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How Can We Improve Care for Patients with Atopic Dermatitis in Portugal?

Como Podemos Melhorar os Cuidados aos Doentes com Dermatite Atópica em Portugal?

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Keywords: Dermatitis, Atopic/epidemiology; Portugal
Palavras-chave: Dermatite Atópica; Portugal

The recent study "Assessing the Burden of Atopic Dermatitis in Portugal through Patient-Centered Experiences" by Michelle Tu *et al*[1] provides a deep insight into the multifaceted burdens faced by individuals with atopic dermatitis (AD) in Portugal. This comprehensive analysis highlights not only the physical and mental health impacts of AD but also the significant financial strain and the suboptimal aspects of current patient management.

Atopic dermatitis, a chronic inflammatory skin condition, affects millions worldwide, causing severe itching, skin lesions, and a substantial reduction in quality of life.[2] In Portugal, the estimated prevalence of AD is approximately 0.6% to 3.5%.[1] The authors of the study conducted a survey of 419 Portuguese adults and caregivers of children with AD (45% were caregivers to pediatric patients and 55% were adult patients) to capture the experience of managing atopic dermatitis in Portugal.

The study's survey revealed critical insights into treatment satisfaction, symptom control, financial burdens, and overall quality of life.

One of the main findings of this study was the moderate overall satisfaction with AD treatments, averaging a 3.15 out of 5 rating. This points to a significant gap in the effectiveness of the current medical management. Patients reported higher satisfaction when treated by dermatologists compared to family physicians, underscoring the critical role of specialized dermatology care and expertise in managing complex AD cases. However, the study also showed that, despite higher satisfaction rates with dermatologists, there was no significant difference in long-term symptom control compared to family physicians. This indicates that, even though specialist care improves patient satisfaction, the quality of care provided by family physicians seems reassuring. Moreover, more effective long-term treatment strategies are needed in both primary and secondary care.

The study highlighted the underuse of shared decision-making and patient education in managing atopic dermatitis. Only 34% of adult patients and 39% of caregivers reported that healthcare providers acknowledged their priorities during visits, and merely 40% of adults and 32% of caregivers received patient education. This suggests that there is a significant gap in patient-centered care, as shared decision-making is vital for aligning treatment plans with patients' values and preferences, thereby enhancing adherence and improving health outcomes. Similarly, patient education empowers individuals to manage their condition more effectively, leading to better symptom control and quality of life. Therefore, there is clearly a high need for comprehensive education programs that cover disease management, treatment options, and self-care strategies to improve patient engagement and satisfaction.

The financial impact of AD on patients and caregivers in Portugal was also found to be high and deeply concerning. Nearly 80% of respondents reported using savings, borrowing money, or reducing spending to cover AD-related costs. This financial strain can exacerbate stress and negatively impact overall health and well-being. In fact, the study found a significant correlation between financial worry and AD severity, indicating that more severe cases of AD are associated with greater financial burden. So, addressing this financial burden is crucial for improving the overall well-being of AD patients.

Finally, this study also confirmed the significant burden of disease, which extends beyond financial concerns and affects patients' quality of life considerably. Portuguese adult patients scored 0.86 out of 1.00 on the EQ-5D, a measure of health-related quality of life, indicating a substantial disease burden. This score suggests that AD patients are willing to trade off 14% of their remaining lifespan to achieve perfect health, underscoring the severe impact of AD on daily life. The average health-related quality of life score identified by the EQ-VAS (another measure of health-related quality of life) in adult Portuguese patients was 73 out of 100, lower than the national average for adults (75/100). This disparity highlights the significant impairment in quality of life experienced by AD patients, pointing to an urgent need for more

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holistic and effective treatment approaches.

The findings of this study have several important implications for healthcare policy and clinical practice in Portugal. Firstly, there is a clear need to improve access to not only family physicians, given their presence in the community and close relationship with their patients, but also dermatologists and other specialists who can provide high-quality care for AD patients. Increasing their availability through the public healthcare system can help address this need. Policymakers should consider strategies to reduce out-of-pocket costs for AD patients, such as subsidizing treatments and providing financial support for those in need. Reducing the financial strain on patients can improve their ability to manage their condition effectively and enhance their quality of life.

Healthcare providers should prioritize shared decision-making and patient education in AD management. Incorporating these elements into routine care can enhance patient satisfaction, adherence to treatment, and improve overall health outcomes. This approach will likely get the patient population more engaged.

In conclusion, the study by Michelle Tu *et al* provides valuable insights into the challenges faced by AD patients and caregivers. The findings underscore the need for improved patient-centered care, enhanced access to both primary and specialist care, increased patient education, and strategies to alleviate the financial burden of AD. By addressing these issues, healthcare providers, researchers, and policymakers can significantly improve the lives of those affected by atopic dermatitis in Portugal. This study serves as a call to action to prioritize the needs of AD patients and to develop comprehensive care strategies that address the multifaceted burdens of this chronic disease.

COMPETING INTERESTS

TT has received consulting fees from AbbVie, Amgen, Almirall, Amgen, Arena Pharmaceuticals, Biocad, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Fresenius-Kabi, Janssen, LEO Pharma, Eli Lilly, MSD, Mylan, Novartis, Pfizer, Samsung-Bioepis, Sanofi-Genzyme, Sandoz and UCB; received payment or honoraria from AbbVie, Almirall, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, LEO Pharma, Eli Lilly, MSD, Mylan, Novartis, Pfizer, Sanofi-Genzyme for lectures, presentations, speakers bureaus, manuscript writing or educational events.

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Rastreio do Cancro do Pulmão em Portugal: Um Projeto Piloto da PULMONALE

Lung Cancer Screening in Portugal: A PULMONALE Pilot Project

Fernanda ESTEVINHO✉[1], Bárbara PARENTE[2,3], Fernando BARATA[4], Isabel MAGALHÃES[5], Manuela FRANÇA[6,7], Paula FIDALGO[8], Paulo SANTOS[9], Venceslau HESPANHOL[10], António ARAÚJO[8,11]
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INTRODUÇÃO

O cancro do pulmão (CP) é o cancro que causa mais mortes na Europa e em Portugal.[1,2] Em Portugal, este é o terceiro tipo de cancro com maior incidência, com 5415 portugueses a serem diagnosticados em 2020, tendo-se registado 4797 mortes.[2] Em média, diagnosticamos, todos os dias, 15 portugueses com CP e 13 morrem devido a esta doença.

Comparativamente a outras neoplasias, como o cancro da mama e colorretal, o CP apresenta uma taxa de sobrevivência muito baixa, sendo que em Portugal a probabilidade de sobreviver cinco anos após diagnóstico é apenas 15%.[3] Esta taxa está associada ao facto de cerca de 75% dos casos serem diagnosticados em estádios avançados da doença.[4] Todavia, em estádios precoces, a taxa de sobrevivência cinco anos após diagnóstico, é de 70% - 90%.[4]

O rastreio do CP com tomografia computorizada de baixa dose (TCBD), demonstrou, nomeadamente nos estudos *National Lung Screening Trial* (NLST)[5] e NELSON,[6] um aumento de diagnósticos em estádios precoces e redução de mortalidade por CP superior a 20%. É de realçar a robustez de ambos os estudos, com o estudo NLST[5] a incluir 53 454 indivíduos com elevada carga tabágica e realização anual de TCBD durante três anos. O estudo NELSON[6] incluiu 15 789 indivíduos com elevada carga tabágica, realização de TCBD no momento da inclusão e após um, três e cinco anos e meio, tendo realizado um seguimento de 10 anos. Ambos demonstraram a segurança e eficácia do rastreio do CP com TCBD, sendo que, no estudo NELSON, o número de TCBD realizadas para prevenir uma morte foi de 130.[7] Adicionalmente, estudos de custo efetividade, nomeadamente o de Gómez-Carballo *et al* (2022) realizado em Espanha, revelaram que o rastreio do CP é custo efetivo na população de risco.[8]

Em 2022, a Comissão Europeia (CE) atualizou as suas recomendações de rastreios de base populacional.[9] Neste seguimento, a CE recomenda que os países europeus iniciem estudos de viabilidade de rastreio do CP a nível nacional usando TCBD, através da implementação de projetos-piloto, associados a programas de cessação tabágica.[9]

Em Portugal, é premente iniciar a implementação de um projeto-piloto, seguindo as recomendações da CE, e permitindo a adaptação do plano de rastreio à realidade portuguesa e a preparação gradual do sistema de saúde para a implementação a nível nacional.

ELABORAÇÃO DO PROJETO-PILOTO DA PULMONALE

A Associação Portuguesa de Luta Contra o Cancro do Pulmão, PULMONALE, reuniu um painel de peritos, incluindo pneumologistas (n = 3), oncologistas (n = 3), radiologistas (n = 1), médicos de família (n = 1) e decisores políticos (n = 1), para a elaboração de um projeto-piloto de rastreio do CP em Portugal. Foram realizadas duas sessões de consenso presenciais focadas em: 1) análise da situação internacional, incluindo principais desafios; 2) mapeamento do projeto piloto, seguidas de reuniões não presenciais para construção de um projeto piloto de rastreio do CP. O projeto final foi consensualizado e aprovado pelos peritos.

RASTREIO DO CANCRO DO PULMÃO

Em Portugal ainda não existem ações concretas para

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a operacionalização do rastreio do CP, apesar de várias entidades e organizações terem vindo a realizar esforços aos níveis científicos, sociais e políticos para demonstrar a urgência da sua implementação.

Este projeto piloto pretende suplantar a atual ausência de ações concretas para a operacionalização do rastreio. O mapeamento do projeto piloto foi desenhado em três grandes áreas – recrutamento, rastreio e orientação para acesso a diagnóstico –, e encontra-se esquematizado na Fig. 1. No seu desenho foram integrados os conhecimentos dos estudos de rastreio do CP, nomeadamente, o estudo NELSON.[6]

Os resultados promissores dos estudos NLST[5] e NELSON[6] fomentaram, pelo mundo, a implementação de projetos de rastreio do CP.[10] Atualmente, existem mais de 129 projetos de rastreio do CP ativos a nível mundial, 49 dos quais são a nível europeu, em países como a Espanha, França, Itália e Alemanha.[11]

O Reino Unido é um dos países que tem demonstrado um forte compromisso em reduzir a mortalidade do CP através do rastreio.[12] O estudo *UK Lung Cancer Screening Pilot Trial* (UKLS), iniciado em 2011, demonstrou um aumento da deteção do CP em estádios precoces, tendo sido realizado tratamento com intuito curativo em mais de 80% dos doentes.[13]

Posteriormente, em 2017, foi iniciada a implementação de projetos-piloto em Manchester.[10] O programa consistiu em disponibilizar o rastreio em diferentes locais de fácil acesso (como supermercados), através de unidades móveis para realização de TCBD, assegurando o acesso da população mais desfavorecida e com dificuldades de acesso a cuidados de saúde.[14] Sessenta e cinco por cento dos casos de CP foram diagnosticados em estádio I, sendo que o sucesso destes projetos levou à sua expansão e à criação, em 2019, do programa *Targeted Lung Health Checks* (TLHC).[10] Desde 2019, o programa TLHC rastreou mais de 120 mil participantes e detetou mais de 1500 casos de CP.[12] Neste contexto, o *UK National Screening Committee* (UKNSC) recomendou, em setembro de 2022, a implementação do rastreio do CP a nível nacional.[10]

Outros países têm vindo a realizar um compromisso para a implementação do rastreio do CP a nível nacional, tendo a Polónia, Croácia e República Checa, já iniciado a implementação.[11] A experiência destes e outros países tem sido essencial para melhorar os protocolos de rastreio, nomeadamente o processo de seleção e recrutamento dos cidadãos elegíveis, assim como o desenvolvimento de tecnologias para colmatar os problemas identificados, designadamente o número insuficiente de radiologistas.[10,12]

A CE tem também demonstrado um compromisso em ajudar os países europeus no processo de implementação de rastreio do CP. Exemplo disso é o projeto *Strengthening the Screening of Lung Cancer in Europe* (SOLACE), que se insere no programa EU4Health.[15] Mais de 10 países europeus participam neste projeto, que tem como principal objetivo apoiar os países no desenvolvimento e implementação de programas de rastreio do CP de forma sustentável e acessível à população de risco.[15]

À semelhança dos desafios reportados por outros países[16] (nomeadamente, dificuldades na identificação dos cidadãos elegíveis, adesão da população desfavorecida e escassez de recursos humanos) a impactarem a realização do rastreio propriamente dito e a posterior abordagem de lesões suspeitas, bem como de outros achados patológicos detetados, também em Portugal se antecipam os mesmos desafios. Assim, foi prioritário refletir sobre um conjunto de ações para antecipar possíveis constrangimentos.

Na nossa perspetiva, é essencial envolver os Cuidados de Saúde Primários (CSP) no recrutamento dos cidadãos elegíveis, assim como desenvolver campanhas de sensibilização direcionadas ao público-alvo, de forma a aumentar a sua adesão. O rastreio do CP deve ser realizado em zonas de fácil acesso a toda a população.

Paralelamente, consideramos, como parte central deste plano, a implementação de consultas de cessação tabágica para todos os cidadãos que decidam participar no rastreio. De forma transversal, propomos a implementação de consultas de apoio psicológico nas diferentes fases do rastreio, especialmente nos casos de resultado positivo.

Por último, este plano pressupõe a criação de vias de referenciação para lesões suspeitas e outros achados adicionais para o Serviço Nacional de Saúde.

CONCLUSÃO

O rastreio do CP pode potencialmente aumentar em mais de 20% a taxa de sobrevivência e permitir o diagnóstico numa fase associada a melhor qualidade de vida. Além disso, os tratamentos em fases iniciais do CP são significativamente menos dispendiosos do que os tratamentos em fases avançadas, estando assim associados, não só, a ganhos em saúde, como a ganhos económicos, prevendo-se que o rastreio seja custo-efetivo.

Face aos benefícios comprovados do rastreio, a CE recomenda a realização de projetos-piloto de rastreio do CP. Neste âmbito, e em linha com o extenso conhecimento adquirido de outros países, a PULMONALE elaborou um projeto-piloto a implementar em Portugal.

Concluindo, é premente a implementação do rastreio do CP em Portugal, que tem o potencial de salvar vidas e assegurar a qualidade de vida dos doentes, contribuindo para aumentar a qualidade dos cuidados prestados.

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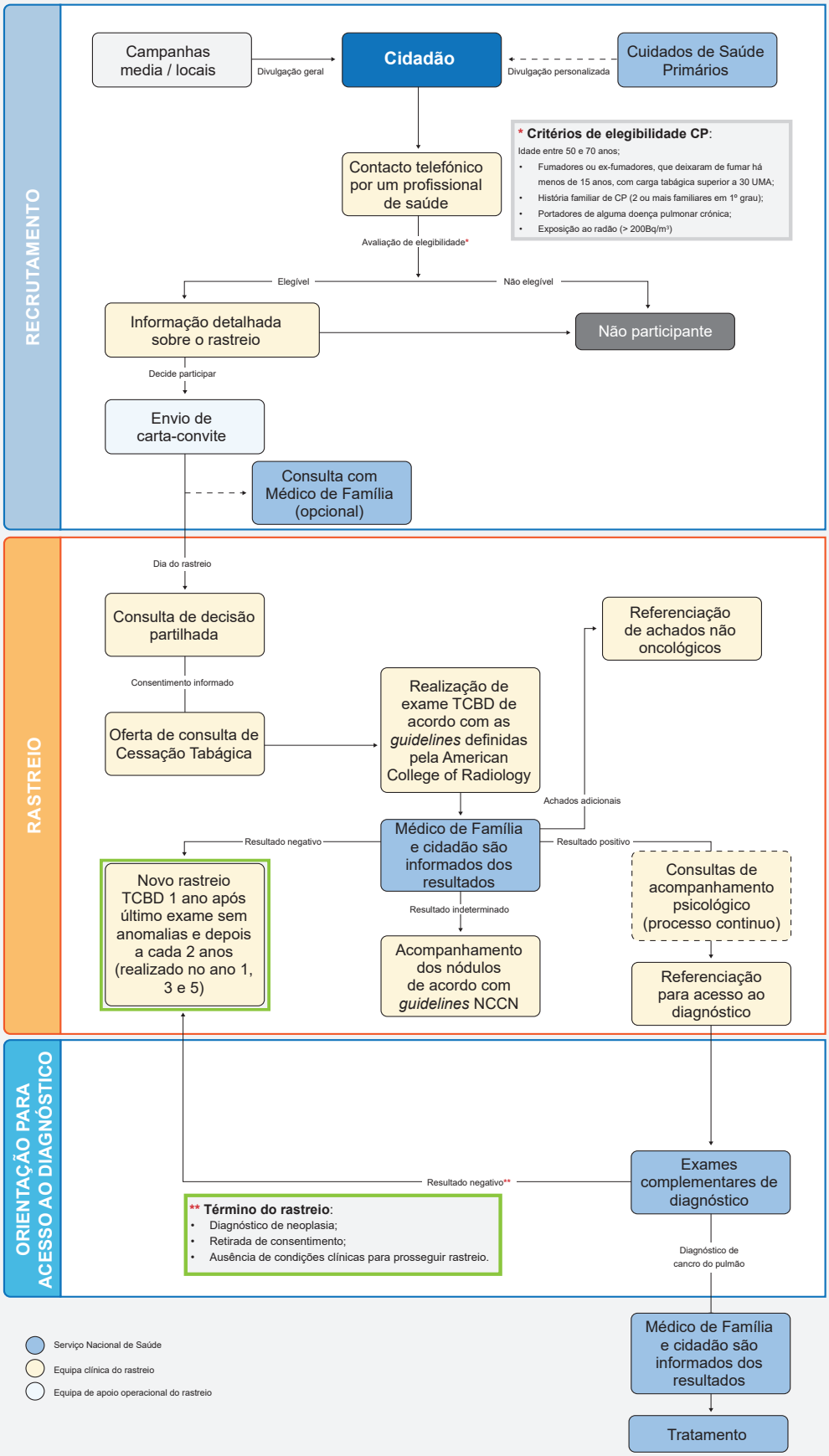

Figura 1 – Mapeamento resumo do projeto-piloto de rastreio do cancro do pulmão
CP: cancro do pulmão; UMA: unidades maço-ano; TCBD: tomografia computarizada de baixa dose; NCCN: *National Comprehensive Cancer Network*.

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CONTRIBUTO DOS AUTORES

FE: Concepção, redação e revisão crítica do manuscrito.

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Todos os autores concordaram com a versão a ser publicada.

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.

CONFIDENCIALIDADE DOS DADOS

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação de dados.

CONFLITOS DE INTERESSE

FE recebeu pagamentos ou honorários para palestras, apresentações, oradores conferências, manuscritos escrita ou educacionais eventos da Takeda, AstraZeneca, Sanofi, BMS, MSD, Roche, Pfizer, Boehringer Ingelheim e Janssen-Cilag; recebeu apoio da MSD, Pfizer, AstraZeneca, Boehringer Ingelgheim, Roche, Takeda, Sanofi, BMS, Novartis, Roche, Lilly e Servier Portugal para a participação em reuniões e/ou deslocações; participou em conselhos consultivos da Janssen-Cilag, BMS, MSD, Merck, Novartis, Boehringer Ingelheim, AstraZeneca, Pfizer.

FB recebeu pagamentos ou honorários para palestras, apresentações, oradores conferências, manuscritos escrita ou educacionais eventos da Eli Lilly Oncology, AstraZeneca, Sanofi, BMS, MSD, Roche, Pfizer, Takeda e Merck; recebeu apoio da MSD, Pfizer, AstraZeneca, Roche, BMS e Takeda para a participação em reuniões e/ou deslocações; participou em conselhos consultivos da Eli Lilly Oncoly, Janssen-Cilag, BMS, MSD, Merck, Roche, Sanofi e Takeda.

PF recebeu pagamentos ou honorários para palestras, apresentações, oradores conferências, manuscritos escrita ou educacionais eventos da Roche, MSD e AstraZeneca; recebeu apoio da MSD e AstraZeneca para a participação em reuniões e/ou deslocações; participou em conselhos consultivos da AstraZeneca, MSD e Roche.

PS recebeu bolsas ou possui contratos com a MSD, GSK e AstraZeneca; recebeu honorários de consultoria da MSD e GSK; recebeu pagamentos ou honorários para palestras, apresentações, oradores conferências, manuscritos escrita ou educacionais eventos da GSK, MSD, AstraZeneca, Medinfar e Tecnimede; recebeu pagamentos da GSK e MSD por testemunho de perito; recebeu apoio da Grunental e Alpha-Wasserman para a participação em reuniões e/ou deslocações; foi presidente do Colégio da Especialidade de Medicina Geral e Familiar.

AA recebeu pagamentos ou honorários para palestras, apresentações, oradores conferências, manuscritos escrita ou educacionais eventos da BMS, MSD, Janssen, Sanofi, Pfizer e Takeda; recebeu apoio da Janssen, Pfizer, Takeda e AstraZeneca para a participação em reuniões e/ou deslocações; participou em conselhos consultivos da MSD, Eli Lilly Oncology, BMS, Takeda, Sanofi, Janssen, Pfizer e Ipsen.

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Burnout Among Portuguese Residents: A Case for Change

Burnout no Internato Médico Português: Uma Perspetiva de Mudança

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Keywords: Burnout, Professional; Internship and Residency; Portugal
Palavras-chave: Burnout Professional; Internato e Residência; Portugal

In the past few years, working conditions in Portugal's public healthcare sector have been deteriorating. Since the identification of the term 'burnout' in the 1970s, the syndrome has been consistently linked to work environments. Therefore, research on burnout among Portuguese healthcare workers is paramount and especially important among doctors, a class of healthcare workers that is particularly affected by this hazard.[1] The significance of this research cannot be understated, as burnout is associated with dire consequences for doctors, their colleagues, their patients, and the healthcare system as a whole.[1] Residency is a time when doctors are particularly vulnerable to burnout because of their young age, high workload, inadequate supervision, lack of autonomy, and the need for continued training/study outside of working hours.

Between August and September 2023, the Portuguese Council of Medical Residents (PCMR), which is a part of the Portuguese Medical Association, launched the first nationwide online survey to evaluate burnout among Portuguese medical residents.[2] There were 1737 participants in the study (16.9% of the invited residents). A validation system by email was used to ensure that there was no duplication of answers. The study concluded that 25% of the medical residents surveyed had severe symptoms of burnout, with 55.3% being at risk of developing the full syndrome in the near future.[2] Taking into account the original definition of Maslach, where burnout is characterized by symptoms of emotional exhaustion, depersonalization or cynicism, and lack of personal accomplishment,[3] we also found meaningful scores in these three dimensions. Therefore, we observed that a high percentage of our sample had severe symptoms of emotional exhaustion (64.7%), depersonalization/dehumanization (45.8%), and lack of personal accomplishment (48.1%). Finally, we found that 35.7% of residents sought psychological or psychiatric help during their residency.[2]

By comparing these results with those of previous studies in Portugal,[4] we observed that burnout syndrome is over three times more prevalent in residents than in specialists (25% *vs* 7%), a finding that underlines the importance of developing preventive measures and strategies tailored specifically to young doctors. In comparison with international studies that used the same definition of burnout, we found similar rates of the syndrome among residents, but higher levels of each dimension of burnout in comparison with studies done in the USA or the Netherlands.[5] Furthermore, the percentage of residents completely engaged in their work in our study was only 5.3%.[2] Although there are no national studies to this day to compare this number directly, this percentage is lower than what has been reported by other countries, where around 20% of residents feel completely engaged in their work.[6]

The most common approaches to burnout have traditionally focused on the healthcare worker, seeking to increase their resilience in the face of extremely adverse working conditions. However, these individualist approaches often ignore many sources of chronic stressors in the workplace, such as excessive workload, staff shortages, and hostile relations among peers. In addition, this kind of strategy may be a problem in itself, as it reinforces burnout as a personal failure that the worker needs to address. The World Health Organization's recent recognition of burnout as an occupational hazard is a call for the need of more organizational strategies to tackle the issue of burnout.[7] Our findings support this call, as we observed a significant number of residents with severe symptoms of emotional exhaustion, a phenomenon closely related with work overload. Indeed, according to our study, medical residents in Portugal worked on average more than 52 hours a week, and only 16.5% reported having a good or very good work/personal life balance.[2]

Work overload usually implies significant compromises to the personal sphere of young doctors, reducing quality

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of life and hampering the creation of coping mechanisms to deal with the stress of work life. As such, a very relevant set of interventions to address the problem of chronic emotional exhaustion could include strategies to manage workplace demands. In contrast, doctors experiencing severe symptoms of depersonalization may benefit from effective interventions taking into account the values of the work institution and the social relationships in the workplace. A particular aspect of residency is the need for continued studying and training outside of working hours, further damaging the quality of life outside of work. This aspect was one of the main themes that appeared in the open-question section of our survey, regarding work-environment difficulties. Therefore, it is essential to allocate protected time for individual study or research in the weekly work schedule to prevent residents from using their time off work to fulfill their training demands. Furthermore, according to the authors' perspective, it is also crucial to review grading and assessment methods across residency programs in order to promote the development of relevant clinical skills and competences instead of focusing on overvaluing checklists for various academic tasks.

In conclusion, this study has shown the urgent need to develop workplace-focused measures to prevent burnout in the Portuguese healthcare workforce, especially among young doctors and residents, as they are at risk of developing the syndrome. Ensuring the quality of postgraduate medical training without risking young doctors' welfare and mental health is crucial to guaranteeing the sustainability of the national health system and the future of healthcare in Portugal.

AUTHOR CONTRIBUTIONS

SM: Conceptualization, writing – original draft.

JB: Conceptualization, methodology, writing – original draft.

CM: Validation, supervision.

FFP: Writing – review & editing, formal analysis.

JD: Writing – review & editing, supervision.

RI: Conceptualization, Writing – original draft, data curation.

All authors approved the final version to be published.

COMPETING INTERESTS

SM and RI are non-paid members of the Portuguese Council of Medical Residents.

JB is a non-paid member of Sociedade Portuguesa de Aplicação de Enteógenos (SPACE).

CM was a non-paid member of the Portuguese Council of Medical Residents and National Board of Medical Residency; is a non-paid member of National Post-Graduation Council

JD is a non-paid member of Portuguese Council of Medical Residents, National Board of Medical Residency and Acta Médica Portuguesa's Scientific Advisory Board.

FFP has declared that no competing interests exist.

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Deprescribing in Older Adults: Attitudes, Awareness, Training, and Clinical Practice Among Portuguese Physicians

Desprescrição nos Idosos: Atitudes, Conhecimento, Formação e Prática Clínica dos Médicos Portugueses

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ABSTRACT

Introduction: The importance of deprescribing in clinical practice is growing, particularly in aging populations with polypharmacy scenarios, making it a crucial matter in Portugal, one of Europe's most aged nations. The aim of this study was to investigate deprescribing awareness, training, attitudes, and practices among Portuguese physicians to inform future healthcare strategies.

Methods: A cross-sectional study using an anonymous online questionnaire was disseminated through the Portuguese Medical Association. It gathered sociodemographic and professional data, and insights into deprescribing awareness, attitudes, training, and practices. Descriptive statistics were summarized as frequencies, percentages, medians, and interquartile ranges. For inferential analysis, the Chi-square test and Fisher's exact test were used to evaluate categorical variables, and the Mann-Whitney U test was used for continuous variables. The significance level was set at $p < 0.05$.

Results: A total of 425 valid questionnaires were included. The participants were mostly women (61.6%), with a median age of 45 (IQR 34 - 42). General practice/family medicine (34.1%) and internal medicine (16.2%) were the most common medical specialties. While 81.2% of the respondents were familiar with the term 'deprescribing', 55.4% reported no training. A vast majority (91.9%) reported practicing deprescribing, but a smaller fraction employed specific methodologies to deprescribe (39.8%) and criteria for identifying potentially inappropriate medications (38.7%). Training in deprescribing was significantly associated with higher deprescribing awareness ($p < 0.001$), the use of specific deprescribing methods ($p < 0.001$), the use of criteria to identify potentially inappropriate medications ($p < 0.001$) and having certification in geriatrics by the Portuguese Medical Association ($p = 0.006$). Family physicians showed higher familiarity with and training in deprescribing than hospital-based specialists ($p < 0.001$). Deprescribing methodologies were adopted more often by family physicians than by hospital-based specialists ($p = 0.004$).

Conclusion: This study highlights widespread deprescribing awareness among Portuguese physicians, while simultaneously uncovering considerable gaps in training and inconsistencies in its application. These findings highlight the pressing need for targeted educational initiatives that could contribute to medication optimization for older adults in the national healthcare system. Furthermore, these findings emphasize the importance of policy development and medical education in promoting safe deprescribing.

Keywords: Aged; Deprescribing; Practice Patterns, Physicians; Portugal; Surveys and Questionnaires

RESUMO

Introdução: A importância da desprescrição na prática clínica tem aumentado, especialmente em populações envelhecidas e com polimedicação, tornando-a uma questão crucial em Portugal, um dos países mais envelhecidos da Europa. Este estudo teve como objetivo investigar a consciencialização, formação, atitudes e práticas de desprescrição entre os médicos portugueses, a fim de informar futuras estratégias e políticas de saúde.

Métodos: Estudo transversal com recurso a um questionário *online* anónimo aos médicos portugueses, disseminado com a colaboração da Ordem dos Médicos. Foram recolhidos dados sociodemográficos, profissionais e relativos à desprescrição (consciencialização, atitudes, formação e prática clínica). A estatística descritiva inclui frequências, percentagens, medianas e intervalos interquartis. Foram aplicados o teste do qui-quadrado e o teste exato de Fisher (variáveis categóricas) e o teste de Mann-Whitney U (variáveis contínuas). A significância estatística foi estabelecida em $p < 0,05$.

Resultados: Foram incluídos 425 médicos, maioritariamente do sexo feminino (61,6%), com média de idade de 45 anos (IQR 34 - 42). As especialidades médicas mais frequentes foram medicina geral e familiar (34,1%) e medicina interna (16,2%). Apesar de 81,2% dos respondentes conhecerem o termo 'desprescrição', 55,4% não possuíam formação na área. A maioria (91,9%) efetuava desprescrição, contudo, uma menor percentagem utilizava metodologias específicas (39,8%) e critérios para identificar medicamentos potencialmente inapropriados (38,7%). Verificou-se uma associação da formação em desprescrição com uma maior consciencialização sobre a mesma ($p < 0,001$), utilização de métodos de desprescrição ($p < 0,001$), uso de critérios para identificar MPI ($p < 0,001$) e competência em Geriatria ($p = 0,006$). Os profissionais de medicina geral e familiar revelaram maior familiaridade e formação em desprescrição do que os especialistas hospitalares ($p < 0,001$), e referiram adotar mais frequentemente as metodologias de desprescrição ($p = 0,004$).

Conclusão: Este estudo destaca uma ampla consciencialização sobre a desprescrição entre os médicos portugueses, mas revela, simultaneamente, lacunas consideráveis na formação e inconsistências na sua aplicação. Estes resultados sublinham a urgente necessidade de iniciativas direcionadas à formação em desprescrição para a otimização da medicação nos idosos no sistema nacional de saúde. Os resultados enfatizam ainda a importância do desenvolvimento de políticas de saúde e da educação médica na promoção de uma desprescrição segura.

