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## Conselho Científico

ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos



# A Transparência da Ciência com o ChatGPT e as Ferramentas Emergentes de Inteligência Artificial: Como se Devem Posicionar as Revistas Científicas Médicas?

# The Transparency of Science with ChatGPT and the Emerging Artificial Intelligence Language Models: Where Should Medical Journals Stand?

Helena DONATO[1,2], Pedro ESCADA[1,3], Tiago VILLANUEVA✉[1,4]
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**Palavras-chave:** Autoria; Ciência/ética; Ética na Investigação; Inteligência Artificial; Publicação
**Keywords:** Artificial Intelligence; Authorship; Ethics, Research; Publishing; Science/ethics

Nos últimos anos, os grandes modelos de linguagem (*large language models* ou LLM) têm gerado debate académico sobre as suas implicações éticas. Com o lançamento do ChatGPT (*Generative Pretrained Transformer*) em acesso aberto, pela OpenAI, em 30 de Novembro de 2022, essa discussão tornou-se mais popular e preocupante. Assim, o Conselho Editorial da Acta Médica Portuguesa (AMP) pretende esclarecer os seus leitores sobre as implicações do aparecimento desta ferramenta de inteligência artificial, ChatGPT I, para o mundo da publicação científica. Esta ferramenta, disponível gratuitamente na versão *web* (https://openai.com/blog/chatgpt) surpreendeu as equipas editoriais das revistas científicas em todo o mundo ao demonstrar ser capaz, por exemplo, de redigir artigos científicos com razoável qualidade ou mesmo de superar exames académicos.[1]

Na semana seguinte ao seu lançamento, mais de um milhão de utilizadores experimentaram o novo *chatbot*.[2]

Um estudo liderado por Catherine Gao, da Northwestern University em Chicago, Illinois, usou o ChatGPT para gerar resumos artificiais de artigos de investigação e testar se os revisores conseguiam identificá-los.[3]

Os autores do estudo pediram ao ChatGPT para escrever 50 resumos de investigação com base numa seleção de artigos publicados na *JAMA, The New England Journal of Medicine, The BMJ, The Lance*t e *Nature Medicine*. Depois, compararam o resultado com os resumos originais, passando-os por um detector de plágio. Pediram ainda a um grupo de investigadores/revisores que identificasse os resumos fabricados.[3]

Os resumos gerados pelo ChatGPT passaram pelo verificador de plágio: a pontuação média de originalidade foi de 100%, o que indica que nenhum plágio foi detectado. Os revisores humanos não se saíram muito melhor: identificaram correctamente apenas 68% dos resumos gerados e 86% dos resumos genuínos, tendo classificado; e incorretamente 32% dos resumos gerados como sendo reais e 14% dos resumos genuínos como sendo gerados.[3]

"ChatGPT escreve resumos científicos críveis", dizem Gao, *et al*. "Os limites do uso ético e aceitável de grandes modelos de linguagem para ajudar a escrita científica ainda precisam ser determinados".[3]

Se não for possível estabelecer a veracidade da investigação, poderão existir "consequências terríveis".[3] Além de ser problemático para os médicos/investigadores, porque correm o risco de basear decisões e investigações em literatura fabricada, há ainda "implicações para a sociedade em geral porque pode significar que as decisões baseadas em investigação disponível podem estar incorrectas", acrescentam os autores do estudo.[3] Em áreas onde informações falsas podem colocar em risco a segurança das pessoas, como a Medicina, as revistas devem adotar uma abordagem rigorosa para verificar se as informações são corretas.

O ChatGPT até já recebeu pelo menos quatro créditos de autoria em artigos científicos publicados.[4,5] Dado o potencial de evolução destas ferramentas, é fundamental que as revistas científicas médicas regulem urgentemente o seu uso, para que possam ser usadas de forma ética e sem comprometer a transparência dos métodos ou a integridade da autoria.

Assim, parecem existir desde já três aspectos fundamentais que importa discutir: a autoria, a transparência e integridade. Relativamente à autoria, parece já existir consenso sobre a impossibilidade de ferramentas LLM como o ChatGPT não reunirem, nos moldes actuais, critérios de autoria. Como sabemos, um dos critérios de autoria extipulados pelo o International Committee of Medical Journal

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Editors (ICMJE) implica que cada autor seja responsável pelo conteúdo e integridade da informação científica do artigo (*accountability*), pelo que é evidente que o ChatGPT não preenche tal critério pois não pode assumir essa responsabilidade.[3] Ao submeter o trabalho a uma revista científica, os autores também têm de assinar uma declaração certificando que o trabalho é original. Assim, o texto escrito pelo ChatGPT não é aceitável, já que é plagiado a partir do ChatGPT. Também parece ser consensual para já que a sua utilização deve ser sempre declarada, na secção de Métodos ou nos Agradecimentos (*Acknowledgements*). Se o uso de texto gerado por inteligência artificial não for adequadamente citado pode ser considerado plágio.[3]

É obrigatório especificar que o texto gerado pelo ChatGPT [ou qualquer outra ferramenta de inteligência artificial (IA)] não pode ser usado no trabalho, nem figuras, imagens ou gráficos podem ser produto de tais ferramentas, sem que isso seja devidamente reconhecido. é fundamental esclarecer que um programa de IA não pode ser autor. A violação dessas políticas constituirá má conduta científica, não diferente de manipulação de imagens ou plágio de trabalhos existentes.[1]

Conseguem os editores detectar texto gerado por ferramentas de LLM? Neste momento, a resposta é 'talvez'. Actualmente, as LLMs ainda não podem citar fontes para documentar e dar validade científica. Mas, no futuro, os investigadores de IA poderão contornar esse problema ao estabelecer ligações a ferramentas de citação de fontes.

Finalmente, o âmbito da sua utilização é ainda incerto e discutível. Há quem compare os LLM a serviços de polimento linguístico, pelo que poderão ser particularmente apelativos a autores cuja língua materna não é o inglês.

A Turnitin, LCC – empresa americana líder de mercado a nível de *software* de detecção de plágio e outras ferramentas projetadas para incentivar o trabalho original, como os programas Ithenticate e Turnitin, usados por revistas científicas médicas e instituições académicas e de investigação em todo o mundo, incluindo a AMP – já anunciou que planeia a melhoria dos seus produtos em 2023 e que está atenta ao uso indevido do ChatGPT, encontrando-se a desenvolver novas funcionalidades para detetar artigos escritos por LLM.[4]

Várias editoras, como a *Springer Nature,* anunciaram alterações às suas normas de publicação e a introdução de novas políticas editoriais com vista a regulamentar o uso destes recursos na escrita de artigos submetidos às revistas do grupo, sendo provável que a maioria das revistas científicas médicas adopte em breve posturas semelhantes.[5]

Pretendemos assim alertar os nossos leitores para este fenómeno emergente dos LLM e para as implicações que a sua utilização poderá ter nos artigos submetidos futuramente a revistas como a AMP. Para já, subscrevemos as políticas editoriais do grupo *Springer Nature* e iremos estar atentos à necessidade de reformular, neste contexto, as nossas normas editoriais.

## OBSERVAÇÕES

Comissionado; sem revisão por pares.

## CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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ACTA MÉDICA PORTUGUESA
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# COVID-19 Vaccination in the Portuguese Medical Community: An Unprecedented Campaign Coordinated by the Portuguese Medical Association

# Vacinação COVID-19 na Comunidade Médica Portuguesa: Uma Campanha sem Precedentes Coordenada pela Ordem dos Médicos

Miguel GUIMARÃES[1], Rubina CORREIA[1], Susana VARGAS[1], Filipe FROES✉[1]
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**Keywords:** COVID-19; Pandemics; Physicians; Portugal; Portuguese Medical Association; Vaccination
**Palavras-chave:** COVID-19; Médicos; Ordem dos Médicos; Pandemia; Portugal; Vacinação

## INTRODUCTION

The COVID-19 pandemic is an ongoing global public health emergency caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The World Health Organization (WHO) declared the outbreak a pandemic on the 11th March 2020, after three months of viral spreading from China to all continents.[2]

The pandemic management was a worldwide effort with the involvement of governments, academia, industry, and citizens. Infrastructural, medical, pharmaceutical, and public health measures were adopted worldwide to control viral spreading. In the context of medical and pharmaceutical advances, the development of SARS-CoV-2 vaccines has been a priority since the early days of the outbreak. As such, several pharmaceutical companies worked intensively on new vaccines aiming to provide effective and safe products as soon as possible. The development of effective vaccines proved to be a relevant turning point for managing this unprecedented threat by reducing COVID-19-related morbidity and mortality, protecting healthcare systems, and resuming social-economic activities.[3]

### SARS-CoV-2 pandemic and the global vaccination campaign

As with other widespread diseases, COVID-19 confirmed the existing deep healthcare inequalities in both developed and developing countries. Even though the management of vaccine distribution around the world has been debated based on ethical and global health concerns, COVID-19 vaccines were first distributed and commercialized in Western Europe and in the United States of America.[4]

After several months of intense research and development efforts, COVID-19 vaccination campaigns began to be structured by the end of 2020 all around the globe. The first SARS-CoV-2 vaccine was administered in the United Kingdom on the 8th December 2020, nine months after WHO declared the novel coronavirus outbreak as a global pandemic.

In general, the campaigns were designed and implemented by governments worldwide to guarantee preferential immunization of the populations with higher morbidity and mortality risks – including the elderly and patients with chronic and autoimmune diseases – along with healthcare providers, to keep health and social care systems operational, in terms of human resources.[3]

As of December 2022, a total of 13 073 712 554 vaccine doses have been administered worldwide, and as of June 2022, 68 WHO Member States had vaccinated more than 80% of their healthcare workers.[3,5]

### The Portuguese vaccination campaign

In Portugal, the vaccination schedule was presented by the Vaccination Coordinating Team and the Portuguese government on the 3rd December 2020, with the identification of priority groups and an estimation of 300 000 administrations per week.[6] The process began on the 27th December 2020, with the symbolic administration of the first COVID-19 vaccine to a physician – the Head of the Infectious Diseases Department of a major hospital of the Portuguese National Health Service (in Portuguese, "Serviço Nacional de Saúde"). This symbolic act intended to send to the Portuguese population a message of trust in the effectiveness and safety of vaccines and reinforced the commitment of healthcare professionals with the most extensive vaccination campaign in history.

As of January 2023, more than 27 million vaccine doses have been administered, and the vaccination plan was on the phase of: i) seasonal booster dose administration for healthcare providers and people over 50 years of age; ii) booster dose administration for those between 18 and 49 years of age; and iii) primary vaccination of all those above 12 years of age.

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**Vaccination of Portuguese physicians: the role of the Portuguese Medical Association**

The priority groups, defined at the launch of the campaign, included all the physicians in accordance with international and national guidance.[6,7] However, physicians without working contracts with the public healthcare system and those who had already retired, but were still professionally active, were not contemplated.

Since the presentation of the vaccination schedule, the Portuguese Medical Association (in Portuguese, "Ordem dos Médicos") assumed the intention to cooperate with the Portuguese government in all aspects related to the management of the pandemic by medical professionals and to the vaccination of the medical community. The exclusion of retired and private practice professionals was a concern for the association that manifested its positioning by means of public statements through its website and communication platforms. On the 2nd February 2021, the Portuguese Medical Association expressed its availability to coordinate the vaccination of the medical professionals that remained unvaccinated and launched a petition to be signed by all medical doctors in solidarity with all those who were not included in the priority groups. At the same time, the association released a questionnaire to be filled out by all medical doctors, with the objective of assessing the extent of the unvaccinated group. Along with these initiatives, the Portuguese Medical Association kept permanent communication with the Portuguese government and with the Portuguese COVID-19 Task Force to firmly state its commitment to the vaccination campaign. By the end of February 2021, the coordination of the Task Force was restructured, and Vice-Admiral Henrique Gouveia e Melo assumed the executive management of the national vaccination campaign. This change became the turning point of the Portuguese vaccination process, including that of the medical community.

By the 4th March 2021, the Portuguese Medical Association announced that the government and the Task Force had transferred the operationalization of the vaccination of all medical professionals that remained unvaccinated to the association.

In this context, the Portuguese Medical Association assembled and managed a nationwide vaccination campaign between the 27th February and the 15th July 2021, directed to the medical community that remained unvaccinated until

Table 1 – Distribution of vaccine administration per region, date and trademark

| Local/date | AstraZeneca | Moderna | Pfizer | Total |
|---|---|---|---|---|
| **Algarve** | 208 | 31 | 168 | 407 |
| March 2021 | 110 | | 168 | 278 |
| May 2021 | | 17 | | 17 |
| June 2021 | 98 | 14 | | 112 |
| **Coimbra** | 428 | | 783 | 1211 |
| March 2021 | 242 | | 342 | 584 |
| April 2021 | | | 339 | 339 |
| May 2021 | 6 | | 32 | 38 |
| June 2021 | 180 | | 70 | 250 |
| **Lisboa** | 839 | | 2711 | 3550 |
| March 2021 | 778 | | 1422 | 2200 |
| April 2021 | | | 893 | 893 |
| May 2021 | 36 | | 156 | 192 |
| June 2021 | 2 | | 240 | 242 |
| July 2021 | 23 | | | 23 |
| **Porto** | 1176 | | 1486 | 2662 |
| February 2021 | | | 630 | 630 |
| March 2021 | 587 | | 630 | 1217 |
| April 2021 | | | 17 | 17 |
| May 2021 | 541 | | 125 | 666 |
| June 2021 | 25 | | 83 | 108 |
| July 2021 | 23 | | 1 | 24 |
| **Total** | 2651 | 31 | 5148 | 7830 |

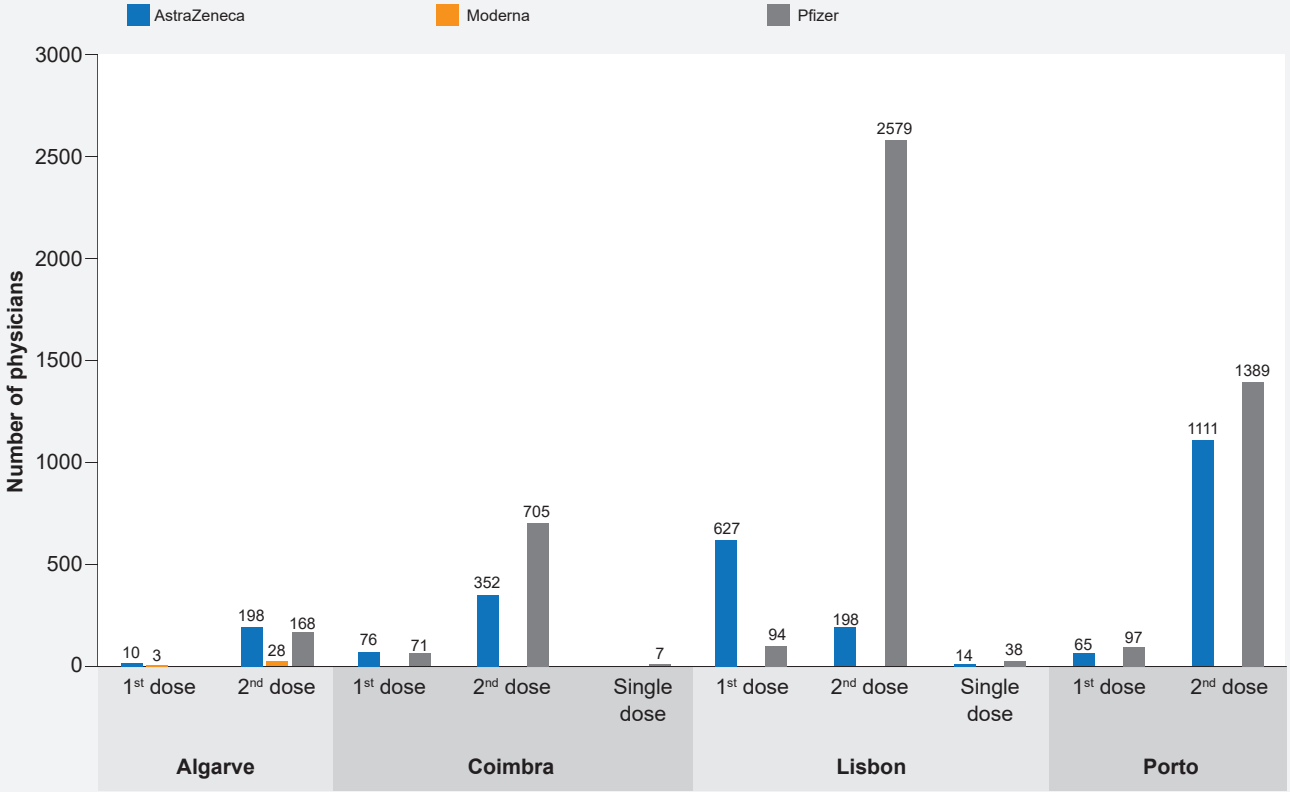


Figure 1 – Distribution of vaccine administration per dose and trademark in each region

that date. All the association's human resources were allocated to this endeavor, which also benefited from cooperation with the national armed forces (in Portuguese, "Forças Armadas Portuguesas"). Regarding logistics, the medical community was vaccinated at both military and civilian hospital facilities in Lisbon, Porto, Coimbra, and Faro.

Overall, 6171 physicians were notified by the Portuguese Medical Association to be present at a specific vaccination spot on a specific date. Of all the notified physicians, 4466 were effectively vaccinated. This difference was due to either ongoing SARS-CoV-2 infection[7] or previous vaccination of the physician in the scope of another campaign.

The physicians were immunized with vaccines produced with three different technologies. From the 7830 administered doses (Table 1, Fig. 1), 65.7% were BNT162b2 (BioNTech/Pfizer), 33.9% were ChAdOx1-S (AstraZeneca/University of Oxford), and 0.4% were mRNA-1273 (Moderna). The vaccines were supplied by the Portuguese COVID-19 Task Force, thus ensuring the strategic planning of the immunization campaign without availability constraints.

The mean age of the vaccinated physicians was 60 years (min: 24, max: 91), and the subgroup of physicians above 65 years received, mainly, the Pfizer vaccine. No adverse events were registered, including hypersensitivity reactions in the 30 minutes after administration. During the whole period, the Portuguese Medical Association did not receive any safety notification, and no vaccine dose was wasted or left unadministered. This illustrates the strict planning of the campaign and the commitment of all the involved healthcare professionals to the sustainability of the process at a critical time in terms of resources.

To the best of our knowledge, the Portuguese Medical Association was the only non-governmental and non-healthcare institution worldwide to have been given access to COVID-19 vaccines in the initial phase of the vaccination campaign. For this and for its results, the operation was unprecedented on a global scale. Moreover, it conveyed a powerful pro-vaccine example to the general population, which may have contributed to the high vaccination rates among the Portuguese population.

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de Lisboa, Hospital das Forças Armadas de Porto, Centro de Saúde Militar de Coimbra, and Centro Hospitalar e Universitário do Algarve.

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## AUTHOR CONTRIBUTIONS

MG: Conceptualization, resources, writing, review, editing.

RC: Project administration, writing, review, editing.

SV: Conceptualization, resources.

FF: Writing, original draft, writing, review, editing.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## COMPETING INTERESTS

FF is the Principal Investigator of "SPHERE Study – Burden of Invasive Pneumococcal Disease in Adults hospitalized in 2017 and 2018" and has received payment from MSD; received honoraria from Pfizer, Bial, AstraZeneca, GSK, Gilead, MSD and Sanofi for lectures and presentations; participated in advisory boards for AstraZeneca, MSD and Sanofi.

The remaining authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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# The Genetic Psychosocial Risk Instrument (GPRI): A Validation Study for European Portuguese

# O Instrumento de Avaliação do Risco Genético Psicossocial (GPRI): Estudo de Validação para Português Europeu

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## ABSTRACT

**Introduction:** Screening instruments specifically developed to identify genetic testing applicants who may need professional psychosocial support are much needed. However, there are no screening instruments validated for the Portuguese language. This paper presents the translation, adaptation, and validation process of the Genetic Psychosocial Risk Instrument in a sample of 207 Portuguese applicants to genetic testing in the context of inherited cancer risk.

**Material and Methods:** Participants were mainly female (84.06%), with a mean age of 40.08 (SD = 12.89) and were recruited from the Portuguese Oncology Institute of Porto. Confirmatory factor analysis was conducted to confirm the Genetic Psychosocial Risk Instrument factorial structure. Convergent validity was assessed with the Impact of Events Scale, the Clinical Outcome Routine Evaluation – Outcome Measure, and the Hospital Anxiety and Depression Scale.

**Results:** A model composed by the factors 'Internal Impact of Genetic Testing', 'External Impact of Genetic Testing' and 'History of Mental Health Concerns' was confirmed. These factors showed good internal consistency, convergent and discriminant validity. The factor 'Personal Loss to Cancer' proposed in the Canadian and French versions did not converge. We propose excluding this factor from the European Portuguese version of the scale.

**Conclusion:** The European Portuguese version of the Genetic Psychosocial Risk Instrument is a reliable and valid instrument, although more research is needed to effectively use it in routine clinical oncogenetic departments.

**Keywords:** Genetic Counseling; Genetic Testing; Neoplastic Syndromes, Hereditary; Psycho-Oncology; Psychometrics; Translation; Validation Study

## RESUMO

**Introdução:** A literatura tem apontado a necessidade de instrumentos de rastreio de risco psicossocial desenvolvidos especificamente para o contexto do teste genético. No entanto, de acordo com o nosso melhor conhecimento, não existe nenhum instrumento com estas características que esteja validado para a língua portuguesa. Este artigo apresenta o processo de tradução, adaptação e validação do Instrumento de Risco Psicossocial Genético numa amostra de 207 utentes convidados à realização de testes genéticos no contexto de risco de cancro hereditário.

**Material e Métodos:** Os participantes são maioritariamente do sexo feminino (84,06%), com média de idade de 40,08 (DP = 12,89) e foram recrutados no Instituto Português de Oncologia do Porto. Foi realizada uma análise fatorial confirmatória para estudar a estrutura fatorial do Instrumento de Risco Genético Psicossocial. A validade convergente foi avaliada com a Escala de Impacto de Eventos, a Escala da Avaliação de Rotina de Resultado Clínico - Medida de Resultado e a Escala de Ansiedade e Depressão Hospitalar.

**Resultados:** Confirmou-se um modelo composto pelos fatores 'Impacto Interno do Teste Genético', 'Impacto Externo do Teste Genético' e 'Histórico de Preocupações com a Saúde Mental'. Estes fatores apresentaram boa consistência interna, validade convergente e discriminante. O fator 'Perda Pessoal para o Cancro' proposto nas versões Canadiana e Francesa não convergiu. Propomos excluir este fator da versão portuguesa da escala.

**Conclusão:** A versão portuguesa do Instrumento de Risco Genético Psicossocial é um instrumento confiável e válido, embora seja necessária mais investigação para que seja integrado efetivamente na prática de rotina.

**Palavras-chave:** Aconselhamento Genético; Estudo de Validação; Psico-Oncologia; Psicometria; Síndromes Neoplásicas Hereditárias; Teste Genético; Tradução

## INTRODUCTION

Hereditary cancer syndromes are adult-onset hereditary diseases caused by genetic pathogenic variants that increase the lifetime probability of developing cancer, compared with the general population.[1,2] These pathogenic variants are identified through genetic testing (GT), which can be offered to healthy individuals from families with suspected or confirmed hereditary cancer syndromes. Once identified as pathogenic variant carriers, individuals may work with geneticists and other healthcare professionals to implement personalized prevention programs (PPP) to prevent the onset of cancer. Nevertheless, effective PPP often involve considering invasive life-altering procedures, such as organ-removal surgeries (e.g., prophylactic bilateral mastectomy), which are associated with important

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psychosocial challenges.[3] Research has consistently shown that a subgroup of GT applicants may experience long-term psychological maladjustment.[4] Pathogenic variant carriers may feel increased distress, anxiety, cancer worry, anger, and guilt for possibly having transmitted the pathogenic variant to their children.[4-7] Moreover, siblings who are non-carriers may experience distress and feelings of survivor guilt towards family members who are pathogenic variant carriers.[8] Therefore, identification of applicants who may need additional psychosocial support in the process of adaptation to GT and its results is an important care step.

Several instruments have been used to screen for psychosocial issues in GT applicants (e.g., Impacts of Events Scale[9]; Multidimensional Impact of Cancer Risk Assessment Questionnaire),[10] but they are either too broad or do not consider GT-specific risk-factors.[11] To fill this gap, Esplen *et al* developed a measure specifically for routine assessment of psychosocial risk in GT applicants. In its original version, the Genetic Psychosocial Risk Instrument (GPRI) has shown good psychometric properties, clinical utility, and acceptability.[11]

Portuguese is the sixth most spoken language in the world, being the official language of over 250 million people.[12] However, to our knowledge there are no specific instruments to assess psychosocial risk in GT applicants being used in any Portuguese speaking countries. Therefore, a Portuguese version of the GPRI is much needed to assist Portuguese speaking geneticists and genetic counsellors in their routine practice. In this sense, our aim with this study was to present the European Portuguese version of the GPRI and to validate its factorial structure for the Portuguese population. We anticipated that the European Portuguese version of the GPRI would replicate the factorial structure of the original version and correlate significantly with measures of anxiety, depression, and distress. Additionally, based on prior research about genetic testing psychological adjustment,[4,13] we expected that cancer patients would have greater psychosocial risks than pre-symptomatic applicants, and that the number of children would be positively correlated with the psychosocial risk.

## MATERIAL AND METHODS

### Participants and procedure

Study participants were 207 patients from the Portuguese Oncology Institute of Porto (IPO-PORTO), aged 18 or over who opted to undergo genetic testing to assess the presence of the following hereditary cancer syndromes: hereditary breast and ovarian cancer (HBOC), hereditary non-polyposis colorectal cancer (HNPCC), hereditary gastric diffuse cancer (HGDC), and familial adenomatous polyposis (FAP). Both pre-symptomatic and participants diagnosed with cancer were included. Participants were excluded if they were not able to understand the context of GT and the implications of GT results or did not have sufficient literacy. This work is part of an ongoing project approved by the IPO-PORTO Ethics Committee (Doc. CES-IPOP 04_2017).

Data collection took place between September 2018 and March 2020. A medical geneticist invited applicants to participate during their first genetics consultation. Applicants who decided to participate were referred to a researcher, who presented the study in detail and asked for written informed consent. After giving consent, participants completed a battery of questionnaires composed by the Genetic Psychosocial Risk Instrument,[11] the Impact of Events Scale,[9] the Hospital Anxiety and Depression Scale[14,15] and the Clinical Outcome Routine Evaluation – Outcome Measure Scale.[16,17]

### Scale translation

The translation of the scale was performed independently by two researchers with extensive experience in translating and adapting psychometric scales, one senior psycho-oncologist and one senior medical geneticist. An initial version was obtained by consensus, and a bilingual Portuguese researcher performed the back translation. The semantic content of some of the items was discussed with the author of the scale. The initial translated version was tested in a sample of five applicants (not included in the study) to assess the clarity of items and instructions. Applicants' uncertainties around the meaning of items were considered, and the wording of a few items was changed after careful consideration by the five researchers involved in the translation process, until a final version was accomplished.

### Instruments

#### Genetic Psychosocial Risk Instrument (GPRI)

The GPRI[11] is a 20-item scale that measures the psychosocial risk of applicants undergoing genetic testing. Of these 20 items, 12 are to be answered according to a five-point Likert scale and eight items are Yes or No questions. The GPRI is composed by three factors: (1) perceived impact and personal adjustment to genetic testing; (2) history of mental health concerns and (3) personal history/family history/loss to cancer. The GPRI has shown high internal consistency (Cronbach's α = 0.81), convergent and discriminant validity. It was able to identify 84% of participants displaying post-GT results distress, as assessed by a battery of measures composed by the Hamilton's Anxiety Rating Scale,[18] the Hamilton's Depression Rating Scale,[19] the Brief Symptom Inventory,[20] and the Impact of Events Scale.[9] To date, the GPRI was validated for the Canadian population[11] and for the French population.[21] However, the French version of the GPRI (GPRI-F) has a slightly different factorial structure, despite exhibiting high reliability (Cronbach's α =

0.81) as well. Specifically, the GPRI-F is composed by four factors: (1) Anticipated or experienced impact of having a disease risk or genetic pathogenic variant; (2) Anticipated or likely external impact from having a disease risk or genetic pathogenic variant; (3) Personal history of or vulnerability to mental health issues or symptoms and (4) Personal or family history of the genetic disease being tested in the clinic.

**Impact of Events Scale**

The Impact of Events Scale (IES[9]) is a 15-item Likert scale used to measure distress triggered by a stressor or life event. The IES comprises two domains: (1) 'Intrusion', which relates to intrusive thoughts and feelings about the event or stressor and (2) 'Avoidance', which relates to patterns of avoidance in terms of thoughts, feelings, and behaviors. The IES has been frequently used with genetic populations and has shown good psychometric properties.

**Hospital Anxiety and Depression Scale**

The Hospital Anxiety and Depression Scale (HADS[14,15]) is a well-known instrument assessing symptoms of depression and anxiety. The HADS has shown good psychometric properties, both in the original[14] and the Portuguese version.[15]

**Clinical Outcome Routine Evaluation-Outcome Measure**

The CORE-OM[16,17] is a five-point Likert scale of global distress (GD), comprising 34 items and four dimensions: subjective well-being, commonly experienced problems or symptoms, social/life functioning, and risk to self and others. The CORE-OM has shown good psychometric properties both in its original version[16] as well as in the Portuguese version.[17]

**Data analysis**

All analyses were performed in R, using the Lavaan and semTools packages. First, we conducted descriptive statistics and calculated an inter-item correlation matrix, using tetrachoric, biserial, and Pearson's coefficients to account for both continuous and dichotomous variables. Then, we evaluated the GPRI factor structure, using confirmatory factor analysis (CFA) to test the original GPRI factor structure, proposed by Esplen *et al*.[11] This three-factor solution measures patients' (a) 'Personal/family history of/Loss to Cancer' (PLC; 3 items), (b) 'Perceived Impact of Genetic Testing' (PIGT, 12 items), and (c) 'History of Mental Health Concerns' (HMHC, five items). We then tested alternative factor structures and used nested model comparisons to achieve the best fitting model. We employed the weighted least squares mean and variance adjusted (WLSMV) estimator for testing the models, since the indicators of PLC and HMHC were defined as categorical. Indicators measuring PIGT ranged from 1 to 5 and were modeled as continuous.[22] The percentage of missing values was quite low (0.05%). Missing data were handled using pairwise deletion, which is considered the most efficient method in this situation.[23] Chi-square goodness-of-fit statistic, the root mean square error of approximation (RMSEA), the comparative fix index (CFI) and the standardized root mean square residual (SRMR) were used to assess model fit. Values lower than 0.06 for RMSEA, greater than 0.95 for CFI, and lower than 0.80 for SRMR indicate good model fit.[24]

After inspecting GPRI internal consistency (Cronbach's alpha), we investigated its convergent and discriminant validity by considering the direction and magnitude of associations with the following measures: Impact of Events Scale (IES); Hospital Anxiety and Depression Scale (HADS); and the CORE Outcome Measure (CORE-OM). We also analyzed the relations between the GPRI scores and distinct aspects of personal/family history (e.g., previous cancer diagnosis) and demographic features (e.g., number of children), using *t*-test for independent samples.

## RESULTS

Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16497/6690) displays the items' frequencies and descriptive statistics. The PLC items showed relatively high frequencies, with nearly 50% of participants indicating they have taken care of a very ill parent or close relative in the past (item 2) or lost a close family member to the disease for which they were being tested (item 3). Overall, participants reported moderate scores on the items tapping PIGT. These items were normally distributed, showing reduced levels of skewness (range -0.60 to 0.88) and kurtosis (range -1.07 to 0.30). A relatively low percentage of participants were seeing a counselor due to emotional concerns (item 18), and few of them reported emotional problems associated with suicidal thoughts (item 17).

The inter-item correlation matrix, including dichotomous and continuous variables, is also presented in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16497/6690). The average correlation among items from the same subscale was 0.12, 0.37, and 0.67 for PLC, PIGT, and HMHC, respectively. The correlation between items 14 ("I have had emotional problems in the past") and 17 ("I have had emotional problems that led me to have thoughts about suicide") from the HMHC subscale was close to 1.0, suggesting these items are highly redundant.

