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Terapêutica Substitutiva com Imunoglobulina G Polivalente: Particularidades de um Coorte Português

Immunoglobulin G Replacement Therapy: Particularities of a Portuguese Cohort

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Palavras-chave: Imunoglobulina G/uso terapêutico
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Os defeitos primários de produção de anticorpos constituem uma indicação óbvia para tratamento substitutivo com imunoglobulina G (IgG) polivalente.[1,2] Esta terapêutica pode também ser ponderada em doentes com imunodeficiências secundárias[2] que apresentem infeções graves/recorrentes e hipogamaglobulinémia.[1] Os objetivos do tratamento substitutivo com IgG são a redução da incidência/gravidade de infeções, controlo de danos a longo prazo de órgãos-alvo e melhoria da qualidade de vida de doentes com defeitos de produção de anticorpos.[3]

A IgG polivalente pode ser administrada por via endovenosa (IgEV) ou subcutânea (IgSC), ambas com eficácia e segurança demonstradas,[4] e diferentes vantagens/desvantagens. Estas, pelos seus possíveis impactos na adesão ao tratamento devem ser cuidadosamente consideradas aquando da seleção da via de tratamento.[1] A IgEV é habitualmente administrada a cada três/quatro semanas e a IgSC com periodicidade semanal ou bissemanal. Em Portugal, apenas a via IgSC é passível de ser auto-administrada no domicílio. O limite inferior de IgG sérica recomendado em doentes com defeitos primários de produção de anticorpos é de 700 - 800 mg/dL, mas é frequentemente necessário atingir concentrações basais/pré-infusão mais elevadas, para garantir resposta adequada a infeções graves/recorrentes ou em presença de algumas comorbilidades.[3,5]

Há recomendações internacionais que sugerem que a terapêutica substitutiva com IgG polivalente deve ser ajustada às diferentes fases da vida dos doentes, com os necessários acertos de dose, formulação, frequência, via e local de administração (hospital/domicílio).[1] A escolha da via mais adequada a cada doente deve ser ponderada com base na dose mensal de IgG, no risco de ocorrência de reações adversas/tolerância às diferentes vias, e, fundamentalmente, valorizando a sua aptidão/preferência.[3]

São muito escassos os dados nacionais relativos à prática da terapêutica substitutiva com IgG polivalente, perfil dos doentes e impacto deste tratamento nas respetivas rotinas. Neste contexto, procurámos avaliar a experiência de doentes com defeitos primários de anticorpos em tratamento substitutivo com IgEV ou IgSC quanto às suas motivações, preocupações e aos efeitos secundários relacionados com o mesmo. Foram seguidas as recomendações do Comité de Ética e da Associação Médica Mundial (Declaração de Helsínquia, revista em 2013). O consentimento informado foi obtido para todos os doentes.

Avaliámos 67 doentes em seguimento numa consulta de imunodeficiências primárias (IDP) do adulto de um hospital terciário e sob tratamento substitutivo com IgG humana polivalente, solicitando o auto-preenchimento de um questionário em formato *online* ou presencial. A maioria dos doentes incluídos (n = 41, 61%) encontrava-se sob IgEV. A caracterização demográfica da população está detalhada na Tabela 1. A maioria das mulheres encontrava-se sob terapêutica com IgEV (71%), enquanto os homens se distribuíam equitativamente pelas duas vias. A distribuição etária, por idade no início do tratamento e a distribuição por diagnóstico clínico foi muito semelhante entre os dois grupos analisados. A maioria dos doentes tinha imunodeficiência comum variável, seguida de défice de anticorpos específicos e agamaglobulinémia ligada ao X. É interessante constatar que, enquanto os doentes com escolaridade secundária/superior e os doentes com emprego estável apresentavam distribuição semelhante pelas duas vias de tratamento, aqueles com escolaridade primária ou não-empregados estavam na sua vasta maioria sob terapêutica endovenosa.

Os doentes sob IgEV reportaram com maior frequência efeitos secundários sistémicos, incluindo cansaço (20/41),

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Tabela 1 – Caraterização demográfica e clínica da população

	Via IgEV n = 41	Via IgSC n = 26
Sexo, n (%)		
Feminino	27 (65,9)	11 (42,3)
Idade, anos		
Média ± DP (mínimo - máximo)	46 ± 14 (24 - 80)	39 ± 11 (23 - 63)
Escolaridade, n (%)		
Educação Primária	15 (36,6)	3 (11,6)
Educação Secundária	8 (19,5)	7 (26,9)
Educação Superior	18 (43,9)	16 (61,5)
Situação de emprego, n (%)		
Empregado	24 (58,5)	25 (96,2)
Desempregado	5 (12,2)	1 (3,8)
Reformado	10 (24,4)	
Estudante	2 (4,9)	
Diagnóstico, n (%)		
IDCV	30 (73,2)	17 (65,4)
XLA	4 (9,8)	2 (7,7)
Defeito de anticorpos específicos	4 (9,8)	4 (15,4)
Defeito de CD40 Ligando	1 (2,4)	1 (3,8)
Síndrome Good	0	2 (7,7)
Síndrome WHIM	1 (2,4)	0
STAT1 GOF	1 (2,4)	0
Idade de início do tratamento, anos		
Média ± DP (mínimo - máximo)	33 ± 17 (4 - 75)	30 ± 14 (1 - 62)

n: número total de doentes; DP: desvio-padrão; IDCV: imunodeficiência comum variável; XLA: agamaglobulinémia ligada ao X; WHIM: verrugas, hipogamaglobulinemia, infeções e mielotaxia; GOF: STAT1 gain-of-function
As variáveis categóricas foram apresentadas como valores absolutos (n) e frequências relativas (%). As variáveis contínuas foram apresentadas como média e desvio padrão (DP), mínimo e máximo.

cefaleias (6/41) e sonolência (6/41), conforme detalhado na Tabela 2, havendo necessidade de pré-medicação com paracetamol em 16 doentes para resolução destas queixas. A maioria dos doentes sob IgSC reportou queixas no local da administração, nomeadamente eritema (18/26), com diâmetro inferior a 10cm, sem necessidade de quaisquer medidas farmacológicas. Apenas quatro doentes referiram queixas sistémicas, também sem necessidade de pré-medicação.

É importante salientar que não se registaram diferenças significativas entre os dois grupos relativamente à avaliação da dor relacionada com o tratamento, quantificada pelos doentes através de uma escala visual (0 - 10 pontos). Mais de 85% dos doentes pontuou abaixo de 5 pontos, com média de 1,9 pontos na IgEV e 2,5 pontos na IgSC (Tabela 2).

Relativamente aos fatores mais valorizados pelos doentes quanto às vias de administração, a preferência pela IgEV resultou da sua periodicidade mensal (28/41), possibilidade de contacto frequente com a equipa médica/de enfermagem (22/41) e receio da auto-administração na IgSC (11/41). A maioria dos doentes considerou a via endovenosa um procedimento simples e prático (36/41). De salientar que 12 doentes sob IgEV tinham realizado previamente IgSC, tendo optado depois pela via endovenosa por falta de adaptação (n = 4), aumento do número de infeções (n = 3) e/ou má tolerância de reações locais (n = 3).

Os doentes sob IgSC, todos em regime de administração no domicílio, justificaram a sua preferência por esta via pelo menor tempo despendido no tratamento e menor absentismo laboral (19/26), maior flexibilidade no horário de administração (17/26), necessidade de menos idas ao hospital (11/26), possibilidade de realização de outras atividades durante o tratamento (9/26) e diminuição dos custos de deslocação associados (8/26). A maioria destes doentes considera a auto-administração de IgSC um procedimento

Tabela 2 – Efeitos secundários e custos reportados pelos doentes em tratamento com IgEV ou IgSC

Caraterísticas	Grupo IgEV Total (n = 41)	Grupo IgSC Total (n = 26)
Escala visual de dor (1-10 pontos)		
Média ± DP (mínimo - máximo)	1,9 ± 2,2 (0 - 8)	2,5 ± 2,1 (0 - 8)
Efeitos secundários sistémicos, n (%)		
Fadiga	20 (48,8)	4 (15,4)
Cefaleia	6 (14,6)	4 (15,4)
Sonolência	6 (14,6)	0
Febre	5 (12,2)	0
Mialgias	4 (9,8)	0
Efeitos secundários locais, n (%)		
Eritema	-	18 (69,2)
Edema	-	8 (30,8)
Dor no local da injeção	-	2 (7,7)
Equimose	-	2 (7,7)
Prurido	-	1 (3,8)
Pré-medicação, n (%)	16 (39)	0
Absentismo, dias/ano		
Média (mínimo - máximo)	10 (0 - 180)	4,5 (0 - 15)
Custos relacionados com o tratamento, n (%)		
< 20€	6 (14,6)	22 (84,6)
20 - 50€	21 (51,2)	4 (15,4)
> 50€	14 (34,1)	0
Tempo despendido no hospital, horas		
Média (mínimo - máximo)	3,5 (0,17 - 5)	1 (0,25 - 2)

n: número total de doentes; DP: desvio-padrão.
As variáveis categóricas foram apresentadas como valores absolutos (n) e frequências relativas (%). As variáveis contínuas foram apresentadas como média e desvio padrão (DP), mínimo e máximo.

simples e prático (17/26), sendo a possibilidade de praticar em hospital de dia e de contactar frequentemente com a equipa médica/de enfermagem apontados como fatores decisivos para o sucesso desta via.

Os doentes sob IgEV reportaram custos diretos e indiretos associados ao tratamento mais elevados, nomeadamente relativamente a dias de absentismo laboral/ano (média de 10 dias na IgEV e 4,5 na IgSC), tempo despendido com a realização do tratamento (média 3,5 horas/tratamento IgEV e 1 hora/tratamento IgSC) e custos mensais de transporte/estacionamento (Tabela 2).

Na nossa população, os doentes sob terapêutica com IgSC apresentaram menos frequentemente efeitos secundários, sendo estes maioritariamente locais, tal como descrito na literatura.[6-8] As principais razões associadas à preferência pela via IgSC foram a possibilidade de autoadministração e a menor duração do tratamento, conferindo aos doentes maior flexibilidade e liberdade pessoal. Estes fatores são igualmente valorizados em estudos semelhantes realizados noutros países.[6-8]

Na população adulta que aqui descrevemos, a maioria dos doentes manifestou preferência pela via de administração endovenosa, valorizando a periodicidade mensal, o facto de envolver menos punções em cada tratamento[6,9] e a possibilidade de manter contacto frequente com a equipa médica/de enfermagem. Este achado contrasta com os resultados de estudos internacionais que desde há duas décadas reportam a preferência dos doentes sob terapêutica substitutiva pela via subcutânea.[8,9]

Nos últimos meses foi disponibilizada no nosso país uma formulação de IgG polivalente a 10% para administração por via IgSC facilitada. Esta via consiste na pré-infusão de hialuronidase humana recombinante, aumentando a laxidão do tecido subcutâneo e permitindo a administração subsequente de maiores volumes do concentrado de IgG polivalente.[1]

Na população que avaliámos, 66% dos doentes sob IgEV rejeitaram a hipótese de transitar para IgSC, quando

confrontados com essa possibilidade, mas poderão, contudo, vir a aceitar a via subcutânea facilitada (fSC). A IgG fSC combina vantagens das vias SC e EV, podendo constituir uma alternativa atrativa, na medida em que oferece a possibilidade de auto-administração domiciliária a cada três ou quatro semanas, utilizando apenas um ou dois locais de administração, e diminui os efeitos secundários.[1] Numa fase de aumento exponencial do número de doentes com imunodeficiências primárias e secundárias com indicação para terapêutica substitutiva com IgG,[1] será vantajosa a diminuição da sobrecarga logística hospitalar decorrente da via endovenosa.

