. To compare groups, Fishers' Exact Test was used for categorical variables and One-way ANOVA was used for continuous variables.

Due to the non-normality of the data (quality of life scores), non-parametric tests were used to analyze between-group differences. The Mann-Whitney test or Kruskal-Wallis test was used, followed by multiple comparison tests with Bonferroni correction. Within

group changes (baseline versus after treatment and baseline versus follow-up) were analyzed with the Wilcoxon signed-rank test. Sample size calculations for the RCT have been described previously [32].

IBM SPSS Statistics software - version 27.0 [42] was used for statistical analysis. The statistical tests were performed at a significance level of 5%.

3. Results

Between December 2020 and May 2021, 88 patients receiving maintenance HD were screened. After applying the inclusion criteria, 10 participants were excluded, 6 declined to participate and a total of 72 patients were included and randomly assigned to the study groups. During the interval between the post-treatment assessment and the 12-week follow-up evaluation, one participant in the VA group, two in the SA group, and two in the WL group dropped out due to hospitalization or transplantation. As a result, the complete analysis set consisted of 67 patients, as shown in the trial flow diagram (Figure 1). Although the sample and methodology were the same as in the primary research project, the results described in the present study are a new and different analysis conducted to evaluate the selected dimensions of HRQOL through KDQOL-SFTM 1.3.

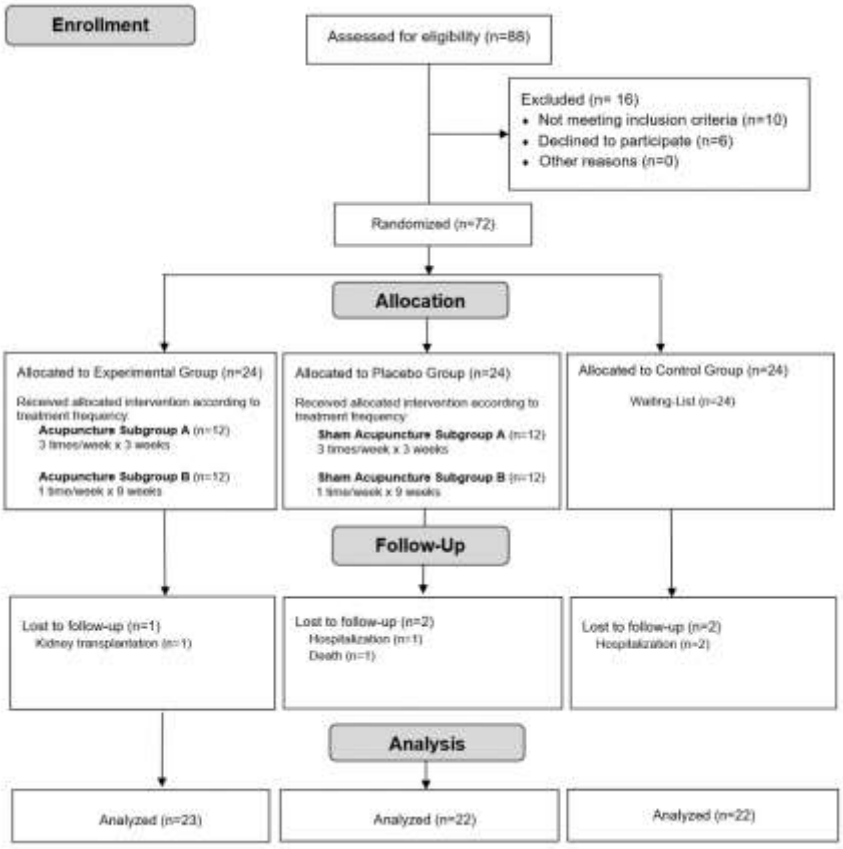

Figure 1. Trial flow diagram. Reprinted with permission from ref. [32]

The baseline sociodemographic, clinical, and laboratorial characteristics of the overall sample categorized by group are presented in Table 2. As previously reported [32], there were no statistically significant differences between the groups in socio-demographic, clinical (including the vascular access type), or laboratory variables ($p > 0.05$).

Table 2. Sample baseline sociodemographic, clinical, and laboratorial characteristics overall and by the group.

Variables	Total (N = 67)	Verum Acupuncture (VA) Group (n = 23)	Sham Acupuncture (SA) Group (n = 22)	Waiting-List (WL) Group (n = 22)	*p*
Sociodemographic					
Gender					
Female	26 (38.8%)	9 (39.1%)	8 (36.4%)	9 (40.9%)	*1.000* (1)
Male	41 (61.2%)	14 (60.9%)	14 (63.6%)	13 (59.1%)	
Age					
Minimum - Maximum	56 - 91	60 – 84	57 - 91	56 - 87	
Mean (SD)	71.6 (7.7)	71.2 (5.1)	72.6 (8.3)	71.0 (9.4)	*0.764* (2)
Level of education					
No literacy	5 (7.5%)	0 (0.0%)	2 (9.1%)	3 (13.6%)	*0.279* (1)
1º Cycle (4 years)	49 (73.1%)	20 (87.0%)	17 (77.3%)	12 (54.5%)	
2º Cycle (6 years)	7 (10.4%)	2 (8.7%)	1 (4.5%)	4 (18.2%)	
3º Cycle (9 years)	1 (1.5%)	0 (0.0%)	0 (0.0%)	1 (4.5%)	
High school (12 years)	5 (7.5%)	1 (4.3%)	2 (9.1%)	2 (9.1%)	
Employment status					
Employed	4 (6.0%)	0 (0.0%)	2 (9.1%)	2 (9.1%)	*0.481* (1)
Self-employed	4 (6.0%)	2 (8.7%)	0 (0.0%)	2 (9.1%)	
Unemployed	2 (3.0%)	1 (4.3%)	1 (4.5%)	0 (0.0%)	
Retired	57 (85.1%)	20 (87.0%)	19 (86.4%)	18 (81.8%)	
Clinical					
Hemodialysis time					
< 12 months	2 (3.0%)	2 (8.7%)	0 (0.0%)	0 (0.0%)	*0.240* (1
12 to 120 months	56 (83.6%)	19 (82.6%)	20 (90.9%)	17 (77.3%)	
> 120 months	9 (13.4%)	2 (8.7%)	2 (9.1%)	5 (22.7%)	
Vascular access					
Arteriovenous fistula (AVF)	61 (91.0%)	22 (95.7%)	18 (81.8%)	21 (95.5%)	*0.306* (1
Central venous catheter (CVC)	6 (9.0%)	1 (4.3%)	4 (18.2%)	1 (4.5%)	
Laboratorial	Mean (SD)				
Hemoglobin (g/dL)	10.93 (1.03)	10.88 (0.94)	10.86 (1.05)	11.05 (1.12)	*0.797* (2)
Potassium (mEq/L)	5.44 (0.81)	5.52 (0.89)	5.35 (0.81)	5.45 (0.74)	*0.799* (2)
Calcium (mg/dL)	9.11 (0.51)	9.13 (0.55)	9.10 (0.49)	9.10 (0.51)	*0.970* (2)
Phosphorus (mg/dL)	4.74 (1.13)	4.71 (1.17)	4.70 (1.25)	4.80 (1.00)	*0.944* (2)
Sodium (mg/dL)	138.1 (3.0)	138.5 (2.9)	138.6 (3.8)	137.3 (2.0)	*0.296* (2)
Albumin (g/dL)	3.91 (0.28)	3.98 (0.27)	3.81 (0.27)	3.95 (0.29)	*0.101* (2)
Urea (before HD) (mg/dL)	152.6 (37.5)	161.0 (37.9)	145.3 (36.2)	151.0 (38.3)	*0.369* (2)
Creatinine (mg/dL)	9.94 (2.12)	10.15 (2.26)	9.51 (1.94)	10.16 (2.16)	*0.514* (2)
Parathyroid hormone (pg/mL)	418.0 (243.2)	454.2 (256.9)	358.2 (193.3)	439.9 (271.5)	*0.370* (2)
Cholesterol (mg/dL)	162.8 (37.1)	166.0 (47.2)	155.5 (35.8)	166.6 (25.0)	*0.536* (2)

[(1)] significance value of value Fisher's Exact Test; [(2)] significance value of ANOVA. Reprinted with permission from ref. [32].

As the study sample mainly included older (Mean age = 71.6; SD=7.7) and retired people (85.1%), the KDQOL-SFTM 1.3 subscales "Work status" and "Sexual function" were not considered for analysis. Also, "Social support", "Dialysis staff encouragement" and "Patient satisfaction" were not analyzed because the research team considered that the subscales scores were not dependent on the acupuncture protocol developed and applied.

The selected HRQOL dimension scores, when compared with the frequency of acupuncture treatment (3 treatments per week for 3 weeks vs. 1 treatment per week for 9 weeks), showed that changes at baseline vs. after treatment and at baseline vs. 12-week follow-up did not differ significantly in either the verum acupuncture group (VA) or the sham acupuncture group (SA) ($p > 0.05$), as shown in Table 3.

Table 3. Comparison of the changes in HRQOL dimensions scores between treatment frequency, within Verum Acupuncture (VA) and Sham Acupuncture (SA) groups.

	Verum Acupuncture (VA) Group			**Sham Acupuncture (SA) Group**		
HRQOL domains	**Treatment Frequency 3x3** (n = 12)	**Treatment frequency 1x9** (n = 11)	p	**Treatment frequency 3x3** (n = 12)	**Treatment frequency 1x9** (n = 10)	p
Kidney disease targeted areas						
Symptom/ problem list	**78.0 ± 15.6**	**81.6 ± 10.1**		**81.6 ± 10.6**	**89.6 ± 8.4**	
Baseline - after treatment	10.9 ± 8.4	9.3 ± 4.8	0.709	0.6 ± 3.3	-0.7 ± 1.9	0.214
Baseline – 12-week follow-up	0.5 ± 4.5	-1.1 ± 3.3	0.281	-2.5 ± 2.5	-1.1 ± 2.9	0.768
Effects of kidney disease	**65.6 ± 15.9**	**62.5 ± 20.1**		**71.0 ± 24.0**	**79.8 ± 11.9**	
Baseline - after treatment	4.4 ± 4.3	3.1 ± 3.4	0.352	-0.5 ± 5.0	-3.1 ± 4.4	0.146
Baseline – 12-week follow-up	1.0 ± 4.3	-0.3 ± 5.5	0.296	-2.3 ± 2.7	-1.6 ± 2.2	0.833
Burden of kidney disease	**34.4 ± 17.4**	**36.9 ± 16.2**		**38.0 ± 31.8**	**30.6 ± 21.3**	
Baseline - after treatment	2.1 ± 6.2	0.6 ± 3.4	0.445	-0.6 ± 6.0	2.1 ± 7.9	0.335
Baseline – 12-week follow-up	-1.0 ± 3.6	-3.4 ± 7.6	0.594	-1.6 ± 1.8	-0.3 ± 3.5	0.883
Cognitive function	**83.9 ± 19.2**	**81.2 ± 14.2**		**91.1 ± 11.1**	**88.7 ± 7.7**	
Baseline - after treatment	3.3 ± 6.7	6.7 ± 8.4	0.315	-1.7 ± 5.8	-0.7 ± 3.8	0.766
Baseline – 12-week follow-up	-1.4 ± 2.8	-0.4± 3.1	0.158	-1.1 ± 2.6	0.0 ± 0.0	0.298
Quality of social interaction	**83.9 ± 18.1**	**78.8 ± 20.6**		**79.4 ± 17.2**	**84.0 ± 6.4**	
Baseline - after treatment	0.6 ± 9.6	3.2 ± 9.6	0.746	-2.8 ± 4.5	-0.7 ± 3.8	0.179
Baseline – 12-week follow-up	-9.7 ± 8.7	-11.8 ± 19.0	0.924	-7.9 ± 14.9	-5.7 ± 3.2	0.800
Sleep	**65.0 ± 20.5**	**63.0 ± 21.2**		**57.9 ± 18.1**	**68.3 ± 12.8**	
Baseline - after treatment	4.0 ± 15.0	6.1 ± 8.4	0.615	-5.2 ± 10.1	-5.8 ± 9.7	0.840
Baseline – 12-week follow-up	-7.5 ± 5.8	-10.5 ± 11.7	0.283	0.6 ± 5.4	-4.0 ± 18.7	0.642
Overall Health	**63.3 ± 17.8**	**56.4 ± 10.3**		**58.3 ± 18.5**	**49.0 ± 5.7**	
Baseline - after treatment	2.5 ± 7.5	4.5 ± 9.3	0.598	-1.7 ± 11.1	1.0 ± 5.7	0.393
Baseline – 12-week follow-up	-1.7 ± 7.2	0.0 ± 6.3	0.677	-4.2 ± 13.8	2.0 ± 6.3	0.245
36-item health survey (SF-36)						
SF12- Physical composite	**37.8 ± 10.9**	**36.1 ± 7.8**		**37.3 ± 10.4**	**38.9 ± 12.4**	