As originally proposed by Esplen *et al*,[11] the CFA model for the GPRI included three oblique factors: PLC, PIGT, and HMHC. No residual covariances were specified. This

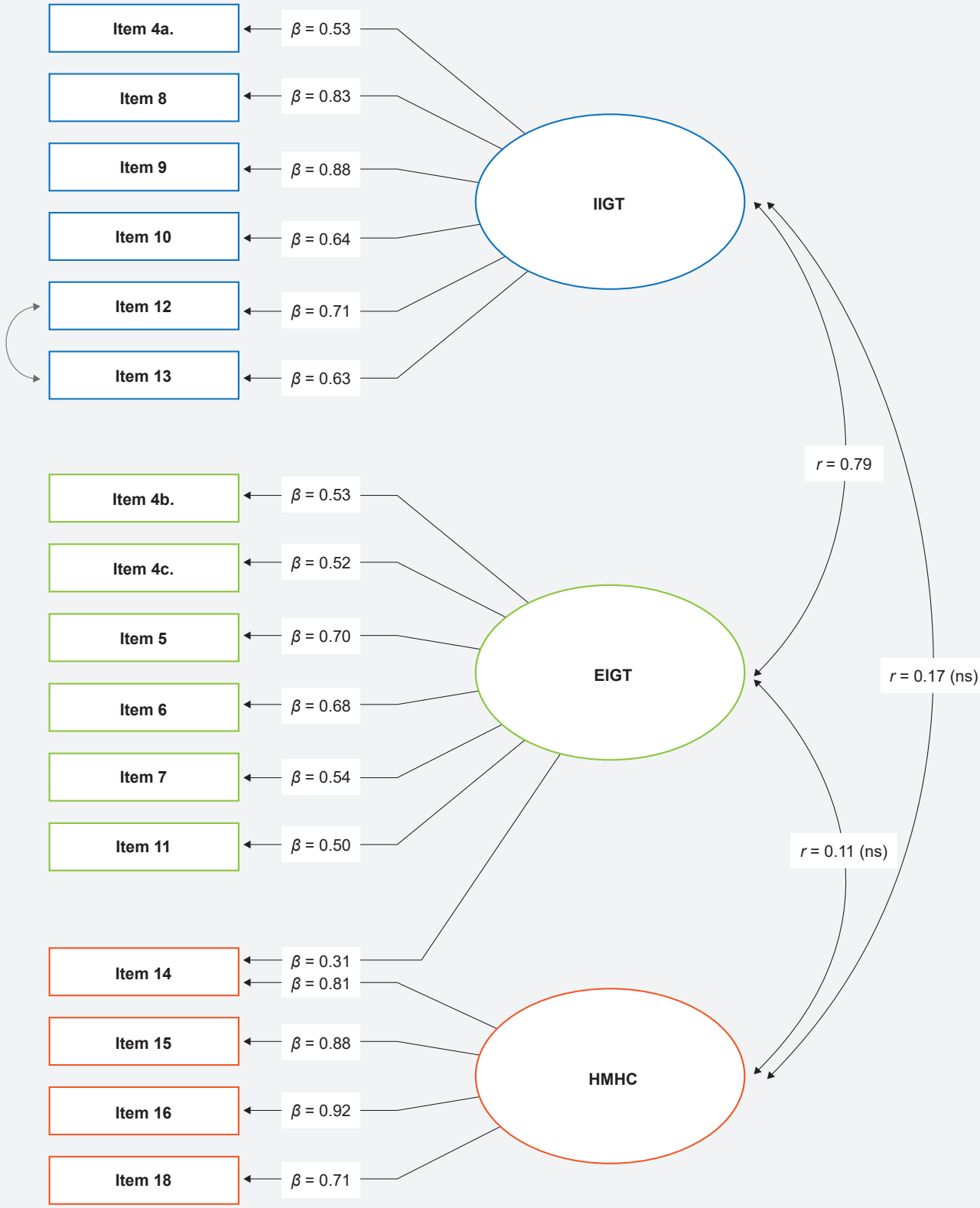


Figure 1 – Confirmatory factor analysis model examining the factor structure of the Genetic Psychosocial Risk Instrument.
IIGT: Internal Impact of Genetic Testing; EIGT: External Impact of Genetic Testing; HMHC: History of Mental Health Concerns.
All parameters are significant at $p < 0.01$ unless otherwise indicated; ns = non-significant.

baseline model (Model 1) did not converge, perhaps because of the existing collinearity between items 14 and 17. To tackle this issue, we decided to drop item 17 from the model, because the scores of this item showed very low variability. As Table 1 displays, the CFA model excluding item 17 (Model 2) showed less than adequate fit to the data, $\chi^2(149) = 226.26$, $p < 0.001$, RMSEA = 0.05 [90% CI (0.04; 0.06)], CFI = 0.89, SRMR = 0.09. We used the modification indices (MI) to identify potential sources of significant model improvement. Model fit improved by specifying residual covariances between items 12 ("I have generally felt sad in the past month") and 13 ("I have generally felt nervous and anxious in the past month") and between items 4c ("I will have difficulties in my family relationships") and 6 ("I am worried that my test result will impact on my relationship with my significant other (or future partner)"). In addition, we allowed a cross-loading of the item 14 ("I have had emotional problems in the past") to the factor measuring the perceived impact of genetic testing (PIGT). Results from the likelihood ratio test in Table 1 indicated that this model (Model 3) fitted the data significantly better than Model 2, $\Delta\chi^2(3) = 30.41$, $p < 0.001$. Despite Model 3's adequate fit, the estimation process resulted in some improper solution (also known as Heywood cases) involving the factor representing PLC, namely estimated negative factor variance and correlations between factors with absolute values > 1.0. Furthermore, all PLC factor loadings were non-significant.

We tested the alternative GPRI 4-factor solution proposed by Maheu *et al.*[21] In this CFA model (Model 4), we reproduced the original PLC and HMHC (except item 17) factors. The 12-item PIGT factor was decomposed into two six-item factors measuring the internal impact of genetic testing (IIGT) and external impact of genetic testing (EIGT). Based on the MI, the residual covariance between items 12 and 13 and the cross-loading of the item 14 to the PIGT were also specified. As shown in Table 1, Model 4 provided significantly better fit to the data than Model 3, $\Delta\chi^2(2) = 6.11$, $p = 0.047$. Nevertheless, like Model 3, the estimation of Model 4 resulted in inadmissible, improper solutions for some of the PLC's factor parameters.

Given the PLC non-significant factor loadings, and to avoid Heywood cases, we tested models 3 and 4 without the PLC factor. Model 5 specified two factors, PIGT (12 items) and HMHC (4 items), whereas Model 6 specified three factors, IIGT (6 items), EIGT (6 items), and HMHC (4 items). Both models provided good fit to the data (Table 1), thus eliminating the estimation issues previously described. We retained Model 6 because it fitted the data better than Model 5, $\Delta\chi^2(1) = 4.10$, $p = 0.043$. Fig. 1 presents the standardized coefficients for this Model 6 and Appendix 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16497/6691) presents estimates, standard errors, confidence intervals and correlation of errors.

As depicted in Fig. 1, all factor loadings were significant at $p < 0.01$. Except for the EIGT cross-loading on item 14, all the standardized factor loadings were higher than 0.50. This CFA model also estimated the error-free correlations between the factors representing IIGT, EIGT, and HMHC. As expected, results indicated a strong association between IIGT and EIGT ($r = 0.79$, $p < 0.001$).

Regarding internal consistency, we opted to use the Cronbach's alpha for the IIGT and EIGT subscales because these subscales' observed variables are continuous and The Kuder-Richardson Formula 20 (KR-20) for the HMHC subscale because the observed variables pertaining to this subscale are dichotomous. In this sense, the Cronbach's alpha for the IIGT and EIGT subscales was 0.75 and 0.85 respectively, and the KR-20 for the HMHC subscale was 0.76, which suggests overall good internal consistency. For establishing the GPRI convergent and discriminant validity, we examined the associations between the scores on these GPRI's subscales and the scores obtained by Impact of Events Scale (IES), the Hospital Anxiety and Depression Scale (HADS), and the CORE outcome measure (CORE-OM). These are well-established measures of psychological adjustment and distress in the face of disease. We also investigated GPRI ability to discriminate genetic psychosocial risk across patients with and without a known diagnosis of cancer and within different demographic subgroups. Results in Table 2 indicate the psychosocial risk to genetic testing measured by the IIGT, EIGT, and HMHC subscales was positively associated with higher levels of intrusion, avoidance, anxiety, depression, and psychological distress.

Table 1 – Goodness of fit statistics for the GPRI's CFA models and nested model comparisons

| **Model tested** | $\chi^2$(df) | **RMSEA** (90% CI) | **CFI** | **SRMR** | **Compared Model** | $\Delta\chi^2(\Delta df)$ |
|---|---|---|---|---|---|---|
| Model 1 | --- | --- | --- | --- | --- | --- |
| Model 2 | 226.26 (149)** | 0.05 (0.04; 0.06) | 0.89 | 0.09 | --- | --- |
| Model 3 | 184.48 (146)* | 0.04 (0.02; 0.05) | 0.94 | 0.08 | Model 2 | 30.41 (3)** |
| Model 4 | 176.08 (144)* | 0.03 (0.01; 0.05) | 0.95 | 0.07 | Model 3 | 6.11 (2)* |
| Model 5 | 125.92 (100)* | 0.04 (0.01; 0.05) | 0.96 | 0.07 | --- | --- |
| Model 6 | 118.88 (99) | 0.03 (0.00; 0.05) | 0.97 | 0.06 | Model 5 | 4.10 (1)* |

*: $p < 0.05$; **: $p < 0.01$

Table 2 – Pearson correlations and descriptive statistics

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Genetic Psychosocial Risk Instrument** | | | | | | | | | | | | | |
| 1. IIGT | --- | | | | | | | | | | | | |
| 2. EIGT | 0.60** | --- | | | | | | | | | | | |
| 3. HMHC | 0.18* | 0.17* | --- | | | | | | | | | | |
| **Impact of Events Scale** | | | | | | | | | | | | | |
| 4. Intrusion | 0.58** | 0.49** | 0.24** | --- | | | | | | | | | |
| 5. Avoidance | 0.48** | 0.40** | 0.21** | 0.66** | --- | | | | | | | | |
| 6. IES total score | 0.58** | 0.48** | 0.25** | 0.89** | 0.93** | --- | | | | | | | |
| **Anxiety and Depression Scale** | | | | | | | | | | | | | |
| 7. Anxiety | 0.58** | 0.37** | 0.32* | 0.62** | 0.43** | 0.57** | --- | | | | | | |
| 8. Depression | 0.55** | 0.37** | 0.24** | 0.50** | 0.40** | 0.50** | 0.75** | --- | | | | | |
| **Core Outcome Measure** | | | | | | | | | | | | | |
| 9. Distress | 0.61** | 0.36** | 0.30** | 0.62** | 0.43** | 0.58** | 0.83** | 0.78** | --- | | | | |
| **Demographic variables** | | | | | | | | | | | | | |
| 10. Age | 0.11 | 0.04 | 0.15* | 0.03 | 0.06 | 0.05 | 0.07 | 0.11 | 0.07 | --- | | | |
| 11. Education (Years) | -0.20** | -0.15* | -0.08 | -0.16* | -0.04 | -0.11 | -0.13 | -0.13 | -0.006 | -0.29** | --- | | |
| 12. Income | -0.25** | -0.18* | -0.07 | -0.19* | 0.02 | -0.08 | -0.13 | -0.04 | -0.1 | 0.06 | 0.43** | --- | |
| 13. Number of children | 0.16* | 0.09 | 0.10 | 0.15 | 0.12 | 0.14 | 0.13 | 0.05 | 0.05 | 0.70** | -0.19* | 0.06 | --- |
| **M** | 2.86 | 2.36 | 0.30 | 8.73 | 12.38 | 21.10 | 6.00 | 3.71 | 0.85 | 40.08 | 11.88 | 2.43 | 1.24 |
| **SD** | 0.86 | 0.80 | 0.34 | 7.16 | 8.52 | 14.32 | 3.71 | 3.40 | 0.56 | 12.89 | 3.76 | 1.14 | 0.90 |
| **Range** | 1 - 5 | 1 - 5 | 0 - 1 | 0 - 31 | 0 - 36 | 0 - 61 | 0 - 17 | 0 - 17 | 0.0 - 2.97 | 18 - 69 | 4 - 19 | 1 - 5 | 0 - 4 |

PLC: Personal Loss to Cancer; PIGT: Perceived Impact of Genetic Testing; HMHC: History of Mental Health Concerns; M: mean; SD: standard deviation
*: $p < 0.05$; **: $p < 0.01$

The IIGT and EIGT scores were negatively correlated with participants' years of education and income. Patients' age and number of children were associated with increasing levels of IIGT and HMHC, respectively.

Finally, we conducted independent-sample *t*-tests to examine differences between women and men, and between those with and without a confirmed diagnosis of cancer on psychosocial risk to genetic testing. Results are presented in Table 3. The GPRI's subscales measuring IIGT and HMHC seem to discriminate male patients from female patients, as well as between patients with and without cancer diagnoses. Compared to men, women showed higher average rates of internal impact to genetic testing and a more evident history of mental health concerns. As expected, patients with a confirmed diagnosis of cancer displayed higher levels of IIGT and HMHC. Results indicated the scores from the EIGT subscale discriminate between women and men but not between patients with and without a cancer diagnosis. Male patients presented significant higher scores of EIGT than female patients.

## DISCUSSION

Identifying individuals at risk for psychosocial issues is essential to promote psychological adjustment and quality of life in GT applicants. A screening instrument with this purpose should be clinically practical, reliable, and adapted to the population it intends to be used on. The results of this study confirm the reliability and validity of the Portuguese version of the GPRI with Portuguese GT applicants in the context of hereditary cancer.

We started by testing the original three factor model proposed by Esplen *et al*[11] and the alternative four factor model proposed in the French version, by Maheu *et al*.[21] However, our data could not fit either of these models adequately. The best fitting model for our data was composed by two factors proposed by Maheu *et al*[21]: (1) 'Internal Impact of Genetic Testing' (IIGT) and (2) 'External Impact of Genetic Testin'g (EIGT), plus one factor proposed by Esplen *et al*[11]: (3) 'History of Mental Health Concerns' (HMHC). It is worth noting that the initial factor 'Perceived Impact of Genetic Testing' (PIGT) proposed by Esplen *et al*[11] also provided a good fit for the data, but the subdivision of this factor in two (IIGT and EIGT) resulted in a better adjustment. One major difference between our results and prior versions concerned the factor 'Personal Loss To Cancer' (PLC). Our analysis found non-significant factor loadings for PLC, thus failing to

Table 3 – Descriptive statistics (mean and standard deviation) and mean comparison (*t*-test) for GPRI's subscales across female and male patients, with and without cancer diagnosis

| | **M** (SD) | *t* | df | d |
|---|---|---|---|---|
| **Internal Impact of Genetic Testing** (IIGT) | | | | |
| Female | 2.93 (0.86) | 2.85** | 46.03 | 0.53 |
| Male | 2.48 (0.83) | | | |
| Without cancer diagnosis | 2.71 (0.81) | -2.54* | 173.95 | 0.38 |
| With cancer diagnosis | 3.05 (0.91) | | | |
| **External Impact of Genetic Testing** (EIGT) | | | | |
| Female | 2.28 (0.81) | 2.94** | 46.29 | 0.54 |
| Male | 2.45 (0.80) | | | |
| Without cancer diagnosis | 30.25 (8.61) | -1.44 | 171.70 | 0.22 |
| With cancer diagnosis | 35.46 (8.67) | | | |
| **History of Mental Health Concerns** (HMHC) | | | | |
| Female | 0.33 (0.35) | 3.78** | 61.53 | 0.56 |
| Male | 0.14 (0.24) | | | |
| Without cancer diagnosis | 0.21 (0.30) | -3.45** | 172.84 | 0.51 |
| With cancer diagnosis | 0.38 (0.34) | | | |

*: $p < 0.05$; **: $p < 0.01$

confirm the existence of this latent construct. Although having been a caregiver of a cancer patient or having experienced personal loss of a family member due to cancer might affect psychological adjustment to hereditary cancer risk,[26] our results do not confirm the existence of the PLC subscale in the European Portuguese version of the GPRI. More research is needed to understand why this occurs. However, it is plausible that it may be due to sociocultural differences between Portuguese, French and Canadian populations. Another difference between our model and prior versions that could be related with cultural differences relates with the option to drop item 17 ("I have emotional problems that led me to thoughts about suicide") due to the existing collinearity with item 14 ("I have had emotional problems in the past").

Construct validity of the three subscales (EIGT, IIGT and HMHC) composing the final model was supported by our study, showing very good indicators of internal consistency (Cronbach's α = 0.85, 0.75, for EIGT and IIGT, and KR-20 = 0.76 for HMHC), discriminant and convergent validity. As expected, and consistent with the Canadian[11] and French versions,[21] the GPRI correlated with measures of depression, anxiety and distress, suggesting that it can identify GT applicants in need of psychological support. The results also indicated that female patients and patients diagnosed with cancer present higher scores regarding the HMHC and the IIGT factors. This is in line with prior research, that found that, in general, female patients tend to report higher levels of cancer-worry,[25] anxiety[26] and depression[27] than male participants, and that cancer patients are more susceptible to feelings of anxiety and depression.[28] Moreover, we found that participants with children displayed higher levels of IIGT and HMHC, which is in agreement with the literature. Research with pathogenic variant carriers from hereditary cancer families has consistently shown that concerns about possibly transmitting the pathogenic variant to children and communicating with children about test results tend to be central themes.[8,29,30] As the provision of genetic testing in Portuguese hospitals and clinics increases, clinicians will need a practical, reliable, and brief way to screen patients who may be at risk of maladjustment to GT and GT results. Global measures of distress or screening instruments may be less apt to identify specific genetic-testing contextual issues that could be addressed with tailored interventions.

Our results suggest confidence in the use of the GPRI by Portuguese genetic counsellors and medical genetics experts working in oncology departments. The validated tool may be used in routine practice to rapidly identify applicants who may be at risk of psychological adjustment issues and promptly refer them to psychological support services. Nevertheless, to integrate the Portuguese Version of the GPRI effectively in routine practice as a screening instrument, further research should be conducted to establish cut-off scores.

## Limitations

Two important limitations should be noted. Our sample had a low proportion of male participants and only included applicants undergoing GT for hereditary cancer syndromes. A second limitation is related with the fact that we could not

replicate the factorial structure of both the original version and the French version. This may hamper the applicability of the instrument in research settings because it may be significantly more difficult to compare outcomes across studies conducted in different countries and cultures. In this sense, given these results, we suggest that a cross validation study with diverse countries should be carried out.

## CONCLUSION

The Portuguese version of the GPRI is a reliable and valid screening measure of the psychological adjustment in the context of genetic cancer testing. Our results suggest that GPRI-P is composed by 16 items and three dimensions referring to 'History of Mental Health Concerns', 'Internal Impact of Genetic Testing' and 'External Impact of Genetic Testing'.

## AUTHOR CONTRIBUTIONS

PG: Data acquisition, drafting and approval of the final version of the manuscript.

TF: Data analysis, drafting and approval of the final version of the manuscript.

PMM, CMDS: Design and conception of the study. Critical review and approval of the final version of the manuscript.

ES: Data acquisition. Critical review and approval of the final version of the manuscript.

JS: Critical review and approval of the final version of the manuscript.

MJE: Critical review and approval of the final version of the manuscript.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## COMPETING INTERESTS

The authors have declared that no competing interests exist.

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# Addictive Potential of Social Media: A Cross Sectional Study in Portugal

# Potencial Aditivo das Redes Sociais: Um Estudo Transversal em Portugal

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## ABSTRACT

**Introduction:** The use of social media is an extremely popular activity, with an average time spent of two and a half hours daily. The number of users continues to rise, with 4.65 billion around the world in 2022, approximately 58.7% of the world population. A rising number of studies show that a minority of these persons will develop a behavioral addiction on social media. The aim of this study was to understand if the use of a specific social media platform predicts increased addictive potential.

**Material and Methods:** A cross-sectional sample of 300 persons (aged 18 years-old or older, 60.33% female), completed an online survey including sociodemographic questions, data regarding the use of social media and the Bergen Social Media Addiction Scale (BSMAS). Linear and logistic regression models were performed to determine the risk for each media platform.

**Results:** Instagram® use was a significant predictor of higher scores on the BSMAS (*B* 2.51; $p < 0.0001$; CI 1.33 - 3.69). The use of other platforms including Facebook® (*B* -0.31), Twitter® (*B* 1.38) and Pinterest® (*B* -0.15) was not found to predict a higher risk of social media addiction.

**Conclusion:** Instagram® scored a higher grade in BSMAS scale, with statistical significance, which could suggest a higher addictive potential. More research is needed to establish the direction of this relationship, since the cross-sectional study design does not allow inferences about directionality.

**Keywords:** Behavior, Addictive; Internet; Internet Addiction Disorder; Psychiatric Status Rating Scales; Social Media

## RESUMO

**Introdução:** A utilização de redes sociais é uma atividade bastante popular nos dias de hoje, com um tempo médio de utilização diária de duas horas e meia. O número de utilizadores continua a aumentar, perfazendo 4,65 mil milhões em 2022, aproximadamente 58,7% da população mundial. Um número crescente de estudos mostra que uma minoria destes utilizadores irá desenvolver uma adicção comportamental às redes sociais. O objetivo deste estudo é compreender se o uso de uma plataforma de rede social específica é um preditor de maior potencial adictivo.

**Material e Métodos:** Uma amostra de 300 pessoas (idade igual ou superior a 18 anos, 60,33% sexo feminino), completou um questionário online, com fatores sociodemográficos, dados acerca do uso de redes sociais e a *Bergen Social Media Addiction Scale* (BSMAS). Foram feitas análises de regressão linear e logística para determinar o potencial de adicção de cada plataforma.

**Resultados:** A utilização do Instagram® foi um preditor significativo para pontuações mais altas na BSMAS (*B* 2,51; $p < 0,0001$; CI 1,33 - 3,69). O uso de outras plataformas, incluindo o Facebook® (*B* -0,31), o Twitter® (*B* 1,38) e o Pinterest® (*B* -0,15) não pareceu ser um preditor de maior risco adictivo

**Conclusão:** O Instagram® atingiu uma maior classificação na BSMAS, com significância estatística, o que pode sugerir um maior potencial adictivo. É necessária mais investigação para estabelecer a direção desta relação, visto que o desenho transversal não permite inferências sobre a direccionalidade.

**Palavras-chave:** Comportamento Aditivo; Escalas de Classificação do Estado Psiquiátrico; Internet; Social Media; Transtorno de Dependência de Internet

## INTRODUCTION

Social media (SM) has changed individuals' everyday life. It is everywhere, from the way people communicate, to how they read the news or keep up with the latest events, with an average time spent by the users of two and a half hours daily.

The first social networking site dates back to 1997,[1] and the most accessed SM platform of all times, Facebook®, was created in 2004.[2] Since then, the number of SM users has increased to 4.65 billion around the world in 2022, approximately 58.7% of the world population.[3]

Due to the rising popularity of SM, there is emerging scientific literature reporting a myriad of its consequences, namely, body image concerns – both in men[4] and women[5–7] – disordered eating,[8] sleep difficulties,[9] loneliness,[10] depression[11] and impaired self-reported work and academic performance.[12] Additionally, several scholars have suggested that a minority of users develop a behavioral addiction on SM.[2,13–17] When distinguishing between addictive and non-addictive behavior, several addiction criteria have been used. These criteria include (1) mood modification: SM is used to induce mood changes, either pleasurable feelings or a numbing effect; (2) salience: SM use may become the single most important activity that they engage in; (3) tolerance: ever-increasing time and energy are required to achieve the same feelings that occurred in the initial phases of usage; (4) withdrawal symptoms; experiencing negative psychological and physical symptoms when SM are restricted; (5) conflict; interpersonal and intrapsychic problems arise as a consequence of SM usage; (6) relapse: rapid reinstatement of problematic use after an abstinence

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period.[15,17,18]

The addictive potential of a certain substance or behavior is the result of the combination of these different characteristics. Therefore, based on the undeniable differences between the SM platforms, so can the addictive potential vary. For instance, Facebook® allows users to post pictures, videos, articles, or even their own thoughts without a size limit; Instagram® is a pictorial platform where one can share personal videos and photos; Twitter® is a text network, where one can post messages up to 140 characters long and is partly focused on people discussing current events or expressing their opinions and ideologies; Pinterest® allows the user to share and save more impersonal theme-based pictures, offering ideas on interior design or outfits, for example. Some studies consider personality traits such as 'extroversion', 'socialization', 'narcissism' or 'neuroticism' could influence addictive potential to SM.[16]

As far as the authors know, no studies have assessed the addictive potential between each different SM platform. We then hypothesize that different social media platforms may also have different additive potentials. For example, the rapid delivery reward associated with Twitter® and Instagram®, the variety of possible social interactions on Facebook® or the more time-consuming pattern of using Pinterest® may contribute to different additive potentials between SM platforms.

In this study, we aimed to investigate if SM platforms were associated with addictive risks.

## MATERIAL AND METHODS

### Study design

A cross-sectional study was carried out. For this purpose, an anonymous online questionnaire including simple demographic data (age, sex, and education level), the SM networks used by the participants selected by leading social media site visit share in Portugal and the Bergen Social Media Addiction Scale was developed.[19]

The invitations to participate in the survey were sent by email, including a link to the questionnaire. Information about the study and informed consent were provided in the first page. All data were collected anonymously, and no monetary or material incentive was provided.

### Participants

Our inclusion criteria were age equal to or above 18 years old and using at least one SM platform. Exclusion criteria were less than 18 years old and absence of SM platform usage. The questionnaire was shared on multiple online platforms and the participants were contacted via SM platforms and e-mail.

The sample was made up of 300 people, with academic qualifications from primary education to doctorate, with the majority of participants having a master's degree.

This study was approved by the Ethics Committee of the Centro Hospitalar Universitário Lisboa Norte (CHULN) and Centro Académico de Medicina de Lisboa (CAML).

### Sample size calculation

Considering a significance level of 0.05 and a power of 0.8 we calculated a minimum sample of 96 people based on a 10% maximum prevalence of Facebook® addiction[20] and 33,5% maximum prevalence of Instagram® addiction.[16]

### Measures

The Bergen Social Media Addiction Scale (BSMAS)[19] is a modified version of the previously validated Bergen Facebook Addiction Scale (BFAS).[21] The modification involves using the words "Social Media" instead of the word "Facebook". This scale was constructed based on addiction criteria previously noted, namely mood modification, salience, tolerance, withdrawal symptoms, conflict, and relapse.[18] BSMAS assesses SM use experiences over the last 12 months through a 6-item questionnaire with a 5-point Likert scale, ranging from (1) Very rarely, (2) Rarely, (3) Sometimes, (4) Often and (5) Very Often. Higher scores indicate greater SM addiction. The scale was translated to Portuguese and then back translated by independent translators. The back-translation was then compared with the original scale and adjustments were made, as necessary.

### Analysis

The statistical analysis was executed using Stata software (version 14.2; StataCorp, Texas, USA). Descriptive statistics were presented as mean ± standard deviation.

To study the addictive potential of different media networks, the outcome was defined as the total score of the BSMAS, and the predictors were each type of social network. As many participants used different networks, we created binary variables for each network (1 = uses Facebook®, 0 = does not use Facebook®; 1 = uses Pinterest®, 0 = does not use Pinterest®; 1 = uses Instagram®; 0 = does not use Instagram®; 1 = uses Twitter®, 0 = does not use Twitter®). Sex, age, and education level, defined as categorical variables, were included as covariates.

First, we performed a multivariate linear regression model including all types of networks, analyzed separately in the model, using the binary variables, and all the potential confounding factors entered as covariates. We tested whether the data met assumptions for linear regression, namely, multicollinearity, using the variance inflation factor (VIF) post estimation test, normality, and the homoscedasticity of residuals.

Then we defined a new outcome variable using a previously suggested cut-off of 12 as an indicator of addictive

behavior problems.

Measures of association were expressed as coefficients (*B*) for linear regression and odds-ratio (OR) for logistic regression. A *p*-value ≤ 0.05 was considered statistically significant. Confidence intervals (CI) were also included in the results.

## RESULTS

### Socio-demographic and clinical characteristics of the sample

An initial sample of 301 persons was reduced to 300 persons, since one individual did not use any social network. The sample comprised 119 men (39.67%) and 181 women (60.33%). Most participants (75%) were in the age group that ranged from 25 to 34 years old. The sample represented a broad range of educational levels, from elementary school to doctoral degrees, and the most representative education category was master's degrees.

Regarding social media networks, most participants used two social media networks, followed by three and one social media networks.

The main SM used was Facebook® (94.67%), followed by Instagram® (73.33%).

Table 1 – Socio-demographic characteristics of the participants

| | |
|---|---|
| **Age categories**, n (%) | |
| 18 - 24 years | 29 (9.67) |
| 25 - 34 years | 226 (75.33) |
| 35 - 44 years | 17 (5.67) |
| > 45 years | 28 (9.33) |
| **Males**, n (%) | 119 (39.67) |
| **Education categories**, n (%) | |
| Elementary school | 1 (0.33) |
| Middle or high school | 34 (11.33) |
| Bachelor's degree | 57 (19.00) |
| Master's degree | 202 (67.33) |
| Doctoral degree | 6 (2.00) |
| **Social media networks**, n (%) | |
| Uses only one social media network | 70 (23.33) |
| Uses two social media networks | 138 (46.00) |
| Uses three social media networks | 82 (27.33) |
| Uses four social media networks | 9 (3.00) |
| Uses five or more social media networks | 1 (20.33) |
| **Social media networks**, types | |
| Uses Facebook® | 284 (94.67) |
| Uses Instagram® | 220 (73.33) |
| Uses Pinterest® | 76 (25.33) |
| Uses Twitter® | 29 (9.67) |

The socio-demographic characteristics of the sample are described in Table 1.

Regarding clinical characteristics, the mean value of BSMAS was 32.92 ± 11.90.

### Results from the multivariate analysis

Including all predictors in the linear regression multivariate model, Instagram® was found to be a significant predictor of higher BSMAS scores (*B* 2.51; $p < 0.0001$; CI 1.33 - 3.69). Due to multicollinearity, the variable education level (VIF 72) was not included in the final analysis. The final results are represented in Table 2. Normality of residuals was confirmed. However, we detected heteroscedasticity of residuals after using a fitted value *versus* residual plot.

Then we performed the analysis using a multivariate logistic regression model that found that Instagram® was a significant predictor of a BSMAS score higher than the defined cut-off of 12 (OR 2.56; $p = 0.008$; CI 1.28 - 5.12).

## DISCUSSION

The aim of our study was to investigate if the addiction risk differs according to the SM platform. We found that Instagram® was a significant predictor of higher BSMAS scores, suggesting a greater addictive risk even after controlling for age and sex.

Facebook® was the most accessed SM in our study, which is in line with the literature on the subject.[2] Nonetheless, regarding the differential addictive potential between different platforms, Instagram® users showed the highest BSMAS scores.

Instagram® is a platform specially designed for smartphones,[17] that is devoted to posting and sharing photographs, with more than 1 billion users worldwide.[22] Its association with higher BSMAS scores might be explained by different reasons. The fact that Instagram® is a visual SM is probably the most important factor. Since its users can easily edit photos and videos, receive comments, and 'likes', broadcast live streams, follow other profiles, and be followed by others, this multiplicity of actions seems to

Table 2 – Results from the multivariate model

| **Age categories**, n (%) | **Coeficcients** (*B*) | ***p*-value** |
|---|---|---|
| 25 - 34 years | -0.24 | 0.78 |
| 35 - 44 years | -0.49 | 0.71 |
| > 45 years | -2.29 | 0.05 |
| **Males**, n (%) | 0.96 | 0.07 |
| **Social media networks**, types | | |
| Uses Facebook® | -0.31 | 0.97 |
| Uses Instagram® | 2.51 | 0.00 |
| Uses Pinterest® | -0.15 | 0.79 |
| Uses Twitter® | 1.38 | 0.10 |

contribute to its excessive use. In fact, statistics show a total of around 544 million posts daily,[23] guaranteeing that the user has always something new to watch, in a seemingly endless scroll, keeping users online longer. Moreover, the explore page algorithm shows photos and videos based on previous research, customizing the pages to show according to everyone's interests, making it easier to spend even more time on the app.

Additionally, Instagram® stories (photos or short videos available for 24 hours only), may help to explain its association with higher BSMAS scores since the user can tailor these snaps with stickers, questions, or polls to obtain reactions from followers, which may act as an immediate reward, positively reinforcing the dysfunctional behavior when it is turned into an addiction. Besides, the stories are shown continuously one after the other and they are also the first thing one sees when opening the app.

Lastly, Instagram® was specifically designed as a smartphone app, enabling its use on the go. In fact, 91% of SM users access the platforms through mobile devices,[24] and the number of smartphone users in 2020 is estimated to be 3.5 billion worldwide.[25]

The present study has some limitations. We recognize that the cross-sectional study design does not allow us to prove the directionality of our findings or demonstrate causality. Another limitation of our study is being an open access poll, leading to an imbalance in sex and age groups, However, these differences were controlled for in the multivariate models. Also, individual variables that could lead to higher addictive tendencies, such as personal or family history of addictive disorders, or personalities with a greater tendency to addiction, were not controlled in this study. The limitation of the Bergen Social Media Addiction Scale (scale used to assess addiction in the questioned social networks) not having been validated for Portuguese, which does not seem to us to be a very significant limitation, since the previous version of the scale (Bergen Facebook Addiction Scale) has been validated for European Portuguese by Pontes *et al*.[26] Additionally, the sample size is relatively modest. Nevertheless, the sample is comprised of the general population, and potentially representative of the population that has more access and use of SM.

Even though SM addiction has been reported in several studies, to the best of our knowledge, this is the first study to compare the addictive risk of different SM platforms that has a diverse sample with convenient size.

## CONCLUSION

Instagram® had the highest score in the BSMAS scale, with statistical significance, which could suggest a higher addictive potential. Further studies, preferably using more representative samples and with an experimental methodology, should be conducted to understand the directionality of the findings and long-term consequences.

## AUTHOR CONTRIBUTIONS

BCR: Conception of the work; methodology; fata collection; writing of the manuscript.

CC, PCP, IDS: Data collection; critical review, editing and approval of the manuscript.

FN: Conception of the work; methodology; data collection and analysis; critical review, editing and approval of the manuscript; supervision of the work.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## COMPETING INTERESTS

PCP has received support for attending meeting and/or travel from Lundbeck.

FN has received payment or honoraria for lectures, presentations, speakers, bureaus, manuscript writing or educational events from Tecnifar and Lundbeck; received support for attending meetings and/or travel from Angelini.