Apesar de ser baseado em auto-reporte, este estudo é revelador do perfil dos doentes sob terapêutica substitutiva. Particularidades culturais e da organização dos serviços de saúde nacionais poderão ter influenciado os resultados obtidos, que contrastam com a realidade de outros países, valorizando assim este trabalho como uma ferramenta extremamente útil para reflexão futura e planeamento a nível nacional.

À escala individual, os nossos dados reforçam a necessidade de reavaliar periodicamente as motivações/preocupações dos doentes sob terapêutica substitutiva com IgG, contribuindo para a melhoria da sua qualidade de vida e maior adesão à terapêutica, favorecendo assim o seu prognóstico.[1,3,6-10]

CONTRIBUTO DOS AUTORES

SCF, JV, MITS, SLS: Conceptualização, recolha, análise e discussão de resultados e redação do manuscrito.

SPS, JC, EP: Validação, supervisão e revisão do manuscrito.

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

CONFIDENCIALIDADE DOS DADOS

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

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

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Strategies to Reduce the Burden of Respiratory Syncytial Virus Infections in Children in Portugal: Results from the Focus Group RSV Think Tank

Estratégias para Reduzir o Impacto das Infeções por Vírus Sincicial Respiratório em Crianças em Portugal: Resultados do Focus Group RSV Think Tank

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Palavras-chave: Criança; Infecções por Vírus Respiratório Sincicial/prevenção e controlo; Portugal

INTRODUCTION

Respiratory syncytial virus (RSV) is the primary cause of acute lower respiratory infections (ALRI) in children under five years of age,[1,2] with bronchiolitis being the most common clinical presentation.[3] This virus affects people of all ages,[2] and it is estimated that by the time children reach the age of three, virtually all would have been infected at least once.[4] Despite the higher likelihood of complications in infants younger than six months or with risk factors, such as prematurity and pulmonary or cardiac disease, the disease progression is unpredictable and can cause severe illness in healthy children.[3]

In Portugal, the annual seasonal epidemics of RSV historically occur during the autumn and winter months.[5] During this period, RSV may be responsible for more than 80% of ALRI in children aged under one year,[2] as well as the main cause of hospitalizations.[6] This has significant consequences for health expenditure, resource management, stress levels of healthcare professionals, and quality of healthcare services.[7-9] Conversely, the associated RSV diseases have a high burden on families, both economically and emotionally.[8] The economic costs are associated with direct out-of-pocket payments, such as medical appointments, hospital/clinic visits and treatments, and indirect costs capturing absenteeism from work and loss of productivity, which represent a high cost for society.[8]

Despite the high burden of RSV in Portugal,[10] the country lacks an adequate prevention strategy. Thus, the 'RSV Think Tank initiative – *Inspirar à mudança'* was created to address this issue. This initiative comprised a multidisciplinary panel of Portuguese experts (n = 20), including pediatricians, neonatologists, public health physicians, nurses, economists, parent associations, and decision-makers, which participated in three discussion sessions focusing on different topics: RSV burden, challenges, and barriers (session 1); economic and psychosocial burden (session 2); future strategies (session 3).

With the aim of improving the management of RSV infections in Portugal, we collated the 10 most important actions to be implemented in Portugal that were developed during the RSV Think Tank, which are grouped into three categories: literacy actions, non-pharmacological preventive actions, and pharmacological preventive actions. These are summarized in Table 1, and detailed in the Appendix 1 (https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20620/15361).

Literacy actions

The lack of literacy regarding RSV is widespread. Based

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Table 1 – Summary of the literacy actions, non-pharmacological preventive actions and pharmacological preventive actions developed by the experts during the RSV Think Tank initiative

	Objective	Actions
Literacy actions	Increase the literacy of parents/caregivers and the general public regarding respiratory infections, particularly RSV.	Disseminate information about RSV through physical, digital, and media campaigns.
	Promote the literacy of parents/caregivers, through the provision of reliable information during the appointment.	Develop an informative brochure about RSV that is given to parents during appointments.
	To directly intervene in communities, increasing the health literacy levels of society and stimulating the adoption of health-promoting behaviours.	Increase the role of municipalities in promoting health literacy and disease prevention among the general population..
	Promote knowledge about respiratory infections, particularly RSV, and preventive measures, among educators and teachers in schools and day-care	Implement specialized training in schools and day-care centres for educators and teachers about respiratory infections.
	Increase parents'/caregivers' knowledge about respiratory infections caused by RSV and promote behavioural changes through healthcare professionals.	Update the "Boletim de Saúde infantil e juvenil" by adding specific discussion topics for each age group regarding respiratory infections.
	Promote healthy habits and disease prevention among educators/teachers, parents, and children, equipping the new generation with the necessary tools to become promoters of their health.	Create a multidisciplinary team between Primary and Secondary Care, Municipalities, and Schools to work on school health promotion.
Non-pharmacological preventive actions	Reduce the spread of respiratory infections in daycare centres.	Facilitate the bureaucratic process associated with parental absenteeism from work due to their child's respiratory infection.
	Reduce premature babies' contact with other children during an early and high-risk period for respiratory infections and complications. Ensure minimal financial impact on parents during this period.	Increase the duration of maternity/paternity leave for premature babies' parents.
Pharmacological preventive actions	Prepare the country for the discussion, analysis, decision-making, and implementation of preventive technologies being developed against RSV infection, to promote a prompt decision-making process by political entities based on scientific evidence.	Create a national task force dedicated to RSV or restructure the existing task force (DGS).
	Reduce the clinical, economic, and psychosocial impact of RSV infections, directly, equitably, and universally, promoting the reduction of the incidence of moderate to severe disease, with a significant impact on the reduction of hospitalizations and emergency department visits in all children.	Implement a preventive method against RSV for all children.

on our experience, there is limited knowledge regarding the burden of RSV on families, the healthcare system and potential long-term health effects on children. We consider this the main factor for the inefficient management of RSV respiratory infections in Portugal.

In order to improve the management of RSV, it is essential to increase awareness among parents, educators, policymakers, and society at large. Prioritized actions include the development of informative materials to be given to parents during medical appointments, increasing the role of local authorities in promoting health literacy and educating teachers, parents, and caregivers about preventive measures, as well as modifiable risk factors, such as smoke exposure. The promotion of individual protective measures, especially at home and in the school and childcare setting, is essential to help prevent the spread of respiratory viruses and therefore reduce the burden of RSV.

Increasing literacy about symptoms and the natural progression of RSV infections will help reduce the psychological impact on parents and minimize the burden on healthcare services. When parents recognize the natural progression of these infections, they do not feel the need to rush to an emergency service, resorting to other healthcare sources for guidance, such as the contact center of the National Health Service (SNS24), pediatric appointments and primary care.

Educators and healthcare professionals have a crucial role in promoting literacy and disseminating information to parents and children. However, in the current healthcare landscape, healthcare professionals often do not have the

time to promote parental literacy. Therefore, policymakers should prioritize the development of communication strategies and training programs to support healthcare professionals, starting at an undergraduate level, and create conditions for their implementation (e.g., longer appointments or allocated times for health literacy dissemination).

Non-pharmacological preventive actions

The lack of prioritization of RSV infections on health policies has led to the absence of measures to empower families to manage these infections effectively. For example, there are bureaucratic obstacles that sometimes force caregivers to adopt behaviors that increase the spread of RSV, putting vulnerable populations at risk (e.g., taking a sick child to daycare due to difficulties in obtaining a timely absence from work certificate).

Priority actions have been developed to enable families to effectively prevent the spread of RSV, such as simplification of the process to obtain an absence from work certificate, elimination of the medical certificate required for childcare return and increasing the duration of maternity/paternity leave for parents of premature babies, who are at greater risk of severe disease, especially in the first two years of life.

Pharmacological preventive actions

The management of RSV infections is at a turning point. The availability of new preventive methods urges the development of a technical and scientific decision-making mechanism focusing on RSV to evaluate the best preventive strategy for the Portuguese population. This can be achieved by creating a national working group dedicated to RSV or restructuring the existing working group in the Portuguese Directorate General of Health (DGS). This will help to ensure quick policy decisions and the development of an adequate implementation strategy with sufficient time for operational preparation, thus ensuring a successful implementation and equitable access.

The implementation of a universal preventive measure for all children has the potential to significantly reduce the number of RSV infections, emergency department visits, hospitalizations, absenteeism, and emotional and economic impact on families.

CONCLUSION

There is a high number of RSV infections in the pediatric population in Portugal, leading to short- and long-term respiratory problems in children. This burden is high, having a negative economic and emotional impact on families and a high cost for society due to absenteeism and lost productivity. Additionally, the high number of RSV infections causes a strain on the healthcare system, particularly during seasonal outbreaks, leading to increased healthcare spending and increased stress and exhaustion levels among healthcare professionals.

Given that the current prevention strategy is insufficient, there is a consensus about the need to prioritize the fight against RSV infections in Portugal. To this effect, we developed a set of actions to reduce the burden of this virus, including educating parents/caregivers, educators, and the society at large about RSV, and developing a technical-scientific decision-making mechanism in Portugal to evaluate, determine and implement the best pharmacological preventive strategy.

The success of the actions developed will depend on whether the prevention of RSV becomes a priority for policymakers. This is of the utmost importance, as investing in the prevention of RSV could lead to a more efficient use of healthcare resources, thus contributing to a more sustainable healthcare system.

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AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

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RM received grants or contracts from the EU Commission for the PANDEM2 Project; received medical writing fees, payment for expert testimony and support for attending meetings from Pfizer; was president of Associação

Nacional dos Médicos de Saúde Pública from 2015 to 2021.

EC and PG received payment or honoraria from Sanofi for participating in a debate on the impact of RSV infections.

TB received grants and symposium fees, honoraria for lectures and presentation, support for manuscript writing and attending meetings from Sanofi; participated on a Data Safety Monitoring Board or Advisory Board for BI.

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All other authors have declared that no competing interests exist.

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Monthly Analysis of Infant Mortality Rate in Portugal during the COVID-19 Pandemic: Insights from Continuous Monitoring

Análise Mensal da Taxa de Mortalidade Infantil em Portugal durante a Pandemia de COVID-19: Perceções a partir da Monitorização Contínua

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ABSTRACT

Introduction: The COVID-19 pandemic significantly impacted global public health. Infant mortality rate (IMR), a vital statistic and key indicator of a population's overall health, is essential for developing effective health prevention programs. Existing evidence primarily indicates a decrease in IMR during the COVID-19 pandemic. We conducted a national-level analysis to calculate IMR and describe its course over the years (from 2016 until 2022), using a month-by-month analysis.

Methods: Data on the number of deaths under one year of age was collected from the Portuguese E-Death Certification System (SICO), and data on the number of monthly live births was obtained from Statistics Portugal. The IMR was calculated per month, considering the previous 12 months' cumulative number of deaths under one year of age and the number of live births.