Palavras-chave: Desprescrição; Idoso; Inquéritos e Questionários; Padrões de Prática Médica; Portugal

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KEY MESSAGES

- Deprescribing Awareness and Implementation Gaps: Although most Portuguese physicians are aware of deprescribing and its benefits, there is a significant gap in the consistent application of structured methods and the use of PIM identification criteria.
- Training in deprescribing is associated with higher awareness and more frequent use of specific deprescribing methodologies and criteria to identify PIMs.
- Specialty-Based Variations in Deprescribing: Family physicians and internal medicine specialists are more actively engaged in deprescribing practices than other specialties, indicating a disparity that needs to be addressed.
- Policy, Educational, and Training Recommendations: These findings advocate for the development of national deprescribing policies and educational programs to address current gaps and promote safer medication practices for older adults.

INTRODUCTION

As populations age globally, healthcare systems face the challenge of effectively managing complex medication regimens. This requires the adoption of evidence-based practices and a shift towards personalized medication management.[1-3] Geriatric health care presents challenges owing to the high prevalence of polypharmacy and multimorbidity. Clinical trials often exclude older adults, resulting in guidelines that do not account for the unique pharmacokinetic and pharmacodynamic changes associated with aging and multimorbidity.[4,5] Consequently, managing inappropriate polypharmacy in older adults has become a complex issue for healthcare professionals.

Deprescribing is the process of withdrawing inappropriate medication, supervised by a healthcare professional, and is a key strategy for managing polypharmacy and improving health outcomes.[6] Recognizing its importance, the World Health Organization (WHO) released, in 2024, a comprehensive policy brief titled “Medication Without Harm”, which followed the WHO Global Patient Safety Challenge: Medication Without Harm released in 2017. This brief outlines a global strategy for ensuring medication safety and urges countries to develop national action plans to address medication errors and prevent medication-related harm.[7,8]

Deprescribing interventions can significantly reduce potentially inappropriate medications (PIMs), potential prescribing omission (PPOs), and the incidence of adverse drug events (ADEs); improve medication adherence; and enhance medication safety and health outcomes in older patients.[9] Furthermore, evidence supports that deprescribing interventions are cost-effective in various contexts and countries.[10]

Deprescribing includes a structured approach that entails creating a comprehensive medication history; identifying PIMs; assessing cessation feasibility; prioritizing medications; implementing withdrawal; and monitoring, supporting, and documenting the entire process. Shared decision making with patients or caregivers is vital during this process.[11]

An umbrella review published in 2023 aimed to identify guidelines to assess medication appropriateness and aid deprescribing. It revealed the existence of 95 tools and 9 guidelines to assist healthcare professionals.[12] In Portugal, some of the adapted tools include the Beers Criteria[13], EU(7)-PIM list[14], and STOPP/START criteria.[15]

Despite expanding evidence, various barriers at the level of healthcare professionals, patients, and systems make it difficult to implement deprescribing practices.[16-18] Deprescribing is a patient-centered approach involving multiple healthcare providers who face numerous challenges and barriers. Physicians have recognized several barriers to deprescribing, such as fear of withdrawal symptoms, disease relapse, insufficient knowledge, lack of evidence-based deprescribing, patient resistance, time constraints, fragmented healthcare with a lack of communication between different prescribing specialists, fear of disrupting relationships with other specialists, and fear of legal consequences.[16-18] Portugal, along with Italy, has the highest proportion (24%) of the population aged 65 years and over in Europe[19] and one of the highest rates of polypharmacy (36.7%) based on Wave 6 of the Survey of Health, Ageing, and Retirement in Europe (SHARE) database.[20] Nationwide studies have underscored the high prevalence of polypharmacy (77%)[21] and potentially inappropriate medications (PIMs) among older Portuguese adults. A retrospective nationwide population-based study revealed a frequency of 9.2% of PIMs in older adults,[22] while a cross-sectional study reported 68.9% of PIMs in this demographic.[23] These findings emphasize the need for implementing policies aimed at optimizing medication use. Furthermore, in Portugal, several studies have been conducted to evaluate the barriers and facilitators of deprescribing using diverse methodologies.[24-27] However, none have comprehensively and quantitatively addressed, at a national level, Portuguese physicians’ awareness, training, use of specific deprescribing methods, or criteria to identify PIMs. This gap in the literature underscores the need for more targeted research

to inform and optimize deprescribing practices across the country.

The objective of our study is to significantly contribute to the existing body of knowledge on deprescribing in Portuguese clinical practice. Specifically, the aim of our study was to evaluate the current state of deprescribing in Portuguese physicians' clinical practice, with a particular focus on awareness, training, attitudes, and practices related to this topic.

METHODS

Study design

A national cross-sectional study using a web survey targeted physicians registered with the Portuguese Medical Association (OM).

Participants and recruitment

Participants were selected based on the following inclusion criteria: being physicians registered with the OM, having an email address in the OM database, and actively practicing in the country. The web survey dissemination employed a strategic sequential approach, using two different channels of communication to reach the widest audience of Portuguese physicians and promote a higher response rate. The first phase of the study was launched in September 2021 through OM's newsletter, which introduced the study and invited participation through a hyperlink to the survey. In the second phase, the survey was sent via email by the Central Portugal Regional Section of the OM (first in April and a reminder in May 2023). Data were extracted in October 2023. The process was encrypted to comply with the General Data Protection Regulation (GDPR), ensuring anonymization of the collected data.

Data collection and questionnaire

The questionnaire is part of a research project entitled "Deprescribing in Older Adults: The Physician's Perspectives". This project consists of two studies: the current study that examines the knowledge, training, and practices of Portuguese physicians regarding deprescribing, and a second study, to be presented in a separate paper, that explores the barriers and facilitators of deprescribing from the physicians' perspective. The web survey was developed to answer the research questions on physicians' deprescribing awareness, training, and practices. Additionally, questions focusing on physicians' attitudes and perceptions were also included, using main themes and sub-themes from the literature on barriers and facilitators to deprescribing.[16,28,29-33]

Five independent physicians pilot-tested the questionnaire to assess its clarity, feasibility, and completion time, which took approximately 10 minutes. The comprehensive questionnaire consisted of nine questions on sociodemographic and professional data and 14 multiple-choice questions on polypharmacy and deprescribing (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21677/15515). The survey was divided into four sections: sociodemographic and professional data, polypharmacy and deprescribing awareness, attitudes and practices, and facilitators/barriers to deprescribing. This study analyzed the results from the first three sections. The questionnaire was developed using Microsoft Forms® software and stored on the University of Aveiro's server.

Ethics

Informed consent and participant information document

The emails containing the hyperlink to access the questionnaire included an introductory text that invited physicians to participate in the study. This text provided an outline of the study's objectives and framework, and introduced the researchers who were responsible for it. The participants were then presented with an informed consent form that had to be agreed upon before accessing the questionnaire [see Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21677/15515)].

Ethics committee approval

This study was approved by the Ethics and Deontology Committee of the University of Aveiro (reference no. 28-CED/2021) and was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013).[34] All data were confidentially maintained and used exclusively in this study.

Statistical analysis

To assess data normality, we used the Kolmogorov-Smirnov test and visual inspection of histograms. Descriptive statistics were summarized as frequencies and percentages. For categorical variables, the Chi-Square test and Fisher's exact test were used, and Cramer's V test was used to measure the association strength. The Mann-Whitney U test was used for continuous and ordinal variables, and the effect size r was calculated using the formula $r = |Z|/\sqrt{n}$, with missing data excluded from the analysis.

In the statistical analysis, all participants were considered for the general characterization of the sample concerning professional and demographic variables. Nevertheless, pediatric specialists were excluded from the remaining statistical analyses because their specialty does not cater to older adults. The association between participants' socio-professional characteristics and their training in deprescribing, as well as their competency in geriatrics and the number of years of medical experience, was explored. The

categorization of medical specialties into four groups was designed to capture the complexities and nuances of medical practice. This methodology was adopted to differentiate between hospital- and non-hospital-based specialties, further subdividing hospital-based specialties into surgical and non-surgical categories. Internal medicine and family medicine, both of which provide comprehensive care to older patients, were categorized individually. These specialties are crucial for overseeing the health care of the aging population and emphasizing their comprehensive approach to patient care. We transformed several variables to streamline the analysis: "years of medical degree" were converted to "decades" and the question "Do you have training in deprescribing" was classified as either "No" (lacking training) or "Yes" (having received training through literature, conferences, or from employers). Lastly, the question "Do you agree that deprescribing is beneficial in older patients when indicated?" was simplified to a binary choice: "Disagree" (combining "disagree" and "no opinion") and "Agree" (including "agree" and "strongly agree").

Adjusted residuals were used to analyze the contingency table results among the categorized medical specialties and deprescribing-related variables, including awareness, perceived benefits, training, implementation in clinical practice, use of deprescribing methodologies, and application of established criteria to identify PIMs. The Critical Z value (1.96 for a 95% confidence interval) was applied to assess the statistical significance of the adjusted residuals. Values outside ± 1.96 were considered significant at $p < 0.05$. Statistical analysis of the data was conducted using the Statistical Package for the Social Sciences (SPSS) – IBM® Statistics Version 29 for MacOS.

RESULTS

Participants characteristics

The web survey had 577 entries; 116 were excluded due to the absence of responses, and from the remaining 461 entries, 36 were excluded for not meeting the inclusion criteria. This process yielded 425 entries that were considered appropriate for the study as they met the inclusion criteria. The survey distributed through the OM weekly newsletter resulted in 122 responses out of 60 178 Portuguese physicians, yielding a response rate of 0.20%. Later, the OM sent the survey via email to 10 234 physicians, receiving 303 responses, for a response rate of 2.96%.

The respondents had a median age of 45 years (IQR: 34 - 62 years) and were primarily women (61.6%). The median number of years since graduating from medical school was 21 (IQR: 10.5-39). The largest group of participants (32.2%) graduated between 2010 and 2019. Senior consultant (*assistente graduado*) was the most common professional category (36.5%). Among the 425 participating physicians, 57 (13.4%) has certification in geriatrics certification from the OM. Table 1 presents a detailed description of the participants.

Participants representing 35 medical specialties were included in the study, with the most common being family physicians (34.1%), followed by internal medicine (16.2%) and psychiatry (4.9%). Among the 57 physicians with certification in geriatrics, 70.2% were family physicians and internal medicine specialists (45.6% and 24.6%, respectively). Within their respective specialties, 34.1% of the family physicians and 16.2% of the internal medicine specialists had certification in geriatrics. The distribution of participants according to medical specialty and certification in geriatrics is shown in Appendix 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21677/15516).

Following the question "Are you familiar with the term 'deprescribing?'", 40 participants ceased to respond to the questionnaire. A significant association ($p = 0.001$) was observed between unfamiliarity with the term and cessation of responding to the questionnaire. Specifically, 20% of those who were not familiar with the term ceased responding, while only 7% of those who were familiar with the term did so.

Global characterization of patients managed by participating physicians: age distribution and polypharmacy patterns

Most physicians (53.5%) had more than half of their patients aged ≥ 65 years, whereas 95.5% reported that polypharmacy was more common in older adults. For patients aged ≥ 65 years, respondents considered polypharmacy either frequent (51.1%) or very frequent (45.2%). See Table 1.

Awareness, training, attitudes, and clinical practice of participating physicians regarding deprescribing

Most physicians (81.8%) were familiar with the term deprescribing, but more than half (54.7%) reported having no training in this field. The majority (98.9%) agreed on the benefits of deprescribing in older adults, and 92% deprescribed medications in their daily practice. However, most participating physicians (59.9%) did not use a specific method and 61.4% did not use specific criteria to identify PIMs. See Table 2.

Physicians' deprescribing training: associations with deprescribing awareness, attitudes, competency in geriatrics, and clinical practice

The findings of the study indicate a substantial discrepancy in participants' familiarity with the term deprescribing based on their training backgrounds. A statistically significant association was observed between awareness of the

Table 1 – Demographic and professional characteristics of the participating physicians (n = 425)

Age	
Median (IQR)	45 (34 - 62)
Sex	n (%)
Female	262 (61.6)
Male	163 (38.4)
Academic degree	
Medical degree	201 (47.3)
Master's degree	199 (46.8)
Doctorate	25 (5.9)
Professional category	
Senior Consultant	155 (36.5)
Consultant	107 (25.2)
Specialty medical resident	61 (14.4)
Senior consultant	54 (12.7)
Specialist physician with no affiliation to the Portuguese NHS	41 (9.6)
Physician without specialization	4 (0.9)
Intern (common year)	3 (0.7)
Certification in geriatrics	
Yes	57 (13.4)
No	368 (86.6)
Medical specialty[a] (n = 425)	
General practice/family medicine	145 (34.1)
Internal medicine	69 (16.2)
Psychiatry	21 (4.9)
Others	190 (44.7)
Considering your patients, is polypharmacy, defined as the use of 5 or more medications, more frequent in: (n = 425)	
Older adults (≥ 65 years)	406 (95.5)
Children and adolescents	3 (0.7)
In adults	16 (3.8)
Among all your patients, the approximate percentage of adults aged ≥ 65 years is: (n = 424)	
None	8 (1.9)
< 25% of older adults	42 (9.9)
25% - 49% of older adults	147 (34.7)
50% - 74% of older adults	170 (40.1)
≥ 75% of older adults	57 (13.4)
Among your older patients (age ≥ 65 years), polypharmacy is: (n = 425)	
Rarely present	8 (1.9)
Occasionally present	8 (1.9)
Frequently present	217 (51.1)
Very Frequently present	192 (45.2)

IQR: interquartile range; NHS: national health service.
a: Frequencies and percentages of the three most frequent specialties are presented individually, while all other specialties are grouped as 'others'. Detailed data on medical specialties can be found in Appendix 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21677/15516).

Table 2 – Physicians' deprescribing training: associations with deprescribing awareness, perception of benefit, certification in geriatrics, and deprescribing clinical practice

	Total	Training in deprescribing		*p*-value
		Yes	No	
Years of medical graduation (n = 417)				
Median (IQR)	20 (10 - 39)	16 (8.50 - 38.00)	26.5 (11.25 - 40.00)	**0.008**[a]
Years of medical graduation by decades (n = 417)				
1970 - 1979	64 (15.3)	26 (13.8)	38 (16.7)	
1980 - 1989	74 (17.7)	30 (15.9)	44 (19.3)	
1990 - 1999	53 (12.7)	15 (7.9)[d]	38 (16.7)[d]	**0.007**[b]
2000 - 2009	81 (19.4)	38 (20.1)	43(18.9)	(χ^2 (5) = 15.955, V = 0.196)
2010 - 2019	135 (32.4)	77 (40.7)[d]	58 (25.4)[d]	
2020	10 (2.4)	3 (1.6)	7 (3.1)	
Certification in geriatrics (n = 417)		n (%)	n (%)	
Yes	57 (13.7)	35 (18.5)	22 (9.6)	**0.007**[c]
No	360 (86.3)	154 (81.5)	213 (90.4)	(χ^2 (1) = 6.889, V = 0.129)
Workplace setting (n = 417)				
NHS hospital[e]	127 (30.5)	78 (41.3)[d]	135 (59.2)[d]	
NHS primary health care[f]	77 (18.5)	80 (42.3)[d]	47 (20.6)[d]	**< 0.001**[c]
Private sector[g]	127 (30.5)	31 (16.4)	46 (20.2)	(χ^2 (2) = 23.307, V = 0.236)
Are you familiar with the term 'deprescribing'? (n = 417)		n (%)	n (%)	
Yes	341 (81.8)	188 (99.5)	153 (67.1)	**< 0.001**[c]
No	76 (18.2)	1 (0.5)	75 (98.7)	(χ^2 (1) = 72.633, V = 0.417)
Do you have training in deprescribing? (n = 417)				
Yes	189 (45.3)	-	-	-
No	228 (54.7)	-	-	-
Do you agree that deprescribing is beneficial in older patients when indicated? (n = 369)		n (%)	n (%)	
Disagree	4 (1.1)	1 (0.6)	3 (1.6)	0.624[b] (χ^2 (1) = 0.875, V = 0.049)
Agree	365 (98.9)	177 (99.4)	188 (98.4)	
In your daily clinical practice, do you deprescribe medications in patients when indicated? (n = 367)		n (%)	n (%)	
Yes	338 (92.0)	173 (97.2)	165 (87.3)	**< 0.001**[c]
No	29 (7.9)	5 (2.8)	24 (12.7)	(χ^2 (1) = 12.319, V = 0.183)
Do you have a specific methodology for deprescribing medications? (n = 367)		n (%)	n (%)	
Yes	147 (40.1)	102 (57.3)	45 (23.8)	**< 0.001**[c]
No	220 (59.9)	76 (42.7)	144 (76.2)	(χ^2 (1) = 42.829, V = 0.342)
What criteria do you use to identify PIM? (n = 370)		n (%)	n (%)	
No specific criteria to identify PIMs	227 (61.4)	77 (33.9%)	150 (66.1%)	**< 0.001**[c] (χ^2 (1) = 47.356, V = 0.358)
STOPP-START criteria	103 (27.8)	80 (77.7%)	23 (22.3%)	**< 0.001**[c] (χ^2 (1) = 49.966, V = 0.367)
Beers Criteria (American Geriatric Society)	93 (24.8)	77 (82.8%)	16 (17.2%)	**< 0.001**[c] (χ^2 (1) = 59.874, V = 0.402)

IQR: interquartile range; PIM: potentially inappropriate medication; V: Cramer´s V.
a: Mann Whitney test; **b**: Fisher exact test, **c**: Chi-square test, and all cells have an expected count greater than 5; **d**: Cells with statistical significance after post-hoc analysis of contingency tables, considering adjusted residuals and using 1.96 as the critical Z-value; **e**: includes physicians working solely in NHS hospitals and those practicing in both NHS hospitals and the private sector; **f**: includes physicians in NHS primary healthcare and dual practitioners in NHS primary healthcare and the private sector; **g**: includes physicians working in the private sector.

term deprescribing and deprescribing training ($p < 0.001$). Nearly all participants (99.5 %) familiar with the term had received training, whereas the majority (98.7%) of those unfamiliar with the term had not undergone such training.

Additionally, this study revealed that deprescribing training was associated with fewer years of clinical practice. The Mann-Whitney test showed a significant difference ($p = 0.008$) between the group with training (n = 189, Md = 16) and the group without training (n = 228, Md = 26.5).

Moreover, deprescribing training was significantly associated with physician certification in geriatrics ($p = 0.009$). Among the participants with certification in geriatrics, a substantial majority (61.4%) had received deprescribing training, whereas only a minority (38.6%) of those without certification had undergone such training.

The study also underscored a significant association between training in deprescribing and practice of deprescribing among Portuguese physicians ($p < 0.001$). Among those with deprescribing training 97.2% reported deprescribing during their clinical practice, compared to 87.3% of those without training.

Furthermore, among those who received deprescribing training, 57.3% used a specific method to deprescribe, whereas only 23.8% of those without training used a specific method. Most participants (76.3%) without deprescribing training did not use any specific deprescribing methods. A significant association was found between receiving training and using a method for deprescribing ($p < 0.001$).

The results indicated significant associations between deprescribing training and the use of the PIM identification criteria. Participants who applied established criteria to identify PIMs had a higher prevalence of deprescribing training. Specifically, 77.7% of those who adopted the STOPP/START criteria ($p < 0.001$) and 82.8% of those who used the Beers criteria ($p < 0.001$) had undergone deprescribing training. Conversely, a significant proportion of the respondents who reported not using specific criteria to identify PIMs (66.1%) lacked deprescribing training ($p < 0.001$).

Interestingly, training in deprescribing was not associated with physicians' perspectives regarding the benefits of deprescribing in older adults, when deemed appropriate ($p = 0.624$).

Table 2 presents these results.

Associations between certification in geriatrics and deprescribing practices

A statistically significant association was identified between certification in geriatrics and physicians' years of clinical experience ($p = 0.048$), deprescribing awareness ($p = 0.043$), deprescribing training ($p = 0.009$), adoption of deprescribing methodology ($p = 0.022$), and the use of the STOPP/START criteria to identify PIMs ($p = 0.028$). Deprescribing in clinical practice and agreement on deprescribing benefits in older patients showed no significant association with having such certification. Further details of this analysis are presented in Table 3.

Associations between years of medical experience and deprescribing awareness, deprescribing attitudes, certification in geriatrics, and prescribed clinical practices

Physicians who graduated more recently were more familiar with the term 'deprescribing' ($p = 0.007$) and had more deprescribing training ($p = 0.008$). Physicians with certification in geriatrics had more years of graduation ($p = 0.048$). Fewer years of clinical experience were associated with using the STOPP/START and Beers Criteria to identify PIMs ($p < 0.001$ for both). Additionally, years of graduation were not associated with deprescribing in clinical practice, employment of a methodology for deprescribing, or physicians' agreement with the benefits of deprescribing in older adults (all $p > 0.05$). The results are presented in Table 4.

Deprescribing awareness, training, attitudes, and practices: associations with medical specialties

A difference in awareness of 'deprescribing' was found across medical specialties ($p < 0.001$), with higher levels of familiarity among family physicians (93.1%) and internal medicine specialists (95.7%) compared to hospital-based medical specialists (68.9%) and medical-surgical specialists (46.2%).

Substantial differences in deprescribing training were observed among medical specialties, with 63.9% of the family physicians and 62.3% of internal medicine specialists having received training, compared to 25.3% of hospital-based specialties and 11.5% of medical-surgical specialists ($p < 0.001$).

Significant differences were observed in the adoption of deprescribing methodology. Only 31.2% of hospital medical specialty physicians reported having a deprescribing methodology compared to 48.1% of the family physicians ($p = 0.004$).

Within hospital-based medical specialties, 78.6% of physicians did not use specific criteria to identify PIMs. In contrast, only 46.2% of family physicians did not use specific criteria to identify PIMs. This difference was statistically significant ($p < 0.001$).

Significant differences were observed in the use of the STOPP/START criteria between specialties ($p < 0.001$). Family physicians had the highest adoption rate within their specialty (43.8%), accounting for 60.6% of all users of these criteria. In contrast, only 4.5% of the medical-surgical specialists used these criteria, representing only 1.1% of the total users.

Differences in Beers criteria usage were observed

Table 3 – Analysis of associations between certification in geriatrics and years of clinical practice, workplace setting, awareness, training attitudes, and clinical practice regarding deprescribing

	Certification in geriatrics		
	Yes	No	*p*-value
Years of experience since medical graduation (n = 418)			
Median (IQR)	27 (13 - 43)	20 (10 - 38)	**0.048**[a]
Workplace setting (n = 418)			
NHS hospital[d]	25 (43.9)	188 (52.1)	0.235[b] (χ^2 (2) = 2.899, V = 0.083
NHS Primary health care[e]	17 (29.8)	111 (30.2)	
Private sector[f]	15 (26.3)	62 (17.2)	
Are you familiar with the term 'deprescribing'? (n = 418)	n (%)	n (%)	
Yes	52 (91.2)	289 (80.1)	**0.043**[b] (χ^2 (1) = 4.089, V = 0.099)
No	5 (8.8)	75 (19.9)	
Do you have training in deprescribing? (n = 417)	n (%)	n (%)	
Yes	35 (61.4)	154 (42.8)	**0.009**[b] (χ^2 (1) = 6.889, V = 0.129)
No	22 (38.6)	206 (57.2)	
Do you agree that deprescribing is beneficial in older patients when indicated? (n = 369)	n (%)	n (%)	
Disagree	2 (3.9)	2 (0.6)	0.094[c] (χ^2 (1) =4.444, V= 0.110)
Agree	49 (96,1)	316 (99.4)	
In your daily clinical practice, do you deprescribe medications in patients when indicated? (n = 367)	n (%)	n (%)	
Yes	45 (88.2%)	293 (92.7)	0.266[c] (χ^2 (1) = 1.214, V = 0.058)
No	6 (11.8%)	23 (7.3)	
Do you have a specific methodology for deprescribing medications? (n = 367)	n (%)	n (%)	
Yes	28 (54.9)	119 (37.7)	**0.022**[b] (χ^2 (1) = 5.438, V = 0.122)
No	23 (45.1)	197 (62.3)	
What criteria do you use to identify PIMs? (n = 370)	n (%)	n (%)	
No specific criteria to identify PIMs	26 (51)	201 (63)	0.121[b] (χ^2 (1) = 2.683, V = 0.085)
STOPP-START criteria	21 (41.2)	82 (25.7)	**0.028**[b] (χ^2 (1) = 5.239, V = 0.119)
Beers Criteria (American Geriatric Society)	15 (29.4)	78 (24.5)	0.487[b] (χ^2 (1) = 0.575, V = 0.039)

a: Mann-Whitney test; **b**: Chi-square test, and all cells have an expected count greater than 5; **c**: Fisher's exact test; **d**: Includes physicians working solely in NHS hospitals and those practicing in both NHS hospitals and the private sector; **e**: Includes physicians in NHS primary health care and dual practitioners in NHS primary health care and the private sector; **f**: Physicians working in the private sector.

among specialties ($p < 0.001$). Medical surgical and hospital-based medical specialties had the lowest proportions at 4.5% and 9.2%, respectively, whereas internal medicine and family physicians had the highest proportions at 37.3% and 35.4%, respectively. The latter specialty represented 54.8% of the total Beers Criteria users, and internal medicine accounted for 29.8%.

No significant differences were found between specialties associated with the benefits of deprescribing in older adults ($p = 0.878$) or with deprescribing in clinical practice ($p = 0.110$). The results are summarized in Table 5.

Associations of physicians' sex with their deprescribing awareness, training, attitudes, and practices

Physicians' sex was associated with years of experience ($p < 0.001$), deprescribing awareness ($p = 0.015$),

Table 4 – Association between years of medical experience and deprescribing awareness, training in deprescribing, certification in geriatrics, deprescribing benefit in older adults, use of a deprescribing method, and use of criteria to identify PIM

Variable	Category	Median (IQR) Years since graduation	Mann-Whitney U	Z	*p*-value	*r* (effect size)
Are you familiar with the term 'deprescribing'? (n = 418)	No	29 (16.5 - 39.5)	10 565.000	-2.678	**0.007**	0.130
	Yes	18 (10.0 - 39.0)				
In your daily clinical practice, do you deprescribe medications to patients when indicated? (n = 367)	No	26 (9.0 - 30.5)	4604.500	-0.541	0.588	0.028
	Yes	19 (10.0 - 38.0)				
Do you have certification in geriatrics? (n = 418)	No	20 (10.0 - 38.0)	8611.500	-1.979	**0.048**	0.096
	Yes	27 (13.0 - 47.0)				
Do you agree that deprescribing is beneficial in older patients when indicated? (n = 369)	No	22.5 (20.5 - 37.5)	559.000	-0.806	0.420	0.041
	Yes	19 (10.0 - 27.5)				
Do you have training in deprescribing? (n = 417)	No	26.50 (11.25 - 40.0)	18 284.500	-2.663	**0.008**	0.130
	Yes	16 (8.5 - 38.0)				
Do you have a specific methodology for deprescribing medications? (n = 367)	No	18.5 (10.0 - 30.4)	147 375.000	-1.803	0.071	0.094
	Yes	20 (11.0 - 42.0)				
What criteria do you use to identify PIMs? - No specific criteria to identify PIMs (n = 370)	No	15 (8.0 - 34.0)	13 390.000	-2.837	**0.005**	0.147
	Yes	23 (12.0 - 39.0)				
What criteria do you use to identify PIMs? - STOPP/START Criteria (n = 370)	No	23 (12.0 - 39.0)	9678.500	-4.419	**< 0.001**	0.230
	Yes	13 (8.0 - 24.0)				
What criteria do you use to identify PIMs? - Beers Criteria (n = 370)	No	23 (12.0 - 39.0)	8951.500	-4.404	**< 0.001**	0.229
	Yes	12 (8.0 - 23.0)				

V: Cramer's V; PIM: potentially inappropriate medication
The Mann-Whitney U test was used to assess associations between the variable years of medical experience and other variables. The effect size *r* was calculated using the formula $r = |Z|/\sqrt{n}$.

certification in geriatrics (p = 0.003), perception of deprescribing benefits (p = 0.022), and the use of criteria to identify PIMs (p = 0.003). Specifically, male physicians had more years of experience after graduation and were more frequently certified in geriatrics training. By contrast, female physicians were more familiar with the benefits of deprescribing, agreed more with the term deprescribing, and were more likely to use criteria to identify PIMs. The detailed results are presented in Appendix 2 - Table 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21677/15516).

DISCUSSION

This study provides novel insights into Portuguese physicians' awareness, attitudes, behaviors, and clinical practice concerning deprescribing, which contributes to a broader understanding of its implications in clinical practice. A striking paradox emerged: Although most physicians were familiar with deprescribing, recognized its benefits, and implemented it regularly, the majority lacked adherence to a specific deprescribing method or criteria for identifying PIMs. Notably, a significant proportion of the participants did not receive deprescribing training. In fact,

discrepancies were observed between participants' high awareness of deprescribing (81.2%), agreement on its benefits for older adults (98.9%), and deprescribing in clinical practice (91.9 %). In contrast, a smaller fraction of participants adopted a specific deprescribing methodology (39.4%) and did not employ specific criteria for PIMs (44.6%). This discrepancy may be attributable to the substantial proportion of physicians (55.4%) lacking training in deprescribing. Furthermore, there is cause for concern regarding the fact that less than half of those applying deprescribing in practice embraced a methodological approach specific to deprescribing, since deprescribing ought to be a structured, evidence-based process that leverages available tools for identifying PIMs and follows guidelines when they exist. It should be a patient-centered process that involves shared decision-making.[35] Merely discontinuing PIMs without a defined methodology can undermine safety and effectiveness.

Training appears instrumental in shaping deprescribing practice. We identified significant associations, with effect sizes greater than 0.3 between receiving deprescribing training and increased awareness of deprescribing, more frequent use of deprescribing methodologies, and more prevalent use of criteria for identifying PIMs. Furthermore, a significant modest association was found between deprescribing training and the active integration of deprescribing into clinical practice. These results suggest the need of increased training and education regarding deprescribing among Portuguese physicians.

The outcome that 98.8% of the participants agreed on the benefits of deprescribing, despite only 81.2% being initially familiar with the term, was likely due to the questionnaire including a definition of deprescribing after asking about familiarity with the term and before inquiring about its perceived benefits for older patients.