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# Consensus for the Early Identification of Secondary Progressive Multiple Sclerosis in Portugal: a Delphi Panel

# Consenso Português para a Identificação Precoce de Esclerose Múltipla Secundária Progressiva: Painel Delphi

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## ABSTRACT

**Introduction:** Multiple sclerosis is a disease with a heterogeneous evolution. The early identification of secondary progressive multiple sclerosis is a clinical challenge, which would benefit from the definition of biomarkers and diagnostic tools applicable in the transition phase from relapsing-remitting multiple sclerosis to secondary progressive multiple sclerosis. We aimed to reach a Portuguese national consensus on the monitoring of patients with multiple sclerosis and on the more relevant clinical variables for the early identification of its progression.

**Material and Methods:** A Delphi panel which included eleven Portuguese Neurologists participated in two rounds of questions between July and August of 2021. In the first round, 39 questions which belonged to the functional, cognitive, imaging, biomarkers and additional evaluations were included. Questions for which no consensus was obtained in the first round (less than 80% of agreement), were appraised by the panel during the second round.

**Results:** The response rate was 100% in both rounds and consensus was reached for a total of 33 questions (84.6%). Consensus was reached for monitoring time, evaluation scales and clinical variables such as the degree of brain atrophy and mobility reduction, changes suggestive of secondary progressive multiple sclerosis. Additionally, digital devices were considered tools with potential to identify disease progression. Most questions for which no consensus was obtained referred to the cognitive assessment and the remaining referred to both functional and imaging domains.

**Conclusion:** Consensus was obtained for the determination of the monitorization interval and for most of the clinical variables. Most questions that did not reach consensus were related with the confirmation of progression taking into account only one test/domain, reinforcing the multifactorial nature of multiple sclerosis.

**Keywords:** Consensus; Multiple Sclerosis, Chronic Progressive/diagnosis; Portugal

## RESUMO

**Introdução:** A esclerose múltipla é uma doença de evolução heterogénea. A identificação precoce da forma secundária progressiva é um desafio clínico, carecendo da definição de biomarcadores e ferramentas de diagnóstico aplicáveis na fase de transição da forma surto-remissão para a forma secundária progressiva. Este trabalho teve como objetivo estabelecer um consenso nacional português sobre a monitorização dos doentes e das variáveis clínicas mais relevantes para a identificação precoce da progressão da esclerose múltipla.

**Material e Métodos:** Um painel Delphi constituído por 11 neurologistas portugueses respondeu a duas rondas de perguntas entre julho e agosto de 2021. Na primeira ronda foram incluídas 39 questões relacionadas com a avaliação funcional, cognitiva, imagiológica, de biomarcadores e outras, e na segunda, as questões para as quais não foi atingido consenso (menos de 80% de concordância) na primeira ronda voltaram a ser submetidas a avaliação pelo painel.

**Resultados:** A taxa de resposta foi de 100% em ambas as rondas e 33 das 39 questões (84,6%) atingiram concordância. Foi atingido consenso relativamente ao tempo de monitorização dos doentes, às escalas de avaliação a empregar e a variáveis clínicas tais como o grau de atrofia cerebral ou redução da mobilidade, cuja alteração é sugestiva de esclerose múltipla secundária progressiva. Adicionalmente, os dispositivos digitais foram considerados ferramentas com potencial para identificar a progressão da doença. A maioria das questões para as quais não foi obtido consenso dizem respeito à avaliação cognitiva, estando as restantes inseridas nos domínios funcional e imagiológico.

**Conclusão:** Foi obtido consenso para a determinação do intervalo de monitorização e para a maioria das variáveis clínicas. A maioria das questões sem consenso estavam relacionadas com a confirmação do diagnóstico de progressão tendo em conta apenas um teste/domínio, realçando a natureza multifatorial da esclerose múltipla.

**Palavras-chave:** Consenso; Esclerose Múltipla Crónica Progressiva/diagnóstico; Portugal

## INTRODUCTION

Multiple sclerosis (MS) is a chronic, autoimmune and neurodegenerative condition that affects approximately 2.8 million people worldwide and a range of 34.3 to 64.4 per 100 000 people in Portugal, being the most common cause of

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non-traumatic disability in young adults.[1-8] As symptoms usually appear in individuals who are between 30 and 40 years old and, therefore, at a highly productive stage of life, it can have a profound social and economic impact.[6,7,9]

In general, MS patients are initially diagnosed with relapsing-remitting MS (RRMS), characterized by the occurrence of relapses or lesions that cause neurological damage, followed by partial or complete recovery and no disease progression between relapses.[10,11] The duration of the RRMS phase is variable, but approximately 50% of untreated patients will progress to a later stage of disease, secondary progressive MS (SPMS), within 15 years after the onset of the first symptoms.[11] SPMS is associated with a higher degree of disability, an inherent deterioration of the patients' health status and with few or no relapses, as after the start of progression only approximately 30% of patients experience relapses.[12,13]

Due to the heterogeneous clinical presentation of MS and the lack of diagnostic tools and criteria, SPMS is usually retrospectively diagnosed considering increased disability and neuronal loss.[10,11] However, early SPMS diagnosis would allow patients to start treatments aimed at this phase of the disease before developing severe disability, thus maximizing the benefit of such drugs.[12] The identification of clinical presentations suggestive of progression to SPMS are, therefore, of the utmost importance for a timely diagnosis and treatment of SPMS.[10,12]

The aim of this study was to identify the clinical variables and the most adequate follow-up timings for the early identification of progression for SPMS.

## MATERIAL AND METHODS

A Delphi panel[14] with two rounds was conducted between July and August 2021, to evaluate the most appropriate timings and clinical variables to monitor and assess MS progression. Eleven Portuguese Neurologists with extensive expertise in the monitorization and treatment of MS were invited to the Delphi panel. The questionnaire was adapted from a survey developed to reach a national consensus on the relevant clinical variables to predict progression to SPMS in Spain[15] with the help from the two experts responsible for the coordination of the project. The survey was divided into 39 questions/statements that belonged to five different assessment domains: functional, cognitive, imaging, biomarkers and additional assessments.

All the questions/statements were rated using three Likert scales that evaluated levels of agreement (completely disagree, disagree, agree, completely agree), recommendation (do not recommend at all, do not recommend, recommend, fully recommend) and applicability (medium/long term applicability, short term applicability, not applied in clinical practice but useful, already applied in clinical practice). The questionnaire was made available online and the answers were anonymous. The questions were considered to have reached consensus at equal to or greater than 80% of agreement. In between rounds, the results were analyzed and sent to the Delphi panel. To facilitate the interpretation of the results, the evaluations completely disagree/disagree and agree/completely agree, as well as the evaluations do not recommend at all/do not recommend and recommend/fully recommend were pooled under the evaluations disagree, agree, do not recommend, and recommend.

## RESULTS

The response rate in both rounds was 100%. In the first round, consensus was obtained for 28 questions (71.8%). The remaining 11 questions were appraised during the second round and consensus was achieved for five questions (45.5%). Thus, in total, consensus was obtained for 33 of the 39 questions (84.6%) (Fig. 1). The percentages for each question are detailed in the Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18543/15036).

### Functional evaluation

Regarding the functional domain of SPMS, six and three months were consensually agreed as the most adequate time interval for monitoring patients under disease modifying therapies who are clinically and imagiologically stable or unstable, respectively. Nevertheless, it was also consensual that when progression is suspected the patient should be monitored on a case-by-case basis.

Consensus was also reached regarding the Expanded Disability Status Scale (EDSS) as the best measure to define progression. Moreover, an increase of 20% in the 25-foot walk test (25FTW) and in the 9-hole peg test (9HPT) or in EDSS Plus (which includes 25FTW, 9HPT and EDSS) was considered sufficient to suspect and confirm the diagnosis of progression. Even without changes in the EDSS,

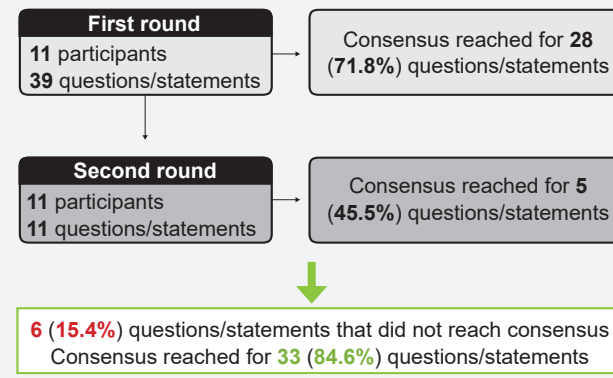


Figure 1 – Flow chart of the Delphi panel results

confirmed worsening of 2-points in any functional system (except the visual) was considered to allow the suspicion and confirmation of a progression diagnosis if disease duration was 10 to 20 years and/or if the patient was older (over 45 years-old).

Defining progression as an increase in confirmed disability, measured by EDSS, regardless of the existence of relapses, achieved 90.9% of consensus. In addition, the minimum time needed to confirm the diagnosis of progression not associated with relapses, independently of the variable used, was considered to be 12 months.

Decreases in mobility, such as the transition from walking independently to needing support or help and a reduction from 500 to 300 m in the distance that the patient can walk without needing rest, were regarded as suspicious of disease progression, but the panel unanimously highlighted the need to use more accurate progression diagnostic tools. Accordingly, the experience of repeated falls, reflecting a clear loss of physical endurance, even without changes in the EDSS score or other evaluation tools, was deemed to suggest the diagnosis of progression. Nevertheless, consensus was not reached on the use of this clinical evaluation as confirmation of a disease progression diagnosis.

**Cognitive evaluation**

Regarding the cognitive domain, consensus was reached for performing at least one cognitive assessment per year since MS diagnosis. In addition, the frequency of this assessment was considered to depend on the clinical situation of the patient and on the recommendation of the neurologist. Moreover, it was considered that the cognitive assessment should include the largest number of domains possible, being recommended the application of at least one battery of intermediate duration, such as the Brief Repeatable Battery of Neuropsychological tests (BRB-N). However, if it is not possible to apply a battery of intermediate duration, a short duration battery such as the Brief International Cognitive Assessment for MS (BICAMS) should be applied. If this short battery can also not be applied, it was considered appropriate to apply a test such as the Symbol Digit Modalities Test (SDMT). Consensus was not reached on whether a battery like BICAMS needed to be applied by a neuropsychologist to obtain a reliable assessment. Nevertheless, if progression of cognitive decline is suspected after application of a short or intermediate battery of tests, it was considered that a comprehensive neuropsychological study by a neuropsychologist should be performed.

Concerning the changes in the cognitive domain suggestive of SPMS, consensus was obtained for how a confirmed worsening of 20% in at least two subtests of the BRB-N or BICAMS battery of tests, after exclusion of other factors, is sufficient to confirm a progression diagnosis. Also, a confirmed 20% reduction in SDMT was considered sufficient to suspect disease progression. No consensus was obtained on whether an isolated worsening of cognitive function was sufficient to diagnose or even suspect disease progression. Likewise, a confirmed 20% reduction in SDMT was not considered sufficient to confirm a diagnosis of progression.

**Imaging evaluation**

Changes in the degree of brain or spinal cord atrophy which are maintained and/or confirmed over time were consensually considered to be suggestive of disease progression. However, no consensus was reached on the presence of diffuse hyperintensity leading to the suspicion of disease progression.

**Biomarkers**

Increased levels of serum neurofilament light chain (sNfL) and changes in optical coherence tomography (OCT) were considered important biomarkers to identify disease progression. Additionally, digital devices were regarded as relevant tools for the early diagnosis of SPMS.

**Additional assessments**

It was consensually agreed that, since the diagnosis of MS, patients should complete a scale/questionnaire which evaluates depression, fatigue and quality of life, as well as a scale that assesses spasticity (if changes in the pyramidal function system occur), at least once a year. Accordingly, deterioration of the patient's quality of life and/or worsening of spasticity were considered to be good indicators for the need to use more precise diagnostic tools. However, changes in scales that measure fatigue and depression were considered insufficient to confirm an SPMS diagnosis. Regarding the informal assessment of patients, it was agreed that patients should be asked proactively and in a structured manner if they noticed some change in their symptoms that could suggest disease progression.

## DISCUSSION

The transition between RRMS and SPMS is difficult to identify due to the overlap between the two conditions. The different modulation by environmental, genetic and epigenetic factors affects the clinical course, symptoms, and therapy. Additionally, the central nervous system compensatory processes can cause a delay in the manifestation of progressive disease.[11] Thus, the time between the onset of disease progression and confirmation of diagnosis has been estimated to be three years, on average.[13,16] This delay can result in needless deterioration of quality of life and increase in costs, as patients may continue relapse-reducing disease modifying therapies, which are ineffective for slowing SPMS, and, therefore, lose the opportunity to

tackle early SPMS with therapies that may delay disability progression.[13,16]

In this Delphi panel, consensus for disease monitoring time intervals was dependent on the degree of stability of patients. Nevertheless, the achievement of 100% of agreement for a case-by-case analysis reflects the heterogeneity of MS, impacting the timing for medical appointments. This tailored-made medicine is especially relevant if there is suspicion of progression.

EDSS is widely regarded as the most used tool to measure MS outcomes, having been accepted internationally as a primary endpoint in clinical trials, allowing cross-study comparisons.[17] Similarly, it was deemed the best measure available in clinical practice to define progression in this study. The definition of progression has been challenging due to the difficulties in identifying SPMS early.[18] Recently, a new definition has been suggested: it considers that if a patient presents a minimal value of 4 in the EDSS score, a pyramidal function system of ≥ 2, and had confirmation of progression for at least three months, an increase of 1 point in the EDSS score if the initial score was ≤ 5.5, or an increase of 0.5 points if the initial score was ≥ 6, confirms disease progression.[19] However, no consensus was reached by this panel, with only 63.6% of the participants considering that this is an appropriate definition of progression. This might be explained by the observation that this definition implies that disability progression can be confirmed during the follow-up at three months.[18] It has been previously suggested that, at this time, diagnosis should be done carefully and confirmed in a later follow-up.[18] Accordingly, this panel considered that 12 months was the minimum time needed to confirm the diagnosis of disability progression not associated with relapses. The selected time interval is explained by the observation that 30% of patients which had a confirmed progression at the three or six months follow-up can still show clinical improvements during the 12 or 24 months follow-up, especially if the EDSS changes are small or if patients are younger.[18] However, and given that waiting 24 (or 18) months could delay treatment[18], 12 months was the selected time interval. In this case, the definition of progression as an increase in confirmed disability at three, six or 12 months, measured by EDSS, regardless of the existence of relapses, reached consensus.

It has been previously shown that the risk of developing SPMS increases with age.[20] Moreover, it was shown that approximately two thirds of untreated RRMS patients will progress to SPMS within 10 to 20 years.[6] Thus, this panel also agreed that for patients who are over 45 years old and have had MS for 10 to 20 years, a worsening of 2-point in any functional system (except the visual), even without changes in the EDSS, can confirm a diagnosis of progression.

Multiple sclerosis causes motor symptoms such as muscle weakness, abnormal walking mechanisms and balance problems.[21] Thus, it is not surprising that consensus was reached for suspicion of progression when patients experience repeated falls, which reflect a clear loss of balance, even without changes in other evaluation tools; when patients reduce the distance that they are able to walk without help or rest from 500 to 300 m; or when the patient transitions from walking independently to needing support or help to do so. However, repeated falls with evident loss of balance alone were not considered sufficient to confirm a progression diagnosis. Changes in other tests would be needed to confirm it. Accordingly, consensus was obtained for confirmation of progression diagnosis when there is a confirmed 20% increase in the 25FTW (which measures ambulation) and 9HPT (which measures upper limb function) or in the EDSS Plus (which combines the two previously mentioned tests and EDSS).[18]

Most questions for which no consensus was obtained belonged to the cognitive performance domain. Cognitive impairment can manifest itself early in the course of the disease and impacts the patients' employability, social interactions, and quality of life.[22] Additionally, it affects approximately 40% to 70% of MS patients in North America and Europe.[23] Thus, it is a major contributor to the burden of MS. However, assessment of cognitive dysfunction is a challenge as it is difficult to define what is considered normal cognition.[22] Moreover, impairment in cognitive function is present in various neurological diseases and depends on the involvement of different brain structures, extent of neuronal damage, and the cognitive reserve and performance of patients.[22,24] Therefore, the importance of cognitive impairment, on one hand, and the difficulty in defining it, on the other hand, may explain why no consensus was reached on the suspicion or confirmation of SPMS diagnosis based on the isolated worsening of cognitive function. Also, no consensus was reached on confirmation of progression based only on a 20% worsening measured by SDMT. This lack of agreement may be due to SDMT being a test that only evaluates one aspect of cognitive impairment (cognitive processing speed) and thus might not reflect the decline of cerebral functions over time which might occur in MS patients.[25] Moreover, the frequency of use of this test seems to impact the results. A recent study, which used original data from the ASCEND trial, where the SDMT test was applied every four weeks during follow-up, reported a steady increase of SDMT scores during this period, which suggests the existence of a practice effect and, thus, the inability to correctly reflect the steady cognitive decline that MS patients experienced.[26] However, in the EXPAND trial, where the original SDMT and two alternative forms (shown to have the same degree of difficulty), were presented in

an alternate pattern every six months, a steady increase in SDMT scores was not observed for patients under treatment with placebo.[27] Thus, although a 20% confirmed reduction on SDMT can suggest progression, it cannot alone confirm the diagnosis. A more thorough evaluation using batteries of tests such as the BRB-N (preferentially) and BICAMS could provide more information on the cognitive status of patients.

No consensus was reached on whether a battery of tests such as BICAMS should be applied by a neuropsychologist to obtain a reliable cognitive assessment. The lack of agreement may be explained by the fact that this battery of tests was developed to be applied by an individual without expertise in cognitive assessment, even though the person applying the test needs to be able to interpret the results, taking into account several confounding variables (MS physical symptoms, demographic factors, other neurological disorders, concurrent medication, and a modest degree of depression).[28]

Due to the relevance and prevalence of cognitive problems, evaluation of the patients' cognitive abilities is recommended in order to monitor disease progression and predict cognitive impairment.[18] In this case, a consensus of one evaluation per year was reached, while also considering that the condition of the patient and the opinion of the neurologist should be taken into account to adjust this time period, if needed.

Magnetic resonance imaging (MRI) is the most common tool for routine surveillance of MS patients, and in a study where Neurologists were interviewed, 68.8% of the physicians reported that their SPMS diagnosis was usually based on MRI scans.[29,30] Our panel reached consensus for suspecting progression when there were changes in the degree of brain atrophy or of spinal cord atrophy. However, no consensus was reached on whether the presence of diffuse hyperintensity in the brain white matter or confluence of lesions would suggest progression. This might be explained by the fact that white matter hyperintensities are not specific to MS and can be detected in individuals with other disorders and even in seemingly healthy individuals, especially with aging.[31] Thus, to reach a diagnosis, it is necessary to combine the characteristic clinical presentations of SPMS with images of lesions that have the morphology and location that are usually associated with MS.[31]

The identification of biomarkers would advance the monitoring of MS and facilitate SPMS diagnosis. However, only a small number of biomarkers are validated, and even a lower number have been translated into clinical practice.[32] Increased sNfL has been associated with brain fraction loss and consequently with cognitive ability, with the increase in sNfL levels being significantly faster, in MS patients experiencing disability worsening, when compared with MS patients that remained stable.[32-34] Also, OCT has been increasingly applied for the study of MS, as it allows quantification of neuronal loss.[35] Accordingly, the Delphi panel agreed that changes in these biomarkers could suggest disease progression. Moreover, the panel considered that digital devices could be relevant for the early detection of SPMS. This is in line with the results of Ziemssen *et al*, that reported that 11 in 16 Neurologists would prefer a digital tool to help evaluate the early and subtle symptoms that are suggestive of SPMS.[30] Also, digital devices, such as wrist accelerometers to measure gait, which allow real-time monitoring, are considered promising for the early detection of progression.[18]

As MS can cause spasticity and fatigue, and usually promotes feelings of depression, highly impacting the quality of life of patients,[21,36] the need to assess these variables was discussed by this panel. Consensus was reached on the importance of frequently assessing these symptoms and how their worsening can be suggestive of progression. However, due to the variety of factors that can cause depression and fatigue, their changes alone cannot confirm progression.

Comparing the agreement and recommendation scales, they both follow the same trend, with the questions that reached agreement being also the most recommended. In terms of applicability there was a more varied distribution, reflecting different clinical practices of the members of the Delphi panel. Interestingly, there were some measures not applied in clinical practice, whose applicability was deemed to be useful, namely: confirmation of the diagnosis of progression due to worsening of 2-points in any functional system (except the visual), even without changes in EDSS, if disease duration is greater than 20 years and if the patient is between 25 to 45 years old; suspicion of progression due to 20% worsening in at least two subtests of the BRB-N or BICAMS battery of tests, after excluding other factors; suspicion of progression due to change of the degree of brain atrophy maintained and/or confirmed over time; applying at least once per year a scale/questionnaire that evaluates fatigue and depression or fatigue and spasticity; and the use of more accurate progression diagnostic tools if there is a worsening in spasticity.

In summary, the main recommendations of our panel for the early identification of SPMS are as follows:

- Timing of clinical monitoring of disease modifying-treated patients: determined by the physician on a case-by-case basis, being recommended every three or six months, in cases of clinical and radiological instability or stability, respectively.
- Definition of progression: increase in confirmed disability measured by EDSS, regardless of relapses; if progression is suspected, the patient should be evaluated on a case-by-case basis. A 20% increase in the EDSS Plus or in 25FTW and 9HPT suggests disease progression and a decrease in the ability to

move independently indicates the need to use more accurate progression diagnostic tools.

- Cognitive evaluation: should be performed annually, ideally with a comprehensive battery; progression can be suspected upon a confirmed worsening of 20% in at least two subtests of the BRB-N or BICAMS battery of tests.
- Imaging: a maintained change in the degree of brain or spinal cord atrophy should lead to the suspicion of disease progression.
- Biomarkers: increased levels of sNfL and OCT changes can be important biomarkers of progression.
- Additional evaluations: the assessment of depression, fatigue and quality of life must be performed annually, although changes in those parameters should not be considered as isolated prognostic factors; a scale that assesses spasticity should be applied in patients with worsening of pyramidal functions.

### Strengths and limitations

The composition of a Delphi panel is a determining question for ensuring its validity. In this study, the specialists involved have extensive clinical practice in treating MS patients, and work in some of the largest hospitals in the country. Additionally, these hospitals included the main regions of mainland Portugal and Madeira, being therefore representative of the Portuguese reality. Nevertheless, to adapt the questionnaire to the realities of different hospitals in different regions of the country, some specific techniques and/or resources were not included in the questionnaire. Moreover, the multifactorial nature of MS makes it difficult to approach all domains in detail. Thus, due to feasibility constraints, some more specific statements such as the types of digital devices that could be useful and how to perform specific assessments were not included.

## CONCLUSION

Consensus was achieved for most of the questions/statements included in this Delphi panel. From all the analyzed domains, the cognitive domain was the one for which more uncertainty was present, possibly due to both the complexity and difficulty in cognitive assessment. Nevertheless, cognitive assessment is clinically relevant as highlighted by the consensus obtained for annual cognitive assessment, with a 20% reduction in SDMT considered sufficient to suspect SPMS progression. The questions for which no consensus was achieved focused mainly in SPMS diagnosis using only one clinical variable, which reflects the multidomain nature of MS. Assessments using imaging techniques and biomarkers seem very promising, even though more research is needed to establish them as diagnostic tools. Also, development of digital tools and devices might facilitate the early diagnosis of SPMS.

This study increases awareness about the importance of early identification of progression and the reached consensus provides a complete set of criteria for the early diagnosis of SPMS.

## AWARDS AND PRIOR PRESENTATIONS

Part of the data described in this manuscript were orally presented at the Congresso Nacional de Neurologia 2021, Albufeira, Portugal, Oct. 27-30, 2021.

## AUTHOR CONTRIBUTIONS

MJS and LS: Conception of the work, members of Delphi panel, critical review and approval of the final version to be published.

CB, CC, JJC, IM, AM, JCS, VS, AMS, JV: members of the Delphi panel, critical review and approval of the final version to be published.

## COMPETING INTERESTS

CC received fees from Janssen, Merck e Roche, Almirall, Biogen, Bristol Myers Squibb, Novartis, Sanofi-Genzyme, Teva and Bayer.

JJC has received fees from Biogen, Novartis, Roche, Merck, Bial Foundation, Fundação para a Ciência e Tecnologia, Almirall, Zambon, Bristol Myers Squibb and Janssen, and is a member of the Multiple Sclerosis Study Group.

JCS received fees from Novartis, Roche, Merck, Biogen, Bristol Myers Squibb and Sanofi Aventis.

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# The Obsessive-Compulsive Inventory-Revised (OCI-R): Translation and Validation of the European Portuguese Version

# Obsessive-Compulsive Inventory-Revised (OCI-R): Tradução e Validação da Versão Portuguesa

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## ABSTRACT

**Introduction:** The Obsessive-Compulsive Inventory-Revised has been developed to evaluate the severity of obsessive-compulsive symptoms in both clinical and non-clinical individuals. The aim of this study was to evaluate the psychometric properties of the Portuguese version.

**Material and Methods:** This questionnaire was applied to 90 people with obsessive-compulsive disorder and 246 without a known mental illness. In addition to this clinical evaluation instrument, participants completed other clinical assessment scales that helped characterize the two study groups.

**Results:** Given the objective of this study, to evaluate the structure by six factors, a confirmatory factor analysis was performed [patient group: $\chi2(120, n = 90) = 205.779$, $p < 0.01$; CFI = 0.916; GFI = 0.814; RMSEA = 0.0890. Control group: $\chi2(120, n = 246) = 224.762$, $p < 0.01$; CFI = 0.938; GFI = 0.904; RMSEA = 0.060]. To assess the internal consistency of the scale, Cronbach's alpha was determined (patient group: α = 0.913; control group: α = 0.888). Convergent validity was tested by determining the Spearman correlation between the scores obtained in the Obsessive-Compulsive Inventory-Revised and Y-BOCS in the patient group (r = 0.651; $p < 0.01$).

**Conclusion:** Obsessive-Compulsive Inventory-Revised has proved to be a consistent, valid, and reliable instrument with good psychometric properties to determine the severity of obsessive-compulsive symptoms in the Portuguese population.

**Keywords:** Obsessive-Compulsive Disorder; Portugal; Psychiatric Status Rating Scales; Psychometrics; Reproducibility of Results; Translating

## RESUMO

**Introdução:** A escala *Obsessive-Compulsive Inventory-Revised* foi desenvolvida para avaliar a gravidade dos sintomas obsessivo-compulsivos em contexto clínico e não clínico. O objectivo deste estudo foi avaliar as propriedades psicométricas da sua versão portuguesa.

**Material e Métodos:** O questionário em estudo foi aplicado a 90 pessoas com perturbação obsessivo-compulsiva e 246 pessoas sem doença psiquiátrica conhecida. Além deste instrumento de avaliação clínica, os participantes preencheram outras escalas de avaliação clínica que ajudaram a caracterizar os dois grupos de estudo.

**Resultados:** Dado o objetivo deste estudo, para avaliar a estrutura por seis fatores foi realizada uma análise fatorial confirmatória [grupo de doentes: $\chi2(120, n = 90) = 205,779$, $p < 0.01$; CFI = 0,916; GFI = 0,814; RMSEA = 0,0890. Grupo controlo: $\chi2(120, n = 246) = 224,762$, $p < 0,01$; CFI = 0,938; GFI = 0,904; RMSEA = 0,060]. Para avaliar a consistência interna da escala foi determinado o *alpha* de Cronbach (grupo de doentes: α = 0,913. grupo controlo: α = 0,888). A validade convergente foi testada através da determinação da correlação de Spearman entre as pontuações obtidas no *Obsessive-Compulsive Inventory-Revised* e Y-BOCS no grupo de doentes (r = 0,651; $p < 0,01$).

**Conclusão:** O *Obsessive-Compulsive Inventory-Revised* revelou-se um instrumento consistente, válido e fiável com boas propriedades psicométricas para determinar a gravidade dos sintomas obsessivo-compulsivos na população portuguesa.

**Palavras-chave:** Escalas de Graduação Psiquiátrica; Perturbação Obsessivo-Compulsiva; Portugal; Psicometria; Reprodutibilidade dos Testes; Tradução

## INTRODUCTION

Obsessive-compulsive disorder (OCD) is a condition that has a worldwide estimated 12-month prevalence between 1.1% and 1.8%[1] and an estimated lifetime prevalence of 2.3%.[2] In Portugal, the 12-month prevalence is estimated at 4.4% and the lifetime prevalence at 5.3%.[3]

OCD is associated with high levels of anxiety and suffering[4,5] and, as the name suggests, is characterized by the presence of obsessions, which are recurrent thoughts, impulses, or images experienced as intrusive and unwanted that usually trigger compulsions that are repetitive behaviors or mental acts that an individual feels compelled to perform according to strict rules that they set.[1]

Although established as a single condition, OCD has significant heterogeneity concerning the spectrum of symptoms experienced by patients, making the diagnosis and the follow-up and treatment of patients with this disorder challenging.[6-8] Therefore, over time, several studies have been conducted in order to develop tools that facilitate the task of clinicians and enable them to gather as much pertinent information as possible about the disorder. Examples of this are psychometric rating scales such as the Obsessive-Compulsive Inventory (OCI)[9] and its shortened version

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Obsessive-Compulsive Inventory-Revised (OCI-R),[10] the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS),[11,12] the Padua Inventory[13] or the Clark-Beck Obsessive-Compulsive Inventory.[14]

The OCI is one of the most recent assessment tools and was created to address the instrument's failures that preceded it. Consisting of 42 items, this self-applied instrument has good internal consistency, reliability, and validity, fulfilling its task concerning disorder assessment.[9]

The OCI is considered a substantial advance over other instruments within the different existing scales, given its characteristics. However, the OCI has some limitations, such as its extension, making the response rate to this instrument low. In this sense some changes and improvements were suggested to optimize its use.[9,10] Therefore, the OCI-R assumes itself as a simplified and improved version of the OCI, meeting the same assumptions as the original scale.

The OCI-R consists of 18 equally divided items in six categories: Hoarding, Checking, Ordering, Neutralizing, Washing, and Obsessing. Several studies have tested this scale to evaluate its psychometric properties, and the results obtained were consistent and demonstrated similar values to those obtained for OCI.[10,15-17]

Considering the good psychometric properties, similar to those of OCI, and given the small number of items, the OCI-R is an instrument with remarkable clinical applicability. Therefore, this instrument was translated into different languages, and all different versions were subsequently validated. Also noteworthy is the transversality in the psychometric properties that corroborate the values initially pointed in the development and validation of this instrument.[18-27]

Looking at the national scenario, psychometric properties of OCI-R have been described in two non-clinical samples,[28] but a Portuguese version of this scale duly validated in a clinical population does not exist. For this reason, the aim of this study was to address that gap and assess the psychometric properties of the Portuguese version of the scale in a clinical sample with OCD patients and a non-clinical sample with healthy controls.

## MATERIAL AND METHODS

### Population and sample

This study was conducted using two groups, one with patients with OCD and another group with individuals without the disorder. The minimum sample size per group was estimated based on the number of OCI-R items: five participants per item, totaling 90 participants.[29,30]

### Clinical sample

The clinical sample included patients diagnosed with OCD according to the diagnostic criteria established in DSM-5. Ninety OCD patients (46 women and 44 men) were recruited from the Psychiatry outpatient clinic of Hospital de Braga (Portugal) by their psychiatrists. All participants were aged 18 years or older and voluntarily agreed to participate in this study. Failure to complete at least one of the assessment instruments applied constituted an exclusion factor.

The age of the participants varied between 18 and 67 [mean (M) = 32.64; standard deviation (SD) = 11.40] years and their years of education ranged between four and 19 (M = 12.18; SD = 3.03).

Within the patient group, women had a mean age of 35.30 (SD = 13.05; Min = 18; Max = 67) years, while the average age of men was 29.86 (SD = 8.66; Min = 18; Max = 50) years. Overall, women with the disorder were significantly older than men (independent samples *t*-test $t(88) = -2.34$; $p = 0.02$; Cohen's effect size $d = -0.49$). The group of women had an average schooling of 11.89 (SD = 3.29; Min = 4; Max = 18) years, and men had an average schooling of 12.48 (SD = 2.73; Min = 6; Max = 19) years. Regarding education, there were no significant sex differences.

For these individuals, data were collected using different psychometric assessment scales after consultation. The remaining data, when not obtained from the participants, were collected from their clinical records.

### Non-clinical sample

The non-clinical sample (control group) included persons without a known history of mental disorders and aged 18 years and older who voluntarily answered a set of online questionnaires. Therefore, a history of mental illness or addictive behaviors were considered exclusion criteria. Failure to complete at least one of the assessment instruments applied constituted an exclusion factor.

The non-clinical group consisted of 246 people, 168 women and 78 men. Their age ranged between 18 and 60 years (M = 29.32; SD = 8.39), and education varied between nine and 25 years (M = 16.28; SD = 2.70).

Within the control group, women had an average age of 28.47 (SD = 8.28; Min = 18; Max = 57) years and men an average age of 31.12 (SD = 8.38; Min = 19; Max = 60) years. From the age comparison between groups, men were significantly older than women [$t(244) = 2.32$; $p = 0.02$; $d = 0.32$]. The group of women had an average schooling of 15.93 (SD = 2.50; Min = 12; Max = 25) years and men an average of 17.03 (SD = 2.98; Min = 9; Max = 25) years of learning. There were significant differences between women and men in terms of education, with men having more years of education than women [$t(244) = 1.31$; $p < 0.01$; $d = 0.18$].

All data were collected through a Google Forms (Google®, USA) questionnaire sent via email to all students, teachers, and non-teachers at the University of Minho.

### Ethical considerations

The OCD patients gave written informed consent while the control participants provided online informed consent before participating in the study. The study was performed following the Declaration of Helsinki and was approved by the Ethics Subcommittee for the Life and Health Sciences of the University of Minho, Portugal (CEICVS 064/2019), and by the Ethics Committee of Hospital de Braga, Portugal (CESHB 138_2019).