Baseline - after treatment	3.1 ± 5.3	3.6 ± 4.4	0.518	-0.7 ± 3.1	-1.4 ± 3.2	0.509
Baseline – 12-week follow-up	-0.9 ± 5.1	-1.7 ± 4.5	0.782	-2.3 ± 4.5	-4.2 ± 5.1	0.176
SF12 - Mental composite	**50.8 ± 10.6**	**43.4 ± 10.3**		**44.3 ± 8.7**	**44.0 ± 7.3**	
Baseline - after treatment	3.9 ± 7.5	2.8 ± 6.9	0.601	-0.5 ± 3.0	0.2 ± 1.7	0.741
Baseline – 12-week follow-up	-2.4 ± 3.8	-1.5 ± 6.5	0.406	-0.7 ± 3.2	1.4 ± 3.9	0.373

NOTES: 1) for each HRQOL dimension: the first row (bold) shows the mean (M) and standard deviation (SD) of the domain score, the second row shows the difference from baseline to after treatment, and the third row shows the difference from baseline to 12-week follow-up; 2) Treatment frequency 3X3 – 3 treatments a week for 3 weeks, Treatment frequency 1x9 – 1 treatment a week for 9 weeks; 3) p – p-value of Mann-Whitney test for the comparison of the changes (baseline vs. after treatment and baseline vs. follow-up) between treatment frequency within Verum Acupuncture group and within Sham Acupuncture group.

Since no significant differences were found among the treatment frequency, subgroups A and B were combined to compare VA, SA and WL groups. Subsequently, a new statistical analysis was conducted, excluding the factor treatment frequency, as shown in Table 4 and Figure 2. These illustrate the effect of the group interventions at each time point in terms of the difference between baseline, after-treatment, and 12-week follow-up assessments of HRQOL dimensions.

No baseline differences between the groups ($p > 0.05$) were observed. As for the changes between baseline and after treatment, the scores of the KDQOL-SFTM subscales symptom/problem list, effects of kidney disease, cognitive function, sleep, overall health, PCS and MCS increased significantly in the VA group ($p < 0.05$), but not in the SA or in WL groups ($p > 0.05$). Significant differences between groups ($p < 0.05$) were found in all these HRQOL dimensions, except in the MCS ($p = 0.415$). The scores of burden of kidney disease and quality of social interaction did not change significantly in any of the groups ($p > 0.05$).

Regarding the changes from baseline to follow-up, there were no statistically significant differences between groups ($p > 0.05$). However, score of the sleep ($p = 0.026$) subscale decreased significantly in the VA group ($p < 0.01$) but not in SA or WL groups ($p > 0.05$); the symptom/problem list and effects of kidney disease scores did not change in the VA and WL groups ($p > 0.05$), but decreased in the SA group ($p < 0.05$); the PCS score did not change in the VA group ($p > 0.05$), but decreased in the SA and WL groups ($p > 0.05$); the overall health score did not change in the VA and SA groups ($p > 0.05$), but decreased in the WL group ($p < 0.05$). The burden of kidney disease, cognitive function and MCS scores did not change between the baseline and the follow-up in any of the groups ($p > 0.05$). The quality of social interaction score decreased significantly in the 3 groups ($p < 0.05$).

Table 4. Descriptive of HRQOL dimensions scores and comparison of the changes from baseline to after treatment and from baseline to 12-week follow-up between groups.

HRQOL domains/ KDQOL-SF™ 1.3 scores	Verum Acupuncture (VA) Group (n = 23)	Sham Acupuncture (SA) Group (n = 22)	Waiting-List (WL) Group (n = 22)	*P*
Primary Outcome				
Physical composite summary (PCS)	**37.0 ± 9.4**	**38.1 ± 11.1**	**38.2 ± 8.5**	0.953
Baseline - after treatment	3.34 ± 4.77 **	-1.02 ± 3.11 ^{A}	-2.27 ± 5.61 *^{A}	**<0.001**
Baseline - follow-up	-1.29 ± 4.72	-3.18 ± 4.73 *	-3.50 ± 5.03 *	0.283
Secondary Outcomes				
Kidney disease targeted areas				
Symptom/ problem list	**79.7 ± 13.1**	**85.2 ± 10.3**	**83.0 ± 8.8**	0.320
Baseline - after treatment	10.14 ± 6.83 **	0.09 ± 3.18 ^{A}	-1.04 ± 2.47 ^{A}	**<0.001**
Baseline – 12-week follow-up	-0.27 ± 3.99	-1.80 ± 2.67 *	-1.14 ± 3.20	0.409
Effects of kidney disease	**64.1 ± 17.6**	**74.7 ± 20.5**	**70.0 ± 19.4**	0.151
Baseline - after treatment	3.80 ± 3.88 **	-1.70 ± 4.80 ^{A}	-1.85 ± 2.67 *^{A}	**<0.001**
Baseline – 12-week follow-up	0.41 ± 4.83	-1.99 ± 2.47 *	-0.57 ± 1.57	0.244
Burden of kidney disease	**35.6 ± 16.5**	**34.7 ± 27.2**	**43.5 ± 23.9**	0.337
Baseline - after treatment	1.36 ± 4.97	0.57 ± 7.19	-3.69 ± 9.18	0.084
Baseline – 12-week follow-up	-2.17 ± 5.84	-0.57 ± 2.67	-4.26 ± 12.56	0.586
Cognitive function	**82.6 ± 16.7**	**90.0 ± 9.6**	**87.6 ± 12.6**	0.431
Baseline - after treatment	4.93 ± 7.58 **	-1.21 ± 4.88 ^{A}	-3.94 ± 8.40 *^{A}	**0.001**
Baseline – 12-week follow-up	-0.87 ± 3.05	-0.61 ± 1.96	-2.12 ± 8.82	0.944
Quality of social interaction	**81.4 ± 19.1**	**81.5 ± 13.3**	**80.3 ± 15.2**	0.789
Baseline - after treatment	1.74 ± 9.69	-1.82 ± 4.21	-2.42 ± 13.58	0.096
Baseline – 12-week follow-up	-10.72 ± 14.32 **	-6.97 ± 11.17 **	-5.76 ± 13.22 *	0.199
Sleep	**64.0 ± 20.4**	**62.6 ± 16.4**	**59.7 ± 16.4**	0.488
Baseline - after treatment	4.89 ± 12.69 *	-5.45 ± 9.69 *^{A}	-4.55 ± 13.84 *^{A}	**0.001**
Baseline – 12-week follow-up	-8.80 ± 9.62 **	-1.48 ± 13.06 ^{A}	-2.61 ± 13.53 ^{A}	**0.026**
Overall Health	**60.0 ± 14.8**	**54.1 ± 14.7**	**60.5 ± 17.0**	0.270
Baseline - after treatment	3.48 ± 8.32 *^{A}	-0.45 ± 8.99 ^{AB}	-3.18 ± 7.16 *^{B}	**0.048**
Baseline – 12-week follow-up	-0.87 ± 6.68	-1.36 ± 11.25	-5.45 ± 9.12 *	0.084
36-item health survey (SF-36) scale				
Mental composite summary (MCS)	**47.2 ± 10.9**	**44.1 ± 7.9**	**40.2 ± 6.5**	0.078
Baseline - after treatment	3.35 ± 5.06 *	-0.18 ± 2.49	0.61 ± 2.48	0.415
Baseline – 12-week follow-up	-1.98 ± 5.18	0.27 ± 3.64	-0.46 ± 2.40	0.228

NOTES: 1) for each HRQOL dimension: the first row (bold) shows the mean (M) and standard deviation (SD) of the domain score at the baseline, the second row shows the difference from baseline to after treatment, and the third row shows the difference from baseline to 12-week follow-up; 2) p – p-value of Kruskal-Wallis test for the comparison between groups; A,B groups with a superscript letter in common do not differ significantly: $p > 0.05$ in the multiple comparison tests with Bonferroni correction; 3) within group changes baseline vs. after treatment and baseline vs. 12-week follow-up were assessed by Wilcoxon signed-rank test: * $p < 0.05$ and ** $p < 0.01$.

