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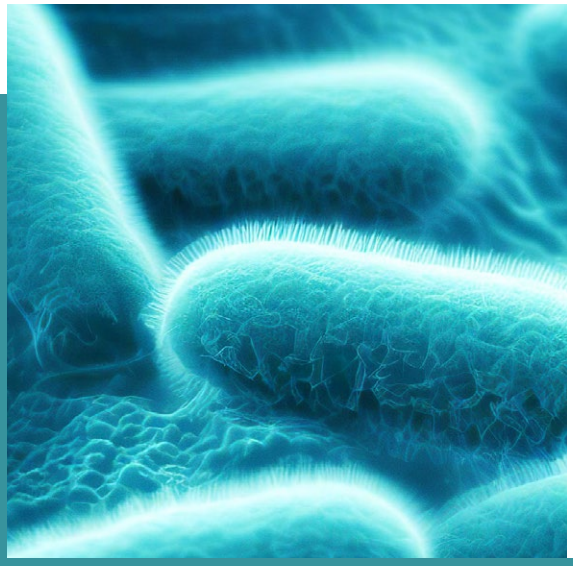

HIGHLIGHT

RESEARCH ARTICLE

Trends in Antibiotic Consumption and Resistance in Portugal, 2013–2023

PERSONALITIES: ONE LIFE IN MEDICINE

Germano de Sousa

RESEARCH ARTICLE

Interstitial Lung Disease in Mixed Connective Tissue Disease: A Single-Center Cohort Study

RESEARCH ARTICLE

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HISTORICAL ARTICLE

Revisiting Deolindo Couto (1902–1992): From National Patron to Transatlantic Diplomat

PFIZER RESEARCH AWARDS 2025

JORNAL DA SOCIEDADE DAS CIÊNCIAS MÉDICAS DE LISBOA

Published since 1835, the Journal of the Society of Medical Sciences of Lisbon (JSCMed) is the official organ of the Society of Medical Sciences of Lisbon, one of the oldest medical-scientific associations in the world, today more than 200 years old. True to its original purpose, JSCMed still undertakes today the mission of constituting one of the main dissemination forums in the biomedical area in Portugal.

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Sociedade das Ciências Médicas de Lisboa
Instituto Bento da Rocha Cabral
Calçada Bento da Rocha Cabral, 14
1250-047, Lisboa
Email: scmed@scmed.pt | Tel: 962610164
Website: https://www.scmed.pt

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Faculdade de Medicina · NOVA MEDICAL SCHOOL · CATÓLICA MEDICAL SCHOOL LISBOA

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JORNAL DA SOCIEDADE DAS CIÊNCIAS MÉDICAS DE LISBOA

EDITORIAL

The Journal of the Society of Medical Sciences of Lisbon
From Historical Legacy to Renewed Responsibility

Susana Oliveira Henriques [1]
Head of the Library and Information Division, Faculty of Medicine, University of Lisbon

[1] Lisbon School of Medicine, University of Lisbon; Centre for Science and Technology Studies (CWTS), Leiden University; School of Arts and Humanities, Centre for Classical Studies, University of Lisbon; Member of the Editorial Board, JSCMed.

> *Society journals are uniquely positioned to advance publishing models grounded in academic responsibility rather than commercial interests.*

First published in 1835, the Journal of the Society of Medical Sciences of Lisbon (JSCML) is inextricably linked to the evolution of biomedical science in Portugal and its growth within the international scientific community. As the official journal of one of the oldest medical-scientific societies in the world, it has long served as a qualified platform for the dissemination of knowledge, critical discussion, and scientific exchange. Its continuity over nearly two centuries stands as a testament to a sustained commitment to science as a collective and public endeavour.

From its earliest decades, JSCML demonstrated a relevance that extended well beyond national boundaries. The contributions of international authors, along with its inclusion in the catalogues of institutions such as the Wellcome Collection Library, the British Library, and the National Library of Medicine, reflect the embedding of the journal in a broad international network. This is also evident in historical collections held by more than thirty libraries across Europe, the Americas, and other regions around the globe, including Macau. Thus, international collaboration and visibility are foundational elements of the journal's identity.

The current scholarly landscape poses significant challenges that threaten the sustainability of this legacy. Research assessment practices are predominantly guided by quantitative indicators, particularly those at the journal level, such as the impact factor and the *h*-index. While these metrics may provide relevant insights in certain contexts, they have increasingly been regarded as proxies

for scientific quality. This reliance on metrics shapes publication strategies, academic careers, and institutional evaluations. Consequently, these practices tend to privilege a narrow segment of commercial and for-profit journals while marginalizing the contributions of well-established scientific society journals, whose value is not properly captured by these metrics.

This reality directly affects JSCML. Once a pivotal entity in sharing biomedical knowledge, the journal now operates in an environment where relevance frequently hinges on quantitative metrics rather than on the principles of editorial rigour, community engagement, or societal value. The consequence is not only a reduction in diversity within scholarly communication, but also the gradual erosion of trusted spaces for reflective, context-aware scientific discourse.

At the same time, this moment presents an opportunity for society journals to demonstrate their genuine commitment to serving the academic community. Society journals are uniquely positioned to tackle the limitations of metric-driven evaluation by advancing publishing models grounded in academic responsibility rather than commercial interests. The JSCML exemplifies this approach through its firm commitment to so-called Diamond Open Access, operating without publication fees (Article Processing Charges) for authors and without subscription costs for readers.

By eliminating financial barriers on both sides of the publication process, the journal actively fosters equitable access to knowledge sharing and consumption, thereby reinforcing the purpose of science as a public good. This aligns closely with the ongoing Open Science transition and embodies the principles articulated in the UNESCO Recommendation on Open Science, particularly its core values of quality and integrity, collective benefit, equity and fairness, and diversity and inclusiveness. It also demonstrates that quality, transparency, and sustainability do not need to be competing objectives; they complement each other when scholarly publishing is guided by academic values.

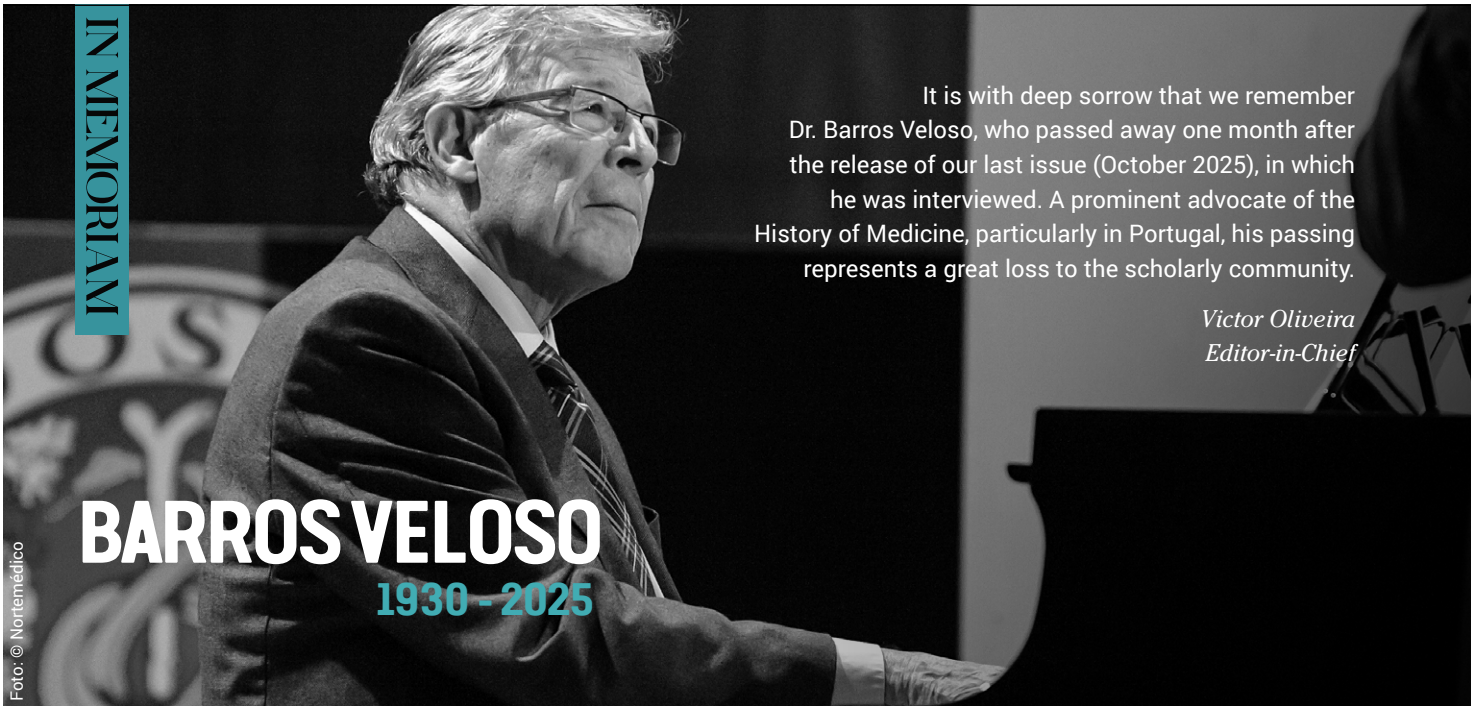
By prioritising rigorous peer review, editorial independence, and the contextual evaluation of research outputs, society journals contribute to a more equitable and responsible culture of research assessment, fully in line with influential international initiatives such as the Coalition for Advancing Research Assessment (CoARA), which seeks to move away from simplistic metrics towards evaluation frameworks that are more just and meaningful. In this context, JSCML has the opportunity to play an important role in supporting the goals and commitments of the Portuguese CoARA National Chapter, thereby contributing to advancing a modern future-oriented research system in Portugal.

> *For JSCML, enhancing its relevance does not mean replicating commercial publishing strategies or competing on the basis of impact metrics.*

Through its editorial practices and publishing model, JSCML prioritises scholarly quality, integrity, and societal value in assessing research. For JSCML, enhancing its relevance does not mean replicating commercial publishing strategies or competing on the basis of impact metrics. Rather, it involves reclaiming its historical position as a central channel for the dissemination of biomedical knowledge, grounded in scientific integrity, openness, and service to the research community. In doing so, the journal not only builds on its historical legacy, but also actively fosters a more plural, fair, and sustainable future for scholarly communication.

In this context, JSCML warmly invites the scientific community, especially early-career researchers, to actively engage with its pages. By submitting original research, critical reflections, and diverse perspectives, authors can take part in a collective effort to strengthen the role of a community-led society journal committed to openness, quality, and integrity. Through this shared engagement, the journal aspires to reinforce its position as a trusted platform for the dissemination of knowledge that propels biomedical science forward and improves people's health and well-being.

Susana Oliveira Henriques
Member of the Editorial Board, JSCMed



It is with deep sorrow that we remember Dr. Barros Veloso, who passed away one month after the release of our last issue (October 2025), in which he was interviewed. A prominent advocate of the History of Medicine, particularly in Portugal, his passing represents a great loss to the scholarly community.

Victor Oliveira
Editor-in-Chief

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JORNAL DA SOCIEDADE DAS CIÊNCIAS MÉDICAS DE LISBOA

EDITORIAL, *by the Editor*

Consolidating Our Editorial Vision

Victor Oliveira [1]
EDITOR-IN-CHIEF

1 MD, PhD. Neurologist; Board Member of the Sociedade das Ciências Médicas de Lisboa; Principal Investigator at Faculdade de Medicina – Universidade de Lisboa

With this February 2026 issue, JSCMed enters the third year of its renewed phase, continuing to consolidate the editorial model we have been building.

Over the past two years, several sections have become firmly established. In addition to the invited Editorial in each issue, we regularly publish original academic work, Letters to the Editor, Clinical Cases, biographical profiles, and articles addressing historical themes in medicine. This diversity reflects our commitment to both scientific rigor and the broader intellectual traditions of medicine.

The Journal has experienced steady growth in engagement from both authors and readers. Our usage metrics now exceed 800 monthly interactions, with peaks reaching 1,500, reflecting increasing visibility and readership.

We are also grateful for the continued support of our sponsors, whose commitment enables the Journal to meet the inherent costs of high-quality scientific publication.

Importantly, JSCMed has consolidated its academic standing as the official journal of the three medical schools in Lisbon — the Faculty of Medicine of the University of Lisbon, the Nova Medical School, and the Faculty of Medicine of the Portuguese Catholic University. This recognition strengthens our institutional responsibility and our ambition for further scholarly development.

In these evolving times, we remain committed to innovation while honoring the traditions that define our Society.

Victor Oliveira
Editor-in-Chief, JSCMed

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JORNAL DA SOCIEDADE DAS CIÊNCIAS MÉDICAS DE LISBOA

LETTER TO THE EDITOR

Pilates method and back pain: Physiotherapy and epistemology

Luís Coelho [1]

[1] Escola Superior de Saúde do Alcoitão

✉ Luís Coelho. Rua Actor Vale 10, r/c esq., 1900-025 Lisboa

coelholewis@hotmail.com

KEYWORDS: Posture; Movement; Therapeutic Relationship; Physiotherapy; Philosophy

Whether through fashion, whim, or commercial or professional strategy, Pilates method has been subjugating physiotherapy and physical exercise market, moving us from the illusion of merely manual intervention to the illusion of selling a methodology that claims to be unique and exemplary. We will see that there is no justification for physiotherapy, and fitness, to be represented by this model.

We will focus on the topic of back pain, because it is this that best addresses methodological and epistemological questions that encompass the entire field of "therapies". A cursory review of the literature provides us with several systematic reviews unanimously concluding that Pilates is not superior to other forms of exercise[1-11] or physiotherapy [9, 12, 13] in treating back pain, especially in the long term [1, 4, 5].

Wells et al. [4] report that Pilates offers similar benefits to massage. Indeed, it is the "exercise" factor that seems to transcend Pilates, with benefits, once again, especially in the long term. In the review by Chou et al. [14], the authors report that, despite the importance of exercise, in the short term, the only therapy with good evidence is superficial heat. Other authors compare the effects of exercise with manual therapy [15].

According to Wells et al. [16], it is the "posture" variable that seems to be most present in research that crosses Pilates with "low back pain" and it is also this variable that invites us most to belief and dogma.

Literature still largely fails to understand the role of "posture" in low back pain, if this relationship doesn't even consider it a consequence of the pain. Old myths, such as the effectiveness of swimming and superficial abdominal strengthening, no longer seem to be of interest to research (and the (lack of) evidence is clear). Even core training lacks the same evidence as Pilates, and only a few reviews place it above other forms of exercise [17-19] in the treatment of low back pain (but, again, only in the short term).

> *Pilates offers similar benefits to massage. Indeed, it is the 'exercise' factor that seems to transcend Pilates, with benefits, once again, especially in the long term.*

It is the "movement" that communicates local methodologies with collective ones, anti-symptomatic approaches with "psychosocial" ones, with the former being able to create new challenges for the latter, and the latter being able to exhaust themselves to reduce the great models to their prescriptive ingredients.

In this "vicious cycle" context, only a global intervention encompassing multiple variables can recreate stability. Literature should be brought into the patient's ecological arena as an "end in itself", with clinical reasoning being the ultimate decision-maker. Collective approaches, on the other hand, will essentially serve placebo needs, fostering a process that pleases the "vanitas" of the patient-therapist group, multiplying the cycle that will ultimately question the role of physical therapy itself as something mandatory, or as something not to be compensated for in the battle of therapeutic virtues. If we consider, for example, the fact that most experimental studies lack a "placebo group", coupled with the limitations of questionnaire-based studies, we clearly see that in the world of therapies, everything remains to be done, a terrain where it is difficult to define what is "falsifiable" (Popper). It is also important to define the therapeutic safety zone; the excesses of Pilates, as well as Postural Reeducation, represent the dogmatic hegemonies that, to the extent that they placebo, disguise the disaster zone, and this viaticum of illusions contaminates, just as much, the therapist, pregnant with needs.

It is essential that "posture" be respected in its "life cycle", recognizing within it the ingredients that will create "totality" and establish the stage for scientific "commonality", for "ethos", reducing the context of physical and psychosocial distress. Only then can this nomothetic, clinical terrain begin to act at the group level, in a sufficiently safe and parsimonious manner, preserving the set of elements that allow postural balance to be compatible with the nature of physiological harmony, as far as pain management is concerned. This work requires a retreat and a clinical respect that a physiotherapy granted to "Fitness" does not contemplate. When dialectical reasoning, clinical phenomenology, assumes the grotesque simplicity currently seen, the fulcrum is definitively lost, and this Physiotherapy is destined to play the inexhaustible "puzzle" of an "eternal return" that loses and vulgarizes it. Its appearance as a "physiology of pain" must be restored, draining the stage of parasitic and intermittent variables, and only then should the product be topped with the capital of psychic variables that, if not well managed, are destined to modify the "focus" of psychosocial violence.

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Diplexil R

Valproato Semisódico

CONFIANÇA NUMA VIDA COM QUALIDADE[1,2]

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO

▼Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas. Para saber como notificar reações adversas, ver secção 4.8 do RCM.