Results: In Portugal, the IMR decreased before and during the COVID-19 pandemic. The lowest values were observed in September and October 2021 (2.15 and 2.14 per 1000 live births, respectively). The IMR remained below the threshold of three deaths per 1000 live births during the pandemic's critical period.

Conclusion: Portugal has achieved remarkable progress in reducing its IMR over the last 60 years. The country recorded its lowest-ever IMR values during the COVID-19 pandemic. Further studies are needed to fully understand the observed trends.

Keywords: COVID-19; Infant Mortality; Infant, Newborn; Pandemics; Portugal

RESUMO

Introdução: A pandemia da COVID-19 teve um impacto significativo na saúde pública mundial. A taxa de mortalidade infantil (TMI), uma estatística vital e indicador-chave da saúde geral de uma população, é essencial para o desenvolvimento de programas de prevenção eficazes no sector da saúde. Evidências existentes indicam uma diminuição da TMI durante a pandemia da COVID-19. Realizou-se uma análise a nível nacional para calcular a TMI e descrever a sua evolução ao longo dos anos (de 2016 até 2022) usando uma análise mês a mês.

Métodos: Os dados sobre o número de óbitos com menos de um ano de idade foram obtidos do Sistema de Certificação Eletrónica de Óbitos (SICO) e os dados sobre o número de nascimentos mensais foram obtidos a partir do Instituto Nacional de Estatística. A taxa de mortalidade infantil (TMI) foi calculada por mês, considerando o número acumulado de óbitos com menos de um ano de idade e o número de nascidos vivos nos 12 meses anteriores.

Resultados: Em Portugal, a TMI diminuiu antes e durante a pandemia da COVID-19. Os valores mais baixos foram observados em setembro e outubro de 2021 (2,15 e 2,14 por 1000 nascimentos vivos, respetivamente). A TMI permaneceu abaixo do limiar de três mortes por 1000 nascimentos vivos durante o período crítico da pandemia.

Conclusão: Portugal alcançou um progresso notável na redução da sua TMI ao longo dos últimos 60 anos. O país registou os valores mais baixos de sempre da TMI durante a pandemia da COVID-19. Estudos adicionais são necessários para compreender completamente as tendências observadas.

Palavras-chave: COVID-19; Mortalidade Infantil; Pandemia; Portugal; Recém-Nascido

INTRODUCTION

The COVID-19 pandemic has been a major public health crisis, resulting in over 774 million cases and 7 million deaths globally as of January 7th, 2024.[1] Vital statistics have played a crucial role in informing health authorities about the pandemic's impact on mortality,[2] including infant mortality rate (IMR), which is defined as the probability of a child born in a given period (e.g., year) dying before one year of age.[3] Infant mortality rate is a key indicator of a population's overall health and is essential for developing and evaluating effective health interventions and policies.[4]

Existing evidence on infant mortality during the COVID-19 pandemic primarily indicates a decrease in

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IMR.[5,6] COVID-19 displayed a U-shaped pattern that paralleled all-cause mortality, which was disproportionally low in children under 12, with a slight increase in newborns and children during their first year. This U-shaped mortality pattern was also observed in pneumonia or influenza.[7]

In Portugal, IMR has significantly improved over the past six decades, with the lowest rates recorded during the pandemic in 2020 and 2021. Reviewing the official IMR – classically measured with whole data of each civil year[8] – high values were observed in the decades of 1960 (ranging from 88.8 to 54.8 per 1000 live births) and 1970 (ranging from 55.5 to 26.0 per 1000 live births). After the Portuguese National Health Service (SNS) was established in 1979, a steady decrease was observed in the IMR until the beginning of the 21st century, systematically registering numbers below 4.0 deaths per 1000 after 2004. In 2010, an unexpected IMR of 2.5 was observed, and subsequently, an oscillation of this rate around the value of 3.0 deaths per 1000 live births was observed up to 2019. An increase in the IMR could have been caused by the pandemic, as it was observed in other mortality indicators, e.g. excess all-cause mortality.[9] However, the opposite was observed, with the best IMR in Portugal being registered during the pandemic, in 2020 and 2021. To clarify this trend, we conducted a national-level analysis relying on publicly available data calculating the IMR and describing its course over the years (from 2017 until 2022) using a month-by-month analysis.

METHODS

Data

We obtained the number of deaths under one year of age from the Portuguese E-Death Certification System (SICO)[10] and the number of monthly live births from Statistics Portugal.[11,12] The data covered the period from January 1, 2014, to December 31, 2022.

Calculation of annual Infant Mortality Rate per month

We calculated the IMR for each month considering the cumulative number of deaths under one year of age and the number of live births for the previous 12 months.[13]

$$IMR_{mt} = \frac{\Sigma_{j=0}^{11} Deaths < 1\ year_{mt-j}}{\Sigma_{j=0}^{11} Live\ births_{mt-j}},$$

$$mt = December\ 2016, January\ 2017, (...), December\ 2022$$

This study used publicly available data and did not require ethics committee intervention. All data analyses were conducted in accordance with relevant guidelines and regulations, ensuring individual privacy.

RESULTS

In Portugal, the IMR steadily declined before and during the COVID-19 pandemic (Fig. 1). The lowest values were

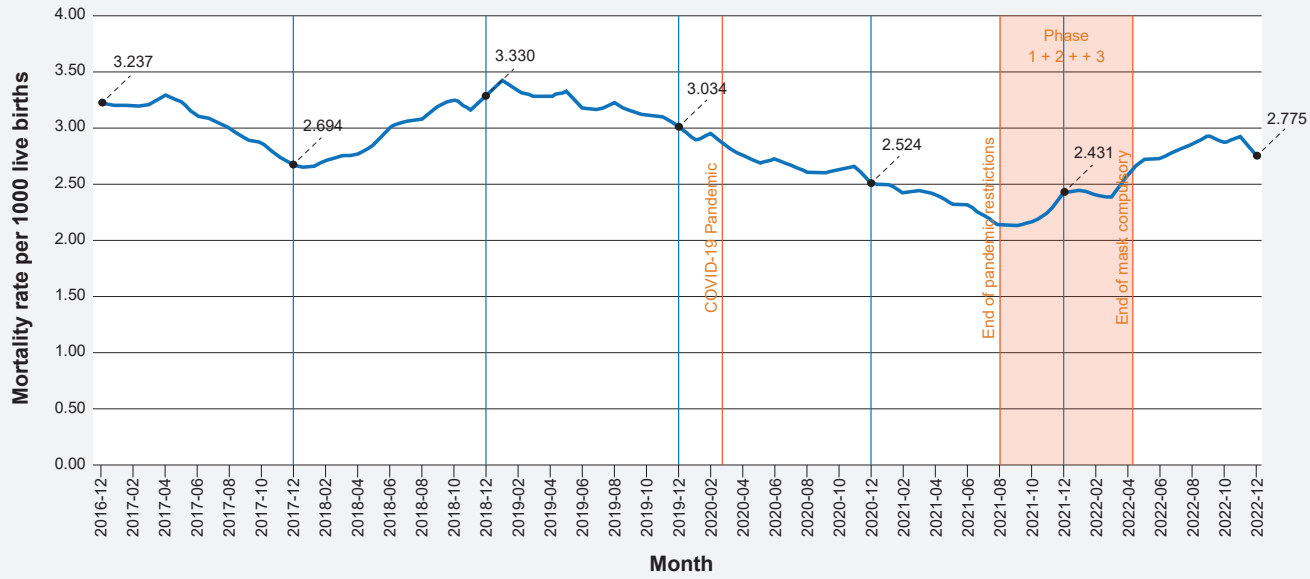

Figure 1 – Monthly evolution of the Annual (previous 12 months) Infant Mortality rate in Portugal. Vertical blue lines: end of year (moment of official IMR calculation); vertical orange lines: important moments of the COVID-19 pandemic. Phases 1, 2, and 3 refer to the pandemic easing strategy proposed by the Portuguese government (https://eportugal.gov.pt/noticias/covid-19-restricoes-vao-ser-levantadas-em-3-fases-ao-ritmo-da-vacinacao)

observed in September and October 2021 (2.15 and 2.14 per 1000 live births, respectively), coincident with the lowest-ever recorded number of live newborns in the country (Table 1). These lowest IMR monthly values followed the lifting of the most severe pandemic restrictions imposed by the government. However, this trend was not observed during the period of easing of pandemic restrictions, followed by a monthly increase in IMR values for more than one year. The peak of this 'post-pandemic' trend was observed in the last trimester of 2022. Nevertheless, the overall IMR remained below the critical threshold of 3.0 deaths per 1000 live births during the pandemic's critical period and until the end of 2022.

DISCUSSION

We herein introduced the monthly evolution of the IMR in Portugal, a novel approach that enables a closer monitoring of this vital statistic, which is essential for population health assessment.[4] Our analysis revealed a consistent decrease in IMR during the COVID-19 pandemic with the trend reversing following the easing of pandemic restrictions. While the usual end-of-year IMR rate would also show a global decreasing trend from 2018 to 2021 with a slight increase in 2022, the monthly dynamics provide more compelling insights that require further understanding.

Potential reasons contributing to this decrease might be related to the COVID-19 public health measures implemented, such as mandatory mask usage, social distancing, and school closures. Another hypothesis for this decrease may be prematurity[15,16] (an important component of IMR), where a decrease in preterm birth and deaths, particularly associated with extreme prematurity, was previously described.[17] Similarly, a decline in other infectious diseases, such as respiratory tract infections[18] and gastroenteritis,[19] was also registered and may have contributed to the decrease in IMR. However, further analysis is required to ascertain the causes of this effect.

Our findings highlight the importance and benefits of continuous IMR monitoring, which we believe to be feasible with a 3- to 4-month lag. This approach enables a timelier identification of trends, allowing a prompter design of potential interventions to improve infant health outcomes.

Our analysis provides a comprehensive view of the IMR in Portugal over a significant period, including during the COVID-19 pandemic. The use of publicly available data from reliable sources, such as the SICO and Statistics Portugal, adds credibility to the analysis. The month-by-month analysis approach allows for a more granular understanding of trends and fluctuations in IMR. However, the study has some limitations. The analysis is limited to data available up until December 2022, and therefore may not reflect more recent trends. Moreover, as the study relies on the accuracy and completeness of the data sources used, any errors or gaps in these data sources could impact the findings. Lastly, the analysis does not delve into the specific causes of the observed trends in IMR, which could be influenced by a variety of factors beyond the scope of this study.