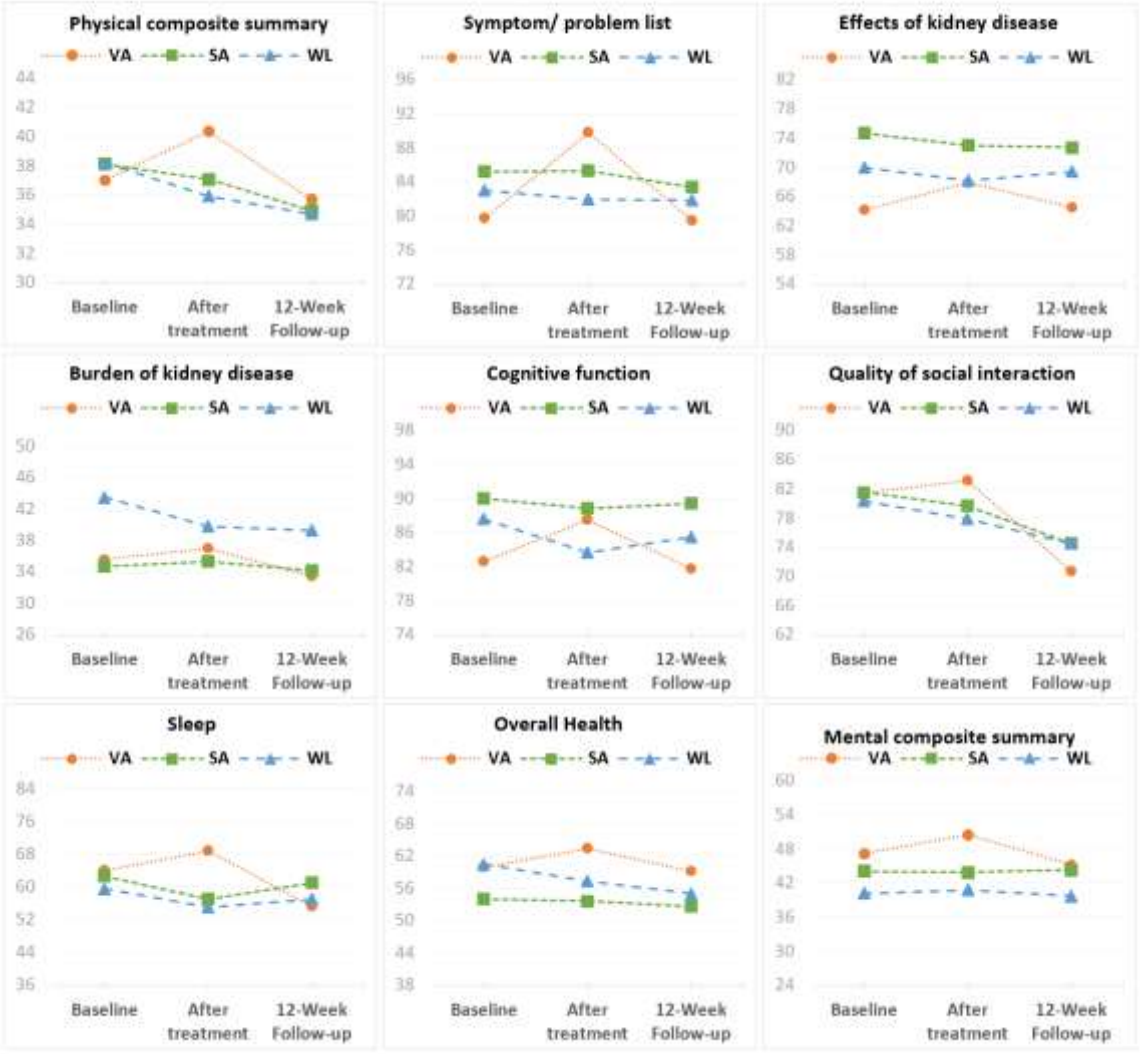

Figure 2. Mean HRQOL dimensions scores in the baseline, after treatment, and 12-week follow-up for Verum Acupuncture (VA), Sham Acupuncture (SA), and Waiting-List (WL) groups.

To assess the success of blinding, patients were asked which type of acupuncture treatment they believed they had received (VA or SA). Most patients answered that they did not know (70% in the VA group and 68% in the SA group), and 31% believed they had received verum acupuncture (30% in the VA group and 32% in the SA group) – none of the patients believed he/she had received sham acupuncture treatment. Blinding Index (0.84 – 95% CI: 0.78–0.91) shows that the participant blinding was successful [32].

The absence of any reported unfavorable incidents by patients, caregivers, or physicians suggests that applying acupuncture throughout the HD sessions was harmless.

4. Discussion

Advanced CKD leads to kidney failure and often requires KRT. HD is a demanding treatment that is time-consuming for patients and limits their professional, familiar and social activities. In addition, HD can cause both physical and emotional distress, which negatively impacts quality of life [6,43,44].

In this study, new data not described in the primary analysis of our previously conducted RCT [32], were analyzed to verify the effectiveness of acupuncture in the HRQOL improvement. For the assessment of the HRQOL dimensions, the KDQOL-SFTM 1.3 was chosen, since it is a validated instrument in CKD patients [40,41] and includes a generic core that has been widely used as a measure of quality of life.

In comparison with sham acupuncture or non-intervention, verum acupuncture improved the HRQOL after-treatment, as shown by the increase in KDQOL-SFTM 1.3, physical component summary (PCS) score, which included physical functioning, role functioning/physical, bodily pain, general health, vitality and social functioning. The after-treatment results are consistent with those obtained in our previous study [32], where acupuncture improved functional capacity and peripheral muscle strength in patients undergoing HD.

As regards the frequency of treatment, and in line with a prior study [32] in which no significant differences were observed indicating that three treatments per week do not seem to provide better results than one treatment per week on functional capacity and muscle strength in patients undergoing HD, the outcomes of the present study did also not depend on the acupuncture treatment frequency. Therefore, three acupuncture treatments per week did not seem to result in higher HRQOL compared to one treatment per week.

Some recent studies have explored the influence of acupuncture frequency on other clinical conditions, and the results are inconclusive and lack consistency. For instance, a study reported that three acupuncture sessions per week were more effective in treating knee osteoarthritis compared to 1 session per week, with improvements persisting for at least 16 weeks [45]. In addition, a pilot study for postprandial distress syndrome showed that three sessions per week tended to improve symptoms and quality of life more than once a week after four weeks of treatment [46]. Finally, another study has shown that acupuncture treatment for lumbar disc herniation was equally effective, whether administered once every day or every two days. Both were more effective than receiving treatment once every three days [47]. Regardless, based on the results of the present study, it cannot be concluded that a higher frequency of acupuncture treatments leads to more

significant therapeutic effects and further research with robust results is needed to confirm the findings of this study.

Besides the increased PCS score, verum acupuncture also increased the scores of some kidney disease targeted areas (symptom/problem list, effects of kidney disease, cognitive function and sleep), the overall health score and the mental component summary (MCS) score, which is indicative of improvement in HRQOL. Sleep and cognitive function are two key components for the HRQOL of kidney patients. Improved sleep quality may be reflected in a better mood and social interaction. On the other hand, cognitive decline is frequent in advanced kidney disease, removing the patient from reality and reducing his autonomy. Thus, the improvement of these two clinical parameters with acupuncture may contribute to the improvement of the patient's global condition.

Verum acupuncture did not improved the scores of burden of kidney disease and quality of social interaction. Although short-term improvement was observed, the long-term effects were not sustained in the VA group, as none of the HRQOL dimensions showed significant improvement three months after the intervention.

As for the specific effect of acupuncture compared to placebo (sham acupuncture), the results obtained are supported by earlier RCT´s in other medical conditions that have demonstrated the superiority of manual acupuncture over sham acupuncture and usual care in preventing episodic migraine without aura [48]. In addition, true acupuncture has been shown to be effective in reducing joint pain in postmenopausal women with early-stage breast cancer and aromatase inhibitor-related arthralgias, compared to sham acupuncture or waitlist control [49]. Moreover, acupuncture has been found to be more effective than sham acupuncture in increasing response rate and elimination rate of all 3 cardinal symptoms (postprandial fullness, upper abdominal bloating, and early satiation) in patients with postprandial distress syndrome [46].

As far as the authors know currently there is no RCT assessing the effectiveness of acupuncture in improving HRQOL in patients receiving maintenance HD. Bullen et al. (2018) conducted a pre-post test design to assess the impact of acupuncture and massage on health-related quality of life during HD, observing a tendency towards overall HRQOL improvement [30]; Rehman et al. (2021) conducted a study to investigate the effectiveness of zolpidem 10 mg and acupressure therapy on foot acupoints and verified an improvement in both sleep quality and overall quality of life among HD patients experiencing CKD-associated pruritus [50]; Yıldırım Keskin and Taşci (2021) showed that acupressure had a beneficial impact on patients receiving HD treatment by increasing the amount of saliva, reducing the severity of visual analog scale thirst, and positively affecting the HRQOL physical component sub-dimension [51]. Attending to the methodological limitations, the

use of other TCM practices rather than acupuncture and the heterogeneity of the instruments used to assess the quality of life, the results of this study cannot be compared.

Evidence from recent research showed the effect of acupuncture or electroacupuncture in HRQOL on different medical conditions. A systematic review and meta-analysis conducted by Hsieh et al. (2019) suggested that acupuncture therapy im-proves HRQOL in patients under medical treatment with chronic obstructive pulmonary disease [26]. Bao et al. (2021) assessed the impact of acupuncture on HRQOL outcomes in patients with solid tumors with chemotherapy-induced peripheral neuropathy, where statistically significant improvements in quality of life, anxiety, insomnia, and fatigue were achieved [52]. A pilot study conducted by Zhu et al. (2022), showed promising effects of electro-acupuncture in improving HRQOL, controlling symptom burden, and reducing toxicity during adjuvant chemotherapy in gastric cancer patients [27].

Low HRQOL scores in patients receiving maintenance HD have been associated with a higher risk of hospitalization and mortality [10,53-55], poorer mental health [56] and nutritional status [57], fatigue [58], chronic pain [59], depressive and anxiety symptoms [44,60,61].

The findings of this study are promising as acupuncture proved to be a safe practice, contributing positively to the PCS score and improved HRQOL in the studied clinical population. As the PCS score is associated with a more impaired functional status [62], an increase in this HRQOL parameter could mean an important contribution to the reduction of adverse outcomes or mortality related to the progression of CKD. The specific effect of acupuncture compared to sham acupuncture is reinforced by the results obtained in the previous RCT [32] in which increased functional capacity and peripheral muscle strength were also reported. Therefore, the results may also support clinicians considering the adoption of integrative and non-pharmacological practices for appropriate interventions in order to improve the HRQOL of patients undergoing HD.

Some limitations can be assigned to this study. In addition to those already widely discussed in the primary research [32], namely the sample size, the non-blinding of the TCM practitioner who provided the acupuncture treatment and the insufficient follow-up time to assess the long-term effect of acupuncture, this study relied only on the analysis of a patient-reported outcome measure for its primary outcome. Also, the assessment of other HRQOL-related variables of the clinical population under study could have been considered, such as sleep quality, anxiety and depression symptoms.

Based on the results presented here, future research is required to evaluate the efficacy of the acupuncture protocol employed in the study and confirm its clinical benefits in a larger sample of CKD patients receiving maintenance HD. It would be also interesting to compare this group with CKD patients on peritoneal dialysis over a longer follow-up

period. Further studies should address the effect of acupuncture on HRQOL, also considering the complete assessment of mental health status and sleep quality. In order to validate integrative approaches in the care provided to CKD G5 patients, researchers might consider incorporating an active control group into the design of a new study. For instance, the effect of acupuncture could be compared with another TCM practices, such as acupressure or auricular acupuncture.

5. Conclusions

The use of integrative medicine practices may be a promising approach to improve HRQOL in CKD G5 patients undergoing HD.

Compared to sham acupuncture or no-acupuncture groups, verum acupuncture increased PCS score, MCS score, overall health and specific kidney disease targeted areas (symptom/problem list, effects of kidney disease, cognitive function, sleep). These positive effects were observed in the short term but did not persist three months after treatment.

Although acupuncture treatment tends to improve overall HRQOL, further investigation will be needed to validate the results of this study.

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Chapter V Research Paper 4

Integrating Acupuncture into a Dialysis Center

Marta Correia de Carvalho [1], Pedro Azevedo [2], Carlos Pires [3], Jorge Pereira Machado [1,4], Manuel Laranjeira [1,5] and José Nunes de Azevedo [2]

[1] ICBAS–School of Medicine and Biomedical Sciences, University of Porto, 4050-313 Porto, Portugal.
[2] TECSAM-Tecnologia e Serviços Médicos SA, 5370-530 Mirandela, Portugal.
[3] Center for Research in Neuropsychology and Cognitive and Behavioral Intervention (CINEICC), Faculty of Psychology and Educational Sciences, University of Coimbra, 3000-115 Coimbra, Portugal.
[4] CBSin—Center of BioSciences in Integrative Health, 4000-105 Porto, Portugal.
[5] INC–Instituto de Neurociências, 4100-141 Porto, Portugal.