NOME, COMPOSIÇÃO QUALITATIVA E QUANTITATIVA e FORMA FARMACÊUTICA DO MEDICAMENTO: Diplexil-R 250 mg (269,1 mg de valproato semisódico) comprimidos gastrorresistentes cor de pêssego. Excipiente(s) com efeito conhecido: Amarelo sunset (E110) – 0,2 mg, Sódio: 18,5 mg por comprimido. Diplexil-R 500 mg (538,2 mg de valproato semisódico) comprimidos gastrorresistentes cor-de-rosa. Excipiente(s) com efeito conhecido: Carmoisina (E122) - 0,104 mg, Vermelho de ponceau 4R (E124) - 0,091 mg, Sódio: 37,0 mg por comprimido. **INDICAÇÕES TERAPÊUTICAS:** Epilepsias generalizadas e parciais: Generalizadas primárias: Pequeno e grande Mal, epilepsias mioclónicas; Parciais: simples e complexas. Generalizadas secundárias: síndroma de Lennox-Gastraut, síndroma de West; Formas mistas. Epilepsias especiais: Convulsões febris na criança. Privação do sono. Alterações do comportamento associados à epilepsia. Tratamento de episódios maníacos na doença bipolar quando o lítio está contraindicado/ não é tolerado. Considerar a continuação do tratamento após a ocorrência de episódios maníacos em doentes que responderam ao valproato semisódico na mania aguda. Em: Doentes com ciclos rápidos; bipolares difíceis (idosos e doentes em situações de comorbilidade com abuso de substâncias). - Tratamento profilático dos seguintes tipos de cefaleias: Enxaqueca, Cefaleia Crónica Diária (Enxaqueca Transformada e enxaqueca Persistente e Resistente) e Cefaleia em salvas. **POSOLOGIA E MODO DE ADMINISTRAÇÃO:** Via oral. Se tratamento prévio com Ácido valpróico, iniciar a terapêutica com a mesma dose diária e esquema posológico. Após estabilização do doente poderá instituir-se um esquema posológico de 2 a 3 tomas diárias. A frequência de efeitos adversos (particularmente enzimas hepáticas elevadas) pode estar relacionada com a dose. Avaliar benefício-risco de doses mais elevadas. Concentrações de Fenitoína no sangue podem ser afetadas com aumento de dosagem. Para os doentes que se queixam de irritação gastrointestinal, recomenda-se a administração do fármaco durante as refeições, e aumento gradual da dose a partir de um nível inicial baixo. Epilepsia: dose inicial recomendada:15 mg/kg/dia 3 x dia, com aumentos de 5 a 10 mg/kg/dia em intervalos de uma semana até controlo das crises ou até dose tolerável. A dose máxima recomendada é de 60 mg/kg/dia. Se exceder os 2500 mg, esta deverá ser administrada em doses repartidas. Para a maior parte dos doentes, as concentrações séricas terapêuticas de Valproato situam-se no intervalo de 50-100 mcg/ml. Caso a posologia diária seja igual ou superior a 50 mg/Kg/dia, recomenda-se monitorizar níveis sanguíneos. Episódios maníacos na doença bipolar: Em adultos: A dose diária deve ser estabelecida e controlada pelo médico. Dose diária inicial recomendada é de 750 mg. Em ensaios clínicos, a dose inicial de 20 mg de valproato/kg de peso corporal também demonstrou um perfil de segurança aceitável. A dose deve ser aumentada tão rapidamente quanto possível, de forma a atingir a dose terapêutica mais baixa que produza o efeito clínico desejado. Ajustar a dose à resposta clínica. A dose média diária varia, habitualmente, entre 1000 a 2000 mg de valproato. Se doses superiores a 45 mg/kg de peso corporal, monitorizar. A continuação do tratamento deve ser adaptada individualmente usando a dose mínima eficaz. Em crianças e adolescentes: A segurança e a eficácia de Diplexil-R para o tratamento de episódios maníacos na doença bipolar não foram avaliadas em doentes com idade inferior a 18 anos. Crianças do sexo feminino e mulheres em idade fértil: O valproato deve ser iniciado e supervisionado por um especialista com experiência no tratamento da epilepsia, perturbação bipolar ou enxaqueca. O valproato não deve ser utilizado em crianças do sexo feminino e mulheres em idade fértil a não ser que outros tratamentos sejam ineficazes ou não tolerados. O valproato é prescrito e dispensado de acordo com o Programa de Prevenção do valproato na Gravidez. O valproato deve ser prescrito preferencialmente em monoterapia e na dose eficaz mais baixa, se possível numa formulação de libertação prolongada. A dose diária deve ser dividida pelo menos em duas tomas únicas. Homens: Recomenda-se que Diplexil seja iniciado e supervisionado por um especialista com experiência no tratamento da epilepsia ou perturbação bipolar ou enxaqueca. Cefaleias: A dose mínima eficaz é de 250 mg 2x dia e o tratamento deverá ter a duração mínima de 3 meses. A dose média é de 1000 a 1500 mg/dia. Em doentes com insuficiência renal: pode ser necessário diminuir a dosagem, ou aumentar a dosagem em doentes em hemodiálise. Valproato é dialisável. A dosagem deve ser modificada de acordo com a monitorização clínica do doente. Diplexil-R só deve ser iniciado e supervisionado por um especialista com experiência no tratamento da enxaqueca. O tratamento só deve ser iniciado se outros não forem eficazes ou tolerados e os benefícios e riscos devem ser cuidadosamente reavaliados em revisões regulares do tratamento. **CONTRAINDICAÇÕES:** Diplexil-R está contraindicado nas seguintes situações: - Hipersensibilidade às SA ou excipientes. - Doença hepática ou disfunção significativa. - Antecedentes pessoais ou familiares de hepatite grave, nomeadamente medicamentosa. - Porfiria hepática. - Doentes que tenham doenças mitocondriais causadas por mutações no gene nuclear que codifica a enzima mitocondrial polimerase gama (POLG), por exemplo a síndrome de Alpers-Huttenlocher, e em crianças com menos de 2 anos de idade em que se suspeita de terem doenças relacionadas com a POLG. - Doentes com distúrbios do ciclo da ureia. Tratamento da epilepsia: - Na gravidez, a não ser que não exista um tratamento alternativo adequado. - Em mulheres em idade fértil, a não ser que as condições do programa de prevenção da gravidez sejam cumpridas. Tratamento da perturbação bipolar e profilaxia de crises de enxaqueca: - Na gravidez. - Em mulheres em idade fértil, a não ser que as condições do programa de prevenção da gravidez sejam cumpridas. **ADVERTÊNCIAS E PRECAUÇÕES ESPECIAIS DE UTILIZAÇÃO:** trombocitopénia, alterações da hemostase/coagulação, hiperamonemia com ou sem letargia, alterações nos testes de função da tiroide, insuficiência hepática, muito raramente pancreatites graves, reações adversas cutâneas graves e angioedema. **Programa de Prevenção de Gravidez:** O valproato tem um elevado potencial teratogénico e as crianças expostas ao valproato in utero têm um elevado risco de malformações congénitas e perturbações do desenvolvimento do sistema nervoso. Ver RCM. Foram relatados casos de ideação e comportamentos suicidas em doentes tratados, com medicamentos antiepiléticos, para várias indicações terapêuticas. Não é recomendado o uso concomitante de ácido valpróico/ valproato de sódio com os antibióticos do grupo dos cabapenemos. Doentes com doença mitocondrial conhecida ou presumida: O valproato pode desencadear ou agravar sinais clínicos de doenças mitocondriais subjacentes causadas por mutações do ADN mitocondrial bem como do gene nuclear que codifica a POLG. Se há suspeita de uma deficiência no ciclo enzimático da ureia, devem ser feitos estudos metabólicos antes do tratamento, devido ao risco de hiperamoniemia com o valproato. Poderá ocorrer aumento de peso no início do tratamento. Doentes com uma deficiência tipo II em carnitina palmitoiltransferase subjacente (CPT) devem ser advertidos do risco aumentado de rabdomiólise. Nos insuficientes renais pode ser necessário proceder-se a uma diminuição da dosagem. Excipientes. **INTERAÇÕES MEDICAMENTOSAS E OUTRAS FORMAS DE INTERAÇÃO:** Efeitos do valproato semisódico nos outros medicamentos: Neurolépticos, antidepressivos, benzodiazepinas e barbitúricos; Fenobarbital e Primidona; Fenitoína; Carbamazepina; Etossuximida; Lamotrigina; Zidovudina; Felbamato; Olanzapina; Rufinamida; Propofol; Nimodipina. Efeito de outros medicamentos sobre o valproato de sódio: Antiepiléticos; Mefloquina; Fármacos com ligação elevada às proteínas plasmáticas; Anticoagulantes; Cimetidina ou eritromicina; Fluoxetina; Carbapenemos; Rifampicina; Inibidores de protéase; Colestiramina; Medicamentos que contêm estrogénio; Metamizol; Outras interações: Topiramato ou acetazolamida; Quetiapina; Álcool; Lítio; Clonazepam; Clozapina. Ver RCM. **EFEITOS INDESEJÁVEIS:** Os efeitos indesejáveis notificados mais comuns para o valproato são perturbações gastrointestinais, as quais ocorrem em aproximadamente 20% dos doentes. Têm sido observados casos de lesões hepáticas graves (ou mesmo fatais), especialmente em crianças tratadas com doses elevadas ou em combinação com outros antiepilépticos. Os efeitos indesejáveis foram classificados por ordem de frequência segundo a seguinte convenção: Neoplasias benignas, malignas e não especificadas (incl. quistos e polipos): Raros: Síndrome mielodisplásico. Doenças do sangue e do sistema linfático: Frequentes: Trombocitopenia, leucopenia. Pouco frequentes: Hemorragia. Raros: Anemia macrocítica, macrocitose. Muito raros: Perturbações da medula óssea, concentração reduzida de fibrinogénio e/ou de fator de coagulação VIII, alteração da agregação plaquetária, tempo de coagulação prolongado, linfocitopénia, neutropénia, pancitopénia, anemia ou aplasia da linhagem de células vermelhas. Desconhecido: Agranulocitose. Doenças do sistema imunitário: Pouco frequentes: Angioedema. Raros: Lúpus eritematoso, erupção medicamentosa com eosinofilia e sintomas sistémicos (síndrome DRESS). Desconhecido: Reações alérgicas (ver também "pele e perturbações dos tecidos subcutâneos"), síndrome da resposta inflamatória sistémica. Doenças endócrinas: Raros: Hiperandrogenismo (hirsutismo, virilismo, acne, alopécia com aparência típica masculina e/ ou aumento dos níveis de androgéneos), hipotiroidismo. Doenças do metabolismo e da nutrição: Frequentes: Hiperamonemia, aumento do peso (fator de risco para a síndrome do ovário poliquístico, requer monitorização cuidadosa) ou diminuição de peso; aumento ou diminuição de apetite. Pouco frequentes: Síndrome de secreção inapropriada de hormona antidiurética (SIADH). Raros: Hiperinsulinemia, baixos níveis da IGFBP-1 (insulin-like growth factor binding protein 1), obesidade. Muito raros: Foram relatadas anomalias das provas da função tiroideia, com relevância clínica duvidosa. Hiponatremia. Vasculopatias: Raros: Vasculites. Perturbações do foro psiquiátrico: Frequentes: Agressividade*, agitação*, atenção alterada*. Raros: Irritabilidade, alucinações, confusão, comportamento anormal*, hiperatividade psicomotora*, perturbação da aprendizagem*. * Estas reações adversas são observadas principalmente na população pediátrica. Doenças do sistema nervoso: Frequentes: Sonolência, tremores, parestesias, defeito de memória, nistagmo, torturas. Pouco frequentes: Coma transitório, em alguns casos associado a aumento da frequência das crises, ataxia. Raros: Cefaleias, hiperatividade, espasticidade, estupor, perturbação cognitiva, diplopia. Muito raros: Encefalopatia, demência associada a atrofia cerebral (reversível após a descontinuação do tratamento), distúrbios extrapiramidais p. ex. síndrome parkinsónica (reversível). Desconhecido: Agravamento das crises, sedação, letargia. Afeções do ouvido e do labirinto: Muito raros: Perda de audição (reversível ou irreversível), acufenos. Doenças respiratórias, torácicas e do mediastino: Pouco frequentes: Derrame pleural (eosinofílico). Doenças gastrointestinais: Muito frequentes: Dores, náuseas, vómitos. Frequentes: Diarreia, perturbação gengival (principalmente hiperplasia gengival), estomatite. Raros: Pancreatite (por vezes fatal), hipersalivação, ileus, obstrução intestinal. Afeções hepatobiliares: Frequentes: Alterações nas provas da função hepática. Raros: Lesão hepática grave que inclui insuficiência hepática. Afeções dos tecidos cutâneos e subcutâneos: Frequentes: alopecia, enfraquecimento do cabelo e aparecimento de cabelo encaracolado, alterações nas unhas e leito ungueal. Raros: Exantema, eritema multiforme. Muito raros: Síndrome de Stevens-Johnson, Síndrome de Lyell. Desconhecido: Hirsutismo (por ex. resultante da síndrome do ovário poliquístico), hiperpigmentação. Afeções musculosqueléticas e dos tecidos conjuntivos: Raros: Rabdomiólise. Desconhecido: Foram notificados casos de densidade mineral óssea diminuída, osteopenia, osteoporose e fraturas ósseas em doentes sob tratamento prolongado com valproato. Ainda não se conhece o mecanismo pelo qual o valproato afeta o metabolismo ósseo. Doenças renais e urinárias: Frequentes: incontinência urinária. Muito raros: Síndrome de Fanconi (com acidose metabólica, fosfatúria, aminoacidúria, glicosúria, reversíveis após a descontinuação do tratamento), enurese nas crianças. Desconhecido: Insuficiência renal, nefrite intersticial, deterioração da função renal. Doenças dos órgãos genitais e da mama: Frequentes: Amenorreia, dismenorreia. Raros: Síndrome de ovário poliquístico, infertilidade masculina. Desconhecido: Espermatogénese anormal (com contagem reduzida de espermatozóides e/ou motilidade). Afeções congénitas familiares e genéticas: Malformações congénitas e alterações no desenvolvimento. Perturbações gerais e alterações no local de administração: Raros: Hipotermia, edema. Exames complementares de diagnóstico: Raros: Redução dos fatores de coagulação (pelo menos um), testes de coagulação anormais (tais como prolongamento do tempo de protrombina, prolongamento do tempo parcial de tromboplastina ativada, prolongamento do tempo de trombina, valor de INR aumentado), carência de biotina/biotinidases. População pediátrica: Existe risco particular de lesão hepática grave em bebés e crianças pequenas, especialmente com idade inferior a 3 anos, e de pancreatite em crianças pequenas. Estes riscos diminuem com o aumento da idade. Transtornos psiquiátricos como agressão, agitação, perturbação da atenção, comportamento anormal, hiperatividade psicomotora e transtorno de aprendizagem são observados principalmente na população pediátrica. **Para mais informações deverá contactar o Titular da AIM:** TECNIFAR - Indústria Técnica Farmacêutica, S.A. 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TECNIFAR - Indústria Técnica Farmacêutica, S.A. Rua José Da Costa Pedreira, Nº 11 – B - Torre Sul - 1750-130 Lisboa | Tel. 210 330 700 - Fax. 210 330 709 | Email: grupotecnifar@tecnifar.pt www.tecnifar.pt | Linha Farmacovigilância: 213 860 929 | Email: farmalerta@tecnifar.pt | NIF: 500280436 | DMK.DIPR.001.02.2025_02/2025/PUB. Exclusivo para profissionais de saúde.

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JORNAL DA SOCIEDADE DAS CIÊNCIAS MÉDICAS DE LISBOA

VIEWPOINT

Scientific and Ethical Challenges in Gender Equality in Sports: A Critical Perspective

António Gentil Martins [1]

[1] Retired Head, Department of Pediatric Surgery of Lisbon's Children's Hospital D Estefânia and Instituto Português de Oncologia Francisco Gentil); Former President of the Portuguese Medical Association (Ordem dos Médicos) and Former President of the Word Medical Association; Paediatric Surgeon, Paediatric Oncologist and Plastic, Reconstructive and Esthetical Surgeon; Doctor Honoris Causa by the European University; Founder and former President of the Portuguese Olympic Athletes Association; Athlete at the Rome Olympic Games -1960 (Rapid fire pistol shooting).

ABSTRACT: This paper addresses two basic principles related to Olympic ethics: the possibility that male transgender or transsexual individuals try to compete as if they were real females. Essentially, it clearly rejects the possibility that men, having "administratively" changed their sex registration, can compete as if they were "true females." It also considers it mandatory that, in all sports modalities where strength is relevant, women must have previously undergone a testosterone evaluation.

KEY WORDS: Olympic Ethics; Gender Identity; Sports Competition

Scientific and ethical issues in sport, as in life, are inseparable. We believe that before addressing any problem, it is essential to clarify the concepts and principles one follows. It is undoubtedly discriminatory to treat what is obviously different as equal. This leads us to reflect on the politically imposed concept of equality between sexes, which are anatomically and physiologically distinct. Equal rights are essential, but it is crucial to avoid simulation and fraud, considering the excessive desire to be the best.

The Olympic Code of Ethics clearly defines fundamental principles that must be fully respected. Article 1.2 emphasizes the universality and neutrality of the Olympic Movement, and Article 1.4 rejects all forms of discrimination, irrespective of the reason (race, language, political opinion, nationality, social origin, or any other situations).

Unfortunately, we believe the concept of amateur sports is at risk, as we cannot forget that the original Olympic Games, which began in 776 BC, ended approximately 1,000 years later in 393 AD (during the reign of Roman Emperor Theodosius).

We maintain that sports should remain independent of political ideologies, and no athlete should ever be precluded from participating in the Olympic Games due to their country's political choices or errors. Furthermore, we believe

the Olympic Truce should be effective from the moment athletes leave their country until they return, not just within the Olympic Village. We all remember the Olympic Truce and its rule of free circulation and the cessation of hostilities, starting one week before and ending one week after the Games.

It is scientifically evident that hormonal levels differ according to biological sex, which is established at the union of the spermatozoon and ovum. Since the dawn of humanity (and we hope it continues to exist...), we need males and females, who are anatomically (and even psychologically) distinct but obviously complementary and essential for the continuation of humanity. Some individuals who have decided to change their sex have neglected the need to clearly distinguish between the different types of sports.

a) ***Physical Exercise:*** Aimed at health and well-being, promoting both physical and mental harmony, and often considered amateur.
b) ***Sports Competition:*** Focused on participation, not just winning, also considered amateur.
c) ***High-Performance Sports:*** Such as the Olympic Games and World Championships, where the main goal is to win, often blurring the lines between amateurism and professionalism.

There are two major issues that need addressing: one is the participation of "transgender" or "transsexual" individuals in women's competitions, and the other is hyperandrogenism.

No one denies the significant muscular differences that clearly distinguish women from men. Blood haemoglobin levels, which provide the essential oxygen supply to muscles and promote their development, range from 13.2 to 16.6 g/dL in men and from 11.6 to 15 g/dL in women. We also know that autotransfusions and the use of drugs to increase blood oxygen levels are already considered doping.

However, it is essential that women also have the opportunity to practice sports in safe conditions, ensuring their rights and dignity. As far as we know, no woman has ever wished to compete in men's competitions. It is, however, crucial to ascertain the true sex of all competitors to avoid fraud by men who have, even administratively, registered as the opposite sex. If a man were to do this, it would clearly violate Article 1 of the 1994 Brighton Declaration.

In men, androgens (especially testosterone) predominate, whereas in women, oestrogens prevail. The most striking physical differences are particularly evident during adolescence and young adulthood, due to the significant hormonal action of androgens during this period. Men have historically been stronger, with a larger heart, more red blood cells, and higher haemoglobin levels, which help transport oxygen to muscle mass and facilitate growth.

These biological differences are evident and can be clearly demonstrated through the results in sports competitions.

		Olympic Records		World Records	
Competition	Unit	Men	Women	Men	Women
100 m	s	9.63	10.61	9.58	10.49
400 m	s	43.03	48.25	43.03	47.60
1500 m	min:s	3:28.32	3:53.11	3:26.00	3:49.11
Marathon	h:min:s	2:06:32	2:23:07	2:02:35	2:11:53
4×100 m	s	36.84	41.60	36.84	40.82
High Jump	m	2.39	2.06	2.45	2.09
Long Jump	m	8.90	7.40	8.95	7.52
Shot Put	m	23.30	22.41	23.56	22.63
Discus Throw	m	69.89	72.30	74.35	76.80
Javelin Throw	m	90.57	71.53	98.48	72.28

In 1968 (Mexico City), the international Olympic Committee (IOC), reacting to rumours that men might attempt to compete in women's events, sought a scientifically safe and non-degrading solution—thus, the karyotype test was introduced (though this method has since been largely forgotten!).

Many sports are gender-segregated due to these evident physical differences. However, the Los Angeles Declaration of 1981, which unanimously approved a series of recommendations for gender equality in sports, aims to improve women's lives globally. It is important to note, however, that excessive exercise may delay puberty and induce menstrual irregularities, requiring careful medical evaluation.

According to the International Olympic Committee, (IOC) for a new sport to be included in the Olympic Games, there must be both a male and a female competition. We believe that this is not justified, as sexual parity should not be the primary concern; instead, the athletes' characteristics should determine the appropriate competition structure.

What scientifically distinguishes men and women are their chromosomes: two X chromosomes (XX) for females and one X and one Y chromosome (XY)

for males. However, there are congenital conditions such as Klinefelter Syndrome (XXY) and Turner Syndrome (X), where individuals may be biologically male or female but possess atypical chromosomal patterns. Additionally, a lack of sensitivity to androgens (testosterone and dihydrotestosterone) can occur.