### Measures

This project required the application of different psychometric assessment instruments. The individuals belonging to the clinical sample were assessed with the OCI-R and Y-BOCS. In the non-clinical sample, only the OCI-R was applied.

The OCI-R is a self-administered questionnaire consisting of 18 items equally divided into six categories/factors: Hoarding, Checking, Ordering, Neutralizing, Washing, and Obsessing. It is a Likert-scale instrument with answers given on a scale between 0 (not at all) and 4 (extremely). The total score ranges from 0 to 72, and the total score for each subscale ranges from 0 to 12.

Considering its characteristics, it allows the determination of the symptoms that most affect the patient and, by adding the scores obtained in all items, assess the severity of the disorder. The higher the score, the more severe the symptoms are.

The original English version of the OCI-R was obtained from Dr. Edna Foa and translated into Portuguese. Subsequently, an independent bilingual translator back-translated the scale, which was sent for approval by the original authors, thus making the Portuguese version of the OCI-R available for application in the populations under study.

The Y-BOCS is a questionnaire applied by a trained healthcare professional. The Y-BOCS consists of 10 Likert-scale questions in which the answers are given on a scale between 0 and 4. The 10 items are divided into two groups of five questions: the obsessions and the compulsions subscales. The total score ranges from 0 to 40, and the total score of each subscale ranges from 0 to 20. The total score obtained allows us to determine the disorder's presence and severity, and the subscales scores enable us to evaluate the type of symptoms that affect patients the most, namely obsessions or compulsions.

### Statistical analysis

Both groups were characterized concerning the different variables under study.

Continuous variables with normal distribution were characterized by mean (M) and standard deviation (SD); when this was not the case, the median (Mdn) and interquartile range (IQR) were used.

A comparison between groups for continuous variables was performed using the *t*-test for independent samples, and the effect size measurement was calculated using Cohen's *d* value.[31] When normal distribution was not followed, the comparison between groups was performed using the Mann-Whitney test, and the effect size measurement was calculated using the value of *r*.[31,32]

A confirmatory factor analysis was performed to confirm the factor structure proposed by the original version of the OCI-R. Thus, for both groups, chi-square ($\chi^2$), confirmatory factor index (CFI), goodness of fit index (GFI), and root mean square error of approximation (RMSE) were determined.[33,34]

To evaluate the scale's internal consistency, Cronbach's alpha (α) was determined among the items that constitute the OCI-R.[35,36] This same indicator was determined for each of the six-factors considered. We also assessed the correlation between the six-factors and the total OCI-R score to understand how they relate to each other and the scale globally. In this sense, the Spearman Correlation Coefficient (*r*) was determined.[37]

To assess the convergent validity in the patient group, the correlation between the total score obtained in the instrument under validation and the total score obtained in the Y-BOCS was determined using the Spearman Correlation Coefficient (*r*). In parallel, the OCI-R items were divided into two groups, the obsessions group and compulsions group, and the Spearman Correlation Coefficient (*r*) was determined between the obtained scores and the Y-BOCS equivalent.[37]

Statistical significance was assumed in all tests for *p* values under 0.05. Statistical analysis was performed using IBM® SPSS® Statistics 26 (IBM®, USA) and Microsoft Office Excel 2017 (Microsoft®, USA) software.

## RESULTS

### Comparison between groups

No participants were excluded during the data analysis. The total OCI-R score was calculated for each individual belonging to the OCD and control groups. As the score obtained in the patient group did not follow a normal distribution, the comparison between groups was performed using the Mann-Whitney test. Significant differences between groups were observed, with patients scoring significantly higher ($U = 5892.50$; $p < 0.01$; effect size $r = 0.36$). The same was true for the comparison of scores between genders (Table 1).

When comparing individuals with the disorder and individuals without the disorder for the scores obtained for each of the six factors that constitute the OCI-R, the OCD subjects scored significantly higher than control subjects,

Table 1 – Comparison between study groups for the total scores obtained in OCI-R

| Variable | Group | Median (IQR) | Mann-Whitney test | Effect size |
|---|---|---|---|---|
| OCI-R total | OCD (n = 90) | 30.5 (23.2) | $U$ = 5892.50, $p$ < 0.01* | $r$ = 0.36 |
| | Control (n = 246) | 15.0 (16.0) | | |
| | OCD women (n = 46) | 35.5 (24.2) | $U$ = 1826.00, $p$ < 0.01* | $r$ = 0.37 |
| | Control women (n = 168) | 14.0 (14.2) | | |
| | OCD men (n = 44) | 28.5 (20.2) | $U$ = 1006.50 $p$ < 0.01* | $r$ = 0.34 |
| | Control men (n = 78) | 18.0 (17.0) | | |

OCI-R: Obsessive-Compulsive Inventory-Revised; OCD: obsessive-compulsive disorder; n: number of individuals; SD: standard deviation; IQR: iInterquartile range: *U*: calculated value for Mann-Whitney test; *p*: significance probability; *r*: effect size value.
*: $p$ < 0.05, two-tailed.

except for the Hoarding factor, in which no significant differences were observed between groups (Table 2). When comparing the scores obtained for each sex subgroup between OCD and the control group, we concluded that both women and men with OCD had significantly higher scores than women and men without the disorder, except for the Hoarding factor in men and women and the Ordering factor in men (Table 2).

### Factor structure

Considering, *a priori*, that the Portuguese version of the OCI-R follows the six-factor structure established by the original version of this instrument, confirmatory factor analysis was performed separately with the data from OCD patients and individuals belonging to the non-clinical group.

In general, it can be said that the results obtained are not entirely favorable for admitting that the OCI-R imperatively follows the originally established 6-factor structure. However, the excellent results obtained at the CFI and GFI levels should be highlighted in both groups [for the patient group $\chi2(120, n = 90) = 205.779$, $p < 0.01$; CFI = 0.916; GFI = 0.814; RMSEA = 0.0890; for the control group: $\chi2(120, n = 246) = 224.762$, $p < 0.01$; CFI = 0.938; GFI = 0.904; RMSEA = 0.060.]

### Internal consistency

For both groups under study, the Cronbach's alpha ($\alpha$) value was calculated for the full scale and the different subscales that constitute it, according to the six-factors (Table 3).

The $\alpha$ value recorded in the patient group for the full scale was considered extremely high ($\alpha$ = 0.913), suggesting an excellent internal consistency of the scale. The $\alpha$ values for the different subscales showed an internal consistency from acceptable to good ($\alpha$ 0.783 - 0.876).

For the control group, the $\alpha$ value for the OCI-R was considered good ($\alpha$ = 0.888), reflecting a good internal consistency of the scale. The $\alpha$ values for the different factors suggested an acceptable to good internal consistency ($\alpha$ 0.713 - 0.817), except for the Neutralizing factor, which had a questionable internal consistency ($\alpha$ = 0.692).

At the same time, the correlation between the OCI-R and the different subscales that constitute it, as well as among the different subscales, was evaluated by determining the Spearman's Correlation Coefficient. As shown in Table 4, in the patients' group, the correlation between the total OCI-R score and its subscales was strong ($r$ 0.658 - 0.794; $p$ < 0.01), and among the different subscales, the correlation was considered weak to moderate. These findings suggest that, globally, the different subscales had a good correlation with the OCI-R total score and, although related, the information collected by each of them was not redundant. In the control group, the correlation between the total OCI-R score and its subscales was strong ($r$ 0.630 - 0.796; $p$ < 0,01) and, among the different subscales, the correlation was considered weak to moderate.

### Convergent validity

To assess the convergent validity, Spearman's Correlation was performed between the scores obtained in the OCI-R and Y-BOCS within the patient group. Considering that Y-BOCS evaluates two OCD dimensions, obsessions and compulsions, the items that constitute the OCI-R were divided into two groups: the obsessions group and the compulsions group. The Spearman's Correlation was evaluated between these groups and the equivalents outlined in the Y-BOCS. The correlation between Y-BOCS and OCI-R total scores was strong ($r$ = 0.651; $p$ < 0.01) and, among the dimensions of these previously considered instruments, the correlation was strong for compulsions ($r$ = 0.642; $p$ < 0.01) and moderate for obsessions ($r$ = 0.513; $p$ < 0.01).

## DISCUSSION

The present study evaluated the psychometric properties of the Portuguese version of the OCI-R in two samples: a clinical sample of people with OCD and a non-clinical sample of persons without the disorder. The evaluation of these properties aimed to validate this version of the instrument.

Having used two different samples, we proceeded to

Table 2 – Comparison between study groups for the scores obtained for the OCI-R factors

| Variable | Group | Mean ± SD | *t*-test | Effect size |
|---|---|---|---|---|
| Hoarding | OCD (n = 90) | 3.40 ± 3.26 | *t*(334) = -0.40, *p* = 0.69 | *d* < 0.01 |
| | Control (n = 246) | 3.54 ± 2.86 | | |
| | OCD women (n = 46) | 3.13 ± 3.07 | *t*(212) = -1.00, *p* = 0.316 | *d* = 0.01 |
| | Control women (n = 168) | 3.63 ± 2.98 | | |
| | OCD men (n = 44) | 3.68 ± 3.44 | *t*(120) = 0.54, *p* = 0.59 | *d* = 0.01 |
| | Control men (n = 78) | 3.36 ± 2.58 | | |
| Checking | OCD (n = 90) | 5.40 ± 3.85 | *t*(334) = 7.47, *p* < 0.01* | *d* = 0.08 |
| | Control (n = 246) | 2.78 ± 2.45 | | |
| | OCD women (n = 46) | 5.72 ± 3.94 | *t*(212) = 5.09, *p* < 0.01* | *d* = 0.10 |
| | Control women (n = 168) | 2.62 ± 2.34 | | |
| | OCD men (n = 44) | 5.16 ± 3.78 | *t*(120) = 3.14, *p* < 0.01* | *d* = 0.06 |
| | Control men (n = 78) | 3.14 ± 2.64 | | |
| Ordering | OCD (n = 90) | 5.62 ± 3.87 | *t*(334) = 2.55 *p* < 0.01* | *d* = 0.03 |
| | Control (n = 246) | 4.59 ± 3.05 | | |
| | OCD women (n = 46) | 5.98 ± 3.93 | *t*(212) = 2.18, *p* = 0.03* | *d* = 0.04 |
| | Control women (n = 168) | 4.61 ± 3.10 | | |
| | OCD men (n = 44) | 5.25 ± 3.82 | *t*(120) = 1.07, *p* = 0.29 | *d* = 0.02 |
| | Control men (n = 78) | 4.54 ± 2.98 | | |
| Neutralizing | OCD (n = 90) | 3.62 ± 3.53 | *t*(334) = 5.12, *p* < 0.01* | *d* = 0.14 |
| | Control (n = 246) | 1.59 ± 2.13 | | |
| | OCD women (n = 46) | 3.91 ± 3.29 | *t*(212) = 4.50, *p* < 0.01* | *d* = 0.08 |
| | Control women (n = 168) | 1.60 ± 2.19 | | |
| | OCD men (n = 44) | 3.32 ± 3.78 | *t*(120) = 2.84, *p* < 0.01* | *d* = 0.06 |
| | Control men (n = 78) | 1.58 ± 2.02 | | |
| Washing | OCD (n = 90) | 4.89 ± 3.97 | *t*(334) = 7.51, *p* < 0.01* | *d* = 0.10 |
| | Control (n = 246) | 1.57 ± 2.20 | | |
| | OCD women (n = 46) | 5.24 ± 4.34 | *t*(212) = 5.70, *p* < 0.01* | *d* = 0.11 |
| | Control women (n = 168) | 1.48 ± 2.07 | | |
| | OCD men (n = 44) | 4.52 ± 3.55 | *t*(120) = 4.54, *p* < 0.01* | *d* = 0.09 |
| | Control men (n = 78) | 1.78 ± 2.46 | | |
| Obsessing | OCD (n = 90) | 6.89 ± 3.70 | *t*(334) = 9.02, *p* < 0.01* | *d* = 0.12 |
| | Control (n = 246) | 3.04 ± 2.73 | | |
| | OCD women (n = 46) | 7.09 ± 3.93 | *t*(212) = 6.48, *p* < 0.01* | *d* = 0.11 |
| | Control women (n = 168) | 3.10 ± 2.71 | | |
| | OCD men (n = 44) | 6.68 ± 3.47 | *t*(120) = 6.15, *p* < 0.01* | *d* = 0.12 |
| | Control men (n = 78) | 2.92 ± 2.80 | | |

OCI-R: Obsessive-Compulsive Inventory-Revised; OCD: obsessive-compulsive disorder; n: number of individuals; SD: standard deviation; *t*: calculated value for *t*-test; *p*: significance probability; *d*: Cohen's effect size.
*: *p* < 0.05, two-tailored.

the evaluation and comparison of different factors between them. Additionally, a comparison was also made between the results obtained for the evaluation instruments applied.

When analyzing the results obtained for the assessment instruments applied, the differences between the patient and control groups were evident, as expected and as widely described in the literature. The patient group had higher total scores on the OCI-R and its subscales as expected.[10,15-27] There were no significant differences between men and women, which indirectly indicates that the scale in

Table 3 – Evaluation of OCI-R internal consistency through Cronbach's alpha (α) determination

| Variable | **OCD** (n = 90) | **Control** (n = 246) |
|---|---|---|
| OCI-R total | α = 0.913 | α = 0.888 |
| Hoarding | α = 0.850 | α = 0.747 |
| Checking | α = 0.870 | α = 0.713 |
| Ordering | α = 0.876 | α = 0.817 |
| Neutralizing | α = 0.783 | α = 0.692 |
| Washing | α = 0.855 | α = 0.770 |
| Obsessing | α = 0.869 | α = 0.798 |

OCI-R: Obsessive-Compulsive Inventory-Revised; OCD: obsessive-compulsive disorder; n: number of individuals.

question has, *a priori*, equal value for both sexes. Also, in the group of patients, it should be noted that the factor with the average minimum score was the Hoarding factor, a finding described in several studies.[10,22,26]

The control group presented global and partial OCI-R scores that are higher than those described in the literature for disorder-free groups.[19,23,24] This can be explained by different factors such as the fact that this group has a high education level or the fact that the information was collected through an online questionnaire, not allowing to identify individuals with undiagnosed disorders. Within this group, there were no differences between men and women, which supports the hypothesis that OCI-R has the same value regardless of sex.

Comparisons between the OCD and control groups showed significant differences for both total and subscales scores. These findings are extremely conjecturable given that the OCI-R is a scale that evaluates obsessive-compulsive symptoms and concurs with results described globally in different manuscripts.[21,22,24-26] It should be noted, however, that for the Hoarding factor, there were no significant differences between groups. This result is most likely related to the fact that this is the factor with the lowest average score in patients, as mentioned above.

Confirmatory factor analysis was performed to assess whether the Portuguese version of the OCI-R follows the six-factor structure proposed when the original version of this instrument was developed. Although it was foreseeable that the Portuguese version would follow this structure, the results obtained discredited this presumption. The results obtained for both samples do not entirely support the structure of the six-factors. However, even if not all requirements

Table 4 – Spearman's correlations among the six OCI-R factors and OCI-R total score for both groups under study

| Variable | Hoarding | Checking | Ordering | Neutralizing | Washing | Obsessing |
|---|---|---|---|---|---|---|
| **OCD** (n = 90) | | | | | | |
| Checking | $r$ = 0.327, $p$ < 0.01* | | | | | |
| Ordering | $r$ = 0.550, $p$ < 0.01* | $r$ = 0.582, $p$ < 0.01* | | | | |
| Neutralizing | $r$ = 0.429, $p$ < 0.01* | $r$ = 0.465, $p$ < 0.01* | $r$ = 0.553, $p$ < 0.01* | | | |
| Washing | $r$ = 0.294, $p$ < 0.01* | $r$ = 0.351, $p$ < 0.01* | $r$ = 0.400, $p$ < 0.01* | $r$ = 0.471, $p$ < 0.01* | | |
| Obsessing | $r$ = 0.464, $p$ < 0.01* | $r$ = 0.344, $p$ < 0.01* | $r$ = 0.358, $p$ < 0.01* | $r$ = 0.544, $p$ < 0.01* | $r$ = 0.380, $p$ < 0.01* | |
| OCI-R total | $r$ = 0.658, $p$ < 0.01* | $r$ = 0.722, $p$ < 0.01* | $r$ = 0.792, $p$ < 0.01* | $r$ = 0.794, $p$ < 0.01* | $r$ = 0.664, $p$ < 0.01* | $r$ = 0.694, $p$ < 0.01* |
| **Control** (n = 246) | | | | | | |
| Checking | $r$ = 0.360, $p$ < 0.01* | | | | | |
| Ordering | $r$ = 0.349; $p$ < 0.01* | $r$ = 0.558, $p$ < 0.01* | | | | |
| Neutralizing | $r$ = 0.380, $p$ < 0.01* | $r$ = 0.480, $p$ < 0.01* | $r$ = 0.500, $p$ < 0.01* | | | |
| Washing | $r$ = 0.250, $p$ < 0.01* | $r$ = 0.381, $p$ < 0.01* | $r$ = 0.479, $p$ < 0.01* | $r$ = 0.471, $p$ < 0.01* | | |
| Obsessing | $r$ = 0.334, $p$ < 0.01* | $r$ = 0.367, $p$ < 0.01* | $r$ = 0.429, $p$ < 0.01* | $r$ = 0.458, $p$ < 0.01* | $r$ = 0.367, $p$ < 0.01* | |
| OCI-R total | $r$ = 0.641, $p$ < 0.01* | $r$ = 0.734, $p$ < 0.01* | $r$ = 0.796, $p$ < 0.01* | $r$ = 0.709, $p$ < 0.01* | $r$ = 0.630, $p$ < 0.01* | $r$ = 0.696, $p$ < 0.01* |

OCI-R: Obsessive-Compulsive Inventory-Revised; OCD: obsessive-compulsive disorder; n: number of individuals; *r:* Spearman's correlation coefficient; *p:* significance probability.
*: $p$ < 0.05, two-tailored.

are met, the values obtained were substantially similar to the results presented in the scale creation studies.[10,16,17] On the other hand, although cutoff points were defined for the parameters evaluated in this process, the literature argues that we should not stick to them because different factors can influence the results obtained in confirmatory factor analysis, from the number of individuals that constitute the sample, to the type of distribution that the variables follow, and the type of content the scale evaluates.[31,32] In this way, considering that the results obtained were similar to those obtained in other studies and that the literature advocates a holistic approach to the scale rather than an approach focused on specific parameters evaluated by factor analysis, we assumed that the Portuguese version of OCI-R follows the model of the six-factors.

Regarding internal consistency, the results obtained are in line with the results presented by scale development studies[10,16,17] and presented by translation studies for different languages.[19,21,24-26] Therefore, Cronbach's alpha values demonstrated an excellent internal consistency for the OCI-R as a whole and an acceptable to good internal consistency for the different subscales for patients. This means that, overall, the items constituting the questionnaire strongly support the scale and the different subscales, in the sense that the information collected is strongly related to each other and contributes to the same end.

Concerning internal consistency, the results obtained for the correlation between the different factors and the scale as a whole should be mentioned, as well as between the different factors, which, once again, attests that the content collected presents a consistent and solid basis. These findings are consistent with previously described results.[10,16,17,19-27]

The inferences drawn for the patient group for internal consistency also applied to the control group. However, the values obtained were slightly lower, probably due to the nature of the parameters assessed by the OCI-R.

Considering that the OCI-R is an evaluation instrument whose main objective is to evaluate the disorder in people with OCD, the correlation between the Portuguese version of this instrument and the Y-BOCS was determined. The results show a strong correlation between both psychometric assessment scales allowing us to infer that the OCI-R is a good instrument in the assessment of OCD. The findings are corroborated with results from similar studies.[10,15,24] Notably, the correlation coefficients were slightly higher than those described in the literature, indicating a stronger relationship between these two instruments in the present study. Considering the dimensions of the obsessions and compulsions evaluated by the Y-BOCS, their correlation with the equivalent dimensions for the OCI-R version under study was also assessed. Although no known literature considers this type of assessment, the results concur with the previously inferred insofar as OCI-R and Y-BOCS present a good correlation. However, it should be noted that OCI-R is not a scale that assesses the disorder in the two dimensions considered, which may limit the interpretation of these results.

## CONCLUSION

The Portuguese version of OCI-R has overlapping characteristics with the original version of the instrument and other versions duly validated in different languages. In addition to the overlapping results, this version of OCI-R follows the six-factor structure and has excellent internal consistency and good convergent validity. An appropriate cut-off point for the distinction between individuals with and without disorder is left to be determined. Considering that this instrument is meant to be used in clinical practice to measure disorder severity, it is not crucial to determine this cutoff point since applying this scale should happen after adequate clinical evaluation.

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## AUTHOR CONTRIBUTIONS

GVC: Data collection and analysis, writing of the manuscript.

PSM: Study design, data collection and analysis, writing of the manuscript.

MMS: Data collection, writing of the manuscript.

TC: Scale translation and validation, data collection, writing of the manuscript.

MPP, SF: Data collection and analysis, writing of the manuscript.

PM: Study design, scale translation and validation, data collection, writing of the manuscript, supervision.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

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ACTA MÉDICA PORTUGUESA
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# Burnout among Physicians Working in Palliative Care During the COVID-19 Pandemic in Portugal: A Cross-Sectional Study

# Burnout nos Médicos que Trabalham em Cuidados Paliativos durante a Pandemia de COVID-19 em Portugal: Um Estudo Transversal

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## ABSTRACT

**Introduction:** Physicians working in palliative care have a greater risk of burnout. Burnout has three dimensions: emotional exhaustion, depersonalization and reduction of personal accomplishments. Burnout is associated with different consequences for the professionals like less professional satisfaction and increase of overall levels of exhaustion. Burnout in healthcare professionals has an impact in the patients with increased probability of clinical erros. In order to monitor the quality of the care it is mandatory to assess overall levels of burnout. This study aimed to determine burnout levels and associated variables of physicians working in the Portuguese national network of palliative care.

**Material and Methods:** A cross-sectional, exploratory and quantitative design was employed and participants were sampled using convenience and snowball technique. The Copenhagen Burnout Inventory was used to determine burnout levels of physicians working in the Portuguese National Network of Palliative Care. The contributions of personal, work and COVID-19 variables were evaluated in three subclasses: work, personal and patient-related burnout. The results obtained enabled the identification of healthcare professionals at risk, comparison with previous results published and to assess the impact of COVID-19 in their non COVID-19 activity.

**Results:** Seventy-five physicians participated. Socio-demographic characterization was conducted and the levels of burnout and determinants were explored. High levels of personal, work and patient-related burnout were present in 32 (43%), 39 (52%) and 16 (21%) physicians, respectively. The majority agreed that COVID-19 had an impact on their activities. Exclusive dedication to palliative care and type of palliative care unit were associated with lower levels of patient and work-related burnout. Weekly physical activity was associated with lower levels of work and personal burnout. Self-perceived health status was associated with lower levels of burnout for all subclasses.

**Conclusion:** There was a high level of burnout among physicians working in the Portuguese National Network of Palliative Care. Measures to identify and prevent burnout are necessary in order to protect these professionals.

**Keywords:** Burnout, Professional; Burnout, Psychological; COVID-19; Palliative Care; Physicians; Portugal

## RESUMO

**Introdução:** Os médicos que trabalham em cuidados paliativos apresentam um risco mais elevado de *burnout*. Esta perturbação psicológica carateriza-se por três dimensões – exaustão emocional, despersonalização e redução da realização pessoal – e está associada a diversas consequências para os profissionais como a diminuição da satisfação profissional ou o aumento dos níveis de exaustão. Ao afetar os profissionais de saúde, o *burnout* tem também impacto nos utentes, visto causar um aumento da probabilidade de erros clínicos. Com vista a monitorizar a qualidade dos cuidados prestados é fundamental monitorizar os níveis de *burnout*. O objetivo deste estudo foi o de determinar os níveis de *burnout* e varíaveis associadas dos médicos que trabalham na Rede Nacional de Cuidados Paliativos em Portugal.

**Material e Métodos:** Estudo transversal, exploratório e quantitativo com amostragem por conveniência e bola de neve. Foi utilizado o questionário *Copenhagen Burnout Inventory* para determinar os níveis de *burnout* de médicos que exercem funções na Rede Nacional de Cuidados Paliativos. As contribuições das varíaveis pessoais, laborais e decorrentes da pandemia de COVID-19 foram analisadas segundo três subclasses: *burnout* pessoal, *burnout* relacionado com a atividade profissional e *burnout* relacionado com o utente. Os resultados obtidos permitiram identificar profissionais em risco, fazer uma comparação com resultados prévios na literatura e determinar o impacto da COVID-19 na atividade assistencial não relacionada com COVID-19.

**Resultados:** Setenta e cinco médicos participaram neste estudo. Foi realizada a caraterização socio-demográfica e determinados os níveis de *burnout* e variáveis associadas. Níveis elevados de *burnout* pessoal, relacionados com a atividade profissional e para com o utente estavam presentes, respetivamente, em 32 (43%), 39 (52%) e 16 (21%) dos participantes. A maioria considerou que a COVID-19 teve um impacto na sua atividade clínica. A dedicação exclusiva em cuidados paliativos e o tipo de unidade de cuidados paliativos estavam associados a menor nível de *burnout* relacionado com atividade profissional e para com o utente. A autopercepção de saúde estava associada a menores níveis de *burnout* em todas as subclasses.

**Conclusão:** Foi observado um elevado nível de *burnout* nos médicos que trabalham na Rede Nacional de Cuidados Paliativos. São necessárias medidas para identificar e prevenir o *burnout* nestes profissionais, com vista à sua proteção.

**Palavras-chave:** COVID-19; Cuidados Paliativos; Esgotamento Profissional; Esgotamento Psicológico; Médicos; Portugal

## INTRODUCTION

Average life expectancy has been rising worldwide according to the World Health Organization (WHO).[1] The long-term consequences of the coronavirus disease 2019 (COVID-19) pandemic are still unknown. Nevertheless, it has exacerbated the discrepancies in access to health care.[2] As a result of the gradual aging of the world's population, healthcare systems are facing new problems and a need to offer new answers[3] involving palliative care delivery.

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The WHO defines palliative care as an approach that improves the quality of life of patients who are facing an incurable or serious illnesses and their families. This is done through the prevention and relief of suffering by early identification and treatment of different problems[4] and it can help with a variety of disorders that are not terminal, including cancers.[5]

The Portuguese National Network of Palliative Care (NNPC) was developed as a response to the country's demand for palliative care. This network is comprised of different types of units.[6] Palliative Care units (PCUs) provide inpatient care and belong to the Portuguese National Health Service or to private hospitals that have an agreement with it. Hospital support Palliative Care teams (HSPCTs) provide support to inpatients in hospitals in which they are integrated, as well as support to families or informal caregivers. Home Palliative Care teams (HPCTs) assist the community including patients in their homes and their informal caregivers or families.[7]

Clinical care teams in palliative care usually include groups of different healthcare professionals.[8] Working teams face different difficulties while working in palliative care, which have been exacerbated due to COVID-19[9]: professionals in palliative care always need to be scientifically up to date,[10] face ethical dilemmas[11] or have to deal with the expectations and suffering.[12-14] The low number of professionals working in palliative care also leads to an increased workload.[8] Physicians may have a lower risk of burnout as they are more prepared to deal with their patient's death,[15] but all the previous reasons mentioned could also increase the risk of burnout in palliative care physicians.[16-18]

Freudenberger was one of the first to describe the symptoms of exhaustion and burnout.[16] Burnout was described as a constellation of non-specific symptoms that are usually related to helping professions (healthcare workers). Maslach and Leiter[17] further developed the concept of burnout. It shifted from being a crisis while helping or working with people to a crisis related to the environment at work.[17,18] Burnout can thus be defined as a "state of physical, emotional and mental exhaustion that results from long-term involvement in work situations that are emotionally demanding".[19] Maslach and Jackson[20] also characterized burnout syndrome through three dimensions: depersonalization, emotional exhaustion and a lack of personal accomplishment.[21,22] As for burnout syndrome in healthcare workers, it is also important to focus the effects of this syndrome in patients.[23] The WHO defines burnout as "a syndrome conceptualized as resulting from chronic workplace stress that has not been successfully managed. It is characterized by three dimensions: 1) feelings of energy depletion or exhaustion; 2) increased mental distance from one's job or feelings of negativism or cynicism related to one's job and 3) a sense of ineffectiveness and lack of accomplishment".[24] Burnout in healthcare professionals is related to a lot of consequences like reduction in work performance or increased probability of errors.[14,21,25] Burnout syndrome could be less prevalent among physicians working in palliative care compared to other medical specialties.[16,26,27] However, it is important to be aware of the importance of early screening of physicians who are at risk as the early detection can lead to the implementation of measures to avoid and mitigate burnout. It is also important to highlight that it is only possible to deliver high-quality care when professionals are satisfied and committed.[23] The real impact of burnout on palliative care physicians during the pandemic is still unknown and we could only retrieve one relevant study in the literature that has been published after the outbreak of COVID-19.[28] The COVID-19 pandemic has been a challenge for palliative care practitioners[29,30]: some of the patients in palliative care have died alone, contact with families and friends has been impossible and some resources have not been available.[31]

The aim of this study was to evaluate the level of burnout among physicians working in Portuguese NNPC using the Copenhagen Burnout Inventory (CBI).[32] This study also examined whether there was any significant association of different socio-demographic and professional variables in this population with the three burnout dimensions. As far as we know, this study is the second of its kind worldwide and the first in Portugal to evaluate the levels and the associations of burnout among palliative care physicians during the COVID-19 pandemic. The first article published[28] only evaluated the level of burnout of home palliative care physicians and nurses, whereas our study focuses on all palliative care physicians in the country. Since this study was conducted during the COVID-19 pandemic, the findings were also compared with previous results in the literature before the outbreak of COVID-19. Measurement of the level of burnout was done using the CBI[32] and this study also examined whether there was any significant association of different socio-demographic and professional variables in this population with the three burnout dimensions.

## MATERIAL AND METHODS

In this exploratory, quantitative and cross-sectional study, physicians working in NNPC in Portugal were sampled by convenience and snowball techniques. This study was approved by the Ethics Committee of São João Hospital Centre (approval number 195/2020 on June 15, 2020) and followed ethical procedures complying with the Declaration of Helsinki. All physicians provided informed consent online in accordance with the General Data Protection Regulation Guidelines.[33] The author responsible for the validation of the CBI for Portuguese language gave permission for the use of this scale.[34]

Personal and work-related variables were collected using a self-administered questionnaire that we developed. The personal variables collected were gender, age, marital status, parental responsibility of underage children, weekly physical exercise and self-perceived health status. The work-related variables collected were academic degree, medical specialization, exclusive dedication to palliative care (yes/no), years of activity in palliative care, unit type as the place of work in NNPC: HPCTs, HSPCTs, PCUs and weekly hours in palliative care. Regarding the impact of COVID-19, physicians were asked whether their work in palliative care was affected by COVID-19 and if they were transferred from palliative care activity to COVID-19 units.

The target population and inclusion criteria of this study were all the palliative care physicians working in NNPC in Portugal. A questionnaire was made on Google Forms (Google, Mountain View, California, United States) and comprised a section with socio-demographic and professional questions followed by the validated Portuguese version of the CBI.[34] There were no missing data. The response rate was impossible to estimate as there are no official data concerning the total number of physicians working in NNPC. The survey was distributed via the institutional e-mails of all the teams that work in NNPC,[35] as well as the social networks LinkedIn® (Microsoft®, Mountain View, California, United States) and Facebook® (Meta Inc, Menlo Park, California, United States). The questionnaire was available for online responses and data were collected between July 20th, 2020 to November 1st, 2020. This project was supported by the Portuguese Association of Palliative Care and the University of Oporto which promoted this questionnaire.

Burnout was evaluated using the Portuguese validated version of the CBI.[34] This scale has 19 questions that are related to three subscales of burnout: personal, work-related, and client-related (reformulated to patient-related). Questions were answered on a 5-point Likert response scale. Each question of the different subscales has five different possible answers that are scored as 0, 25, 50, 75, or 100 according to the authors' instructions.

The personal burnout subscale (six questions) evaluates the degree of physiological, physical, and personal feeling of exhaustion. The work-related burnout subscale (seven questions) evaluates the degree of physical and psychological fatigue and the personal sensation of exhaustion towards work. The patient-related burnout subscale (six questions) assesses the degree of physical and psychological fatigue and personal feeling of exhaustion related to working with patients. The total score for each subscale is the calculated mean of the scores of that subscale's answers, which ranged from 0 to 100. If the total score of a subscale was greater than or equal to 50, it was considered a high level of burnout for that subscale.[22,24] All subscales have high internal consistency with Cronbach's alpha (α) in the original version ranging from 0.84 to 0.87. In the Portuguese version, α for personal burnout was 0.85, that for work-related burnout was 0.87, and that for client-related burnout was 0.84.[34] In our sample, α was 0.84, 0.90, and 0.87, respectively. Additionally, the correlations item-total were in the range (0.61 - 0.82) for personal burnout, (0.41 - 0.83) for work-related burnout and (0.55 - 0.68) for client-related burnout, emphasizing the internal consistency of the CBI Portuguese version.