Our study revealed that younger physicians with less clinical experience received more deprescribing training than their older and more experienced counterparts. This difference in training may be the reason why physicians with less clinical experience reported a significantly higher awareness of

Table 5 – Physicians deprescribing awareness, training, perception of benefits, and deprescribing practices and their association with medical specialties[a]

		General Practice/ Family Medicine	Internal Medicine	Hospital Medical Specialties[b]	Medical-Surgical Specialties	*p*-value
Are you familiar with the term 'deprescribing'? (Yes) (n = 391)		135 (93.1%)	66 (95.7%)	104 (68.9%)	12 (46.2%)	**< 0.001**[c]
	Adjusted residual	4.7	3.4	-4.9	-4.7	(χ^2 (3) = 59.501, V = 0.387)
Do you have training in deprescribing? (Yes) (n = 390)		92 (63.9%)	43 (62.3%)	40 (25.3%)	3 (11.5%)	**< 0.001**[b]
	Adjusted residual	5.8	3.2	-6.4	-3.5	(χ^2 (3) = 61.572, V = 0.397)
Do you agree that deprescribing is beneficial in older patients when indicated? (Yes) (n = 344)		128 (99.2%)	66 (98.5%)	124 (98.4%)	22 (100%)	0.878[c]
	Adjusted residual	0.5	-0.3	-0.6	0.5	(χ^2 (3) = 0.688, V = 0.045)
In your daily clinical practice, do you deprescribe medications in patients when indicated? (Yes) (n = 342)		124 (96.1%)	63 (94%)	113 (90%)	18 (85.7%)	0.130[c]
	Adjusted residual	1.8	0.4	-1.4	-1.3	(χ^2 (3) = 5.042, V = 0.130)
Do you have a specific methodology for deprescribing medications? (Yes) (n = 345)		62 (48.1%)	34 (50.7%)	39 (31.2%)	5 (23.8%)	**0.005**[c]
	Adjusted residual	2.2	1.9	-2.9	-1.6	(χ^2 (3) = 13.499, V = 0.194)
Criteria used to Identify PIM: (n = 345)						
Does not use specific criteria to identify PIMs		60 (46.2%)	37 (55.2%)	103 (78.6 %)	17 (77.3%)	**< 0.001**[b]
	Adjusted residual	-4.7	-1.3	5.0	1.5	(χ^2 (3) = 32.709, V = 0.311)
STOPP-START criteria		57 (43.8%)	21 (31.3%)	15 (11.5%)	1 (4.5%)	**< 0.001**[b]
	Adjusted residual	5.4	0.8	-4.9	-2.5	(χ^2 (3) = 41.192, V = 0.338)
Beers criteria		46 (35.4%)	25 (37.3%)	12 (9.2%)	1 (4.5%)	**< 0.001**[b]
	Adjusted residual	3.7	2.8	-4.9	-2.2	(χ^2 (3) = 36.129 V = 0.316)

a: Responses from all medical specialists were considered in the analysis. Specialties, according to their frequency and the nature of their clinical activity, were grouped into four categories: family medicine, internal medicine, hospital-based medical specialties (excluding internal medicine), and medical-surgical specialties. All hospital medical specialties except internal medicine.; **b**: Chi-square test. All the cells had an expected count greater than 5; **c**: Fisher's exact test

deprescribing concepts and more frequently used specific criteria to identify PIMs. However, despite the clear statistical association between fewer years of clinical experience and greater engagement with deprescribing practices, the overall impact of this relationship appeared modest, with effect sizes for these associations being lower than 0.3. These discrepancies in deprescribing training based on age and clinical experience may be because the concept emerged in the literature only in 2003,[6] meaning that doctors with more years of experience likely did not have access to deprescribing training during their undergraduate or specialty training. However, the length of clinical experience did not significantly affect deprescribing practices or agreement on its benefits, possibly because physicians treating many older patients with polypharmacy experience the need to deprescribe PIMs despite having less training than their less experienced peers. In addition, certification in geriatrics training was associated with more years of clinical experience. As geriatrics is not a medical specialty in Portugal, many practitioners may have obtained this certification only after completing their specialty training, resulting in more years since graduation.

Further analysis demonstrated that possessing certification in geriatrics training was associated with a heightened awareness and training in deprescribing, a stronger conviction in its benefits for older adults, the use of a specific deprescribing method, and the use of the STOPP/START criteria to identify PIMs.

The STOPP/START criteria exhibit a tailored approach to addressing the specific needs of older adults, combined with a practical and evidence-based nature that likely contributes to their adoption by the participants with certification in geriatrics. Furthermore, the results suggested that education and training were crucial in shaping deprescribing attitudes and practices, as medication management for older patients is a fundamental aspect of geriatrics.

As for the differences observed across specialties, our study showed that family physicians, along with internal medicine specialists, exhibited higher deprescribing awareness, increased deprescribing training, more frequent use of criteria for identifying PIMs, and greater adoption of deprescribing methodologies. These differences may arise from the focus of these specialties in older adults, which inherently affects the existence of knowledge and skills in deprescribing. Other specialties catering to older patients with a holistic care approach require more expertise in medication safety and efficacy, and demand advanced deprescribing training and practice. Nonetheless, all specialties must develop deprescribing skills, improve communication between colleagues, and ensure a patient-centered approach and optimal medication management outcomes.

National policies on deprescribing with a structured approach are necessary to enhance physicians' knowledge and practice of deprescribing. This involves developing and implementing targeted educational interventions that integrate deprescribing principles, guidelines, and evidence-based practices into healthcare curricula across all levels of education and continuing professional development.[36,37] A multidisciplinary collaboration among educators, healthcare professionals, policymakers, and relevant stakeholders, including patients and caregivers, is crucial for ensuring a comprehensive and structured approach to deprescribing education and practice. Furthermore, policies aimed at promoting deprescribing should align with good prescribing practices and be multifaceted, considering the distinct barriers and facilitators present in various healthcare settings while also allocating the necessary resources accordingly.[38,39]

Comparison to existing literature

We found that most physicians (98.9%) agreed with deprescribing benefits for older patients, which is generally in line with other studies, but with varying rates: 92% among Indian hospital physicians in internal medicine and nephrology,[40] 71.8% in another large Indian study across all specialties,[41] and 66% in a Singaporean study of internal medicine physicians.[42] Physician awareness of deprescribing in our study matched that of a smaller study of 70 physicians (80% awareness)[43] but exceeded that of a qualitative study of 15 physicians, most of whom were unfamiliar with deprescribing.[44] Variability likely arises from differences in the sample size, specialty, organizational culture norms, socio-cultural aspects of the professionals involved, and healthcare systems.

The prevalence of deprescribing training among physicians has demonstrated considerable variability in the literature. For instance, a study conducted within a Nigerian hospital reported that only 21.4% of physicians had received such training.[43] In contrast, our more comprehensive and heterogeneous study, which spanned various specialties, revealed that 44.6% of physicians were trained in deprescribing. A cross-sectional study conducted in Portugal using an online survey of family physicians found that 11% of the family physicians reported a lack of training and knowledge as factors that might influence deprescribing when answering an open-ended question.[24] This differs from our study, which specifically inquired about training in deprescribing. Additionally, among our subgroup of geriatric-competent physicians, 61.4% received deprescribing training, which is close to the reported 72% in a 31-country European web-based survey on deprescribing practices, habits, and attitudes of geriatricians and geriatricians-in-training.[45]

Strengths and limitations

Our study has limitations, such as the relatively low response rate, which may be due to factors such as time constraints, survey fatigue, or a perceived lack of relevance of the study's subject matter to recipients. Additionally, there is a potential for non-response bias since physicians with a heightened interest in deprescribing may be more likely to participate. Indeed, our investigation uncovered a relationship between familiarity with the research subject, deprescribing, and the completion of the questionnaire. However, our study's strength is that our sample size was commendable and only exceeded by a European study spanning 31 countries that garnered 964 responses.[45] Furthermore, the sample of 425 physicians was representative of the overall population of 60 178 physicians affiliated with the OM, with a 95% confidence interval and a margin of error of 4.75%. The sample proportions for male and female physicians were also representative, with a margin of error of 4.64%. Among the top three medical specialties with the highest response rates, family physicians comprised 34.1% of the sample (compared to 23.96% nationally), internal medicine accounted for 16.2% (compared to 5.48% nationally), and psychiatry accounted for 4.9% (compared to 2.19% nationally). The 95% confidence intervals and margins of error indicate that the samples for these specialties are representative of their respective populations, with margins of error of 2.05% for family physicians, 4.67% for internal medicine, and 5.23% for psychiatry. Another strength is that our study included physicians across 35 medical specialties, achieving national coverage and having the largest number of nationwide participants in exploring Portuguese physicians' deprescribing knowledge, training, and clinical practice. In contrast, a recently published study evaluating primary healthcare physicians' perspectives on deprescribing included 63 participants from a regional health administration in northern Portugal.[26]

CONCLUSION

This study illuminates the paradox within Portuguese medical practice: despite physicians recognizing and agreeing with the benefits of deprescribing, there was a clear discrepancy in the consistent and effective application of methods to deprescribe or criteria to identify PIMs. Consequently, our findings underscore the pressing need for enhanced deprescribing education and training among Portuguese physicians. Such an intervention is crucial and holds paramount importance for medication optimization in Portuguese older adults. Future research should examine additional barriers to deprescribing beyond educational and training factors. This will allow the development of comprehensive deprescribing policies that ensure medication optimization for older adults in Portugal.

AUTHOR CONTRIBUTIONS

AP: Conceptualization, methodology, formal analysis, investigation, resources, data curation, writing original draft, writing, reviewing, editing, and project administration.

MV: Conceptualization, methodology, investigation, writing, reviewing, editing, and supervision.

OR: Conceptualization, methodology, investigation, resources, writing, reviewing, editing, and supervision.

All authors approved the final version to be published.

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.

DATA AVAILABILITY

The data supporting the findings of this study are available upon request from the corresponding author.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Logistic Regression: Limitations in the Estimation of Measures of Association with Binary Health Outcomes

Regressão Logística: Limitações na Estimação de Medidas de Associação com Desfechos de Saúde Binários

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ABSTRACT

Introduction: Logistic regression models are frequently used to estimate measures of association between an exposure, health determinant or intervention, and a binary outcome. However, when the outcome is frequent (> 10%), model estimates for relative risks and prevalence ratios might be biased. Despite the availability of several alternatives, many still rely on these models, and a consensus is yet to be reached. We aimed to compare the estimation and goodness-of-fit of logistic, log-binomial and robust Poisson regression models, in cross-sectional studies involving frequent binary outcomes.

Methods: Two cross-sectional studies were conducted. Study 1 was a nationally representative study on the impact of air pollution on mental health. Study 2 was a local study on immigrants' access to urgent healthcare services. Odds ratios (OR) were obtained through logistic regression, and prevalence ratios (PR) through log-binomial and robust Poisson regression models. Confidence intervals (CI), their ranges, and standard-errors (SE) were also computed, along with models' relative goodness-of-fit through Akaike Information Criterion (AIC), when applicable.

Results: In Study 1, the OR (95% CI) was 1.015 (0.970 - 1.063), while the PR (95% CI) obtained through the robust Poisson mode was 1.012 (0.979 - 1.045). The log-binomial regression model did not converge in this study. In Study 2, the OR (95% CI) was 1.584 (1.026 - 2.446), the PR (95% CI) for the log-binomial model was 1.217 (0.978 - 1.515), and 1.130 (1.013 - 1.261) for the robust Poisson model. The 95% CI, their ranges, and the SE of the OR were higher than those of the PR, in both studies. However, in Study 2, the AIC value was lower for the logistic regression model.

Conclusion: The odds ratio overestimated PR with wider 95% CI and higher SE. The overestimation was greater as the outcome of the study became more prevalent, in line with previous studies. In Study 2, the logistic regression was the model with the best fit, illustrating the need to consider multiple criteria when selecting the most appropriate statistical model for each study. Employing logistic regression models by default might lead to misinterpretations. Robust Poisson models are viable alternatives in cross-sectional studies with frequent binary outcomes, avoiding the non-convergence of log-binomial models.

Keywords: Logistic Models; Models, Statistical; Odds Ratio; Outcome Assessment, Health Care; Poisson Distribution

RESUMO

Introdução: A regressão logística é frequentemente utilizada para estimar medidas de associação entre uma exposição, determinante de saúde ou intervenção e um desfecho binário. No entanto, quando o desfecho é frequente (> 10%), estas estimativas podem ser enviesadas. Apesar de existirem modelos estatísticos alternativos, muitos estudos continuam a aplicar modelos de regressão logística indiscriminadamente. O objetivo deste estudo foi comparar as estimativas e o ajuste de modelos de regressão logística, log-binomial e Poisson robustos, em estudos transversais com desfechos binários frequentes.

Métodos: Realizaram-se dois estudos transversais. O Estudo 1 foi um estudo representativo a nível nacional sobre o impacto da poluição atmosférica na saúde mental. O Estudo 2 foi um estudo local sobre o acesso de imigrantes a serviços de urgência. Obtiveram-se *odds ratio* (OR) através de regressões logísticas e razões de prevalência (RP) através de modelos log-binomiais e Poisson robustos. Foram ainda obtidos intervalos de confiança a 95% (IC 95%), suas amplitudes, os erros-padrão (EP) das estimativas e comparados os valores *Akaike Information Criteria* (AIC).

Resultados: No Estudo 1, a OR (IC 95%) foi de 1,015 (0,970 - 1,063) e a RP (IC 95%) obtida através do modelo de Poisson robusto foi de 1,012 (0,979 - 1,045). O modelo de regressão log-binomial não convergiu. No Estudo 2, a OR (IC 95%) foi de 1,584 (1,026 - 2,446), a RP (IC 95%) para o modelo de regressão log-binomial foi de 1,217 (0,978 - 1,515) e para o modelo de Poisson robusto foi de 1,130 (1,013 - 1,261). Os IC 95%, as suas amplitudes e os EP das OR foram superiores ao das RP, em ambos os estudos. No entanto, no Estudo 2, o valor do AIC foi inferior no modelo de regressão logística.

Conclusão: As OR sobrestimaram as RP, com IC 95% mais amplos e EP superiores. A magnitude da sobrestimação foi tanto maior quanto mais prevalente o desfecho em estudo, em linha com estudos prévios. No Estudo 2, a regressão logística foi a que melhor se ajustou aos dados. Este exemplo ilustra a necessidade de avaliar vários critérios para selecionar o modelo estatístico mais apropriado. Os modelos de Poisson robustos são uma alternativa viável em estudos transversais com desfechos binários frequentes e evitam o problema de não convergência dos modelos log-binomiais.

Palavras-chave: Avaliação de Processos e Resultados em Cuidados de Saúde; Distribuição de Poisson; Modelos Estatísticos; Modelos Logísticos; Rácio de Probabilidades

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KEY MESSAGES

- Researchers should avoid defaulting to logistic regression, in studies with frequent binary outcomes (frequency > 10%), as it may lead to misinterpretations of data.
- The Robust Poisson regression is a viable alternative to the logistic regression, in cross-sectional studies with frequent binary outcomes, as it provides less biased estimates for prevalence ratios and avoids the convergence issues often encountered with log-binomial models.
- Careful consideration of the outcome's frequency and appropriate model selection are crucial to ensure accurate estimates.
- The Akaike Information Criterion (AIC) can be used to assess the goodness-of-fit for different models, but a lower AIC does not necessarily mean the model provides the most appropriate estimates for measures of association, as illustrated by the better fit of logistic regression in Study 2, despite its overestimation.

INTRODUCTION

In medical research, logistic regression models are frequently used to estimate measures of association between an exposure, treatment or health determinant and a binary outcome.[1,2] These models are employed mostly in cross-sectional and case-control studies to estimate odds ratios (OR), the odds of disease occurrence between the exposed and unexposed.[1] Logistic regression models are very attractive due to their simplicity and effectiveness.

The equivalent of the relative risk or risk ratio (RR) of prospective studies is the prevalence ratio (PR) in the case of cross-sectional studies. Although under certain conditions OR might allow to infer PR/RR, in many other cases, these inferences should not be made as they introduce bias.[1] If the outcome of the study is rare (≤ 10%), logistic regression models may appropriately estimate PR/RR. However, if the outcome is frequent (> 10%), OR might not be a suitable estimator of PR/RR.[2,3]

In the case of a frequent outcome, OR tend to overestimate PR/RR when their values are greater than one, or to underestimate them when values are lower than one.[2,4] A study reported that 40% of the papers that employed logistic regression models estimated OR which deviated by over 20% from the corresponding RR.[5] Odds ratio is also mistakenly portrayed as PR/RR, which is reflected in the results section of some research papers where 'risk' and 'probability' are wrongly used instead of the correct 'odds' and 'possibility' to refer to OR.[2,3]

While alternative methods to estimate valid adjusted PR/RR in the presence of frequent binary outcomes have been suggested, a consensus on the matter is yet to be reached. Log-binomial,[6-8] and modified Poisson regression models[6,7,9] are the most widely accepted.

The Poisson regression model is the nominal model for count data, being commonly used in cohort studies to estimate RR.[7,9] In cross-sectional studies with binary data, the computed ratios can still be interpreted, but as an approximation to the PR.[7,9] This approach yields correct estimates of the PR directly like log-binomial models, but typically with larger variances and standard errors.[7,9] Modified Poisson regression models, as the robust Poisson model, address this issue. Robust standard errors, determined through the Huber sandwich estimation (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21435/15510), correct the Poisson model for data overdispersion (when variance is higher than the mean). This robust estimator performs well even when data does not perfectly meet the model's requirement, as in the case of Poisson regression models applied to cross-sectional binary data.[9]

Since methodological consistency is essential to epidemiological and clinical research, and given the potential impact of biased estimates on clinical practice, policymaking, communication and community behaviour, selecting the appropriate statistical models holds paramount importance. This study aimed to compare the estimation and goodness-of-fit of logistic, log-binomial, and robust Poisson regression models, in cross-sectional studies with frequent (> 10%) binary outcomes.

METHODS

We carried out two cross-sectional studies (Study 1 and Study 2) to estimate the measures of association between two different exposures and two different frequent (> 10%) binary outcomes that were adjusted for several variables identified as potential confounders through directed acyclic graphs, elaborated based on a literature review of the associations in the study.

We conducted a comparative analysis of the estimates of the measures of association (OR in the case of logistic regression models, and PR in the case of log-binomial and robust Poisson regression models), in terms of their magnitude and significance. The estimates' confidence intervals, their ranges and standard errors were also compared.

The maximum likelihood estimation method was

employed in all the computed models, even for those using complex survey data (Study 1). In this case, we fitted models to complex data incorporating the sampling weights in a designed-based analysis (a statistical analysis of survey data that took the survey design, its stratification and clustering, and the sampling weights into consideration).

As the Akaike Information Criterion (AIC) is a widely used tool in model selection and allows to compare the relative goodness-of-fit of different models, AIC values were obtained for every model in study fitting non-complex data (Study 2) and compared. The optimal model should be the one with the minimum AIC value. Any model yielding an AIC value within two units of the minimum AIC value might also be an appropriate candidate.[10]

All statistical analyses were conducted using Stata®, version 15. The significance level was established at 5%.

Study 1: Association between long-term exposure to ambient air, depression and anxiety

Particulate matter smaller than 10 μm (PM_{10}) accounts for much of the impact of air pollution on health.[11,12] Some studies have assessed the association between long-term exposure to PM_{10} and common mental disorders (CMD), namely depressive and anxiety disorders, but evidence is inconsistent.[13-18] To estimate the association between long-term exposure to PM_{10} and the frequency of probable diagnosis of CMD, a population-based, nationally representative cross-sectional study was conducted, in mainland Portugal.

Long-term exposure to PM_{10} was estimated through one-year average concentrations of PM_{10}, calculated with data from the Portuguese Environment Agency's air quality monitoring stations, and attributed to each individual considering their seven-digit postal codes of residence. The probable diagnosis of CMD was ascertained through the scores obtained in the 5-item Mental Health Inventory (MHI-5) [Appendix 2 – Fig. 2.1 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21435/15511)].[19-21] A score ≤ 52 in the MHI-5 represents a situation that implies proper clinical evaluation by a doctor (a "Probable diagnosis of CMD"), while a score > 52 represents a situation that does not imply proper clinical evaluation. The MHI-5 scores and the independent variables' data were obtained from a restricted sample of the participants of the first Portuguese National Health Examination Survey (INSEF).[22] The study participants were the INSEF participants from mainland Portugal who consented on data linkage, had their seven-digit postal codes of residence available in the database, were living within a 30-km radius from a background air quality monitoring station (with available data on PM_{10} atmospheric concentration), like previously detailed,[23-26] and who had answered all the five items of the MHI-5. Data on area-level socioeconomic deprivation, the Portuguese version of the European Deprivation Index, was available online.[27] Individually allocated one-year average temperatures were obtained through a similar methodology to the one applied to estimate exposure to PM_{10}, making use of one-year average temperatures collected from the National Oceanic and Atmospheric Administration data.[23,24,26] Data on area-level walkability was obtained through the weighted sum of residential density, street connectivity, and a land use mix index, for all the parishes of mainland Portugal, and is available at request, in terciles of increasing walkability.

We performed single-level multivariable analyses since, even if we used individual and aggregated variables (at parish level) in our models, the assumptions for carrying out a multilevel analysis were not met [some parishes had just one individual) (models' specifications in Appendix 2 – Table 2.1 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21435/15511)]. All estimates were weighted to account for different selection probabilities resulting from the complex sampling design, and to match the population distribution in terms of geographic region, age group and sex, unless specifically stated.

Study 2: Association between immigration status and urgent care use in a paediatric population

Foreign residents have been increasing in Portugal, in the past years.[28] One of the biggest challenges immigrants face in the host countries is to obtain access to healthcare services.[29] The Portuguese National Health Service offers universal and free healthcare services for children up to 18 years old, irrespective of their immigration status.[30] Several studies have already reported the increased urgent care use by migrants, compared to non-migrants,[31-33] but evidence is inconsistent,[31,34-38] and differences exist according to migrants' characteristics and to countries' different healthcare systems.[31,39] To estimate the association between being an immigrant and the urgent care use, in the paediatric population living in Amadora, a population-based, non-representative cross-sectional study was conducted there, in the most densely populated Portuguese municipality, and the second with the highest density of foreign residents.[30]

Data was obtained from the participants of the first wave of the CRIAS (Health Trajectories of Immigrant Children in Amadora) cohort, implemented in Portugal from June 2019 to March 2020. The CRIAS targeted children born in 2015, aged four or five years old, who had records of attending at least one of the primary healthcare centres of Amadora in the two years before the assessment time, also targeting their parents. Self-reported data on the families' demographic and socioeconomic characteristics, migration history, and on the children's lifestyle and health was collected and integrated with data on the children's healthcare

use, obtained through electronic health records.[30] From the CRIAS participants, those with missing data on the variables of immigration status or urgent care use were excluded from the present study.

Immigration status was categorized as "immigrant" (born to non-native parents, even if in Portugal) and "non-immigrant" (born in Portugal, to native parents). Urgent care use was categorized as "yes" or "no" according to the children having, or not, at least one visit to the urgent care service of the Hospital Professor Doutor Fernando Fonseca, in 2019.

The AIC values were obtained for all the fitted models [models' specifications in Appendix 3 – Table 3.1 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21435/15512)].

Ethical considerations

In this study, no ethical or legal issues of confidentiality were raised, since all the data came from anonymized databases.

The INSEF had its scientific protocol approved by the Ethics Committee for Health of the National Health Institute Doutor Ricardo Jorge (INSA) (Internal Note No. 7/2011), by the National Data Protection Commission (Authorization No. 199/2001), and by the Ethics Commissions of the Northern Portugal Regional Health Administration (Authorization No. 91/2014), the Central Portugal Regional Health Administration (Authorization No. 44/2014), the Lisbon and Tagus Valley Regional Health Administration (Authorization No. 17/2014), the Algarve Regional Health Administration (Authorization No. 2742 of 04/03/2015), and the Health Service of the Autonomous Region of Madeira (Authorization No. 32/2014). All the participants were asked to sign a declaration of informed consent to participate in INSEF, which consisted of accepting to respond to a general health interview, perform a physical examination and donate a blood sample for testing.

The protocol of this study was also approved by the INSA Ethics Committee and by the Institutional Review board of INSEF (INSA-IM60_05/February 2023).

The CRIAS cohort involves human participants and was approved by the Health Ethics Committee of the Lisbon and Tagus Valley Regional Health Administration of, Portugal (001/CES/INV/2019). The parents signed a written information and consent form to participate in the study, including permission to assess data from the child's health centre and hospital medical records.

RESULTS

Study 1

A total of 2398 individuals were included in the study, following the application of the inclusion and exclusion criteria [Appendix 2 – Fig. 2.2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21435/15511)]. Included and excluded individuals were similar regarding most of the analysed characteristics. Differences between these two groups were only found regarding the individual allocated one-year average temperature, and the area-level walkability terciles [Appendix 2 – Table 2.2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21435/15511)].

The study population had higher percentages of female participants (52.6%, 95% CI: 50.2 - 55.1) and individuals belonging to the age groups 35 - 49 years (34.1%, 95% CI: 32.0 - 36.4) and 50 - 64 years (31.5%, 95% CI: 29.4 - 33.7) [Appendix 2 – Table 2.3 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21435/15511)]. The median [interquartile range (IQR)] individual allocated one-year average PM_{10} concentration was 18.6 (15.3 - 19.3) µg/m³ [Appendix 2 – Table 2.4 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21435/15511)]. A probable diagnosis of DMC was found in 22.7% (95% CI: 20.0 - 25.6) of the study population [Appendix 2 – Table 2.3 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21435/15511)].

The adjusted logistic regression model obtained an OR (95% CI) = 1.015 (0.970 - 1.063), and the robust Poisson model a PR (95% CI) = 1.012 (0.979 - 1.045). The adjusted log-binomial regression model did not converge. Adjusted OR overestimated the adjusted PR obtained through the robust Poisson model by 0.003 and presented wider 95% CI (95% CI range: 0.093 *vs* 0.066, respectively) and a higher standard-error (0.022 *vs* 0.016, respectively) (Table 1).

No statistically significant association between long-term exposure to PM_{10} and the frequency of probable CMD diagnosis was observed in any of the models after adjustment.

Study 2

From the CRIAS participants, 410 children were included in the study, since 10 were excluded due to missing data in the variable urgent care use.

Most of the children were male (50.7%), being most of their caregivers (or questionnaire respondents) female (87.6%) with a median (IQR) age of 34 (18 - 75) years old [Appendix 3 – Table 3.2 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21435/15512)]. Among the children in study, 50.5% were immigrants [Appendix 3 – Table 3.2 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21435/15512)]. Approximately 48.0% of all children used urgent care services (58.4% of them being immigrants) [Appendix 3 – Tables 3.2 and 3.3 (Appendix 3:

Table 1 – Characteristics of logistic, log-binomial and robust Poisson regression models fitted for the estimation of measures of association between the exposure to particulate matter with an aerodynamic diameter equal than or lower to 10 micrometres and the frequency of common mental disorders

	Logistic	Log-binomial	Robust Poisson
Number of individuals included in the adjusted models	2210	2210	2210
Adjusted OR/PR* (95% CI)	1.015 (0.970 - 1.063)	Did not converge	1.012 (0.979 - 1.045)
95% CI range	0.093	Did not converge	0.066
Standard-error of the adjusted estimates	0.022	Did not converge	0.016

OR: odds ratio; PR: prevalence ratio; 95% CI: 95% confidence interval; PM10: particulate matter with an aerodynamic diameter less than or equal to 10 micrometres.
* Adjusted for sex, age groups, education level, employment status, professional occupation, area-level socioeconomic deprivation terciles, individual allocated one-year average temperature, area-level walkability terciles, degree of urbanization (OR for logistic and log-binomial regression models, PR for robust Poisson regression model).

https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21435/15512)].

The adjusted logistic regression model obtained an OR (95% CI) = 1.584 (1.026 - 2.446), the adjusted log-binomial regression model a PR (95% CI) = 1.217 (0.978 - 1.515), and the robust Poisson regression model a PR (95% CI) = 1.130 (1.013 - 1.261). The adjusted OR overestimated the adjusted PR obtained through the log-binomial and robust Poisson regression models by 0.367 and 0.454, respectively, presented wider 95% CI (95% CI range: 1.420 *vs* 0.537 and 0.248, respectively) and higher standard-errors (0.351 *vs* 0.136 and 0.063, respectively). However, the AIC value was lower for the logistic regression model than for the log-binomial and robust Poisson models (1.345 *vs* 1.350 and 1.656, respectively) (Table 2).

Only logistic and robust Poisson regression models showed statistically significant associations between immigration status and urgent care service use, in the adjusted models. The log-binomial model, however, did not yield statistically significant associations.

DISCUSSION

This study, based on two distinct real-life epidemiological examples involving outcomes with different prevalence (22.7% in Study 1, and 48.0% in Study 2), contributed to the knowledge about the estimation of measures of association, in cross-sectional studies with frequent outcomes, in different settings. Study 1 assessed a nationally representative sample of 2398 individuals, whereas Study 2 focused on a local sample of 410 individuals. Study 1 estimated the association between a continuous exposure and a binary outcome, adjusting for nine independent variables (including one continuous variable); and Study 2 estimated the association between a binary exposure and a binary outcome, adjusting for three covariates.

In Study 1, the log-binomial regression model did not converge. This likely happened due to the inclusion of two continuous independent variables in the model (one variable which was a potential confounder and the exposure in study).[8,40,41] When in the presence of quantitative variables, the maximum likelihood estimate can lie on the boundary of the parameter space which can lead to model non-convergence as the instantaneous slope of the likelihood may not reach zero at this boundary.[6] This inability to find a solution that fits the model to the data supports authors who advocate for the robust Poisson regression model as the

Table 2 – Characteristics of logistic, log-binomial, and robust Poisson regression models fitted for the estimation of measures of association between immigration status and urgent care use

	Logistic	Log-binomial	Robust Poisson
Number of individuals included in the adjusted models	389	389	389
Adjusted OR/PR* (95% CI)	**1.584 (1.026 - 2.446)**	1.217 (0.978 - 1.515)	**1.130 (1.013 - 1.261)**
95% CI range	**1.420**	0.537	**0.248**
AIC for the adjusted model	1.345	1.350	1.656
Standard-error of the adjusted estimate	0.351	0.136	0.063

OR: odds ratio; PR: prevalence ratio; 95% CI: 95% confidence interval; AIC: Akaike information criteria.
* Adjusted for caregiver's age, education level and professional occupation (OR for logistic and log-binomial regression models, PR for robust Poisson regression model). Results in bold are those statistically significant.

preferred choice to logistic models, when addressing frequent outcomes in cross-sectional studies, instead of log-binomial models.[40,41]

As, in Study 1, the obtained point estimate for the measures of association was higher than 1, the OR overestimated the PR obtained through the robust Poisson regression model. The magnitude of the overestimation was 0.003 units (OR = 1.015 *vs* PR = 1.012). The precision of the OR was lower than the precision of the PR, which presented a narrower 95% CI, with the 95% CI range for the OR being 0.027 units higher than the obtained for the PR through the robust Poisson regression model (0.093 *vs* 0.066, respectively). Consistently, the standard-error was 0.006 units lower for the robust Poisson (robust Poisson: 0.016 *vs* logistic: 0.022, respectively).

In Study 2, the obtained measures of association were also higher than 1, with the consequent overestimation of PR by OR already reported in Study 1. The magnitude of the overestimation was higher when the OR was compared with the PR obtained through the robust Poisson model, than with the PR obtained through the log-binomial model (overestimations of 0.454 and 0.367 units, respectively). This happened because the robust Poisson model obtained a lower value for the PR than the log-binomial model (PR: 1.130 *vs* 1.217, respectively). The robust Poisson model also obtained the most precise estimate (the one with the lowest 95% CI range), followed by the log-binomial and, lastly, by the logistic regression model (95% CI ranges: 0.248, 0.537, and 1.420, respectively), as well as the lowest standard-error for the estimate. However, the AIC values were lower for the logistic regression model, followed by the log-binomial model, and, lastly, by the robust Poisson model, indicating that the logistic was the one better fitting to the data, which was counterintuitive. This might have been because the binomial distribution is ultimately more appropriate to module binary outcomes than the Poisson distribution, and because the mean and the variance of the outcome were different in this study (variance = 0.250, mean = 0.480), affecting the fit of the Poisson model, even if a robust estimator was being used.[7] This example illustrates why relying solely on the AIC value for the selection of the most appropriate statistical model is not adequate.