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Abstract: A growing interest in integrating Traditional Chinese Medicine (TCM) and Conventional Medicine (CM) to create a more comprehensive approach to healthcare has been verified. Scientific evidence supports acupuncture as an integrative treatment for specific health conditions. The aim of this study was to assess the acceptance and feasibility by patients and healthcare professionals of integrating acupuncture in a dialysis center. Individuals undergoing hemodialysis (HD) who participated in a patient-assessor-blinded randomized controlled trial that evaluated the effect of acupuncture on functional capacity and quality of life were included. Acceptance was measured by adherence (percentage of patients who completed treatments and dropouts) and patients' and healthcare professionals' opinions toward acupuncture (pre- and pro-intervention questionnaires). Feasibility was measured by safety (number of reported adverse) and effectiveness (changes in functional capacity, peripheral muscle strength, and health-related quality of life scores after treatment). Forty-eight patients were included, and forty-five (93.8%) were analyzed. No adverse events were reported. All patients completed the treatment, and only three patients (6.2%) were lost to the 12-week post-treatment follow-up. The attitudes of patients and health professionals were favorable to acupuncture, namely in relation to its use, degree of discomfort, recommendation to others, and interference with routine care and clinical setting. Integrating acupuncture into a dialysis center seems viable and well-accepted by patients with kidney failure on maintenance HD, doctors and nurses.

Keywords: integrative medicine; traditional Chinese medicine; acupuncture; hemodialysis; dialysis center; acceptance; feasibility.

1. Introduction

Traditional, complementary and integrative medicine has been rising in developing countries with well-established health system structures [1]. According to the World Health Organization (WHO), it encompasses various healthcare practices and therapies, such as Traditional Chinese Medicine (TCM), that fall outside the scope of conventional medical treatments [2]. The significant increase in the prevalence of traditional and complementary medicine (T&CM) use in the last two decades has led regulators to discuss issues related to safety, equity of access, and integration into health systems. As a result, through its first Traditional Medicine Strategy, the WHO has defined global policies with national and regional rules to promote the regulation of products, practices, and practitioner education and training to ensure the rational, safe, and effective use of T&CM [3].

While it is not yet widespread, a few countries have completely incorporated certain T&CM practices into their healthcare systems. For instance, in China, TCM and conventional medicine (CM) are administered together across all levels of healthcare, and both are covered by public and private insurance [2].

Also, research indicates an increasing interest in verifying the combined effect of both T&CM and CM. For example, recent systematic reviews and meta-analyses reported that combining TCM with Western medicine (WM) may be a helpful approach for improving both quality of life and clinical outcomes in breast cancer patients and reducing the incidence of adverse reactions, toxic side effects, traditional and tumor markers [4]; in patients with atopic dermatitis, the combined use of Chinese medicine and WM was found to be more effective than using only WM, enhancing clinical symptoms and quality of life and lowering the recurrence rate [5]. In addition, combining TCM and conventional WM was a viable therapeutic approach for enhancing the clinical symptoms of COVID-19 patients, with no increased adverse events [6].

In the context of Portugal, the designation adopted for these practices is Non-Conventional Therapies (NCT). Their regulation began in 2003 [7] and reached its recognition in 2019 [8] as one of the bases of the Portuguese health system. NTCs include: acupuncture, phytotherapy, homeopathy, traditional Chinese medicine (TCM), naturopathy, osteopathy, and chiropractic. This action towards regulation resulted, so far, in the attribution of 6311 professional licenses [9,10] which contributed to the client's safety when using the NCTs with the certainty that an accredited practitioner provided them. Of the NCTs described, only homeopathy has not been awarded professional certification and it is still in the process of regulation. It is worth mentioning that acupuncture and TCM have the highest number of certified professionals following osteopathy [10,11].

Although the Portuguese healthcare system is transitioning towards an integrative approach that incorporates both conventional medicine (CM) and T&CM, NCT is currently not accessible at hospitals and health centers of the National Health System. Its treatments are not covered by health insurance reimbursement [11].

Numerous studies have explored the practicality of incorporating acupuncture into healthcare facilities, and making it accessible to the clinical population, while benefiting jointly from the potential of T&CM and CM [12-15]. According to the conceptual framework proposed by Zhang et al. (2022), successfully integrating acupuncture in Western hospitals involves converting evidence into clinical practice primarily. Also, the attitudes of healthcare professionals play a pivotal role in the effective integration of any innovation into healthcare systems [16]. Their attitudes toward acupuncture can vary based on several factors, including their training, cultural background and personal experiences with the therapy. As such, some healthcare professionals may view it with skepticism, while others may be more open to its potential benefits; their attitudes toward acupuncture are complex and multifaceted and may be influenced by various factors [16-19].

Our prior studies evaluated the impacts of acupuncture on the functional capacity and quality of life of patients undergoing hemodialysis, pointing to the possibility of integrating this practice during HD sessions [20,21]. Given the promising results obtained and the limited number of national studies in this field, this paper aims to assess the opinions and perceptions of patients and health professionals regarding the acceptance of incorporating acupuncture as an integrative approach in the context of a Portuguese health services and conventional medicine.

2. Methods

2.1 Study design and participant criteria

This exploratory study aims to assess patients' and healthcare professionals' knowledge, perceptions and opinions about the integration of acupuncture as a complementary therapy for chronic kidney disease (CKD) patients undergoing HD.

Eligible participants were individuals with renal failure on weekly hemodialysis treatment for more than three months, male and female, older than eighteen, with a medically stable state, who had participated in a prior patient-assessor randomized trial and had received acupuncture treatment. Individuals with comorbidities such as hypertension and poorly controlled coronary heart disease, angina pectoris, unstable diabetes mellitus control, mental illness, cognitive limitation, or impairment were excluded. In addition, all participants who refused to participate or demonstrated an inability to cooperate with the study procedures were excluded.

Concerning the inclusion criterion, “having received acupuncture treatment”, eligible participants were randomly allocated into the verum and sham acupuncture groups with an allocation ratio of 1:1 through a simple randomization process carried out by an independent researcher, using Microsoft® Excel® for Microsoft 365 MSO to generate randomization series. The participants, outcome assessor, and statistician were blinded to the group allocation, except the TCM practitioner. The acupuncture intervention followed a standardized and reproducible protocol designed by the research team, including a comprehensive procedure description according to the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) 2010 Checklist [22,23]. Briefly, the verum acupuncture (VA) group underwent a total of 9 manual acupuncture sessions, using acupoints Taixi (KI3), bilateral, Sanyinjiao (SP6), bilateral, Zusanli (ST36), bilateral, Shenmen (HT7), unilateral in the arm without arteriovenous fistula, and Guan Yuan (CV4), unilateral with manual stimulation. On the other hand, sham acupuncture (SA) received superficial needling (5mm depth) at non-acupuncture points with no stimulation. Both groups received 25-minute needle retention time, and sterilized stainless steel needles (0.25x25mm) were used [22].

Healthcare professionals considered eligible for the study were physicians and nurses working at the dialysis center, providing medical and nursing care related to HD sessions during the administration of acupuncture treatments (from August 2021 to February 2022) , and consented to participate. Conversely, those healthcare professionals not present during the acupuncture treatment sessions were excluded from the study. After screening for eligibility, written informed consent was obtained from each participant who agreed to participate.

2.2 Data collection

Acceptance was measured by adherence: first, in terms of the percentage of subjects who completed nine acupuncture sessions and dropped out from the initial assessment to the follow-up assessment, and second by patients' and health professionals' views of acupuncture. For this purpose, pre-and post-intervention questionnaires were administered to patients and to health care professionals.

In order to protect the privacy and confidentiality of study participants, a code was assigned to each questionnaire to ensure data anonymization. Throughout the HD session, patients maintained a supine position with restricted use of the upper limbs, specifically the arm with the arteriovenous fistula. Due to this fact, the questionnaires were administered by an independent researcher who had received previous appropriate training.

The pre-intervention questionnaire (Supplementary materials) was applied at the baseline and before acupuncture treatment. It included questions about patients' knowledge of acupuncture, whether they had ever been treated with acupuncture and for what purpose, and whether they would be willing to receive it. After nine acupuncture treatments, the patients answered the post-intervention questionnaire (Supplementary materials), which contained questions about the discomfort felt when the acupuncture needle was punctured, the discomfort felt during the acupuncture treatment, whether they would recommend it to others, and whether the acupuncture interfered with their HD treatment routine.

A self-administered paper-and-pen format was applied to the doctors and nurses (Supplementary materials) after the patients completed nine acupuncture treatments, i.e., in the after-treatment time point. It consisted of generic questions about age, gender, profession, and education level. The other questions concerned their knowledge, use, and general opinion about acupuncture and its clinical effectiveness and applicability. They were also asked whether they had ever suggested acupuncture to their patients, whether the treatments provided during the hemodialysis session interfered with their care delivery and clinical routine, whether adverse events of acupuncture were observed, and their opinion about the possibility of integrating acupuncture into the dialysis center. In addition to closed questions ("Yes" or "No"), the other questions could be rated according to the Likert 5-point scale. The options were "very positive", "positive", "neither positive nor negative", "negative", and "very negative".

Concerning the development of the questionnaire items, clear and concise questions were drawn up to collect the participants' opinions regarding their knowledge, use, general opinion and recommendation of acupuncture, using simple and appropriate language for the target population. Prior to administering the questionnaires to patients and healthcare professionals, an independent investigator conducted a trial on a small group of patients and healthcare professionals who were unavailable to participate in the study but who met all other inclusion criteria in order to identify problems related to the formulation and understanding of the questions. In this essay, all questions were validated and considered well formulated.

The feasibility of acupuncture was evaluated by measuring its safety and effectiveness.

The number of adverse events reported by patients and healthcare professionals was recorded to assess safety. Patients and healthcare professionals were informed of potential adverse events associated with acupuncture before treatment. As acupuncture was administered during the HD session, healthcare professionals were instructed to promptly observe and report any incidents. To facilitate this, a checklist (Appendix A, Figure A1) was made available in the dialysis room for reference during acupuncture treatments.

The effectiveness of acupuncture was assessed by analyzing the results obtained by the changes between baseline and post-treatment of acupuncture's effect on FC and HRQOL.

2.3 Statistical analysis

Patients' sociodemographic and clinical characteristics, and the answers to the questionnaire were described, by group, through frequencies (n and %). Minimum, maximum, mean, and standard deviation were used for age. Fishers' Exact Test and the two sample t-test were used for group comparisons. Normality of data was assessed and validated with Shapiro-Wilk test. The same descriptive measures were used for healthcare professionals' sociodemographic characteristics and their answers to the questionnaire.

A significance level of 5% was considered for the statistical tests. Statistical analysis was performed with IBM SPSS Statistics software - version 27.0 [24].

3. Results

A total of forty-five patients were included, aged between 57 and 91, with a mean age of 71.9 (SD=6.8). Most were men (62.2%), lived in rural areas (62.2%), with low education levels (≤6 years of schooling) (93.3%), and retired (86.7%). In terms of clinical features, diabetes mellitus (44.4%) was the leading causes for CKD; most underwent HD between 10 and 120 months (86.7%), with arteriovenous fistula (88.9%) being the most common method of vascular access, as shown in Table 1. The group of patients who received verum and sham acupuncture did not differ significantly (p>0.05) regarding sociodemographic or clinical characteristics.

Table 1. Patients' sociodemographic and clinical characteristics.