All the data from Google Forms® were exported to an Excel® 2016 spreadsheet (Microsoft®, Washington, United States) and data analysis was performed using SPSS Statistics® (version 26.0; SPSS Inc., Chicago, Illinois, United States) and Jamovi software (The Jamovi project (2021), Jamovi (Version 1.6) (Computer Software) (Sydney, Australia). Absolute and relative frequencies [n (%)] were used to describe the categorical variables. In the case of normally distributed quantitative variables, the mean and standard deviation were used to describe the variables. If the quantitative variables were non-normally distributed, they were described using medians and interquartile intervals (Q1, Q3). The observation of histograms was used for verification of normality. For each independent variable (personal, work and COVID-19 related), a simple linear regression was performed for each outcome: personal burnout, work and patient-related burnout. If the variables were related to the outcomes ($p \leq 0.20$), these variables were included in the multiple linear regression analyses for each outcome.[36] In the final model, only the significant ($p \leq 0.05$) independent variables were maintained for each outcome and the results of linear regressions are shown with unstandardized coefficients (B), 95% confidence intervals (95% CI), and *p*-values.

Standardized β and semi-partial squared-correlations (sum-of-squares of the effect divided by the total sum-of--square, $\eta^2$) for the final models are also presented. The final multivariable models were evaluated using F statistics, *p*-values, and coefficients of determination ($R^2$). The assumptions of the linear regression models were verified as follows. Normality of residuals was assessed by visual analysis of histograms, *t*-tests were employed to test whether average residuals were zero, and homoscedasticity was checked using scatter plots of residuals versus the predictive values. The absence of multicollinearity was verified assessing the tolerance for each independent variable in the final model, which should be close to 1, and the variance inflation factor (VIF), using VIF < 5 as the cut-off point.[37] In all tests, values of $p \leq 0.05$ were considered significant.

## RESULTS

Seventy-five physicians participated in this study. The

majority were women (n = 58, 77.3%), and the median (Q1, Q3) age of all physicians was 44 (36, 48) years old. Most of them (n = 52, 69.3%) did not work entirely in palliative care, but the majority had formal training in palliative care (n = 71, 94.7%). Nineteen physicians (25.3%) worked in HPCTs, 42 physicians (56%) worked in HSPCTs and 14 physicians (18.7%) worked in a PCUs. The majority (n = 62, 82.7%) believed that their clinical activity in palliative care was affected by COVID-19, and were not allocated to other clinical functions in COVID-19 units (n = 51, 68%). Regarding the number of years working in palliative care, the median (Q1, Q3) was 6 (3, 9) years. Most physicians reported a good health status (n = 40, 53.3%) or very good health status (n = 13, 17.3%), but almost half (n = 30, 40%) did not report having any regular physical activity. The most frequent medical specialties were internal medicine (n = 35, 46.7%) and family medicine (n = 24, 32%). The full characterization of all participants is summarized in Table 1.

The physicians' level of burnout for each subscale was divided between low and high levels (final scores equal or above 50). High levels of personal burnout were found in 32 physicians (43%), high levels of work-related burnout in 39 physicians (52%) and high levels of patient-related burnout in 16 physicians (21%).

The personal, work, and COVID-19 variables that were eligible for the multiple linear regression models ($p \leq 0.20$ in the simple regression) were different for each subscale of burnout (Table 2). For personal burnout, the variables were gender, weekly hours of physical activity, self-perceived health status and type of unit. For work-related burnout, the variables included were gender, weekly hours of physical activity, exclusive dedication to palliative care, self-perceived health status, years and weekly hours of activity in palliative care and type of palliative care unit. For patient-related burnout the variables included were weekly hours of physical activity, exclusive dedication to palliative care, self-perceived health status, type of palliative care unit and weekly hours of activity in palliative care.

In the final multiple linear regression model for personal burnout, the significant variables were weekly hours of physical exercise and self-perceived health status. The final model explained approximately 50% of the total data variance (Table 3). For work-related burnout, the significant variables were weekly hours of physical exercise, exclusive dedication to palliative care, self-perceived health status and type of palliative care unit. The final model explained approximately 47.6% of the total data variance (Table 3). For patient-related burnout, the significant variables were exclusive dedication to palliative care, self-perceived health status and type of palliative care unit. The final model explained approximately 30.2% of the total data variance (Table 3). Self-perceived health status represented the

Table 1 – Sample characterization (n = 75)

| Characteristics | n | % |
|---|---|---|
| Gender | | |
| Male | 17 | 22.7 |
| Female | 58 | 77.3 |
| Marital status | | |
| Married/civil union | 46 | 61.3 |
| Divorced/separated | 8 | 10.7 |
| Single | 21 | 28.0 |
| Underage children | | |
| Yes | 32 | 42.7 |
| No | 43 | 57.3 |
| Nationality | | |
| Portuguese | 72 | 96 |
| Non-Portuguese | 3 | 4.0 |
| Exclusive dedication to PC | | |
| Yes | 23 | 30.7 |
| No | 52 | 69.3 |
| Specialization in PC | | |
| No | 4 | 5.3 |
| Bachelor's degree or post-graduation | 38 | 50.7 |
| Master's or PhD degree | 33 | 44.0 |
| Type of PC unit | | |
| HPCT | 19 | 25.3 |
| HSPCT | 42 | 56.0 |
| PCU | 14 | 18.7 |
| PC affected by COVID-19 | | |
| Yes | 62 | 82.7 |
| No | 13 | 17.3 |
| Allocated to COVID-19 units | | |
| Yes | 24 | 32.0 |
| No | 51 | 68.0 |
| Weekly hours of activity | | |
| Less than 20 | 26 | 34.7 |
| Between 20 and 40 | 34 | 45.3 |
| More than 40 | 15 | 20.0 |
| Self-perceived health status | | |
| Very good | 13 | 17.3 |
| Good | 40 | 53.3 |
| Not good or bad | 16 | 21.3 |
| Bad or very bad | 6 | 8.0 |
| Medical specialty | | |
| Anaesthesiology | 6 | 8.0 |
| Family medicine | 24 | 32.0 |
| Internal medicine | 35 | 46.7 |
| Others | 10 | 13.3 |
| Workplaces | | |
| Northern Portugal | 18 | 24.0 |
| Central Portugal | 15 | 20.0 |
| Lisbon | 21 | 28.0 |
| Alentejo | 17 | 22.7 |
| Algarve | 2 | 2.7 |
| Autonomous Region of Azores | 1 | 1.3 |
| Autonomous Region of Madeira | 1 | 1.3 |

PC: Palliative Care; HPCT: home Palliative Care teams; HSPCT: hospital support Palliative Care teams; PCU: Palliative Care units

Table 2 – Unstandardized regression coefficients of univariable models for the subscales of burnout according to Copenhagen Burnout Inventory as outcomes and personal, work and coronavirus disease 2019 (COVID-19) variables as predictors

| Variables | Personal burnout B [95% CI] | Work-related burnout B [95% CI] | Patient-related burnout B [95% CI] |
|---|---|---|---|
| Gender | | | |
| Male | Ref | Ref | Ref |
| Female | **14.6 [4.66; 24.00]**** | **13.9 [4.61; 23.20]**** | -1.27 [-11.90; 9.40] |
| Age (years) | 0.07 [-0.35; 0.49] | 0.07 [-0.34; 0.47] | -0.24 [-0.67; 0.20] |
| Marital status | | | |
| Married/Civil union | Ref | Ref | Ref |
| Divorced/Separated/Single | 0.96 [-7.83; 9.74] | -0.58 [-9.06; 7.9] | -1.76 [-10.9; 7.41] |
| Underage children | | | |
| No | Ref | Ref | Ref |
| Yes | -2.35 [-11.00; 6.28] | -3.71 [-12.00; 4.60] | 1.96 [-7.07; 11.00] |
| Weekly physical exercise | | | |
| No regular practice | Ref | Ref | Ref |
| Less than 75 min | **-18.70 [-27.30; -10.00]***** | **-14.90 [-23.50; -6.32]***** | **-15.20 [-25.30; -5.15]**** |
| 75 min or more | **-22.40 [-31.20; -13.70]***** | **-20.70 [-29.40; -11.97]***** | **-12.10 [-22.30; -1.87]**** |
| Exclusive dedication to PC | | | |
| No | Ref | Ref | Ref |
| Yes | -3.93 [-13.20; 5.30] | **-6.62 [-15.40; 2.20]**+** | **-7.51 [-17.00; 2.02]**+** |
| Self-perceived health status | | | |
| Bad /Not good or bad | Ref | Ref | Ref |
| Good / Very Good | **−20.43 [−28.47; −12.40]**** | **−17.13 [−25.40; −8.84]***** | **−15.00 [−23.50; -6.48]***** |
| Years of activity in PC | -0.17 [-1.11; 0.77] | **-0.61 [-1.51; 0.29]**+** | -0.43 [-1.41; 0.55] |
| Type of PC unit | | | |
| HPCT | Ref | Ref | Ref |
| HSPCT | **-7.91 [-18.00; 2.22]**+** | **-8.61 [-18.40; 1.14]**+** | **-14.60 [-24.80; -4.39]**+** |
| PCU | -3.15 [-16.10; 9.76] | -4.70 [-17.10; 7.72] | **-11.90 [-24.90; 1.08]**+** |
| Weekly hours of activity | | | |
| Less than 20 | Ref | Ref | Ref |
| Between 20 and 40 | -3.50 [-13.10; 6.13] | -4.36 [-13.60; 4.85] | 0.88 [-8.97; 10.73] |
| More than 40 | -6.90 [-18.90; 5.07] | **-9.55 [-21.00; 1.91]**+** | **-11.10 [-23.36; 1.16]**+** |
| Allocated to COVID−19 units | | | |
| No | Ref | Ref | Ref |
| Yes | 0.12 [-9.05; 9.29] | -0.72 [-9.57; 8.13] | 3.56 [-5.98; 13.10] |

PC: Palliative Care; HPCT: home Palliative Care teams; HSPCT: hospital support Palliative Care teams; PCU: Palliative Care units; Ref: reference category; B: unstandardized coefficient; CI: confidence interval
+: $p \leq 0.20$; *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$

most relevant variable in terms of variance explained for all burnout dimensions (Table 3). No problems of multicollinearity were present, as the final model presented variance inflation factors between 1.09 and 1.20 for personal burnout, between 1.05 and 1.22 for work-related burnout and between 1.02 and 1.05 for patient-related burnout.

The personal burnout levels of physicians who perceived their health status as very good or good were 21.2 points lower on average than those of physicians who perceived their health status as bad or not good or bad. In addition, physicians who weekly exercised 75 minutes or more had lower levels of personal burnout. On average, their personal burnout levels were 11.7 points lower than those of physicians with no regular physical activity (Table 4).

Table 3 – Standardized regression coefficients and semi-partial squared correlations in multivariable models for the subscales of burnout according to Copenhagen Burnout Inventory as outcomes and personal, work and coronavirus disease 2019 (COVID-19) variable as predictors

| Variables | Personal burnout | | Work-related burnout | | Patient-related burnout | |
|---|---|---|---|---|---|---|
| | Standardized β | $\eta^2$ | Standardized β | $\eta^2$ | Standardized β | $\eta^2$ |
| Exclusive dedication to PC | | | | | | |
| No | - | - | Ref | 0.05 | Ref | 0.69 |
| Yes | | | -0.48* | | -0.59** | |
| Self-perceived health status | | | | | | |
| Bad / Not good or bad | Ref | 0.19 | Ref | 0.13 | Ref | 0.12 |
| Good / Very good | -1.10*** | | -0.96*** | | -0.78*** | |
| Weekly physical exercise | | | | | | |
| No regular practice | Ref | | Ref | | - | - |
| Less than 75 min | -0.42 | 0.05 | -0.32 | 0.06 | | |
| 75 min or more | -0.63** | | -0.67** | | | |
| Type of PC unit | | | | | | |
| HPCT | - | - | Ref | | Ref | |
| HSPCT | | | -0.44* | 0.03 | -0.79** | 0.10 |
| PCU | | | -0.35 | | -0.69* | |
| $R^2$ | 0.50 | | 0.48 | | 0.30 | |
| F | **23.70*** ** | | **10.30*** ** | | **7.56*** ** | |

PC: Palliative Care; HPCT: home Palliative Care teams; HSPCT: hospital support Palliative Care teams; PCU: Palliative Care unities; Ref: reference category; β: standardized coefficient; $\eta^2$: semi-partial squared-correlations; $R^2$: determination coefficient; F: F statistics.
*: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$.

Work-related burnout levels of physicians who perceived their health status as very good or good were 17.1 points lower, on average, in comparison with physicians who perceived their health status as bad or not good or bad. Physicians who exercise who weekly exercised 75 minutes or more had lower levels of work-related burnout, with a reduction of 12 points, on average, compared with physicians with no regular physical activity. Physicians who worked exclusively in palliative care showed lower levels of work-related burnout with a reduction of 8.9 points on average in comparison with physicians that did not work exclusively in palliative care. Physicians working at HSPCTs had lower levels of work-related burnout by 7.8 points on average compared to physicians working in HPCTs (Table 4).

Patient-related burnout levels of physicians who perceived their health status as very good or good were 15 points lower, on average, in comparison with physicians who perceived their health status as bad or not good or bad. Physicians who worked exclusively in palliative care showed lower levels of work-related burnout with a reduction of 11.4 points, on average, in comparison with physicians that did not work exclusively in palliative care. Physicians working at HSPCTs and PCUs had lower levels of patient-related burnout by 15.2 and 13.2 points, on average, compared to physicians working in HPCTs. These results are summarized in Table 4.

## DISCUSSION

A difference between the prevalence of high levels in personal (43%), work-related (52%) and patient-related (21%) burnout was found. The results indicated higher levels of burnout in comparison to other studies.[16,17,38] It is important to note that this study was conducted during the COVID-19 pandemic, thus leading to higher levels of burnout being reported.[29] Most physicians (n = 62, 82.7%) agreed that COVID-19 had an impact on their palliative care work, but the majority were not allocated to COVID-19 units which could have had a protective effect on the overall levels of burnout.

The impact of COVID-19 on non-COVID-19 situations like palliative care activity has already been described.[30] There are different variables that could be related to higher levels of burnout[39] in healthcare workers: depression,[40] resilience,[40] stress,[41] previous psychological problems[42] or traumatic events in relation with COVID-19.[42]

Health is defined by the WHO as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[43] Being deployed to a COVID unit could have an impact on one or more of these elements and lead to higher levels of burnout. It is also now clear that even more than after the outbreak, COVID-19 will continue to be a challenge and a possible source of burnout for all healthcare workers. It is mandatory that institutions protect

Table 4 – Unstandardized regression coefficients of multivariable models for the subscales of burnout according to Copenhagen Burnout Inventory as outcomes and personal, work and coronavirus disease 2019 (COVID-19) variable as predictors

| Variables | Personal burnout B [95% CI] | Work-related burnout B [95% CI] | Patient-related burnout B [95% CI] |
|---|---|---|---|
| Exclusive dedication to PC | | | |
| No | - | Ref | Ref |
| Yes | | **-8.89 [-15.90; -1.83]*** | **-11.4 [-20.10; -2.78]**** |
| Self-perceived health status | | | |
| Bad / Not good or bad | Ref | Ref | Ref |
| Good / Very good | **-21.21 [-29.30; -13.14]***** | **-17.13 [-25.4; -8.84]***** | **-15.00 [-23.50; -6.48]***** |
| Weekly physical exercise | | | |
| No regular practice | Ref | Ref | |
| Less than 75 min | -7.77 [-16.20; 0.68] | -5.62 [-14.20; 2.95] | - |
| 75 min or more | **-11.65 [-20.20; -3.14]**** | **-11.99 [-20.80; -3.18]**** | |
| Type of PC unit | | | |
| HPCT | | Ref | Ref |
| HSPCT | - | **-7.80 [-15.60; -0.01]*** | **-15.20 [-24.80; -5.71]**** |
| PCU | | -6.20 [-16.60; 4.16] | **-13.20 [-25.50; -0.96]*** |
| $R^2$ | 0.50 | 0.48 | 0.30 |
| F | **23.70***** | **10.30***** | **7.56***** |

PC: Palliative Care; HPCT: home Palliative Care teams; HSPCT: hospital support Palliative Care teams; PCU: Palliative Care unities; Ref: reference category; B: unstandardized coefficient; CI: confidence interval; $R^2$: determination coefficient; F: F statistics.
*: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$.

their workers and offer tools for early detection of professionals at risk.[9] The high levels of burnout in this study were in agreement with some of the results in the literature.[38,41,44] It is important to note that this study was, to the best of our knowledge, the second study worldwide to assess the levels of burnout in palliative care physicians after the COVID-19 outbreak. Our study focuses on all palliative care physicians in the country and is the first national study of its kind in Portugal to be conducted after the outbreak of COVID-19. It is necessary to highlight that the prevalence of burnout varies in studies involving healthcare workers in palliative care and the majority used the Maslach Burnout Inventory and were conducted before the outbreak of COVID-19, which makes it more difficult to compare the results.[45] One review found no major differences between physicians and nurses,[45] and the burnout levels of nurses working in palliative care in Portugal during the COVID-19 pandemic were similar to the results in this study[30] which supports the conclusions of this study. The most recent report of the NNPC also supports our conclusions in this study about the median age of the physicians, the number of years of working in palliative care and weekly hours of work in NNPC.[8]

For the three burnout dimensions, the personal and work variables that were included in the final model were different. Patient-related burnout is related to individuals' exhaustion in relation to their work with patients. The personal and work variables that were included in the final model of patient-related burnout were exclusive dedication to palliative care, self-perceived health status and type of unit. Depersonalization can be harmful to patients as it leads to detachment from patients, colleagues and the organization.[44] According to our final model, exclusive dedication to palliative care was significantly associated with less burnout in both patient-related and work-related burnout. These results can seem like a paradox, but in fact, other studies had the same results.[17,26] Several reasons could be related to the fact that physicians working in palliative care[47] have a lower probability of burnout. For example, they have a higher degree of job satisfaction, a less stressful working environment or better conditions to do their job.[26] Furthermore, while working with only palliative care patients, the risk of becoming infected or infecting other patients with COVID-19 is lower, which could have an effect on overall levels of burnout.

Engaging in weekly physical activity was also associated with lower levels of personal and work-related burnout which is supported by the literature.[46] The type of unit was related with different levels of burnout in work and patient-related burnout in accordance with another study.[17] The levels of work (not statistically significant) and patient-related burnout of physicians working in the HSPCTs and PCUs were 7.8, 6.2 points and 15.2, 13.2 points lower on

average, respectively, in comparison with those in home palliative care teams. These differences could be associated with the organization of NNPC.[6] Physicians working in HSPCTs or PCUs have a different work environment and better support in contrast with HPCTs. HSPCTs have the advantage of working in a hospital with better support from different specialties and from other professionals like nurses. In contrast, physicians working in HPCTs have a more demanding environment[47] and fewer resources available.[17] Physicians working in PCUs can also count on the support of the institution and other workers in contrast to HPCTs. Overall, having better support from the work environment and other professionals could be responsible for the lower levels of work and patient-related burnout.[17] It is important to note that COVID-19 required a modification of the normal procedures across all the teams, but the impact could be higher in HPCTs in terms of burnout while having clinical meetings in their homes such as the need to protect patients and their caregivers while having clinical meetings.[28]

Self-perceived health status was the only variable present in the three final models. The notion of very good or good health status was significantly related to less personal, work, and client-related burnout, as expected. These results are also supported by the literature, which indicates that physicians who perceived having a better health status are more likely to be able to control situations that could increase overall levels of burnout.[48]

We could not find any other study similar to this one that was conducted after the outbreak of COVID-19. This study offers the first possibility to assess the impact of the new reality of these healthcare workers during the COVID-19 pandemic. The majority (83%) agreed that COVID-19 had an impact on their clinical activity. As expected, patient-related burnout levels were low, but the high prevalence of personal and work-related burnout requires measures and solutions from institutions. The authors note the limitation of the sample size that could have influenced the overall results. In future studies it would be important to have a bigger sample size. However, as far as the authors know, this study has the biggest sample size concerning palliative care physicians in Portugal, which offers the possibility to provide new insights about burnout in these professionals.[49,50] We are also aware that COVID-19 could have contributed to higher levels of burnout. During the period of data collection, Portugal was experiencing the COVID-19 pandemic crisis, which could have influenced the overall burnout levels. Another limitation that this study could have is lower representation of physicians who use the internet less as the data were collected entirely through electronic means. This study was a cross-sectional study with no follow-up of the physicians over time or during different phases of the COVID-19 pandemic. Other variables related with COVID-19 could have an influence on the overall results of burnout levels, like physicians or their relatives being infected with COVID-19 during the period of data collection. It would be important to have more studies in the literature conducted after the outbreak of COVID-19 in order to make the comparison with the obtained results. Lastly, although this study was also totally anonymous, participants could still have a tendency to rate themselves in a better position while answering the questions related to burnout levels.

We are now in a different phase of the COVID-19 pandemic with fewer cases and a majority of the population being vaccinated in some countries. Thus, it would be interesting to see whether these factors have had an impact on overall levels of burnout by replicating this study in the same population. These high levels of burnout in physicians demonstrate the importance of applying measures in the National Health Service to identify physicians who are at risk and to decrease overall levels of burnout to protect these healthcare workers and deliver high-quality health care services to their patients.

## CONCLUSION

The prevalence of personal burnout, work-related burnout, and patient-related burnout was 43%, 52% and 21%, respectively. We have found high levels of burnout in comparison with other studies, but the COVID-19 pandemic situation could have influenced the overall levels of burnout.

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## AUTHOR CONTRIBUTIONS

JVG, LC: Design of the study, data acquisition and analysis, draft and critical review of the manuscript.

RN, GR: Data analysis, draft and critical review of the manuscript.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## COMPETING INTERESTS

All authors report no conflicts of interest.

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# Co-Administration of Albumin and Furosemide in Acute Heart Failure with Diuretic Resistance

# Coadministração de Albumina e Furosemida na Insuficiência Cardíaca Aguda com Resistência aos Diuréticos

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**ABSTRACT**

Acute heart failure is a frequent cause of hospital admission in Portugal, and has an increasing tendency given the aging population. Although most admissions for acute heart failure are caused by congestive conditions, not all patients have a congestive phenotype, reflecting the complexity of a process with multiple pathophysiological pathways. The use of diuretics, usually loop diuretics, is the mainstay of treatment for congestion. However, many patients develop resistance, thus constituting a challenge with no consensual solution to date, despite extensive debate over the years. Despite its frequent use in clinical practice, the co-administration of albumin and furosemide remains controversial in the management of patients with acute heart failure, hypoalbuminemia, and diuretic resistance. This review addresses the pathophysiological mechanisms of congestion in patients with acute heart failure and explores the theoretical basis that supports the co-administration of albumin and furosemide in this clinical context. It is intended to clarify the potential benefit of the combined approach in this specific population and identify possible gaps in the literature that could be the subject of future studies.
**Keywords:** Albumins; Diuretics; Drug Resistance; Furosemide; Heart Failure; Sodium Potassium Chloride Symporter Inhibitors

**RESUMO**

A insuficiência cardíaca aguda é uma causa frequente de internamento hospitalar em Portugal, com tendência a aumentar devido ao envelhecimento da população. Apesar de a maioria dos internamentos por insuficiência cardíaca aguda ser motivada por quadros congestivos, nem todos os doentes apresentam um fenótipo congestivo, o que reflecte a complexidade de um processo com múltiplas vias fisiopatológicas. A utilização de diuréticos, habitualmente diuréticos de ansa, constitui a base do tratamento da congestão. No entanto, muitos doentes desenvolvem resistência, constituindo assim um desafio sem solução consensual até à data, apesar do extenso debate ao longo dos anos. Apesar da sua utilização frequente na prática clínica, a coadministração de albumina e furosemida permanece controversa na gestão de doentes com insuficiência cardíaca aguda, hipoalbuminémia e resistência aos diuréticos. Esta revisão aborda os mecanismos fisiopatológicos da congestão nesses doentes e explora a base teórica que suporta a coadministração de albumina e furosemida no respectivo contexto clínico. Pretende-se clarificar o potencial benefício da estratégia combinada nesta população específica e identificar possíveis lacunas na literatura que possam ser alvo de estudos futuros.
**Palavras-chave:** Albuminas; Diuréticos; Furosemida; Inibidores de Simportadores de Cloreto de Sódio e Potássio; Insuficiência Cardíaca; Resistência a Medicamentos

## INTRODUCTION

Acute heart failure (AHF) is a frequent cause of hospital admission in Portugal and represents a challenge in terms of therapeutic management.[1] With no prognostic impact, diuretic therapy including loop diuretics (LD) such as furosemide, is a cornerstone in decongestive therapy.[2] However, up to one third of patients with heart failure (HF) become resistant to diuretics, which is related to poor clinical outcomes.[3–5] In these cases, a combined therapeutic approach may prevent sodium reabsorption and promote water excretion.[6] This may include sodium and water restriction, increasing doses of diuretics and the sequential blockage of the nephron. Despite this combined approach, some patients remain congestive and become resistant to diuretic therapy, with progressive deterioration of their clinical condition and quality of life, particularly if they have hypoalbuminemia.[7] The underlying mechanisms behind diuretic resistance are incompletely understood.[8] So far, there is not enough evidence to support the generalized use of a furosemide and albumin combined approach in clinical practice. This article discusses the pathophysiological mechanisms of AHF with congestion and the potential role of albumin-furosemide co-administration to address diuretic resistance.

## MATERIAL AND METHODS

The authors conducted a literature search in the PubMed/Medline and Cochrane databases for articles

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including the Medical Subject Headings (MeSH) terms 'heart failure', 'albumin', 'diuretics' and/or 'diuretic resistance'. The search included articles published from 1986 until September 2021. The methodological approach applied for the selection of articles to include in the main text is summarized in Fig. 1. An initial screening was independently conducted by two authors. Duplicates and titles that did not mention at least one of the MeSH terms were excluded. The same authors independently selected the abstracts for full text assessment if they included information focusing on albumin and furosemide co-administration regardless of the index disease. Documents that did not include information about HF and/or diuretic resistance or the co-administration of albumin and furosemide were considered irrelevant and excluded. From this selection, relevant articles were included in the main text.

## RESULTS

Four hundred and ninety titles were selected from the database search and, based on their relevance, 91 titles were selected for abstract screening. A second selection excluded 34 records: two due to repetition and 32 due to irrelevance (Fig.1). From the 57 articles selected, 38 were literature reviews (1 - 7, 10 - 16, 44, 45, 48 - 50, 17 - 33, 35 - 37), five were prospective studies (9, 46, 38, 52, 54), six were retrospective studies (8, 51, 36, 39, 43, 55) and eight

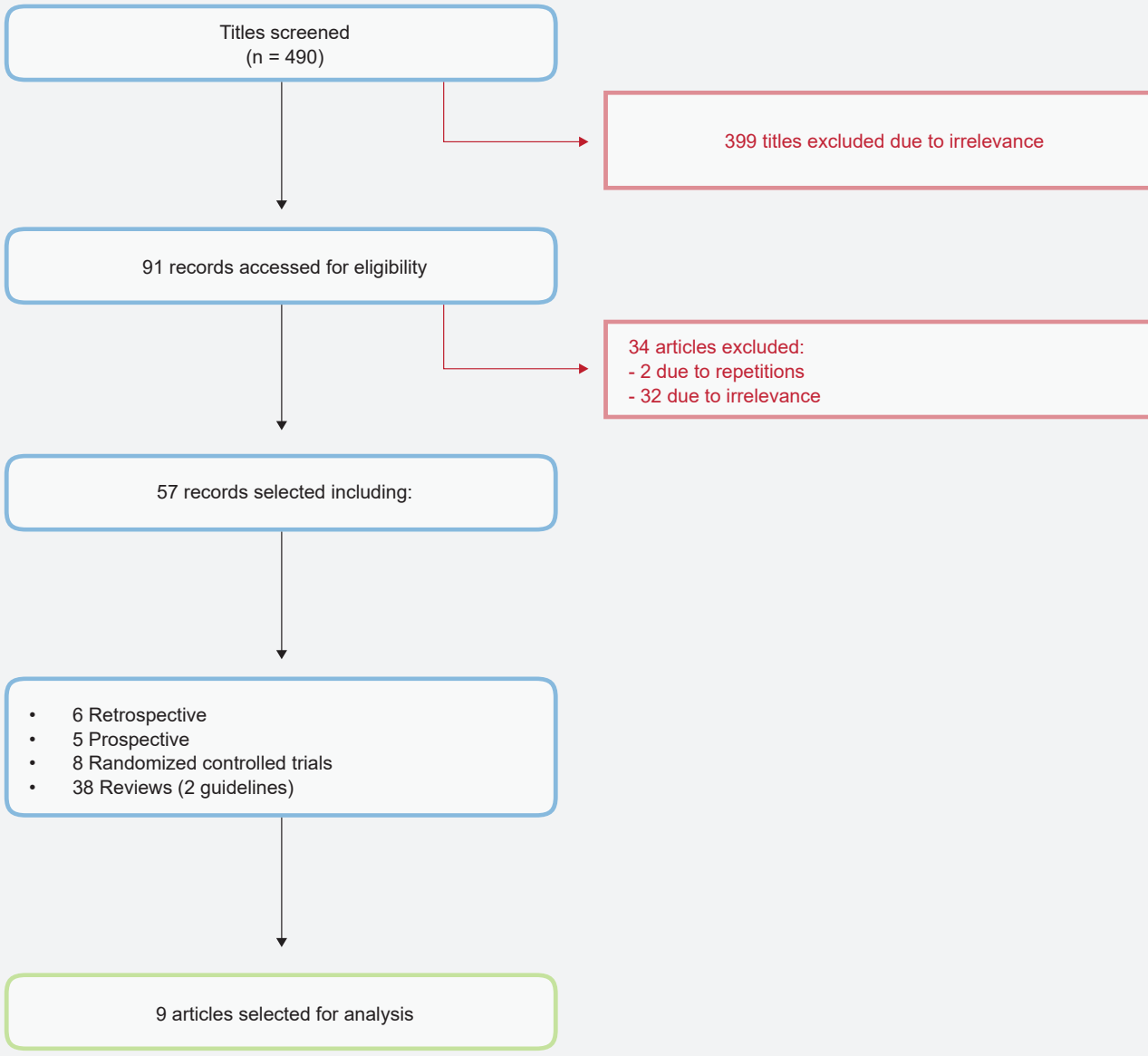


Figure 1 – Results. Included and excluded articles according to predefined criteria.

were randomized controlled trials (RCT) (46, 47, 40 - 42, 53, 57, 58). Nine studies focused on the co-administration of albumin and furosemide and were included in the analysis: five concluded in favour of co-administration strategy (7, 41, 42, 47, 53) but one did not focus on diuretic resistant patients (47); four articles concluded against the co-administration strategy (4, 40, 46, 55). From these nine studies, only one clearly included HF patients (46). The articles focusing on the co-administration of albumin and furosemide are listed in Tables 1 and 2.

## DISCUSSION

### Acute heart failure, congestion, and diuretic resistance

Several mechanisms may be involved in AHF, and congestion appears to be the consequence of a complex, multi-pathophysiological process. This process leads to increased intra-cardiac filling pressures which appears to be the starting point for the congestive state. Trends in weight and volume status act as surrogate markers for congestion which is one of the main targets of the current strategies for HF management. However, fluid retention is not evident in all patients and this heterogeneity in clinical presentation suggests that other mechanisms may increase cardiac filling pressures and subsequently trigger AHF.[9] Blood volume redistribution between different vascular compartments may be one contributing mechanism.[10]

Diuretic resistance suggests impaired sensitivity to diuretics and results in reduced sodium and water excretion, limiting the possibility to achieve an euvolemic state.[11] There is not a universal definition for diuretic resistance, but

Table 1 – Articles that favor the co-administration of furosemide and albumin (regardless of the index disease) by order of appearance in the main text

| Study | Design | Cohort | Findings |
|---|---|---|---|
| Duffy *et al*, 2015[7] | Review | Nephrotic syndrome patients | Combination therapy should be considered in patients with diuretic resistance. |
| Martin *et al*, 2005[47] | Crossover, prospective | 40 patients with acute lung injury/ acute respiratory distress syndrome and albumin < 6g/dL | Combination therapy in patients with hypoproteinemia significantly improves oxygenation, with greater net negative fluid balance and better maintenance of hemodynamic stability. |
| Fliser *et al*, 1999[41] | Crossover, prospective | 9 patients with nephrotic syndrome | Co-administration of human albumin potentiates the action of furosemide, but only modestly. |
| Phakdeekitcharoen *et al*, 2012[42] | Crossover, prospective | 24 patients with CKD and hypoalbuminemia | Combination therapy has a superior short-term efficacy over furosemide alone in enhancing water and sodium diuresis. |
| Inoue *et al*, 1987[53] | Crossover | 20 patients with hypoalbuminemia (diverse aetiologies) | Combination therapy allowed effective diuresis in patients with diuretic resistance. |

NA: non-applicable; CKD: chronic kidney disease

Table 2 – Articles that do not support the co-administration of furosemide and albumin (regardless of the index disease) by order of appearance in the main text

| Study | Design | Cohort | Findings |
|---|---|---|---|
| Ellison *et al*, 2019[4] | Review | NA | Did not support the use of combination therapy in diuretic resistant patients. |
| Makhoul *et al*, 1997[46] | Observational, prospective | 30 patients with acute respiratory failure due to cardiogenic pulmonary oedema | Combining continuous furosemide infusion with albumin offers no advantage over the use of continuous furosemide alone. |
| Chalasani *et al*, 2001[40] | Crossover, prospective | 13 patients with cirrhosis (variable causes) | Combination therapy did not enhance diuretic effects in patients with cirrhosis and ascites. In addition, the administration of albumin did not alter the pharmacokinetics or pharmacodynamics of furosemide. |
| Doungngern *et al*, 2012[55] | Retrospective | 31 ICU patients (variable causes) | Addition of albumin to a furosemide infusion did not enhance diuresis obtained with furosemide alone in critically ill patients. |

NA: non-applicable; ICU: intensive care unit

clinical and laboratory markers of poor diuretic response have been described.[12] The 'reference diuretic dose' is consistently determined as 40 mg of furosemide or equivalent among studies. Accordingly, clinical surrogates of poor diuretic response may include diuresis below 1400 ml or a net weight change of 0 to 2.7 kg. Laboratory markers for poor diuretic response include fractional excretion of sodium at baseline < 0.2%, lower chloride levels at baseline (97 to 103 mEq/L) and/or a urinary sodium and urinary furosemide concentration ratio below 2 mmol/mg.[12–16]

**The splanchnic circulation and 'effective blood volume'**

The 'effective circulatory volume' is one of the main determinants of preload to the heart and refers to blood in the arterial system and in non-splanchnic venous vessels.[17] In a similar manner, the highly compliant venous system acts as a reservoir for blood and is actively involved in the regulation of preload to the heart and cardiac output.