We also observed that, in Study 2, the log-binomial model could not obtain a statistically significant association, while the logistic and robust Poisson models did. This might have been due to the conjunction of the estimation of a not-so-inflated estimate through the log-binomial model, as through the logistic model, with wider 95% CI for the log-binomial than for the robust Poisson model.

Moreover, in Study 2, the magnitude of the overestimation exceeded the overestimation observed in Study 1 (Study 2: 0.454 and 0.367 units, Study 1: 0.003 units), which was also verified in terms of the 95% CI range. This discrepancy was likely due to the higher prevalence of the outcome in Study 2 compared to Study 1 and illustrates that higher outcome prevalence represents larger OR inflations.[1,3]

In both Study 1 and Study 2, the robust Poisson model exhibited greater precision (narrower 95% CI and lower 95% CI ranges) than log-binomial and logistic regression models. This characteristic is particularly relevant when a study aims to estimate unbiased measures of association (where the expected value is identical to the population parameter being estimated), but not so when the aim is solely to comprehend the general trend or direction of it.[2]

In both examples, we observed that OR obtained through logistic regression models provide biased estimates of PR, in the presence of frequent binary outcomes, and also wider confidence intervals, magnifying the probability of a type II error. Additionally, we verified that the extension of the bias became more pronounced as the prevalence of the outcome increased, consistent with findings from prior studies.[4,6,8,40-44] The challenges associated with estimating measures of association through logistic regression models when there are frequent outcomes in study are not limited to cross-sectional designs. Longitudinal studies and randomized clinical trials might encounter similar estimation issues, and also need to be investigated.[5]

This study reinforces the viability of alternative statistical models and reopens a discussion that has yet to reach a definitive solution. These alternative models are readily accessible within commonly used statistical software packages like SPSS®, Stata® and R Studio®. Nonetheless, they have potential disadvantages that could lead researchers to discard them and stick to the logistic regression models. A disadvantage of the log–binomial regression is that the model might not converge, like in Study 1.[45] Despite robust Poisson regression not showing convergence issues, this model, like the log-binomial, may yield individual predicted probabilities above 1. The robust Poisson regression is indeed a suitable method to obtain valid, unbiased estimates, but not to predict individual probabilities (as in diagnostic or prognostic studies).[3,7,9] Moreover, both models lack reciprocity, underscoring the importance of being mindful of the reference category selected.[4] While other options exist, the log-binomial and the robust Poisson regression models are relatively straightforward to apply, easy to interpret, and offer the ability to control for confounding.[7,9]

Given the curriculum requirements that often compel medical doctors and other health professionals to publish, recognizing the time constraints clinicians face to master research methodologies and statistics, and considering the need for consistency in research, establishing a standardized approach for the selection of the most suitable model to

employ in a study would be useful. Several processes have been proposed. One of them involves constructing a contingency table between the exposure and the outcome and comparing the OR and RR/PR obtained through epidemiological formulas of calculation. Relevant disparities between the values would suggest the employment of a model that estimates RR/PR instead of OR (such as the log-binomial and robust Poisson models).[44] However, this methodology is too simplistic, can only be applied in the presence of a categorical exposure, and does not help to choose between log-binomial and robust Poisson models. Another proposal was made by a group of authors who created a flowchart to support researchers, but its interpretation could be complex as it requires some methodological knowledge, and it was not agreed upon consensus.[46]

Strengths and limitations

This study has several strengths. First, it contributed to reigniting the discussion around the validity of the OR to infer RR/PR in the context of frequent binary outcomes, in cross-sectional studies. Second, it used real-life datasets applied to different settings – in terms of topics investigated (the health impact of air pollution, and the access to healthcare services), types of exposure assessed (continuous, and categorical), types of independent variables included (categorical and continuous, or just categorical), and outcome prevalence (22.7%, and 48.0%) – allowing for a comprehensive discussion, pertinent to several different scientific fields and aims. Third, the example studies were conducted according to robust and previously published methodological approaches, allowing us to diminish biases and confounding, and to add findings relevant to the scientific literature.

Some limitations should also be noted. First, a simulation study to calculate the exact relative risk was not performed. Second, the assessed associations did not have substantial effect magnitudes, making the estimates' values closer to one and, across models, to each other (due to reduced variability). Third, logistic regression models were compared against log-binomial and robust Poisson regression models, and not all the possible models. This choice was made not only based on the appropriateness of these models to the studies developed, but also on their popularity and user-friendliness. However, we acknowledge that each model has its own assumptions and limitations

CONCLUSION

Even if both the OR and the RR/PR might be appropriate to understand the direction of a certain measure of association, in a study whose aim is to obtain unbiased estimates, using the OR might lead to misinterpretations. The OR should not be interpreted as RR/PR in cross-sectional studies whose outcomes are not rare. Robust Poisson models could be a viable alternative to logistic regression models, avoiding the non-convergence of log-binomial models.

There is not a standardized approach to the selection process of the most suitable model. The type of outcome variable, the aim of the study (the need or not of unbiased estimates), its intent, the fulfilment of the assumptions for causal inference, and the fulfilment of the assumptions of the available statistical models should guide the decision. Several statistical measures could be used to support the models' selection, including models' estimates, standard-errors, 95% CI, and AIC values. This study emphasizes that no single value should serve as the sole criterion to determine the most appropriate model to employ.

More studies could be conducted to compare other alternatives to logistic regression models (modified Cox, quasi-Poisson, negative binomial, and probit models), not only within cross-sectional, but also in longitudinal studies and clinical trials, provided these studies aim to obtain unbiased estimates. Simulation studies could be useful to fix relative risks. A standard approach to the estimation of measures of association involving frequent binary outcomes would be helpful to guide researchers in the process.

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AUTHOR CONTIBUTIONS

LPG: Conceptualization, methodology, software, formal analysis and investigation, writing – original draft preparation.

CM: Investigation, writing – review & editing.

MROM: Conceptualization, resources, validation, writing – review & editing, supervision.

All authors approved the final version to be published.

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.

DATA AVAILABILITY

The datasets analysed during the current study are not publicly available due to ethical restrictions. Data is available from the authors upon reasonable request.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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Assessing the Burden of Atopic Dermatitis in Portugal through Patient-Centered Experiences

Avaliação da Carga da Doença Atribuída à Dermatite Atópica em Portugal através de Experiências Centradas no Doente

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ABSTRACT

Introduction: Adult patients and caregivers of children with atopic dermatitis experience high physical, mental, and financial burden in Portugal. We outline the experience of atopic dermatitis management and how the current medical care model impacts patient-centered concerns such as financial burden, quality of life, disease burden, and treatment satisfaction.

Methods: We conducted a survey of 419 Portuguese adults and caregivers of children to capture the experience of managing atopic dermatitis in Portugal.

Results: Respondents reported average satisfaction with treatment, with a mean satisfaction rating of 3.15/5.00 (SD = 0.77). Adults reported slightly better control of atopic dermatitis symptoms (mean = 56.6) than pediatric patients (mean = 55.9, caregiver reported). Nearly 34% of adults and 39% of caregivers of children and adolescents indicated that their healthcare providers asked about their priorities at the last medical visit. Additionally, only 40% of adult patients and 32% of caregivers reported that patient training was offered to them. Respondents seeing dermatologists reported higher satisfaction than those seeing other healthcare providers (p = 0.01) but there were no differences in long-term control of symptoms by provider type (p = 0.85) when controlling for severity. Portuguese adult patients scored 0.86/1.00 on the EQ-5D (where 0 = death and 1 = perfect health). Financial concern was high as nearly 80% of patients and caregivers reported using savings, borrowing money, and/or reducing spending to cover atopic dermatitis-related costs.

Conclusion: Portuguese patients with atopic dermatitis and caregivers experience financial burden, lower health-related quality of life, higher disease burden, and treatment satisfaction issues with their current medical care. These factors often deteriorate as the disease's severity increases. Providers, researchers and policymakers should focus on better addressing patient-centered concerns for individuals suffering from atopic dermatitis to improve care and health outcomes.

Keywords: Cost of Illness; Decision Making, Shared; Dermatitis, Atopic/epidemiology; Dermatitis, Atopic/therapy; Patient Education; Portugal; Quality of Life

RESUMO

Introdução: Em Portugal, os doentes adultos e os cuidadores de crianças com dermatite atópica encontram-se sobrecarregados com elevadas responsabilidades a nível físico, mental e financeiro. Neste artigo, descreve-se a experiência da gestão da dermatite atópica e o impacto que o atual modelo de cuidados médicos representa a nível dos encargos financeiros, da qualidade de vida do doente, do peso da doença e da satisfação com o tratamento.

Métodos: Realizou-se um inquérito a 419 adultos portugueses e a cuidadores de crianças para conhecer a experiência de gestão da dermatite atópica em Portugal.

Resultados: Os inquiridos referiram uma satisfação média com o tratamento, com um índice de satisfação médio de 3,15/5,00 (DP = 0,77). Os adultos referiram um controlo ligeiramente melhor dos sintomas da dermatite atópica (média = 56,6) do que os doentes pediátricos (média = 55,9, relatado pelo prestador de cuidados). Cerca de 34% dos adultos e de 39% dos prestadores de cuidados de crianças e adolescentes com dermatite atópica indicaram terem sido questionados sobre as suas prioridades na última consulta médica. Além disso, apenas 40% dos doentes adultos e 32% dos prestadores de cuidados referiram que foi oferecida formação aos doentes. Os inquiridos que consultaram dermatologistas relataram maior satisfação do que os que consultaram outros prestadores de cuidados de saúde (p = 0,01), mas não houve diferenças no controlo a longo prazo dos sintomas por tipo de prestador (p = 0,85) ao controlar a gravidade. Os doentes adultos portugueses obtiveram uma pontuação de 0,86/1,00 no EQ-5D (em que 0 = morte e 1 = saúde perfeita). A preocupação financeira foi elevada, uma vez que quase 80% dos doentes e prestadores de cuidados referiram recorrer a poupanças, pedir dinheiro emprestado e/ou reduzir as despesas para cobrir os custos relacionados com a dermatite atópica.

Conclusão: Os doentes portugueses com dermatite atópica e os seus cuidadores identificam encargos financeiros, menor qualidade de vida relacionada com a saúde, mais despesas com a doença e problemas de satisfação com o tratamento e com os seus cuidados médicos atuais. Estes fatores tornam-se com frequência mais significativos à medida que a gravidade da dermatite atópica aumenta. Os prestadores de cuidados de saúde, os investigadores e os decisores políticos devem concentrar-se em abordar melhor as preocupações centradas no doente para os indivíduos que sofrem de dermatite atópica, a fim de melhorar os cuidados e os resultados em termos de saúde.

Palavras-chave: Custo da Doença; Dermatite Atópica/epidemiologia; Dermatite Atópica/terapia; Educação do Doente; Portugal; Qualidade de Vida; Tomada de Decisão Partilhada

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease[1] that is associated with a high physical and mental health burden in patients and caregivers.[2,3] Globally, patients with AD and their caregivers report substantial negative financial impact, lower satisfaction with treatment (especially for those with more severe disease), and lack of

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adequate symptom control.[4] Moreover, individuals with AD may have difficulty accessing specialized care that incorporates their values, preferences, and perspectives.

In Portugal, the estimated prevalence of AD is approximately 0.6% to 3.5%.[3,5,6] Current research suggests that nearly 30% of all individuals with AD in Portugal do not have frequent medical visits and 37% report that their AD causes them to have some degree of disability whereas those who have more severe AD suffer from a greater impact on quality of life.[3] Furthermore, health, psychosocial, and financial outcomes worsen with disease severity.[6] There is a lack of data on the patient and caregiver experience in Portugal on a larger set of patient-centered care factors such as shared decision-making, patient education, treatment satisfaction, access to specialists, and financial impact.

The primary aim of this study is to examine patient-centered experiences among patients and caregivers in Portugal, specifically those linked to health-related quality of life, long-term control of symptoms, shared decision-making, and patient education, satisfaction with treatments, financial impact and psychosocial burden. The results reveal opportunities for innovative approaches to improving the experience of patients and their families.

METHODS

We developed and conducted an anonymous electronic survey with up to 53-items for AD patients and caregivers between March 2023 and July 2023. This study was part of a larger global survey of adults and caregivers of children in eight countries that examined health-related quality of life, long-term control of symptoms, satisfaction with treatments, the financial burden, and the prevalence of patient-centered care.[7] A committee of eleven AD advocacy organizations representing eight countries selected the survey questions covering seven domains of AD management:

1. Treatment satisfaction;
2. Access to medical specialists;
3. Shared decision-making and patient education;
4. Long-term control;
5. Burden of disease;
6. Quality of life;
7. Financial impact.

The survey used the AD Control Tool[8] which is a validated six-question self-assessment tool to measure long-term control of AD symptoms and the EQ-5D[9] to measure quality of life and burden of disease. We adapted treatment satisfaction questions from instruments validated for other diseases (i.e., PsoSat Patient Questionnaire). Where no reasonable instrument was available (i.e., access to medical specialists, shared decision-making and patient education, and financial impact), we developed questions *de novo*. This research was reviewed and approved by Advarra Institutional Review Board (Pro00055632). Respondents were initially asked demographic questions about their age, the child's age (if a caregiver), sex, country of residence and AD severity.

The survey was offered in five languages and distributed by social media, newsletters, and publications of the participating patient organizations. All respondents provided informed consent. Statistical analyses were conducted using R 4.2 (R Core Team, Vienna, Austria). At the end of the survey, participants had the option of entering a drawing for a gift card worth US $100. This paper reports the data provided by Portuguese participants.

RESULTS

Participants

A total of 419 Portuguese respondents completed the survey. Of those, 45% (n = 189) were caregivers to pediatric patients and 55% (n = 230) were adult patients. Respondents were predominantly female: 96% of patients (n = 182) and 85% of caregivers (n = 195). The mean age was 36 years for adult patients and eight years for children (caregiver reported) (Table 1).

Treatment Satisfaction

Overall, respondents reported average satisfaction with treatment, with a mean satisfaction rating of 3.1/5.0 (SD = 0.77) (1 = least satisfied to 5 = most satisfied) as measured by the PsoSat Patient Questionnaire adapted for AD. However, satisfaction was highly dependent upon symptom severity and respondents with the highest AD severity reported the lowest treatment satisfaction at 2.08/5.00 (SD = 1.30) ($p < 0.001$) compared to all less severe groups combined (Fig. 1). Satisfaction was significantly higher when the provider was a specialist ($p = 0.01$), which is driven largely by lower satisfaction with family physicians/ than dermatologists ($p = 0.04$).

Shared decision-making and patient education

Patient-centered medical care was evaluated with two measures: the presence of shared decision-making during the medical appointment and patient training for AD management after the visit that was offered by the provider. Nearly 34% of adults and 39% of caregivers indicated that their providers asked about their priorities at the last medical visit. Additionally, 40% of adult patients and 32% of caregivers reported that patient training was offered to them. By contrast, a minority of respondents (adults: 6%, caregivers: 2%) said their healthcare provider suggested they attend a formal AD training program.

Table 1 – Respondent demographics and survey responses

	Caregiver (n = 189)	Adult (n = 230)	All patients (n = 419)	*p*-value
Respondent age				< 0.001
n-Missing	6	5	11	
Mean (SD)	40 (6.7)	36 (10.4)	38 (9.2)	
Range	20 - 63	18 - 69	18 - 69	
Respondent sex	**n (%)**	**n (%)**	**n (%)**	**< 0.001**
Male	7 (3.7%)	35 (15.2%)	42 (10.0%)	
Female	182 (96.3%)	195 (84.8%)	377 (90.0%)	
Patient age				**n/a**
n-Missing	42		47	
Mean (SD)	8.4 (5.5)		25.1 (16.2)	
Range	1 - 25		1 - 69	
Patient sex	n (%)		n (%)	n/a
Male	93 (49.2%)		128 (30.5%)	
Female	96 (50.8%)		291 (69.5%)	
Mean treatment satisfaction 0 - 5 (SD)	3.1 (0.50)	3.2 (0.96)	3.2 (0.77)	0.026
Primary provider	**n (%)**	**n (%)**	**n (%)**	**< 0.001**
Dermatologist	102 (54.5%)	168 (74.0%)	270 (65.2%)	
Pediatrician	51 (27.3%)	0 (0.0%)	51 (12.3%)	
Primary care physician / Family physician	28 (15.0%)	54 (23.8%)	82 (19.8%)	
Allergist	0 (0.0%)	1 (0.4%)	1 (0.2%)	
Dermatology nurse	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Nurse practitioner	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Other	6 (3.2%)	4 (1.8%)	10 (2.4%)	
Shared decision-making	**n (%)**	**n (%)**	**n (%)**	
Asked about priorities	74 (38.9%)	78 (34.1%)	152 (36.3%)	0.43
If asked, priorities included in treatment plan	90 (47.8%)	96 (41.6%)	186 (44.4%)	0.66
Offered training/education	53 (31.7%)	85 (40.1%)	138 (36.4%)	0.093
Recommended > 6 hours training	2 (1.2%)	6 (2.8%)	8 (2.1%)	0.272
Recommended external training	3 (1.8%)	12 (5.7%)	15 (4.0%)	0.055
Mean long-term control				
0 - 100 (SD) ADCT (Adequate control > 70.8)	57.3 (27.6)	56.6 (24.5)	56.9 (25.8)	0.82
Mean burden of disease				
EQ-5D Utility 0 (worst possible) - 1 (best possible) (SD)	n/a	0.86 (0.15)	n/a	n/a
Mean quality of life				
EQ-VAS 0 (worst possible) -100 (best possible) (SD)	n/a	72.6 (17.8)	n/a	
Mean financial worry				
1 = none, 5 = extremely (SD)	2.8 (1.0)	2.6 (0.93)	2.7 (0.99)	< 0.001
Funding AD related costs	**n (%)**	**n (%)**	**n (%)**	
Used savings	49 (26%)	61 (27%)	110 (26%)	0.89
Borrowed money	7 (4%)	17 (7%)	24 (6%)	0.11
Spent less on essentials	31 (16%)	33 (14%)	64 (15%)	0.56
Spent less on nonessentials	84 (44%)	108 (47%)	192 (46%)	0.61
No impact	32 (17%)	54 (24%)	86 (21%)	0.10

Long-term control of symptoms

Long-term control was measured using the AD Control Tool where a score greater than 70.8 indicates adequate control. Respondents with moderate to severe AD scored far below adequate control. Overall, adults reported slightly better control of AD symptoms (mean = 56.6) than pediatric patients (mean = 55.9, caregiver reported). Additionally, and even though long-term control of AD symptoms was negatively associated with severity (Fig. 2), there was no significant association between long-term control of AD symptoms and provider type.

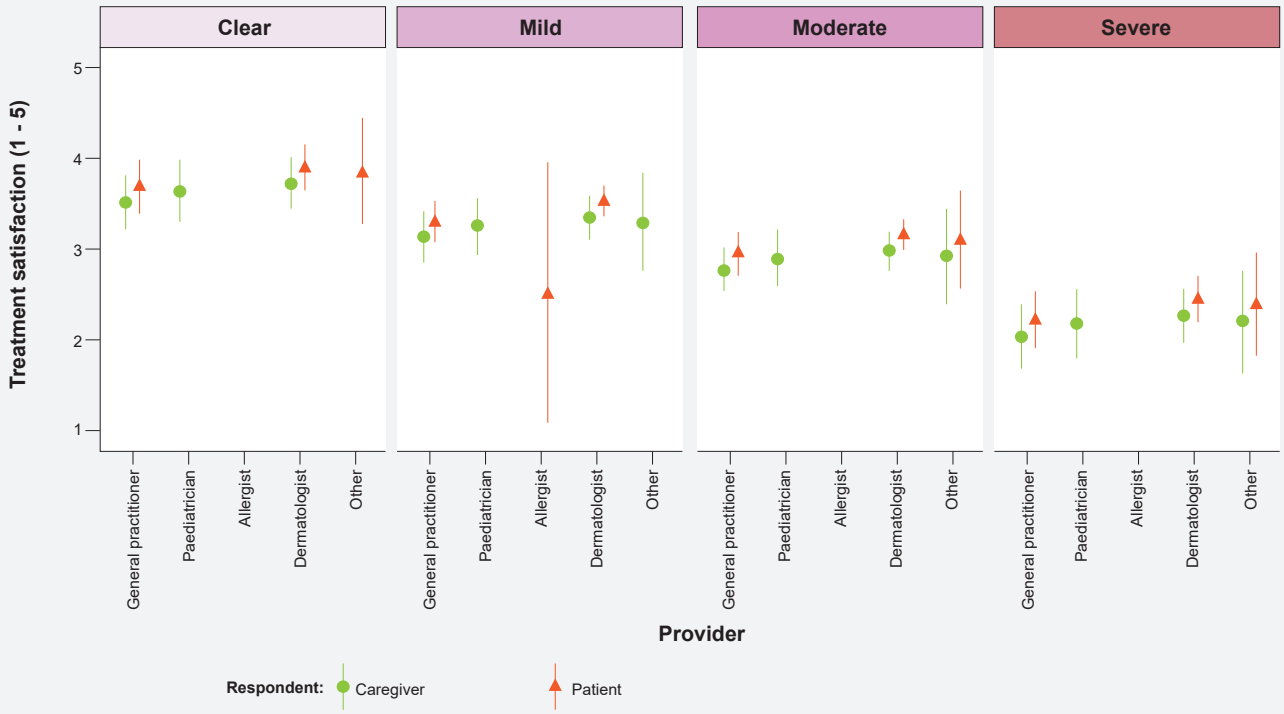

Figure 1 – Predicted mean satisfaction with AD treatments (1 = least satisfied to 5 = most satisfied) stratified by respondent type, provider type, and severity, adjusted for patient age as reported by patients and caregivers in Portugal. Treatment satisfaction score is shown separately for caregiver reported (circles) and patient reported (triangles). Whiskers represent 95% confidence intervals.

Type of specialist care

Respondents were most likely to consult with a dermatologist for AD care (74% of adults, 55% of caregivers) or a family physician (24% of adults, 15% of caregivers). Less than 0.5% of Portuguese AD patients consulted with an allergist. Respondents seeing dermatologists reported higher satisfaction than those seeing other providers (p = 0.01) but no difference in long-term control of symptoms (p = 0.85) when controlling for severity.

Burden of disease and quality of life

Portuguese adult patients scored 0.86/1.00 on the EQ-5D which measures burden of disease where 0 = death to 1 = perfect health. This was higher compared to normal values for Portuguese adults (0.76/1.00).[10] By translation, this score indicates that Portuguese adult patients are willing to trade off 14% of their remaining lifespan to be restored to perfect health. This indicates that AD still poses a burden to those affected with the disease. Data are not reported for this subpopulation since the EQ-5D does not have a version available for caregivers. The average health-related quality of life score identified by the EQ-VAS in adult Portuguese patients was 73/100.

Financial impact

Patients and caregivers in Portugal reported significant financial impact due to AD. Nearly 80% of patients and caregivers reported using savings, borrowing money, and/or reducing spending to cover AD-related costs. In particular, almost 46% of Portuguese respondents report spending less on non-essentials to pay for AD-related expenses (Table 1). Financial worry in Portugal was strongly positively correlated with AD severity (Spearman's ρ = 0.26, p < 0.001).

DISCUSSION

Challenges associated with AD management in Portugal are common especially for patient-centered experiences such as treatment satisfaction, shared decision-making, financial impact, and long-term symptom control. Overall, while Portuguese patients are moderately satisfied with their AD treatment, those with severe AD (10.3%) had the lowest treatment satisfaction. Moreover, higher satisfaction was associated with care provided by dermatologists. Even though there are only 4.3 dermatologists per 100 000 individuals in Portugal, the majority of patients in this study had medical appointments with dermatologists (65.2%). Increasing access to dermatologists, more education efforts, and access to innovative treatments for those with more

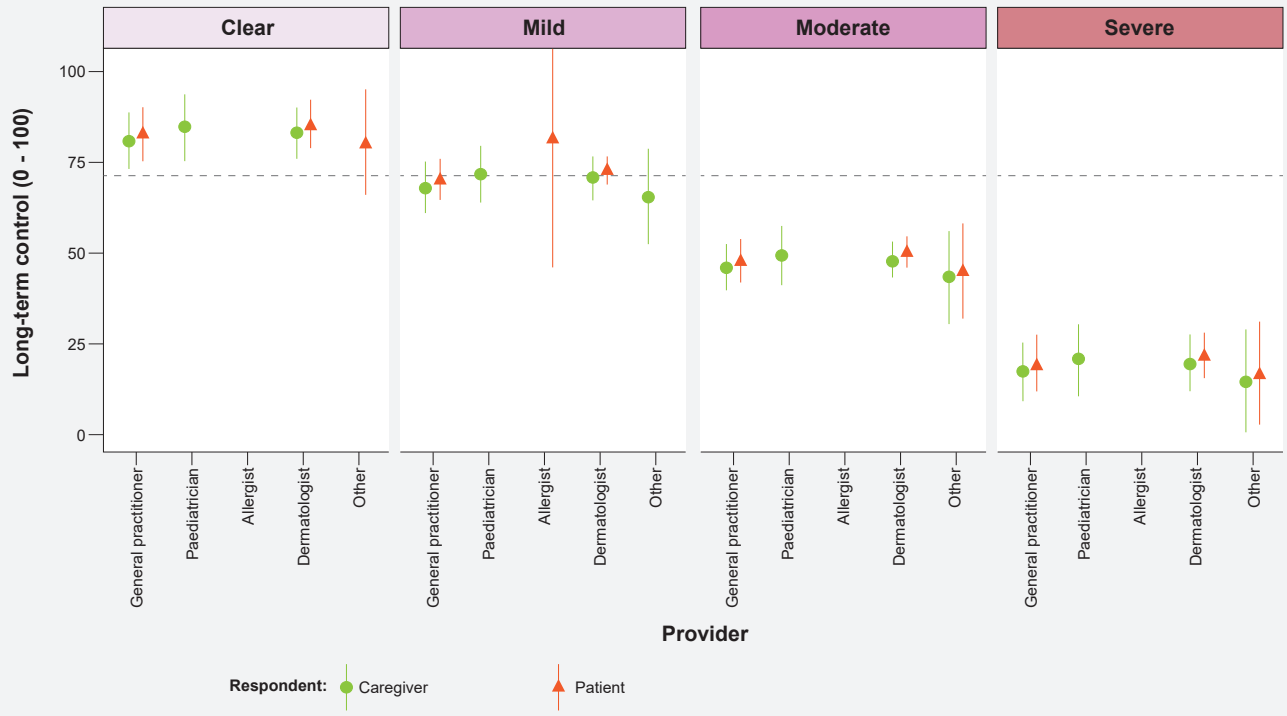

Figure 2 – Predicted mean long-term control (0 - 100) using the rescaled AD Control Tool stratified by respondent type, provider type, and severity, adjusted for patient age. Scores below 70.8 indicate poor control. Long-term control score is shown separately for caregiver reported (circles) and patient reported (triangles) results. Whiskers represent 95% confidence intervals.

severe AD may help improve treatment satisfaction rates and improve overall AD management. Solutions to address the lack of access to providers could include increasing education and training efforts (e.g., using evidence-based clinical practice guidelines on AD[11]) for family physicians in order to add them into the pool of providers that may successfully treat AD.

Shared decision-making is not a common practice in Portugal (66% of adults and 61% of caregivers not being asked about their priorities during the most recent medical visit). Increased efforts to train providers to engage in shared decision-making with patients and caregivers should incorporate patient-centered care practices that encourage participation. This may help increase the number of patients engaging in their own care, increase adherence to treatment, and improve health outcomes. Similarly, most patients and caregivers indicated that they had not been offered any training to address AD. A minority of respondents (6% of adults and 2% of caregivers) said their provider suggested that they attend an AD training program. However, current practice often recommends educational programs for more challenging cases of AD. New initiatives to increase the number of training programs such as eczema schools and similar educational programs that are already being organized, will allow patients and caregivers the opportunity to be more educated on their condition and manage symptoms more effectively.

Considerable financial impact was seen in adult patients and caregivers resulting from AD. An overwhelming majority of adult patients and caregivers (80%) reported that they used savings, borrowed money, or reduced their spending to cover AD-related costs. Increasing financial concern was significantly associated with the severity of AD. As a result, this financial burden may significantly affect the overall financial health of patients or caregivers. This underscores the importance of quickly and effectively providing access to effective and safe treatments, and optimally managing symptoms early in order to prevent disease progression and significant unnecessary long-term spending by patients or caregivers.

In Portugal, access to medical professionals and pharmaceuticals occurs predominantly through the national health service (SNS) which provides universal coverage for its citizens. Patients can access healthcare services, including consultations with dermatologists or other specialists through public hospitals, health centers, or clinics affiliated with the SNS. Pharmaceutical access is facilitated through pharmacies where prescribed medications are often subsidized or partially covered by the SNS depending on the patient's eligibility and the specific medication. While

private healthcare options also exist in Portugal, the majority of the population relies on the national health service for their healthcare needs. Health policy decisions that help lower AD-related costs which may not be covered by healthcare systems or identifying novel payment mechanisms for individuals with moderate to severe AD could help alter the financial burden patients and caregivers face. Larger policy decisions that reduce healthcare costs to the patient should be considered within the healthcare system.

Portuguese respondents with moderate or severe AD (53%) did not have adequate control of symptoms compared to those with clear or mild AD (47%). This underscores the need to focus on and address the root cause of uncontrolled symptoms for those with more severe AD. Health-related quality of life for adults with AD (73/100) was lower compared to average adult scores for the whole country (75/100) which suggests an area of opportunity for improvement. Additional research into lifespan trade-off data may help identify best practices or how to better manage AD in the population.

The limitations of this study include recruitment only via online messaging through AD communities. As a result, participants were potentially more likely to be active in these communities and experiencing more impact from AD than others. Patients who take initiative to join these organizations may also be more informed about AD care in general. As this was a cross-sectional study, cause and effect relationships could not be evaluated. Lastly, *de novo* questions did not go through formal validity testing but were framed in simplistic language or yes/no answer choices. Future research should identify what treatments patients are taking and their association with patient-centered attributes such as symptom control and treatment satisfaction.

CONCLUSION

Our results demonstrate that Portuguese patients with AD and caregivers experience financial burden, lower health-related quality of life, higher disease burden, and treatment satisfaction issues. These factors often deteriorate as AD severity increases. Providers, researchers, and policies should focus on addressing patient-centered concerns for individuals suffering from AD in order to improve care and health outcomes. This includes more efforts to train clinicians and incorporate evidence-based clinical guidelines into practice, increasing awareness of eczema schools or educational programs for patients, approving safe and effective treatments, and developing policy decisions to reduce the cost of care. Future research should examine how adequate treatment or psychodermatological approaches could improve health outcomes[12] and how psychosocial factors impact AD.