This study contributes to the literature by providing a detailed examination of IMR trends in Portugal, particularly during the COVID-19 pandemic. It highlights the

Table 1 – Monthly numbers of live births in Portugal

Year*	2016	2017	2018	2019	2020	2021	2022	2016 - 2021†
January	7070	7114	7188	7298	7328	6003	6393	7000
February	6544	6344	6209	6437	6359	5734	6237	6271
March	7003	7110	6823	6971	7167	6653	6715	6955
April	6937	6684	6751	6820	6956	6304	6224	6742
May	7489	7258	7554	7238	7244	6810	6953	7266
June	7382	6933	7087	6809	6829	6546	6735	6931
July	7542	7515	7385	7647	7445	7009	7339	7424
August	7632	7318	7897	7665	7224	7159	7716	7483
September	8069	7587	7888	8055	7676	7246	7783	7754
October	7538	7772	7897	7863	7393	6840	7450	7551
November	7139	7641	7367	7259	6859	6565	7303	7138
December	7095	7222	7335	6964	6316	6926	7131	6976
Total	**87 440**	**86 498**	**87 381**	**87 026**	**84 796**	**79 795**	**83 979**	**85 489**
Average	**7287**	**7208**	**7282**	**7252**	**7066**	**6650**	**6899**	**7124**

* Statistics Portugal (https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&indOcorrCod=0007286&contexto=bd&selTab=tab2); * Statistics Portugal (https://www.ine.pt/xportal/xmain?xpid=INE&xpgid=ine_indicadores&indOcorrCod=0008086&xlang=pt&contexto=bd&selTab=tab2);
† month average.
Data available on April 1st, 2023.

unexpected decrease in IMR during the pandemic and the subsequent reversal of this trend following the easing of pandemic restrictions. Additionally, this study also proposes a method for continuous monitoring of IMR, offering timely insights and presenting new challenges for future research. Furthermore, it underscores the importance of IMR as a key indicator of a population's overall health, reinforcing its significance in public health research and policy development.

CONCLUSION

Portugal has remarkably reduced its IMR in the last 60 years. In recent years, before the COVID-19 pandemic, the IMR fluctuated around 3.0 per 1000 live births. During the pandemic, Portugal recorded its lowest-ever IMR values. Further studies are needed to fully understand this observed trend. Nevertheless, the continuous monitoring approach we propose for Portugal offers timely insights and new challenges for the future.

AUTHOR CONTRIBUTIONS

PJN: Study design, data analysis, drafting, critical review and approval of the manuscript.

CC, RFS, ASC, MAN, LBN, CF, CE: Drafting and critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

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All other authors have declared that no competing interests exist.

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Strategic Communication for Local Public Health Services in Portugal: A Delphi Study

Estudo Delphi sobre a Comunicação Estratégica em Unidades de Saúde Pública em Portugal

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ABSTRACT

Introduction: Strategic communication plays a decisive role in public health planning and project implementation. However, Portuguese Local Public Health Units, which are responsible for community interventions, still lack guidance models, tools, specialized resources, and training in health communication. The aim of this study was to develop a conceptual model of strategic organizational communication for local public health services, in Portugal.

Methods: This study presents a conceptual model of strategic organizational communication for Local Public Health Units, which was developed through a three-round, modified Delphi online panel. Thirty-seven Portuguese specialists in public health, communication, and community members were invited to analyse a proposed framework, based on an up-to-date literature review. High retention rates were observed in all rounds (first = 22 valid participations; second = 21 valid participations; third = 18 valid participations).

Results: Most participants believed that Portuguese Public Health Units were not prepared to communicate effectively and that they would benefit from adequate planning and identification of a communication lead or team. Websites and social media were also identified as essential for effective communication. The validated conceptual model integrated different partners in health and in the community, with emphasis on the relationships with the national network of health authorities, other Public Health Units, primary health care units, municipalities, and schools. The preferred channels identified for communicating with these partners included interpersonal relationships, email, and mobile phone. No consensus was obtained for preferred communication channels between Local Public Health Units and the media.

Conclusion: Strategic planning based on the proposed conceptual model involving different stakeholders, has potential to improve the effectiveness of internal and external communication and facilitate the implementation of public health programs and projects. The proposed model needs to be validated in Local Public Health Units, considering the potential human, material, and financial constraints.

Keywords: Delphi Technique; Health Communication; Portugal; Public Health Administration; Strategic Planning

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Strategic Communication for Local Public Health Services in Portugal: A Delphi Study

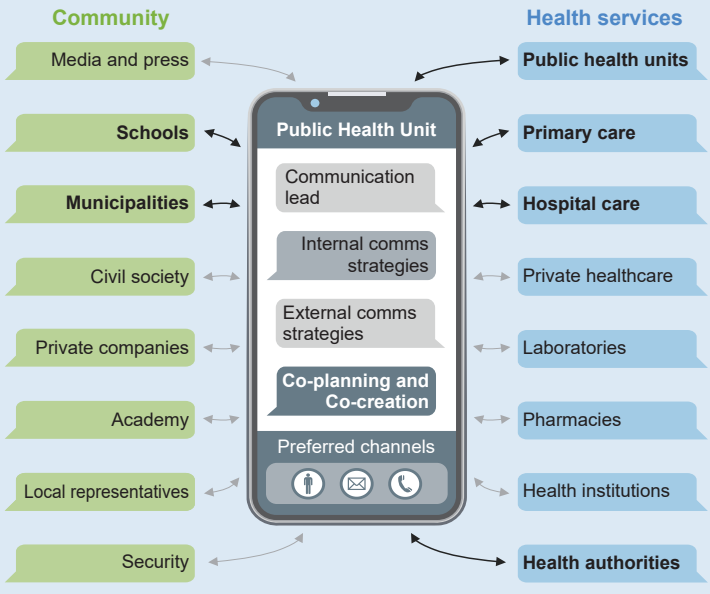
VISUAL ABSTRACT

Local Public Health Units lack guidance models, tools, specialized resources and training in health communication. **Strategic communication** plays a decisive role in local public health planning:

- ✓ Improves internal & external communication;
- ✓ Improves health projects' implementation.

Literature review for developing a strategic organizational communication for Local Public Health Units.

3-round Modified Delphi online panel including 18 to 22 experts in public health communication and community members.



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RESUMO

Introdução: A comunicação estratégica desempenha um papel fundamental no planeamento e implementação de projetos em saúde pública. No entanto, as Unidades de Saúde Pública em Portugal, responsáveis por intervenções comunitárias, carecem de modelos orientadores, ferramentas, recursos especializados e formação em comunicação em saúde. O objetivo deste estudo foi desenvolver um modelo conceptual de comunicação organizacional estratégica aplicável pelas Unidades de Saúde Pública, em Portugal.

Métodos: Este estudo apresenta um modelo conceptual de comunicação organizacional estratégica para Unidades de Saúde Pública em Portugal, desenvolvido através de um painel online Delphi modificado de três rondas. Trinta e sete especialistas portugueses em saúde pública, comunicação e membros da comunidade foram convidados a analisar um modelo proposto, com base numa breve revisão da literatura. Foram observadas elevadas taxas de participação em todas as rondas (primeira = 22 participações válidas; segunda = 21 participações válidas; terceira = 18 participações válidas).

Resultados: A maioria dos participantes afirmou que as Unidades de Saúde Pública em Portugal não estavam preparadas para comunicar de forma eficaz e que beneficiariam de um planeamento adequado e definição de um responsável ou equipa de comunicação. *Websites* e redes sociais também foram identificados como essenciais para uma comunicação efetiva. O modelo conceptual validado considerou diferentes parceiros na saúde e na comunidade, com destaque para as relações com a rede nacional de autoridades de saúde, outras Unidades de Saúde Pública, cuidados de saúde primários, municípios e escolas. Os canais preferenciais identificados para comunicação com esses parceiros incluem relacionamentos interpessoais, correio eletrónico e telefone. Não houve consenso sobre os canais de comunicação preferenciais entre as Unidades de Saúde Pública e a comunicação social.

Conclusão: O planeamento estratégico baseado no modelo conceptual proposto, envolvendo diferentes parceiros da saúde e da comunidade, tem potencial para melhorar a efetividade da comunicação interna e externa e facilitar a implementação de programas e projetos de saúde pública. O modelo proposto deverá ser validado em Unidades de Saúde Pública, considerando potenciais restrições humanas, materiais e financeiras.

Palavras-chave: Comunicação em Saúde; Gestão de Serviços de Saúde Pública; Painel Delphi; Planeamento Estratégico; Portugal

INTRODUCTION

The Health communication is a research topic that includes both an individualized clinical approach and the transmission of messages to populations, among others. In 1962, Neal framed some of the main applications of health communication, namely the communication of scientific information, communication between health teams, communication between patients and healthcare professionals, communication between healthcare institutions, and mass communication.[1]

More recently, health communication was defined by Schiavo as a multidisciplinary area of research and practice related to the exchange of health information and the influence, support, and empowerment of individuals, communities, and organizations to adopt behaviors aimed at improving individual and community health. It should be people-centered, evidence-based, multidisciplinary, strategic, process-oriented, cost-effective, creative, segmented, promote relationships, behavior-driven, and inclusive of vulnerable groups.[2]

Health communication is deeply related to health literacy, which encompasses a comprehensive perspective of health information, integrating citizens' empowerment, and including an active role in their own health management, both in an individual and a community context.[3] During the COVID-19 pandemic, the role of risk communication and health education to promote the adoption of preventive behaviors to control infectious diseases and counteract misinformation was crucial.[4] Therefore, behavioral sciences are fundamental to develop effective health communication. A vast number of behavioral change techniques are known and can be used in specific contexts.[5] Social marketing also emerged as a solution to involve communities and promote behavior change through personalized and segmented strategies.[6]

In fact, advocacy communication and social mobilization for health are considered essential public health operations, highlighting the relevance of health literacy to reduce risk, prevent disease, promote health, and ease the navigation of healthcare systems.[7]

Organizational models and strategic communication

According to Lammers and Barbour, organizational communication includes all communication activities that take place within organizations, including daily practices, routines, beliefs, and regulations, among others.[8] Kunsch considers that organizational communication includes four dimensions that should be balanced according to organizational goals: instrumental, human, cultural, and strategic.[9] Organizations may find it difficult to achieve their goals if they rely on communication that is horizontal, informal and dominated by personal relationships and emotions. Organizational commitment is mainly determined by vertical and strategic communication, and that is applied to management processes.[10] Strategic communication considers communication used to achieve organizational objectives involving managers and employees, including components such as public relations, corporate communication, business communication, advertising, among others.[11,12] It is evidence-based, user-centered, oriented towards results and benefits, intervenes at multiple levels, promotes community and partner participation, and uses various media and multimedia channels.[13] However, not all communication developed in organizations is strategic, including administrative, social, and emotional components.[14] In healthcare, strategic communication can influence agendas, increase the visibility of organizations, develop a credible public image, and build networks with other organizations.[15]

Internal and external communication

Internal communication plays an important role in organizational models and workers' motivation and must be coherent throughout the organization. According to Clampitt and Downs, efficient internal communication increases productivity, reduces absenteeism and strikes, encourages innovation, and increases services and the quality of products while reducing costs.[16] Aligning internal communication processes with the organization's objectives facilitates the understanding of the organizational strategy, promotes continuous improvement, and brings professionals closer to managers, supporting them in their actions through formal and informal information flow processes.[17] One of the problems identified is the inability of managers to take an active part in the construction of consistent internal communication systems, whether due to excessive workload, little time to dedicate to assistant managers, or a lack of feedback mechanisms.[18]

On the other hand, external communication encourages knowledge sharing with partners and improves the public perception of organizations, contributing to their unique identity.[19] Health services should develop health information materials, but they should also be prepared to analyze how they are perceived and used by patients to adapt these materials to their needs.[20]