The splanchnic vascular compartment is a major reservoir for blood and can accommodate or release most of the volume change in circulating blood.[10,18] It has an abundance of adrenergic receptors, with an asymmetrical distribution, with higher density of adrenergic terminals on veins.[19] This causes a stronger venous vasomotor response compared to other vascular regions and makes the splanchnic circulation an important component of effective circulatory volume regulation.

In healthy individuals, the baroreflex prevents fluid shift from the splanchnic reservoir by providing a sympathetic-inhibitory influence on this vascular bed.[20] Increases in sympathetic tone should recruit blood from the splanchnic and peripheral compartment to the heart, which increases filling pressures. In HF patients, a decreased baroreflex function inhibits the capacity to buffer eventual rises of effective circulatory volume, especially in acute disease states.[21,22] In HF, a 'fast track' for decompensation stems from autonomic imbalance with overactivity of the sympathetic nervous system (SNS), resulting in increased preload and extravascular edema. A slower mechanism, also mediated by the SNS, causes sodium retention resulting in splanchnic congestion. Finally, in HF, the storage capacity of splanchnic vasculature may be impaired *per se*, reducing its ability to buffer extra fluid. This fluid redistribution mechanism accelerates the increase in central filling pressures and might play a significant role in the pathophysiology of AHF.[23]

**The cardiorenal interaction and 'renal congestion'**

The cardiorenal interaction in AHF remains poorly understood. Coexistent renal dysfunction may complicate the treatment of HF and the use of LD to treat congestion may worsen renal function.[24] Renal dysfunction in HF patients is traditionally associated with decreased renal perfusion and altered neural-hormonal feedback mechanisms. New findings point to a major role of venous congestion in the pathophysiology of renal dysfunction in AHF. In fact, persistent venous congestion explains several changes observed in HF: hormonal and endothelial activation, increased intra-abdominal pressure, excessive tubular sodium reabsorption and volume overload. Among others, these mechanisms lead to further renal dysfunction and increased cardiac filling pressures.[24–26] Moreover, irreversible renal dysfunction due to persistent renal hypoperfusion or venous congestion may lead to inefficient decongestion. Addressing and solving the reversible causes of renal dysfunction, should facilitate effective decongestion.[27]

**Glycocalyx loss and albumin**

The glycocalyx is a complex layer of membrane-bound proteins that lines the luminal surface of the endothelium. Among other functions, it regulates vascular permeability, contributing to the vascular homeostasis.[28] Albumin integrates the structure and stabilizes the glycocalyx. Under physiological conditions, the glycocalyx inhibits the shift of albumin across the endothelium and plays a major role in the regulation of hydrostatic and oncotic pressure gradients through the capillary beds.[29,30] Moreover, changes in capillary pressure may impose changes in the composition of the fluid under the glycocalyx. In contrast, the interstitial fluid composition may take longer to adjust to changes in vascular pressure.[31] Glycocalyx loss can occur in any vascular bed, but it can be easily detected in the kidneys since albuminuria is measured in the urine.[30] This process is normally reversible and may occur in the absence of glomerular structural injury. Detecting glycocalyx loss is important as it may constitute a reversible cause of albuminuria and renal dysfunction, and due to its influence in fluid shift across compartments.

**Loop diuretics**

To be effective, LD must transit to the kidney via the circulation, undergo secretion by the proximal tubule, be delivered to the luminal surface of thick ascending limb cells, and bind to and inhibit the Na-K-2Cl cotransporter. More than 95% of the absorbed LD circulate bound to albumin and are transported in its inactive form. In their active site, they inhibit sodium reabsorption promoting natriuresis and water excretion.[4,32]

The natriuretic effect of LD may be modified by processes upstream or downstream from their active site. Hepatorenal or cardiorenal syndromes, occur frequently in HF patients and may promote fluid overload and poor response to diuretic therapy. Moreover, conditions such as liver cirrhosis or nephrotic syndrome may cause protein deficiency

or loss impacting LD pharmacokinetics and challenging the evaluation of its true diuretic effect.[4,32] Knowing which of these conditions plays the dominant role, could change the treatment approach.

**Hypoalbuminemia and diuretic response to LD in HF patients**

Albumin is a major player in maintaining cardiovascular homeostasis due to its oncotic properties and seems to be a powerful risk predictor, even within normal ranges.[33] It is also a marker of inflammation, arterial stiffness, liver and kidney disease, which may occur in HF patients. Hypoalbuminemia is a frequent condition in HF patients and is associated with the malnutrition-inflammation complex syndrome, which translates the relation between malnutrition, inflammation and atherosclerosis-related cardiovascular disease.[34] Other conditions that may increase the severity of hypoalbuminemia in the elderly, comorbid patient include: hemodilution; altered albumin synthesis in liver disease; vascular dysfunction with increased transcapillary escape rate; kidney disease (mainly end-stage kidney disease) with reduced synthesis and increased albumin degradation; and enteral loss.[35–37] Hypoalbuminemia induces a low plasma oncotic pressure, which facilitates transcapillary fluid shift causing pulmonary edema, even in patients without increase in pulmonary capillary hydrostatic pressures. It also favors myocardial edema, volume overload, diuretic resistance and exacerbation of oxidative stress and inflammation, contributing to the progression of HF.[35] In fact, hypoalbuminemia is considered a risk factor for the development of HF and is predictive of mortality in patients with acute and chronic HF.[38,39] Evidence is growing that hypoalbuminemia independently predicts incident HF in patients with end-stage renal disease and elderly patients, as well as mortality in patients with HF regardless of left ventricular ejection fraction and clinical presentation.[35]

Theoretically, hypoalbuminemia should affect LD pharmacokinetics by indirectly increasing the volume of distribution, increasing the odds of resistance. Also, an excess of albumin in the renal tubules may act as a scavenger for the unbound LD forcing its excretion, thus contributing to diuretic resistance.[40] On the other hand, administration of albumin should positively impact renal hemodynamics, increasing oncotic pressure in the circulatory system and improving the glomerular filtration rate and effective renal plasma flow.[41,42] In patients with AHF receiving intravenous diuretics, moderate/severe hypoalbuminemia as determined by the nadir (not necessarily serum albumin level at admission) is associated with a greater risk of acute worsening of renal function and the need for intravenous vasoactive therapy. Therefore, the timing of serum albumin level assessment may influence the utility of albumin as a biomarker of short-term clinical outcomes in patients with AHF.[39]

The discussion regarding the impact of albumin concentration on the mechanism of action of LD makes sense. However, its clinical relevance, particularly in the range of values routinely found in clinical practice, has not yet been proven in patients with HF.[8,36,43]

**Co-administration of albumin and furosemide throughout the decades**

Numerous strategies for the management of HF with congestion and diuretic resistance have been investigated.[44,45] One of them consists in the intravenous co-administration of albumin and furosemide in patients with HF and hypoalbuminemia. Although there is a rationale for the addition of colloids to diuretic therapy, only a few studies addressed this problem in AHF and none proved its beneficial role.[46–49] Presently, there are no evidence-based recommendations for this combined therapy in diuretic resistant AHF patients with hypoalbuminemia.[50,51]

Monzo *et al*, confirmed a strong correlation between congestion and hypoalbuminemia.[9] Peterson *et al*, found a trend toward greater diuresis in patients with normal albumin levels versus hypoalbuminemia.[39] A trial carried out by Phakdeekitcharoen *et al*, concluded that the combination of furosemide and albumin had superior short-term efficacy over furosemide alone in enhancing water and sodium diuresis in hypoalbuminemic patients with chronic kidney disease.[42] In another way, a pre-clinical study showed that proteinuria may compromise the benefit of albumin and furosemide in hypoalbuminemic patients with nephrotic syndrome.[52] Inoe *et al* tested a small subset of hypoalbuminemic patients (mean serum albumin concentration of 2.0 g/dL), in which the furosemide-albumin complex effectively increased the urine volume.[53]

More recently, Charokopos *et al* showed an association of hypoalbuminemia with poor diuretic efficiency but failed to maintain this correlation when the effects of inflammation on serum albumin concentration were addressed after adjustment for IL-6 levels.[54] Doungngern *et al* conducted a retrospective study on 31 intensive care patients who received furosemide as a continuous infusion with and without 25% albumin for more than six hours.[55] The authors concluded that the addition of albumin to a furosemide infusion did not enhance diuresis compared with furosemide alone in critically ill patients. However, the previous level of albumin was not considered.

In 2014, Kitsios *et al* conducted a meta-analysis focusing the co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia.[56] The studies considered included mainly patients with nephrotic syndrome and cirrhosis and none of them mentioned HF patients and diuretic resistance.

A statistically significant increase in the amount of urine volume and sodium excreted at eight hours was found, favoring the combined therapy but these differences were no longer statistically significant at 24 hours. A subgroup analysis with nephrotic syndrome as the index disease, demonstrated an increase in urinary volume, both at eight hours and 24 hours after albumin-furosemide administration compared with furosemide alone, with an absolute magnitude larger than in the main analysis. Of note, the furosemide daily dose ranged from 30 to 220 mg per day across studies, which is probably considered a low dose in the context of HF and diuretic resistance. Finally, despite the potential beneficial effect of albumin on diuresis no significant effects on natriuresis were found.[56]

Kitsios *et al* mentioned the large heterogeneity between studies as a limitation, with some including patients with cirrhosis and kidney disease with or without nephrotic syndrome.[56] Regarding methods, there were several differences between studies: only some measured serum creatinine, proteins in 24 hours urine and urinary sodium; the definition of hypoalbuminemia differed (cut-off from 1.1 to 3.1 g/dL); and doses of furosemide and albumin in individual studies were remarkably variable. Nonetheless, it was noted that a significant diuretic effect from albumin administration was detected only when associated with smaller doses of furosemide (60 mg or less in the studies with statistically significant results on the outcome of urinary volume). The authors also mentioned the possible relation between the severity of hypoalbuminemia and the extension of diuretic resistance, which could impact the effect of co-administration of albumin and furosemide.[56] They concluded that effects of the combined therapy in patients with hypoalbuminemia were modest and transient (in the first eight hours after administration of albumin) and none of the results would support a change in clinical practice.[56]

Bleske *et al* studied a cohort of 162 patients with AHF treated with continuous diuretic infusion to compare diuretic response (measured as urine output) between two groups: one with hypoalbuminemia defined as albumin ≤ 3 g/dL); and a control group without hypoalbuminemia. Unlike what has been observed in nephrotic syndrome, this study did not demonstrate that hypoalbuminemia decreased diuretic effectiveness.[43] The authors stated that diuretic effectiveness could be related with the type and degree of hypoalbuminemia and hyperalbuminuria in patients with AHF when compared with patients with nephrotic syndrome. In patients with nephrotic syndrome, a decrease in serum albumin is more probably related with albuminuria. However, in patients with HF, hypoalbuminemia may stem from hemodilution, although malnutrition, cachexia, and inflammation can also contribute. Another factor positively affecting diuresis may be the aggressive diuretic approach employed to treat patients with congestive AHF. Aggressive diuresis may overcome any effect hypoalbuminemia may have on diuretic efficacy by increasing the amount of drug at the site of action. Finally, the authors proposed that continuous infusion of furosemide, especially in higher doses, provided a continuous level of diuretic therapy above the threshold and less rebound effect, possibly increasing the diuretic effect of furosemide.[43]

The DOSE trial compared the method and dose of administration of furosemide in patients with AHF. The groups were assigned to receive furosemide administered intravenously either by bolus or continuous infusion and at a low dose (previous oral dose) or high dose (2.5 times the previous oral dose). Despite the high-dose strategy association with greater relief of dyspnea, greater fluid and weight loss and fewer serious adverse events, there was no statistically significant difference regarding the primary efficacy end point (the patient's global assessment of symptoms) and safety end points. The same was found in the bolus versus continuous infusion groups, concerning the primary efficacy endpoint.[57] Both the DOSE-AHF and the ROSE-AHF trials also provided a well-characterized cohort regarding albumin concentrations and diuretic response. In these trials, an unequivocal relationship between a lower baseline albumin level (hypoalbuminemia defined as serum levels < 3 - 3.5 g/L) and decreased response to decongestive therapies was not found, which does not support the use of albumin in hypoalbuminemia.[57,58]

**Co-administration of albumin and furosemide in HF patients with hypoalbuminemia and diuretic resistance: the present and the future**

Clinical experience seems to support the use of albumin as a therapeutical strategy to mobilize edema fluid in dialysis patients with hypoalbuminemia and decreased effective arterial volume. In AHF patients with hypoalbuminemia and diuretic resistance, the access to the extravascular compartment is difficult. Raising the vascular oncotic pressure may allow the mobilization of excessive extravascular fluid and promote ultrafiltration by pulling extravascular fluid into the intravascular compartment.[37] Nevertheless, this beneficial role of albumin-furosemide co-administration needs to be proven in a large RCT.

Several considerations should be made regarding studies focusing on the correlation between albumin administration and LD effectiveness in HF: there are few studies including patients with AHF; cohorts included are usually of small size, have heterogenous populations and endpoints are somewhat variable across studies; the general approach to AHF is heterogeneous and may include the use of vasoactive drugs or diuretics other than furosemide, which contributes to the heterogeneity among studies.

All these considerations make it difficult to compare results and find generalizable assumptions.

Additionally, the definition of hypoalbuminemia is variable among studies, and it seems that severe hypoalbuminemia may favor the use of albumin to overcome diuretic resistance. Albumin levels should be measured in several time points and the nadir should be considered to define hypoalbuminemia. Ideally, studies should be performed in HF patients without nephrotic syndrome, cirrhosis, or any kind of other inflammatory or infectious disease, in order to reduce possible confounding factors. Hypovolemia should be identified and excluded, and other pathophysiologic mechanisms should be explored to gauge poor diuretic response.

Ultimately, a standardized definition of diuretic resistance is mandatory. Urine output and sodium excretion are specific endpoints that have demonstrated the beneficial role of albumin-furosemide administration in patients with conditions other than HF. Such specific endpoints should also be chosen over less specific ones in future studies regarding HF patients. Future RCTs should evaluate the efficacy of albumin-furosemide administration for different degrees of hypoalbuminemia, since there is just a generalized assumption that albumin is more effective in severe hypoalbuminemia, a term that also lacks definition. The timing of albumin administration (generally prior to furosemide) should also be addressed since it is known that higher doses of furosemide could make the addition of albumin less effective and that the maximal effect of albumin in expanding intravascular volume occurs in the first hour after administration.[7] For this reason, drug doses, methods and timing of administration should also be defined.

The large heterogeneity between concepts and the lack of RCTs in AHF are major limitations of this review. The consequence is that there are more questions than answers being raised, which, in another way, may be possible starting points for future studies.

## CONCLUSION

Congestion in acute heart failure arises from a complex interaction between multiple pathophysiological pathways and compensatory mechanisms. The resulting increased sympathetic activity, excessive volume overload, and dysfunctional fluid redistribution ultimately lead to increased intra-cardiac filling pressures which appear to be the starting point for congestion. The specific physiologic mechanisms of diuresis enhancement and hemodynamic improvement after the co-administration of albumin and furosemide remain unclear but this combined approach seems to overcome diuretic resistance in selected patients with acute heart failure. This strategy seems to be reasonable on pathophysiological grounds and has been supported by clinical experience. However, its beneficial role in this specific population has not yet been proven and remains controversial. The variability in selection criteria, experimental design, and clinical endpoints may justify this controversy. A standardized measurable definition for congestion, diuretic resistance and hypoalbuminemia would allow for a more accurate selection of patients who could benefit from this combined approach. Large-scale randomized controlled trials are therefore needed to make recommendations regarding the use of albumin and furosemide in acute heart failure patients with diuretic resistance.

## AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## COMPETING INTERESTS

The authors have declared that no competing interests exist.

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# Surgical Resection Combined with Adjuvant Radiotherapy and Non-Steroidal Anti-Inflammatory Drugs in the Treatment of Heterotopic Ossification Following Total Hip Arthroplasty

# Tratamento da Ossificação Heterotópica Após Artroplastia Total da Anca: Excisão Cirúrgica Combinada com Radioterapia e Anti-Inflamatórios Não Esteróides

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**ABSTRACT**

Heterotopic ossification (HO) is a well-known complication following total hip arthroplasty (THA), with an average incidence of 30%. Patients are classified according to Brooker's staging system. In advanced stages (III and IV), HO may limit hip motion and cause intolerable pain. For these symptomatic stages, surgical excision is mandatory, usually combined with prophylaxis of recurrence with non-steroidal anti-inflammatory drugs (NSAIDs) and/or radiotherapy. We present the case of a 70-year-old woman who developed Stage IV HO after undergoing THA for left hip osteoarthritis. Surgical excision of the HO was performed eighteen months after THA, with adjuvant radiotherapy and indomethacin. After two years of follow-up, the patient had a good hip function with no recurrence of HO. Several authors have studied the effect of NSAIDs and radiotherapy in HO prophylaxis and in HO treatment but there is lack of reports concerning the combination of the two strategies with surgery in the postoperative period. We therefore report this successful case of post-THA HO treatment with surgical excision and post-operative radiotherapy and NSAIDs.
**Keywords:** Anti-Inflammatory Agents, Non-Steroidal; Arthroplasty, Replacement, Hip; Ossification, Heterotopic/drug therapy; Ossification, Heterotopic/radiotherapy

**RESUMO**

A ossificação heterotópica (OH) é uma complicação frequente após artroplastia total da anca (ATA), com uma incidência média de 30%. Os doentes são classificados de acordo com o sistema de estadiamento de Brooker. Nos estádios avançados (Brooker III e IV), a OH pode restringir a mobilidade da anca e causar dores insuportáveis. Nestes estádios sintomáticos, o tratamento indicado consiste na excisão cirúrgica combinada com profilaxia da recorrência com anti-inflamatórios não esteróides (AINEs) e/ou radioterapia. Apresentamos o caso de uma mulher de 70 anos que desenvolveu OH grau IV após ATA por osteoartrose da anca esquerda. Realizou-se excisão da OH um ano e meio após a ATA, com radioterapia e indometacina adjuvantes. Após dois anos de seguimento, não se verifica recorrência da OH e apresenta uma boa função da anca. O efeito dos AINEs e radioterapia adjuvante na profilaxia e no tratamento da HO está bem estabelecido, mas não há muitos relatos das duas estratégias combinadas com cirurgia no pós-operatório. Descrevemos, portanto, um caso de tratamento de OH pós-ATA com excisão das ossificações e radioterapia e AINEs no pós-operatório.
**Palavras-chave:** Anti-Inflamatórios não Esteroides; Artroplastia Total da Anca; Ossificação Heterotópica/radioterapia; Ossificação Heterotópica/tratamento farmacológico

## INTRODUCTION

Heterotopic ossification (HO) is a well-known complication following total hip arthroplasty (THA). Although the literature is not totally consistent, it is thought to be more frequent with the lateral approach.[1-3] Its reported incidence varies widely, with values ranging from 1% to almost 90%.[1–4] Zhu *et al* reported a cumulative mean incidence of 30% in their recent meta-analysis.[1] Overall, 9% of patients with HO are symptomatic, which can hinder the results achieved with THA.[2]

Several risk factors have been proposed for HO, with the most important being previous HO, ankylosing spondylitis, bilateral hip replacement, cemented technique, male gender and hip ankylosis.[1,3] Table 1 outlines the four types of HO, according to Brooker.[4]

HO can be well tolerated in its less severe stages. However, in more advanced stages, patients can become symptomatic and develop groin pain and loss of range of motion.[3] Surgical excision is the only treatment available, and prophylaxis of recurrence with non-steroidal anti-inflammatory drugs (NSAIDs) and/or radiotherapy (RT) has been suggested as the most effective regimen.[5–7]

There are few reports describing the association of surgery, NSAIDs and radiotherapy to treat HO after THA. The case we present illustrates the successful outcome of a protocol combining these three methods in the treatment of post-THA HO.

## CASE REPORT

We report the case of a 70-year-old woman with a medical history of arterial hypertension, obesity, and degenerative lumbar spine disease. The patient was referred to the outpatient clinic due to hip osteoarthritis in 2017 (Fig. 1A), for which she underwent left hip uncemented THA through a posterior approach (Fig. 1B).

Three months after surgery, the patient started experiencing pain, decreased left hip motion and a flexion

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Table 1 – Brooker's grading system for HO around the hip joint[4]

| Class | Definition |
|---|---|
| I | Islands of bone within the soft tissues about the hip |
| II | Bone spurs from the pelvis and/or proximal end of the femur; > 1 cm of space |
| III | Bone spurs from the pelvis and/or proximal end of the femur; < 1 cm of space |
| IV | Apparent bone ankylosis of the hip |

contracture of the left hip. The radiograph (Fig. 1C) showed abnormal ossifications. One year after surgery the symptoms increased, and the patient had already developed Stage IV HO (Fig. 1D) with apparent bone ankylosis of the hip joint. She had no motion of the left hip and was not capable of walking without crutches. The Harris Hip Score (HHS) was 44 (0 - 100) and the Visual Analogue Scale (VAS) 1 (0 - 10).

Since there was no progression of HO in sequential radiographs, surgical excision of the ossifications was performed (Fig. 2) 18 months after the THA. A similar surgical approach was used, resulting in the immediate recovery of hip range of motion intra-operatively, after debriding and clearing the surrounding tissues of any residual heterotopic bone.

Adjuvant radiotherapy was initiated the day after surgery, according to the following protocol: after computed tomography (CT) scan planning to define the isocentre, the isocentric technique (using a common focus point to all radiation beams) was used in order to minimize damage to healthy tissues, with 15 MV photon beams. The left proximal femur and the surrounding tissues were irradiated with a dose of 2 Gray (Gy)/session/day, five days per week, with a total cumulative dose of 20 Gy after two weeks. The patient was also given indomethacin 75 mg/day for six weeks.

One month after surgery, the patient reported a relief of symptoms and was able to walk without crutches. The radiograph (Fig. 1E) showed evidence of improvement when compared to the one before excision (Fig. 1D), with only some minor residual HO.

Two years after revision surgery, the patient was asymptomatic, had a left hip motion of 85º of flexion, 25º of internal rotation, 20º of external rotation and 30º of abduction. The HHS was 87 and the VAS was 1. The radiograph (Fig. 1F) did not present evidence of HO recurrence. No adverse effects from either radiotherapy or Indomethacin were noticeable nor have been reported by the patient.

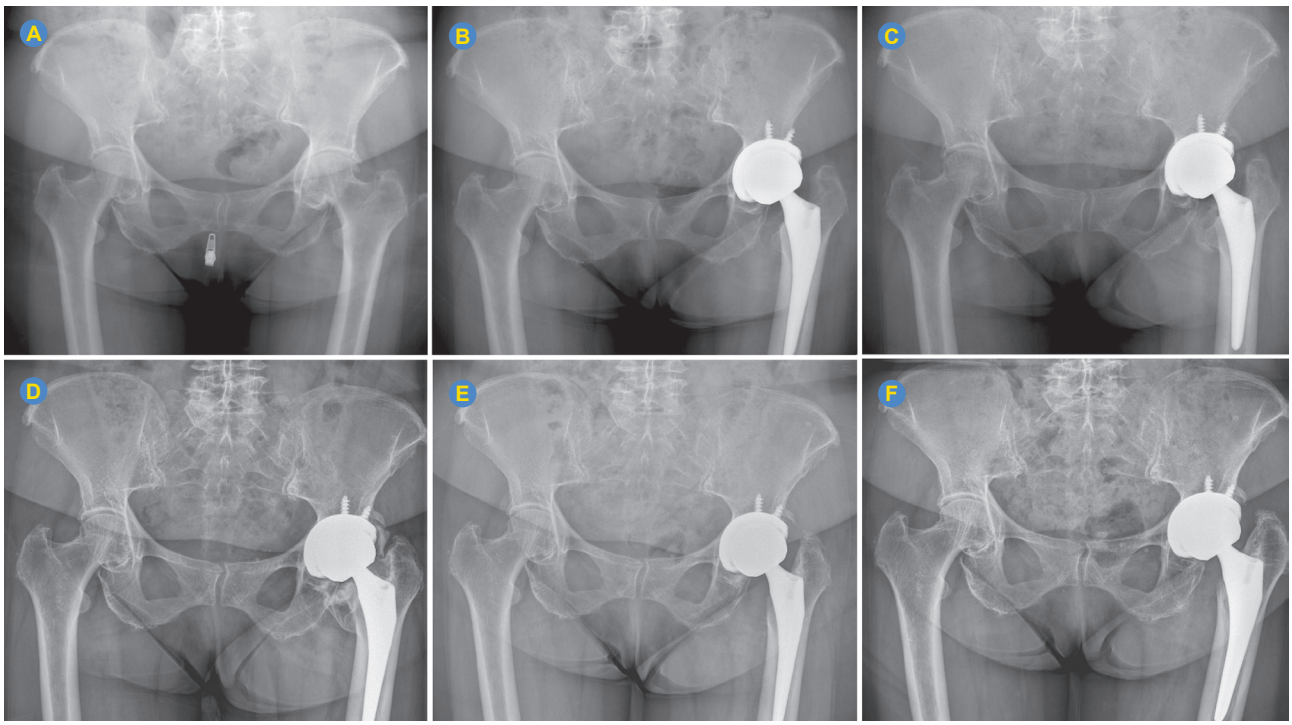


Figure 1 – Radiographic evolution: pelvis antero-posterior radiographs of the patient in different treatment phases; (A) Presentation with left hip osteoarthritis; (B) Post-operative control after total left hip arthroplasty; (C) Three months after THA, HO Brooker Grade II; (D) One year after THA, HO Brooker Grade IV; (E) One month after HO excision and RT; (F) Two years after HO treatment.

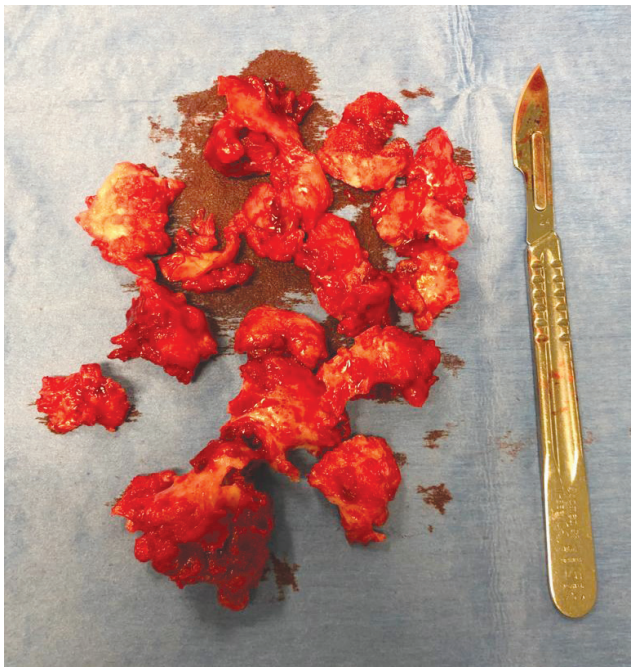

Figure 2 – Heterotopic ossification excision

## DISCUSSION

This case highlights the synergistic effects of three different treatment methods in treating HO and preventing its recurrence after a THA performed through the posterior approach.

Surgical excision is the only method to remove HO once it becomes established. The surgical procedure is technically demanding, and complications include sciatic nerve injury, iatrogenic femoral fracture, and infection.[5] A wide surgical exposure is needed, and care must be taken to protect the sciatic nerve and avoid damaging the original bone. In this case, no complication was registered.

Since it prevents HO formation by inhibiting osteoblast activity, the inclusion of adjuvant RT has been reported by many authors with good results, using many different schemes.[5–8] Chao *et al* compared the efficacy of several different RT regimens (cumulative doses of 6 to 20 Gy and single-dose *versus* fractionated) and found there were no statistically significant differences between the different schemes.[6] We used the dose of 20 Gy fractionated 10 times, which achieved a good result without recurrence or adverse effects.

NSAIDs are also used to prevent HO after THA and to prevent its recurrence after HO excision as they decrease the inflammatory status around the hip joint, thus decreasing the number of mesenchymal cells that would further differentiate into osteoblasts. Indomethacin has been used as the main NSAID in HO prophylaxis due to its cost effectiveness and good results. In a recent meta-analysis, Joice *et al* found similar results with indomethacin and other non-selective NSAIDs as well as selective NSAIDs decreasing the prevalence of HO after THA.[9] Our patient took 75 mg of indomethacin daily, for six weeks, without complications.

The three methods have been described by many authors, with clinical reports consisting mainly of combinations for prophylaxis of HO after THA with RT and NSAIDs and treatment of installed HO with surgery and either RT or NSAIDs.[7,9-11] In a prospective study, Pakos *et al* compared the results of post-operative prophylaxis of HO with either indomethacin alone or with combined post-operative single dose radiotherapy of 7 Gy and indomethacin. They found that the combined radiotherapy and indomethacin regimen was more effective in preventing HO after THA.[11] Macheras *et al* reported a recent case series using the three methods for the treatment of HO (only 23% after THA), with no severe HO recurrence.[5] However, RT was performed pre-operatively whereas in this case we used a combined post-operative treatment regimen.

The gain in the HHS obtained (from 44 to 87 points) suggests that this approach has obtained the desired endpoint. The patient had a good hip function for someone who underwent the two aforementioned surgeries and who suffers from lumbar spine disease which prevents her from achieving a higher HHS score.

In conclusion, this case report illustrates the positive results of a therapeutic scheme that combines RT, NSAIDs and surgical excision, which has been well tolerated by the patient. There are no widely accepted guidelines for the treatment of HO after THA. Since NSAIDs and RT inhibit the formation of HO in different phases of its pathogenesis, we believe it is a good option to combine these two techniques with the surgical excision. A limitation of this article is that it reports a single, retrospective, case. Further studies are necessary to define a universally applicable scheme that should encompass efficacy, cost-effectiveness, and patient tolerance in order to decrease the rate of HO after THA and to decrease the occurrence of complications from its treatment.

## AUTHOR CONTRIBUTIONS

TO: Literature review, draft of the manuscript.
JL, OT: Literature review, draft of the manuscript.
RS: Critical review of the manuscript.
AV: Draft and critical review of the manuscript.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## PATIENT CONSENT

Obtained.

## COMPETING INTERESTS

All authors report no conflict of interest.

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# Life-Threatening Wunderlich Syndrome Associated with Apixaban and the Complexity of Anticoagulation Management in Bleeding Patients: A Case Report

# Síndrome de Wunderlich Associada ao Apixabano e à Complexidade de Gestão de Anticoagulação em Doentes com Hemorragia: Um Caso Clínico

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**ABSTRACT**

Wunderlich syndrome is a rare and possibly life-threatening haemorrhagic syndrome presenting as spontaneous nontraumatic renal rupture with subcapsular and perinephric haemorrhage. Apixaban, a direct oral anticoagulant recommended in patients with atrial fibrillation, has previously been associated with atraumatic solid organ rupture but, to date, no case of apixaban-related Wunderlich syndrome has been reported. We report a rare case of Wunderlich syndrome associated with apixaban while addressing the difficulties face by clinicians when managing anticoagulation in bleeding patients.
**Keywords:** Acute Kidney Injury; Anticoagulants/adverse effects; Hemorrage; Kidney Diseases/chemically induced; Rupture, Spontaneous

**RESUMO**

A síndrome de Wunderlich é uma síndrome hemorrágica rara caracterizada por rutura renal espontânea, não-traumática, com hemorragia subcapsular e peri-renal. O apixabano, um anticoagulante oral direto recomendado em doentes com fibrilação auricular, foi associado no passado a rutura atraumática de órgãos sólidos mas, à data, nenhum caso de síndrome de Wunderlich associada ao apixabano foi reportado. Reportamos um caso raro de síndrome de Wunderlich associada ao apixabano abordando concomitantemente as dificuldades na gestão da anticoagulação em doentes com hemorragia.
**Palavras-chave:** Anticoagulantes/efeitos adversos; Doenças do Rim/induzida quimicamente; Hemorragia; Lesão Renal Aguda; Ruptura Espontânea

## INTRODUCTION

Direct oral anticoagulants (DOAC) are associated with spontaneous haemorrhage and, in rare cases, atraumatic solid organ rupture.[1,2] Yet, to date, no reports exist of renal rupture, or Wunderlich syndrome (WS), associated with DOAC use. To the best of our knowledge, we present the first-ever case report of WS associated with apixaban while highlighting the difficulties clinicians face in managing patients with a high-bleeding and high-thrombotic risk.

## CASE REPORT

A 79-year-old female with a medical history of permanent atrial fibrillation (AF) diagnosed two years prior and currently under apixaban and previous right (seven years ago) middle cerebral artery (RMCA) stroke was admitted to the emergency department due to sudden and intense left-flank pain. She denied fever, chills, night sweats, dysuria, supra-pubic/abdominal pain or trauma. She did not have any known clotting/bleeding disorders. Vital signs were stable and the physical examination only revealed abdominal tenderness. Blood tests showed a hemoglobin of 9.2 g/dL (down from a baseline of 11.1 g/dL 12 months prior), platelet count 188 x $10^9$/L, creatinine 2.05 mg/dL (up from a baseline of 0.85 mg/dL) and c-reactive protein of 5.0 mg/dL. Urinalysis revealed numerous leucocytes. An initial diagnosis of acute pyelonephritis was assumed, and the patient was discharged with antibiotics and paracetamol for pain management.