A case in point was a Spanish athlete who was wrongly disqualified from a World University Sports competition due to an XY karyotype, despite having female physical characteristics. It is well-known (though fortunately rare) that sexual ambiguities at birth can lead to questions about the newborn's sex, a decision that the physician must make. This is one reason we strongly oppose Law 38/2018, which should be urgently revoked. It is nonsensical to delay sex assignment until the child has grown and is allowed to choose their gender identity, as if biology were irrelevant.

The Universal Declaration of Human Rights (10/12/1948) and the Universal Declaration of Children's Rights (20/11/1959) clearly state that all children have an inalienable right to receive treatment for medical conditions, and congenital malformations are considered "diseases" requiring timely medical intervention. Medical practitioners, in accordance with the Hippocratic Oath, must correct any existing congenital malformations as soon as possible, not wait for the child to make a decision later in life.

According to the law, after birth, the child must be registered by the parents in the Civil Registry as either male or female. Curiously, in Portugal, a child has already been officially registered with a gender-neutral name: "Gentil".

In females (XX), virilization can occur, leading to an enlarged clitoris resembling a penis, as seen in conditions like congenital adrenal hyperplasia and polycystic ovary syndrome, which can cause pathological hyperandrogenism and thus require careful medical assessment. In males (XY), the penis may be malformed, hypoplastic, or retracted. Rarely, true hermaphroditism occurs, where the newborn possesses both testes and ovaries, with a karyotype of 46 XY / 45 XO.

Physiologically, after the initial embryonic phase, hormones are what most clearly define sex, with testosterone predominating in males and oestrogens in females (though both sexes have both hormones, albeit at very different levels). These issues arise during early infancy and do not affect high-performance athletes, such as Olympians.

It is clear that no athlete should be disadvantaged because of natural attributes that confer a sporting advantage, as opposed to doping. Strangely, during the 2016 Rio Olympics, a simple declaration of sex sufficed for participation, though WADA (World Anti-Doping Agency) did not endorse this.

In 1968, the International Olympic Committee (IOC), responding to rumours that men might attempt to compete as women, introduced the karyotype test as a scientifically safe method to determine sex, even using saliva to conduct it. However, the method was not entirely reliable and was eventually abandoned.

Following a vote by American psychiatrists, the concept of "Gender Dysphoria" was introduced, defining individuals who feel their anatomy does not match their gender identity. These individuals are now termed transgender (or transsexual if they have undergone surgery). However, it has been shown that individuals who undergo sex change surgery have higher rates of severe depression and suicide.

Additionally, hormones used by transgender individuals may pose health risks, such as blood clots, cardiovascular disease, and certain cancers, requiring close medical supervision. Furthermore, individuals who regret transitioning have formed organizations advocating for the reversal of these irreversible surgeries.

In November 2015, at an IOC "Consensus Meeting on Sex Identification and Hyperandrogenism," Dr. Richard Burgett, then IOC Medical and Scientific Director, disclosed that female athletes' testosterone levels should be below 10 nmol/L for at least one year prior to the Olympic Games (though how this would be monitored remains unclear). Hormonal levels can also be altered by anti-androgens, such as spironolactone or cyproterone acetate.

The IOC suggested that testosterone levels up to 10 nmol/L would be acceptable for women, a threshold that seems arbitrarily high, given that healthy women typically have testosterone levels below 3.9 nmol/L. We believe that a maximum level of 5 nmol/L would be more appropriate.

For women with hyperandrogenism, the simplest solution would be to introduce a separate category for competitions, as is done in other sports like weightlifting, judo, and boxing. A simple testosterone test would clarify this issue, enabling fair decisions. We suggest creating two categories: one for values below 2.5 nmol/L and another for values above 2.5 nmol/L.

The case of Caster Semenya is noteworthy, as she was reinstated as the rightful winner of her Olympic gold medal in the 800m after her initial disqualification. This demonstrates the importance of respecting an athlete's dignity when their situation is the result of natural development rather than doping. Other Olympic athletes, such as Allyson Felix and Margaret Wambui, have also spoken out about living with hyperandrogenism.

A biologically female athlete can, of course, compete in men's competitions, though this has yet to occur. We believe that sex changes prior to puberty have little effect on athletic performance, but administrative changes after puberty pose significant challenges, as the individual may not lose the advantages given by testosterone prior to the transition.

While the IOC asserts that transgender individuals should not be excluded from sports competitions, it seems they have overlooked the biological truths that have shaped humanity for millennia. Regrettably, instead of taking a clear stance, the IOC continues to delegate responsibility for determining policies to individual sports federations.

In many so-called "developed countries", including the USA, transgender women have already competed in women's events, sometimes winning. This troubling trend is gaining momentum, as reported by publications such as The Washington Stand.

CONCLUSIONS

We believe that transgender and transsexual individuals should not be allowed to compete in women's sports competitions. The issue became starkly evident at the Paris Olympics, where a biologically male boxer (Imane Khelif) was awarded a "female" gold medal. The IOC's silence on this issue was disgraceful and unacceptable.

Sadly, the Olympic Games have increasingly become commercial enterprises rather than preserving their original ethos. While the Games continue to provide excitement and spectacle, we long for a return to Pierre de Coubertin's original vision of the Olympics as a philosophy of life, promoting the unity of body, will, and spirit, and aiming for a society rooted in peace and human dignity. The classical motto, *"Mens sana in corpore sano,"* should remain at the core of the Olympic spirit, reminding us that the true value of the Games lies in the pursuit of excellence through effort, fair play, respect, and solidarity.

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JORNAL DA SOCIEDADE DAS CIÊNCIAS MÉDICAS DE LISBOA

ONE LIFE IN MEDICINE

Germano de Sousa

By
Victor Oliveira

MD, PhD. Neurologist; Board Member of the Sociedade das Ciências Médicas de Lisboa; Editor-in-Chief JSCML; Principal Investigator at Faculdade de Medicina – Universidade de Lisboa

✉ voliveira98@hotmail.com

Germano Rego de Sousa was born in Vila do Nordeste (São Miguel, Azores). At the age of seventeen, he moved to mainland Portugal to pursue medical studies at the University of Coimbra. In keeping with academic tradition, he resided in one of the student "Republics" – self-governed student residences – joining the *República dos Corsários das Ilhas,* which was composed primarily of students from the Azores.

His vocation for medicine was reportedly influenced by a great-uncle who served as *Enfermeiro-Mor* (Chief Medical Administrator) of the Civil Hospitals of Lisbon.

During his time in Coimbra, he held positions of student leadership and became actively involved in the academic protest movement of 1964–1965. As a consequence of this engagement, he was denied access to the general medical internship by the political police of the regime (PIDE).

He subsequently fulfilled his compulsory military service and was deployed to Angola (1968–1970), where he carried out clinical duties both at the military hospital and at the civil hospital in the town of Luso (now Luena).

Upon returning to Portugal, he began his residency in Clinical Pathology (Laboratory Medicine) at the Central Hospitals of Lisbon, specifically

Germano de Sousa's professional trajectory combines clinical leadership, institutional responsibility, and a sustained commitment to the History of Medicine.

at Hospital do Desterro, where he later became Director of the laboratory. He subsequently moved to the newly inaugurated Hospital Dr. Fernando da Fonseca (Amadora), where he established its Clinical Pathology laboratory.

In parallel with his hospital career, he developed a private practice, founding a laboratory that would progressively become one of the largest enterprises of its kind in Portugal and a national reference in laboratory diagnostics: Laboratório Germano de Sousa.

He also served as a professor at NOVA University Lisbon and at Universidade Atlântica.

Between 1999 and 2005, he was President (Bastonário) of the Portuguese Medical Association (Ordem dos Médicos), where he was particularly noted for his defense of ethical standards rooted in the Hippocratic tradition.

Alongside his professional career, he cultivated a longstanding interest in the History of Medicine, a passion that dated back to his adolescence. Among his contributions in this field were the republication of *História da Medicina* by Maximiano de Lemos during his tenure as President of the Portuguese Medical Association, as well as the re-edition of *Tractado del Mal Serpentino* by Ruy Gómez de Isla. His most significant original contribution is *A Medicina dos Descobrimentos* ("Medicine of the Discoveries"), recently published in a second edition. This work represents a major contribution to the understanding of Portuguese medicine during the Age of Discoveries, a period that remains comparatively underexplored. An English-language edition is currently in preparation.

FIGURE 1. Germano de Sousa was President (Bastonário) of the Portuguese Medical Association (Ordem dos Médicos) from 1999 to 2005.

FIGURE 2. Germano de Sousa and his 18th-century statues representing the 3rd-century twin martyrs Saints Cosmas and Damian, patrons of medicine and pharmacy.

FIGURE 3. Interior view of the museum space created by Germano de Sousa at the headquarters of his laboratory.

As a culmination of his interest in medical history, he founded a museum at the headquarters of his laboratory. The collection includes historically significant artifacts, such as a Roman unguentarium accompanied by small surgical instruments. It also features dozens of microscopes from various periods, as well as rare books, including an edition of *Vesalius* and a 1572 edition of *Pierre André Matthioli's Commentaires*.

The museum was inaugurated on 26 December 2025 by the President of the Portuguese Republic.

Professor Germano de Sousa continues to direct his laboratory while maintaining an active and enthusiastic commitment to the History of Medicine.

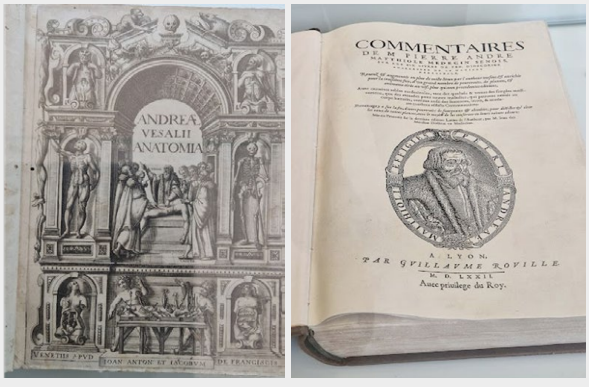

FIGURE 4. Old and rare books in exhibition

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Special Issue

II Luso-Galician Congress on the History of Medicine

Following the II Luso-Galician Congress on the History of Medicine, held in Porto on 21–22 November 2025, JSCMed is pleased to announce the publication of a Special Issue featuring selected works presented at the meeting.

This issue reflects the scientific contributions and collaborative spirit that marked the Congress and highlights the ongoing dialogue in the field of History of Medicine.

We invite our readers to explore this volume, published concurrently with the present issue.

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RESEARCH ARTICLE

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Interstitial Lung Disease in Mixed Connective Tissue Disease: A Single-Center Cohort Study

Khea Direndra Hasmucrai[1], **Filipa Costa**[2], **Inês Sopa**[2], **Nikita Khmelinskii**[1,2], **João Eurico Fonseca**[1,2], **Gonçalo Boleto**[2]

[1] Faculdade de Medicina da Universidade de Lisboa

[2] Rheumatology Department, Unidade Local de Saúde Santa Maria, Centro Académico de Medicina de Lisboa, Lisbon, Portugal

✉ **Corresponding author:**
Dr. Gonçalo Boleto
Rheumatology Department, Unidade Local de Saúde Santa Maria, Centro Académico de Medicina de Lisboa, Lisbon, Portugal
Tel.: +351 217805139

Email address:
goncalo.boleto@ulssm-min.saude.pt

ABSTRACT: **Background**: Mixed connective tissue disease is a rare systemic autoimmune condition characterized by overlapping features of different connective tissue diseases and the presence of anti-U1-ribonucleoprotein antibodies. Its association with interstitial lung disease represents one of the main causes of morbidity and mortality in affected patients. **Objective:** To characterize the clinical, immunological, and radiological phenotype of patients with mixed connective tissue disease-associated interstitial lung disease, and to evaluate the evolution of pulmonary function over time. **Methods:** All patients had at least one high-resolution computed tomography scan and two pulmonary function tests available during the 48 ± 12 months follow-up period. The extent of lung involvement was assessed using semi-quantitative visual evaluation of high-resolution computed tomography scans. Severe progression was defined as an annual ≥10% absolute decline in forced vital capacity or a ≥15% absolute decline in diffusion capacity of the lungs for carbon monoxide. **Results:** Thirteen patients were included. Raynaud's phenomenon, puffy fingers, and arthritis were the most common manifestations. Anti-SSA/Ro antibodies were detected in 4 patients. Dyspnea was reported in 7 patients. The predominant radiological pattern was nonspecific interstitial pneumonia, present in 9 patients. Three patients exhibited interstitial lung disease involvement >20%. At baseline, mean predicted FVC and DLCO values were significantly reduced (72.7% ± 17.3% and 58.0% ± 11.9%, respectively). Throughout follow-up, there was a mean increase of 2.5% ± 8.3% in forced vital capacity and a mean decrease of 2.2% ± 11.0% in total lung capacity; diffusion capacity of the lungs for carbon monoxide remained unchanged, with a mean variation of -0.5% ± 10.6%. A total of two patients experienced major interstitial lung disease progression during the follow-up period. **Conclusions:** In this cohort, pulmonary function remained relatively stable over time, with few cases of severe pulmonary function decline, suggesting a slow progression of interstitial lung disease in mixed connective tissue disease.

KEYWORDS: Mixed Connective Tissue Disease; Interstitial Lung Disease; Progression; Prognosis

INTRODUCTION

Mixed connective tissue disease (MCTD) is a rare systemic autoimmune disease characterized by overlapping features of systemic lupus erythematosus, dermatomyositis, systemic sclerosis, and rheumatoid arthritis. MCTD is associated with the presence of specific autoantibodies, namely anti-U1-ribonucleoprotein (anti-U1-RNP) antibodies, which serve as key immunological markers for diagnosis[1]. Raynaud's phenomenon (RP) is among the most prevalent clinical manifestations, alongside puffy fingers[2].

No diagnostic criteria have been universally established for MCTD; however, four classification criteria are commonly used: those proposed by Sharp, Kasukawa, Alarcón-Segovia, and Khan[3,4].

Interstitial lung disease (ILD) represents a severe complication of connective tissue diseases and significantly impacts morbidity and mortality[5]. In MCTD, pulmonary involvement affects up to 78% of patients, with dyspnea being the most frequently reported symptom[6]. Other respiratory symptoms may include dry cough, pleuritic chest pain, hemoptysis, and wheezing.

Nonspecific interstitial pneumonia (NSIP) is the most common radiological pattern, observed in up to 90% of patients. Usual interstitial pneumonia and organizing pneumonia patterns are observed less frequently[3,7]. Pulmonary function tests (PFTs) may reveal a reduced diffusing capacity for carbon monoxide (DLCO), forced vital capacity (FVC), and forced expiratory volume in one second (FEV1), consistent with a restrictive ventilatory pattern[8].

ILD and pulmonary hypertension (PH) are the two leading causes of mortality in patients with MCTD, with longer disease duration correlating with worse outcomes[3]. Several factors have been identified as associated with the presence of ILD in patients with MCTD, including older age, skin thickening, upper gastrointestinal symptoms, FVC <80%, DLCO <80%, anti-topoisomerase (Scl-70) autoantibodies, anti-SSA/Ro antibodies, cryoglobulinemia, and elevated C-reactive protein. Digital ulcers (DU) were identified as a risk factor for FVC decline >10% and mortality was higher in patients with MCTD-associated ILD (MCTD-ILD)[9].

MCTD remains a rare and understudied condition in the literature. Its association with ILD is even less common, and consequently, few studies have evaluated the clinical progression and long-term prognosis of affected patients.

This study aims to characterize the phenotype of MCTD-ILD at the time of diagnosis and to evaluate its evolution over time in a cohort of patients followed at our tertiary center.

METHODS

This was a retrospective, single-center cohort study conducted in the Rheumatology Department of ULS Santa Maria, Centro Académico de Lisboa, Portugal.

Inclusion criteria were as follows:[1] age ≥18 years at diagnosis;[2] a diagnosis of MCTD fulfilling one of the four accepted classification criteria (Sharp, Kasukawa, Alarcón-Segovia, or Kahn) and positive anti-U1-RNP antibodies;[3] diagnosis of ILD by high-resolution computed tomography (HRCT) at baseline;[4] availability of at least two PFTs, one at diagnosis and one during follow-up.

ILD was diagnosed based on the presence of typical HRCT features, including ground-glass opacities, consolidations, reticular pattern, interlobular septal thickening, traction bronchiectasis, or honeycombing. Imaging findings were not standardized and were reported according to our local radiology team[10,11].

Clinical data were extracted in a standardized manner from medical records, including sex, smoking status (current, passive, or never smoker), age at MCTD diagnosis, age at ILD diagnosis, interval between MCTD and ILD diagnoses, clinical manifestations, PFTs, immunological profile, and treatment. Baseline was defined as the time of ILD diagnosis ± 12 months.

Clinical features assessed included RP, DU, puffy fingers, limited or diffuse cutaneous thickening, arthritis, myositis, upper and/or lower gastrointestinal involvement, and PH.

Lung involvement was evaluated by the presence of dyspnea and through HRCT (to assess ILD pattern and extent) and PFTs, including FVC, total lung capacity (TLC) and DLCO, all expressed as a percentage of the predicted value. These parameters were assessed at ILD diagnosis and annually thereafter (± 6 months), when available.

The immunologic profile comprised the analysis of antinuclear antibodies (ANA), anti-double-stranded DNA (dsDNA), anti-SSA/Ro, anticentromere, anti-Scl-70, anti-cyclic citrullinated peptide (CCP), and anti-polymyositis/scleroderma (Pm/Scl) autoantibodies.

Recorded immunosuppressive therapies included glucocorticoids, hydroxychloroquine (HCQ), methotrexate (MTX), mycophenolate mofetil (MMF), azathioprine (AZA), rituximab (RTX), cyclosporine, le-

flunomide, tacrolimus, tumor necrosis factor inhibitors (TNF inhibitors), belimumab, cyclophosphamide, and intravenous immunoglobulin (IVIG).

ILD severity – ILD extent was assessed using semi-quantitative visual evaluation of HRCT scans, with lung involvement categorized as mild (<10%), moderate (10-20%), or severe (>20%), based on the extent of the lesions. The >20% threshold was selected as it represents the most commonly used cutoff in the literature[12].

ILD progression during Follow-up – Annual assessment periods were analyzed to classify ILD functional progression throughout the follow-up period. Patients were stratified into three subgroups according to annual changes in predicted FVC and DLCO, assessed over a follow-up of 48 ± 12 months. Severe ILD progression was defined as an annual ≥10% absolute decline in FVC or ≥15% absolute decline in DLCO. Moderate ILD progression was defined as an annual 5-10% decline in FVC or a 10-15% decline in DLCO. Pulmonary function was considered stable or improved when the annual variation in FVC and DLCO was less than 5% and 10%, respectively, regardless of whether this represented a decrease or an increase from the previous assessment.

Ethical considerations – This study was approved by the Ethics Committee of Centro Académico de Medicina de Lisboa (CAML) (reference number 319/25), in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis – Data normality was assessed using the Shapiro-Wilk test. Continuous variables were reported as mean ± standard deviation (SD) for normally distributed data or median [interquartile range, IQR] for non-normally distributed data.

RESULTS

BASELINE ANALYSIS

Study Population And Patient Characteristics – The study population consisted of 13 patients with MCTD-ILD. Of these, 12 were female (92.3%), and 1 patient (7.7%) reported either active or passive tobacco exposure. At the time of MCTD diagnosis, the median age was 35.0 [16.5] years, while the median age at MCTD-ILD diagnosis was 37.0 [14.0] years. The median time from MCTD to MCTD-ILD diagnosis was 14.0 [21.0] months (see Table 1).