		VA Group (n = 23)	**SA Group (n = 22)**	**Total (N = 45)**	***p-value***
Sociodemographic					
Age	Minimum–Maximum	60–84	57–91	57–91	*0.496* [2]
	Mean (SD)	71.2 (5.1)	72.6 (8.3)	71.9 (6.8)	
		n (%)	n (%)	n (%)	
Gender	Female	9 (39.1)	8 (36.4)	17 (37.8)	*1.000* [1]
	Male	14 (60.9)	14 (63.6)	28 (62.2)	
Residence	Urban	9 (39.1)	8 (36.4)	17 (37.8)	*1.000* [1]
	Rural	14 (60.9)	14 (63.6)	28 (62.2)	
Education level	No literacy	0 (0.0)	2 (9.1)	2 (4.4)	*1.000* [1]
	1° Cycle (4 years)	20 (87.0)	17 (77.3)	37 (82.2)	
	2° Cycle (6 years)	2 (8.7)	1 (4.5)	3 (6.7)	
	High school (12 years)	1 (4.3)	2 (9.1)	3 (6.7)	
Professional status	Employed	0 (0.0)	2 (9.1)	2 (4.4)	*0.782* [1]

	Self-employed	2 (8.7)	0 (0.0)	2 (4.4)	
	Unemployed	1 (4.3)	1 (4.5)	2 (4.4)	
	Retired	20 (87.0)	19 (86.4)	39 (86.7)	
Clinical		n (%)	n (%)	n (%)	
CKD causes	Diabetes mellitus	10 (43.5)	10 (45.5)	20 (44.4)	*0.202* (1)
	Chronic rejection	1 (4.3)	4 (18.2)	5 (11.1)	
	Hypertensive nephropathy	3 (13.0)	0 (0.0)	3 (6.7)	
	High blood pressure	0 (0.0)	1 (4.5)	1 (2.2)	
	Glomerulonephritis	1 (4.3)	0 (0.0)	1 (2.2)	
	Interstitial tubular necrosis	0 (0.0)	2 (9.1)	2 (4.4)	
	Other	3 (13.0)	1 (4.5)	4 (8.9)	
	Unknown	5 (21.7)	4 (18.2)	9 (20.0)	
Hemodialysis time	< 12 months	2 (8.7)	0 (0.0)	2 (4.4)	*0.544* (1)
	12 to 120 months	19 (82.6)	20 (90.9)	39 (86.7)	
	> 120 months	2 (8.7)	2 (9.1)	4 (8.9)	
Vascular access	Arteriovenous fistula	22 (95.7)	18 (81.8)	40 (88.9)	*0.187* (1)
	Central venous catheter	1 (4.3)	4 (18.2)	5 (11.1)	

VA=Verum Acupuncture; SA=Sham Acupuncture; (1) significance value of Fisher's Exact Test; (2) significance value of two sample t-test

Regarding the sociodemographic profile of the participating health professionals (Table 2), 41.7% were female and 58.3% were male, with an average age of 51.2 (SD=13.7). The majority held a bachelor's degree (83.3%), with 41.7% being doctors and 58.3% being nurses. Among the doctors, 3 (60.0%) were specialists in General Practice/Family Medicine and 2 (40.0%) in Nephrology. The 3 nurses who were specialists were in the areas of medical-surgical, rehabilitation and public health.

Table 2. Healthcare professionals' sociodemographic characteristics (N=12).

		n (%)
Gender	Female	5 (41.7)
	Male	7 (58.3)
Age	Minimum–Maximum	23–73
	Mean (SD)	51.2 (13.7)
Education level	Bachelor's Degree	10 (83.3)
	Master's Degree	2 (16.7)
Profession	Doctor	5 (41.7)
	Nurse	7 (58.3)
Medical specialty	General Practice/Family Medicine	3 (60.0)
(Doctors: N=5)	Nephrology	2 (40.0)
Nursing specialty	Medical-surgical	1 (14.3)
	Rehabilitation	1 (14.3)
	Public health	1 (14.3)
(Nurses: N=7)	None	4 (57.1)

3.1. Acceptance

3.1.1. Adherence

All participants completed acupuncture treatment throughout the study period, indicating a 100% adherence rate. However, three dropouts occurred between the post-treatment and follow-up assessment due to kidney transplantation, hospitalization and death, resulting in a 6.6% dropout rate (Table 3).

Table 3. Number of participants at each evaluation time point.

	VA Group (n)	**SA Group (n)**	**Total (n/%)**	***p-value*** *(1)*
Baseline assessment	24	24	48 (100)	
Treatment	24	24	48 (100)	
Post-treatment assessment	24	24	48 (100)	
12-week follow-up assessment	23	22	45 (93.4)	
Lost in follow-up/Dropout	1	2	3 (6.6)	
Reason	Kidney transplantation	Hospitalization, death		
Analyzed - n (%)	23 (95.8%)	22 (91.7%)	45 (93.4%)	*1.000*

VA=Verum Acupuncture; SA=Sham Acupuncture; (1) significance value of Fisher's Exact Test.

3.1.2. Patients' and healthcare professionals' attitudes toward acupuncture

From the pre-intervention questionnaire data (Table 4), out of the 45 participants, more than half (55.6%) had no knowledge about acupuncture. Concerning acupuncture use, only one participant (2.2%) had had acupuncture treatment for osteoarticular pain more than three months before. However, all were receptive to receiving acupuncture treatment (100%). No statistically significant differences were found between the groups (p>0.05).

Table 4. Pre-intervention patient' questionnaire.

		VA Group (n = 23)	**SA Group (n = 22)**	**Total (N = 45)**	***p-value*** *(1)*
		n (%)	n (%)	n (%)	
Do you know what Acupuncture is?	No	11 (47.8)	14 (63.6)	25 (55.6)	*0.373*
	Yes	12 (52.2)	8 (36.4)	20 (44.4)	
Have you received any Acupuncture treatment before your participation in this study?	No	23 (100.0)	21 (95.5)	44 (97.8)	*0.489*
	Yes	0 (0.0)	1 (4.5)	1 (2.2)	
If so, how long ago has it been?			> 3 months		-
And for what purpose?			Osteoarticular pain		-

Are you willing to receive an Acupuncture treatment?	No	0 (0.0)	0 (0.0)	0 (0.0)	-
	Yes	23 (100.0)	22 (100.0)	45 (100.0)	

VA=Verum Acupuncture; SA=Sham Acupuncture; (1) significance value of Fisher's Exact Test.

From the post-intervention questionnaire data analysis (Table 5), regarding the degree of discomfort felt when puncturing the acupuncture needle, 31.1% answered "uncomfortable," 48.9% "neither comfortable nor uncomfortable," and 20% "comfortable." Regarding the degree of discomfort felt during acupuncture treatment, 17.8% answered "neither comfortable nor uncomfortable," 35.6% answered "comfortable," and 46.7% "very comfortable." Furthermore, the majority (91.1%) would recommend acupuncture treatment to others. All participants considered that acupuncture treatments did not interfere with the hemodialysis routine. There were no statistically significant differences between the groups ($p>0.05$).

Table 5. Post-intervention patient' questionnaire.

		VA Group (n = 23)	**SA Group (n = 22)**	**Total (N = 45)**	***p-value*** *(1)*
		n (%)	n (%)	n (%)	
Degree of discomfort felt when puncturing the acupuncture needle.	Totally uncomfortable	-	-	-	*0.858*
	Uncomfortable	8 (34.8)	6 (27.3)	14 (31.1)	
	Neither comfortable, nor uncomfortable	11 (47.8)	11 (50.0)	22 (48.9)	
	Comfortable	4 (17.4)	5 (22.7)	9 (20.0)	
	Totally comfortable	-	-	-	
Degree of discomfort during acupuncture treatment.	Totally uncomfortable	-	-	-	*0.488*
	Uncomfortable	-	-	-	
	Neither comfortable, nor uncomfortable	3 (13.0)	5 (22.7)	8 (17.8)	
	Comfortable	10 (43.5)	6 (27.3)	16 (35.6)	
	Totally comfortable	10 (43.5)	11 (50.0)	21 (46.7)	
Would you recommend acupuncture treatment to others?	No	2 (8.7)	2 (9.1)	4 (8.9)	*1.000*
	Yes	21 (91.3)	20 (90.9)	41 (91.1)	
In your opinion, did the Acupuncture treatments interfere with your hemodialysis routine?	No	23 (100.0)	22 (100.0)	45 (100.0)	-
	Yes	-	-	-	

VA=Verum Acupuncture; SA=Sham Acupuncture; (1) significance value of Fisher's Exact Test.

Regarding the results from health professionals' questionnaire (Table 6), all participants were aware of what acupuncture entailed. Furthermore, 33.3% of the respondents had received acupuncture treatment for osteoarticular pain and/or muscle pain

more than three months. In addition, all the health professionals would recommend acupuncture treatment to others, and 91.7% expressed openness to receiving acupuncture treatment themselves.

In terms of general opinion about acupuncture, 16.7% answered "neither negative nor positive," 66.7% answered "positive," and 16.7% "very positive." As for acupuncture's efficacy and clinical applicability, 8.3% evidenced a neutral stance opinion, while 75% evidenced "positive" and 16.7% "very positive." All considered that the acupuncture treatments provided to patients did not interfere with routine hemodialysis.

Only 8.3% of the respondents expressed a neutral stance about integrating acupuncture in patient care during hemodialysis, while the rest held “positive” (33.3%) or “very positive” (58.3%) opinions.

Table 6. Healthcare professionals' questionnaire (N=12).

		n (%)
Do you know what Acupuncture is?	No	-
	Yes	12 (100.0)
Have you ever received any acupuncture treatment?	No	8 (66.7)
	Yes	4 (33.3)
If so, how long ago has it been?	> 3 months	4 (100.0)
And for what purpose?	Osteoarticular pain	2 (50.0)
	Muscle pain	3 (75.0)
Would you recommend acupuncture treatment to others?	No	-
	Yes	12 (100.0)
Would you be receptive to receiving acupuncture treatment?	No	1 (8.3)
	Yes	11 (91.7)
What is your general opinion on Acupuncture?	Very negative	-
	Negative	-
	Neither negative nor positive	2 (16.7)
	Positive	8 (66.7)
	Very positive	2 (16.7)
What is your opinion on the efficacy and clinical applicability of Acupuncture?	Very negative	-
	Negative	-
	Neither negative nor positive	1 (8.3)
	Positive	9 (75.0)
	Very positive	2 (16.7)
Have you ever suggested acupuncture to a patient?	No	4 (33.3)
	Yes	8 (66.7)
In your opinion, did the acupuncture treatments provided to patients interfere with the hemodialysis routine?	No	12 (100.0)
	Yes	-
What is your opinion on the integration of acupuncture into the care of patients on hemodialysis?	Very negative	-
	Negative	-
	Neither negative nor positive	1 (8.3)
	Positive	4 (33.3)
	Very positive	7 (58.3)

3.2. Feasibility

3.2.1. Safety

Throughout the trial period, patients or health professionals observed or reported no acupuncture-related adverse events, suggesting the safety of using acupuncture during hemodialysis sessions.

3.2.2. Effectiveness

The effectiveness of acupuncture was assessed by scrutinizing the overall results described in a previous RCT [20,21]. The group that received verum acupuncture (VA) demonstrated better results, compared to the group that received sham (SA) acupuncture and a control group. Specifically, they walked a greater distance, exhibited increased peripheral muscle strength in their lower limbs and handgrip strength. Additionally, they achieved higher scores in health-related quality of life (HRQOL), as evidenced by an increase in KDQOL-SFTM 1.3 Physical component summary (PCS) score, which includes physical functioning, role functioning/physical, bodily pain, general health, vitality, and social functioning, as well as in Mental component summary (MCS) score, overall health and specific areas targeted by kidney disease (symptom/problem list, effects of kidney disease, cognitive function, sleep).

The participant blinding was assessed by asking patients which type of acupuncture treatment they believed they received. Most patients in the VA and SA groups were uncertain about their treatment allocation. However, 31% of patients believed they received verum acupuncture, with similar percentages in both groups. None of the patients believed they received sham acupuncture. The calculated Blinding Index (0.84 – 95% CI: 0.78–0.91) indicated successful participant blinding.

4. Discussion

Integrating traditional and complementary medicine, such as acupuncture, into public or private conventional healthcare services is contingent on multiple considerations. In this regard, we assessed its acceptance and feasibility to determine the possibility of incorporating acupuncture as an adjuvant and complementary therapy in a dialysis center.