Six hours later she developed new-onset obnubilation, leading to re-admission to the emergency department. The patient was now hypotensive, lethargic and blood gas analysis showed mixed acidemia with a pH of 6.9 (reference value: 7.35 - 7.45), pCO2 76 mmHg (reference value: 35 – 45 mmHg) and lactate of 13.0 mmol/L (reference value: < 2.0 mmol/L). The blood tests also revealed a hemoglobin of 6.4 g/dL (reference value: 12.0 - 15.0 g/dL), an international normalized ratio (INR) of 1.2 and creatinine of 3.31 mg/dL (reference value 0.50 - 0.90 mg/dL). Therefore, a diagnosis of hemorrhagic shock was assumed. The patient was transferred to an intensive care unit for vasopressor support, orotracheal intubation and mechanical ventilation. Apixaban was suspended and the presumed volume loss replaced with 2000 mL of normal saline followed by three units of packed red blood cells, after which hemodynamic stability was achieved. A contrast-enhanced abdomino-pelvic computed tomography (CT) was ordered, revealing an upper-left renal rupture with extensive perirenal hemorrhage (Figs. 1 and 2), without active contrast extravasation. Therefore, a diagnosis of WS was made. The CT showed

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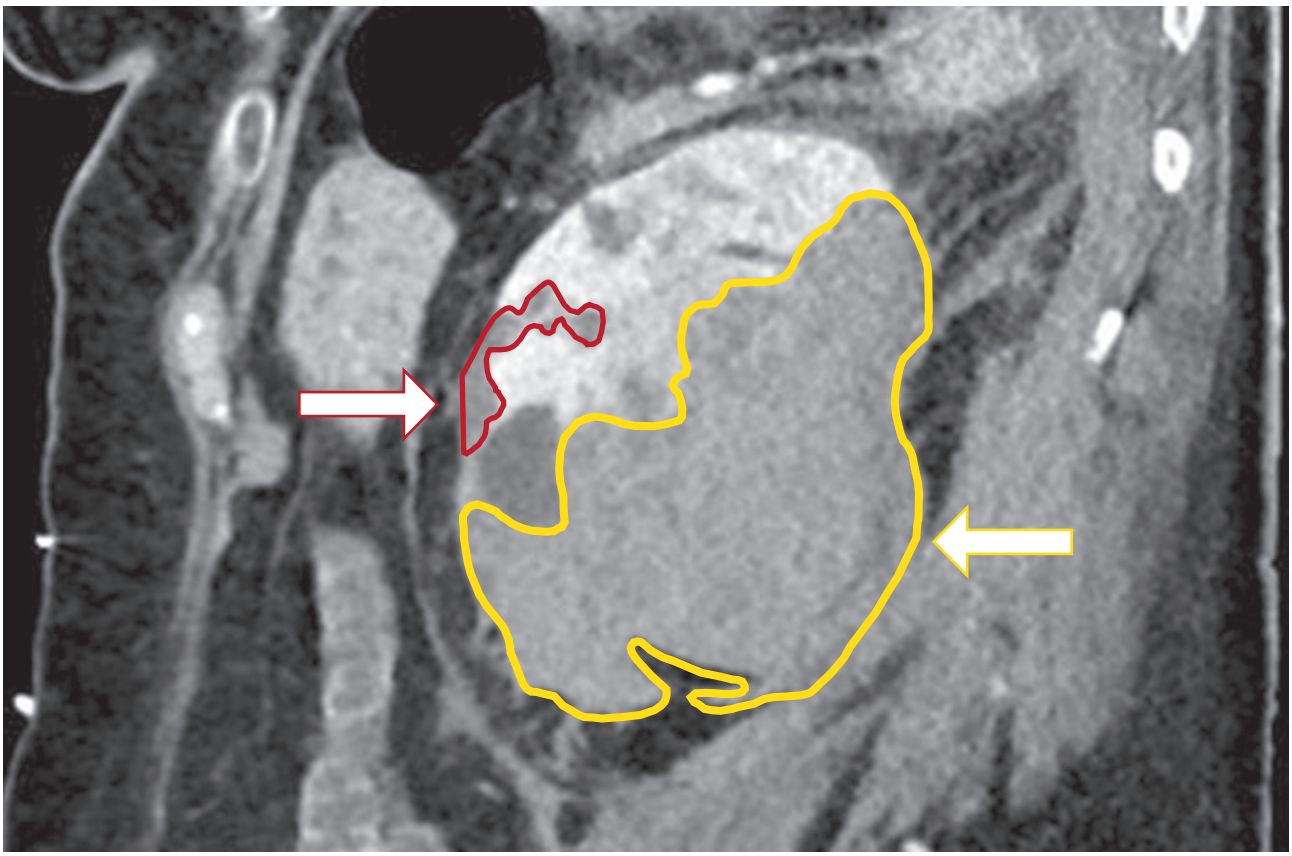

Figure 1 – Abdominal computed tomography (sagittal plane) revealing extensive left perirenal haemorrhage (yellow outline; yellow arrow) and left upper renal rupture (red outline; red arrow)

no renal masses or malignant lesions. Due to hemodynamic stability after blood transfusion, she was managed conservatively with bed rest and surveillance. A follow-up CT scan was done before discharge, showing significant renal subcapsular hematoma reabsorption and no parenchymal disease.

On day seven of admission, at a time when anticoagulation was still suspended, the patient woke up with nausea and left-arm paresis, with a National Institute of Health Stroke Scale (NIHSS) score of 5. A cranial CT confirmed a RMCA M2-segment occlusion, left vertebral artery occlusion and subacute left cerebellar infarction. Intravenous thrombolysis was contraindicated due to recent life-threatening bleeding. Given the low NIHSS score, distal-vessel occlusion and need of periprocedural heparin, mechanical thrombectomy was discarded after multidisciplinary discussion, including intensive care/internal medicine/neurology/neuroradiology consultation. The patient was therefore started on a single-antiplatelet strategy with aspirin and apixaban remained suspended. Yet, a follow-up cranial CT scan showed a new right posterior cerebral artery infarction and hemorrhagic transformation of a previous cerebellar infarction. Therefore, anticoagulation was again considered prohibitive and aspirin was maintained. After a third cranial CT scan revealed complete cerebellar hemorrhage reabsorption and no other bleeding events, anticoagulation resumption was deemed safe. Finally, on day 47 of admission, the patient was discharged on apixaban to a short-term physical-rehabilitation facility, with ongoing improvement of neurological deficits and normal renal function.

## DISCUSSION

WS is a rare and possibly life-threatening disease defined by non-traumatic renal haemorrhage.[3] Patients may present a classic 'Lenk's triad' comprising of sudden or insidious flank/abdominal pain, palpable flank mass and hypovolemic shock.[4] Renal neoplasms (e.g. angiomyolipoma or renal cell carcinoma) are the most frequent aetiologies and underly WS in up to 60% of patients.[3] In rare situations no cause is found.[4] Contrast-enhanced CT has 100% sensitivity in identifying perirenal haemorrhage and is the standard imaging technique in diagnosing WS.[5] CT can also assess renal vasculature, neoplasms or other structural changes that may underly WS.[5] During our patients' assessment, CT scan did not show any renal lesions concerning neoplasms nor parenchymal/vascular renal disease. Moreover, her

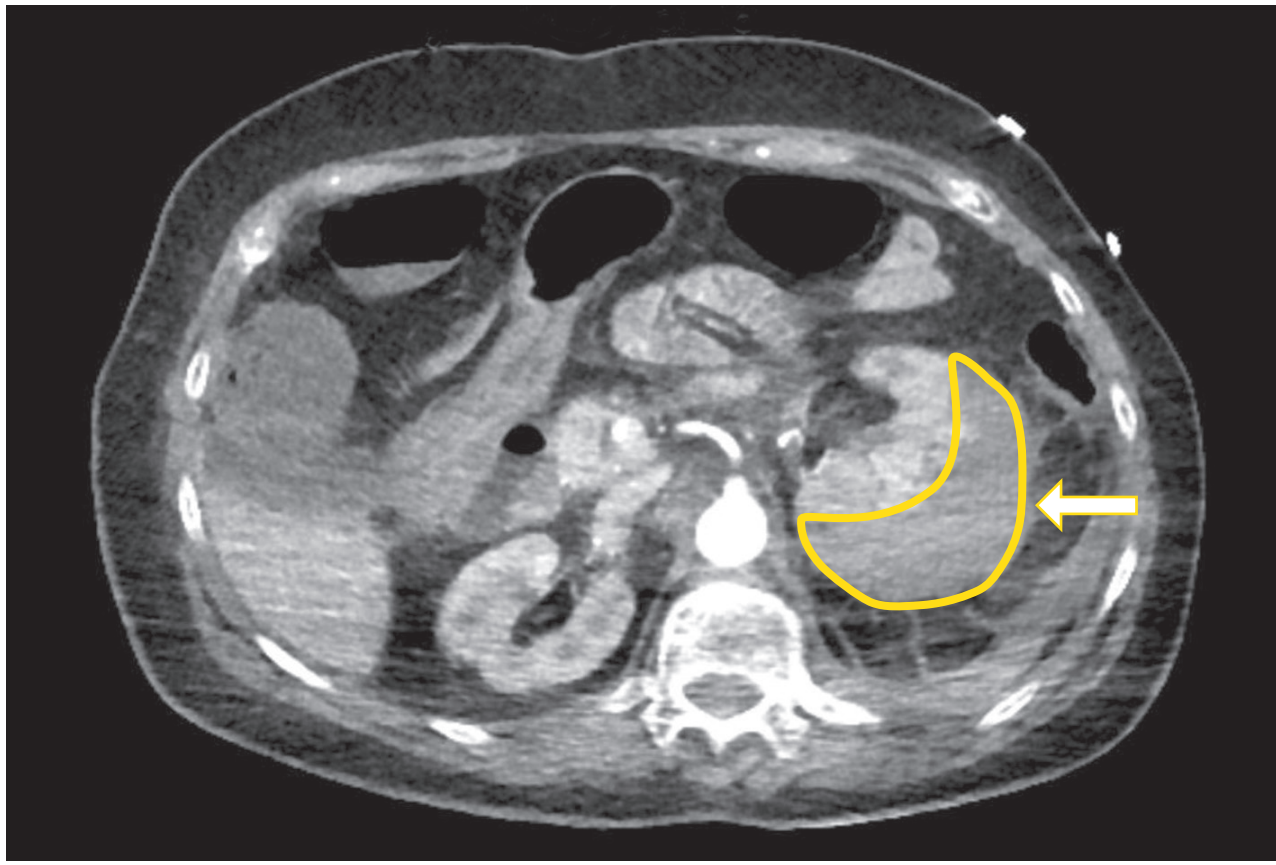

Figure 2 – Abdominal computed tomography (transverse plane) with extensive left perirenal haemorrhage (yellow outline; yellow arrow)

past medical history, current symptoms and baseline blood and urine tests did not point to any other possible causes of WS (e.g. vasculitis, nephritis or coagulation disorders).

Currently, no guidelines for WS management exist.[6] Treatment should rely on anticoagulation discontinuation/reversal, immediate fluid resuscitation and angioembolization or emergent nephrectomy in clinically deteriorating patients.[6] Due to scarcity of cases, optimal management is controversial. While some urologists favour early exploratory surgery or selective arterial embolization, others may prefer a more conservative approach.[7] Indeed, some authors recommend radiological re-evaluation following hemodynamic stability to avoid unnecessary nephrectomy.[8]

Apixaban is a DOAC and a reversible inhibitor of free and clot-bound forms of activated factor X.[7] In the ARISTOTLE trial, apixaban was superior to warfarin in reducing the risk of stroke or systemic embolism in nonvalvular AF while also causing less bleeding events and lowering overall mortality.[9] Therefore, current European Society of Cardiology AF guidelines recommend apixaban and other DOACs over warfarin in the majority of patients with nonvalvular AF.[10] Despite DOACs' superior safety, several case reports of atraumatic solid-organ rupture, mainly spontaneous splenic rupture, still exist.[1,2] To our knowledge, no reports of WS associated with apixaban have been published.

Concerning thromboembolic prevention after a major bleeding event, guidelines provide limited guidance regarding the optimal timing for anticoagulation resumption. Indeed, our patient developed multiple embolic strokes seven days after anticoagulation cessation. Due to haemorrhagic transformation, apixaban resumption was contra-indicated.

Our case highlights the importance of prompt consideration of renal or intra-abdominal haemorrhage in all anticoagulated patients presenting with new-onset flank pain, raised creatinine levels and declining haemoglobin levels, even in the absence of an obvious trauma. Moreover, this case underlines the importance of an urgent imaging study among those presenting with acute kidney injury and abdominal or flank pain in the emergency department. It also emphasizes the challenging decision of restarting anticoagulation after a life-threatening bleeding event. Given the absence of clear guidelines, the decision to resume anticoagulation should be individually tailored.

## CONCLUSION

To our knowledge, we present the first-ever case report

of WS associated with DOAC. WS is a rare and potentially life-threatening event. A high level of suspicion must be maintained in all patients presenting with flank pain and haemorrhagic shock, especially in those under anticoagulants or platelet-inhibitors. Management of patients with active bleeding while on DOAC is complex, particularly when simultaneous thromboembolic events occur. This case highlights the difficulties faced in deciding the appropriate timing to resume anticoagulation in patients with severe haemorrhage.

## AUTHOR CONTRIBUTIONS

SM: Draft of the paper.

CCG, FS, MR: Draft and critical review of the paper.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

## PATIENT CONSENT

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## COMPETING INTERESTS

The authors declare that there are no competing interests.

## FUNDING SOURCES

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ACTA MÉDICA PORTUGUESA
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# Diffuse Large B-Cell Lymphoma with Axillary Cutaneous Invasion in a HIV Positive Patient

# Linfoma Difuso de Grandes Células B com Invasão Cutânea Axilar num Doente com Infeção VIH

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**Keywords:** HIV Infections; Immunoproliferative Disorders; Lymphoma, Large B-Cell, Diffuse
**Palavras-chave:** Infecções por HIV; Linfoma Difuso de Grandes Células B; Síndrome de Imunodeficiência Adquirida; Transtornos Imunoproliferativos

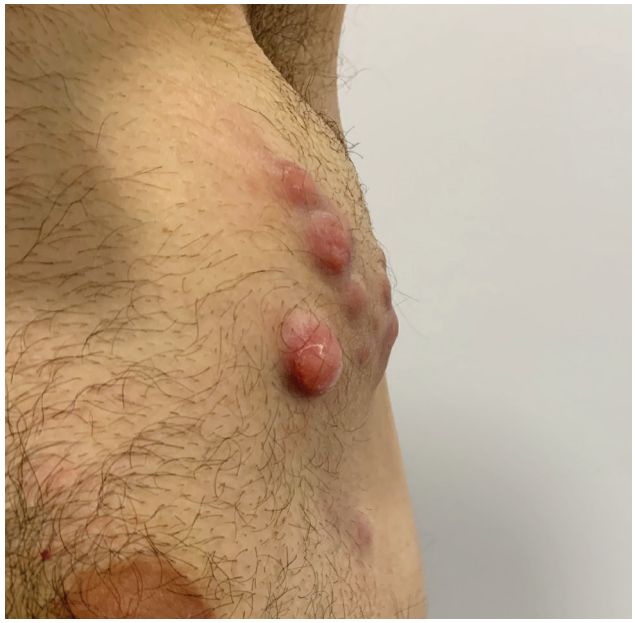

Figure 1 – Axillary cutaneous invasion by diffuse large B-cell lymphoma

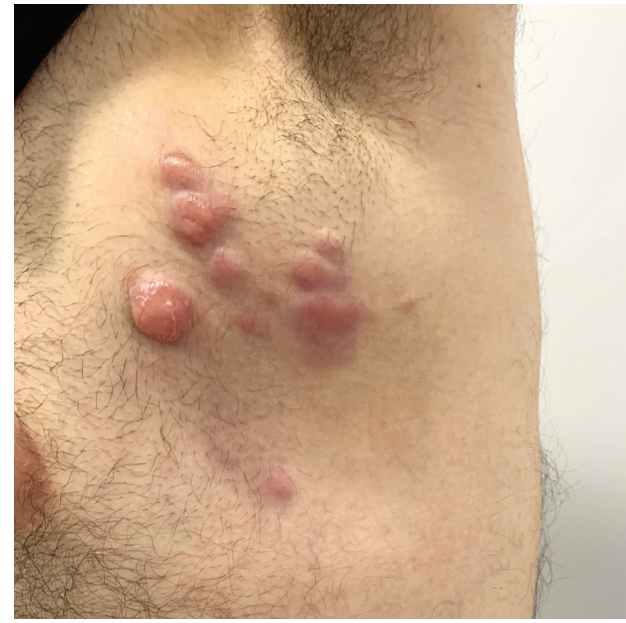

Figure 2 – Axillary cutaneous invasion by diffuse large B-cell lymphoma

A 34-year-old man with untreated HIV-1 infection was admitted due to obstructive jaundice and progressive, non-tender swelling in the left axillary region. The HIV viral load was 412 000 copies/mL and CD4⁺ T-cell count was 133 cells/mm³ (11.8%). The computed tomography (CT) scan showed an expansive 3.2 cm lesion in the pancreatic head along with multiple hypodense liver lesions. Both a therapeutic endoscopic retrograde cholangiopancreatography (ERCP) and a liver biopsy were performed, confirming stage IV diffuse large B-cell lymphoma NOS, type CCG, MYC and BCL6 double expression, with a R-IPI score of 3.[1]

The antiretrovirals tenofovir/emtricitabine plus dolutegravir and prophylactic trimethoprim-sulfamethoxazole with acyclovir were started, along with R-CHOP chemoimmunotherapy. The CD4⁺ T-cell count increased to 371 cells/mm³ (16.9%).

The PET-CT showed complete metabolic response after six cycles, and the patient remains on follow-up.

The risk of mature B-cell neoplasms is increased in HIV patients.[1,3] Treatment relies on the selection of antiretrovirals[3] and chemotherapy protocols, and prophylaxis against other opportunistic diseases must be ensured, since it leads to better outcomes for HIV patients.[3,4]

## AUTHOR CONTRIBUTIONS

AD: Responsible for the intellectual integrity of the manuscript, evaluation of the patient, draft of the paper.

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FM: Critical review of the manuscript.

## PROTECTION OF HUMANS AND ANIMALS

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## DATA CONFIDENTIALITY

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## PATIENT CONSENT

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## COMPETING INTERESTS

The authors have declared that no competing interests exist.

## FUNDING SOURCES

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ACTA MÉDICA PORTUGUESA
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# The Role of High-Resolution Ultrasound in the Assessment of Surgical Candidates for Transoral Endoscopic Thyroidectomy Via Vestibular Approach (TOETVA)

# Papel da Ecografia de Alta Resolução na Avaliação dos Candidatos a Tiroidectomia Endoscópica Trans-Oral por Acesso Vestibular (TOETVA)

Beatriz REBELO✉[1], Ricardo NOGUEIRA[2], Mariana HORTA[1,3]
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**ABSTRACT**

The approach of surgical techniques has evolved significantly over the last decade, with natural orifice surgeries replacing traditional open approaches. In 2016, Angkoon Anuwong, in Thailand, demonstrated it was possible to perform thyroidectomies in a series of patients by a transoral endoscopic approach – transoral endoscopy thyroidectomy vestibular approach (TOETVA) – with similar complication rates when compared to conventional surgeries. This transoral surgery has become a safe alternative with better cosmetic results, compared to conventional open-route procedures, like Kocher cervicotomy. Indeed, it is an option to surgically treat neoplastic and functional thyroid diseases. The technique is performed through a median incision in the oral vestibule, plus two bilateral incisions, followed by the insertion of three trocars, one centrally for a camera, and two laterally for working instruments. Although revolutionary, TOETVA has its technical limitations. Therefore, it is important to precisely define the preoperative eligibility criteria for this type of surgical approach. High-resolution ultrasound is the first imaging modality for the assessment of thyroid nodules, lymph node metastases and surgical field. The aim of this article is to outline the sonographic technique and the role of high-resolution ultrasound in the presurgical evaluation of TOETVA.
**Keywords:** Endoscopy; Natural Orifice Endoscopic Surgery; Thyroid Neoplasms/surgery; Thyroidectomy

**RESUMO**

Em muitas técnicas cirúrgicas, o acesso tem evoluído significativamente ao longo da última década, com a substituição das técnicas abertas tradicionais pela utilização dos orifícios naturais. Em 2016, na Tailândia, Angkoon Anuwong demonstrou, numa série de doentes, não só ser possível realizar tiroidectomias por via endoscópica oral, de que é exemplo a *transoral endoscopy thyroidectomy vestibular approach* (TOETVA), como também provou obter, com o mesmo acesso, taxas de complicações comparáveis às da cirurgia convencional. Esta cirurgia transoral tem-se tornado uma alternativa segura e com resultados cosméticos superiores aos procedimentos realizados pela cirurgia aberta, baseada na clássica cervicotomia de Kocher. De facto, é uma opção para o tratamento cirúrgico de doenças neoplásicas e funcionais da tiroide. A TOETVA é realizada através de uma incisão mediana no vestíbulo oral e duas incisões laterais, seguida da inserção de três trocartes, um central, que alberga a óptica e dois laterais para os instrumentos cirúrgicos de trabalho. A TOETVA, apesar de revolucionária, tem as suas limitações técnicas. Assim, é importante definir os critérios de elegibilidade numa avaliação pré-cirúrgica. A ecografia cervical de alta resolução é a modalidade de escolha na avaliação dos nódulos tiroideus, de eventuais metástases ganglionares e do campo cirúrgico. O objetivo deste artigo é descrever a técnica e o papel da ecografia cervical de alta-resolução na avaliação pré-cirúrgica da TOETVA.
**Palavras-chave:** Cirurgia Endoscópica de Orifício Natural; Endoscopia; Neoplasias da Tiróide/cirurgia; Tiroidectomia

## INTRODUCTION

The prevalence of nodular thyroid disease is high in developed nations. In Portugal, the incidence of thyroid neoplasms is estimated at 19 and 4 per 100 000 individuals in women and men, respectively, being the ninth most common cancer, with 1700 new cases every year nationwide.[1] As total or partial thyroidectomies are the standard treatment for nodular thyroid disease, these procedures are common in developed countries. In the last century, thyroidectomies have been performed through a medial cervical incision (Theodor Kocher technique), causing a permanent anterior cervical scar, which is associated with variable degrees of dissatisfaction, body image concerns and religious issues.[2,3]

With the advent of minimally invasive surgery, many surgical approaches have been developed for the treatment of thyroid disease with variable results.[4] Over the past few years, transoral thyroidectomy with endoscopic vestibular approach (TOETVA) has been considered to be a safe alternative to traditional techniques in the management of thyroid nodular disease with easier post-surgical management, less trauma and better cosmetic results.[5-8] This technique is performed through a subplatysmal median incision in the oral vestibule, where the surgical scar is located, plus two bilateral incisions, followed by the insertion of three trocars, one centrally for a camera, and two laterally for working instruments,[9] allowing access to the thyroid gland without any external neck incisions (Fig. 1). Although revolutionary, this approach has its own limitations that are mainly due to the small operative field plus anatomical considerations. Therefore, it is important to precisely define the eligibility criteria

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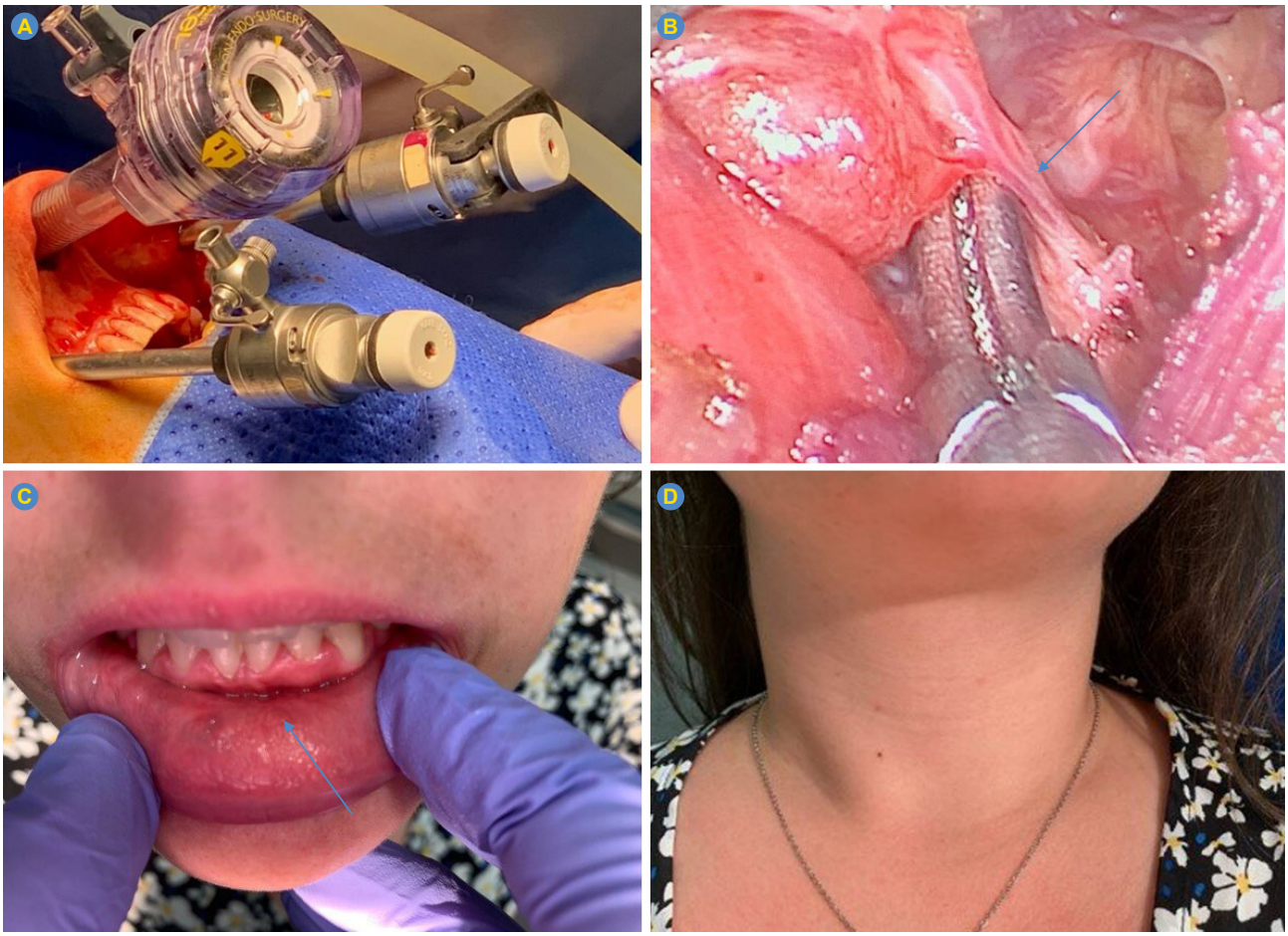


Figure 1 – Surgical TOETVA technique (A, B), showing the positioning of trocars (A), the medial thyroid vein and inferior laryngeal nerve (arrow in B), the surgical scar in the oral vestibule, barely noticeable (C), and the patient's neck, without any scars (D).

for this type of surgical technique (Table 1).

High-resolution ultrasound is the first imaging modality for the assessment of thyroid nodules, lymph node metastases and surgical field. It is an affordable, available, non-invasive, radiation-free, real-time imaging modality, with higher resolution than cross-sectional imaging. The aim of this article is to outline the technique and the role of high-resolution ultrasound in the presurgical evaluation when considering transoral route thyroidectomies, as our institution is a national pioneer in this surgical approach.

The first section of this article outlines the surgical indications for TOETVA and how it is performed in our Institute. The second section covers our technique of high-resolution ultrasound in the presurgical evaluation of these patients, and finally, the third section will focus on specific ultrasonographic criteria that are necessary for this type of surgery.

## 1. Surgical indications for TOETVA

Thyroid surgery is the primary treatment for thyroid cancer and provides a definitive diagnosis of suspicious thyroid nodules, making it one of the most frequently performed surgeries worldwide. Any novel surgery technique, when applied to thyroid cancer, must be safe.

Understandably, the current indications for TOETVA are conservative, in order to achieve optimal oncological outcomes.

In our institution, we currently perform partial thyroidectomies using the TOETVA technique for thyroid nodules with a cytology result of atypia of undetermined significance/follicular lesion of undetermined significance (corresponding to a Bethesda III classification, according to the Bethesda Classification of Thyroid Nodule Fine Needle Aspirations) and papillary microcarcinomas.[10]

All patients with thyroid cancer should undergo formal screening for nodal metastatic disease. Ultrasound is the most sensitive imaging modality for identifying cervical lymph node metastatic disease. We are not performing this surgical technique in patients with suspected lymph node metastatic disease at the moment. Ultrasound also enables the estimation of thyroid gland volume, nodule size and

Table 1 – Eligibility criteria for the TOETVA approach

| Thyroid disease | Nodular disease of Bethesda III or papillary microcarcinoma cytological diagnosis |
|---|---|
| **Thyroid size and distribution** | |
| - Total thyroid volume | < 15 mL, $cm^3$ |
| - Total thyroid gland diameter (combined transverse diameter) | < 10 cm |
| - Superior lobe border | Gland/tumours not extending beyond cricoid cartilage superior border |
| - Inferior lobe border | - |
| - Isthmus anterior-posterior diameter | Preferably < 1 cm |
| **Node size and location** | |
| - Size | < 3 cm |
| - Location | Not at the superior pole<br>Not at the retro-thyroid region |
| - Relation with surrounding structures | Not abutting the course of the recurrent laryngeal nerve |
| **Inflammation** | Absence of acute cervical inflammation/infection (i.e., abscess)<br>Absence of sonographic signs of chronic inflammation – oedema, fibrosis, previous cervical radiation therapy<br>Presence of thyroid inflammatory conditions – Hashimoto's thyroiditis, Graves' thyroiditis |
| **Disease extension** | Absence of locally advanced disease and cervical lymph node metastases |

important anatomical landmarks for surgical planning.

In the setting of thyroid cancer, chronic thyroid inflammation can be associated with prior high-dose radiation exposure. This procedure should not be considered in patients with prior radiation. If signs of chronic inflammation are present (i.e., oedema, fibrotic changes), they should be noted and described, since such cases may be more safely managed with an open approach. Prior neck surgery is currently an exclusion criterion.

## 2. Technique of high-resolution thyroid ultrasound

The sonographic examination of the thyroid gland and cervical lymph nodes should be performed with a high-frequency linear transducer (7 – 18 MHz) in order to obtain high-resolution images. The preoperative ultrasound protocol of the thyroid gland must include paramedian transverse and longitudinal sweeps obtained with the patient in the supine position. Having the neck and head well positioned is especially important when measuring lobe diameter and volume.[11] If patients cannot sufficiently hyperextend their necks, a small pad may be placed under their shoulders.

### First step: thyroid volume and extension

To calculate thyroid volume, right and left lobe volumes should be measured separately. One can start with a paramedian transverse plane of one lobe and find the view where the gland reaches the greatest width (Fig. 2). The maximal transverse and anteroposterior diameter of that lobe should be measured separately, with the depth measurement at a 90-degree angle to the skin surface and the width measurement at 90 degrees to the depth measurement. Afterwards, a longitudinal sweep should be performed, and the greatest longitudinal length should be measured. The ultrasound volume tool should be used to calculate the volume of that lobe. The procedure can be repeated for the other lobe and the sum of both volumes could be calculated. In the median transverse plane, the anterior-posterior diameter of the isthmus should be measured. In the paramedian transverse sweeps, the location of the upper poles of both lobes can be accessed, especially their relation to the upper border of the cricoid cartilage, and of the lower poles and their relation to the mediastinum. Any posterior extension of the thyroid gland into the tracheal-oesophageal grooves should be assessed.

### Second step: nodule evaluation

The node that will be surgically removed should be identified and measured on its transverse, anterior-posterior, and longitudinal diameters. The lesion at the superior, medium, or inferior, as well as at the anterior or posterior poles of the gland should be located precisely.[12] The sonographic characteristics of the node according to a risk stratification score should be described (i.e., ACR TIRADS™, EU-TIRADS) and its relation to the thyroid border and the presence of possible extra-thyroid extension should be evaluated.