TABLE 1. Patient characteristics

	MCTD-ILD (n=13)
Demographics	
Female, n (%)	12 (92.3)
Smoking, n (%)	1 (7.7)
Clinical features	
Age at diagnosis of MCTD, years, median [IQR]	35.0 [16.5]
Age at diagnosis of ILD, years, median [IQR]	37.0 [14.0]
Time from MCTD to MCTD-ILD diagnosis, months, median [IQR]	14.0 [21.0]
Raynaud's phenomenon, n (%)	12 (92.3)
Digital ulcers, n (%)	5 (38.5)
Puffy hands/fingers, n (%)	9 (69.2)
Limited skin thickening, n (%)	1 (7.7)
Diffuse skin thickening, n (%)	0 (0.0)
Arthritis, n (%)	9 (69.2)
Myositis, n (%)	4 (30.8)
Upper and lower gastrointestinal tract involvement, n (%)	1 (7.7)
Pulmonary hypertension, n (%)	1 (7.7)
Pulmonary features	
NSIP, n (%)	9 (69.2)
Dyspnea, n (%)	7 (53.8)
Extent of CT findings	
<10%, n (%)	3 (23.1)
10-20%, n (%)	7 (53.8)
>20%, n (%)	3 (23.1)
FVC (%), mean ± SD	72.7 ± 17.3
TLC (%), mean ± SD	78.4 ± 14.7
DLCO (%), mean ± SD	58.0 ± 11.9
Biological features	
ANA, n (%)	13 (100.0)
Anti-dsDNA, n (%)	2 (15.4)
Anti-SSA/Ro, n (%)	4 (30.8)
Anticentromere, n (%)	0 (0.0)
Anti-Scl-70, n (%)	0 (0.0)
Anti-CCP, n (%)	2 (15.4)
Anti-Pm/Scl, n (%)	0 (0.0)
Treatment	
Prednisolone, n (%)	12 (92.3)
Hydroxychloroquine, n (%)	9 (69.2)
Methotrexate, n (%)	8 (61.5)
Mycophenolate mofetil, n (%)	5 (38.5)
Azathioprine, n (%)	3 (23.1)
Rituximab, n (%)	2 (15.4)
Cyclophosphamide, n (%)	0 (0.0)
Others, n (%)	3 (23.1)

Legend: IQR = interquartile range; **SD** = standard deviation; **ANA** = antinuclear antibody; **Anti-CCP** = anti-cyclic citrullinated peptide antibody; Anti-dsDNA = anti-double-stranded DNA antibody; Anti-Pm/Scl = anti-polymyositis/scleroderma antibody; Anti-SSA/Ro = anti-Sjögren's syndrome-related antigen A/Ro antibody; CT = computed tomography; DLCO = diffusing capacity of the lungs for carbon monoxide; FVC = forced vital capacity; ILD = interstitial lung disease; MCTD = mixed connective tissue disease; NSIP = nonspecific interstitial pneumonia; TLC = total lung capacity.

Regarding clinical features, RP was the most frequent manifestation, observed in 12 patients (92.3%), followed by puffy fingers and arthritis in 9 patients (69.2%). DU were documented in 5 patients (38.5%) and myositis in 4 patients (30.8%). Limited cutaneous thickening was present in 1 patient (7.7%), whereas diffuse cutaneous thickening was not observed in any patient. Upper and lower gastrointestinal tract involvement, as well as PH, were each reported in one patient (7.7%).

Baseline Pulmonary Involvement – Regarding clinical manifestations, dyspnea was reported by 7 patients (53.8%). On HRCT, the most frequently identified lung pattern was NSIP, observed in 9 patients (69.2%).

Regarding the extent of radiological abnormalities on HRCT, 3 patients (23.1%) had less than 10% involvement, 7 patients (53.8%) had 10–20% pulmonary involvement and 3 patients (23.1%) had more than 20% involvement.

PFTs showed a mean FVC of 72.7% ± 17.3%, mean TLC of 78.4% ± 14.7%, and mean DLCO of 58.0% ± 11.9%.

Immunologic Profile – All 13 patients (100%) tested positive for ANA. Anti-SSA/Ro antibodies were positive in 4 patients (30.8%). Anti-CCP antibodies were positive in 2 patients (15.4%), as were anti-dsDNA antibodies (15.4%). All patients tested negative for anticentromere, anti-Scl-70, and anti-Pm/Scl antibodies.

Treatment – Prednisolone was the most frequently used immunosuppressant, prescribed to 12 patients (92.3%), followed by HCQ, prescribed to 9 patients (69.2%). MTX was prescribed to 8 patients (61.5%) and MMF to 5 patients (38.5%). The least commonly used immunosuppressants were AZA, prescribed to 3 patients (23.1%), and RTX, prescribed to 2 patients (15.4%).

LONGITUDINAL PULMONARY FUNCTION ANALYSIS

Overall Cohort Analysis (Baseline To Last Visit) – The median follow-up period was 40.0 [30.0] months.

From baseline until the last available data time point, we observed an overall increase in mean FVC by 2.5% ± 8.3%, a decrease in TLC, of 2.2% ± 11.0%, and stability in DLCO, with a variation of -0.5% ± 10.6% (see Table 2).

TABLE 2. Changes in pulmonary function parameters in MCTD-ILD until the last visit.

Variables	Baseline	Last Visit	Variation
FVC (%), mean	72.7	75.2	+2.5 ± 8.3
TLC (%), mean	78.4	76.2	-2.2 ± 11.0
DLCO (%), mean	58.0	57.6	-0.5 ± 10.6

Time Point Specific Analysis – The longitudinal analysis considered five time points: at diagnosis, and at 12, 24, 36, and 48 months of follow-up. Data availability varied across time points (13 patients at baseline, 9 at 12 months, 5 at 48 months).

12-Month Early Follow-Up Analysis – At 12 months of follow-up, an improvement in pulmonary function was observed. Regarding general data available for this time point, mean FVC increased from 72.7% ± 17.3% to 78.6% ± 15,6% (corresponding to an absolute change of 5.9% ± 8.9%), as well as mean TLC, which rose from 78.4% ± 14.7% to 80.2% ± 14.7% (1.8% ± 5.0%). However, mean DLCO decreased from 58.0% ± 11.9% to 56.7% ± 9.2% (-1.3% ± 12.9%).

By this time point, 1 patient experienced severe ILD progression, with predicted DLCO decreasing from 88% to 54%, which corresponds to an absolute decrease of 34%; 2 patients experienced moderate ILD progression and 6 patients experienced stable or improved ILD disease.

48-Month Late Follow-Up Analysis – At 48 months of follow-up, FVC showed a mean value of 71.6% ± 11.8%, reflecting an absolute change of -1.1% ± 9.0% from baseline. TLC decreased to a mean value of 71.4% ± 9.7%, representing an absolute change of -7.0% ± 11.7%. DLCO reached 56.6% ± 7.4%, corresponding to a change of -1.4% ± 1.5%.

Longitudinal changes in lung function at different time points, including 24 and 36 months, are presented in Table 3 and Figure 1.

TABLE 3. Pulmonary function parameters evolution over time.

Parameter	Baseline n=13	12 Months n=9	24 Months n=7	36 Months n=4	48 Months n=5
FVC (%)	72.7 ± 17.3	78.6 ± 15.6	77.4 ± 14.1	*73.3 ± 10.2*	*71.6 ± 11.7*
TLC (%)	78.4 ± 14.7	80.2 ± 14.7	77.9 ± 18.1	*78.8 ± 13.5*	*71.4 ± 9.7*
DLCO *(%)*	*58.0 ± 11.9*	*56.7 ± 9.2*	*59.6 ± 12.7*	*64.7 ± 5.5*	*56.6 ± 7.4*

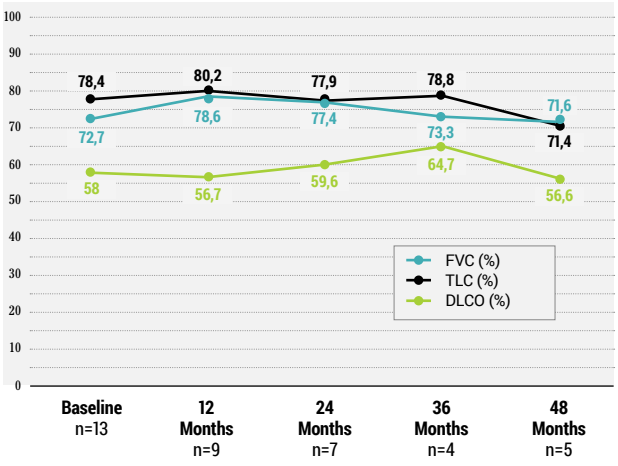

FIGURE 1. Evolution of FVC (%), TLC (%) and DLCO (%) over time

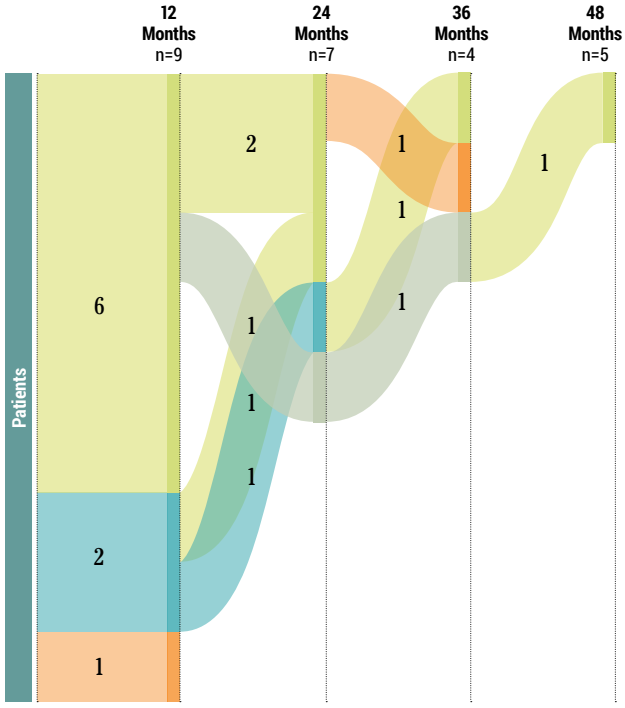

FIGURE 2. Sankey diagram showing annual transitions in ILD progression status over 48 ± 12 months of follow-up. Flow width represents the number of patients in each category. Categories include stable or improved disease (green), moderate progression (orange), severe progression (red), and missing data (gray).

Disease Progression Classification – Annual assessment periods were analyzed to classify ILD functional progression throughout the follow-up period and a total of 16 patient-assessment periods were analyzed.

As stated in the Methods section, disease progression was defined as follows:

- ***Severe:*** ≥10% decline in FVC or ≥15% decline in DLCO;
- ***Moderate:*** 5-10% decline in FVC or 10-15% decline in DLCO;
- ***Stable/Improved:*** <5% decline or any improvement in FVC or <10% decline or any improvement in DLCO.

Of the 16 analyzable annual periods, functional progression was classified as follows (see Figure 2):

- ***Severe progression:*** 2 periods (12.5%), occurring in 2 different patients at different time points;
- ***Moderate progression:*** 3 periods (18.8%);
- ***Stable/Improved:*** 11 periods (68.8%).

MORTALITY

No deaths were documented during the follow-up period.

DISCUSSION

ILD is a clinically significant manifestation of MCTD, standing as a major contributor to long-term morbidity and mortality[5]. In this single-center retrospective cohort study, we analyzed the clinical, radiological, and functional characteristics of 13 patients with MCTD-ILD over a median follow-up period of 40.0 [30.0] months, aiming to characterize the trajectories of pulmonary function in this population and identify potential patterns of disease progression. Given the rarity of MCTD and the even lower frequency of MCTD-ILD, our findings provide valuable insights to an underexplored area of the literature.

In this cohort of 13 patients, consistent with the known clinical spectrum of this disease, RP, puffy fingers, and arthritis were the most prevalent clinical features[2]. Myositis and DU were less frequently observed, and gastrointestinal involvement or PH were rare.

From a pulmonary standpoint, dyspnea was reported in 53.8% of patients, underscoring its relevance as a key clinical symptom of ILD. Regarding imaging findings, the NSIP pattern was the most common, identified in 69.2% of patients, aligning with current evi-

dence that this is the predominant radiologic pattern in MCTD-ILD[3]. As for PFTs, mean predicted FVC and DLCO values at diagnosis were already significantly reduced (72.7% ± 17.3% and 58.0% ± 11.9%, respectively), findings that reflect a restrictive ventilatory pattern, and suggest that ILD was functionally advanced at the time of diagnosis.

In the longitudinal analysis of pulmonary function, overall variations were minimal, with a general trend toward stability with minimal changes in FVC and DLCO. However, a more detailed evaluation of mean values at each time point revealed a biphasic trajectory. An initial phase of mild functional improvement was observed at 12 and 24 months, especially in FVC and TLC. This was followed by a subsequent gradual decline in all evaluated parameters, from 36 months onward, becoming more evident in the last year of follow-up. This pattern may reflect an initial positive therapeutic response to early diagnosis and prompt initiation of immunosuppressive treatment, followed by a stable course of ILD. The initial improvement may represent a "window of opportunity" during which MCTD-ILD is more responsive to immunomodulatory therapy. These variations should be interpreted with caution due to the small sample size and the already impaired pulmonary function at baseline.

Despite the overall trends observed in mean pulmonary function, individual trajectories varied considerably. While some patients experienced a decline in pulmonary function, others remained stable, and a few even improved. The overall prognosis in our cohort appeared favorable, with only a minority of patients exhibiting major functional decline and no deaths during follow-up. During follow-up, only two patients fulfilled the criteria for severe ILD progression. There were also three episodes of moderate progression, while the majority of assessments (eleven episodes) indicated stability or improvement in ILD progression.

This study emphasizes the heterogeneity of MCTD-ILD progression: while some patients stabilize or improve, others experience decline, underscoring the need for extended and regular monitoring beyond the first years, even in cases that initially appear stable. Early recognition of functional deterioration and timely therapeutic adjustment may have an important role in mitigating irreversible pulmonary damage.

More than one-third of patients had DU, which has been reported as a risk factor for ILD progression. In out cohort, most patients nonetheless had mild or stable disease. Similarly, while anti-SSA/Ro antibodies have been linked to severe ILD in MCTD, most patients in our cohort maintained mild or stable disease. Although baseline reduced FVC and DLCO are considered risk factors for ILD in MCTD, our cohort exhibited these values while maintaining a favorable pulmonary course. This apparently favorable pulmonary outcome may reflect the overall low prevalence of other high-risk features: cutaneous skin thickening was uncommon, advanced age was rare, only one patient had upper gastrointestinal involvement, and no patients had anti-Scl-70, an antibody associated with worse pulmonary outcomes[13]. In fact, among the two patients who experienced severe disease progression, neither had anti-SSA/Ro antibodies, and only one had a prior history of DU (data not shown).

When compared to the study from Kawano-Dourado et al.[14], which followed 39 patients with MCTD-ILD over 10 years, our findings regarding FVC are consistent with the ones shown in this study, supporting the overall stability of this parameter over time. The relative preservation of PFTs values in both cohorts aligns with existing literature describing MCTD-ILD progressing less aggressively than other ILD subtypes.

This study has several limitations. First, the small sample size, although expected due to the rarity of the disease. The second limitation relates to the study design, single-center and retrospective, which restricts the generalizability of findings. In addition, incomplete data, particularly at later time points, which may have introduced bias or underestimated the real rate of ILD progression. A final limitation is that the study did not explore the impact of specific or cumulative immunosuppressive regimens on pulmonary function trajectory.

In spite of these limitations, this study contributes to the scarce literature on MCTD-ILD, as well as reinforces existing data regarding its pulmonary course. The findings support the concept of heterogeneity of disease progression at the individual level and highlight the importance of personalized monitoring strategies. Lastly, future prospective multicentric studies are needed to validate these findings and to assess the impact of therapeutic interventions, including antifibrotic agents, in patients with progressive phenotypes of MCTD-ILD.

CONCLUSION

This study allowed for a detailed characterization of MCTD-ILD patients followed at our center, the Department of Rheumatology of ULS Santa Maria, and, more importantly, the evolution of their respiratory function over a mean follow-up period of 48 ± 12 months.

Baseline PFTs revealed a significant restrictive pattern. However, during follow-up, results showed that pulmonary function remained relatively stable. Individual analysis of patients demonstrated notable heterogeneity in disease progression, with the majority of cases showing stability or improvement, and only a few experiencing significant ILD progression.

These findings suggest that ILD progression in MCTD is generally slow in our cohort. The data obtained contribute to the understanding of this rare entity and reinforces the need for prospective multicentric studies to further explore the role of different therapeutic regimens.

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Ethical Compliance: *This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee, with reference number 319/25, of the Centro Académico de Medicina de Lisboa (CAML) signed off on 26 November 2025.*
Written informed consent was waived by the Ethics Committee considering the retrospective nature of this study and the appropriate measures that were taken to ensure compliance with the General Data Protection Regulation (GDPR) (EU).
Conflicts of Interest: *The authors declare no conflicts of interest.*
Data Availability Statement*: The data underlying this article will be shared on reasonable request to the corresponding author. The data are not publicly available due to data protection.*

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RESEARCH ARTICLE

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Misdiagnosis of Surgical Conditions in ALS Patients: Analysis of a single-center experience and review of the literature

Miguel Martins[1*], **Marta Gromicho**[1*], **Miguel Oliveira Santos**[1,2], **Mamede de Carvalho**[1,2]

[1] Medicine ULisboa for Health, Clinical Research and Innovation (MUHCRI), Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal

[2] Serviço de Neurologia, Departamento de Neurociências e Saúde Mental, ULS de Santa Maria, Lisboa, Portugal.

[*] These two authors contributed equally to this work

✉ **Corresponding author:**
Prof Mamede de Carvalho
Institute of Molecular Medicine, Faculty of Medicine, University of Lisbon
Av. Professor Egas Moniz,
1648-028 Lisbon, Portugal
Email: mamedemg@mail.telepac.pt

ABSTRACT: Introduction: In amyotrophic lateral sclerosis (ALS) late or incorrect diagnosis significantly reduces the therapeutic window, while also increasing the risk of inappropriate interventions, with a negative impact on disease progression rate. **Objectives:** We aim to identify and characterize the clinical profile of ALS patients followed in our center who underwent surgeries due misdiagnosis, and to review the literature. **Methods:** We conducted a prospective observational study of patients newly diagnosed with ALS at our center between 2021 and 2024. Patients were categorized into two groups: those who underwent surgical intervention (Surgery Group, n=17) and those who did not (non-Surgery Group, n=284). Variables analyzed included demographic characteristics, onset region, diagnostic delay, baseline disease progression rate (ΔFS), the first specialist consulted, upper motor neuron (UMN)/lower motor neuron (LMN) predominance, and presence of fasciculations at onset. English medical literature was reviewed. **Results:** Of 301 ALS patients, 17 (5.6%) underwent surgery due to initial symptoms. These patients had a significantly longer diagnostic delay (median 14.95 vs. 8.99 months, p=0.010) and all had spinal-onset ALS (p=0.014). No significant differences were found in sex (p=0.354), progression rate (p=0.453), UMN/LMN predominance (p=0.708), or fasciculations at onset (p=0.129). **Conclusion:** Surgical misdiagnosis in ALS, particularly in spinal-onset cases, remains a clinical concern. Surgeries may delay diagnosis and bypass early neurological assessment. We advocate for increased ALS awareness among non-neurologists and emphasize the necessity of neurological evaluation prior to elective spinal surgery in patients exhibiting progressive motor symptoms.