The adherence indicators and the patient and health professional opinion questionnaire were used to check acceptance. A complete adherence rate was found from baseline to post-treatment evaluation, constituting an important indicator of commitment to acupuncture treatment.

The literature review reports a low frequency of traditional and complementary medicines for individuals in maintenance HD [25]. The same was found in our sample of patients, where only one had performed acupuncture treatment for osteoarticular pain before they participated in this study.

Regarding the patient's experience of receiving acupuncture, although some discomfort has been reported when puncturing the acupuncture needle, this did not occur during treatment. Acupuncture was well accepted by the patients, as evidenced by their high level of recommendation for the treatment to others and the fact that it did not disrupt their hemodialysis routine.

The optimal implementation of innovative health and centered-patient care strategies relies not only on patients' knowledge and beliefs but also the attitudes of healthcare professionals [16]. The healthcare professionals' survey outcomes indicated that doctors and nurses from TECSAM's dialysis center revealed knowledge about acupuncture, and the majority expressed their willingness to receive acupuncture treatment. However, while a few held a neutral general opinion of acupuncture and its efficacy and clinical applicability, most had an optimistic perspective. Doctors and nurses were also unanimous in that acupuncture treatments did not interfere with the dialysis routine. Most of them held a favorable opinion regarding including acupuncture as a part of regular care for patients undergoing hemodialysis. It appears that the level of knowledge of health professionals on the subject may have influenced the results obtained, considering that the dialysis center where the study was conducted is known to adopt an integrative approach in the care of patients undergoing HD. In addition, health professionals' direct observation of acupuncture treatments during HD may have contributed to this fact. Finally, the authors highlight the importance of providing information and training to health professionals on the scientific evidence of the application of acupuncture in clinical practice to broaden the acceptance of these complementary therapeutic approaches.

Unfortunately, given the lack and heterogeneity of studies evaluating health professionals' attitudes toward acupuncture and other T&CM practices, it was not possible to obtain comparative results. Despite this limitations, some studies have reported similar results. The study conducted by Zhang et al. (2022) found that doctors and nurses held positive viewpoints on acupuncture and acupressure use in perioperative care [26]; Shao

et al. (2005) reported broadly positive attitudes of general practitioners and hospital doctors toward traditional acupuncture [18]; Lipman et al. (2003) study findings, suggested that the majority of general practitioners were supportive of making acupuncture readily accessible within the National Health Service (NHS) [19]. Recent reviews have also shown positive attitudes toward acupuncture among healthcare professionals [27].

Concerning the feasibility, assessed in terms of safety and efficacy, no adverse effects acupuncture-related were reported or recorded. Furthermore, its effectiveness in improving FC and HRQOL has been verified [20,21].Despite the limited number of randomized clinical trials examining the safety and efficacy of acupuncture in CKD patients receiving maintenance HD, these parameters have been extensively investigated and established across diverse medical conditions [28-34]. Nevertheless, the results of a recent review and meta-analysis indicate that acupuncture may be a safe and effective therapeutic alternative for uremic pruritus in patients undergoing HD. Additionally, the combination of acupuncture and HD effectively alleviated uremic pruritus symptoms compared to HD alone [35]. In line with what these studies point out, the results of the present study indicate that acupuncture is safe and effective for patients receiving maintenance HD.

As the limitation of the study, it is worth noting the small sample size of healthcare professionals and the fact that only the questionnaire's content and construct validity assessment was conducted without a pilot study to evaluate its validity and reliability.

Based on the findings obtained from this study, acupuncture should be considered and incorporated as an integrative approach in CM health services. In addition to the patient's and healthcare professionals' acceptance, it is also essential to carefully consider the views of healthcare management and administrative boards and the acceptance of other stakeholders.

Future larger RCTs to validate the safety and effectiveness of acupuncture on patients undergoing HD are required. Also, further research should involve cost-benefit analyses, comparing outcomes and acupuncture treatment costs with other conventional therapies (e.g., physiotherapy) on patient functional capacity. Finally, it will be necessary to create a conceptual framework to address logistical issues associated with integrating acupuncture into conventional care and verify its clinical applicability to other populations or settings.

5. Conclusions

In conclusion, the acceptance and feasibility assessment outcomes of integrating acupuncture into a dialysis center suggest that it may be a viable and very useful complementary treatment option in managing chronic kidney disease symptoms burden and quality of life of patients receiving maintenance HD. Extended future research is required.

Appendix A

Acupuncture-related adverse events checklist (*)

Participant ID [ ]

	Date of occurrence								
Acupuncture-related adverse events	/ /	/ /	/ /	/ /	/ /	/ /	/ /	/ /	/ /
Fainting									
Excessive pain during needling									
Stuck needle									
Bent needle									
Broken needle									
Pneumothorax									
Nerve injury									
Vascular injury									
Organ injury									

Obs.: In the same participant, adverse events are counted by type rather than frequency. If an adverse event happens multiple times within a single participant, it is still considered as one adverse event.
(*) Based on WHO benchmarks for the practice of acupuncture. Geneva: World Health Organization; 2020. License: CC BY-NC-SA 3.0 IGO.

Reported by:_____

Figure A1. Acupuncture-related adverse events checklist

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Chapter VI General Discussion

1. Discussion

In this chapter, the General Discussion of this Thesis, we intend to systematize, integrate and analyze the main results of the three empirical studies presented above. This articulated set of research sought to respond to the initial general and specific objectives.

Specifically, it was intended to determine whether acupuncture positively impacts the patient's functional capacity (FC) and health-related quality of life (HRQOL). Additionally, we sought to verify the difference in the acupuncture frequency treatment and compare the specific effects of acupuncture with a placebo. Finally, we were interested in investigating whether the beneficial effects of acupuncture are sustained over the long term and if it is possible to integrate acupuncture into the hemodialysis (HD) care routine.

The discussion of the results is structured according to the variables evaluated, congruent with the sequence in which the studies were presented.

A parallel patient-assessor blinded RCT was conducted to assess the impact of acupuncture on FC **(Research Paper 2)** [1] and HRQOL **(Research Paper 3)** [2] in chronic kidney disease with GFR category 5 (CKD G5) patients receiving maintenance HD. The results demonstrated that nine manual acupuncture sessions resulted in improved FC, increased peripheral muscle strength, and overall HRQOL in the experimental group (verum acupuncture) compared to the placebo (sham acupuncture) and control (waiting-list) groups.

Regarding the specific effect of acupuncture compared with placebo (sham acupuncture), after treatment verum acupuncture (VA) group was found to increase walked distance. Conversely, the sham acupuncture (SA) or no-acupuncture treatment (WL) group did not enhance walked distance after treatment. Identical results were observed for muscle strength, where verum acupuncture led to increased muscle strength and a decline in muscle strength was observed from baseline to post-treatment in the SA and WL groups. VA treatment also improved handgrip strength immediately after treatment, and no improvement in handgrip strength was observed in either the SA or WL group.

Increasing FC in HD patients is a favorable outcome since it can significantly improve the quality of life of these patients. HD is a demanding treatment that requires considerable energy and can leave patients feeling fatigued and debilitated. Augmenting FC implies that patients can perform their daily activities more easily, achieve greater independence, and reduce reliance on caregivers or family members.

In addition, improved FC can lead to greater participation in social and physical activities, thus improving the patient's overall mental and physical health.

In individuals with kidney failure undergoing hemodialysis (HD), the distance walked during the 6-minute walk test (6MWT) is considered a predictor of mortality independent of other factors. The reported survival rate of HD patients increased by approximately 5% for every hundred meters walked during the 6MWT [3]. Furthermore, handgrip strength predicts all-cause mortality in both men and women undergoing maintenance HD [4-6]. Hence, improving FC parameters contributes to patient survival and decreased mortality risk. Coupled with better overall health, improved FC can assist in preventing medical complications, improve patient response, and increase treatment compliance, resulting in more profitable health outcomes. In addition, it may allow patients to engage in regular physical activity, which can help maintain muscle mass, reduce inflammation, and improve cardiovascular function. Furthermore, since a substantial percentage of hemodialysis patients are elderly and require assistance in walking, improved handgrip strength may provide a more robust support system for their ambulation.

In light of the findings from our research, it may be proposed that the observed enhancements in functional capacity and muscle strength were attributable to the impact of acupuncture needle stimulation on augmented blood flow, cytokine levels, and growth factor expression. These effects may, in turn, have engendered modifications to the connective tissue milieu, leading to the modulation of sensory input afferents [7,8].

The post-treatment HRQOL outcomes indicate a significant improvement in the VA group compared to SA or WL group **(Research Paper 3)**, as evidenced by the increase in the physical component summary (PCS) score of KDQOL-SF™ 1.3, which encompasses physical functioning, role functioning/physical, bodily pain, general health, vitality, and social functioning. Furthermore, verum acupuncture improved scores in several kidney disease-specific domains, including symptom/problem list, effects of kidney disease, cognitive function, and sleep. The overall health score and mental component summary (MCS) score were also increased, suggesting an improvement in HRQOL. These post-treatment outcomes are consistent with the functional results described above.

In patients undergoing maintenance HD, low scores on HRQOL assessments have been linked to a heightened risk of hospitalization and mortality [9-12], as well as a range of adverse health outcomes, including poorer mental health [13] and nutritional status [14], fatigue [15], chronic pain [16], and depressive and anxiety symptoms [17-19].

The enhancement of both physical and mental well-being among patients, as evidenced by a concomitant improvement in their HRQOL, has the potential to mitigate the psychological distress and burden associated with symptoms related to HD treatment. Furthermore, enhanced sleep quality and cognitive function are essential to HRQOL in individuals receiving maintenance. On the other hand, cognitive decline is a typical manifestation of advanced kidney disease, and patients may experience a decrease in autonomy. Hence, the improvement of these two clinical parameters through acupuncture may have a positive impact on the patient's overall well-being.

Verum acupuncture did not improve the burden of kidney disease and the quality of social interaction scores. These outcomes may be attributed to the multifaceted nature of social interaction and symptom burden in chronic kidney disease, which can be influenced by a diverse range of factors, including the adequacy of social support and the subjective experience of the disease.

Regarding the specific results of acupuncture versus placebo, no similar study was found that could be compared with ours. However, within different medical conditions previous RCTs in other medical conditions have demonstrated the superiority of manual acupuncture over sham acupuncture and usual care in preventing episodic migraine without aura [20]. In addition, verum acupuncture has demonstrated efficacy in decreasing joint pain among postmenopausal women with early-stage breast cancer and aromatase inhibitor-related arthralgias compared to sham acupuncture or waitlist control [21]. Furthermore, in individuals with postprandial distress syndrome, acupuncture has exhibited greater effectiveness than sham acupuncture in improving the response rate and elimination rate of all three cardinal symptoms, namely postprandial fullness, upper abdominal bloating, and early satiation [22]. Although the comparison is not possible due to methodological discrepancies, it is possible to state that our results follow the same tendency as the prior RCTs.

As for the evaluation of short-term (after-treatment) and long-term (12-week follow-up) results shows VA group maintained the increased walking distance beyond the 12-week follow-up period **(Research Paper 2)**. In contrast, the SA group and WL show a decreased tendency from baseline to the 12-week follow-up period.

The VA group improvement observed in muscle strength did not persist beyond the 12-week follow-up period. Furthermore, the declining trend in muscle strength was observed from after-treatment to the 12-week follow-up period in the SA and WL groups.

Regarding the handgrip strength, during the 12-week follow-up period, the VA group showed no significant differences compared to post-treatment measurements, so the effect did not last over time. Also, no improvement in handgrip strength was observed in either the SA or WL group at any of the evaluation time points.