Communication between public health institutions and community partners is essential to achieve each other's goals. It might be done through annual reports, websites, newsletters, pamphlets, meetings, training sessions, media kits, press releases and news articles, among other formats. In addition to traditional media such as television, radio, magazines, newspapers and billboards, digital media integrate social networks (including Facebook®, Instagram®, LinkedIn®, Twitter®, YouTube®, Pinterest®, Reddit® and Tumblr®), text messages (by phone or applications such as WhatsApp® and Facebook Messenger®), email, websites, blogs, and video games.[21] Audience segmentation according to populations' social, media and digital skills, such as internet and social media use, can improve the effectiveness of public health interventions.[22]

An integrated approach to organizational communication includes three perspectives: public relations and institutional communication; internal and administrative communication; and marketing.[9]

Health communication practices in public health services in Portugal

Portuguese public health services are organized at a national, regional, and local level. At a local level, there are 56 public health units (PHU), integrated into community health clusters (CHC), including several professional groups: public health doctors, specialist nurses, environmental health officers, among others. In 2024 there was a profound reorganization of local health services, now included in 39 local health units, along with primary and secondary healthcare services. According to legislation, based on essential public health operations, PHU are responsible for "ensuring people's awareness, maintaining and improving communication about health and social mobilization for individuals and communities, towards public health".[7,23] Core competencies of public health doctors also include collaboration with the community, collaboration with healthcare institutions, and health communication targeting the population.[24]

According to data from the latest Portuguese Health Literacy Survey, in 2019, 70% of Portuguese population had a sufficient or excellent general level of health literacy. However, approximately 55.5% considered that literacy related to the navigation of the healthcare system was problematic or inadequate.[25]

Although Portugal has a strong health information system, it is mostly based on individual data. It lacks a population-based approach that considers the management of projects and partnerships, monitoring, and evaluation of communication processes.[26] In Portugal, most health communication is focused on the hospital context, is reactive and focused on individuals, and lacks comprehensive planning.[27] In public health services, there is a lack of adequate training and application of communication techniques, despite their importance. Research in public health communication is also scarce.

Therefore, the aim of this study was to develop a framework for strategic communication in PHU, detailing the most relevant communication channels used according to specific audiences.

METHODS

The aim of this non-interventional qualitative study was to develop a consensus on a framework for strategic communication in PHU, through a three-round, modified Delphi panel, as shown in Fig. 1. Such qualitative research methodology allows a description of complex communication flows, considering perspectives from experts to develop a topic lacking scientific evidence and implementation guidelines,[28] such as strategic communication in local public health services.

Literature review

An initial framework was developed following a rapid literature review on strategic organizational communication in health institutions. The inclusion criteria for this review were studies published until 2019, in Portuguese or English, that focused on strategic organizational communication in public health institutions and were available on PubMed, the Open Access Scientific Repositories in Portugal (RCAAP),

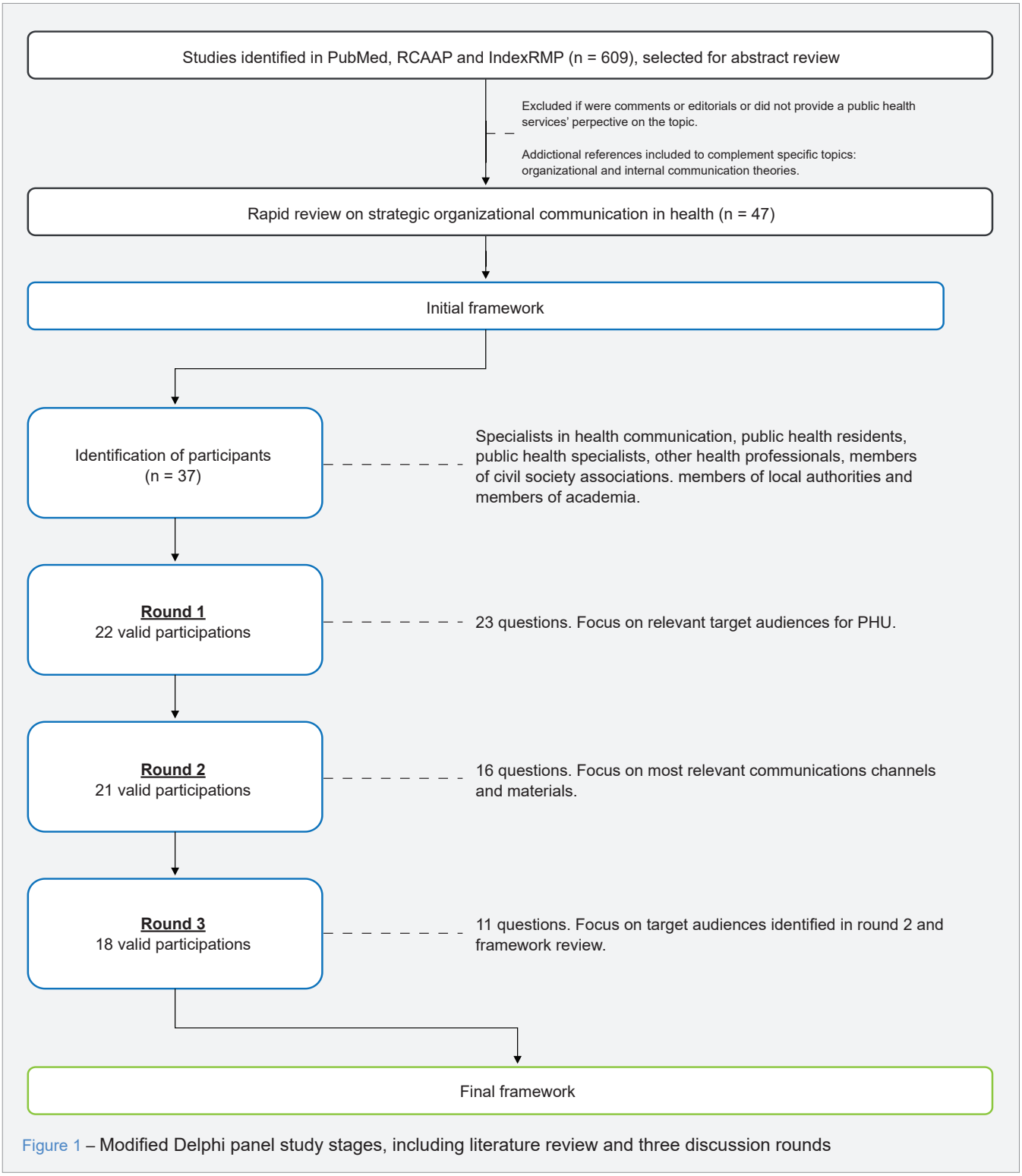

Figure 1 – Modified Delphi panel study stages, including literature review and three discussion rounds

and the Index of Portuguese Medical Journals (IndexRMP). These repositories were screened for articles including the following Portuguese and English terms in the title or abstract: "public health communication"; "health communication plan*"; "strategic communication"; "organizational communication"; "internal communication".

The RCAAP were also screened for master's and postdoctoral theses including "health communication" in

the title or abstract. A total of 609 articles, master's theses and post-doctoral theses were identified. Articles that were commentaries, editorials, or didn't provide a public health services' perspective on the topic were excluded. Additional references identified during article analysis were included to complement more specific topics, such as organizational and internal communication theories. After title and abstract analysis, 47 articles were identified to support the initial framework.

The most relevant frameworks that were considered to produce the initial proposed framework included: internal communication proposed by Yates[29]; PHU stakeholders' management proposed by Beaufort and Rohrer[30]; and institutional organizational communication proposed by Lammers and Barbour.[31]

Participants in Delphi panel

Thirty-seven experts were invited via e-mail to participate in this Delphi panel, including 22 women and 15 men. Different perspectives were considered[32]:

- Sixteen healthcare professionals, including public health doctors, family physicians, community health nurses, environmental health officers, and teachers with background in public health. Among these, eight experts worked in local public health units, providing insightful feedback about the usability of the proposed framework;
- Fourteen communication professionals, including journalists, researchers, and teachers with background in health communication;
- Seven community stakeholders, including school directors, members of patient associations, members of the city council and politicians, with interventions in health topics.

Experts were selected based on convenience, knowledge about health communication, experience at the local level and availability to participate.[33]

Data collection

Data was collected between August and October 2020 through a digital questionnaire on Google Forms®, shared via blind carbon copy emails, ensuring participants' confidentiality.[34] The collected data included only the participants' e-mail addresses as potentially identifiable information, to avoid repeated answers. In all rounds of discussion, the participants provided their voluntary and informed consent to the study's objectives, data collection, and analysis.[35] Each round lasted approximately 10 days, including two reminders sent via email. High retention rates were observed in all rounds (first = 59%; second = 57%; third = 48%). The questionnaire presented successively fewer questions, including open-answer, multiple choice, matrix-format, and Likert scale questions, ensuring that a maximum limit of 26 questions was not exceeded, as suggested in the current scientific literature.[36] Likert scale questions focused on collecting feedback regarding general statements about the importance of communication planning for local public health services. Open-ended questions asked for suggestions regarding internal and external communication in PHU and its main barriers, feedback on the proposed framework, and suggestions for additional audiences and communication channels to be included in the proposed framework. Multiple-choice and matrix-format questions aimed to gather consensus regarding the main barriers and facilitators of internal and external communication, as well as the main audiences and communication channels used in PHU.

Data analysis

Data analysis was performed by the main researcher. Consensus was defined as agreement ('strongly agree' or 'agree') or disagreement ('strongly disagree' or 'disagree') among at least 70% of answers in each round, as suggested in the scientific literature.[37] Qualitative thematic analysis of open-ended answers allowed items to be categorized and included in closed-ended questions in the following rounds (e.g., identification of closed-ended options for barriers to internal and external communication). Descriptive quantitative analysis was performed using Microsoft Excel® software. Results were presented as raw numbers and percentage of agreement or disagreement, considering a 70% threshold, in each round. The data collected and agreed upon in the third round of discussion was integrated into the final framework.

Both an initial and revised protocol for this study were submitted to the Portuguese Institute of Hygiene and Tropical Medicine (IHMT) Ethical Committee before the research was conducted. The protocol N. 07.20 was approved on July 30, 2020.

RESULTS

Retention rates per field of work

Retention rates among 37 invited experts decreased from 59% to 48%, while most participants worked in healthcare (14 in each discussion round). Between two and three academics participated in each round of this Delphi panel, while specialists in communication varied from three in the first round of discussion to one in the last round of discussion. People involved in community services (politicians and school directors) were the least engaged group, including two participants in the first round of discussion and one in the last round of discussion.

Perception about health communication in local public health services

According to the invited experts, "communication is fundamental to public health" and "it is essential to have a functional area dedicated to communication in PHU" represented an agreement consensus of 100% and 95% of participants obtained during the first round of discussion, respectively. Most experts disagreed that "PHU are prepared to communicate effectively" (disagreement consensus of 82%, obtained in the first round of discussion) and believed that "it is essential to have a framework, like the one proposed in this study, to prepare communication in PHU" (agreement consensus of 91%, obtained in the first round of discussion).

Internal communication in local public health services

Public health units include a wide range of healthcare professionals, including public health authorities, public health doctors, nurses, environmental health officers, dental hygienists, technical assistants, operational assistants, among others. Most experts disagreed that "internal communication between these professionals is well developed" (disagreement consensus of 77%) and believe that "for an adequate internal communication planning, it is essential to define someone responsible for communication in PHU" (agreement consensus of 95%, obtained in the second round of discussion).