AUTHOR CONTRIBUTIONS

MT, FM, JC: Study design, drafting, critical review and approval of the manuscript.

AS, KC: Study design, data analysis, drafting, critical review and approval 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

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AS has received consultant fees from Global Parents for Eczema Research.

JC has received contracts/grants from Sanofi, Eli Lilly, Leo Pharma, Pierre Fabre Eczema Foundation, Bayer, AbbVie; received honoraria as patient consultant in projects from Regeneron and Sanofi; received support for attending events from Sanofi, AbbVie and Pierre Fabre Eczema Foundation.

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ACTA MÉDICA PORTUGUESA
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Digital Cognitive-Behavioral Therapy for Insomnia in Cancer Survivors: Protocol for a Pragmatic Clinical Trial

Intervenção Digital para o Tratamento da Insónia em Sobreviventes de Cancro: Protocolo de um Ensaio Clínico Pragmático

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ABSTRACT

Introduction: Insomnia is one of the most prevalent, persistent, and distressing conditions associated with cancer, affecting almost half of all cancer survivors. Although cognitive-behavioral therapy for insomnia is well established as the gold-standard treatment for insomnia, its accessibility is very limited in routine care. We aim to examine the real-world effectiveness and acceptability of a digital cognitive-behavioral therapy for insomnia for cancer survivors with insomnia symptoms through a randomized controlled trial in Portugal.

Methods and Analysis: Our cancer trial will test the effects and acceptability of an accessible internet-delivered self-administered cognitive-behavioral therapy for insomnia digital intervention with clinician support, OncoSleep. This online program includes six interactive, personalized weekly sessions featuring evidence-based techniques targeting psychophysiological hyperarousal and maladaptive conditioning, tailored for cancer survivors. Research study procedures include screening for eligibility in the general population and randomization into one of two arms: the digital CBT-I program or a waitlist control group. Insomnia severity (primary outcome), fatigue, sleep diary outcomes, psychological distress, and quality of life (secondary outcomes) will be assessed at baseline and post-intervention.

Keywords: Cognitive Behavioral Therapy; Digital Health; Neoplasms/complications; Sleep Initiation and Maintenance Disorders

RESUMO

Introdução: A insónia é um dos sintomas associados ao cancro mais prevalentes, persistentes e debilitantes, afetando quase metade das pessoas sobreviventes. Embora a terapia cognitivo-comportamental para a insónia esteja bem estabelecida como o tratamento de referência para a insónia persistente, permanece praticamente inacessível na prática clínica. Pretendemos examinar os efeitos clínicos e a aceitabilidade de uma intervenção digital de terapia cognitivo-comportamental para a insónia para pessoas sobreviventes de cancro com sintomas de insónia através de um ensaio clínico em Portugal.

Métodos e Análise: O nosso ensaio oncológico vai testar os efeitos clínicos e aceitabilidade de uma intervenção digital de terapia cognitivo-comportamental para a insónia com apoio clínico oferecido *online*, o programa OncoSleep. O programa *online* inclui seis sessões semanais, interativas e personalizadas, que envolvem técnicas baseadas na evidência para reduzir a hiperativação psicofisiológica e condicionamentos maladaptativos, adaptadas à sobrevivência oncológica. O recrutamento será realizado na população geral e, após triagem, os participantes elegíveis serão aleatoriamente alocados a um de dois braços: o grupo de intervenção da terapia cognitivo-comportamental para a insónia ou um grupo em lista de espera. A gravidade da insónia (indicador primário), fadiga, indicadores de sono, sofrimento psicológico, e a qualidade de vida (indicadores secundários) serão avaliados pré- e pós-intervenção.

Palavras-chave: Distúrbios do Início e da Manutenção do Sono; Neoplasias/complicações; Saúde Digital; Terapia Cognitivo-Comportamental

INTRODUCTION

More people are surviving cancer than ever before, despite a surge in cancer incidence, particularly early-onset.[1-3] Cancer is increasingly recognized as a chronic condition, with ongoing unmet needs after primary treatment and throughout the cancer journey. Insomnia emerges as a prevalent complaint linked to cancer and its treatments, and tends to persist, affecting between 29% to 64% of cancer survivors months or years after treatment completion.[4-6] Insomnia has been associated with deleterious consequences, including heightened fatigue and pain sensitivity, and reduced quality of life and immune functioning.[7,8] Untread cancer-related insomnia may also contribute to poorer treatment response, increased risk of cancer recurrence, and reduced survival.[9-11]

Insomnia is, however, highly treatable with cognitive-behavioral therapy for insomnia (CBT-I), a behavioral medicine intervention well-established as the treatment of choice for cancer-related sleep disturbances due to its efficacy, long-lasting benefits, and security profile.[12,13] Among people diagnosed with cancer, CBT-I improves key sleep parameters (i.e., insomnia, sleep diary outcomes), while also yielding benefits in psychological well-being, cancer-related symptoms (i.e., fatigue), and quality of life.[14] Cognitive-behavioral therapy for insomnia may be beneficial in addressing insomnia symptoms even when they do not reach the clinical threshold, acting as an important preventative

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measure against the development of more severe insomnia disorder.[15]

Current guidelines recommend CBT-I as the first-line treatment for insomnia, either offered in-person or digitally.[13] However, the accessibility to CBT-I remains extremely limited, particularly in cancer care.[16] As insomnia affects nearly half of all patients diagnosed with cancer, the need for CBT-I far exceeds available resources.[17] Consequently, pharmacotherapy, a second-line intervention, remains the most pragmatic resource,[4] filling the cancer-related insomnia treatment gap despite limited evidence for long-term efficacy, not being curative, side effects (including abuse, dependence, and tolerance), and security profile (e.g., drug-drug and drug-disease interactions).[18] Along with system-level barriers, practical barriers (i.e., travel/disease burden) affect cancer survivors' access to in-person CBT-I, emphasizing the need for more accessible interventions for cancer-related insomnia.[16]

The European Cancer Manifesto for 2024 - 2029 highlights the need to translate available clinical evidence into healthcare systems to support its sustainability and resilience, recognizing the value of comprehensive care models, the pressing need for treatment optimization, and the potential of digital for providing high-quality cancer care for all.[19] Digital CBT-I (dCBT-I) has been proposed to optimize insomnia treatment within cancer care, presenting a promising approach to address the needs of cancer survivors, offering patient convenience, opportunities for efficiency gains, and enhanced access to evidence-based, guideline-concordant insomnia treatment.[16]

The European Society for Medical Oncology (ESMO) clinical practice guideline recommends CBT-I as the standard of care for treating insomnia in cancer survivors (level of evidence I, grade of recommendation A), and offering dCBT-I when in-person CBT-I is not available (II, A). Subsequent treatment options include brief CBT-I or mindfulness-based therapies (II, B) and pharmacological intervention (II, C).[20] The guideline highlights that despite few studies have been conducted, dCBT-I shows highly promising effects for survivors, underscoring the need for high-quality trials to strengthen the evidence base for dCBT-I in people living with and beyond cancer.

By being focused on improving the accessibility of evidence-based digital therapeutics providing care for insomnia and expanding research on dCBT-I for cancer survivors, our goal is to test the real-world effectiveness and acceptability of a web-supported self-administered CBT-I intervention with clinician support, OncoSleep, on insomnia symptom severity in cancer survivors through a clinic-randomized hybrid effectiveness-implementation trial, in Portugal. Our primary aim is to test the clinical effects and acceptability of an accessible internet-delivered CBT-I by comparing post-test outcomes of insomnia severity between the intervention and a waitlist control group for cancer survivors experiencing subclinical or clinically significant insomnia symptoms. Our primary hypothesis is that, compared to the control group, the intervention group will show significantly lower insomnia symptom severity by the end of the intervention, and that the dCBT-I will be a well-accepted treatment for insomnia among cancer survivors.

The daytime consequences of insomnia, including fatigue and mood impairments that affect the quality of life, typically motivate survivors to seek specialized help.[4] Therefore, we will also test if the intervention produces clinically meaningful benefits on these psychosocial outcomes. We will also examine secondary between-group outcomes: sleep diary parameters, fatigue, psychological distress, and quality of life. We hypothesize that, compared to the waitlist control group, participants in the intervention group will report significantly better sleep after treatment, better health-related quality of life, and lower psychological distress and fatigue after treatment.

METHODS AND ANALYSIS

Participants

Survivors, recruited from the general population, will be eligible if they are aged 18 years or older; have a history of cancer, solid or blood malignancy(ies); have completed primary cancer treatment (survivors who are on hormone and/or other long-term maintenance therapies are eligible), and report having at least subclinical symptoms of insomnia [severity scores ≥ 8 in the Insomnia Severity Scale (ISI)],[21,22] emphasizing the unmet needs of this subgroup. Exclusion criteria: inability to read/write in Portuguese, pregnancy, breastfeeding, nightshift work, psychotherapy for insomnia, and self-reported untreated psychiatric condition or a formal diagnosis of another untreated sleep disorder (e.g., sleep apnea syndrome). These criteria were selected to be the most representative of real clinical settings, where it may not be feasible to systematically conduct diagnostic interviews or polysomnographic assessments to confirm insomnia disorder or exclude other sleep disorders. Patients can be on sleep medication if it has been stable for four weeks.

Screening, randomization, and assessments

In this two-armed parallel randomized controlled trial (RCT), the experimental group (dCBT-I via OncoSleep) will be compared to a waitlist control using treatment as usual from baseline to post-treatment (Fig. 1). Survivors will complete surveys at baseline (T0) and post-treatment (T1: eight weeks after randomization). Potential participants will be asked to complete an online screening assessment [including the ISI and the Hospital and Anxiety and Depression Scale (HADS)] to assess eligibility.[23,24] Survivors exhibiting

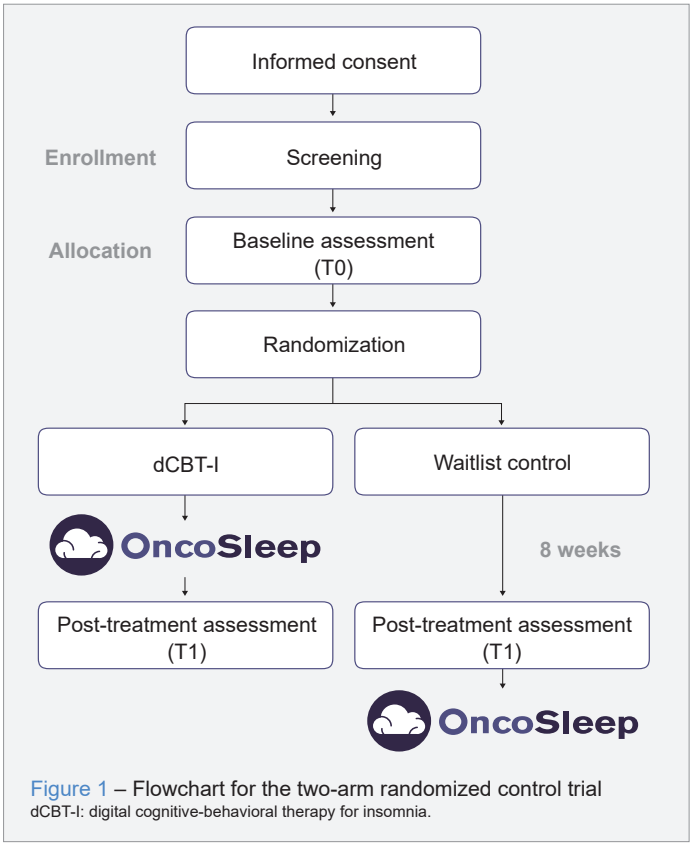

Figure 1 – Flowchart for the two-arm randomized control trial
dCBT-I: digital cognitive-behavioral therapy for insomnia.

severe psychological distress in the screening assessment (score of 21 - 41 in the HADS) will be advised to consider seeking specialized help but are welcome to participate in the study. After informed consent, eligible survivors will be sent links to complete the baseline assessment, including sociodemographic and clinical data, through a brief questionnaire developed for the study (Table 1).

Participants will then be randomized by an automated system either to the intervention group or a waitlist through a computer-generated randomization scheme using randomly varying block sizes (of two and four). Randomization will be stratified according to insomnia severity [based on the Insomnia Severity Index (ISI)] cutoff points[21,22]: subthreshold insomnia (ISI score 8 - 14), moderate insomnia (15 - 21), severe insomnia (22 - 28), sleep medication use ("yes" if using medication at least two times per week, "no" if otherwise), psychological distress ("yes" if HADS score 22 - 42, "no" if < 22),[23,24] and time since completion of cancer treatment ("up to five years", "five or more years").

All outcomes will be assessed online using surveys consisting of a battery of validated questionnaires administered through a secure platform provided by the University of Coimbra. The OncoSleep program integrates an automated online collection of sleep diaries. Researchers remain blind to the allocation until after study completion.

Primary outcome: insomnia severity

Insomnia will be measured using the ISI,[21,22] consisting of seven items rated on a five-point Likert scale. Scores range from 0 - 28, categorized as no insomnia (0 - 7), subthreshold (8 - 14), moderate (15 - 21), and severe insomnia (≥ 22).

Secondary outcomes

Psychological distress

The HADS is a 14-item self-reported questionnaire assessing anxiety and depression (seven items each).[23,24] Psychological distress in the past week will be gauged using the two subscale scores, ranging from 0 - 21. Scores ≤ 7 indicate non-cases, 8 - 10 indicate mild symptoms, 11 - 14 moderate symptoms, and ≥ 15 severe symptoms.

Quality of life

Health-related quality of life in the past two weeks will be evaluated using the World Health Organization Quality of Life–Brief (WHOQOL-BREF),[26,27] covering four domains

Table 1 – Sociodemographic and clinical questionnaire

Sociodemographic and cancer questions	Questions on insomnia and digital treatment
Name and e-mail	Use of sleep medication
Sex	Insomnia symptoms: duration and frequency
Year of birth	Impact of cancer diagnosis in insomnia
Marital status	Daytime complaints
Education level	Known non-insomnia sleep disturbances/other major conditions
Occupational status	Current psychological treatment for insomnia (yes/no)
Working shifts (if applicable)	Digital literacy (0 = very bad to 4 = very good)
Year of cancer diagnosis	
Cancer type	
Cancer treatment(s) and end of active treatment (if applicable)	
Other health conditions (mental or physical)	

(physical health, psychological health, social relationships, and environment). Higher scores indicate better quality of life. Cancer-related quality of life will be assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30).[28,29] Scores range from 0 - 100, with higher scores indicating better functioning/global health status, and higher scores on symptom/single-item scales indicating more significant symptoms.

Fatigue

Fatigue in the preceding week will be assessed with the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF),[30,31] with higher scores indicating more fatigue.

Sleep diary

Sleep diaries capture waking and sleeping time, sleep onset latency (SOL: time it takes to fall asleep after turning off the lights), number of awakenings, total time awake after sleep onset (WASO), total sleep time (TST), time in bed (TIB), and sleep efficiency (SE: percentage of time someone slept while in bed).[32] The diary also measures respondents' sense of morning refreshment (0 = "not at all" to 4 = "very"), sleep quality (0 = "very poor" to 4 = "very good"), and the use of sleep medication/alcohol. Post-test differences in sleep diary estimates between the intervention and control groups will be assessed. Baseline and post-treatment outcomes (weekly averages of daily mean SE, sleep quality, TST, WASO, and SOL) will be established from the week before the intervention and the week of intervention completion. The program will guide behavior change based on participants' SE by suggesting a sleep window.

Intervention

OncoSleep is a web-based CBT-I with six interactive, self-guided weekly sessions (approximately 35 minutes each) plus remote clinician support. OncoSleep is a fully automated program but includes support from a licensed psychologist as an additional feature: after each session, participants receive an email with additional feedback. Participants are also informed they can contact the clinician if they have questions or difficulties.

The treatment was modeled after a well-established protocol but features disease-specific adaptations to target survivor-specific perpetuating factors and address factors that could interfere with treatment adherence.[16,33] Table 2 provides a detailed overview of the sessions' content. The initial session provides psychoeducation on sleep and cancer-related insomnia. Participants learn strategies to manage cancer-related symptoms affecting sleep (e.g., fatigue, night sweats). The second session covers sleep hygiene and relaxation techniques. Relaxation techniques, tailored to accommodate cancer-related effects, are recommended as a strategy to manage the stress that exacerbates cancer-related symptoms, thereby alleviating these symptoms. The third session introduces behavioral techniques stimulus control therapy (SCT) and sleep restriction therapy (SRT). Sleep restriction therapy seeks to restrict sleep opportunity (curtailing TIB based on the current sleep pattern, but not to less than a minimum of five hours) while leveraging heightened sleep pressure to consolidate and regularize sleep. Time in bed is then gradually adjusted weekly (indexed by a SE > 85%) until optimal sleep duration (and daytime functioning) is achieved. SRT is presented as adjusting the sleep window to emphasize the goal is to optimize sleep efficiency rather than limiting sleep. Sleep restriction therapy decreases arousal and improves sleep continuity and sleep depth.[13] Stimulus control therapy strengthens the association between sleep and the conditions under which it typically occurs by eliminating sleep-incompatible activities,

Table 2 – Structure of the intervention

Session	Content	Handouts and resources
1	Overview of the intervention Psychoeducation Defining goals	Understanding sleep Cancer-related insomnia: associations with cancer-related fatigue, night sweats
2	Sleep hygiene Relaxation	Sleep hygiene Relaxation audios
3	Stimulus control Sleep consolidation	Sleep efficiency Sleep window
4	Restructuring dysfunctional beliefs about sleep	Thought record Cognitive distortions (mind traps) Reframing thoughts
5	Restructuring dysfunctional beliefs about cancer Additional adapted cognitive techniques (e.g., cognitive control, paradoxical intention therapy, acceptance and commitment-based strategies)	Mind map Dealing with a racing mind
6	Insomnia relapse prevention	Insomnia cycle overview Personal plan

minimizing awake TIB (e.g., going to bed only when sleepy and getting up when unable to sleep), and regulating the sleep schedule. Behavioral techniques are applied flexibly for participants who have difficulty complying due to illness burden and to prevent sleep loss, which could produce a hyperalgesic response). Adaptations also include addressing unhelpful sleep-related beliefs aiming to overcome resistance to behavioral strategies. The next session focuses on restructuring sleep and cancer-related beliefs (e.g., worry about the impact of insomnia on cancer progression) to decrease cognitive-cortical arousal and short-circuit the self-perpetuating cycle of insomnia. The fifth session features additional cognitive techniques to prevent (daytime) and cope (nighttime) with the racing mind (e.g., "worry time" is taught to reduce the interference of cancer-related worry during nighttime). Entering sleep diary information is a prerequisite for advancing to the next session, guiding personalized techniques, and tracking weekly progress.

Acceptability

Acceptability will be assessed through an online survey using quantitative measures (satisfaction, helpfulness, usability, odds of future technique use, willingness to recommend, and overall enjoyableness, rated on Likert-type scales), along with qualitative insights garnered from an open-ended question inviting participant feedback and suggestions for improvement. To assess satisfaction, the Consumer Report Treatment Satisfaction scale was adapted[25]: "How much do you feel the OncoSleep program has helped you in the following areas?" Items (well-being, coping with stress, energy levels, mood, insomnia, performance) will be rated from "a lot worse" = 0 to "a lot better" = 4. Format, clinician support, and complementary material helpfulness will be rated from "not helpful at all" = 0 to "very helpful" = 3. Usability, odds of future technique use, and willingness to recommend will be rated from "very low" = 0 to "very high" = 3 and overall enjoyableness will be rated from "very dissatisfied" = 0 to "very satisfied" = 3.

Ethical considerations and data management plan

This pragmatic trial, approved by the Deontology Committee for Research of the Faculty of Psychology of the University of Coimbra, is prospectively registered at ClinicalTrials.gov (NCT04898855), follows the Helsinki Declaration, and adheres to both the CONSORT[34] and SPIRIT reporting guidelines.[35] All data that may indirectly identify the participants will be deleted five years following the end of the study, as instructed by Resolution no. 1704/2015 of the Portuguese National Commission for the Protection of Data, enforceable to the treatment of personal data for clinical research.

Power analyses

Based on prior research,[14] we expect a moderate-to-large effect size. To detect a statistically significant ($p < 0.05$) effect of $d = 0.5$ with a statistical power of 80%, the required sample is 64 for each group. Adjusting for an anticipated attrition rate of 20%,[36] the total enrolment goal is 154 participants, 77 per arm. Sample size calculations were carried out in the pwr package in R version 4.4.0.

Statistical analysis plan

Mixed effects models based on an intent-to-treat approach will be used to assess between-group changes over time. All statistical tests will be two-sided. An eight-point clinical margin is considered clinically significant based on previous research.[37] Cohen's *d* will be calculated based on absolute between-group differences post-treatment. Dropouts will be defined as participants failing to complete questionnaires at post-treatment and adherence as the number of sessions completed. Acceptability ratings will be analyzed using descriptive statistics.

DISCUSSION

There is a pressing need to adopt sustainable and innovative care delivery models to alleviate the burden of cancer, aiming to ensure that the rights outlined in the European Code of Cancer Practice are upheld: equal access to affordable and optimal cancer care through multidisciplinary within cancer networks. Considering insomnia tends to adopt a chronic course and has detrimental effects for survivorship and recovery, optimal treatment for cancer-related insomnia should be included in routine care. This article details the study design and protocol for a pragmatic RCT testing a dCBT-I to deliver guideline care in cancer survivorship. We aim to determine if dCBT-I is effective in a diverse setting for cancer survivors with complaints of insomnia and whether it can lead to improvements in patient's psychological distress, fatigue, and quality of life.

To improve equity in access to guideline treatment for insomnia in cancer care, we developed a dCBT-I for cancer survivors. Committed to delivering evidence-based, quality cancer care, we aim to examine its real-world effectiveness and acceptability. Certain limitations are anticipated. First, a self-referred sample of cancer survivors will be recruited, introducing potential selection bias. Our focus is on creating an interactive, user-friendly program with professional support to minimize attrition rates. Second, albeit comparable in efficacy to face-to-face CBT-I, self-guided interventions may result in smaller treatment effects.[14,37,38] To address this limitation and enhance treatment effects, self-administered CBT-I may be supplemented by clinician support,[39,40] helping patients implement treatment strategies, stay engaged in sessions, personalize treatment based on cancer

experiences, and reinforce their self-efficacy.[41] A recent meta-analysis suggested clinician support is preferred when CBT-I is administered digitally.[42] This is in line with another meta-analysis that evaluated various delivery CBT-I formats and found in-person therapies and digital therapy with clinician support to be the most effective approaches.[43] Hence, our choice to include clinician support is informed by this evidence. Lastly, we opted for a waitlist control group to avoid withholding treatment unethically, making long-term between-subjects comparisons unfeasible. Notwithstanding such limitations, our pragmatic cancer trial will offer clinical practice guideline care for insomnia to cancer survivors in Portugal, in a community setting, generating broadly applicable evidence while simultaneously contributing to improved patient outcomes. Currently, pharmacotherapy, a second-line intervention for insomnia, stands as the prevailing treatment despite concerns around its efficacy, side effects, and safety profile, largely due to its accessibility. Telemedicine may be leveraged to enhance access to CBT-I for survivors who would otherwise be limited to pharmacotherapy, a less effective, second-line intervention. Our clinical trial aims to shed light on opportunities for facilitating optimal access to guideline-concordant insomnia treatment in cancer care and translating innovative, evidence-based approaches into clinical practice.

Effective and well-accepted digital therapeutics delivering CBT-I may result in clinical guideline care becoming routine in oncology settings, improving sleep and insomnia daytime consequences, and alleviating cancer burden. Evidence-based digital therapeutics may be integrated into a comprehensive survivorship plan, allowing for a personalized care pathway supported by an interconnected digital ecosystem aimed at enhancing the cancer healing journey.[16]

AUTHOR CONTRIBUTIONS

MIC: Conceptualization, writing – original draft.

AVS: Writing – original draft, review & editing, supervision.

MCC: Writing – review & editing, supervision.

AAG: Conceptualization, writing – original draft, review & editing, supervision.

All authors approved the final version to be published.

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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ACTA MÉDICA PORTUGUESA
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Estimation of 10-Year Cardiovascular Disease Risk in the Portuguese Population Using the Systematic Coronary Risk Evaluation 2 (SCORE2)

Estimativa do Risco a 10 Anos de Doença Cardiovascular na População Portuguesa Utilizando o Systematic Coronary Risk Evaluation 2 (SCORE2)

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ABSTRACT

Cardiovascular diseases are the leading cause of death globally. The objective of this study was to estimate the 10-year cardiovascular risk in the Portuguese population using the new Systematic Coronary Risk Evaluation 2. Data from the first National Health Examination Survey from 2015 were used. Inclusion criteria were age between 40 and 69 years, absence of pregnancy, available information on sex, age, smoking status, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol. Participants who had an acute myocardial infarction or a stroke, had diabetes, chronic kidney disease, or reported taking medication for these conditions were excluded from the analysis. The prevalence of high and very high cardiovascular risk was stratified by sex, age group, marital status, education level, occupational activity, degree of urbanization of the area of residence, health region, and income quintile. The sample consisted of 2817 individuals. In Portugal, in 2015, 36.7% (95% CI: 34.2 - 39.3) and 6.1% (95% CI: 4.8 - 7.4) of the individuals aged between 40 and 69 years had a high and a very high risk of having a cardiovascular disease in the following 10 years, respectively. In 2015, there was a high percentage (42.8%) of the Portuguese population aged 40 to 69 years in high or very high risk of developing cardiovascular disease (fatal and non-fatal) in the following 10 years. A possible explanation may be the high prevalence of risk factors for cardiovascular disease in Portugal.
Keywords: Cardiovascular Diseases; Heart Disease Risk Factors; Risk Assessment; Sociodemographic Factors

RESUMO

As doenças cardiovasculares são a principal causa de morte globalmente. O objetivo deste estudo foi atualizar a estimativa do risco cardiovascular a 10 anos na população portuguesa utilizando o novo *Systematic Coronary Risk Evaluation 2*. Foram utilizados dados do Primeiro Inquérito Nacional de Saúde com Exame Físico de 2015. Os critérios de inclusão foram a idade entre 40 e 69 anos, ausência de gravidez, informação disponível sobre o sexo, idade, consumo de tabaco, pressão arterial sistólica, colesterol total e colesterol da lipoproteína de alta densidade. Os participantes previamente diagnosticados com enfarte agudo do miocárdio, acidente vascular cerebral, diabetes, doença renal crónica ou com terapêutica para estas doenças foram excluídos da análise. A prevalência de risco cardiovascular alto e muito alto foi estratificada por sexo, grupo etário, estado civil, nível de escolaridade, atividade profissional, grau de urbanização da zona de residência, região de saúde e quintil de rendimento. A amostra foi constituída por 2817 indivíduos. Em Portugal, em 2015, 36,7% (IC 95%: 34,2 - 39,3) e 6,1% (IC 95%: 4,8 - 7,4) dos indivíduos entre os 40 e 69 anos apresentaram um risco alto e muito alto, respetivamente, de desenvolver uma doença cardiovascular a 10 anos. Em 2015 houve uma elevada percentagem (42,8%) da população portuguesa entre os 40 e 69 anos em risco alto ou muito alto de desenvolver doença cardiovascular (fatal e não fatal) a 10 anos. Uma explicação possível poderá ser a elevada prevalência de fatores de risco para doença cardiovascular em Portugal.
Palavras-chave: Avaliação de Risco; Doenças Cardiovasculares; Fatores de Risco de Doenças Cardíacas; Fatores Sociodemográficos

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of mortality worldwide, accounting for 20.5 million deaths in 2021.[1] The Systematic Coronary Risk Evaluation (SCORE) was developed by the European Society of Cardiology (ESC) in 2003 to estimate cardiovascular (CV) risk, validated for European populations to predict the 10-year risk of fatal events (coronary heart disease, heart failure, stroke, and sudden death), in asymptomatic individuals without a diagnosis of CVD.[2] In 2015, among Portuguese individuals aged 40 to 65 years, SCORE identified a 5.1% high CV risk and a 11.9% very high CV risk of a fatal cardiovascular event within 10 years.[3]

In 2021, the risk of non-fatal CV events (acute myocardial infarction and stroke) was added to SCORE, combining fatal and non-fatal CV risk, naming this update SCORE2.[4] For the application of SCORE2, ESC defined four CV risk zones based on World Health Organization age- and sex-standardized CV mortality rates. Portugal was classified within the moderate-risk category.[4] SCORE2 consists of three categories: low to moderate risk [< 2.5% (< 50 years) or < 5% (50 - 69 years)]; high risk [2.5% - 7.4% (< 50 years) or 5.0% - 9.9% (50 - 69 years)]; and very high risk [≥ 7.5% (< 50 years) or ≥ 10.0% (50 - 69 years)].[4] It uses the variables sex, age, smoking status, systolic blood pressure, and non-high-density lipoprotein cholesterol (non C-HDL).[4] SCORE is recommended for people aged 40 to 69, without documented CVD, diabetes, chronic kidney disease, familial hypercholesterolemia, or other genetic/rare lipid or blood

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pressure disorders.[4,5] As stated in the 2021 ESC Guidelines, individuals with diabetes can have a moderate, high, or very high CV risk *a priori*.[5] 2021 ESC Guidelines do not advise the application of SCORE2 charts in pregnant women.[5]

To the best of our knowledge, no studies have evaluated SCORE2 in the Portuguese population. This study aimed to estimate and characterize the 10-year CV risk using SCORE2 in the Portuguese population aged 40 to 69.

METHODS

Study population

Data from the INSEF, collected between February 2nd and December 21st, 2015, was used.[6] INSEF was an observational, cross-sectional study of a population-based sample, targeting individuals aged 25 to 74 years who had been residing in mainland Portugal or the autonomous regions of the Azores and Madeira for at least 12 months before the interview. The sample was selected using a complex multistage probabilistic design to ensure regional and national representativeness.[6]

For this study, the inclusion criteria were age 40 - 69 years, not being pregnant, available information on sex, age, smoking status, systolic blood pressure, total cholesterol, and C-HDL. Diagnosis of acute myocardial infarction, stroke, diabetes, chronic kidney disease, or undergoing medication for these conditions were excluded.[5] The INSEF indicated the use of medication for high blood pressure, myocardial infarction, stroke, diabetes, and chronic renal failure, without specification of drug.[6]

Statistical analysis

The statistical analysis was performed using the R software for Windows, version 4.3.1.[7] The significance level was set at 5% for all analyses.

The participants were described by sociodemographic variables and relative and absolute frequencies. The prevalence of CV risk was determined using SCORE2 for moderate-risk European countries. The 95% confidence interval (CI) was calculated using the "confint" function in the R program. The adjusted version of the Pearson chi-squared test ("svychisq" function) for complex samples was used to compare the distribution of CV risk. Sample weighting was included in all estimates to account for different selection probabilities,[6] using the "survey" package in R.[7]

Ethical issues

The INSEF study received approval from the INSA Health Ethics Committee, the National Data Protection Authority and from eight regional Ethics Committees.[6] The INSA Health Ethics Committee issued a favorable opinion for the conduct of this research study on February 7, 2023.