The sustained effects of acupuncture treatment may confer an advantage to patients by enabling them to maintain greater functional capacity over time.

In addition, although the short-term improvement was observed, none of the HRQOL **(Research Paper 3)** dimensions showed significant improvement three months after the intervention in the VA group.

Few clinical trials compare the effectiveness of short-term intensive interventions over time to less frequent and prolonged interventions. Despite the widespread discussion on determining the appropriate acupuncture dosage, the role of acupuncture frequency in achieving optimal treatment outcomes remains to be determined. There is no agreement on the standard criteria for determining the optimal acupuncture treatment frequency.

The outcomes were independent of the frequency of acupuncture treatment, as no significant differences were observed. These results suggest that a treatment frequency of three times per week does not confer any superior benefits over a frequency of once per week in improving functional capacity and muscle strength in patients undergoing hemodialysis.

Concerning the frequency of treatment assessed, the outcomes were independent of the acupuncture treatment frequency, as no significant differences were observed in our study. Furthermore, three treatments per week did not seem to provide better results than one treatment per week on functional capacity and peripheral muscle strength **(Research Paper 2)** in patients undergoing HD. Therefore, HRQOL outcomes were also not dependent on the frequency of acupuncture treatment since three times a week acupuncture treatment did not appear to result in a better HRQL than once a week **(Research paper 3)**.

In the clinical population under study, no RCT was found assessing the impact of acupuncture treatment frequency on FC or HRQOL. Current investigations have examined the impact of acupuncture frequency on various clinical conditions, but the findings were unclear and not very conclusive. For instance, three acupuncture sessions per week was superior in treating knee osteoarthritis than one session per week, with beneficial effects persisting for a minimum of 16 weeks [23]. Likewise, a pilot investigation targeting postprandial distress syndrome indicated that receiving three weekly acupuncture sessions led to more significant improvement in symptoms and quality of life than once-weekly sessions after four weeks of treatment [22]. Conversely, data from study on lumbar disc

herniation revealed that daily and alternate-day acupuncture treatments were equally effective but more beneficial than every three days [24].

Incorporating traditional and complementary medicine practices, such as acupuncture, into a private conventional medicine healthcare service requires careful consideration of multiple factors. Hence, we assessed its acceptance and feasibility to evaluate the potential integration of acupuncture as an integrative and complementary therapy within a HD center **(Research paper 4)**.

First, we highlighted the level of complete adherence to acupuncture treatment since all participants completed all treatments scheduled during the study period. Although no statistically significant differences were observed in the socio-demographic and clinical characteristics of the sample, since most participants were elderly, from rural areas, and with a limited level of education could have been a barrier to treatment adherence. Secondly, more than half of the patients did not know about acupuncture, and only one patient had undergone acupuncture treatment for osteoarticular pain before participating in the RCT. These are consistent with the findings from Bahall (2017) reporting the infrequent utilization of traditional and complementary medicine among CKD patients receiving HD [25].

Concerning the patient's experience of receiving acupuncture, it is worth noting that no discomfort was reported during the treatment, despite some discomfort commonly reported when puncturing the acupuncture needle. In addition, patients were receptive to the acupuncture treatment, as indicated by its high level of recommendation to others, and it did not interfere with their HD routine.

The practical implementation of innovative health and patient care strategies depends on patients' knowledge and beliefs and healthcare professionals' attitudes. Results from the survey of healthcare professionals at TECSAM's dialysis center indicated that doctors and nurses possessed knowledge of acupuncture, and the majority expressed a willingness to receive acupuncture treatment. While a few individuals held a neutral stance regarding acupuncture's efficacy and clinical applicability, most expressed an optimistic perspective. Furthermore, the healthcare professionals unanimously agreed that acupuncture treatments did not interfere with the dialysis routine. Most held a favorable opinion regarding acupuncture as a standard component of care for hemodialysis patients. These outcomes may have been influenced by the healthcare professionals' level of knowledge on the subject. We also emphasize the significance of educating healthcare professionals about the existence of acupuncture to expand the acceptance of these complementary therapeutic approaches.

Regrettably, due to the lack and disparity of studies examining the attitudes of healthcare professionals toward acupuncture and other traditional and complementary medicine practices, it was not feasible to obtain comparative outcomes. Nonetheless, some studies have reported similar findings: doctors and nurses exhibited positive perspectives on acupuncture and acupressure utilization in perioperative care [26]; favorable attitudes were reported among general practitioners and hospital doctors toward traditional acupuncture [27]; general practitioners were supportive of facilitating access to acupuncture within the National Health Service (NHS) [28]. In addition, recent review have also revealed positive attitudes toward acupuncture among healthcare professionals [29].

Extensive research has demonstrated the safety and efficacy of acupuncture in different clinical conditions, mainly when used as an adjunct to conventional medical treatments [30-35]. Contrariwise, a paucity of high-quality clinical trials examining the safety and efficacy of acupuncture in CKD patients with KRT was observed. Nevertheless, current review and meta-analysis data indicated that acupuncture might be considered a safe and effective treatment modality for uremic pruritus in patients undergoing HD [36].

Consistent with the conclusions of prior studies, our findings also suggest that acupuncture is a safe and effective therapeutic option for patients undergoing maintenance HD. No adverse events related to acupuncture were reported and improved patients' functional capacity and health-related quality of life were observed.

2. Research Relevance and Limits. Future Research

The findings of our research are encouraging and have the potential to facilitate the integration of acupuncture as an adjunctive therapy for symptom management in patients undergoing HD. CKD progression and the initiation of dialysis are related to unfavorable health outcomes and higher mortality rates. As observed, functional capacity and muscle strength improvements could translate to greater autonomy in performing daily activities and a higher overall functioning level for HD patients. Likewise, acupuncture may be a promising integrative modality in conventional medicine health services. However, in addition to the views of patients and healthcare professionals, it is imperative to carefully consider the perspectives of healthcare management, administrative boards, and other relevant stakeholders regarding its implementation. A thorough evaluation of these opinions can provide valuable insights into the feasibility and acceptance of acupuncture as an integrative approach in the health care system.

Although our research has produced promising outcomes and our study was designed with careful consideration for methodological rigor, there are still some limitations that must be acknowledged. Firstly, the sample size used for comparing different frequencies of acupuncture treatment resulted from the subdivision of participants from the experimental and placebo groups. Secondly, blinding the TCM practitioner who provided acupuncture treatment was not possible due to the nature of the intervention. Thirdly, although the effects of acupuncture treatment on FC were observed 12 weeks after the end of treatment, this timeframe may not have been sufficient to evaluate the long-term effects of acupuncture. Finally, the assessment of the HRQOL relied on the analysis of only one measurement patient-reported outcome measure for its primary outcome.

As strengths of our research, we highlight the comparison of the experimental group with two control groups (sham and non-acupuncture groups); the participants, the evaluator of the results, and the statistician were unaware of the assignment; and the number of dropouts during follow-up was as low as possible.

Further research is required to corroborate the efficacy of our acupuncture treatment protocol on a larger population of CKD patients and to evaluate the long-term effect of acupuncture treatment in CKD patients without kidney replacement therapy, on peritoneal dialysis, or in a healthy population. Comprehensive data on nutritional status would be valuable to establish a correlation with the effects of acupuncture on the parameters assessed in our RCT. An active control group, such as a comparison with a group receiving intradialytic exercise, or other TCM practices, such as acupressure or auricular acupuncture, should be considered. A comprehensive evaluation of sleep quality and mental health status, including anxiety and depression symptoms, should be included.

Additionally, future studies should involve cost-benefit analyses, comparing outcomes and acupuncture treatment costs with other conventional therapies (e.g., physiotherapy) on patient functional capacity. Finally, it will be necessary to create a conceptual framework to address logistical issues associated with integrating acupuncture into conventional care and verify its clinical applicability to other populations or settings.

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Chapter VII Final Conclusion

In this chapter, the Final Conclusion, we summarize our main results and provide a clear and concise answer to the research question.

A parallel group patient-assessor-blinded randomized controlled trial were conducted and the outcomes suggest that the use of acupuncture as a integrative practice may be a promising approach to improve functional capacity and health-related quality of life in chronic kidney disease patients undergoing hemodialysis.

Verum acupuncture has been shown to improve functional capacity and peripheral muscle strength compared to sham or no-acupuncture groups. The effects of verum acupuncture on specific parameters persisted up to 12-weeks follow-up. While once-weekly acupuncture treatment appeared to be as effective as three-times-weekly treatment, further prospective studies are necessary to confirm the optimal treatment frequency.

Concerning the health-related quality of life, verum acupuncture was found to enhance the physical composite summary score, mental composite summary score overall health, and specific areas targeted by kidney disease (such as the symptom/problem list, effects of kidney disease, cognitive function, and sleep) as compared to sham acupuncture or no-acupuncture groups. However, these beneficial effects were observed only in the short term and did not last beyond three months post-treatment.

The assessment of the acceptability and feasibility of incorporating acupuncture into a dialysis center indicates that it could be a viable and beneficial complementary therapeutic approach to address symptom burden and improve the quality of life.

The findings of our study indicate the relevance of using acupuncture as a complementary therapeutic approach for chronic kidney disease patients undergoing hemodialysis, with no harmful effects. Nevertheless, we underscore the significance of conducting further extensive randomized controlled trials to validate the effectiveness of the developed acupuncture protocol.

In conclusion, we hope that the outcomes of this research will aid in developing more comprehensive and integrated public policies and clinical practices, providing safe and feasible integrative treatments to chronic kidney disease receiving maintenance hemodialysis.

Annexes

Anexes Index

A1. Photo front page research article 1.

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Article

Effect of Acupuncture on Functional Capacity and Health-Related Quality of Life of Hemodialysis Patients: Study Protocol for a Randomized Controlled Trial

Marta Correia de Carvalho [1,*], Jorge Pereira Machado [1,2], Manuel Laranjeira [1,3], José Nunes de Azevedo [4] and Pedro Azevedo [4]

[1] ICBAS—Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, 4050-313 Porto, Portugal
[2] CBSin—Center of BioSciences in Integrative Health, 4000-105 Porto, Portugal
[3] INC—Instituto de Neurociências, 4100-141 Porto, Portugal
[4] TECSAM—Tecnologia e Serviços Médicos SA, 5370-530 Mirandela, Portugal
* Correspondence: correiadecarvalho.marta@gmail.com

Abstract: The proposed randomized controlled trial protocol will evaluate the effect of acupuncture treatment on the functional capacity (FC) and health-related quality of life (HRQOL) in chronic kidney disease (CKD) with glomerular filtration rate (GFR) category 5 (CKG G5) patients receiving maintenance dialysis. Patients undergoing hemodialysis (HD) from a dialysis center will be randomly assigned to experimental, placebo and control groups. In order to determine the difference between the same number of treatments performed three times or one treatment a week, experimental (verum acupuncture) and placebo (sham acupuncture) groups will receive a total of nine acupuncture treatments; however, both groups will be divided into subgroups A and B. The same selection of acupuncture points will be applied to both experimental subgroups and the placebo subgroups will receive acupuncture on non-acupuncture points. The results will be assessed by the 6-min Walk Test, Handgrip Test, 30-sec Sit-to-Stand and Kidney Disease Quality of Life-Short Form and will be held at baseline, after treatment and 12 weeks post-treatment follow up. This paper describes the rationale and design for a randomized, patient-assessor blinded controlled trial, which may provide evidence for the clinical application of acupuncture in CKG G5 patients undergoing HD.