KEYWORDS: Amyotrophic Lateral Sclerosis; Diagnostic Errors; Disease Progression; Surgical Procedures

INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a progressive and fatal neurodegenerative disorder primarily affecting motor neurons, leading to progressive muscle weakness, atrophy and paralysis. Despite being a rare disease, ALS is the most prevalent form of motor neuron disease.[1,2]

The global prevalence of ALS is estimated at 4.42 per 100,000 individuals (95% CI: 3.92–4.96), with an incidence of 1.59 per 100,000 person-years (95% CI: 1.39–1.81).[3] Higher prevalence and incidence rates have been reported in more socioeconomically developed regions.[4] ALS typically pre-

sents with focal muscle weakness and atrophy, which spreads as the disease progresses.[2,5] It can be classified by onset site and by predominant motor neuron involvement (upper vs. lower motor neuron, UMN/LMN).[6]

Diagnosis of ALS relies on clinical history, neurological examination, electrodiagnostic studies, and imaging to exclude other mimicking conditions.[7] Early diagnosis remains a challenge due to symptom variability, the lack of definitive biomarkers, and ALS's heterogeneous early presentation, all of which contribute to frequent diagnostic delays and initial diagnostic errors.[7,8] Late or incorrect diagnosis significantly reduces the therapeutic window, limiting access to treatments and clinical trials, while also increasing the risk of inappropriate interventions,[9] with a negative impact on disease progression rate.[10]

Numerous scientific studies have explored and evaluated the factors contributing to the difficulty of diagnosing ALS in its early stages.[9,11-15] First, the site of symptom onset can influence clinical suspicion, as spinal presentation may initially mimic other diseases, such as radiculopathies, spinal myelopathies, multifocal motor neuropathies, nerve entrapment, myasthenia gravis or primary muscle disorders. Age is another determinant; younger patients are more likely to experience a diagnostic error and have a longer diagnostic delay.[15] Additionally, patients rapidly observed by a neurologist earlier have a faster diagnosis.[11,13,15] A significant consequence of ALS difficult diagnosis is the occurrence of unnecessary surgical interventions.[16,17]

This study we aim to identify ALS patients followed in our center who underwent surgical procedures due to misdiagnosis, to characterize their clinical profile and to review the literature.

MATERIAL AND METHODS

Study protocol – Data prospectively collected at the ALS clinic, Centro Académico de Medicina de Lisboa, ULS de Santa Maria, between 2021 and 2024, were analysed. A standardized clinical questionnaire[18] was completed during the initial evaluation by an experienced neurologist (MdC, MOS).

Inclusion Criteria included a confirmed ALS diagnosis based on Gold Coast Criteria, disease progression on follow-up, completion of data questionnaire and informed consent. Exclusion criteria included associated dementia (due to limitations in providing essential clinical information regarding the diagnostic track), other neurological conditions, severe comorbidities, and missing key data. An exception was made for [23] patients (7.6%) who were uncertain about the presence of fasciculations at the time of first motor symptoms.

Subgroup Classification – Patients were classified into two groups: Surgery Group - patients who underwent surgical procedures; non-Surgery Group - patients who did not undergo surgery related to ALS symptoms. Information was confirmed through clinical review, diagnostic tests, and surgical records.

Variables Analysis – We compared demographic and clinical variables between the Surgery and non-Surgery groups. Demographic variables included age at symptom onset and sex. Clinical variables included diagnostic delay (months from symptom onset to ALS diagnosis), disease progression rate, region of onset (spinal vs. non-spinal), presence of fasciculations at onset, and UMN/LMN predominance.

UMN predominance was defined by spasticity with functional impairment, and LMN predominance by weakness and atrophy without spasticity. In mixed cases, LMN predominance was assumed, based on prior literature indicating a higher likelihood of diagnostic uncertainty.[10,16]

The functional rate of progression (ΔFS) at first visit at our ALS clinic was calculated using the Revised ALS Functional Rating Scale (ALSFRS-R) as follows: *ΔFS = (48 – ALSFRS-R at first visit) / duration in months from symptom onset to first visit*.[19] Patients were classified as Slow Progressors (ΔFS < 0.29), Intermediate Progressors (0.29 and 1.03), or Fast Progressors (ΔFS > 1.03), following the thresholds defined in Alves et al., 2025.[19] Moreover, ALSFRS-R decay was calculated during the 3 months following the initial consultation, up to the time of the second consultation. Longer functional decay was not possible due to missing data.

To assess the influence of healthcare pathways on the diagnostic trajectory of ALS, we analysed the first specialist seen for related-ALS symptoms (neurologist, neurosurgeon, general practitioner, orthopaedic surgeon, or other). In the Surgery Group, we also documented the type of surgical procedure and the specialty of the operating physician.

Statistical Analysis – Continuous variables were analysed using independent t-tests (if normally distributed) or the Mann-Whitney U test (if non-normally distributed, assessed by the Shapiro-Wilk test). Categorical variables were analysed using the Chi-square test. A p-value of < 0.05 was considered statistically significant. All statistical analyses were conducted using IBM

SPSS Statistics for Windows, Version 30.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The statistical analysis included 301 ALS patients, of whom 17 (5.6%) underwent surgical procedures. The demographic and clinical characteristics of both groups are shown in Table 1, no significant differences were found between the Surgery and non-Surgery groups in terms of sex (p=0.35) or age at onset (p=0.77).

Diagnostic delay was significantly longer in the Surgery Group (14.95 [10.97 – 20.02] months vs. 8.99 [5.95 – 15.99] months, p=0.01) as seen in Figure 1. Regarding disease onset, there was a significant association with spinal-onset (p=0.014). All patients in the Surgery Group had spinal onset ALS, whereas 26.8% of the non-Surgery Group had a non-spinal onset. No significant differences were found in UMN vs. LMN predominance (p=0.71) and for ΔFS at diagnosis (p=0.453). No significant differences were found in UMN vs. LMN predominance (p=0.708) and for functional decay (ΔFS) at diagnosis (p=0.453). Symptoms of fasciculations at disease onset were assessed in 278 patients, no difference was found between groups (p=0.13).

Among the 17 ALS patients (5.6%) who underwent surgery, the initial specialist varied. General practitioners (GPs) were most frequently seen first (24%), followed by orthopaedic surgeons (18%), neurologists (12%), and neurosurgeons (12%). In 6 cases (35%), the first consulted specialist could not be identified. Common diagnoses included lumbar stenosis (53.0%, n=9), cervical myelopathy (24.0%, n=4) and carpal tunnel syndrome (18.0%, n=3). These led to surgical interventions such as spinal decompression (77.0%, n=13), carpal tunnel release (18.0%, n=3), and other orthopaedic procedures (6.0%, n=1). Most surgeries (64.7%) were performed by neurosurgeons, while the remainder (35%) were conducted by orthopaedic surgeons.

Comparing with prior studies

Our literature review retrieved two articles from the electronic search that investigated inappropriate surgeries in ALS.[16,17] One study reported that 7.9% of ALS patients underwent inappropriate surgical interventions.[16] Srinivasan et al, observed 13% of ALS patients underwent unnecessary procedures.[17] Our findings are consistent with these studies, confirming that patients spinal-onset ALS are often diagnosed as cervical or lumbar compressive disorders. In all three studies, spinal decompression surgeries and carpal tunnel releases were common procedures performed before an ALS diagnosis was established, as presented in Table 2. The total number of surgeries exceeded the number of patients, as some individuals underwent multiple procedures, as described before;[17] in our study, three patients underwent two surgeries related to ALS symptoms. Similar to prior findings, most patients who underwent surgery were initially evaluated by non-neurologists, particularly surgeons.

TABLE 1. Clinical and demographic characteristics of ALS patients in the Surgery and Non-Surgery groups.

Variable	Non-Surgery Group (N=284)	Surgery Group (N=17)	p-value
Sex	Male: 151 (53.2%) Female: 133 (46.8%)	Male: 11 (64.7%) Female: 6 (35.3%)	*0.354 **
Age at Onset (years)	64.1 (52.5 – 71.8)	64.12 (52.30 – 70.54)	*0.770 #*
Diagnostic Delay (months)	8.99 (5.95 – 15.99)	14.95 (10.97 – 20.02)	*0.010 #*
Disease Progression Rate (ΔFS)	0.72 (0.36 – 1.29)	0.64 (0.29 – 1.17)	*0.453 #*
Onset region	Spinal: 208 (73.2%) Nonspinal: 76 (26.8%)	Spinal: 17 (100.0%) Nonspinal: 0 (0.00%)	*0.014 **
UMN vs. LMN at Onset	LMN: 223 (78.5%) Predominant UMN: 61 (21.5%)	LMN: 14 (82.4%) Predominant UMN: 3 (17.6%)	*0.708 **
Fasciculations at Onset (N=278)	Yes: 83 (31.7%) No: 179 (68.3%)	Yes: 8 (50.0%) No: 8 (50.0%)	*0.129 **

Values are presented as median (Q1-Q3) for continuous variables and n (%) for categorical variables.
* Chi-Square test; # Mann-Whitney U test. Statistically significant values p-values (p < 0.05) are noted.

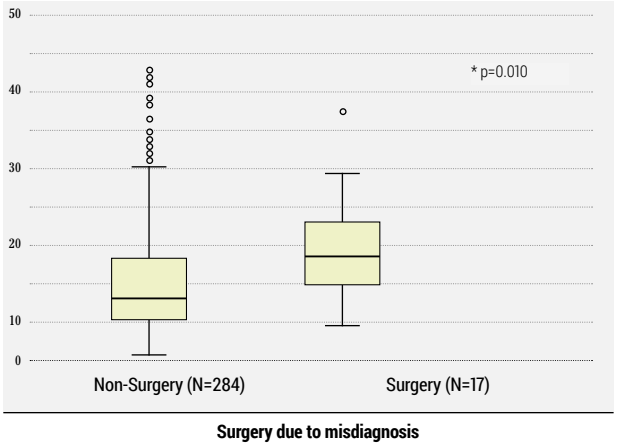

FIGURE 1. Distribution of Diagnostic Delay (in months) in Surgery *vs* Non-Surgery Groups.

Boxplot with the distribution of diagnostic delay in ALS patients in Surgery and Non-Surgery groups. The Surgery Group exhibited significantly longer diagnostic delays (p=0.010)

DISCUSSION

Among the 301 ALS patients included in the study, 17 (5.6%) underwent surgery for symptoms that were later attributed to ALS. These patients who underwent surgery experienced a significantly longer diagnostic delay (p=0.010), and all of them had spinal-onset ALS. However, no significant differences were found for ΔFS, UMN versus LMN predominance, or the presence of fasciculations at onset. Fasciculations at onset and UMN versus LMN predominance were not approached in previous studies.

Our overall findings align with previous studies, reinforcing the persistent challenge in the early recognition of ALS—often resulting in substantial diagnostic delays and mismanagement, including unnecessary surgical procedures.[10,11,17,20] Patients in the Surgery Group had a significantly longer diagnostic delay (median: 14.95 months) compared to the non-Surgery Group, likely due to the initial difficulty in diagnosis, as previously proposed.[10] Contrary to a previous study,[10] we found no evidence of faster disease progression after the surgical intervention; however, the follow-up information in our study was limited due to missing data.

All patients in the Surgery Group had spinal-onset ALS, which shows spinal-onset is more prone to surgical interventions.[10,16,17] In this cohort, predominant UMN signs did not prevent inappropriate surgeries. Contrary to expectation, spasticity and hyperreflexia did not prompt earlier referrals to neurology, possibly due to incidental cervical cord MRI findings. Interestingly, while fasciculations associated with weakness are a hallmark of ALS and strongly suggest the disease,[21] this clinical feature was not relevant in our study, suggesting that future diagnostic red flags should strongly emphasize this finding.

The first specialist consulted significantly influences the ALS diagnostic pathway. Within our Sur-

TABLE 2. Inappropriate surgical interventions in ALS patients: three studies.

Reference	Surgical Cases (N)	First Specialist Consulted (%)	Diagnosis (%)	Surgery Procedures (%)
This Study	*17 (5.6%)*	*Surgeon: 5 (29%)* *Non-Surgeon: 6 (35%)* *Unknown: 6 (35%)*	*Lumbar Sten.: 9 (45%) – 3 OrtS + 6 NS* *Cerv. Myelopathy: 5 (25%) - 5 NS* *CTS: 4 (20%) – 4 OrtS* *Others: 2 (10%) – 1NS + 1OS*	*Spinal Decomp..: 14 (70%)* *CTR: 4 (20%)* *Other: 2 (10%)*
Bakola et al. (2014)16	*13 (7.9%)*	*Surgeon: Not specified* *Non-Surgeon: Not Specified*	*Lumbar Sten.: 7 (54%)* *CTS: 3 (23%)* *Cerv. Myelopathy: 2 (15%)* *Others: 1 (8%)*	*Spinal Decomp.: 9 (69%)* *CTR: 3 (23%)* *Others: 1 (8%)*
Srinivasan et al. (2006)17	*34 (13%)*	*Surgeon: 12 (35%)* *Non-Surgeon: 3 (8.8%)* *Unknown: 19 (55.8%)*	*Knee: 12 (32.4%)* *Lumbar Sten.: 11 (29.7%)* *Cerv. Myelopathy: 3 (8.1%)* *CTS: 5 (13.5%)* *Others: 6 (16.2%)*	*Spinal Decomp.: 14 (37.8%)* *Knee surgery: 12 (32.4%)* *CTR: 5 (13.5%)* *Others: 6 (16.2%)*

Data includes the number and percentage of surgical cases, type of first specialist consulted, most frequent diagnosis, and types of surgeries performed prior to ALS diagnosis. **Cerv. Myelopathy** = Cervical Myelopathy; **Lumbar Sten.** = Lumbar Spinal Stenosis; **CTS** = Carpal Tunnel Syndrome; **Spinal Decomp.** = Spinal Decompression Surgery; **CTR** = Carpal Tunnel Release; **OrtS** – surgery done by orthopedic surgeon; **NS** – surgery done by neurosurgeon; **OS** – surgery done by other surgeon (plastic surgeon).

gery group cohort, 24% of patients initially consulted general practitioners, and 29% consulted surgical specialties (orthopaedics and neurosurgery). The small sample size of the Surgery Group made a comparative analysis of diagnostic pathways infeasible.

This study has several limitations: firstly, the initial specialist consulted was unidentified in 35% of surgical cases; secondly, the single-centre design may restrict the generalizability of findings to healthcare systems with differing referral patterns; [22,23] and the limited sample size of operated patients reduces the statistical power, potentially affecting the robustness of the results.

CONCLUSION

Beyond the clinical implications, inappropriate surgical interventions in ALS patients impose avoidable healthcare costs and psychological distress on patients and families. In our cohort, we found some issues linked to diagnostic delay, including late neurology referrals and potential overreliance on imaging. Improving interdisciplinary referral protocols and integrating neuromuscular triage tools at the primary care level could mitigate these diagnostic issues. Future research should focus on developing diagnostic red flags for early ALS, as the split-hand in patients with non-specific spinal symptoms. [24,25]

Ethical compliance statement: *This study was approved by the Local Ethics Committee (Comissão de Ética do Centro Académico de Medicina de Lisboa, ID number 162/21) and was conducted in accordance with the Declaration of Helsinki. All patients gave signed informed consent. To ensure data privacy, all patient information was anonymized, and databases were stored securely.*
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- **Conselho Diretivo do Instituto Nacional de Saúde Doutor Ricardo Jorge**
- **Direção-Geral da Saúde**
- **Secretaria de Estado da Saúde**

10:30 Painel 1: *Doenças Raras - Perspetiva Local*

Moderação: *Cristina Abreu Santos (INSA), (ULS Alto Alentejo)*

Vera Escoto - ULS Alto Alentejo
Maria do Céu Machado - Plano de Ação para as Doenças Raras: Da estratégia à Pessoa 2025-2030
Agustín Pijerro - Consulta de Enfermidades Minoritarias - Hospital Universitario de Badajoz

12:00 Painel 2: *Doenças Raras - Perspetiva dos Doentes*

Moderação: *AICIB*

Raquel Marques (RD-Portugal)
Diana Franco Frazão (IQVIA)
Mariana Esteves (Associação CTNNB1)

12:30 *Tuberous Sclerosis Complex: Horizons*
(Trabalho vencedor do Concurso *Genética e Raras: Uma Visão, Vários Olhares*)

Moderação: *Glória Isidro*
Joana Leitão

13:00 Almoço

14:00 Painel 3: *Doenças Raras: Perspetiva Nacional e Internacional*

Moderação: *Patrícia Maciel, Francisca Coutinho, Ana Santos Carvalho*

Joint Action JARDIN
Carla Pereira - Direção-Geral da Saúde

Parceria *ERDERA - Perspetiva Nacional*
Anabela Isidro - AICIB
Luís Pereira de Almeida - GeneT, CNC-UC, CiBB, Universidade de Coimbra
Sandra Alves - DGH, INSA, "National Mirror Group" da "European Alliance for Rare Diseases"

Projeto *CPLP Raras*
Filipe Bernardi
Vinicius Lima

16:00 Sessão de Encerramento
Paulo Gonçalves (RD-Portugal)
AICIB

16:15 Coffee-break e Programa Social (Visita à Sé Catedral de Portalegre)

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A Sociedade das Ciências Médicas de Lisboa apoia esta iniciativa.

RESEARCH ARTICLE

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JORNAL DA SOCIEDADE DAS CIÊNCIAS MÉDICAS DE LISBOA

Trends in Antibiotic Consumption and Resistance in Portugal, 2013–2023

Claudio Viera Teixeira [1,2]

[1] Independent Researcher, Lisbon, Portugal

✉ *Email: cvtex@icloud.com*

ABSTRACT: **Introduction:** Antimicrobial resistance (AMR) remains a major public health challenge globally and in Portugal, where antibiotic consumption has historically exceeded European averages. In response, the Plano Nacional de Prevenção da Resistência aos Antimicrobianos (National Programme for the Prevention of Antimicrobial Resistance) 2019–2023 established national targets to reduce inappropriate prescribing, consumption, and resistance. **Objectives:** To analyse national trends in antibiotic consumption and resistance in Portugal between 2013 and 2023, and to evaluate progress relative to the 2019–2023 national program targets. **Methods:** Surveillance data from 2013–2023 were obtained from the European Centre for Disease Prevention and Control (ECDC), the World Health Organization (WHO), and the Direção-Geral da Saúde (DGS). Four indicators were analysed in line with the 2019–2023 National Programme for the Prevention of Antimicrobial. **Resistance targets:** outpatient antibiotic consumption, hospital carbapenem use, prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), and prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp). Results were compared against national targets and EU/EEA averages. **Results:** Between 2013 and 2023, outpatient antibiotic consumption in Portugal increased and exceeded the 2023 national programme target, remaining above the EU/EEA average. Broad-spectrum antibiotics continued to account for a disproportionate share of prescribing. Hospital carbapenem use remained within national ceilings but above EU means. Resistance trends showed marked progress in reducing MRSA prevalence, which fell below the 2023 national programme target (<35%). CR-Kp approached, but did not exceed, the ceiling (15%). Compared with EU averages, Portugal demonstrated higher resistance rates for both MRSA and CR-Kp, though the gap has narrowed over time. **Conclusion:** Portugal achieved measurable progress in stewardship during 2013–2023, particularly in reducing MRSA prevalence. However, outpatient antibiotic consumption increased during this period and exceeded programme targets, and carbapenem resistance in Gram-negative pathogens continues to pose a critical threat. Sustained, targeted stewardship interventions, especially in primary care, are essential to consolidate and expand national progress.