RESULTS

The subsample consisted of 2817 individuals, mostly female (55.5%). Most participants resided in urban areas (73.2%; 95% CI: 70.0 - 76.4) and were married or cohabiting (76.1%; 95% CI:73.9 - 78.3). Nearly one-third of participants (30.9%; 95% CI:28.0 - 33.8) had no formal education or completed primary school, and over one-third (38.1%; 95% CI:32.8 - 43.4) had low-skilled occupations (e.g., farmers, industry, and construction) (Table1). The

Table 1 – Description of INSEF 2015 participants by sociodemographic characteristics

Socio-demographic characteristics	n	%
Sex (n = 2817)		
Female	1570	55.5
Male	1247	44.5
Age group (n = 2817)		
40 - 44 years	589	21.9
45 - 49 years	525	18.6
50 - 54 years	547	19.0
55 - 59 years	433	14.3
60 - 64 years	414	14.6
65 - 69 years	309	11.5
Marital status[a] (n = 2817)		
Married	2136	76.1
Not married	681	23.9
Educational level (n = 2815)		
No education/ basic 1st cycle	941	30.9
Basic 2nd/3rd cycle	1002	35.6
Secondary education	469	18.0
Higher education	403	15.5
Occupational activity[b] (n = 2526)		
A	402	17.1
B	1142	44.8
C	982	38.1
Degree of urbanization (n = 2817)		
Urban	2026	73.2
Rural	791	26.8
Health Region (n = 2817)		
North	441	35.7
Centre	432	17.9
Lisbon and Tagus Valley	342	32.6
Alentejo	392	4.7
Algarve	392	4.4
Autonomous Region of Madeira	422	2.6
Autonomous Region of Azores	396	2.1
Income quintile (n = 2668)		
Low	667	20.7
Medium - low	522	17.0
Medium	503	18.8
Medium - high	450	17.2
High	526	18.8

[a] Married: cohabiting and married; Not married: single, divorced, widowed.
[b] A: armed forces, managers, professionals; B: technicians & associate professionals, clerical support workers, services & sales workers; C: skilled agricultural workers, craft & related trades workers, plant & machine operators, elementary occupations.[3]

characteristics of excluded individuals can be consulted in Table 1 of the Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/21376/15489).

In the 2015 INSEF, of those who qualified for SCORE2 assessment, 42.8% had a high risk [36.7% (95% CI: 34.2 - 39.3)] or very high risk [6.1% (95% CI: 4.8 - 7.4)] of developing CVD within 10 years (fatal or non-fatal). The prevalence was higher in men [high risk of 56.3% [95% CI: 52.6 - 60.0) and a very high risk of 13.4% (95% CI: 10.6 - 16.1)]; older age (65 - 69 years), with a high CV risk prevalence of 71.0% (95% CI: 62.4 - 79.5) and a very high CV risk prevalence of 20.4% (95% CI: 14.7 - 26.1); no education or only primary education [high risk of 43.1% (95% CI: 38.6 - 47.7) and a

Table 2 – Distribution of cardiovascular risk by SCORE2 according to sociodemographic characteristics

	% (95% CI)			
	Low/moderate risk n = 1623	**High risk** n = 992	**Very high risk** n = 202	***p*-value**
Sex (n = 2817)				
Female	78.6 (75.9 - 81.4)	21.1 (18.3 - 23.9)	0.3 (0.0 - 0.6)	< 0.001
Male	30.4 (25.7 - 35.0)	56.3 (52.6 - 60.0)	13.4 (10.6 - 16.1)	
Age group (n = 2817)				
40 - 44 years	71.2 (65.0 - 77.3)	27.3 (22.1 - 32.6)	1.5 (0.1 - 2.9)	< 0.001
45 - 49 years	55.5 (49.5 - 61.5)	41.6 (35.8 - 47.4)	2.9 (1.5 - 4.3)	
50 - 54 years	80.3 (73.0 - 87.6)	18.0 (10.5 - 25.5)	1.7 (0.4 - 3.0)	
55 - 59 years	58.5 (50.0 - 67.0)	34.9 (28.3 - 41.6)	6.6 (2.3 - 10.9)	
60 - 64 years	45.0 (37.7 - 52.3)	43.9 (36.2 - 51.5)	11.2 (7.2 - 15.2)	
65 - 69 years	8.6 (3.7 - 13.6)	71.0 (62.4 - 79.5)	20.4 (14.7 - 26.1)	
Marital status[a] (n = 2817)				
Married	56.8 (53.9 - 59.6)	36.9 (34.4 - 39.4)	6.3 (5.0 - 7.6)	0.8672
Not married	58.4 (50.9 - 65.8)	36.2 (29.7 - 42.7)	5.5 (1.8 - 9.1)	
Educational level (n = 2815)				
No education/ basic 1st cycle	46.4 (42.1 - 50.7)	43.1 (38.6 - 47.7)	10.5 (7.7 - 13.3)	< 0.001
Basic 2nd/3rd cycle	60.2 (55.4 - 65.0)	35.6 (30.4 - 40.7)	4.3 (2.7 - 5.8)	
Secondary education	59.8 (55.6 - 64.1)	34.9 (29.2 - 40.7)	5.3 (1.4 - 9.1)	
Higher education	68.6 (61.3 - 76.0)	28.8 (22.6 - 35.0)	2.6 (0.1 - 5.1)	
Occupational activity[b] (n = 2526)				
A	58.0 (52.3 - 63.4)	36.3 (30.8 - 41.7)	5.8 (1.9 - 9.7)	0.008
B	60.0 (56.6 - 63.4)	34.1 (30.8 - 37.4)	5.9 (4.0 - 7.8)	
C	49.0 (44.3 - 53.6)	43.1 (38.8 - 47.4)	7.9 (6.1 - 9.7)	
Degree of urbanization (n = 2817)				
Urban	57.0 (54.6 - 59.4)	37.1 (35.2 - 39.1)	5.8 (4.4 - 7.3)	0.7252
Rural	57.5 (47.8 - 67.2)	35.6 (27.2 - 44.1)	6.9 (4.6- 9.1)	
Health Region (n = 2817)				
North	59.0 (53.8 - 64.2)	35.5 (31.2 - 39.8)	5.5 (4.3 - 6.8)	0.5333
Centre	52.6 (45.6 - 59.6)	39.9 (32.4 - 47.4)	7.5 (4.9 - 10.1)	
Lisbon and Tagus Valley	57.8 (52.1 - 63.5)	36.8 (33.2 - 40.5)	5.4 (1.3 - 9.4)	
Alentejo	54.9 (50.0 - 59.8)	36.4 (31.8 - 41.1)	8.7 (7.0 - 10.4)	
Algarve	56.4 (51.6 - 61.2)	37.0 (31.2 - 42.9)	6.6 (2.6 - 10.6)	
Autonomous Region of Madeira	63.4 (59.4 - 67.4)	29.2 (24.3 - 34.1)	7.4 (3.3 - 11.4)	
Autonomous Region of Azores	53.9 (48.7 - 59.1)	38.9 (34.8 - 43.0)	7.2 (4.6 - 9.8)	
Income quintile (n = 2668)				
Low	59.8 (52.8 - 66.9)	32.8 (27.2 - 38.5)	7.4 (3.9 - 10.8)	0.6083
Medium - low	54.8 (49.7 - 59.9)	38.7 (32.5 - 45.0)	6.5 (4.2 - 8.8)	
Medium	59.2 (50.9 - 67.5)	36.7 (28.0 - 45.3)	4.2 (1.4 - 7.0)	
Medium - high	58.7 (53.3 - 64.1)	34.8 (28.4 - 41.1)	6.5 (3.3 - 9.8)	
High	53.1 (47.7 - 58.6)	40.1 (34.5 - 45.7)	6.8 (3.9 - 9.7)	
Total (n = 2817)	57.2 (54.2 - 60.1)	36.7 (34.2 - 39.3)	6.1 (4.8 - 7.4)	

[a] Married: cohabiting and married; Not married: single, divorced, widowed.
[b] A: armed forces, managers, professionals; B: technicians & associate professionals, clerical support workers, services & sales workers; C: skilled agricultural workers, craft & related trades workers, plant & machine operators, elementary occupations.[3]

very high risk of 10.5% (95% CI: 7.7 - 13.3)]; and low-skilled occupations (e.g., farmers, industry, and construction) [high risk of 43.1% (95% CI: 38.8 - 47.4) and a very high risk of 7.9% (95% CI: 6.1 - 9.7)]. There were no statistically significant differences in CV risk between categories of marital status, degree of urbanization, health region, and income quintile (Table 2).

DISCUSSION

In the INSEF, the proportion of individuals at risk was higher when evaluated with SCORE2 (42.8%) compared to the 17.1% CV risk determined by SCORE in 2015.[3] A study in Madeira validated SCORE and SCORE2 for ages 40 - 65, finding SCORE2 is more accurate, classifying over 50% of patients in the high-risk group, versus 25.3% with SCORE, indicating SCORE might underestimate risk by excluding non-fatal CV events.[11]

The higher prevalence of high and very high risk in men may be explained by the cardioprotective role of estrogen in premenopausal women.[8] Older adults may have a higher CVD risk due to the deterioration of cardiovascular function with age.[9] Socioeconomic determinants can also modify the calculated risk.[5] The correlation between education and health literacy stands out as being a potential risk factor for CVD.[10]

To ensure SCORE2 accuracy, only individuals with complete data were included. This study faced limitations, such as a 43.9% participation rate, although no differences were found between participants and non-participants. Selection bias may arise from missing data on CVD symptoms or conditions like aortic aneurysm, peripheral artery disease, or documented atherosclerotic CVD on imaging, considered high-risk CV criteria. Future studies should aim to collect more comprehensive data on CVD symptoms and high-risk criteria and consider incorporating additional variables such as socioeconomic status.

These findings support the need to reinforce measures to prevent CV risk factors for the general population while also focusing on early detection and monitoring in the most susceptible individuals, such as men, the elderly, and individuals with low levels of education and low-skilled occupations.

PREVIOUS AWARDS AND PRESENTATIONS

An abstract of this study was submitted to the 23rd Public Health Congress at Culturgest and was accepted for an oral presentation, which took place on June 16th, 2023.

AUTHOR CONTRIBUTIONS

MS: Literature review, data analysis and interpretation, writing, review, and approval of the manuscript.

MU, SN, TG, CD: Manuscript review and approval.

VG: Supervision of the work, manuscript review and approval.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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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Aggressive Giant Extraskeletal Aneurysmal Bone Cyst of the Thigh: Overcoming Challenges with a Multidisciplinary Approach

Quisto Ósseo Aneurismático Extraesquelético Agressivo da Coxa: Ultrapassando Desafios com uma Abordagem Multidisciplinar

António PROENÇA CAETANO✉[1,2], Teresa NEVES[1], Carlos PEDROSA[3], José PORTELA[3], Filipe Veloso GOMES[1], Élia COIMBRA[1], Tiago BILHIM[1]
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ABSTRACT

Aneurysmal bone cysts are vascular benign fibroblastic lesions usually found in bone that are locally destructive, with a greater incidence in the first and second decades of life. Patients usually undergo curettage or, less frequently, surgical resection, which may lead to growth disturbances and deformities in cases of large or complex lesions. Minimally invasive techniques such as sclerotherapy and endovascular embolization have been developed as an alternative or complement to surgery, with promising results. The authors present a rare case of an extraskeletal aneurysmal bone cyst successfully treated with minimally invasive techniques followed by surgical resection and provide a literature review of the current treatment options.
Keywords: Bone Cysts, Aneurysmal; Embolization, Therapeutic; Radiology, Interventional; Sclerotherapy

RESUMO

O quisto ósseo aneurismático é uma lesão benigna, de origem vascular fibroblástica, localmente destrutiva, que se forma tipicamente no osso, em indivíduos nas primeira e segunda décadas de vida. As lesões são tipicamente submetidas a curetagem ou, menos frequente, ressecção cirúrgica, que apresenta risco de complicações como deformidades ósseas ou distúrbios de crescimento, sobretudo em lesões complexas ou volumosas. Técnicas minimamente invasivas como a escleroterapia ou a embolização arterial têm sido desenvolvidas como alternativa ou complemento à cirurgia, com resultados promissores. Os autores apresentam um caso de quisto ósseo aneurismático extraesquelético tratado com sucesso através da combinação de técnicas minimamente invasivas e seguido de ressecção cirúrgica, e revisão da literatura a respeito dos tratamentos atualmente disponíveis.
Palavras-chave: Embolização Terapêutica; Escleroterapia; Quisto Ósseo Aneurismático; Radiologia de Intervenção

INTRODUCTION

Aneurysmal bone cyst (ABC) is a benign fibroblastic tumor that is usually found in bone, with locally aggressive potential due to expansion and destructive nature towards surrounding tissue.[1] It usually affects patients below the age of 20, and 70% of cases are of primary nature. The remaining 30% are associated with other tumors.

In the past, treatment consisted of open resection, which has the potential for 0% recurrence but high morbidity.[2] There has been a current shift to less invasive procedures to treat ABC in order to reduce morbidity and growth disturbance. Curettage and bone grafting remain the gold standard for managing ABC,[3] but several minimally invasive tools have shown efficacy and safety, such as sclerotherapy, radionuclide ablation and endovascular embolization.[4]

In this report, the authors discuss the role of interventional radiology in conjunction with orthopedic surgery in treating a challenging case of peripheral extraskeletal ABC.

CASE REPORT

A 28-year-old Nepalese male patient with a one-month history of progressive posterior left thigh pain and claudication was referred to an Orthopedic surgery clinic. Prior medical history was unremarkable.

On physical examination, a palpable mass was detected in the posterior thigh, as well as range-of-motion limitation performing left knee flexion. There was no evidence of neurovascular compromise.

Contrast-enhanced computed tomography (CT) was performed, which revealed a giant soft tissue mass located in the deep layer of the left posterior compartment of the thigh, with peripheral calcifications and multiple cysts of variable size (Fig. 1). The cyst-like mass had a total volume of 569 cc and was moderately vascularized from several branches of the deep femoral artery, as depicted on CT angiography. No soft-tissue mass component was identified within the multiple cysts besides the multiple septa, but extensive periosteal reaction was evidenced at the proximity with the posterior cortex of the femur.

Magnetic resonance imaging (MRI) was performed for further assessment, confirming a cystic mass with multiple cysts with fluid-fluid levels (Figs. 2A and B), exerting significant mass effect and displacing the surrounding soft tissue structures, including the sciatic nerve. In a 45-day span between CT and MRI assessments, the mass had nearly

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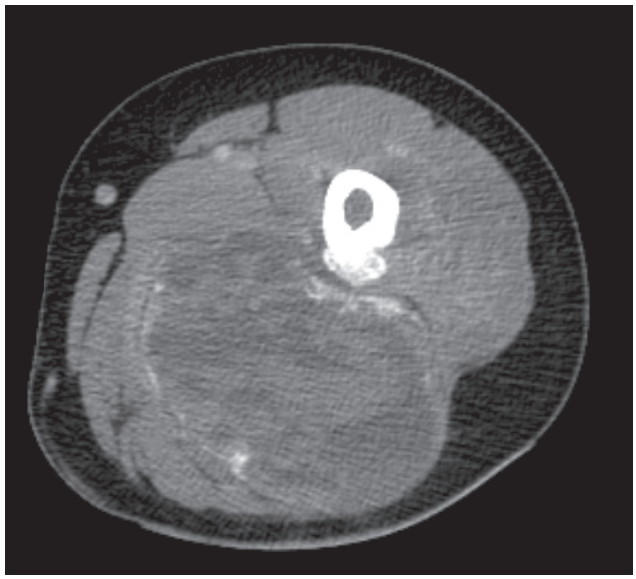

Figure 1 – Computed tomography of the thigh reveals a soft-tissue mass located in the posterior thigh, with thin rim calcifications (axial plane)

doubled in size (936 cc), and the patient had developed increased pain and claudication with the need for a walking aid.

An ultrasound-guided biopsy was performed in-between CT and MRI imaging, with soft-tissue extraction of the cyst septa and fluid aspiration of different cysts for cytologic evaluation. Pathology results heralded findings suggestive of ABC with no signs of underlying malignant tissue. After MRI evaluation, a second biopsy was performed, targeting the soft tissue adjacent to the posterior femoral periosteal reaction, with a similar result.

A multidisciplinary decision-making process opted for minimally invasive treatments to halt progression, induce size reduction, and serve as a bridge for subsequent surgical removal if technically feasible.

The patient underwent arterial embolization, which was achieved with a femoral contra-lateral approach, superselective catheterization of the feeding vessels from the deep femoral artery and embolization with polyvinyl alcohol particles (355 - 500 µm) until stasis was obtained (Fig. 3). An intra-procedural arterial CT was performed which revealed further increase of the mass to 1256 cc.

A follow-up CT one-month post-embolization documented stability of the ABC size and progression to peripheral bone mineralization Combined therapy was proposed, and two sessions of fluid aspiration and subsequent percutaneous polidocanol injection on the largest cysts were performed, each session focusing on a different segment of the mass. Follow-up CT revealed a reduction in the size of the treated cysts and further mineralization, with a small reduction in global tumor size (1105 cc) (Fig. 4).

After discussion with the orthopedic surgery team, surgical removal was deemed feasible and proposed. A second session of pre-operative arterial embolization was done to reduce bleeding during surgery, and the ABC was successfully removed (Figs. 5A and B). Histological analysis revealed a multiloculated cystic lesion without epithelial lining, septs with macrophages and giant multinucleated cells of osteoclast type, bony trabeculae with immature bone and osteoblastic activity, as well as myofibroblast tissue proliferation. The findings were compatible with aneurysmal bone cyst.

Patient was referred for physical rehabilitation. A follow-up MRI one month later documented a large seroma at the

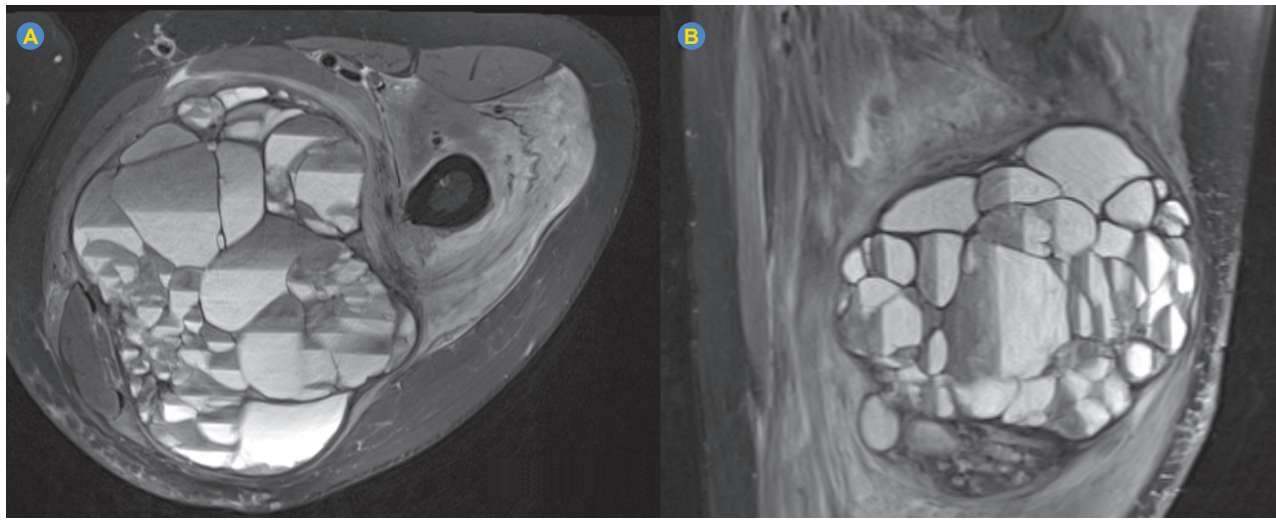

Figure 2 – Magnetic resonance imaging of the thigh revealing a multiloculated soft-tissue mass with fluid-fluid levels [axial (A) and sagittal (B) fat-saturated proton density sequences]

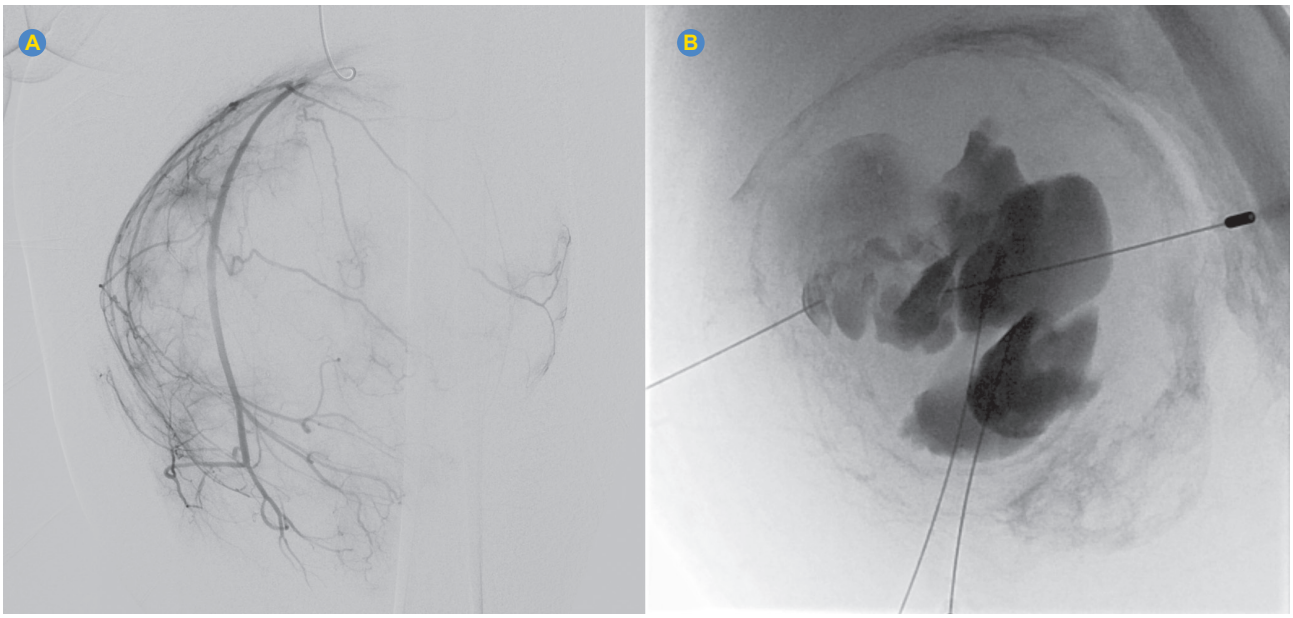

Figure 3 – Arterial embolization of the tumoral vascular supply arising from branches of the deep femoral artery (anteroposterior fluoroscopic image) (A). Percutaneous sclerotherapy using four 22G needles placed in different internal loci of the ABC (B).

resection site and clinical evaluation showed progressive improvement of mobility and pain reduction (Fig. 6). At the time of publication, patient is continuing physical rehabilitation and follow-up by the orthopedic oncology team.

DISCUSSION

Aneurysmal bone cysts are rare expansile benign skeletal tumors that affect the bone during the growth period, with an incidence of 0.14 per 100 000 persons, accounting for 1% to 2% of all primary bone tumors.[5] Pathogenesis is associated with dysplastic vessels and neoplastic proliferation, and 80% occur before the third decade of life. In 30% of cases, an underlying tumor is present, and these are considered secondary ABC.[6]

They most commonly present as an expanding mass with a cyst-like appearance inside the bone. They are composed of multiple blood-filled cysts separated by fibrous septa containing several cell types, including giant cells with or without osteoblasts.

Common complications include pain, local edema or tumefaction, neurological compromise, movement restriction and pathologic fracture.[7]

Extraskeletal ABC are exceedingly rare; there have been anecdotal reports in the literature,[8] and they may mimic a variety of other benign and malignant tumors, such as extraskeletal (telangiectatic) osteosarcoma, soft-tissue giant-cell tumor, tenosynovial giant cell tumor, brown tumor, and myositis ossificans.

Pathogenesis is unknown but it is hypothesized that they may be associated with traumatic events or vascular changes with a pathologic reparative process underlying cystic degeneration and neoplastic formation.[8]

Although conventional x-ray is usually the first diagnostic tool employed, further imaging evaluation with CT and/

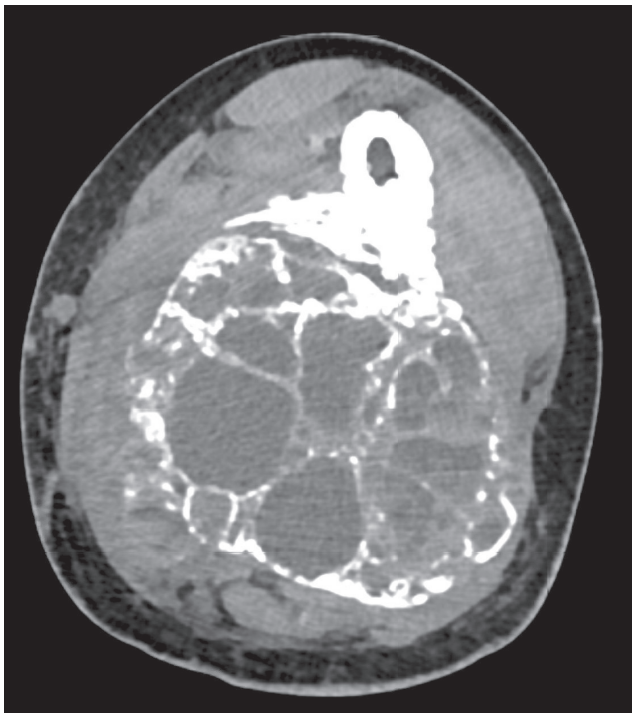

Figure 4 – Follow-up CT post-minimally invasive procedures reveals stabilization of mass size and progressive calcification and reduction of cyst volume

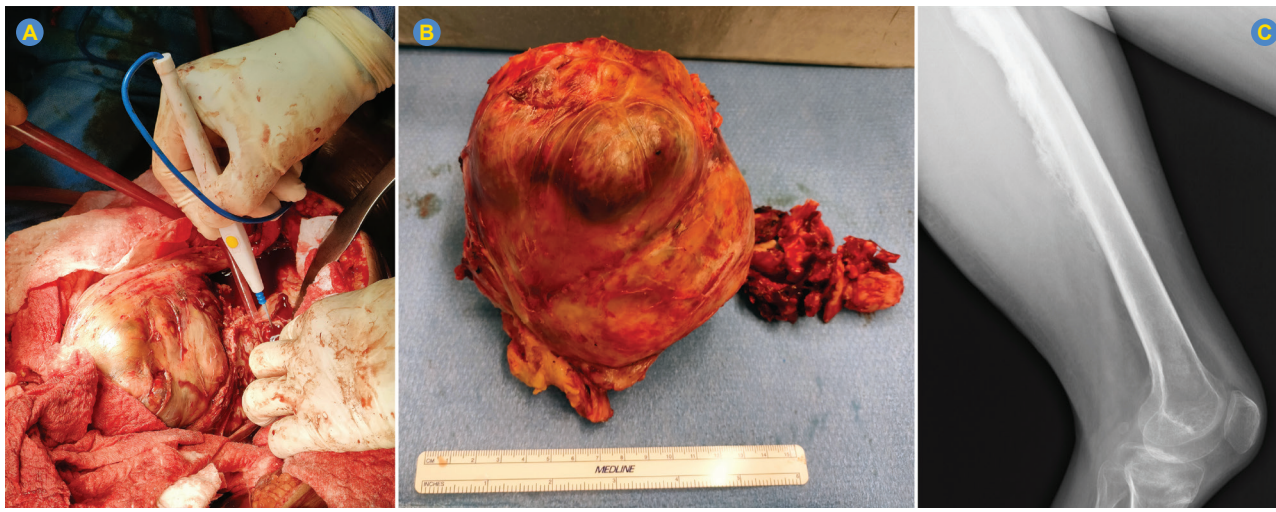

Figure 5 – Intra-operative image during surgical resection of the extraskeletal ABC (A). Surgical specimen (B). Post-surgical x-ray of the thigh, lateral incidence (C).

or MRI is fundamental for a more detailed assessment with regards to size, shape, presence of soft-tissue component, cyst size and number, presence of fluid-fluid levels, grade of mineralization and bone stock, relationship with the underlying bone or soft-tissues, and vascularity.[9,10]

Treatment options include surgical techniques, percutaneous injection or endovascular embolization. Comparative studies are missing and, currently, there is no consensus regarding the preferred type of management.[11]

The gold standard of surgical treatment is curettage with or without mechanical burring, bone grafting, cauterization, argon beam coagulation, polymethyl methacrylate (PMMA), hydrogen peroxide and internal fixation.[2] With curettage, the most commonly employed technique (with or without adjuvants), failure rates range from 0% to 40%. Supplemental use of adjuvants has been shown to decrease recurrence rates.[6] En block resection may also be employed, especially in more aggressive lesions since it has lower recurrence rates but bears greater morbidity.

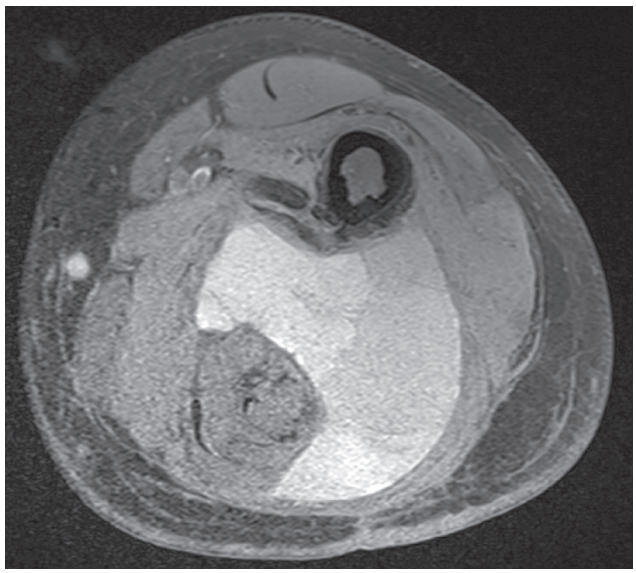

Figure 6 – Post-operative MRI after surgical resection reveals large posterior thigh seroma (axial fat-saturated proton density sequence)

Intralesional curettage with filling up of the remaining cavity with bone substitutes is generally performed in lesions to prevent pathological fractures and in lower-limb lesions with weight-bearing pain. High-speed mechanical burring is used to increase cavity size after curettage. Cauterization, argon beam coagulation and hydrogen peroxide extend the zone of necrosis and eradicate marginal tumor remnants, thus serving as adjuvant therapies.

Growth disturbance and deformity are the most common complications related to surgical treatment groups described in the literature.

Minimally invasive techniques have been increasingly employed for management of ABC, as reported in the literature.[4] Such techniques include intralesional injection of sclerosing agents and arterial embolization.

Sclerotherapy of ABC is an alternative procedure that may act as an adjuvant treatment or bridge to other therapeutic strategies. The radiological efficacy of different sclerosing agents has not been compared, and options include polidocanol, ethibloc, absolute alcohol, calcitonin and steroids, calcium sulfate, doxycycline or a combination of these agents.

Multiple treatments are often needed with injection therapy, reportedly between 1.1 to 6.4,[2] and a failure to heal or recurrence rate of 14.7% has been reported.