External communication in local public health services

During the first round of discussion, external communication was mostly discussed with open-answer questions, and consensus was obtained in the second and third rounds of discussion. All participating experts agreed that "for an adequate external communication planning, it is essential to define someone responsible for communication in PHU" (agreement consensus of 100%, obtained in the second round of discussion). Most participating experts also believed that external communication in PHU

Table 1 – Agreement percentage on the most relevant communication channels to be used by public health units by target audience. Consensus was obtained in the second round of discussion (n = 21), except for audiences in italic lettering, for which consensus obtained in the third round of discussion. No consensus was obtained for the media audience.

Target audience	Communication channel	% agreed
Health authorities	Interpersonal relationships	90
	E-mail	86
	Mobile phone	71
Other PHU	E-mail	89
	Mobile phone	78
	Interpersonal relationships	72
Hospitals	Mobile phone	86
	E-mail	81
	Interpersonal relationships	76
Primary health care	Interpersonal relationships	81
	E-mail	81
	Mobile phone	71
Schools	Interpersonal relationships	100
	E-mail	81
	Mobile phone	67
Community leaders	Interpersonal relationships	89
	E-mail	72
	Mobile phone	56
City councils	Interpersonal relationships	86
	E-mail	81
	Mobile phone	57
Laboratory	E-mail	86
	Mobile phone	76
	Interpersonal relationships	57
Private companies	E-mail	86
	Website	71
	Mobile phone	38
Health institutions	Interpersonal relationships	83
	E-mail	78
	Mobile phone	33
Civil society	Social media	81
	Website	76
	Media	57
Community pharmacies	E-mail	89
	Website	39
	Mobile phone	39
Private healthcare	E-mail	86
	Mobile phone	52
	Website	48
Academia	E-mail	86
	Mobile phone	57
	Interpersonal relationships	52
Security and military	E-mail	81
	Interpersonal relationships	67
	Mobile phone	62
Media	E-mail	61
	Website	61
	Social media	50

should involve an institutional website and social media (agreement consensus of 95% and 90%, respectively, obtained in the second round of discussion).

The most relevant target audiences and stakeholders were identified during the first round of discussion through open-answer questions, while their relevance, preferable communication channels, and materials were agreed upon in the following rounds.

Regarding the relevance to target audiences, no consensus was obtained in the second round of discussion. In the last round of discussion, the most important target audiences included primary health care institutions, health authorities, hospitals, community pharmacies, local councils, and local community leaders (agreement consensus of 100%, obtained in the third round of discussion). Schools, civil society, and healthcare institutions involved in decision-making were considered highly relevant (agreement consensus of 94%, obtained in the third round of discussion). No consensus was obtained on the relevance of academia for PHU.

Regarding the preferred communication approach for target audiences, participating experts considered that PHU should interact via formal communication channels with most stakeholders. Consensus on using formal and informal communication channels was obtained for interaction with other PHU (agreement consensus of 83% and 77%, for formal and informal communication channels, respectively) and schools (agreement consensus of 81%, for both formal and informal communication channels). No consensus was obtained on the preferable communication approach for civil society.

Regarding the preferred communication channels for target audiences, e-mail, mobile phone, and interpersonal relationships were the most agreed-upon overall. Table 1 describes the top three communication channels and agreement percentage (consensus was only considered if more than 70% of participants agreed on the same communication channel) by target audience. While consensus on three communication channels was obtained for interaction with health authorities, other PHU, hospitals, and primary health care, no consensus was obtained for communication with the media. In the second round of discussion, all participants considered that interpersonal relationships were the main communication channel with schools. Interaction with city councils and municipalities was also highlighted by most participants, particularly via interpersonal relationships and e-mail.

Strategic communication framework for local public health services

An initial framework was presented in the first round of discussion, including relevant changes in the following rounds, such as the inclusion of other stakeholders, highlights of the most relevant interactions, bidirectional communication, and most relevant communication channels (after consensus). According to participating experts, internal and external communication strategies were adequately represented in the final proposed framework (agreement consensus of 94%, obtained in the third round of discussion), as shown in Fig. 2.

DISCUSSION

According to 82% of the participants, PHU in Portugal were not ready to communicate effectively with stakeholders and the community. Some suggestions to improve this area included the implementation of a strategic planning process, the identification of a communication lead or team, the reinforcement of human and technological resources, as well as the prioritization of internal and external communication activities. According to at least 90% of the participants, PHU should have websites and social media accounts. In this conceptual model, most participants highlighted the importance of the collaboration with schools, municipalities, other PHU, primary healthcare units, hospitals, and health authorities. At least 70% of the participants considered interpersonal relationships and e-mail as the main communication channels to interact with these stakeholders.

Although communication is considered a key aspect of public health, there are no specific guidelines on how it can be implemented in public health units in Portugal. A modified online Delphi panel enabled the development of a conceptual model involving multiple stakeholders in only two months and without incurring relevant expenses.

Digital and online tools allowed faster data collection, minimizing errors in transcription while maintaining the confidentiality of experts and avoiding biased perspectives due to group interaction.[38] The threshold for consensus was set at 70%, according to previous studies.[37]

Methodological limitations

Although scientific evidence is widely available for organizational communication in hospitals, there is a lack of relevant frameworks applied to primary care and public health services, particularly at local level. Therefore, this study contributes to the improvement of communication planning among public health services and fills that knowledge gap while providing an applicable framework. Using consensus methodology through a Delphi panel of specialists in public health, communication, and community members we were able to overcome the lack of a conceptual model for communication in PHU in Portugal, with low financial costs. Since PHU include different healthcare professionals and interact with multiple health stakeholders, they represent a greater proportion of invited experts. The selection of

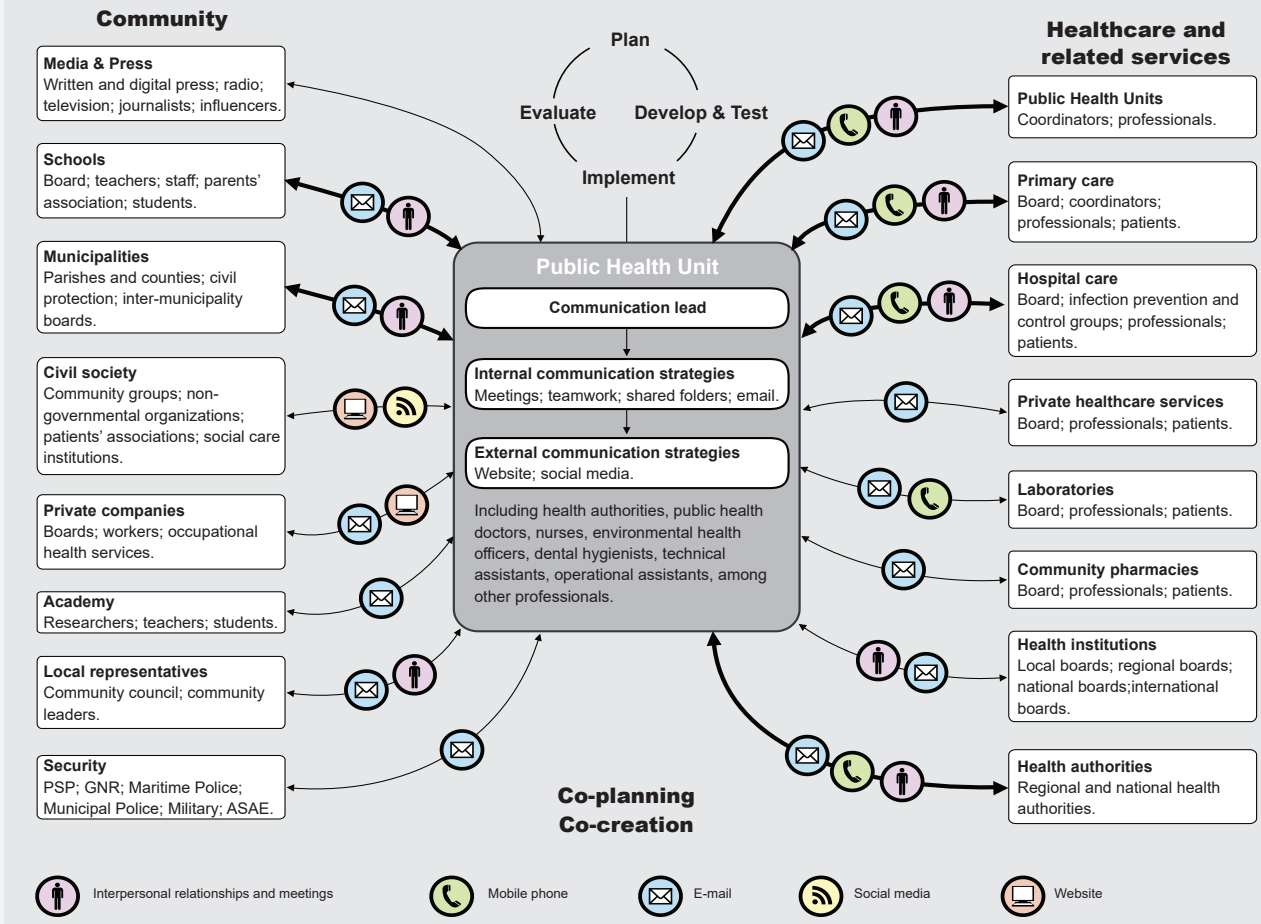

Figure 2 – Validated framework on organizational and strategic communication in public health unit (prepared by the author)

experts was motivated by convenience and availability, which can lead to potential bias and homogeneous thinking.[39]

The proposed initial framework was developed after a rapid review of organizational health communication, a methodological approach chosen due to time constrains that ensured a critical appraisal of current evidence. However, a more comprehensive systematic review could provide a more detailed analysis of the topic.

Data collection through online questionnaires allowed the inclusion of experts from different geographical areas, who provided a broader perspective on the topic. Anonymity during the discussion rounds potentially avoided dominance of one perspective over others, which is a common limitation in focus group methodology. There was a high retention rate of participants, which led to a variety of perspectives, although it decreased in further discussion rounds: 59% in the first round, 57% in the second round, and 48% in the third round. Two reminders were sent via e-mail in each round in order to increase the engagement of participants. The proportion of participants who were healthcare professionals was higher, which could be related to direct involvement in public health units and interest in this topic: 64% in the first round, 70% in the second round and 78% in the third round. Although they were invited, no stakeholders from civil society participated in the Delphi panel, which could perhaps be explained by a lack of interest in the topic. This should be addressed in further studies in order to increase the validation of the conceptual model among community stakeholders with high relevance to public health interventions.

Three healthcare professionals tested the initial questionnaire and suggested minor revisions. In the first round, most participants considered they did not know if formal or informal communication channels were established between PHU and stakeholders, which required minor revisions to the questionnaire.