Keywords: chronic kidney disease; hemodialysis; acupuncture; functional capacity; health-related quality of life; integrative medicine; randomized controlled trial

check for updates

Citation: Correia de Carvalho, M.; Pereira Machado, J.; Laranjeira, M.; Nunes de Azevedo, J.; Azevedo, P. Effect of Acupuncture on Functional Capacity and Health-Related Quality of Life of Hemodialysis Patients: Study Protocol for a Randomized Controlled Trial. *Healthcare* **2022**, *10*, 2050. https://doi.org/10.3390/healthcare10102050

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1. Introduction

Over the last few decades, chronic diseases have become increasingly relevant and, according to the statistics, this type of disease is the leading cause of death worldwide and considered by the World Health Organization (WHO) to be the greatest threat to the health of the population in the 21st century [1].

Chronic kidney disease (CKD) is considered a public health problem due to the increasing incidence and prevalence, as well as to high associated economic costs, substantially affecting the life of the patient and implying a significant burden on the health system [2,3]. Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease defines CKD as abnormalities of kidney structure or function, present for more than 3 months, with implications for health and classified based on cause, glomerular filtration rate (GFR < 60 mL/min/1.73 m^2 and albuminuria (AER ≥ 30 mg/24 h; ACR ≥ 30 mg/g (≥3 mg/mmol)) categories. Glomerular filtration rate (GFR) is generally accepted as the best overall index of kidney function and decreased GFR is associated with a higher risk of complications of CKD [4,5].

Although CKD etiology is diverse and due to diseases, such as glomerulopathies, polycystic kidney disease, autoimmune diseases, systemic infections, recurrent urinary tract

A2. Photo front page research article 2.

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Article

Effect of Acupuncture on Functional Capacity in Patients Undergoing Hemodialysis: A Patient-Assessor Blinded Randomized Controlled Trial

Marta Correia de Carvalho [1,*], José Nunes de Azevedo [2], Pedro Azevedo [2], Carlos Pires [3], Manuel Laranjeira [1,4] and Jorge Pereira Machado [1,5]

[1] ICBAS-School of Medicine and Biomedical Sciences, University of Porto, 4050-313 Porto, Portugal
[2] TECSAM-Tecnologia e Serviços Médicos SA, 5370-530 Mirandela, Portugal
[3] Center for Research in Neuropsychology and Cognitive and Behavioral Intervention (CINEICC), Faculty of Psychology and Educational Sciences, University of Coimbra, 3000-115 Coimbra, Portugal
[4] INC-Instituto de Neurociências, 4100-141 Porto, Portugal
[5] CBSin—Center of BioSciences in Integrative Health, 4000-105 Porto, Portugal
* Correspondence: correiadecarvalho.marta@gmail.com

Abstract: Decreased functional capacity (FC) in patients undergoing hemodialysis (HD) is associated with adverse health events and poor survival. Acupuncture is recognized as a safe and effective integrative treatment. The aim of this study is to evaluate the effect of acupuncture treatment on the FC in chronic kidney disease with GFR category 5 (CKG G5) patients undergoing HD. In this patient-assessor blinded randomized controlled trial, seventy-two KF patients were randomly assigned to experimental ($n = 24$), placebo ($n = 24$) and control groups ($n = 24$). The primary outcome was the improvement in FC assessed by the 6-Minute Walk Test (6-MWT). Secondary outcomes included assessment of peripheral muscle strength by the Handgrip Strength Test (HGS) and the 30-Second Sit-to-Stand Test (STS-30) at baseline, after treatment and at 12-week follow up. A mixed ANOVA with interaction time*group was used. The experimental group increased walk distance ($p < 0.001$), lower limbs strength ($p < 0.001$) and handgrip strength ($p = 0.012$) after nine acupuncture sessions and stabilized in the follow-up ($p > 0.05$). In the placebo and control groups the 6-MWT and 30STS results decreased ($p < 0.001$) and the HGS scores did not change through time ($p > 0.05$). Acupuncture treatment improved FC and muscle strength in patients undergoing HD.

Keywords: chronic kidney disease; hemodialysis; acupuncture; functional capacity; integrative medicine

Citation: Correia de Carvalho, M.; Nunes de Azevedo, J.; Azevedo, P.; Pires, C.; Laranjeira, M.; Machado, J.P. Effect of Acupuncture on Functional Capacity in Patients Undergoing Hemodialysis: A Patient-Assessor Blinded Randomized Controlled Trial. *Healthcare* **2022**, *10*, 1947. https://doi.org/10.3390/healthcare10101947

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1. Introduction

The growing incidence and prevalence of chronic kidney disease (CKD) are associated with increased morbidity, mortality and additional burden and economic cost to the health-care system and social assistance [1,2]. According to the most recent data, in 2016, CKD was ranked as the 16th leading cause of death worldwide, and by 2040 it is expected to be the fifth leading cause of death [3].

The etiology of CKD is diverse, with diabetes and hypertension mainly contributing to the increased prevalence of the disease [4]. Patients who have CKD with glomerular filtration rate (GFR) category 5 (CKG G5) can only be treated by kidney replacement therapy (KRT), in particular peritoneal dialysis (PD), hemodialysis (HD), kidney transplantation (KT) and conservative kidney management [4]. Technological innovation and optimization of medical therapy applied to hemodialysis treatments contributed to patients surviving longer on dialysis and after kidney transplantation, helping to increase worldwide the prevalence of kidney failure [5–7].

HD is the most predominant dialysis modality and is characterized as a complex and demanding treatment regimen. One of the significant problems in patients on maintenance

A3. Photo front page research article 3.

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Article

Effectiveness of Acupuncture on Health-Related Quality of Life in Patients Receiving Maintenance Hemodialysis

Marta Correia de Carvalho [1,*], José Nunes de Azevedo [2], Pedro Azevedo [2], Carlos Pires [3], Jorge Pereira Machado [1,4] and Manuel Laranjeira [1,5]

[1] ICBAS, School of Medicine and Biomedical Sciences, University of Porto, 4050-313 Porto, Portugal
[2] TECSAM-Tecnologia e Serviços Médicos SA, 5370-330 Mirandela, Portugal
[3] Center for Research in Neuropsychology and Cognitive and Behavioral Intervention (CINEICC), Faculty of Psychology and Educational Sciences, University of Coimbra, 3000-115 Coimbra, Portugal
[4] CBSin, Center of BioSciences in Integrative Health, 4000-105 Porto, Portugal
[5] INC, Instituto de Neurociências, 4100-141 Porto, Portugal
* Correspondence: correiadecarvalho.marta@gmail.com

Abstract: Patients with kidney failure (KF) receiving maintenance hemodialysis (HD) experience numerous symptoms that impair their health-related quality of life (HRQOL) and contribute to high mortality rates. Acupuncture is often used for symptom enhancement and HRQOL. This blinded, randomized, controlled patient-assessor trial evaluated the effectiveness of acupuncture compared with sham acupuncture on patients' HRQOL receiving maintenance HD as a secondary analysis. Seventy-two participants were randomly assigned to verum acupuncture (VA), sham acupuncture (SA), or waiting-list (WL) groups. The outcome was an improvement in HRQOL, assessed using the Kidney Disease Quality of Life—Short Form, version 1.3 (KDQOL-SF™ v1.3) at baseline, after treatment, and at 12-week follow-up. Non-parametric tests were used for statistical analysis. Of the 72 randomized patients, 67 were included in the complete analysis set. As for the changes between baseline and after treatment, the VA group showed significantly increased scores on most of the KDQOL-SF™ v1.3 scales compared to SA or WL groups ($p < 0.05$). No statistically significant differences between groups were observed in the changes from baseline to follow-up ($p > 0.05$). Compared to the sham treatment, acupuncture improved the HRQOL in patients receiving maintenance HD after treatment but not at follow-up.

Keywords: chronic kidney disease; hemodialysis; acupuncture; health-related quality of life; integrative medicine; randomized controlled trial

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Citation: Correia de Carvalho, M.; Nunes de Azevedo, J.; Azevedo, P.; Pires, C.; Machado, J.P.; Laranjeira, M. Effectiveness of Acupuncture on Health-Related Quality of Life in Patients Receiving Maintenance Hemodialysis. *Healthcare* **2023**, *11*, 1355. https://doi.org/10.3390/healthcare11091355

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1. Introduction

The increasing number of chronic kidney disease (CKD) patients with category five glomerular filtration rates (CKG G5) is considered a public health concern [1]. The latest data from CaReMe CKD study indicates that the prevalence of CKD is around 10% in the adult population, usually underestimated in most studies, with substantial mortality rates and high health costs [2]. In Portugal, the prevalence of CKD is high compared to other countries, and its diagnostic and therapeutic approaches are more expensive than other very prevalent chronic diseases, such as heart failure, acute myocardial infarction, or peripheral arterial disease [2,3].

CKD is a debilitating disease, and its progression often requires kidney replacement therapy (KRT), such as hemodialysis (HD) treatment.

Patients in maintenance HD have a complex treatment and experience numerous physical and emotional limitations that severely impact their daily living activities and clinical outcomes [4–6]. While innovation and improvements in technologies associated with HD treatment have contributed to an increased life expectancy, patients often experience physical and mental disabilities and a poor HRQOL [5,7,8].

A4. Approval of the Ethics Committee.

Exma. Senhora
Marta Raquel Custódio Correia de Carvalho

| v. referência | v. comunicação | n. referência 1155 | data 6.08.2019

SD/HCC/42 2019-08-02

| assunto 2019/CE/P026(P304/2019/CETI)

Exma. Senhora,

Informa-se que o projeto com o título "*The intervention of Traditional Chinese Medicine in the clinical status of dialysis patients*", com a referência 2019/CE/P026(P304/2019/CETI), submetido à Comissão de Ética conjunta CHUP/ICBAS, foi apreciado em reunião plenária de 31 de julho de 2019, tendo obtido parecer favorável nessa data.

Com os melhores cumprimentos,

O DIRETOR

(Prof. Doutor Henrique Cyrne Carvalho)

LCO

Rua de Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal
Telefone: +351 220 428 000
Fax: +351 220 428 090
www.icbas.up.pt

A5. Permission Statement for the use of KDQOL-SF™ 1.3 Portuguese version

Centro de Estudos
e Investigação em Saúde
da Universidade de Coimbra

Pedro Lopes Ferreira
Professor Associado com Agregação

Email: pedrof@fe.uc.pt
ceisuc@fe.uc.pt

Coimbra, 15 de setembro de 2017

Ex.ª Senhora Drª Marta Custódio Correia:

Em resposta ao pedido que me formalizou é com todo o prazer que envio a versão portuguesa do instrumento de medição KDQOL-SF (*Kidney Disease Quality Of Life Short Form version 1.3*) para aplicar no âmbito do trabalho de investigação que pretende realizar. É um instrumento especifico de avaliação da qualidade de vida para doentes com insuficiência renal em diálise.

A sua validação e a obtenção dos valores normais encontram-se nas seguintes referências:

- Ferreira PL, Anes EJ. Medição da qualidade de vida de insuficientes renais crónicos. Criação da versão portuguesa do KDQOL-SF. Revista Portuguesa de Saúde Pública 2010 Jan-Jun; 28(1): 31-9.
- Anes EJ, Ferreira PL. Qualidade de vida em diálise. Revista Portuguesa de Saúde Pública 2009 Vol Temático: 8:67-82.

Desejo-lhe o melhor êxito para o seu trabalho.

Com os meus melhores cumprimentos.

Prof. Doutor Pedro Lopes Ferreira

Faculdade de Economia da Universidade de Coimbra
Av. Dias da Silva, 1653004-512 COIMBRA •
tel/Fax 239 790 507