KEYWORDS: Antimicrobial Resistance; Antibiotic Consumption; Antimicrobial Stewardship; Portugal; MRSA; *Klebsiella pneumoniae*

INTRODUCTION

In recent decades, AMR has emerged as one of the most pressing global public health threats of the 21st century. The WHO has identified AMR as one of the top ten global health challenges, with resistant infections estimated to cause nearly 1.3 million deaths annually and contributing to almost five million deaths worldwide [1,2]. The main drivers of AMR are the overuse and misuse of antibiotics in human and veterinary medicine, as well as other multisectoral industries, combined with insufficient development of novel antimicrobial agents [3].

Recognising the magnitude of the problem, Portugal has progressively implemented stewardship policies and awareness campaigns since the early 2000s. Early initiatives included the "Uso Prudente de Antibióticos" campaign, aimed at improving public and professional awareness [4]. In 2007, the Programa de Prevenção e Controlo de Infeções e Resistência aos Antimicrobianos (PPCIRA) was established under the Directorate-General of Health, providing a central governance structure for infection prevention and resistance control [5].

These efforts evolved into more structured national strategies, culminating in the Plano Nacional de Prevenção da Resistência aos Antimicrobianos (PNPRAM) 2019–2023, which adopted a One Health framework spanning human, veterinary, agricultural, and environmental sectors [6]. While broad goals were outlined for all sectors, specific quantitative targets were set for human health: (i) reduction of outpatient antibiotic consumption; (ii) limitation of hospital carbapenem use within targeted limits; (iii) reduction in prevalence of Staphylococcus aureus resistant to methicillin; and (iv) reduction in carbapenem-resistant Klebsiella pneumoniae isolates. Importantly, these goals aligned Portugal's strategy with the European Commission's One Health Action Plan Against AMR and the WHO's Global Action Plan on AMR [1,3].

In 2021, PPCIRA published an interim report on PNPRAM implementation, addressing several objectives and providing early insights into Portugal's progress. However, the inclusion of COVID-19 pandemic data complicates interpretation, as reductions in outpatient prescribing during lockdown periods may not reflect sustainable changes in clinical practice [7]. Furthermore, a comprehensive end-of-cycle report for 2023 has yet to be published. A consolidated analysis across the four human health indicators is therefore needed to evaluate true progress, identify persistent gaps, and inform the design of the next national stewardship strategy.

This article aims to assess Portugal's progress towards the PNPRAM 2019–2023 targets within the human health sector. Using national and European surveillance data, we evaluate trends in outpatient antibiotic consumption, hospital carbapenem use, and resistance in Staphylococcus aureus and Klebsiella pneumoniae. By benchmarking outcomes against programme goals, this analysis provides a timely evaluation to inform the next phase of Portugal's antimicrobial stewardship strategy.

METHODS

This study is a retrospective, descriptive analysis of antimicrobial consumption and resistance trends in Portugal between 2013 and 2023. The analysis focused specifically on the four quantitative targets defined for the human health sector in the PNPRAM 2019–2023. These indicators were benchmarked against programme objectives and, where applicable, against European Union (EU) averages.

Data Sources

Antibiotic consumption data were obtained from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), coordinated by the ECDC. These data are reported annually by INFARMED, the Portuguese National Authority of Medicines and Health Products, and expressed as Defined Daily Doses (DDD) per 1,000 inhabitants per day (DHD), in accordance with WHO methodology [8–10].

Hospital consumption data for carbapenems (ATC code J01DH) were extracted from PPCIRA surveillance reports and ESAC-Net submissions [7,8].

Antimicrobial resistance data were obtained from the EARS-Net, coordinated by the ECDC. These data provided annual percentages of resistant isolates for *S. aureus* (resistant to methicillin) and *K. pneumoniae* (resistant to carbapenems), derived from invasive clinical isolates submitted by Portuguese laboratories. National reports published by PPCIRA in 2021 were also consulted, providing interim assessments of PNPRAM implementation [7,11].

European Union comparator data for both consumption (ESAC-Net) and resistance (EARS-Net) were used to contextualise Portugal's performance relative to EU/EEA averages. Where possible, EU weighted means were applied [8,11].

Indicators Assessed

The analysis was structured around the four central PNPRAM human health indicators:

- Outpatient antibiotic consumption: ≤17.0 DHD by 2023.
- Hospital carbapenem consumption: <1.0 DHD.
- *MRSA:* ≤35% prevalence.
- *CR-Kp:* <15% prevalence.

Analytical Approach

Time-series analysis was conducted for each indicator, using annual national data points between 2013

and 2023. Outpatient and hospital antibiotic consumption were plotted as line graphs, with PNPRAM targets superimposed as reference thresholds. For antimicrobial resistance, proportions of resistant isolates were plotted annually, with EU averages included for comparison.

Progress towards PNPRAM objectives was assessed using two complementary approaches:

(i) Absolute target comparison, in which 2023 values were evaluated against national target thresholds; and
(ii) Trend analysis, in which direction and magnitude of changes between 2013 and 2023 were assessed to capture broader dynamics.

Where EU averages were available, benchmarking was performed to evaluate whether Portugal's trajectory was converging with or diverging from EU/EEA norms.

Descriptive statistics (absolute values, percentages, and relative changes) were applied; no inferential statistical testing was undertaken, as the study relied exclusively on aggregated surveillance data.

Limitations

This study is subject to several limitations inherent to secondary data analysis. Firstly, reliance on national and European surveillance platforms means that data accuracy depends on completeness of reporting by participating institutions. While EARS-Net and ESAC-Net maintain quality assurance protocols, variability in laboratory participation and diagnostic capacity across years may influence results.

Secondly, interim assessments such as the PPCIRA 2021 report included trends influenced by the COVID-19 pandemic, particularly reductions in outpatient consumption during lockdowns. These anomalies may overestimate progress towards stewardship objectives and should be interpreted cautiously [7].

Thirdly, at the time of writing, a full end-of-cycle report for PNPRAM 2019–2023 had not been published. While 2023 surveillance data were available through ECDC, national synthesis and policy evaluation remain pending [8,11].

Finally, this study was limited to the human health sector. Although PNPRAM adopted a One Health approach, data from veterinary and environmental sectors were outside the scope of this analysis. The findings should therefore be interpreted as a partial evaluation of the programme's broader goals.

RESULTS

Outpatient Antibiotic Consumption

Between 2013 and 2019, outpatient antibiotic consumption in Portugal steadily increased from 16.1 to 17.9 DHD. Temporary reductions were observed in 2020–2021 during the COVID-19 pandemic (reaching 13.7 DHD in 2020), but these were short lived. Consumption rates rebounded in the following years, reaching 17.99 DHD in 2023. This exceeded the PNPRAM 2019–2023 target of ≤17.0 DHD [6], although it remained slightly below the EU/EEA average of 18.5 DHD for the same year [11], as illustrated in Figure 1.

Hospital Carbapenem Consumption

From 2013 to 2023, hospital carbapenem consumption in Portugal consistently remained below the PNPRAM 2019–2023 target of ≤1.0 DHD [6]. In 2013, usage was 0.113 DHD, gradually declining to 0.082 DHD by 2018. A modest rebound followed during the COVID-19 pandemic years, with consumption rising to 0.089 DHD in 2021 and stabilising thereafter, reaching 0.097 DHD in 2023. Throughout the period, Portuguese values exceeded the EU/EEA mean, which increased from 0.061 DHD in 2013 to 0.070 DHD in 2023 [11]. While national consumption stayed well under the PNPRAM ceiling, the persistent gap above EU/EEA averages highlights opportunities for further optimisation, as illustrated in Figure 2.

Methicillin-resistant *Staphylococcus aureus*

Between 2013 and 2023, the prevalence of MRSA among invasive *S. aureus* isolates in Portugal decreased markedly, from 46.8% in 2013 to 23.1% in 2023 [11]. This represents a sustained downward trend across the decade, with the most notable reductions occurring after 2016. By 2019, MRSA prevalence had fallen below the PNPRAM ceiling of 35% [6] and continued to decline steadily in subsequent years, reaching its lowest recorded level in 2023. These improvements place Portugal closer to, though still above, the EU/EEA average reported over the same period [11], as illustrated in Figure 3.

Carbapenem-resistant *Klebsiella pneumoniae*

Between 2013 and 2023, the prevalence of carbapenem resistance among invasive *K. pneumoniae* isolates in Portugal rose substantially. Resistance increased from 1.8% in 2013 to 11.7% in 2018, before stabilising around 11% between 2018 and 2022. In 2023, prevalence rose again to 13.1%, remaining just below the PNPRAM ceiling of 15% [6]. While Portuguese rates were above EU/EEA averages

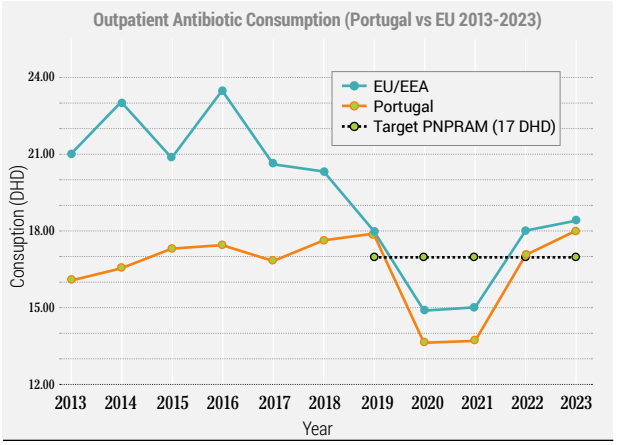

FIGURE 1. Outpatient antibiotic consumption in Portugal *versus* the EU/EEA, 2013–2023, expressed in defined daily doses per 1,000 inhabitants per day (DHD), with PNPRAM target line (≤17.0 DHD). Data from ESAC-Net [8].

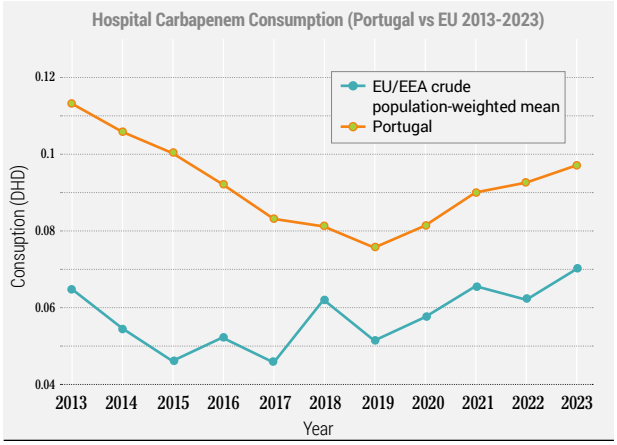

FIGURE 2. Hospital carbapenem consumption in Portugal *versus* the EU/EEA, 2013–2023, expressed in DHD, with PNPRAM target line (<1.0 DHD). Data from ESAC-Net [8].

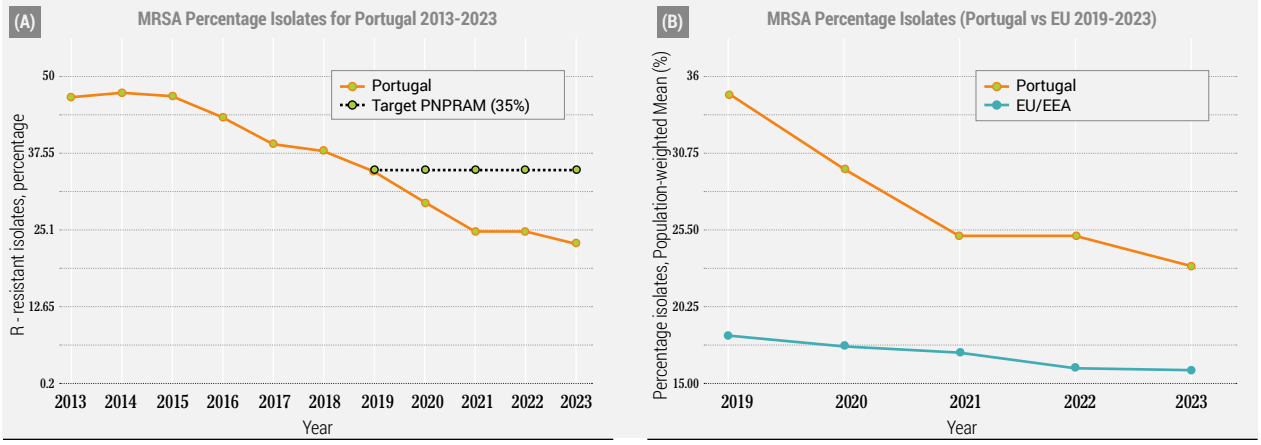

FIGURE 3. Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA). (A) Portugal, 2013–2023, with PNPRAM target line (≤35%). Data from EARS-Net[11]. (B) Portugal *versus* EU/EEA, 2019–2023, population-weighted means. Data from EARS-Net annual epidemiological report[12].

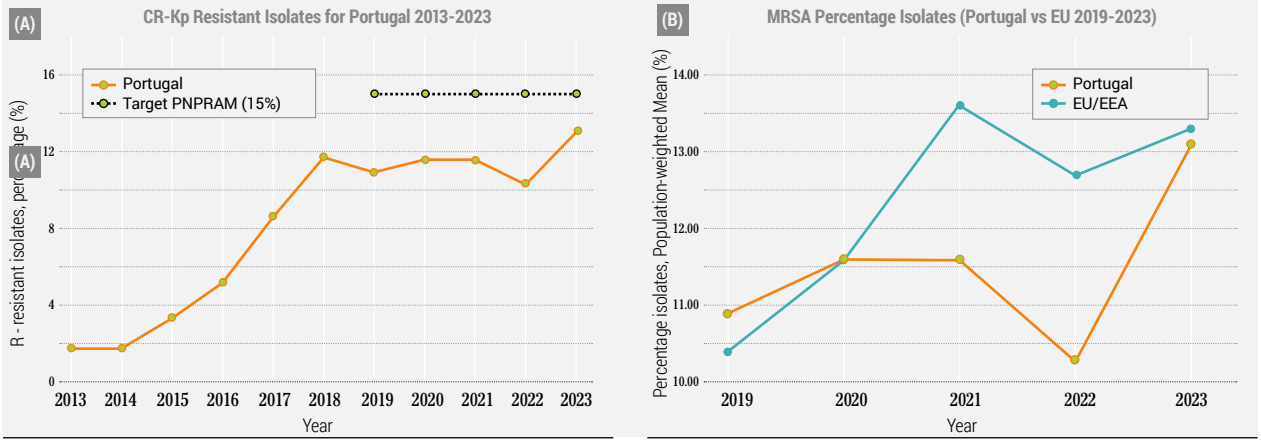

FIGURE 4. Prevalence of carbapenem-resistant *Klebsiella pneumoniae* (CR-Kp). (A) Portugal, 2013–2023, with PNPRAM target line (<15%). Data from EARS-Net [11]. (B) Portugal *versus* EU/EEA, 2019–2023, population-weighted means. Data from EARS-Net annual epidemiological report [12].

earlier in the decade, they have been overtaken since 2020, with both Portugal and EU/EEA showing a persistent upward trajectory as illustrated in Figure 4 [11].

Taken together, these findings show that Portugal achieved measurable progress against PNPRAM 2019–2023 targets [6], particularly with reductions in MRSA prevalence [11] and the containment of carbapenem use within hospital settings [6]. However, outpatient antibiotic consumption remains above the national ceiling [8], and CR-Kp continues to pose a significant challenge [11]. While Portugal has avoided surpassing programme thresholds [6], the persistence of high consumption and resistance rates [11] highlights the need for sustained and strengthened stewardship interventions moving forward.

DISCUSSION

This analysis highlights contrasting patterns in Portugal's progress against PNPRAM 2019–2023 goals, with notable successes in resistance outcomes but persistent challenges in antibiotic consumption.

Outpatient Antibiotic Consumption

The persistently elevated level of outpatient antibiotic consumption remains one of the central challenges for Portugal's stewardship efforts. Despite a temporary decline during the COVID-19 pandemic, community use rebounded to 17.99 DHD in 2023, exceeding the PNPRAM ceiling of 17.0 DHD. This pattern indicates that reductions achieved during periods of restricted social interaction and reduced healthcare utilisation were not sustained once normal prescribing pressures returned. The 2021 PPCIRA interim report highlighted Portugal as one of the five worst-performing countries in Europe regarding the ratio of broad- to narrow-spectrum antibiotics, reflecting diagnostic uncertainty, patient expectations, and regional variability in adherence to prescribing guidelines [7]. Compared with EU/EEA averages, Portugal continues to rank among the higher-consuming countries, underscoring the need for intensified measures in the outpatient sector. Addressing this gap will require stronger integration of rapid diagnostic tools, reinforcement of clinical guideline adherence, and expanded public education to reshape attitudes toward antibiotic use.

Hospital Carbapenem Consumption

Although Portugal's hospital carbapenem use has remained within national ceilings, it consistently exceeds EU/EEA averages, which raises concern considering the parallel rise in CR-Kp isolates [6,12]. This association highlights a central stewardship challenge: even modestly elevated carbapenem consumption can drive selective pressure favouring resistant Gram-negative pathogens. Evidence from European and global studies confirms that higher carbapenem exposure correlates with greater prevalence of CR-Kp and other carbapenemase-producing *Enterobacteriaceae* [13]. Given that CR-Kp has continued to increase in Portugal despite adherence to the <1.0 DHD carbapenem ceiling, it may be necessary to reevaluate this threshold and set a more ambitious national target. Establishing stricter consumption limits – aligned with EU best performers – could provide a stronger safeguard against the expansion of carbapenem resistance.

Methicillin-resistant *Staphylococcus aureus*

The reduction of MRSA in Portugal stands out as one of the clearest successes of national stewardship and infection control policies, with prevalence declining well below the PNPRAM ceiling of 35% [6]. Despite this progress, Portugal still records rates above the EU/EEA mean [12], highlighting the need to consolidate and extend these achievements. The interim PPCIRA 2021 report also documented improvements in other priority pathogens, including a decline in vancomycin-resistant *Enterococcus faecium* (VRE) and reduced prevalence of *Pseudomonas aeruginosa* resistant to carbapenems and piperacillin-tazobactam [7]. These outcomes indicate that targeted stewardship interventions and robust infection prevention measures can yield tangible benefits across multiple species. Looking forward, the strategies that contributed to reducing MRSA should serve as a model for addressing persistent challenges in Gram-negative resistance, particularly CR-Kp.

Carbapenem-resistant *Klebsiella pneumoniae* and other emerging Gram-negative threats

Notably, since 2020, EU/EEA averages have exceeded Portugal's levels, underscoring that this is not only a national but also a pan-European challenge [12]. The persistence of double-digit resistance rates is clinically significant, given the limited therapeutic alternatives and the association of CR-Kp with increased morbidity, mortality, and healthcare costs [13]. While the 2021 PPCIRA interim report highlighted declining resistance rates for several pathogens up to 2020, more recent data reveal renewed increases since 2021. The prevalence of CR-Kp has risen steadily, accompanied by upward trends

in carbapenem-resistant *A. baumannii* and extended-spectrum β-lactamase (ESBL)-producing *E. coli* [7].