Strategic communication frameworks in healthcare

The COVID-19 pandemic exacerbated existing weaknesses in public health communication, a lack of training, and an urgent need of local operationalization of vague theoretical recommendations.[40] According to the existing evidence, most local health plans developed by PHU did not mention proper communication strategies to implement the proposed strategies.[41] As shown in this study, PHU in Portugal lack structural, organizational, and strategic planning to communicate more effectively with different healthcare professionals and stakeholders. Hospitals manage internal communication more effectively, but financial and management autonomy play a relevant role in the operationalization of communications.[27]

Lack of planning, coherence, and assertiveness in public health communication increased during the COVID-19 pandemic, deepening existing problems.[42] The proposed conceptual model could provide the foundations for PHU to better communicate with wider audiences, via healthcare and community stakeholders they usually engage with. Specific local contexts should be considered, as well as stakeholder mapping, through the identification of the most relevant and influential ones.[43] This study did not analyze interactions between community and healthcare stakeholders, which were already in place and did not involve PHU.

Internal communication in PHU

According to this study, having an individual or team responsible for communication in PHU is a key aspect to improve public health communication. In most PHU in Portugal, health authorities usually assume this role informally, regardless of their knowledge and skills in health communication, which could lead to difficulties in communicating during a public health crisis.[44] Since PHU have a diverse workforce, including medical doctors, nurses, environmental health officers, dental hygienists, senior diagnostic and therapeutic technicians, administrative and operational assistants, internal communication processes are particularly relevant to promoting teamwork and good interpersonal relationships.[45]

External communication in PHU

Although communication through digital and online channels can improve population outreach, about 73% of PHU do not communicate via a website, and 89% do not own a Facebook® page. For those who own websites, there is a lack of proper integration with a coherent communication strategy within the Portuguese National Health Service.[13,46] According to this study, websites represent a relevant communication channel between PHU, private companies, and civil society (with consensus), private healthcare services, community pharmacies, and media (without consensus).

E-mail was the most relevant communication channel identified in this study, but public health professionals still lack practical training in managing e-mail inboxes.[47] Interpersonal and telephone communication allow PHU to establish stronger institutional relationships but require more time and commitment.[48] During the COVID-19 pandemic, most in-person meetings were replaced by videoconferences, which saved time and reduced the risk of contagion.[49]

Although mainstream media, such as TV, radio, and newspapers, are relevant communication channels to reach wider audiences, there was no consensus on how PHU can communicate with them. Lack of knowledge about how to communicate with journalists and the need for hierarchical feedback may contribute to this result.[13] According to this study, PHU and academia may have a suboptimal relationship, probably due to a lack of knowledge translation from public health researchers to practitioners, regardless of its potential to strengthen research and outreach capacity.[26]

Communication between PHU and schools using both formal and informal communication channels was considered extremely relevant, which was probably due to long-term relationships and local coordination of the National Program for School Health.[50] Communication with municipalities was also highlighted, probably due to frequent interactions via Civil Protection meetings and local health planning strategies.

Applicability and future perspectives

There is a need to disseminate and validate the proposed conceptual model in multiple PHU, considering potential human, material, and financial constraints. Given the high level of consensus and previous research, the development of PHU websites and discussion regarding social media interaction should be a priority, with proper technical support and training, as mentioned in the Portuguese scientific literature.[46] Considering the engagement of multiple stakeholders that public health requires, the proposed framework provides a structured approach to mapping and discussion about the most relevant communication channels.

Invited experts working at PHU in Portugal ensured relevant feedback on the applicability of the proposed framework in public health services at a local level. Uptake by PHU can be promoted through local workshops focused on identifying communication channels and mapping stakeholders. Lack of human resources, time and strategic planning were constraints identified by the surveyed experts. While this framework could improve strategic planning, further investment in human resources might be required to ensure proper implementation. As agreed by participants in this Delphi panel, creating a communication team and lead, with awareness of the available communication channels,

procedures, and hierarchies, could be a starting point to improve internal communication in PHU.

To encourage a focus on strategic communication planning, annual commissioning between PHU and local healthcare managers could include communication-related indicators.[26]

CONCLUSION

Communication is a core public health area, which lacks adequate strategic and operational planning, particularly in local public health services. The development of strategic and organizational communication plans in PHU, in Portugal, as proposed in this framework, has the potential to enhance internal communication procedures in PHU, improve the implementation of public health programs, and promote better interaction with the community and local stakeholders.

According to the proposed framework, internal and external communication strategies should consider assigning a person or team responsible for communication planning, implementation, monitoring, and evaluation and promoting the use of digital platforms such as e-mail, websites, and social media. To communicate effectively with communities and multiple stakeholders, which is one of the most important competencies of PHU, it is essential to identify communication strategies that integrate community partners, build capacity in local public health services, and prepare communication plans for activities to be developed.

AWARDS AND PREVIOUS PRESENTATIONS

Poster presentation in the 16th World Congress on Public Health (Online, October 2020) and Public Health National Conference 2023 (Lisboa, June 2023).

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PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

DVB is the vice-president of the Portuguese Association of Public Health Doctors.

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ACTA MÉDICA PORTUGUESA
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Effectiveness of Neuropsychological Rehabilitation in the Recovery of Executive Deficits in Patients with Alcohol Use Disorder: A Systematic Review Protocol

Eficácia da Reabilitação Neuropsicológica na Recuperação de Défices Executivos em Doentes com Perturbação por Uso de Álcool: Protocolo de Revisão Sistemática

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ABSTRACT

Introduction: Changes in executive functions associated with alcohol consumption are frequently found in alcohol use disorder. Neuropsychological rehabilitation can play an essential role as an effective treatment in the recovery from these deficits, leading to the maintenance of abstinence. However, there are still some uncertainties regarding its impact on the recovery of deficits in executive functions. Our purpose is to present a protocol for a systematic review aiming to assess which neuropsychological rehabilitation programs are effective in the recovery of executive deficits in patients with alcohol use disorder.

Methods: We will search the following databases: PubMed, Cochrane Library (CENTRAL), Web of Science, and Scopus, as well as the list of references of the identified studies. Screening, data extraction, and synthesis, as well as evaluation of the risk of bias, will be carried out by two reviewers independently, using ROBINS-I and RoB 2. Disagreements will be resolved using a third additional reviewer. Primary outcomes will correspond to changes in executive functions, following a neuropsychological rehabilitation program in patients with alcohol use disorder. The evidence will be synthesized using a narrative description of neuropsychological rehabilitation programs and the indicators of their effectiveness will be identified. The neuropsychological rehabilitation programs for executive functions will be assessed considering their different components and their impact on the recovery of these functions. The review described in this protocol will allow the development of guidelines for the design of more effective rehabilitation programs for clinical populations with alcohol use disorder.

Keywords: Alcoholism; Alcohol Use Disorder; Cognitive Rehabilitation; Executive Functioning

RESUMO

Introdução: Na perturbação por uso de álcool é frequente verificarem-se alterações nas funções executivas associadas ao consumo de álcool. A recuperação destes défices é essencial, podendo promover a eficácia dos tratamentos e levar à manutenção da abstinência. Apesar da reabilitação neuropsicológica poder assumir aqui um papel essencial ainda existem algumas incertezas em relação ao seu impacto na recuperação destes défices. O objetivo deste trabalho é apresentar um protocolo de revisão sistemática da literatura com vista a avaliar que programas de reabilitação neuropsicológica são eficazes na recuperação das funções executivas em doentes com perturbação por uso de álcool.

Métodos: Pesquisaremos nas bases de dados PubMed, Cochrane Library (CENTRAL), Web of Science e Scopus, bem como na lista de referências dos estudos identificados. A triagem, extração e síntese de dados, bem como a avaliação do risco de viés serão efetuadas por dois revisores de forma independente, utilizando o ROBINS-I e o RoB 2. Os desacordos serão ultrapassados com um terceiro revisor. As alterações nas funções executivas obtidas com a reabilitação neuropsicológica em pacientes com perturbação por uso de álcool constituirão os *outcomes* principais. As evidências serão sintetizadas por meio de uma descrição narrativa, sobre os programas de reabilitação neuropsicológica, identificando-se indicadores de eficácia. Serão analisados os programas de reabilitação neuropsicológica para as funções executivas, considerando as suas diferentes componentes e descrevendo o seu impacto na recuperação destas funções. A revisão definida neste protocolo permitirá o desenvolvimento de linhas orientadoras para a definição de programas de reabilitação mais efetivos para a população clínica com perturbação por uso de álcool.

Palavras-chave: Alcoolismo; Funções Executivas; Perturbação por Uso de Álcool; Reabilitação Cognitiva

INTRODUCTION

Alcohol use disorder (AUD) represents a serious public health problem, with multiple repercussions, causing liver disease, heart disease, psychiatric disorders (e.g., depression, anxiety, etc.), oncological diseases, and cognitive impairment,[1] affecting also the quality of life of individuals. In AUD the deficits in cognitive functioning are frequent, including those of executive functions, which may affect the treatment process by affecting motivation and decision-making.[2] All these aspects may increase the risk of relapse.[3] In this context, significant changes in executive functions (EF) are present due to greater impairment in the prefrontal cortex,[4] both in recently detoxified individuals[5] and those with longer periods of abstinence.[6]

Some of the cognitive deficits tend to be restored over the course of abstinence,[4] although others can persist over time.[7] Some studies found improvements after one month of

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abstinence,[8] while others highlighted the presence of cognitive deficits after one and two years.[6,9] Variables such as psychiatric comorbidities, affective aspects,[10] the number of previous detoxifications,[11] age of cessation of consumption,[9] among others, may influence these aspects.

The cognitive impairment and its interference in the day-to-day life of individuals with AUD point to the need to include neuropsychological rehabilitation (NR)/cognitive remediation in the traditional treatments for the disease to minimize its negative impact. This hinges on the premise that repetitive exposure to certain activities can help strengthen and restore cognitive function, facilitating the recovery trajectory compared to spontaneous evolution over time of abstinence.[10] Furthermore, NR is underpinned by neuroplasticity, which reflects the brain's capacity for self-repair, this being enhanced by the cognitively complex environmental experiences to which it is subjected, as is NR.[12]

As far as we know, there is some heterogeneity in results regarding the importance of NR in the recovery of cognitive deficits. Some data show that NR is associated with improved cognitive functioning, promoting recovery from alcohol-induced damage,[13-16] although others do not support this positive association.[17-19] In this area, it becomes increasingly relevant that the NR programs benefit the individuals' functionality, fitting in with their daily needs and demands. It is essential to make them more capable of managing their interpersonal relationships, daily life, and work tasks, as well as avoiding consumption.[20] On the other hand, it is thought that NR may contribute to better efficacy of treatments in AUD,[21] by promoting adherence to them. The protocol presented here describes the rationale, hypothesis, and methods to be followed for a systematic review aiming to assess which NR programs are effective in the recovery of executive deficits in patients with AUD.

METHODS

The protocol was structured, based on Cochrane[22] recommendations for systematic reviews of literature and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P).[23]

Research question

We defined the following research question for the review: 'Which neuropsychological rehabilitation programs are effective in the recovery of executive deficits in patients with alcohol use disorder?'

Inclusion/Exclusion criteria

The inclusion/exclusion criteria[24] were defined as follows:

Study design: randomized and non-randomized controlled clinical trials, longitudinal studies (cohort), case-control studies, and cross-sectional studies.

Population: abstinent adults (≥ 18 years old) with previous history of AUD, with or without a history of other substance use, with different patterns and durations of consumption, and without brain damage. Individuals with traumatic brain injury and neurological conditions caused by alcohol consumption and psychiatric comorbidity will not be eligible, as well as other types of alcohol consumption other than dependence (e.g., binge drinking).