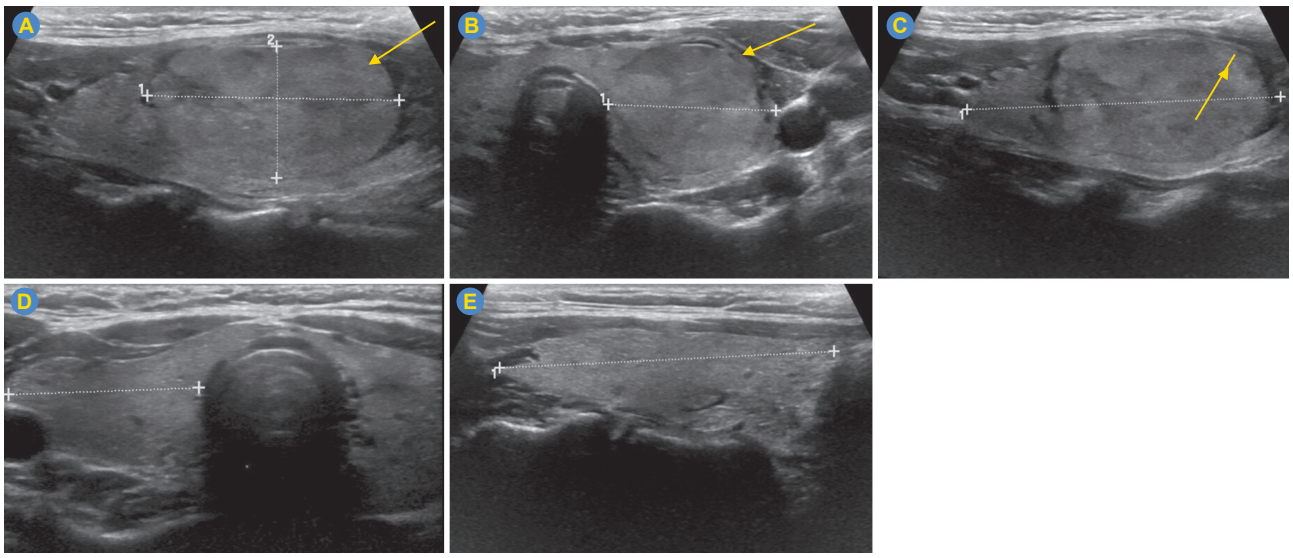


Figure 2 – B-mode ultrasound of the thyroid shows an isoechoic well-defined solid nodule in the left thyroid lobe (arrow), with a fine-needle aspiration result of papillary carcinoma, measuring 3 cm (A). The right and the left lobe diameters are measured in the paramedian transverse and longitudinal planes to determine lobe volume. The total thyroid gland volume was estimated at 12 cc, under 15 cc (B, C, D), making the case suitable for TOETVA approach.

**Third step: cervical node evaluation**

Start with the evaluation of IA, VI, and VII anatomic lymph node neck levels by performing a median transverse sweep over these cervical lymph node regions. Scan from superior to inferior starting at the submentonian region. When reaching the superior border of the manubrium, the probe should be angled inferiorly in order to access the VII lymph node station. To evaluate IB levels, paramedian transverse sweeps of both sides starting at the anterior belly of the digastric muscles and finishing at the submandibular glands should be performed. In order to access the internal jugular (deep cervical) chain (levels II/III/IV) a paramedian transverse sweep starting at the submandibular gland and finishing at the superior border of the clavicle should be performed. The spinal chain (level V) is accessed with a paramedian transverse sweep between the sternocleidomastoid and the trapezius muscles.

## 3. Presurgical ultrasound criteria for TOETVA

**Thyroid volume, thyroid size, and thyroid tissue extension**

In our institution, we use 15 mL of total gland volume and a thyroid gland transverse diameter up to 10 cm (calculated as the sum of the transverse diameter of both lobes) as inclusion criteria,[13-15] excluding the cases exceeding these criteria (Fig. 3). From our own experience so far, more important than the total thyroid volume is the distribution of total thyroid volume in each of the two lobes. If most of the total volume is concentrated in one lobe, even if the total volume is within limits, the case may not be eligible. This criterion is enforced in order to minimize intraoperative bleeding time, as well as to minimize the potential damage of thyroid tissue and of surrounding structures, especially the parathyroids and the laryngeal recurrent nerves.[16] Besides, there is also concern about removing relatively large tissue specimens via small central ports.[17]

The location of the thyroid relative to the laryngeal cartilage is also of interest to the surgical team. A thyroid gland that extends further than the superior border of the cricoid cartilage poses an important surgical challenge, considering the cephalad-to-caudal view afforded by the transoral approach, that can deem the patient not eligible. Successful transoral thyroid surgery also requires transection of the thyroid isthmus, to facilitate medial and anterior thyroid lobe retraction and removal of the surgical specimen. If the thyroid isthmus exceeds 1 cm in anterior-posterior diameter, that step may be more difficult.[16] Thyroid isthmus thickness is not a formal exclusion criterion, but its measurement should be made when scanning the gland.

**Node size and location**

As discussed previously, the surgical working space is limited. Large-size tumours can obscure laparoscopic vision. Therefore, we include in our criteria nodules under 3 cm in diameter, regardless of node histology. Another limitation of this procedure is the manipulation of the superior pole since these are areas that are particularly difficult to reach. This is explained by the oblique cephalad-to-caudal view and the limited medial/superior instrument angulation, as discussed previously. When approaching the superior

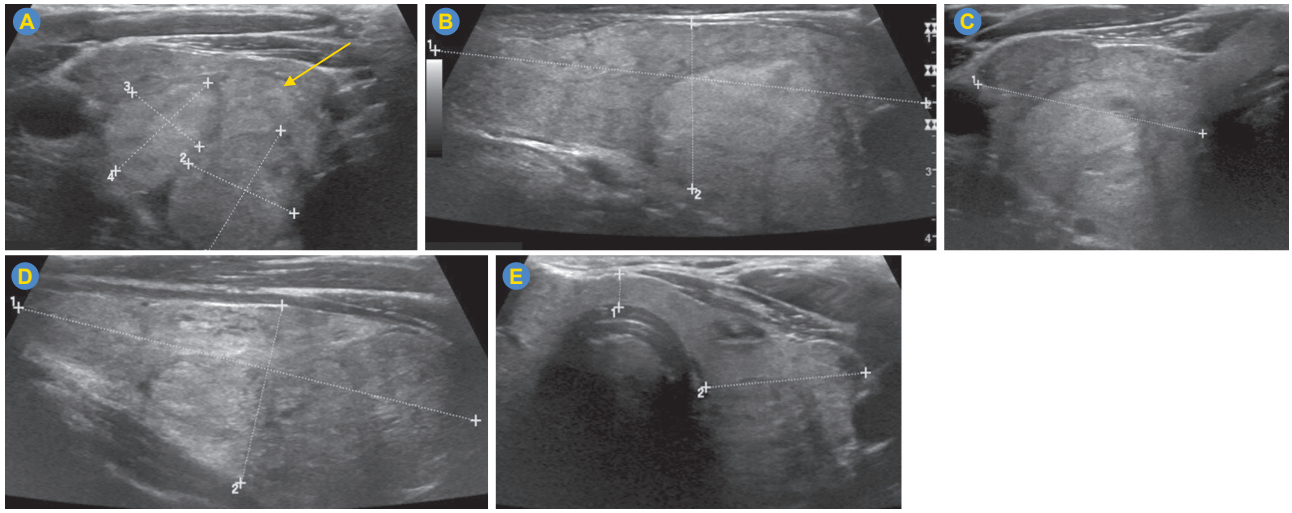


Figure 3 – B-mode ultrasound of the thyroid shows a hypoechoic well-defined solid nodule in the left thyroid lobe (arrow in A), with a fine-needle aspiration result of a follicular lesion of undetermined significance. The right and the left lobe diameters are measured in the paramedian transverse and longitudinal planes to calculate lobe volume, estimated to be 48 cc, exceeding 15 cc, making this case unsuitable for the approach.

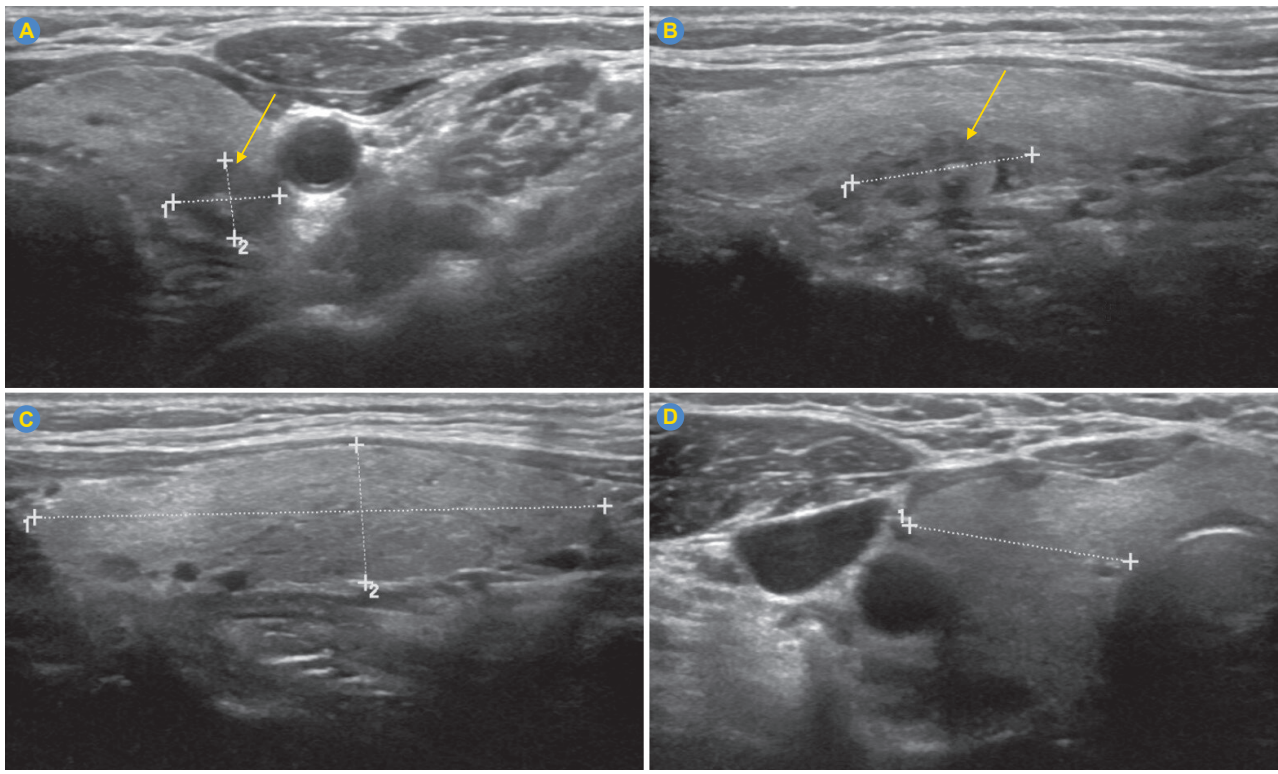


Figure 4 – B-mode ultrasound of the thyroid shows a hypoechoic well-defined solid nodule in the posterior margin of the left thyroid lobe (arrow), with a fine-needle aspiration result of follicular lesion of undetermined significance (A, B). The location of the nodule in the posterior portion of the lobe makes the case unfavorable for the TOETVA approach. The remaining characteristics of the nodule and the gland (C, D) are not impeditive.

pole, the surgeon must apply a skilled technique to avoid leaving the remaining residual thyroid tissue. Moreover, damage to the superior thyroid artery is a concern.[16] Therefore, a node that is located in the superior pole of the thyroid gland might make this procedure inadequate. It is also important to notice if the nodule is in the retro thyroid areas due to the increased risk of recurrent laryngeal nerve damage (Fig. 4). Nodules abutting the expected course of the

recurrent laryngeal nerve should be mentioned, since they may be invading the nerve, which cannot be dealt with this technique.[17]

**Thyroid and perithyroiditis**

The anatomical distortion that comes with chronic inflammation can be a limitation to an endoscopic procedure since it can affect normal tissue dissection. It can also increase tissue friability, which leads to higher complication rates, particularly higher haemorrhagic risk. Inflammatory thyroid diseases such as Graves' or lymphocytic (Hashimoto's) thyroiditis can increase operative difficulty. Sonographic changes associated with Graves' disease include gland enlargement, parenchymal heterogeneity, and increased vascularity. Hashimoto's thyroiditis can present as an enlarged thyroid gland with a heterogeneous echotexture especially in the initial phase, a gland with hypoechoic micronodules surrounded by echogenic septations and a thyroid with a pseudo nodular pattern. Although focal and mild, fine-needle aspiration can also be a cause of local inflammation. As with any surgery, any ongoing infection such as a cervical abscess is an exclusion criterion.

**Cervical and distant metastatic disease**

As mentioned above, any preoperative sonographic evaluation of thyroid node malignancy is incomplete unless a cervical nodal metastatic assessment is made. If a lymph node has sonographic findings associated with malignancy (i.e., loss of the fatty hilum, presence of nodal microcalcifications, rounded rather than elongated nodal shape, cystic changes, nodal hyperechogenicity, or lymph node short axis > 8 mm), fine-needle aspiration biopsy of the suspicious lymph node should be performed. If malignancy is confirmed, then cervical lymph node dissection is needed.

For now, central neck dissection is an exclusion criterion for transoral surgery in our institution, considering we are still on the learning curve of this procedure. Findings of extranodal disease extension or local invasion also exclude the patient as a surgical candidate for TOETVA.

## AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## PATIENT CONSENT

Obtained.

## COMPETING INTERESTS

The authors have declared that no competing interests exist.

## FUNDING SOURCES

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## Femoral Neuropathy Associated with Prophylactic Anticoagulation in a Patient with Severe COVID-19: A Case Report

## Neuropatia do Femoral Associada à Anticoagulação Profilática num Doente com COVID-19 Grave: Caso Clínico

**Keywords:** Anticoagulants/adverse effects; COVID-19/complications; Femoral Neuropathy/chemically induced
**Palavras-chave:** Anticoagulantes/efeitos adversos; COVID-19/complicações; Neuropatia Femoral/induzida quimicamente

To the Editor:

Thromboembolic events have been described among individuals infected with SARS-CoV-2, particularly in critically ill patients, and therefore thromboprophylaxis is recommended in these patients.[1]

A high level of suspicion concerning bleeding complications in patients under anticoagulation is required in order to promptly recognize the hemorrhage and immediately suspend the anticoagulation.

We describe the case of a 72-year-old male with severe COVID-19 who received thromboembolism prophylaxis with enoxaparin.

On the 20th day of admission, he complained of the onset of left groin pain, numbness, difficulty walking with significantly decreased muscle strength during hip flexion and knee extension, with sensory loss of the anterior medial thigh, medial calf and absent patellar tendon reflex. He had a low hemoglobin level, and a computed tomography (CT) scan identified a left iliac muscle hematoma. Femoral nerve injury was suspected due to compression caused by the hematoma. The hematoma was managed conservatively, and enoxaparin was suspended. Due to severe functional impairment, he was admitted to the Rehabilitation Unit. The electrodiagnostic examination (EDX) confirmed the diagnosis. Although the clinical presentation of quadriceps atrophy, decreased muscle strength and sensory loss did not improve, the patient acquired full autonomy, including walking, with a knee orthosis with range-of-motion restriction feature (0º - 30º) and crutches, and was discharged on the 77th day.

Five months later, the EDX showed signs of reinnervation of the iliac muscle. The patient remained stable up to 10 months, when there was an increase in muscle strength during knee extension, a reduction in the hypoesthesia area in the anterior thigh, and gait was possible just with the knee orthosis. A CT scan revealed complete hematoma reabsorption. Two years after the diagnosis, muscle strength during hip flexion had fully recovered as well as sensory function; there was an improvement in muscle strength during knee extension and gait (Table 1).

Isolated femoral neuropathy is uncommon and retroperitoneal hemorrhage is a rare cause.[2]

Although there is no consensus about the therapeutic approach, conservative treatment must be considered when there is no continued bleeding or progressive neurological defects.[3] Therefore close monitoring of the neurological examination of hemodynamic stability and hemoglobin levels are essential in a conservative approach. The evidence of neurological worsening or continued bleeding calls for a surgical evacuation of the hematoma.[3]

Physical and Rehabilitation Medicine interventions include diagnosis, pain management, physical and occupational therapy and orthosis prescribing and, and all play an important role in both the initial care as well as during follow-up. The prognosis and recovery time depend on the degree of axonal loss.[2] In this case, after two years there were still sequelae of the neuropathy with impaired muscle strength during knee extension. However, a conservative approach was well tolerated and a good functional outcome was achieved.

### PREVIOUS PRESENTATIONS

Part of the clinical case was previously presented at the "XXI Congresso Nacional da Sociedade Portuguesa de Medicina Física e Reabilitação", as an oral communication, in October 15th, 2021.

### AUTHOR CONTRIBUTIONS

AAP: Literature research, case description and discussion.

MM: Literature research, contribution to the discussion.

VBS, MAS, ACM: Critical review of the work.

Table 1 - Summary of clinical, radiological and electrodiagnostic findings

| | Day 20th | PRM admission | PRM discharge | 5 months | 10 months | 24 months |
|---|---|---|---|---|---|---|
| **Strength measure** (left lower limb) – MRC score | | | | | | |
| Hip flexion | 1/5 | 2/5 | 2/5 | 2/5 | 3/5 | 5/5 |
| Knee extension | 1/5 | 1/5 | 1/5 | 1/5 | 3/5 | 4/5 |
| **Gait** | with OT and crutches | | | | with OT | without aids |
| **CT scan** | iliac muscle hematoma | | | | complete reabsorption | |
| **Electrodiagnostic examination** | severe axonal lesion of the left femoral nerve associated with probable sensorimotor neuropathy | | | signs of reinnervation of the iliac muscle | | |

CT: computed tomography (electrodiagnostic examination); MRC: Medical Research Council; OT: orthosis; PRM: Physical and Rehabilitation Medicine

## PROTECTION OF HUMANS AND ANIMALS

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## PATIENT CONSENT

Obtained.

## COMPETING INTERESTS

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# Reconciliação Terapêutica na Admissão de um Serviço de Medicina Interna: A Perspetiva dos Cuidados de Saúde Primários

# Medication Reconciliation during Admission to an Internal Medicine Department: The Perspective of Primary Health Care

**Palavras-chave:** Cuidado Transicional; Cuidados de Saúde Primários; Erros de Medicação; Medicina Interna; Reconciliação de Medicamentos; Segurança do Doente
**Keywords:** Internal Medicine; Medication Errors; Medication Reconciliation; Patient Safety; Primary Health Care; Transitional Care

Caro Editor:

Foi com interesse e entusiasmo que lemos o artigo "Reconciliação Terapêutica na Admissão de um Serviço de Medicina Interna: Estudo-Piloto",[1] publicado em novembro de 2022, cujo principal objetivo se prende com a identificação dos recursos necessários para a implementação da reconciliação terapêutica na prática clínica.

Alinhado e em continuidade com o Plano Nacional para a Segurança dos Doentes (PNSD) 2015 - 2020, o PNSD 2021 - 2026 objetiva consolidar e promover a segurança na prestação de cuidados de saúde no sistema de saúde.[2]

As falhas na comunicação são das principais causas de eventos adversos na saúde, ocorrendo a maioria nos momentos de transição de cuidados.[3] Esta transição intra/inter-instituições prestadoras de cuidados de saúde aumenta o risco de incidentes relacionados com a medicação e de admissões hospitalares evitáveis.[4,5]

A reconciliação da medicação é um processo multidisciplinar, centrado no doente, que contribui significativamente para a redução de incidentes relacionados com a medicação.[4]

Para a construção da *best possible medication history* (BPMH), os investigadores recorreram a várias fontes de informação: lista de medicação fornecida pelo doente, saco de medicação, familiar ou cuidador e à Plataforma de Dados de Saúde (PDS). Contudo, o acesso a esta plataforma digital de abrangência nacional apresentou várias limitações: inacessibilidade, indisponibilidade de funcionalidades e desatualização da lista da medicação crónica. Estas dificuldades e limitações são também vivenciadas na prática diária nos Cuidados de Saúde Primários (CSP), afetando a coordenação de cuidados.

Salientamos ainda o impacto que as discrepâncias terapêuticas não documentadas e as omissões transmitidas aquando da alta hospitalar têm na continuidade de cuidados e no tratamento adequado.[2,5]

Os CSP, pelo seu carácter contínuo e longitudinal, desempenham um papel crucial no processo de reconciliação terapêutica, devendo contribuir ativamente para a manutenção de uma lista atualizada e acessível da terapêutica dos doentes.

Concordamos que a reconciliação terapêutica deve ser um processo multidisciplinar, envolvendo todos os

profissionais e instituições que cuidam do doente a cada momento, e salientamos que a par da sensibilização e motivação dos profissionais de saúde urge a implementação e/ou otimização de um sistema universal e acessível.

Congratulamos os autores pela pertinência do estudo que concretiza uma das limitações dos serviços de saúde com impacto na segurança dos utentes.

A cultura de segurança deve ser uma prioridade de todos os que cuidam. Acreditamos que a sistematização, uniformização e acessibilidade do processo de reconciliação terapêutica, tal como proposto pelos autores, serão peças fundamentais deste objetivo comum.

## CONTRIBUTO DOS AUTORES

JF: Pesquisa bibliográfica, organização documental, redação do artigo, aprovação da versão final.

RS: Revisão crítica do conteúdo, edição final do manuscrito, aprovação da versão final.

## PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

## CONFLITOS DE INTERESSE

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## FONTES DE FINANCIAMENTO

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## Valuing Mundane Manifestations of Rare, but Underdiagnosed, Diseases in Portugal: The Example of McArdle Disease

## A Importância de Manifestações Mundanas de Doenças Raras, mas Subdiagnosticadas em Portugal: O Exemplo da Doença de McArdle

**Keywords:** Glycogen Storage Disease Type V/diagnosis; Glycogen Storage Disease Type V/epidemiology; Portugal
**Palavras-chave:** Doença do Armazenamento do Glicogénio Tipo V/diagnóstico; Doença do Armazenamento do Glicogénio Tipo V/epidemiologia; Portugal

Perhaps one of the biggest challenges in primary care and hospital medicine lies in the ability of attending physicians to recognize what are seemingly unsuspected and non-specific symptoms as manifestations of uncommon, yet important, diseases with systemic repercussions.

Paradigmatic examples are found among non-specific manifestations of diseases included within the rare diseases category, such as the glycogen storage disease type V (also referred to as McArdle disease). Among the available indexed literature, only four cases have been reported in Portuguese adult patients,[1-4] with Costa *et al* being one of the first to do so.[2] We have just recently diagnosed what, to the best of our knowledge, would be the fifth reported case of a Portuguese patient to be diagnosed during adulthood. This was a 28-year-old female patient who had been complaining of generalized myalgia and exercise intolerance for several years, and was referred to the Internal Medicine clinic. Her symptoms were mostly induced by intense physical activity, forcing her to rest for several minutes shortly after beginning to exercise. She further explained how these short 10- to 15-minute breaks allowed her to recover and resume exercising. The patient also mentioned her sister presented similar symptoms.

Due to high suspicion of a metabolic disease, she underwent bloodwork and urine tests that revealed creatine

Table 1 – Cases of McArdle disease reported within the Portuguese population (indexed in PubMed)

| Authors | Year | Age of diagnosis | Onset of symptoms | Clinical features | Confirmatory test | Potentially fatal complications |
|---|---|---|---|---|---|---|
| Leite A *et al*[1] | 2012 | 54 | Childhood | Myalgia, early fatigue. Rhabdomyolysis sometimes with myoglobinuria. | Genetic screening: *PYGM* c.148C>T (p.R49X); c.345+ G>A. | None described. |
| Costa R *et al*[2] | 2013 | 38 | Childhood | Myalgia, early fatigue, single myoblobinuria episode, diarrhea. | Muscle biopsy: negative myophosphorylase activity. | Oliguric acute kidney injury requiring hemodialysis. |
| Ferreira MA *et al*[3] | 2014 | 60 | Adulthood | Mostly asymptomatic. Rhabdomyolysis. | Muscle biopsy: negative myophosphorylase activity. | Acute kidney injury requiring hemodialysis (previously known chronic kidney disease). |
| Pinto H *et al*[4] | 2018 | 51 | Childhood | Muscle weakness, early fatigue. Rhabdomyolysis with myoglobinuria. | Genetic screening: *PYGM*, c.2392T>G (p.W798R). | Severe crisis of muscle weakness during swimming. |
| Mateus-Pinheiro *et al*[↑] | 2022 | 28 | Childhood | Myalgia, early fatigue, second-wind phenomenon. Rhabdomyolysis. | Genetic screening: *PYGM* c.148C>T (p.R49X). | None described. |

↑: case reported herein

kinase serum levels of 24 171 U/L (normal value: < 145 U/L), along with the presence of urinary 3-methylglutaric acid and 2-methylglutaconic acid. Genetic testing disclosed a *PYGM* c.148C>T (p.R49X) homozygous mutation, which confirmed McArdle disease. A therapeutic dietary regimen along with avoidance of intense physical activity were recommended to the patient.

We must emphasize how meticulous medical history taking along with a high index of suspicion are essential to diagnose this disease. It usually presents as a syndrome of exercise intolerance, fatigue, and muscle cramps. Moreover, one hallmark of McArdle[5] disease is muscle weakness aggravated with exertion, along with a characteristic recovery phenomenon after a few minutes of rest, that has been called the 'second-wind phenomenon', as patients recover from myalgic symptoms and regain exercise tolerance. These non-specific complaints may remain unaddressed for many years, leading to a delayed diagnosis and treatment (Table 1).

In its latest report on European Centres of Reference, the Rare Diseases Task Force highlighted how appropriate social education and medical expertise on rare diseases are often insufficient among most European states. This often translates into risk of medical complications and late sequelae.

Hence, we encourage both physicians and clinical researchers to focus on implementing training and education programs devoted to increasing medical skills, along with social consciousness related to this group of diseases. We hold the strong conviction that this is the only way to promptly identify patients at risk and to increase the diagnostic rates of rare diseases in Portugal.

## AUTHOR CONTRIBUTIONS

AMP: Conception, design, draft of the paper and critical review.

TC: Conception and draft of the paper.

SM: Conception, critical review of the paper and supervision.

HE: Critical review.

## PROTECTION OF HUMANS AND ANIMALS

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## COMPETING INTERESTS

The authors have declared that no competing interests exist.

## PATIENT CONSENT

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## Treino de Simulação em Saúde: A Perspetiva Atual acerca das Técnicas de Discussão

## Simulation Training in Healthcare: The Current Perspective on Discussion Techniques

**Palavras-chave:** Competência Clínica; Feedback Formativo; Modelos Educacionais; Treino de Simulação
**Keywords:** Clinical Competence; Formative Feedback; Models, Educational; Simulation Training

Caro Editor,

O artigo "Debriefing ou Feedback: Estudo Exploratório do Efeito de Dois Métodos de Discussão Pós-Cenário na Aquisição e Retenção de Competência Não-Técnicas"[1] realiza uma comparação entre dois sistemas de discussão na aprendizagem de competências não-técnicas. A Society for Simulation in Healthcare refere que a simulação confere quatro propósitos: Educação, Avaliação, Investigação e Integração da Segurança do Doente no Sistema de Saúde.[2]

Em Portugal, foi criada em 2011 a Sociedade Portuguesa de Simulação Aplicada às Ciências da Saúde com o objetivo de divulgar a simulação como recurso científico, formativo e de excelência dos cuidados de saúde. Existem atualmente, a nível nacional, 18 centros de simulação credenciados para realização de formação pré e pós-graduada. A simulação assume atualmente um papel fundamental na formação dos profissionais de saúde.

A análise da eficácia das técnicas de discussão relativamente às competências em aprendizagem é muito útil. O estudo evidencia o *debriefing* como a técnica mais eficaz na aprendizagem de competências não técnicas. Os resultados deste estudo vêm corroborar os resultados de outros estudos que sublinham o *feedback* como mais eficaz na aprendizagem das competências técnicas.[3,4]

O *debriefing* é uma metodologia que proporciona aos participantes a oportunidade de refletir, reforçar os comportamentos/atitudes e identificar aspetos a serem melhorados. O *feedback* é baseado num diálogo estruturado de informação unidirecional entre o instrutor e o formando onde se apontam os aspetos positivos e a atitudes a modificar.[1]

Estão definidos quatro pontos de estruturação do processo, originando assim diferentes tipos de *debriefing*, nomeadamente: tempo, dinamizador, fases do processo e técnicas a ser utilizadas.[5] Relativamente ao tempo, o *debriefing* pode ser realizado no meio do evento ou no final. O dinamizador pode ser o facilitador ou pode ser guiado pelos participantes. O processo pode ser estruturado em três ou mais fases, de acordo com o modelo utilizado. Entre as técnicas, as mais utilizadas são as perguntas abertas, questões circulares e a revisão por vídeo.

Seria importante compreendermos que técnicas foram aplicadas e quais as que poderão ter uma maior taxa de sucesso na aquisição de competências.

Pela natureza contínua da aprendizagem e pela importância que a simulação tem na formação, as diversas práticas a utilizar devem ser estudadas para perceber quais as mais eficazes. De salientar ainda o treino do *debriefing*, como ferramenta de reflexão pessoal da prática clínica do profissional de saúde.

### CONTRIBUTO DOS AUTORES

JPA: Contribuição para a concepção escrita e design.
FR: Revisão crítica do artigo.

### PROTEÇÃO DE PESSOAS E ANIMAIS

Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

### CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse relacionados com o presente trabalho.

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## Acute Kidney Injury with Hyperlactatemia: Clues to a Hidden Problem

## Lesão Renal Aguda com Hiperlactacidemia: Pistas para um Problema Escondido


**Keywords:** Acute Kidney Injury; Adolescent; Ethylene Glycol/poisoning; Hyperlactatemia; Suicide, Attempted
**Palavras-chave:** Adolescente; Etilenoglicol/envenenamento; Hiperlactacidemia; Lesão Renal Aguda; Tentativa de Suicídio


Intoxications in children are usually unintentional ingestions. When faced with altered mental status and an incongruent medical history a high degree of suspicion is warranted when investigating a possible intended intoxication.

We present a case of an adolescent male, previously healthy, who presented to the pediatric emergency department with a 12-hour history of headache, abdominal pain, vomiting, lethargy, confusion and altered speech. The physical examination revealed depressed mental status with confused and unintelligible speech, tachypnea, hypertension (144/92 mmHg) and tachycardia (128 beats/minute). Laboratory evaluation (Table 1) showed acute kidney injury (AKI), severe hyperkalemia, hyperphosphatemia, hypermagnesemia and severe high anion gap metabolic acidosis (pH 7.04, $pCO_2$ 15.4 mmHg, $HCO_3$- 7.4 mmol/L, base excess -24.7 mmol/L, anion gap 37 mmol/L) with hyperlactatemia (268 mg/dL). Common toxicological tests were negative. Emergent treatment was immediately started with improvement of potassium levels and metabolic acidosis (pH 7.31, $HCO_3$- 16.7, base excess -11.4, lactate 208 mg/dL), and stable urine output (33 mL/h) and serum creatinine levels.

The AKI investigation revealed calcium oxalate crystals on urinalysis, diffuse increased cortical echogenicity and increased cortical-medullary differentiation on renal ultrasonography and crystal nephropathy on the renal biopsy. The patient consistently denied having ingested any toxic substances but further investigation revealed social isolation and depression in the previous months, and a suspicious pink fluid found in his bedroom that was revealed to be ethylene glycol. Ultimately, he confessed to having drunk 250 mL of antifreeze fluid with suicidal intent.

On day two, due to worsening renal function (serum

Table 1 – Laboratory evaluation at hospital admission and subsequent 24-hour evolution

| Laboratory evaluation | At admission | 3-hours after admission | 24-hours after admission |
|---|---|---|---|
| **Hemoglobin** (g/dL) | 18.6 | 17.4 | 13.8 |
| **Leucocytes** (/µL) | 43 500 | 47 400 | 18 800 |
| **Creatinine** (mg/dL) | 2.00 | 3.62 | 7.27 |
| **Urea** (mg/dL) | 63 | 87 | 160 |
| **Potassium** (mmol/L) | 6.5 | 8.1 | 4.1 |
| **Sodium** (mmol/L) | 144 | 140 | 147 |
| **Chloride** (mmol/L) | 109 | 110 | 105 |
| **Phosphate** (mg/dL) | 5.6 | 5.5 | 6.7 |
| **Magnesium** (mg/dL) | 2.3 | 2.5 | 2.4 |
| **Serum osmolality** (mOsm/kg) | - | 296 | - |

creatinine 7.27 mg/dL), he was started on continuous veno-venous hemodiafiltration, which he maintained for seven days. Hypertension was controlled with amlodipine and atenolol. A psychiatric evaluation revealed a major depressive disorder and psychotherapy was started along with antidepressants. On day 19, he was transferred to a psychiatric centre, where he remained for three weeks, with complete recovery of renal function and suspension of antihypertensive therapy after one month.

Few cases of suicidal attempt in the pediatric age are reported,[1] especially with ethylene glycol, used as antifreeze fluid, deicing solutions and windshield wiper fluids.[2,3] Toxicity is mostly due to its metabolites (glycolic, glyoxylic and oxalic acids) which cause a false-positive elevation in lactic acid and promote calcium oxalate crystal deposits in different tissues.[4,5] An ethylene glycol blood level test is not readily available in most hospitals. Therefore, clinical and analytical clues, such as an increased anion gap acidosis and hyperlactatemia should raise the suspicion of poisoning.[1,4] When available, the first treatment option would be fomepizole, which blocks alcohol dehydrogenase, which is responsible for the metabolism of ethylene glycol (half-life of three to nine hours).[3,4] Another option would be ethanol, whose affinity is 100 times higher for alcohol dehydrogenase compared to ethylene glycol.[3] Whenever there is renal failure, severe metabolic acidosis, severe electrolyte imbalance, very high ethylene glycol concentrations (> 50 mg/dL) and an osmolar gap above 10 mOsm/L, acute renal replacement therapy (hemodyalisis or hemofiltration) must be initiated.[1,2,4] In our case, continuous veno-venous hemodiafiltration was the more readily available treatment option when intoxication was confirmed, given the time of ingestion. Therefore, it is extremely important to promptly initiate adequate treatment to achieve a favourable outcome.

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## PREVIOUS AWARDS AND PRESENTATIONS

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## AUTHOR CONTRIBUTIONS

SIA, SO: Design and conception of the work.

EM, FA: Critical review of the work.

## PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

## PATIENT CONSENT

Obtained.

## COMPETING INTERESTS

The authors have declared that no competing interests exist.

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