These developments point to a shift in Portugal's AMR landscape, where Gram-negative resistance is re-emerging as the most urgent threat. Addressing this requires pathogen-specific interventions, supported by strengthened diagnostic capacity, rapid detection and isolation of carriers, and more robust infection-control practices in both hospital and long-term care facilities. Without targeted responses, the incremental progress achieved against Gram-positive pathogens risks being offset by rising resistance in Gram-negative bacteria.

Improving stewardship outcomes in Portugal will ultimately depend on addressing systemic drivers such as diagnostic uncertainty and variation in prescribing practices, which continue to encourage broad-spectrum use in community care. Strengthening access to rapid diagnostic tools and reinforcing adherence to clinical guidelines could reduce inappropriate prescribing and ease pressure on resistance trends. Looking ahead, the successor to PNPRAM 2019–2023 offers an opportunity to set more ambitious and transparent targets, ensuring that recent gains are consolidated while tackling emerging Gram-negative threats with renewed urgency.

CONCLUSION

Portugal has made measurable progress in antimicrobial stewardship, particularly through reducing MRSA prevalence and maintaining hospital carbapenem consumption below PNPRAM ceilings. These achievements reflect the impact of coordinated national strategies and surveillance frameworks. However, outpatient antibiotic consumption continues to exceed national targets, broad-spectrum prescribing remains widespread, and CR-Kp has emerged as a persistent challenge.

The 2021 PPCIRA interim assessment illustrated success in curbing resistance among several pathogens, but more recent data reveal a resurgence in Gram-negative threats, including carbapenem-resistant *A. baumannii* and ESBL-producing *E. coli*. This shift underscores the need for sustained vigilance, pathogen-specific interventions, and strengthened infection-control measures across both hospital and community settings.

Looking forward, Portugal's stewardship policies must build on prior successes while setting more ambitious goals to reduce antibiotic overuse, expand diagnostic capacity, and reinforce governance. Continued alignment with European and global One Health initiatives will be critical to ensure that the progress achieved is not reversed, and that the next phase of stewardship delivers durable reductions in resistance burden.

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CLINICAL REVIEW

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JORNAL DA SOCIEDADE DAS CIÊNCIAS MÉDICAS DE LISBOA

Chronic Otitis Media in Childhood: Impact on Hearing, Language Development and Cognitive Educational Outcomes

Augusto Cassul [1,2]

[1] Faculdade de Medicina, Universidade de Lisboa

✉ *a.cassul@gmail.com*

ABSTRACT: Otitis media in childhood comprises a spectrum of highly prevalent clinical entities with the potential to produce significant functional consequences, particularly when disease is persistent or recurrent. Within this spectrum, two conditions are especially relevant in the context of chronic otitis: persistent otitis media with effusion (OME), characterized by the presence of middle ear fluid without signs of acute infection, and chronic suppurative otitis media (CSOM), defined by chronic inflammation and infection associated with tympanic membrane perforation and recurrent or persistent otorrhea. These conditions are particularly important because they occur during sensitive periods for language acquisition, consolidation of pre-academic skills and maturation of attentional and self-regulatory processes, potentially resulting in episodes of conductive hearing loss (typically fluctuating in OME and more sustained in CSOM). This narrative overview examines: (1) the epidemiology and pathophysiology of chronic otitis in childhood; (2) the audiological and functional characteristics of the associated hearing impairment; and (3) current evidence regarding impacts on language, learning and cognitive development, including relevant moderating factors. The discussion highlights implications for screening, interdisciplinary assessments and clinical and educational intervention.

KEYWORDS: Childhood; Chronic Otitis Media; Conductive Hearing Loss; Language Development; Cognitive Development

INTRODUCTION

Otitis media is among the most common childhood conditions and represents a substantial component of the global burden of pediatric disease, particularly during the first five years of life. Global reviews indicate that otitis media and its sequelae significantly contribute to avoidable hearing loss and disability, disproportionately affecting socioeconomically vulnerable populations [1,2]. Even mild conductive hearing loss may be clinically relevant in classroom environments, where speech understanding critically depends on signal-to-noise ratio and binaural integration [3,4].

Persistent OME is frequently painless and may therefore be underdiagnosed despite causing bilateral and fluctuating conductive hearing loss. Clinical guidelines recommend careful documentation of effusion, appropriate hearing assessments when effusion persists and identification of children at developmental risk [4,5]. CSOM carries a greater likelihood of persistent hearing loss and complications and remains an important cause of hearing impairment globally [6,7].

Evidence linking otitis media with neurocognitive development is heterogeneous. While meta-analyses sug-

gest small average effects on language, other studies report specific deficits and greater impact in vulnerable subgroups [8–10]. This apparent discrepancy warrants critical synthesis.

METHODS

This article presents a narrative overview of the literature addressing persistent and chronic otitis media in childhood and associated auditory, linguistic, cognitive and educational outcomes. Rather than applying formal systematic review procedures, the aim was to provide a structured and clinically oriented synthesis of relevant evidence.

Key publications were identified through targeted searches of biomedical literature databases (PubMed/MEDLINE), including primary studies, systematic reviews, meta-analyses, clinical practice guidelines and major reference articles addressing the epidemiology, pathophysiology and developmental implications of otitis media. In addition, manual searches of the reference lists of relevant publications were undertaken to identify further pertinent studies. [4,11]. Particular attention was given to studies clearly describing exposure to persistent OME, recurrent otitis media or CSOM, and reporting developmental outcomes using recognised measures. Both prospective and retrospective pediatric studies, as well as population-based investigations of longer-term outcomes, were considered [8,12,13]. Given the methodological diversity across studies, findings are presented narratively and organised into thematic domains.

RESULTS

Epidemiology and Risk

The burden of otitis media is concentrated in early childhood, a critical period for phonological and lexical development [1,2]. Persistence and progression are influenced by social determinants, explaining disproportionate impact in vulnerable populations [7,9]. OME often produces bilateral, fluctuating conductive hearing loss [5]. CSOM may lead to more stable and potentially greater hearing deficits [11,14].

Auditory Processing, Language and Literacy

Meta-analytic evidence suggests small mean effects on global language measures [8]. However, specific vulnerabilities in phonological awareness and emerging literacy have been reported [10]. A recent systematic review indicates potential associations between early OME and altered auditory processing performance in some children [15], supporting the hypothesis that fluctuating hearing loss may influence auditory maturation [16].

Learning, Academic Performance and Cognition

Population studies show small but measurable associations between early otitis media and later cognitive or educational outcomes [13]. In high-prevalence settings, educational impact may be substantial [9]. Reviews highlight heterogeneity in findings and underscore the importance of moderating variables such as disease duration, severity and social context [12]. Mechanistic interpretations frequently emphasize listening effort and language-mediated pathways [3].

DISCUSSION

Listening Effort, Language Mediation and Executive Function

The pathway linking chronic otitis and cognitive outcomes is most plausibly indirect. Degraded auditory input increases processing demands, placing additional strain on working memory and attention. The FUEL model offers a coherent explanatory framework for understanding how listening effort may affect learning in complex acoustic environments [3]. Language development appears central in mediating potential downstream effects. Evidence from broader hearing loss literature indicates bidirectional relationships between language skills and executive functioning [17,18]. Although not specific to otitis media, this body of work strengthens the conceptual plausibility of indirect cognitive impact.

Clinical and Educational Implications

Guideline-based diagnosis and monitoring remain essential [8]. Functional audiological assessment, including evaluation of speech perception in noise, may be warranted in children with persistent academic concerns [19]. Early tympanostomy tube placement does not guarantee long-term developmental gains in unselected populations [20]. The management of CSOM prioritizes infection control and mitigation of persistent hearing impairment [7,14]. Educational accommodations, particularly in vulnerable settings, may reduce functional impact [9].

Limitations and Future Research

The available evidence is limited by hetero-

geneous exposure definitions, incomplete quantification of cumulative disease burden and variability in developmental outcome measures [1,8]. Residual confounding related to socioeconomic and linguistic environments remains a concern [2,9]. Future research would benefit from longitudinal designs incorporating repeated otological and audiological documentation, sensitive functional measures (including speech-in-noise and auditory processing) and explicit modeling of mediation and moderation pathways. The FUEL framework provides a useful conceptual basis for such investigations [3].

CONCLUSIONS

Chronic otitis media in childhood, particularly persistent OME and CSOM, may result in conductive hearing loss during sensitive developmental periods. Although average effects on language appear small, evidence suggests increased risk for specific phonological and literacy difficulties and measurable educational impact in vulnerable subgroups.

A mediated model offers the most coherent interpretation, whereby degraded auditory input increases listening effort and constrains cognitive resources necessary for learning. Risk stratification, functional assessments and integration of clinical and educational support are central to mitigating potential long-term consequences.

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HISTORICAL ARTICLE

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Memory Clinics: On the 25th anniversary of the first Memory Clinic in Portugal

Alexandre de Mendonça[1], **Frederico Simões do Couto**[2], **Manuela Guerreiro**[1], **Rui Alves**[3], **João Garcia**[4]

[1] Faculdade de Medicina da Universidade de Lisboa

[2] Faculdade de Medicina da Universidade Católica Portuguesa

[3] MemoClínica, Lisboa

[4] Instituto Superior Técnico, Universidade de Lisboa

✉ **Corresponding author:**
Alexandre de Mendonça
Faculdade de Medicina da Universidade de Lisboa
Av. Prof. Egas Moniz, 1649-028 Lisboa
mendonca@medicina.ulisboa.pt

ABSTRACT: Memory Clinics have first appeared in the 1980s, in the United States of America and in the United Kingdom, focusing on early stages of cognitive decline. The first memory clinic in Portugal was officially founded on the 4th October 2001, in Lisbon. Since then, *MemoClínica* followed a multidisciplinary approach to the diagnosis and treatment of patients with cognitive complaints, keeping up with scientific advances and novel technologies in the field. Participation in research has also been a priority of *MemoClínica*. The perspectives and challenges that Memory Clinics will possibly face in the near future are briefly discussed.

KEYWORDS: Memory Clinic; Mild Cognitive Impairment; History of Medicine; Portugal

It is generally considered that Memory Clinics have first appeared in the 1980s, in the United States of America and in the United Kingdom.[1,2] Interestingly, the first initiatives toward these clinics adopted different names, *centre de mémoire,* memory clinic, memory disorders research unit, and were not initially subjected to formal publication.[3]

In the following years, the main characteristics of Memory Clinics became established, namely the focus on early stages of cognitive decline, the use of a multidisciplinary team approach, the purpose to promote pharmacological interventions and cognitive therapies, and the vocation to foster research and education for healthcare professionals as well as promotion of mental health in the general population.[4,5] Some evidence that memory clinics might improve psychosocial health related quality of life in caregivers was presented.[6] Practical orientations regarding the set up and the operation of a memory clinic were advanced.[7] The role and utility of Memory Clinics, however, have not been exempt from controversy.[8]

MemoClínica[9] was officially founded on the 4th October 2001, in Lisbon. The founding partners were three neurologists, Carlos Garcia, Helena Coelho (both deceased) and Alexandre de Mendonça, a neuropsychologist, Manuela

Guerreiro, and a general practitioner, Rui Alves. A psychiatrist, Frederico Simões do Couto, joined the society later on. Thus, *MemoClínica* assumed a multidisciplinary approach from the beginning. Several other professionals, including speech therapist, rehabilitation psychologist, nurse, clinical geneticist and endocrinologist, were enrolled as collaborators along the time.

The founders already had extensive clinical experience at a dementia outpatient facility in a large public hospital, Hospital de Santa Maria, where essentially patients with dementia were observed at that time. The founders felt the need to pay more attention to initial stages of cognitive decline. Clearly, it was a time for change. The concept of Mild Cognitive Impairment had been advanced, putative disease-modifying treatments were being tested, the population was ageing and awareness of Alzheimer´s disease was growing in the society. As a consequence, the emphasis on early diagnosis was raising.[10] However, the concept of Memory Clinic was not at all familiar, the famous columnist Eduardo Prado Coelho would write with some surprise *Subia a Avenida António Augusto de Aguiar, quando vi à minha direita uma clínica de memória* (Público, 2004).[11]

In the following years, for an earlier and more precise diagnosis, the clinic had to keep up with ground-breaking scientific advances and novel technologies, developing an informal network including excellence centres of magnetic resonance, genetics, neurochemistry and nuclear medicine. Importantly, the members of *MemoClínica*, as researchers at the Faculty of Medicine, University of Lisbon, participated in main European scientific consortia in the field. As a consequence, *MemoClínica* has been always actively involved in research, essentially devoted to the initial stages of cognitive decline, and its contribution was explicitly acknowledged in full publications in international peer-reviewed scientific journals.

We must recognize that *MemoClínica* could keep a personal, charming character all these years. A showcase exhibits Carlos Garcia´s collection of medical doctors miniatures,[12] generously provided by Engº João Coelho Garcia. On the walls we can see paintings owned by Carlos Garcia and Helena Coelho, as well as a nice didactic drawing from Carlos Garcia (Figure 1).

A final word about the perspectives and challenges that Memory Clinics will possibly face in the near future. A

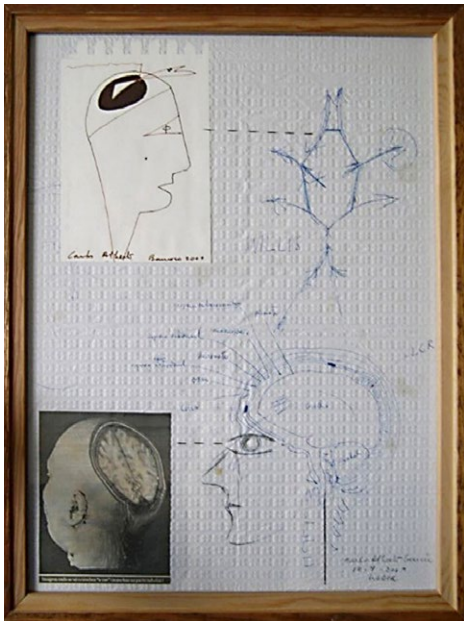

Fig 1. Didactic drawing, by Carlos Garcia, illustrating anatomical aspects of the Willis circle and the meninges. The collage on the top left is a sketch from the visual artist Carlos Barroco. The legend of the collage down on the left is *Imagem onde se vê o cérebro 'a ver'*.

second-generation of memory clinics was recently proposed, the Brain Health Services. In a comparable trend as the concept of Memory Clinics, that was developed to focus on the initial stages of cognitive decline, the Brain Health Services would move still earlier, to the evidence-based prevention of cognitive decline in healthy at-risk individuals.[13] Where Memory Clinics should integrate the dementia care path has been questioned, particularly under the constraints of overwhelmed healthcare systems.[14] How the Memory Clinics will incorporate the novel digital health technologies is also a subject of debate.[15] Another challenge we can anticipate are the recently approved disease-modifying anti-amyloid antibody treatments, requiring demanding conditions of access, selection, administration and side effects monitoring.[16]

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The authors are grateful to all patients and families observed at MemoClínica during these 25 years. They also acknowledge the confidence of the colleagues that have referenced their patients. A special word to the professional collaborators of MemoClínica, for whom we believe the clinic was always a cooperative, friendly and quiet endeavour. Finally, we thank the staff assistants, making an inevitable mention to D. Maria Luísa Pinto, who joined us since the beginning of the clinic, and to the present invaluable assistants, Filipa Marcelo and Maria João Penaguião.

DISCLOSURE STATEMENT

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HISTORICAL ARTICLE

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JORNAL DA SOCIEDADE DAS CIÊNCIAS MÉDICAS DE LISBOA

Revisiting Deolindo Couto (1902–1992): From National Patron to Transatlantic Diplomat

Marleide de Mota Gomes [1]

[1] MD, PhD. Full Professor of Neurology (retired), Laboratory of the History of Psychiatry, Neurology and Mental Health; Institute of Psychiatry; Institute of Neurology, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

✉ mmotagomes@acd.ufrj.br

ABSTRACT: This article revisits the enduring legacy of Deolindo Couto, the esteemed Patron of the Brazilian Academy of Neurology. It explores how Couto's foundational contributions-succeeding Antônio Austregésilo Rodrigues de Lima, the founder of Brazilian neurology, establishing Brazil's first Institute of Neurology, and leading the creation of the Brazilian Academy of Neurology, were intricately linked to his role as a cultural and diplomatic bridge between Brazil and Portugal. By celebrating the scientific achievements of Egas Moniz and embracing the literary heritage of Camilo Castelo Branco, Couto masterfully connected national professional identity with international recognition. His story reveals how the development of a medical specialty in 20th-century Brazil was deeply intertwined with the cultivation of transatlantic prestige and intellectual exchange.

KEYWORDS: History of Medicine; Neurology; Diplomacy; Deolindo Couto; Egas Moniz; Camilo Castelo Branco

Three decades after his passing, the career of Deolindo Augusto de Nunes Couto (1902–1992) continues to inspire reflection and critical examination. His life and work offer more than just a narrative of achievement; they provide a window into the complex forces that shaped Brazilian neurology in the 20th century. Couto's legacy is unique: he is celebrated as the Patron of the Brazilian Academy of Neurology (ABN), a title that underscores his pivotal role in organizing and elevating the specialty nationally, while also serving as a key figure in the Luso-Brazilian intellectual and diplomatic landscape (Figure 1).

Born in Teresina, Piauí, in 1902, Couto's journey began with a medical degree from the National College of Medicine of the University of Brazil (now UFRJ) in 1926. His career was marked by a relentless commitment to excellence and innovation. As a tenured professor at the National Faculty of Medicine in Rio de Janeiro, the Fluminense Faculty of Medicine, and the Rio de Janeiro School of Medicine and Surgery, he influenced generations of neurologists.

Fig 1. Portrait of Deolindo Augusto de Nunes Couto (1902–1992), a pioneering figure in Brazilian neurology and the Patron of the Brazilian Academy of Neurology. *Source: Adapted from the original provided by the National Academy of Medicine (ANM). Reproduced with permission.*

Fig 2. Institute of Neurology Deolindo Couto (INDC/UFRJ), Rio de Janeiro Founded in 1946 by Deolindo Couto, this institution remains a cornerstone of neurological research and education in Brazil. *Source: Photograph by the author (MMG).*

He was a Full Professor of Neurology and later an Emeritus Member at the University of Brazil's National College of Medicine, as well as a Full Professor of Clinical Neurology at the Federal Fluminense University (UFF) and the Federal University of the State of Rio de Janeiro (UNIRIO). His leadership was instrumental in founding and directing the Institute of Neurology in 1946, now called the Institute of Neurology Deolindo Couto (INDC), a groundbreaking institution that became the cornerstone of neurological research and education in Brazil (Figure 2).

Couto's administrative acumen was further demonstrated in his roles as Vice-Rector and Rector of UFRJ, and President of the Federal Council of Education, where he helped shape national higher education policies. His intellectual and cultural contributions were equally remarkable, earning him membership in both the National Academy of Medicine, where he served five terms as President (1955–1959, 1969–1971, 1973–1975, 1977–1979, and 1981–1983), and the Brazilian Academy of Letters, a rare honor for a physician.