The most common complications regarding the most

frequently used agents include induration and hypopigmentation at the size of injection regarding polidocanol and inflammatory reaction with ethibloc.[4]

One single-center randomized controlled trial has compared injection-based therapy and surgical treatment and was not sufficiently powered to detect significant differences with healing as a primary outcome measure.[12] However, surgery was found to result in poorer functional outcomes and a higher number of complications. To the best of the authors' knowledge, there are no other studies comparing surgical and minimally invasive techniques.

Transarterial embolization is another viable option, and can be achieved with coils, polyvinyl alcohol particles or n-butil-cyanoacrilate, among other agents, and has been used for the treatment of ABC.[13] Indeed, it has been shown to halt growth, promote mineralization, and cause pain palliation in several bone tumors.[14] Pre-operative embolization has also been shown to decrease bone loss and transfusion requirements during surgery.

Denosumab is a monoclonal antibody that induces mineralization and has been reported as a useful treatment for giant cell tumors of bone. Some reports have shown efficacy in other fibro-osseous lesions, such as spinal and peripheral ABC, with promising results for local tumor control.[15]

Taking into account the pathogenesis underlying ABC, targeting the dysplastic vessels with endovascular occlusion and filling the cysts with substances that may locally destroy neoplastic cells may produce a synergistic effect. Such combined therapies have the potential to eradicate neoplastic tissue and promote bone remineralization, especially in aggressive, refractory, or unresectable tumors.[10]

The collaboration between the orthopedic oncology and interventional radiology teams at our hospital center has been ongoing for several years, with the intent of providing the best treatments for complex cases such as the one presented in this article. The authors have had good results and feedback with minimally invasive treatments for several complex ABC, successfully reducing or halting tumor growth and promoting sclerosis, which in turn leads to clinical improvement and precludes surgery.

In this case, the choice of performing minimally invasive treatments was not to preclude surgery but to effectively promote sclerosis and fibrosis, decrease tumor size and vascularity in order to facilitate surgical resection, and reduce the risk of complications.

CONCLUSION

Minimally invasive treatment with combined percutaneous and endovascular techniques has been proven to be safe and effective as an alternative or downstaging/adjuvant therapy to facilitate surgery, with significant symptom and quality of life improvement.

Although curettage is the gold standard treatment for ABC, these are often complex lesions that require a distinct case-by-case approach. In light of this, several alternative and adjuvant therapies have been developed, which should be taken into consideration when they pose as available options. However, there are currently no treatment recommendations or guidelines, and further research is needed to compare the different techniques and come up with a rationale to develop adequate therapeutic algorithms.

AUTHOR CONTRIBUTIONS

APC: Study design, data acquisition, writing of the manuscript.

TN: Data acquisition, writing of the manuscript.

CP, FVG, JP, EC, TB: Study design, critical review of the manuscript.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

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PATIENT CONSENT

Obtained.

COMPETING INTERESTS

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

A Case of Giant Cell Tumor of the Fibula

Um Caso de Tumor de Células Gigantes do Perónio

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Keywords: Denosumab/therapeutic use; Fibula; Giant Cell Tumor of Bone/drug therapy; Giant Cell Tumor of Bone/pathology
Palavras-chave: Denosumab/uso terapêutico; Fibula; Tumor de Células Gigantes do Osso/tratamento farmacológico; Tumor de Células Gigantes do Osso/patologia

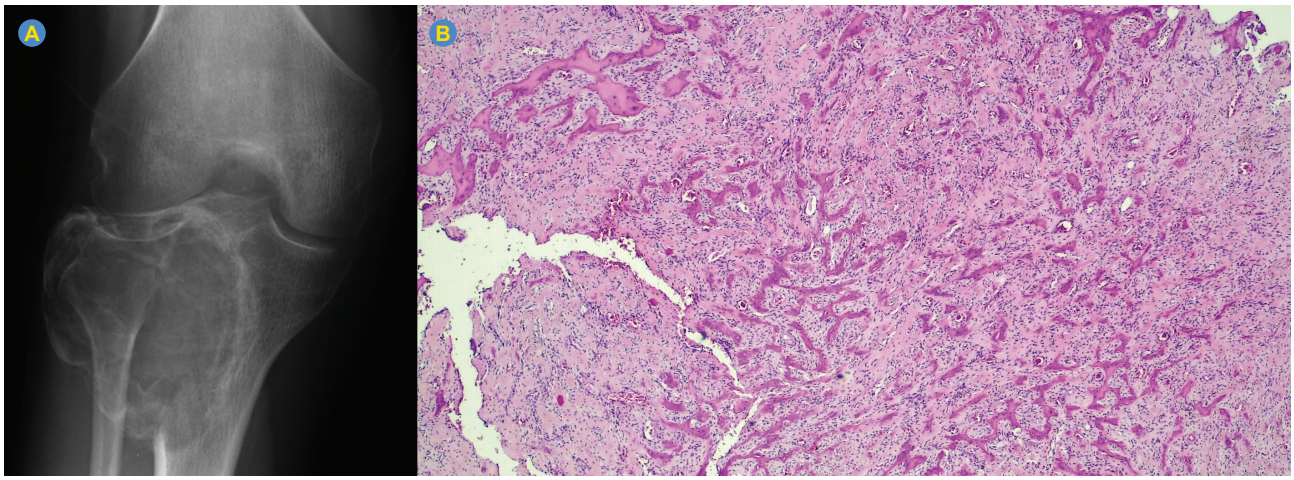

Figure 1 – (A) Giant cell tumour of the fibula. The X-ray, taken before treatment with denosumab, shows a lytic and trabeculated lesion in the epiphysis of the distal fibula. (B) Denosumab-treated giant cell tumor of the bone with the formation of woven bone, between the woven bone there is a proliferation of a fibrous tissue (hematoxilin-eosin 40x)

A 21-year-old male presented to the emergency department with right knee pain and swelling. A diagnosis of giant cell tumor of the bone (GCT) was made on magnetic resonance imaging. The patient started neoadjuvant treatment with denosumab, after which he underwent surgery.

The GCT is a locally aggressive neoplasm, representing 5% of primary bone tumors. It usually occurs between the ages of 20 and 45 and affects the epiphysis of long bones.[1] Radiologically, it is usually lytic, eccentric with trabeculation and has a multilobulated appearance (Fig. 1A).[2]

Denosumab is a human monoclonal antibody against the receptor activator of nuclear factor-κB-ligand that inhibits osteoclastic activity, thus reducing osteolysis, and osteoclast-like cell (OLC) activity (Fig. 1B).[3] The use of neoadjuvant denosumab helps convert an inoperable GCT to a tumor amenable to surgery.[4]

The histological changes induced by denosumab treatment include ossification, fibrosis, and marked decrease/disappearance of OLC. Recognizing these changes is important as they mimic benign fibro-osseous lesions or osteosarcoma.[4]

AUTHOR CONTRIBUTIONS

JMG: Study design, image collection and writing of the manuscript.

RCO: Study design, writing and critical review of the manuscript.

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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

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Abordagem à Infeção pelo Vírus Citomegálico em Doentes Submetidos a Transplante Alogénico de Progenitores Hematopoiéticos

Management of Cytomegalovirus Infection in Allogeneic Hematopoietic Stem Cell Transplant Recipients

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RESUMO

O vírus citomegálico (CMV) é um tipo de vírus de ácido desoxirribonucleico de dupla cadeia que pertence à família *herpesviridae*. Após uma infeção primária, o vírus torna-se latente em vários tipos de glóbulos brancos. A infeção por CMV pode permanecer latente ou tornar-se ativa, especialmente em indivíduos imunodeprimidos, como aqueles submetidos a transplantes de células progenitoras hematopoiéticas (TPH), onde a reativação do CMV pode ocorrer. Neste contexto, a infeção por CMV é comum e associada a elevadas taxas de morbilidade e mortalidade. A pneumonite é uma das complicações mais graves, com taxas de mortalidade superiores a 50%. Além disso, mesmo na ausência de doença específica do órgão, a infeção por CMV está relacionada com um aumento da mortalidade não relacionada com a recidiva da neoplasia hematológica. Dada a frequência e gravidade desta infeção em doentes submetidos a TPH, é crucial implementar estratégias eficazes de monitorização, prevenção e tratamento. Este protocolo foi desenvolvido para identificar os grupos de doentes que se beneficiam de uma abordagem sistematizada para a infeção por CMV e definir a estratégia mais adequada para cada grupo. A monitorização da carga viral de CMV no sangue periférico é fundamental, especialmente em doentes com risco moderado a elevado de infeção ativa. A profilaxia primária com letermovir (fármaco antiviral) é recomendada para reduzir a incidência de infeção ativa, especialmente em doentes com alto risco. A profilaxia secundária com valganciclovir (fármaco antiviral) é recomendada após um episódio de infeção ativa, enquanto o tratamento de antecipação e de doença é baseado na monitorização da carga viral e na resposta clínica. Este protocolo visa melhorar a abordagem da infeção por CMV em doentes submetidos a TPH, garantindo uma abordagem preventiva e terapêutica eficaz e segura.
Palavras-chave: Antivirais/uso terapêutico; Infecções por Citomegalovirus/etiologia; Infecções por Citomegalovirus/prevenção e controlo; Infecções por Citomegalovirus/tratamento farmacológico; Transplantação de Progenitores Hematopoiéticos/efeitos adversos

ABSTRACT

Cytomegalovirus (CMV) is a type of double-stranded deoxyribonucleic acid virus belonging to the *herpesviridae* family. Following a primary infection, the virus becomes latent in various types of white blood cells. Cytomegalovirus infection can remain latent or become active, especially in immunocompromised individuals, such as those undergoing hematopoietic stem cell transplantation (HSCT), where CMV reactivation can occur. In this context, CMV infection is common and associated with high rates of morbidity and mortality. Pneumonia is one of the most serious complications, with mortality rates exceeding 50%. Additionally, even in the absence of organ-specific disease, CMV infection is related to increased mortality unrelated to hematologic neoplasm recurrence. Given the frequency and severity of this infection in HSCT patients, it is crucial to implement effective strategies for monitoring, prevention, and treatment. This guideline was developed to identify patient groups that benefit from a systematic approach to CMV infection and to define the most appropriate strategy for each group. Monitoring CMV viral load in peripheral blood is crucial, especially in patients at moderate to high risk of active infection. Primary prophylaxis with letermovir (an antiviral drug) is recommended to reduce the incidence of active infection, especially in high-risk patients. Secondary prophylaxis with valganciclovir (antiviral drug) is recommended after an episode of active infection, while preemptive and disease treatment is based on monitoring viral load and clinical response. The aim of this guideline is to improve the approach to CMV infection in HSCT patients, ensuring an effective and safe preventive and therapeutic approach.
Keywords: Antiviral Agents/therapeutic use; Cytomegalovirus Infections/drug therapy; Cytomegalovirus Infections/etiology; Cytomegalovirus Infections/prevention & control; Hematopoietic Stem Cell Transplantation/ adverse effects

INTRODUÇÃO

O vírus citomegálico (*cytomegalovirus*, CMV) é um vírus de cadeia dupla de ácido desoxirribonucleico (ADN) que pertence à família *herpesviridae.* Após infeção primária, o vírus torna-se latente em múltiplos leucócitos.[1] A infeção por CMV pode ser classificada como latente ou ativa, sendo que, no contexto de imunossupressão, é possível que ocorra reativação de infeção latente.

No caso específico dos doentes submetidos a transplante de progenitores hematopoiéticos (TPH), o CMV é o vírus que mais frequentemente apresenta reativação, e esta associa-se a morbimortalidade significativa.[2,3] Sem profilaxia, estima-se que aproximadamente 60% a 80% dos doentes seropositivos para CMV submetidos a TPH alogénico apresentem infeção ativa, assim como 20% a 30% dos doentes seronegativos submetidos a TPH alogénico de dadores seropositivos.[4,5] Após a reativação, a evolução para doença de órgão-alvo (pneumonite, colite, retinite, etc.) é comum, sendo a pneumonite a complicação mais grave,

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com taxas de mortalidade superiores a 50%.[5] Destaca-se que, mesmo na ausência de doença de órgão-alvo, a infeção pelo CMV associa-se ao aumento de mortalidade não relacionada com recidiva da neoplasia hematológica.[6]

Considerando a frequência e a gravidade da infeção pelo CMV nos doentes submetidos a TPH, é necessário definir uma estratégia de monitorização, prevenção e tratamento da infeção que seja o mais eficaz possível. É importante que tal estratégia seja segura para os doentes, minimizando os efeitos secundários indesejáveis (tais como mielossupressão, lesão renal ou hepatotoxicidade). O objetivo deste protocolo consiste em identificar os grupos de doentes submetidos a TPH que beneficiam de uma abordagem sistematizada à infeção pelo CMV e definir qual a estratégia de monitorização, prevenção e tratamento mais adequada a cada grupo em questão. Este protocolo foi elaborado pelos Serviços de Doenças Infeciosas, Hematologia Clínica e Unidade de Farmacologia Clínica da Unidade Local de Saúde de São João e aprovado pela sua Comissão de Farmácia e Terapêutica.

DEFINIÇÃO DE CONCEITOS

Com o objetivo de facilitar a compreensão e abordagem do protocolo, definem-se os seguintes conceitos:

- Transplante de progenitores hematopoiéticos alogénico: TPH provenientes de um dador que não o recetor do transplante.
- Transplante de progenitores hematopoiéticos autólogo: TPH provenientes do próprio recetor do transplante.
- Recetor seropositivo para CMV (R+): recetor com exposição prévia ao CMV, demonstrada pela deteção de imunoglobulina G (IgG) específica para CMV.
- Dador seropositivo para CMV (D+): dador com exposição prévia ao CMV, demonstrada pela deteção de IgG específica para CMV.
- Infeção latente: estado de infeção associado a manutenção de genoma vírico com capacidade de replicação, mas sem evidência de replicação vírica.
- Infeção ativa: estado de infeção associado a replicação vírica com deteção de antigénios ou ácidos nucleicos víricos; pode corresponder a primoinfeção ou reativação de infeção latente, independentemente da presença de sintomas.
- Doença citomegálica: infeção ativa pelo CMV com sintomas diretamente atribuíveis; pode ocorrer como síndrome vírica ou doença de órgão-alvo.
- Profilaxia primária: administração de antivíricos com o objetivo de prevenir infeção ativa pelo CMV.
- Tratamento de antecipação (em inglês *preemptive)*: início de tratamento antivírico perante deteção de infeção ativa pelo CMV, com o objetivo de prevenir o desenvolvimento de doença; implica monitorização regular de antigénios ou ácidos nucleicos.
- Profilaxia secundária: administração de antivíricos após tratamento de antecipação ou tratamento de doença, com o objetivo de prevenir recidiva de infeção.

FATORES DE RISCO

O principal preditor de infeção por CMV após TPH é o estado serológico do recetor antes do transplante,[7] mas existem outros fatores de risco a ter em consideração.

INFEÇÃO ATIVA

A infeção ativa pelo CMV ocorre habitualmente nos primeiros 100 dias pós-TPH.[8,9] Os principais fatores de risco para infeção pelo CMV nesta população estão descritos e categorizados na Tabela 1.[10-13]

INFEÇÃO TARDIA

A infeção ativa pelo CMV também pode ocorrer posteriormente ao dia 100 pós-TPH (infeção tardia).[8] Os principais fatores de risco para infeção tardia pelo CMV são[11]:

- Linfopenia (< 100 linfócitos/mm^3);
- Infeção pelo CMV antes do dia 100 pós-TPH;
- Desenvolvimento de doença aguda de enxerto *versus* hospedeiro (DEVH) com necessidade de prednisolona em altas doses (≥ 0,5 mg/kg/dia) ou equivalente;
- Ausência de imunidade de células T específicas para CMV.

MANIFESTAÇÕES CLÍNICAS

O diagnóstico de infeção ativa pelo CMV ocorre frequentemente em doentes assintomáticos.[11] Na ausência de tratamento de antecipação, a infeção pode evoluir para doença com sintomas associados, sendo que as principais síndromes clínicas incluem[5,14]:

- Síndrome vírica caracterizada por febre e mal-estar geral.
- Doença de órgão-alvo:
  - Pneumonite;
  - Doença gastrointestinal:
    - Esofagite;
    - Gastroenterite;
    - Colite;
  - Hepatite;
  - Pancreatite;
  - Retinite;
  - Doença do sistema nervoso central;
  - Doença geniturinária:
    - Nefrite;

  - Cistite;
- Pancitopenia;
- Disfunção multiorgânica.

O diagnóstico de doença de órgão-alvo não deve ser realizado apenas com base na deteção de CMV no sangue periférico e sintomas associados ao órgão com suspeita de envolvimento. Sempre que possível, devem ser colhidas amostras do tecido em questão para deteção do CMV por técnicas de histopatologia, imunohistoquímica, microbiologia ou biologia molecular, permitindo a confirmação do diagnóstico.[5]

MONITORIZAÇÃO

A monitorização de infeção ativa pelo CMV deve ser iniciada precocemente após o alotransplante e realizada através da deteção de ADN de CMV no sangue periférico (carga vírica) com recurso a técnica de *polymerase chain reation* (PCR), uma vez que é mais sensível que a deteção do antigénio pp65 para infeção ativa e permite também melhor quantificação da infeção.[11,15]

A monitorização está recomendada nos seguintes doentes:

- Recetores de TPH alogénico seropositivos para CMV (R+).
- Recetores de TPH alogénico seronegativos para CMV (R-) e dadores seropositivos (D+).

A monitorização deve ser realizada da seguinte forma:

- Pelo menos uma vez por semana desde o dia zero até ao dia 100 pós-TPH.
- Pelo menos uma vez a cada duas semanas desde o dia 100 até ao dia 180 pós-TPH.

A monitorização pode ser diferente em algumas situações:

- Semanalmente desde o dia zero até aos 12 meses pós-TPH nos doentes com fatores de risco para infeção tardia.

A monitorização também pode ser considerada nos seguintes doentes:

- Recetores de TPH alogénico seronegativos para CMV (R-) e dadores seronegativos (D-), com necessidade de múltiplas transfusões pós-TPH.
- Recetores de TPH autólogo e infeção pelo CMV antes do dia 60 pós-TPH ou com transplante com células CD34 positivas, isto é, células progenitoras hematopoiéticas que o vírus tem capacidade de infetar e estabelecer latência.

PREVENÇÃO

Profilaxia primária

A profilaxia primária deve ser complementar a uma estratégia de antecipação e não substituinte desta. A profilaxia primária com letermovir reduz a incidência de infeção ativa pelo CMV e tem menor toxicidade que os fármacos alternativos.[12]

A profilaxia está recomendada nos seguintes doentes (*on-label*)[16,17]:

Tabela 1 – Estratificação de risco tendo em conta situação clínica em casos de TPH alogénico

Categorização do risco	Situação clínica
Risco muito baixo	Transplante autólogo Casos com D-/R-
Risco baixo	Casos com D+/R- (sem outros fatores de risco)
Risco moderado	Casos com D+/R- associados a: • DEVH aguda • Uso de prednisolona numa dose de 1mg/kg/dia ou equivalente • Enxerto com *mismatch* do sistema *human leukocyte antigen* (HLA) • Enxerto de células do cordão umbilical • Enxerto com depleção de células T • Uso de alemtuzumab • Uso de ciclofosfamida • Linfopenia • Idade avançada
Risco elevado	Casos com D+/R+ (sem outros fatores de risco)
Risco muito elevado	Casos com D-/R+ Casos com D+/R+ associados a: • Dador relacionado com pelo menos uma incompatibilidade do gene HLA (A, B ou DR) • Dador não relacionado num dos 4 *loci* do gene *HLA* (A, B, C ou DRB1) • Dador haploidêntico • Enxerto com depleção de células T • Enxerto de células do cordão umbilical • Desenvolvimento de doença de enxerto versus hospedeiro (DEVH) pelo menos de grau 2 com uso de prednisolona numa dose de 1 mg/kg/dia ou equivalente

- Recetores de TPH alogénico seropositivos para CMV (R+) e dadores seronegativos para CMV (D-) – grupo de risco muito elevado.
- Recetores de TPH alogénico seropositivos para CMV (R+) e dadores seropositivos para CMV (D+) – grupo de risco pelo menos elevado.

A profilaxia deverá ser considerada nos seguintes doentes (*off-label*, com avaliação caso a caso):

- Recetores de TPH alogénico seronegativos para CMV (R-) e dadores seropositivos para CMV (D+) – grupo de risco baixo a moderado.

A profilaxia não se encontra recomendada nos seguintes doentes:

- Recetores de TPH alogénico seronegativos para CMV (R-) e dadores seronegativos para CMV (D-) – grupo de risco muito baixo.

O esquema de profilaxia consiste em letermovir 480 mg PO id desde o dia zero até ao dia 100 pós-TPH (deverá ser iniciado no máximo até ao dia 28).[11,16,17]

É de realçar que[11,13,16,17]:

- A profilaxia com letermovir deve ser suspensa se for iniciado tratamento de antecipação ou tratamento de doença por CMV.
- A profilaxia com letermovir não previne reativação de vírus *herpes simplex* (VHS), varicela-zoster (VVZ), Epstein-Barr (EBV) ou adenovírus; a profilaxia com aciclovir ou valaciclovir para VHS e/ou VVZ deve ser mantida, se necessário.
- A utilização de letermovir pode aumentar a concentração sérica de tacrolimus (inibidor da calcineurina), sirolimus (inibidor da mTOR) e ciclosporina (inibidor da calcineurina), pelo que se deve aumentar a monitorização destes fármacos nas duas primeiras semanas após iniciar e depois de terminar o letermovir; também pode reduzir a concentração sérica de voriconazol (antifúngico), pelo que os níveis séricos deste fármaco também devem ser monitorizados.
- A dose de letermovir deve ser reduzida para 240 mg PO id se uso concomitante de ciclosporina.
- A utilização de letermovir está contraindicada se uso concomitante de dabigatrano (anticoagulante oral direto), atorvastatina (estatina), sinvastatina (estatina), rosuvastatina (estatina) ou pitavastatina (estatina).
- As interações farmacológicas e contraindicações devem ser sempre consultadas previamente à prescrição de letermovir.
- O letermovir não é recomendado em doentes com patologia hepática grave (Child-Pugh classe C) e não existem recomendações específicas para doentes com doença renal terminal (com ou sem diálise).
- Se o letermovir não puder ser usado como profilaxia, recomenda-se uma estratégia de monitorização e tratamento de antecipação, não estando recomendada profilaxia com outros agentes.

Tal como referido anteriormente, é necessário manter a monitorização de infeção ativa pelo CMV nos doentes sob profilaxia primária, uma vez que a taxa de infeção pode chegar até 20% nestes doentes. Após término da profilaxia primária no dia 100, é também necessário manter monitorização até pelo menos ao dia 180, tendo em especial atenção que a taxa de infeção tardia após letermovir pode situar-se entre 10% e 20%.[11]

A profilaxia primária estendida (até aos 200 dias pós-transplante) já foi testada em doente com alto risco de reativação tardia de CMV e mostrou-se bem tolerada e eficaz na redução de infeção CMV clinicamente significativa.[18] Contudo, ainda se levantam questões devido ao atraso da reconstituição imune específica anticitomegálica.[19] A profilaxia primária estendida pode ser ponderada nas seguintes situações:

- Ter um dador relacionado com pelo menos uma incompatibilidade num dos três locais genéticos HLA especificados (HLA-A, HLA-B ou HLA-DR);
- Ter um dador não relacionado com pelo menos uma incompatibilidade num dos quatro locais genéticos HLA especificados (HLA-A, HLA-B, HLA-C ou HLA-DRB1);
- Ter um dador haploidêntico;
- Utilizar células de cordão umbilical como fonte;
- Ser recetor de enxertos *ex-vivo* depletados de células T, globulina antitimocítica ou alemtuzumab;
- Doença do enxerto contra hospedeiro (*graft versus host disease*, GVHD) ou outras condições que exijam o uso de prednisona sistémica (ou seu equivalente) numa dose de pelo menos 1 mg/kg de peso corporal por dia, dentro de seis semanas após randomização.

Profilaxia secundária

A profilaxia secundária é feita com valganciclovir 900 mg PO id e está recomendada após um episódio de infeção ativa pelo CMV em todos os doentes submetidos a TPH ou, como alternativa, uma estratégia de monitorização e tratamento de antecipação.[11] A profilaxia pode ser mantida durante várias semanas, permitindo a reconstituição imune.[20]

Nos doentes com um episódio de infeção antes do TPH, o esquema de profilaxia secundária deve ser individualizado e discutido em equipa multidisciplinar, uma vez que o valganciclovir pode apresentar toxicidade hematológica não aceitável durante o TPH. Não existe ainda evidência científica robusta para a utilização de letermovir nestes casos, embora já existam pequenos estudos retrospetivos

que apoiem a sua utilização.[11] A sua utilização pode ser ponderada caso a caso, sendo considerada *off-label*.

TRATAMENTO

Os tratamentos encontram-se resumidos na Tabela 2 e Fig. 1.

Tratamento de antecipação

O tratamento de antecipação é baseado na monitorização de infeção ativa pelo CMV. É importante realçar que não existe um valor de carga vírica estabelecido para diagnóstico de infeção ativa. Existem modelos que apresentam uma estratégia de início de terapêutica de antecipação com base nos valores de carga vírica de CMV e fatores de risco do doente,[21] sendo que as recomendações atuais são que cada instituição deve definir os limiares para início de tratamento.[11] Com base num ensaio bem-sucedido de Marty *et al*,[12] definimos que o início de terapêutica de antecipação deve ocorrer nas seguintes situações:

- Carga vírica de CMV > 130 UI/mL em doentes de risco muito elevado;
- Carga vírica de CMV > 270 UI/mL nos restantes doentes.

Ressalvamos que os valores de ponto de corte devem ser adaptados à técnica utilizada e podem não ser reprodutíveis entre centros.

Após as 14 semanas de transplante (D+100), o limiar para início de terapêutica de antecipação passa a ser 270 UI/mL para todos os doentes.

O uso de letermovir como terapêutica de antecipação não representa a prática clínica atual, sendo pouca a evidência que recomenda o seu uso neste tipo de estratégia.[11] Existem, no entanto, estudos que sugerem uma possível utilização futura do fármaco neste contexto,[22] sendo necessários estudos confirmatórios.

O esquema de tratamento de antecipação de primeira linha consiste em duas semanas (fase de indução) de valganciclovir 900 mg PO de 12 em 12 horas ou, em alternativa, ganciclovir 5 mg/kg EV de 12 em 12 horas caso se verifique ausência de via oral ou na presença de DEVH gastrointestinal grave que condicione a absorção do fármaco.[11,15] Durante o tratamento de antecipação é muito importante vigiar sinais e sintomas sugestivos de doença por CMV, tais como alteração da acuidade visual, sintomas respiratórios, sintomas gastrointestinais e sintomas neurológicos.

Os efeitos secundários comuns associados ao ganciclovir e valganciclovir incluem anemia, neutropenia e trombocitopenia, pelo que devem ser realizadas monitorizações com hemograma pelo menos duas vezes por semana. É necessário ajuste de dose de ganciclovir e valganciclovir à função renal, pelo que esta também deve ser monitorizada com regularidade.[11,15]

Caso o doente se apresente na fase de pré-enxerto ou pós-enxerto precoce, se apresentar intolerância aos fármacos de primeira linha ou se tiver citopenias importantes, deve considerar-se o tratamento de antecipação com foscarnet 90 mg/kg EV de 12 em 12 horas.[11,15,23]

Os efeitos secundários comuns associados ao foscarnet incluem nefrotoxicidade e distúrbios eletrolíticos (potássio, cálcio, magnésio e fosfato),[11,15] pelo que devem ocorrer monitorizações com função renal e ionograma pelo menos duas vezes por semana. É necessário ajustar a dose de foscarnet à função renal, e cada administração deve ser acompanhada de fluidoterapia com 500 a 1000 mL de NaCl 0,9%.

Devido à elevada incidência de nefrotoxicidade, o cidofovir apenas deve ser considerado como terapêutica de terceira linha.[10,11,15,23]

A carga vírica de CMV deve ser monitorizada ao longo das duas semanas da fase de indução do tratamento de antecipação. De acordo com a carga vírica no final das duas semanas, a próxima fase do tratamento deve ser decidida:

Tabela 2 – Quadro-resumo de tratamento de CMV

Profilaxia primária		**Letermovir**
Tratamento de antecipação	1.ª linha	Ganciclovir/Valganciclovir
	2.ª linha	Foscarnet
	3.ª linha	Cidofovir
Tratamento de doença	1.ª linha	Ganciclovir
	2.ª linha	Foscarnet
	3.ª linha	Cidofovir
Tratamento de infeção refratária/resistente	1.ª linha	(Maribavir)
	2.ª linha	Foscarnet
	3.ª linha	Cidofovir
Profilaxia secundária		Ganciclovir/Valganciclovir

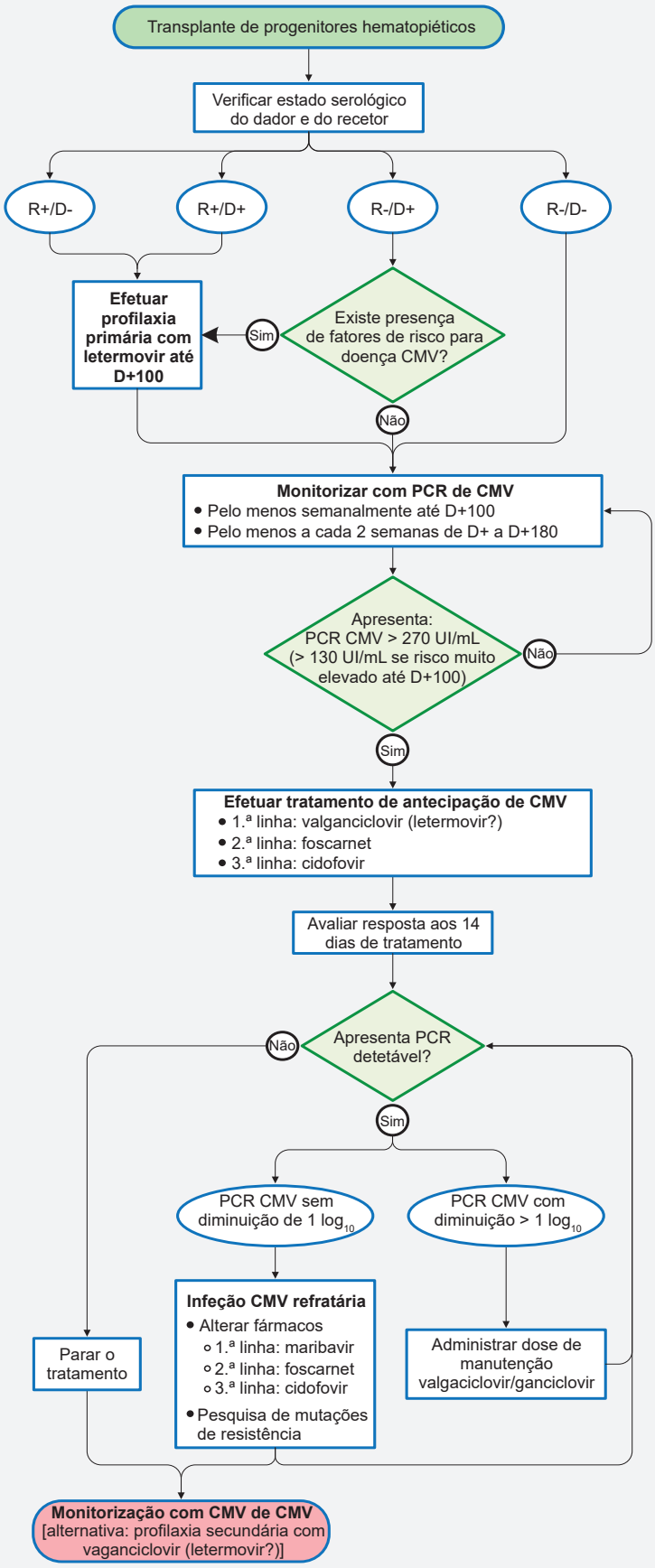

Figura 1 – Fluxograma de tratamento do CMV após transplante de progenitores hematopoiéticos

- Se a carga vírica for indetetável: terminar tratamento de antecipação e manter monitorização.[11] O tratamento de antecipação poderá ser reiniciado posteriormente de acordo com os critérios de monitorização.
- Se a carga vírica estiver em decrescendo (≥ 1 $\log_{10}$): transitar para valganciclovir 900 mg PO id ou ganciclovir 5 mg/kg EV id até que se atinja carga vírica indetetável (fase de manutenção).[11]
- Se a carga vírica for sobreponível ou em decrescendo < 1 $\log_{10}$ (possível infeção refratária) ou se a carga vírica estiver em crescendo ≥ 1 $\log_{10}$ (infeção refratária): considerar prolongar a fase de indução e reavaliar a carga vírica posteriormente e/ou pesquisar a resistência ao ganciclovir/valganciclovir e/ou alterar a terapêutica para outro fármaco (foscarnet, cidofovir ou maribavir 400 mg PO de 12 em 12 horas, representando este último a maior promessa neste contexto).[24,25] A pesquisa de resistências genotípicas deverá ser realizada em centros de referência para a técnica.