Couto's impact extended far beyond Brazil's borders. He represented the country in the World Federation of Neurology and played significant roles in international congresses in Paris, Lisbon, Brussels, and Rome. His honorary memberships in prestigious societies, such as the French Society of Neurology and the American Neurological Association, underscored his global influence. His written works, including *Clínica Neurológica* (1944) and *O tremor parkinsoniano e a via piramidal* (1945), as well as his founding of the *Jornal Brasileiro de Neurologia*, cemented his reputation as a leading voice in the field. Yet, his influence was not limited to academia. He unified Brazil's neurology schools, bridging regional divides, and his name lives on through the INDC/UFRJ, a testament to his enduring legacy.

A defining moment in Couto's career came in 1953 at the 5th International Congress of Neurology in Lisbon. Here, he acted not only as a scientist but also as a diplomat, publicly praising Egas Moniz, the Portuguese Nobel laureate, and highlighting Brazil's role in nominating Moniz for the Nobel Prize. His words *"Science owes him a great deal. I hold the deepest veneration for this wise Lusitanian scholar"* were more than a tribute; they were a strategic affirmation of Brazil's connection to European medical tradition, positioning Couto as a vital link between the two cultures. This mutual respect is immortalized in a photograph of Egas Moniz with a dedication to Deolindo Couto (Figure 3). Couto's book *Dois Sábios Ibéricos* (Two Iberian Sages) praised Egas Moniz and Santiago Ramón y Cajal, both Nobel laureates.

Couto's admiration for Moniz was matched by his passion for the works of Camilo Castelo Branco, whose

Fig 3. Egas Moniz's Tribute to Deolindo Couto (1951) Egas Moniz's dedication to Deolindo Couto, inscribed: *"To the illustrious Professor Dr. Deolindo Couto, a friendly tribute from Egas Moniz, ... 1951."* This photograph symbolizes the transatlantic collaboration between Brazilian and Portuguese neurology. *Source: Museum Collection of the Deolindo Couto Institute of Neurology (INDC/UFRJ). Reproduced with permission.*

Fig 4. Commemorative medal honoring Deolindo Couto (1902–1992), featuring his portrait and the Neurology Institute he founded. *Source: Digital design by MMG.*

literary legacy he championed. This dual engagement with science and culture reflected Couto's unique ability to navigate both worlds, enriching his medical mission with a broader intellectual and diplomatic purpose.

Couto's legacy is complex. He was a demanding yet inspiring mentor, and the institutions he helped build, while foundational, were also products of their time, marked by the hierarchies and inequalities of Brazilian academia. He received numerous honors and medals, including the Medal of the Academy of Sciences of Lisbon and the D. João VI Order of Merit (ANM). His enduring impact is further symbolized by commemorative tributes such as the medal honoring his life and contributions (Figure 4), which celebrates his lasting influence on Brazilian neurology and academia.

Reflecting on Deolindo Couto's career reveals that the history of a medical specialty is not just a chronicle of scientific progress. It is also a story of institutional consolidation, personal diplomacy, and cultural affinity. His life, bridging the roles of national patron and transatlantic diplomat, invites us to consider how professional identity is often shaped by the strategic cultivation of prestige and networks abroad.

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PFIZER RESEARCH AWARDS 2025

CLINICAL RESEARCH

zAvatar-test forecasts patient's treatment outcome in colorectal cancer: a co-clinical study towards personalized medicine

Bruna Costa[1], **Rita Fior**[1]

[1] Champalimaud Research, Champalimaud Foundation, 1400-038 Lisbon, Portugal

✉ **Corresponding author:** *rita.fior@research.fchampalimaud.org*

ABSTRACT: Cancer patients often undergo rounds of trial-and-error to find the most effective treatment because there is no test in the clinical practice for predicting therapy response. Here, we conducted a co-clinical study to validate the zebrafish patient-derived xenograft model (zAvatar) as a fast predictive platform for personalized treatment in colorectal cancer. zAvatars were generated with patient tumor cells, treated exactly with the same therapy as their corresponding patient and analyzed at single-cell resolution. By individually comparing the clinical responses of 55 patients with their zAvatar-test, we developed a tree decision model integrating tumor stage, zAvatar-apoptosis, and zAvatar-metastatic-potential. This model accurately forecasts patient progression with 91% accuracy. Importantly, patients with a sensitive zAvatar-test exhibited longer progression-free survival compared to those with a resistant test. We propose the zAvatar-test as a rapid approach to guide clinical decisions, optimizing treatment options and improving the survival of cancer patients.

KEYWORDS: Colorectal Neoplasms; Disease Models; Animal; Xenograft Model Antitumor Assays; Precision Medicine; Progression-Free Survival

INTRODUCTION

Colorectal cancer (CRC) remains one of the leading causes of cancer-related mortality worldwide. Although surgical resection is often curative, circulating tumor cells or undetectable micrometastases can be present after surgery. Thus, patients with risk factors for metastatic disease have been shown to greatly benefit from post-surgical systemic therapies to reduce the likelihood of relapse and disease progression, such as FOLFOX or FOLFIRI chemotherapy regimens.

Despite the broad equivalence of these regimens, approximately 50% of patients fail to respond, resulting in unnecessary toxicity and loss of critical clinical time. The absence of reliable predictive biomarkers remains a major limitation to personalized oncology, highlighting the need for functional models capable of anticipating individual tumor responses.

We have been developing a fast *in vivo* functional test with unprecedented cellular resolution: the zebrafish patient-derived xenograft model or zAvatar. This assay relies on the injection of fluorescently labelled patient tumor cells into 2 days post fertilization (dpf) zebrafish embryos. Among its numerous advantages, the most important are the ability to analyze metastatic and angiogenic potentials *in vivo*, and the speed of the test: tumor behavior and response to therapy can be accessed in just 10 days, a time frame compatible with oncological clinical decisions.

Therefore, this study aimed to evaluate the predictive capacity of zAvatars for chemotherapy response in patients with CRC.

METHODS

Seventy-nine patients undergoing systemic chemotherapy after surgical resection were recruited, and zAvatar-test was technically feasible in 55 patients, representing 70% of the cohort. These included tumors from the colon, rectum, and liver metastases, spanning clinical stages II to IV. Tumor cells were injected into 2dpf zebrafish embryos, which were then treated with exactly the same chemotherapy regimen prescribed to the corresponding patients. Tumor responses in zAvatars were assessed by measuring apoptosis via activated caspase-3, tumor size, micrometastasis formation, and tumor engraftment. Results from zAvatars were compared in a blinded manner with patient clinical response 12 months after starting chemotherapy.

MAIN RESULTS

Induction of apoptosis in zAvatars strongly predicted patient clinical response, as tumors from patients who did not experience disease progression exhibited significantly higher apoptosis levels upon treatment ($p<0.0001$).

Moreover, the presence of micrometastases in untreated zAvatars strongly correlated with clinical staging and actual post-treatment progression, identifying high-risk patients even among those clinically classified as stage II or III. The model also captured intratumoral heterogeneity: in cases with synchronous primary and metastatic surgeries, zAvatars reproduced phenotypic and therapeutic differences between samples from the same patient.

A multivariate decision-tree analysis incorporating patient tumor stage, apoptosis, and metastatic potential in zAvatars achieved an overall accuracy of 91%, correctly predicting outcomes in 50 of 55 patients. Notably, CRC patients whose zAvatar-test show sensitivity to treatment experienced a significantly longer PFS compared to those whose zAvatars were resistant ($p<0.0001$).

CONCLUSION

These findings demonstrate that the zAvatar-test, with a timeframe of 10 days, has an exceptional predictive value for personalized medicine (Figure 1).

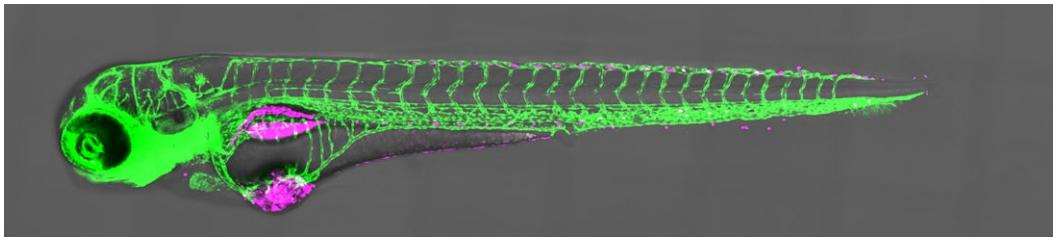

Fig 1. Patient cells (in mangenta) injected in a zebrafish transgenic line with the endothelial vessels depicted in green.

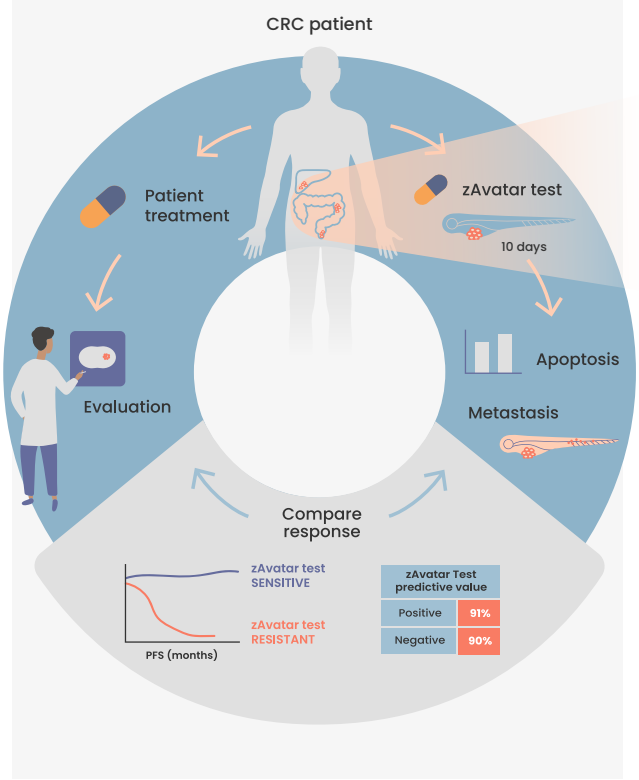

Fig 2. Schematic illustration of the workflow of the zAvatar-test and obtained results. Our findings demonstrate that the zAvatar-test is an accurate screening-platform for predicting colorectal cancer treatment outcomes. Illustration by Marta Correia.

Importantly, this test can be expanded to other types of cancers, by optimizing treatment options, improving PFS, preventing unnecessary toxicities and reducing healthcare costs. Furthermore, it serves as a valuable tool for assessing off-label options, particularly in the case of multi-resistant tumors.

In conclusion, zAvatar-test is a promising platform in personalized oncology, serving as a valuable complement to genetic studies. To introduce the zAvatar-test into clinical practice, it is crucial to perform a randomized clinical trial comparing zAvatar-based therapeutic decisions with physician's-choice (standard of care), a step that is already underway.

ORIGINAL PAPER

Costa B, Estrada MF, Gomes A, et al. Zebrafish Avatar-test forecasts clinical response to chemotherapy in patients with colorectal cancer. *Nat Commun.* 2024;15(1):4771. Published 2024 Jun 5. doi:10.1038/s41467-024-49051-0

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PFIZER RESEARCH AWARDS 2025

BASIC RESEARCH

Neuroimmune interactions control glucagon secretion and glucose balance

Henrique Veiga-Fernandes [1]

[1] Champalimaud Foundation. Champalimaud Centre for the Unknown. Champalimaud Research. Lisbon, Portugal

✉ *henrique.veigafernandes@research.fchampalimaud.org*

KEYWORDS: Neuroimmune Interactions; Glucagon Secretion; Glucose Homeostasis; Innate Lymphoid Cells; Metabolic Regulation

SCIENTIFIC BACKGROUND

Maintenance of stable blood glucose levels is essential for organismal survival, particularly to sustain brain and muscle function during periods of limited nutrient availability. This balance, known as glucose homeostasis, is achieved through coordinated interactions between endocrine organs, metabolic tissues, the nervous system, and the immune system. Central to this process is the pancreas, which regulates blood glucose through the secretion of hormones from the islets of Langerhans.

Insulin and glucagon are the main hormones from the pancreas that regulate blood glucose. Insulin, made by beta cells, helps the body absorb and store glucose after eating. On the other hand, glucagon is released by alpha cells during periods of fasting, physical activity, or low blood sugar, raising glucose levels by prompting the liver to break down glycogen (glycogenolysis) and make new glucose from non-carbohydrate sources (gluconeogenesis). Although insulin resistance and poor insulin secretion are well-known causes of metabolic diseases, problems with glucagon regulation are also becoming recognized as significant yet less understood factors in these disorders.

Glucagon release has been attributed to intrinsic pancreatic mechanisms and direct neural control, particularly through sympathetic innervation of the pancreas. However, recent research has broadened this view by demonstrating that immune cells contribute actively to metabolic regulation. Both adaptive and innate immune cells influence glucose metabolism by shaping inflammation, insulin sensitivity, nutrient absorption, and energy expenditure. Among these, innate lymphoid cells (ILCs) have emerged as important regulators of tissue homeostasis and lipid metabolism.

ILCs are tissue-resident immune cells that respond rapidly to environmental and physiological signals. Type 2 innate lymphoid cells (ILC2) are best known for their roles in barrier tissues, where they contribute to host defense, tissue repair, and type 2 immune responses through the secretion of cytokines such as interleukin-5 (IL-5) and interleukin-13 (IL-13). Beyond immunity, ILC2 have been implicated in metabolic processes, including adipose tissue regulation and insulin sensitivity, suggesting that they may link immune responses to systemic metabolism.

In parallel, the nervous system plays a critical role in sensing energy status and coordinating metabolic responses. Specific brain regions detect changes in blood glucose and relay signals to peripheral organs via autonomic pathways. Importantly, neurons do not operate in isolation but interact closely with immune cells, giving rise to neuroimmune communication networks that regulate physiology across multiple organs.

Together, these observations led to the hypothesis that neuronal and immune signals may cooperate to regulate pancreatic hormone secretion during fasting. The study summarized here investigated whether such neuroimmune interactions contribute to glucagon release and glucose homeostasis, focusing on the role of ILC2 and adrenergic neuronal signaling.

RESEARCH PROJECT

To explore the contribution of immune cells to glucose regulation, the study first examined glucose homeostasis in different mouse models with selective immune deficiencies. Mice lacking both adaptive immune cells and innate lymphoid cells displayed markedly reduced fasting blood glucose levels compared with wild-type animals or mice lacking only adaptive lymphocytes. This reduction became more pronounced during prolonged fasting and was accompanied by increased hepatic glycogen stores and reduced endogenous glucose production.

Importantly, these metabolic alterations were not due to abnormalities in insulin production or action. Insulin gene expression, circulating insulin levels, insulin sensitivity, and glucose tolerance were all preserved in immune-deficient mice. Instead, the defect was linked to glucagon: mice lacking innate lymphoid cells showed reduced expression of the glucagon precursor gene in the pancreas and significantly lower circulating glucagon levels. Administration of exogenous glucagon restored blood glucose levels, indicating that glucagon responsiveness was intact but endogenous glucagon production was impaired.

These findings suggested that innate lymphoid cells play a key role in supporting glucagon secretion during fasting. Further analysis identified type 2 innate lymphoid cells as the relevant population. Under normal conditions, ILC2 were the most abundant innate lymphoid subset in the pancreas. Fasting selectively increased pancreatic ILC2 numbers, whereas other ILC subsets remained unchanged. To determine whether ILC2 were sufficient to restore metabolic function, purified ILC2 were transplanted into immune-deficient mice. This intervention restored fasting-induced glucagon secretion, normalized blood glucose levels, and corrected defects in hepatic glucose production. Conversely, selective depletion of ILC2 in otherwise healthy mice led to reduced glucagon levels, impaired gluconeogenesis, and lower fasting glucose. These complementary approaches demonstrated that ILC2 are both necessary and sufficient for maintaining glucagon-dependent glucose homeostasis during fasting.

The study then addressed how ILC2 influence pancreatic alpha cells. Transcriptomic analyses revealed that alpha cells express receptors for IL-5 and IL-13, both in mice and in humans. In vitro experiments showed that these cytokines directly stimulated glucagon secretion from isolated alpha cells and pancreatic islets. Blocking downstream signaling pathways associated with these receptors reduced glucagon release, confirming a direct functional effect. In vivo, ILC2 were identified as the primary source of IL-5 and IL-13 in the pancreas during fasting, and neutralizing these cytokines reduced glucagon levels. Together, these data established a direct cytokine-mediated pathway by which ILC2 enhance glucagon secretion.

A central question was how ILC2 accumulate in the pancreas during fasting. Analysis of ILC2 distribution across organs revealed a simultaneous decrease in intestinal ILC2, suggesting that the intestine serves as a source of pancreatic ILC2. Using cell-tracking approaches, the study showed that fasting induces ILC2

migration from the gut to the pancreas through mesenteric lymph nodes. This migration was associated with reduced expression of molecules that normally retain ILC2 in the intestinal tissue.

The study then explored the signals driving ILC2 migration. Because the nervous system is a primary sensor of energy status, they tested whether neuronal activity could influence ILC2 trafficking. Using chemogenetic approaches to activate neurons innervating the intestine, they showed that neuronal activation alone was sufficient to induce ILC2 migration to the pancreas, increase glucagon secretion, enhance hepatic glucose production, and raise blood glucose levels. Conversely, elimination of catecholaminergic neurons prevented ILC2 accumulation in the pancreas and blunted glucagon response to fasting.

Adrenergic signaling emerged as a critical mediator of this process. Activation of sympathetic neurons increased intestinal norepinephrine levels, while genetic deletion of the β2-adrenergic receptor specifically in ILC2 prevented their migration and impaired glucose homeostasis. Importantly, adrenergic stimulation reduced the expression of gut-retention molecules on ILC2, providing a mechanistic explanation for their mobilization from the intestine to the pancreas.

Together, these experiments revealed a coordinated neuroimmune mechanism in which adrenergic neuronal signals instruct ILC2 to relocate from the gut to the pancreas, where they directly promote glucagon secretion.

IN SUMMARY

This study identifies a previously unrecognized neuroimmune pathway that regulates glucose homeostasis during fasting. It shows that type 2 innate lymphoid cells are essential contributors to glucagon secretion and endogenous glucose production when energy availability is low.

In response to fasting, adrenergic neuronal signals originating in the intestine trigger ILC2 to migrate from the gut to the pancreas. This migration depends on β2-adrenergic signaling within ILC2 and involves the downregulation of intestinal retention cues. Once in the pancreas, ILC2 produce IL-5 and IL-13, which act directly on alpha cells to stimulate glucagon secretion, thereby supporting hepatic glucose production and maintenance of blood glucose levels.

These findings expand the current understanding of metabolic regulation by demonstrating that immune cells are active regulators of endocrine function, highlight a functional integration of the nervous, immune, and endocrine systems in adapting to fasting. Thus, this work suggests that dysregulation of neuroimmune communication may contribute to metabolic and endocrine disorders characterized by abnormal glucagon secretion. By revealing how neuronal signals shape immune cell behavior to control hormone release, the study opens new avenues for research and potential therapeutic strategies targeting metabolic disease through neuroimmune pathways.

ORIGINAL PAPER

Šestan M, Raposo B, Rendas M, et al. Neuronal-ILC2 interactions regulate pancreatic glucagon and glucose homeostasis. *Science.* 2025;387(6731):eadi3624. doi:10.1126/science.adi3624

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