O marivibir encontra-se autorizado pela Agência Europeia do Medicamento (EMA),[26] mas ainda não foi avaliado pelo Infarmed (à data de junho de 2024), pelo que, caso seja necessária a sua utilização, deverá ser emitida uma autorização de utilização especial (AUE) em articulação com a Comissão de Farmácia e Terapêutica e o Infarmed. Após aprovação, a sua utilização deverá ser equacionada caso a caso, dentro das indicações do RCM (tratamento de infeção por CMV refratária após utilização de um fármaco ativo – ganciclovir, valganciclovir, foscarnet ou cidofovir).

A infeção citomegálica refratária define-se por elevação da carga vírica do CMV sanguínea mais de 1 $\log_{10}$ após pelo menos duas semanas de tratamento antivírico apropriado. A infeção será provavelmente refratária se houver persistência de carga vírica (sem diminuição superior a 1 $\log_{10}$) após pelo menos duas semanas de tratamento antivírico apropriado. É recomendado que na infeção citomegálica refratária e provavelmente refratária haja pesquisa de mutações de resistência do CMV no gene que codifica a *UL97* (codões 460, 520, 594, 595, 603, 607). Estas mutações condicionam resistência ao ganciclovir mas manutenção da sensibilidade ao foscarnet e cidofovir. No caso de suspeita de resistência ao foscarnet ou cidofovir deverá também ser pesquisado mutações no gene que codifica a *UL54*.[15]

Tratamento de doença

O tratamento de doença por CMV é semelhante ao tratamento de antecipação, mas deve ser iniciado com ganciclovir 5 mg/kg EV de 12 em 12 horas durante um período a definir consoante a resposta clínica ao tratamento, a resposta imagiológica (se aplicável) e a evolução da carga vírica sérica (e do líquido cefalorraquidiano, se aplicável). Habitualmente, a duração do tratamento é superior a 14 dias.[27] No caso da retinite, o tempo de tratamento varia entre duas e três semanas. Na doença gastrointestinal, o tempo de tratamento varia entre três e seis semanas, até à resolução dos sintomas. Na doença do SNC, deve-se manter o tratamento até à resolução dos sintomas e à negativação da carga vírica no líquido cefalorraquidiano. Após término do tratamento de doença por CMV, deve ser iniciado um esquema de profilaxia secundária.

No caso da pneumonite por CMV, pode-se considerar a adição de imunoglobulina EV em altas doses ao ganciclovir.[15]

A terapêutica para a doença refratária/resistente é composta pelo uso de foscarnet 90 mg/kg EV de 12 em 12 horas, cidofovir 5 mg/kg semanal ou por uma combinação de cidofovir e foscarnet. O uso de maribavir (400 mg PO a cada 12 horas) poderá ser considerado no caso de doença refratária.[15]

Tal como referido na secção 'Tratamento de antecipação', os principais efeitos secundários associados aos fármacos utilizados devem ser monitorizados, assim como o ajuste de dose à função renal, se indicado.

CONTRIBUTO DOS AUTORES

FS, AM: Revisão bibliográfica, elaboração do rascunho do manuscrito.

PF, DL: Revisão bibliográfica, revisão crítica do manuscrito.

JB, JA, FT: Revisão crítica do manuscrito.

RP, ASP: Conceção, revisão crítica e aprovação da versão final do manuscrito.

CONFLITOS DE INTERESSE

RP participou num conselho consultivo da Takeda.

ASP possui contrato com a MSD; recebeu honorários de consultoria da Pfizer, Takeda e Gilead; recebeu pagamento ou honorários da Gilead e Takeda para participação em palestras, apresentações, gabinetes de oradores, redação de manuscritos ou eventos educativos; recebeu apoio da Pfizer e Gilead para participar em reuniões e/ou deslocações.

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Palmar Psoriasis or Missed Syphilis?

Psoríase Palmar ou Sífilis Disfarçada?

Keywords: Psoriasis/diagnosis; Syphilis/diagnosis
Palavras-chave: Psoríase/diagnóstico; Sífilis/diagnóstico

To the Editor,

Syphilis is a systemic sexually transmitted infection caused by *Treponema pallidum*. The incidence of syphilis in European countries has shown an overall increase since 2000.[1] Moreover, noticeable increases in syphilis among heterosexual men and women have been reported in 2022.[2]

Syphilis is a chronic infection that evolves through several stages. Its clinical manifestations are diverse and often wrongly attributed to other diseases, so this disease is known as 'the great imitator'. Primary infection usually causes a painless ulcer or chancre that heals within weeks and may be undetected by the patient. Hematogenous dissemination of *T. pallidum* up to six months after initial infection causes secondary syphilis. Secondary syphilis manifestation can include skin rash and varied systemic features.[1] If left untreated, besides transmission, secondary syphilis potentially develops into complications and permanent sequelae known as tertiary syphilis.

A 64-year-old heterosexual man with no significant medical history presented with non-pruritic palmoplantar lesions evolving for two months, which did not improve after topical therapy with calcipotriol and betamethasone dipropionate.

Well-defined hyperkeratotic plaques and erythematous macules and papules limited to the palms and soles were observed (Fig. 1). No other mucocutaneous lesions were noticed, except for hypertrophic pink plaques with a smooth and moist surface in the perianal region suggestive of *condyloma lata*.

Molecular test for *T. pallidum* DNA detection from the perianal lesion exudate was positive. Treponema pallidum hemagglutination assay (TPHA) was reactive, with a Venereal Disease Research Laboratory (VDRL) titer of 1:128.

The patient was treated with a single intramuscular dose of benzathine penicillin (2 400 000 U).

After therapy, there was rapid resolution of the palmoplantar lesions (Fig. 2) and the *condyloma lata*. The VDRL titer decreased to 1:32 dilutions two months after treatment.

The multiple manifestations of secondary syphilis can lead to misdiagnosis and late diagnosis. Even though dermatological manifestations of secondary syphilis may be non-specific and may present to non-dermatologists, one important distinguishing feature is the involvement of the palms and soles. Few cases of hyperkeratotic palmar and plantar lesions have been described as a presentation of secondary syphilis, classically known as *clavi syphilitici*.[3,4] This clinical presentation may be mispresented as viral warts, calluses, or palmoplantar psoriasis.

Current guidelines on syphilis management support the key role of benzathine penicillin treatment for all forms of syphilis.[5]

This case reinforces the relevance and the importance of considering syphilis as a diagnostic hypothesis in atypical dermatoses or those not responding to conventional therapy.

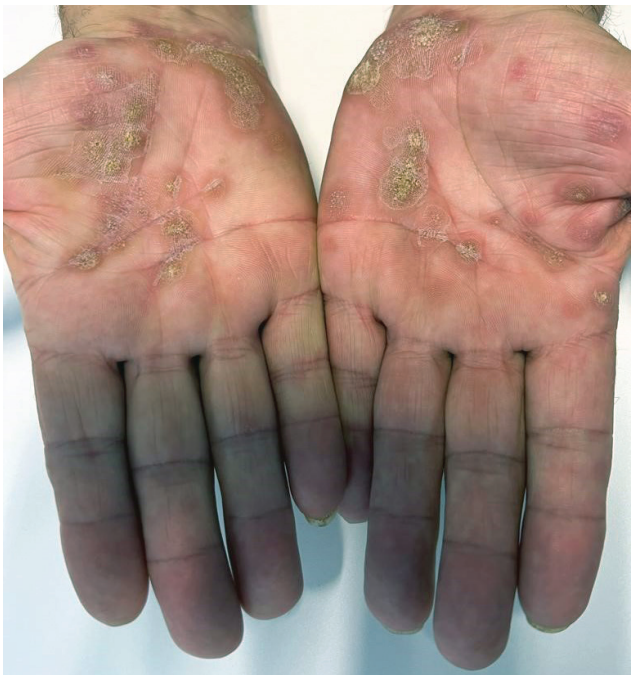

Figure 1 – Hyperkeratotic plaques and erythematous papules and macules on the palms

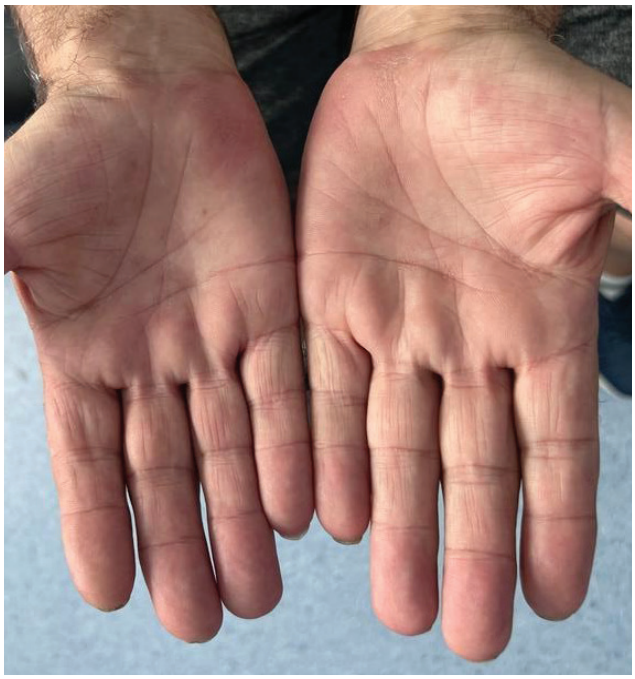

Figure 2 – Resolution of the palmar lesions two months after therapy with intramuscular benzathine penicillin

AUTHOR CONTRIBUTIONS

PRM: Literature search, data acquisition, writing of the manuscript.

BG: Writing of the manuscript.

CL: Critical review of the manuscript.

All authors approved the final version to be published.

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

The authors have declared that no competing interests exist.

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Bridging the Gap: Use of Mental Health Apps in the Adolescent Population

Estabelecendo Pontes: Aplicações Dedicadas à Saúde Mental na População Adolescente

Keywords: Adolescent; Mental Disorders; Mental Health, Mobile Applications
Palavras-chave: Adolescente; Aplicativos Móveis; Perturbações Mentais; Saúde Mental

Dear Editor,

It was with great interest that we read the article "Perspectives on the Implementation of Mental Health Apps on Clinical Interventions in Mental Health" published in the July-August 2024 issue of Acta Médica Portuguesa.[1] In the article, the authors explore the growing interest in mobile mental health apps as a potential tool for managing mental health conditions, but we would like to take the discussion further, focusing on a specific population, namely adolescents.

According to the global assessment of the World Health Organization, one in seven individuals between the ages of 10 and 19 experiences a mental disorder, accounting for 13% of the global burden of disease in this age group.[2] However, the current mental healthcare infrastructure is not built to support and effectively treat the vast number of young people experiencing mental health challenges.[3]

As the article highlights, we are at a crucial point in the integration of digital solutions in the healthcare system,[1] and they may be part of an answer to the large gap between the need and delivery of mental health services for adolescents.[4] However, existing research into the use of mental health apps in the adolescent population indicates that their effectiveness remains uncertain, with most studies focusing on depression and anxiety, and little research into other clinical areas.[4] Adding to this, research shows that most available mental health apps are not evidence based, and they will continue to come from multiple companies, lacking scientific validation and without a structured classification that differentiates content according to users' ages.[5] Even so, as ubiquitous users of new technologies, adolescents will continue to have access to these apps, and we can only speculate about the impact this may have on their mental health, with very few studies tracking the long-term outcomes of digital mental health interventions.[5]

As for chatbots, these software applications can be specially appealing to many youths, since they can deliver information in a conversational, human-like manner, and provide users anonymity, thereby eliminating social stigma as a barrier that often prevents successful linkage with mental health services.[4] But what is easier for an adolescent in distress: to navigate the internet in search of help, or face the disclosure of their problems with an adult in order to get an appointment with a qualified professional?

In times of disparity between the exponential development of artificial intelligence tools and the lack of human resources, mental health apps seem to hold great promise in delivering accessible interventions in mental health,[4] but, until then, we cannot forget how vulnerable our adolescents can be.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Comment on "Assessment of the Implementation of the International Health Regulations during the COVID-19 Pandemic: Portugal as a Case Study"

Comentário ao Artigo "Avaliação da Implementação do Regulamento Sanitário Internacional durante a Pandemia de COVID-19: O Caso Português"

Keywords: Decision Making; Health Policy; International Health Regulations; Pandemics; Preparedness
Palavras-chave: Pandemias; Política de Saúde; Regulamento Sanitário Internacional; Tomada de Decisão

Every year, countries self-assess their compliance with the core capacities of the International Health Regulations (IHR). In Portugal, this assessment is conducted by the Directorate-General of Health (DGS), and the results are published by the World Health Organization (WHO).[1] Since 2021, the second edition of the State Party Self-Assessment Annual Reporting tool (SPAR)[2] has been used.

In the study by Queiroz *et al*,[3] 15 public health residents evaluated the IHR implementation in Portugal based on their perspectives and on publicly available information. As the IHR national focal point, DGS welcomes the initiative and contribution to a broader approach to the IHR's challenges. However, we believe several aspects of the article do not adequately reflect the process and results of the assessment of IHR capacities in Portugal.

Firstly, the article claims that annual updates of the IHR's implementation status do not exist or are not publicly available. However, under the IHR, the yearly national reports of the IHR implementation status and changes over the years of all countries are published by the WHO,[1] based on the submissions of the annual SPAR by each country. Within the context of the pandemic, in 2020 - 2021, there was a short delay in the publication of SPAR updates on the WHO website, but Portugal has maintained its annual reporting.

Secondly, the study incorrectly claims that Portuguese surveillance mainly relies on indicator-based surveillance through the National Epidemiological Surveillance System (SINAVE), whose sources are notifications from physicians and labs. However, there is also an event-based surveillance system in place, and the DGS operates a specialized unit for this purpose, known as the Center for Public Health Emergencies (CESP), with a specific legal framework that includes epidemic intelligence and event-based surveillance. The CESP is actively engaged in continuous, systematic, event-based surveillance, with relevant threats detected, assessed, and communicated weekly to the public health authorities network, relevant partners within the healthcare sector, and other sectors. This includes the RONDA (*Relatório de Observações, Notícias, Dados e Alertas*) weekly meeting and weekly health threats report, shared with the aforementioned stakeholders. Epidemic intelligence,[4] combining event-based and indicator-based surveillance for risk assessment and communication of threats, is a legal responsibility of the DGS and has been operationalized since 2005. Under the epidemic intelligence framework, a study has recently been published presenting all threats reported in RONDA since 2016.[5] We understand that there is room for improvement, namely in technological and artificial intelligence tools and an information system that fully supports event-based surveillance, as well as in the visibility of epidemic intelligence activities and outputs outside the public health network. However, stating that Portuguese surveillance mainly relies on indicator-based surveillance is not aligned with reality.

Thirdly, the article claims that there is a gap between self-reported and peer-assessed IHR implementation in Portugal. To support this, they focus on the Points of Entry (PoE) capacity and compare Portugal's IHR score[1] to the results of a study on PoE published in 2018.[6] While we consider the 2018 study a useful evaluation, we advise against comparing these results, as they differ in their scope and aim, methods, and assessment tools.

Fourthly, the study suggests that the existence of non-publicly available documents would breach the IHR. We clarify that key framework documents, including Portuguese legal[4] and technical ones, are publicly available. However, the execution of the implementation of the IHR and the overall process of articulation and communication with different entities and other sectors' stakeholders is not expected to always be publicized since communication differs considering public health actions and needs in accordance with the threat assessment.

To conclude, we endorse all initiatives that may support the IHR and all efforts to analyze its implementation, and we acknowledge that there is a great deal for improvement in its different spheres of action. However, it is relevant to minimize the risk of factual inaccuracies in publications related to national and international preparedness and response assessment instruments that may lead to an inaccurate interpretation of the national reality.

We hope that this discussion can contribute to the enhancement of the IHR's capacities for public health emergency preparedness and response at the national and subnational levels with different partners, ensuring an adequate response in future acute events through prevention, early detection, assessment, notification, and response to public health risks, while ultimately contributing to global health security.

AUTHOR CONTRIBUTIONS

SVS, PV: Conceptualization and writing of first draft.

VRP, AF, MF, RLS: Conceptualization and critical review of the manuscript.

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The Effect of Globalization on Hemoglobinopathies and its Genetic Inheritance: The Booster Effect of Genetic Combinations

O Efeito da Globalização no Paradigma das Hemoglobinopatias e a sua Herança Genética: Combinações Genéticas Potenciadoras

Keywords: beta-Thalassemia; Hemoglobinopathies/epidemiology; Transients and Migrants
Palavras-chave: Hemoglobinopatias/epidemiologia; Migrantes; Talassemia beta

Hemoglobin E (HbE) is a structural β-hemoglobin variant that presents as asymptomatic or mild disease, similar to β-thalassemia minor.[1] The association between HbE and β-thalassemia (HbE/β-thalassemia) has a variable phenotype that can go from asymptomatic or mild anemia to a life-threatening disorder requiring transfusions from an early age.[2] Worldwide, it is more common in Southeast Asia, but it is rarely described in Europe, representing approximately 50% of the clinically severe β-thalassemia disorders.[1] The pathophysiology is similar to other forms of β-thalassemia.[1] Disease severity depends on the type of mutation, the co-inheritance of α-thalassemia and polymorphisms in genes involved in HbF production.[3]

Children are asymptomatic until six to 12 months when HbF is replaced by HbE. Clinical features include anemia, jaundice, hepatosplenomegaly, growth retardation and thalassemic facies.[1] Severe forms manifest as a β-thalassemia major.[1]

We present the case of an 8-year-old girl (Fig. 1) from Bangladesh with microcytic and hypochromic anemia requiring on-demand transfusions since the age of three. Having migrated to Portugal with her family at the age of seven, she was referred by the family physician to our hospital with the diagnosis of a transfusion-dependent hemoglobinopathy without any written medical information. Electrophoresis showed HbA2 4.2% (N: 2 - 3.5), HbF 23% (N: < 2), HbE 31% and HbA 41.8% (N: 95 - 98) (post-transfusion). Gene analysis showed a compound heterozygote for Hb E/β^0-thalassemia (c.79G>A; p.Glu27Lys(HbE)/c.93-1G>C). Because of disease severity (requiring monthly transfusions) and iron overload (liver iron concentration at 91 µmol/g dry weight), she was started on iron chelation therapy and proposed for stem cell transplantation.

Hemoglobin E/β-thalassemia leads to significant clinical heterogeneity, which makes its management particularly challenging. A study in Sri Lanka found a median survival of 49 years.[4] Poor survival was associated with lower hemoglobin, higher serum ferritin and liver iron levels.[4] To our knowledge there are no survival studies in Europe. Studies of β-thalassemia major show 30 year-overall survival ranging from 83.6% to 93.3%, with improved survival in recent years because of regular transfusions, iron chelation therapy, close monitoring of complications, and stem cell transplantation.[5] We can extrapolate that in developed countries these patients might have a similar evolution as β-thalassemia major, if proper treatment is initiated.

The increase in migration has changed the geographic distribution of hemoglobinopathies. The arrival of immigrants to Europe increases the public health burden.[6] In immigrants with severe disease, it is crucial to be aware of hemoglobinopathy associations for an accurate diagnosis and follow-up, including genetic counseling.

AUTHOR CONTRIBUTIONS

CGF, AFL, AS: Literature search and writing of the manuscript.

AF, ER: Critical review of the manuscript.

All authors approved the final version to be published.

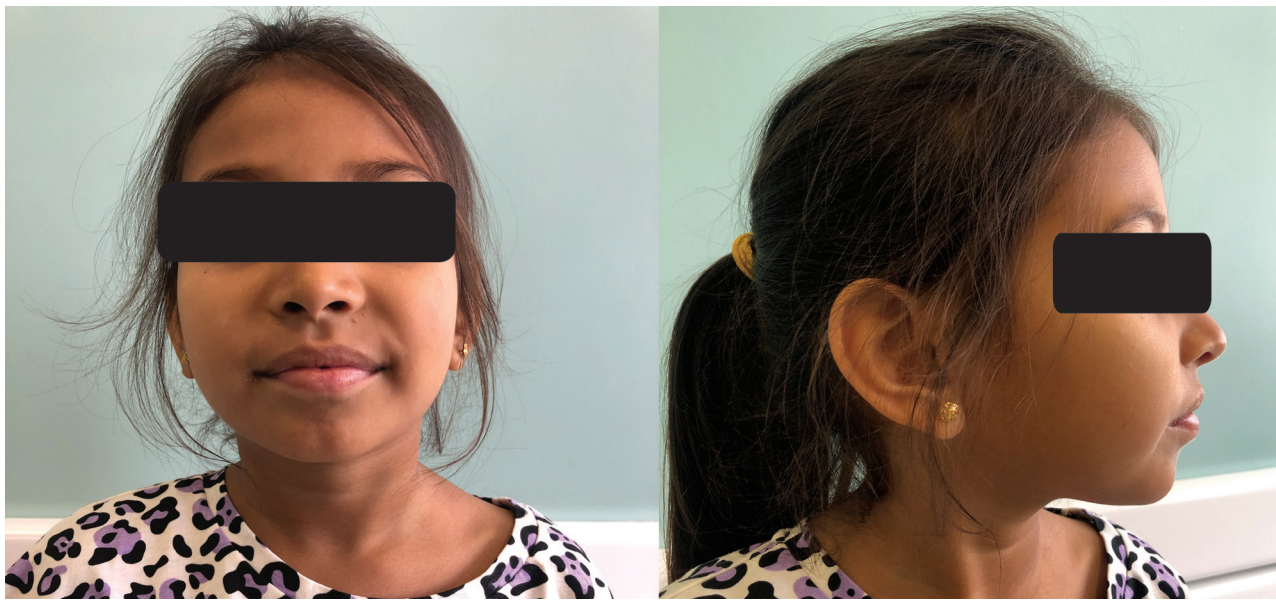

Figure 1 – Patient with HbE/β-thalassemia (characteristic facial features)

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.

PARENTAL CONSENT

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The Role of Dermatology in the Diagnosis of the 'Great Imitators' in Medicine

O Papel da Dermatologia no Diagnóstico das Doenças Denominadas 'Grandes Imitadoras' em Medicina

Keywords: Sarcoidosis/diagnosis; Skin/pathology; Skin Diseases/diagnosis
Palavras-chave: Doenças da Pele/diagnóstico; Pele/patologia; Sarcoidose/diagnóstico

The 'great imitator' is a term used to describe medical conditions featuring diverse manifestations. In dermatology. These imitators might be viral exanthems or uncommon diseases such as cutaneous lymphomas. The best examples are the three ancient infectious diseases — syphilis, tuberculosis, and leprosy — which have long been considered the classic imitators in medicine.[1] In addition to infections, some inflammatory diseases may present nonspecific cutaneous manifestations that mimic several other diseases.

A 47-year-old male patient presented to our dermatology clinic with a disseminated, polymorphic, and pruritic dermatosis characterized by three annular, infiltrated patches with an elevated border on both hands (Figs. 1A and B) and multiple left forearm confluent erythematous papules and plaques with scales with a well-defined, rounded border on the trunk (Fig. 1C). Additionally, the patient reported dysphonia and progressive dyspnea for the past 12 months. We considered the following diagnostic hypotheses: primary cutaneous T-cell lymphoma, a cutaneous manifestation of a systemic lymphoproliferative disease, secondary syphilis, sarcoidosis, and, with a low likelihood, generalized granuloma annulare.

The blood tests revealed no changes apart from a high level of angiotensin-converting enzyme (148 U/l). Infectious serologies were negative. A skin biopsy of an annular skin lesion revealed superficial and deep infiltrate of the dermis with epithelioid cells, lymphocytes, and multinucleate giant cells (Fig. 1D). The microbiologic examination of the skin biopsy was negative. Thoracic computed tomography (CT) showed partial obliteration of the upper airway, including subglottic and tracheal invasion, without lung abnormalities. The patient was diagnosed with systemic sarcoidosis and referred to a pulmonology clinic. The treatment consisted of clobetasol propionate cream 1%, prednisolone 10 mg/day, hydroxychloroquine 400 mg/day, methotrexate 20 mg/week, and infliximab 3 mg/kg every four weeks. The patient maintains follow-up in dermatology and pulmonology clinics.

Sarcoidosis is one of the 'great imitators' in medicine.[2] It is a non-infectious multisystem granulomatous disorder of unknown etiology that predominantly affects the lungs,

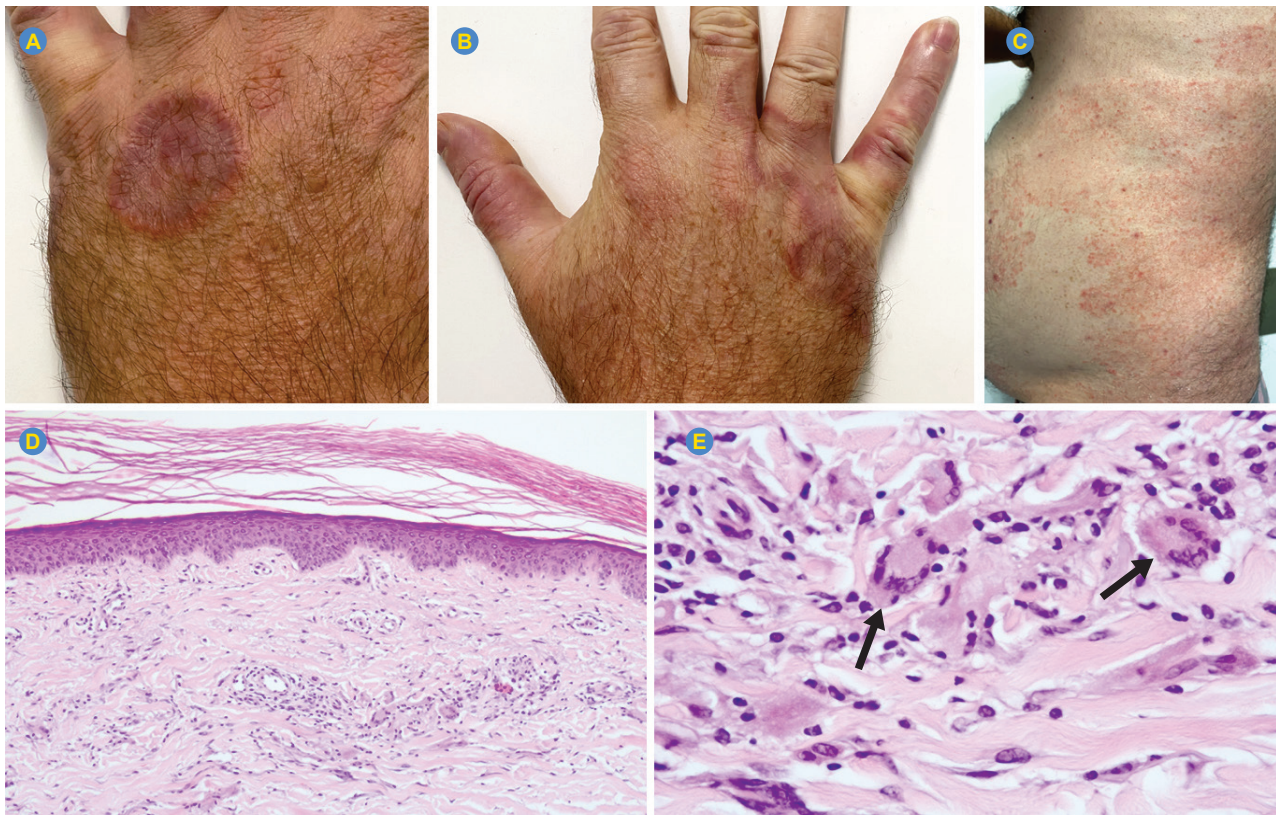

Figure 1 – Clinical images – (A) and (B) annular patches with elevated borders in the dorsum of the left and right hand; (C) multiple confluent erythematous papules and plaques with a rounded border on the trunk. Skin biopsy (D) – H&E 100x superficial and deep infiltrate of the dermis with epithelioid cells, multinucleated giant cells, and lymphocytes; a slight increase in interstitial mucin (E) (H&E 400x) multinucleated giant cells (arrows).

but the skin is the second most frequently involved organ.[3] Cutaneous sarcoidosis is usually an early manifestation of the disease, prompting the need to look for systemic involvement.[2] The skin is a convenient source for histological diagnosis.[3] Naked sarcoidal granulomas are the characteristic histologic finding in sarcoidosis.[4] In our case, the skin biopsy alone was consistent with sarcoidosis or granuloma annulare. However, the clinicopathological correlation was essential to reach a definitive diagnosis. In addition to being one of the great clinical mimickers of many different cutaneous disorders, sarcoidosis may histologically mimic other conditions.[4] The dermatologist is often the first to consider a diagnosis of sarcoidosis, because, on average, 25 % of sarcoidosis cases have cutaneous involvement.[5] Sarcoidosis is a diagnosis of exclusion that relies on epidemiological, clinical, radiographic, and laboratory criteria.[2] Dermatologists and other physicians should be encouraged to become actively involved in the multisystemic evaluations of patients, providing early recognition of cutaneous sarcoidosis, and protecting patients from multisystemic complications.

AUTHOR CONTRIBUTIONS

DM: Study design and writing of the manuscript.
PV, LSA: Writing and critical review of the manuscript.
All authors approved the final version to be published.

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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