Intervention: all NR programs will be integrated, with no limitations in terms of intervention context, treatment phase, abstinence time, or trained executive functions. We will include different interventional strategies. Transcranial magnetic stimulation will be excluded.

Comparator: usual treatment in AUD and/or some type of NR with different characteristics (technical and frequency) of the experimental group, or cases of no intervention of any type.

Context: we will include all contexts of intervention in AUD, such as outpatient, inpatient, and therapeutic community.

Results: The main results will be assessed as changes (improvement/ worsening) in the EF with NR, particularly in inhibition, working memory, cognitive flexibility, planning, problem-solving, decision-making, and abstract thinking, using data from the cognitive tests used in the studies. We will also analyze changes in other cognitive domains or other EF components (transfer effect). As secondary outcomes, changes in alcohol consumption patterns will be described, such as reduction/increase in consumption or abstinence time and the number of relapses during treatment, based on reports and tests related to consumption.

Studies published in English, Spanish, French, Italian, and Portuguese will be included.

Only reports with empirical data will be included. We will exclude opinion or literature review studies, conference abstracts, and books or book chapters.

Information sources and research strategies

PubMed, Cochrane Library (CENTRAL), Web of Science, and Scopus will be used to conduct the proposed review. The only filter used in the research will be the language.

The search strategy will include text words, and search terms adjusted to the specificities of the different databases. Keywords or database-specific subject headings (e.g., MeSH) and the Boolean operators 'OR' and 'AND' will be used to combine the search terms. The keywords included will be 'alcoholism', 'alcohol', 'cognitive training', and 'cognitive remediation'. Keywords will be grouped into three combined free-text blocks, one on alcohol, one on cognitive domains, and another one on NR. An example of the

research strategy that will be used for one of the databases is presented in Appendix 1 (https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19804/15224).

The reference list of systematic reviews and meta-analyses identified in this review, as well as from other papers that match the defined inclusion criteria will also be handsearched.

Study selection

The titles of the reports found in the different databases will be extracted and duplicates eliminated using Mendeley reference management software (keeping only the most recent versions, when applicable). Titles and abstracts will be independently assessed by two authors of this review in order to select the reports that potentially match the inclusion criteria [see Appendix 2 (https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19804/15225)]. Disagreements regarding the eligibility of the reports will be resolved using a third researcher to reach a consensus. Reports with no full text available will be excluded. A list of the reports eliminated will be drawn up and the reasons for the exclusion will also be described.

Data extraction/synthesis

The extracted data will be included by one of the researchers in a standardized table and checked by another researcher. This table will include the article author's name, year of publication, study design, inclusion criteria, exclusion criteria, population and characterization of the participants (number, age, gender, comorbidity, type of consumption, other consumptions and participation rate), the NR characterization (objective, tasks, strategies, cognitive domains trained, intervention context, number of rehabilitation sessions/hours), simultaneous interventions, control group, transfer effect, follow-up, outcome measure (the instruments and moments of evaluation), the main outcome (changes in cognitive domains) and other outcomes, such as alcohol consumption pattern, emotional aspects, functionality in daily life.

The information described above will be included in a narrative synthesis, illustrated with tables because the diversity of interventions and comparators makes a meta-analysis difficult to perform.

Risk of bias assessment

Two reviewers will independently assess the methodological quality of the selected studies. The risk of bias in randomized controlled trials will be evaluated using the Cochrane Collaboration tool (RoB2). The risk of bias in non-randomized studies of interventions will be assessed using ROBINS-I.[25,26]

DISCUSSION

The proposed review is expected to aggregate a heterogeneity of results, some of which will point to the efficacy of NR on EFs,[13,14] while others will not highlight significant differences between baseline and follow-up data.[17,18]

On the other hand, it is expected that the NR of EFs may interfere with other variables in the daily life of this population specifically on the reduction of alcohol consumption[12] or the promotion of abstinence, which influences adherence and motivation for treatment,[2] as well as behavioral change. Neuropsychological rehabilitation for a particular cognitive function can improve the performance of that function and generalize the benefit of untrained tasks.[27]

Previous systematic reviews of the literature, despite not having controlled for some of the variables that may interfere with data analysis (inclusion of certain psychiatric conditions or the simultaneous use of pharmacological therapy), have shown improvement at the cognitive level with NR in AUD. However, the data does not appear to be robust, especially regarding the degree of impact of NR on cognitive functioning and/or functionality, in consumption and social adaptation of individuals with AUD,[27] causing the underlying mechanisms of those improvements not to be understood.[28]

The analysis of different NR programs, in different rehabilitative contexts and with different methodologies, in comparison with the usual treatments in AUD, may allow the identification of the most efficient interventions in this field. Nonetheless, the diversity found in studies, concerning the NR and the studied population, may constitute challenges in drawing conclusions regarding this issue. It is expected that this review may facilitate a better understanding of these aspects, by including structural elements of NR, specifically the duration/number of sessions and diversified interventional strategies, among others. Examining and better characterizing NR programs will allow us to assess whether there are methodologies with greater impact on the rehabilitation of executive deficits in AUD. This review will provide guidance for the design of more effective NR therapies for AUD and will identify possible profiles of individuals who may benefit from them, demonstrating their relevance in AUD therapeutic plans.

A possible limitation of this review relates to the risk of not including unpublished studies, which may not be covered by the search strategy. Furthermore, the risk of bias may persist, namely the difficulties in combining the various studies, with differences in the studied populations, interventions, and comparators, as well as methodological limitations of the primary studies, which may affect the analysis of results.

This review will examine the effectiveness of NR of EFs in AUD. Its strengths relate to the attempt to control

variables that may interfere with the analysis of the effectiveness of the NR programs, such as brain injuries or psychiatric conditions, attending to more structural elements of the NR, and facilitating the characterization of the rehabilitative processes. All these aspects may allow a more solid analysis of the NR in this population.

AUTHOR CONTRIBUTIONS

SF: Conceptualization, data curation, formal analysis, investigation, methodology, writing of the original draft, critical review.

AV: Conceptualization, formal analysis, investigation, methodology, writing and critical review of the original draft, supervision.

CR, SP, LBN: Writing and critical review of the original draft, supervision.

STUDY REGISTRATION

Submission to Prospero was carried out to record the systematic literature review (registration number: CRD42023393730).

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
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Trauma Associado às Touradas à Corda nos Açores: Um Estudo Transversal

Trauma Injuries Associated with Rope Bullfights in the Azores: A Cross-Sectional Study

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RESUMO

Introdução: O objetivo deste estudo foi caracterizar as lesões traumáticas tauromáquicas ocorridas nas touradas à corda nos Açores no que diz respeito à causa do incidente, mecanismo de trauma, área anatómica mais afetada e gravidade das lesões.

Métodos: Estudo unicêntrico, transversal, com a colheita prospetiva de dados realizada durante dois anos. Foram incluídos os doentes que consecutivamente recorreram ao serviço de urgência do hospital local por lesões traumáticas ocorridas por trauma direto com o animal ou quedas aquando da fuga ou manuseio da corda. Foram colhidos dados demográficos gerais, características da lesão, tratamentos efetuados, necessidade de internamento hospitalar e mortalidade. Foi realizada uma análise estatística descritiva com recurso ao *software* estatístico SPSS.

Resultados: Registaram-se 56 admissões hospitalares e 80 lesões traumáticas. A principal causa de traumatismo foi o trauma direto com o animal (37; 66,07%) e o mecanismo de lesão foi o trauma fechado (56; 100%). As áreas anatómicas mais afetadas foram a cabeça e pescoço (27; 33,75%). A mediana de *Injury Severity Score* foi de 4 à admissão hospitalar. Cinco doentes (8,92%) apresentaram trauma *major*. Dez doentes (17,85%) necessitaram de internamento hospitalar com uma mediana de dias de internamento de sete (IIQ 4,5 dias). Três (30%) dos doentes internados necessitaram de internamento em unidade de cuidados intensivos. Seis doentes (10,71%) foram submetidos a cirurgia.

Conclusão: A principal causa de traumatismo foi o trauma direto com o animal e o mecanismo de lesão foi o trauma fechado. As áreas anatómicas mais afetadas foram a cabeça e pescoço. Estes dados constituem um alerta para o impacto destes eventos no que diz respeito aos custos económicos que acarretam, aos custos para a saúde da população local, às medidas de segurança atualmente implementadas e à disponibilidade dos meios necessários para tratar estes doentes.

Palavras-chave: Feridas e Lesões; Ferimentos não Penetrantes; Índice de Gravidade de Doença; Trauma Múltiplo

ABSTRACT

Introduction: The aim of the study was to describe trauma injuries associated with rope bullfights in the Azores, Portugal, regarding the cause of the incident, trauma mechanism, most affected anatomical areas, and injury severity.

Methods: Two-year cross-sectional study in the local hospital with prospective data collection. Patients who were consecutively admitted to the local hospital's emergency department with trauma injuries from the bull's direct impact or from falls either during the bull's escape or when handling the rope, were included. Data on general demographics, lesion characteristics, treatments, need for hospitalization and mortality were collected.

Results: Fifty-six incidents and 80 trauma injuries were identified. The main cause of trauma was the bull's direct impact (37; 66.07%) and the mechanism of injury was blunt trauma in all patients (100%; 56). Head and neck injuries (27; 33.75%) were the most common. The median Injury Severity Score at the emergency department admission was 4. *Major* trauma was noted in five patients (8.92%). Ten patients (17.85%) needed hospitalization with a median hospital stay of seven days. Three of the 10 hospitalized patients (30%) were previously admitted to the intensive care unit. Surgery was performed in six patients (10.71%).

Conclusion: The main cause of trauma was the bull's direct impact, and the mechanism of injury was blunt trauma. The most affected anatomical areas were the head and neck. These findings are a wake-up call to the impact of these events regarding the economic costs they entail, the costs for the health of the local population, the safety measures currently implemented and the availability of the necessary means to treat these patients.

Keywords: Multiple Trauma; Severity of Illness Index; Wounds and Injuries; Wounds, Nonpenetrating

INTRODUÇÃO

Touradas à corda são eventos festivos tradicionais da Região Autónoma dos Açores caracterizados pela corrida de touros, presos pelo pescoço a uma corda guiada por seis pastores ao longo de um arraial montado numa rua. Estes eventos são bastante populares nesta região, ocorrendo diariamente entre maio e outubro. Mais de 99% destes eventos ocorrem na Ilha Terceira, com uma pequena percentagem a ocorrer nas restantes oito ilhas dos Açores. Todos os anos, recorrem aos serviços de urgência dos hospitais locais doentes vítimas de traumatismos decorrentes de traumas diretos com os animais, ou de quedas aquando da fuga ou manuseio da corda.

A literatura científica internacional sobre lesões traumáticas por corno de gado bovino é escassa. A sua incidência é maior em áreas geográficas e sociedades onde o gado coexiste no mesmo espaço que as pessoas,[1] relacionada com acidentes de trabalho com campinos, maiorais e ganadeiros, ou em países com tradição tauromáquica como Portugal, Espanha, Sul de França e países da América Latina.[2,3] As séries publicadas descrevem maioritariamente acidentes

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decorrentes em touradas de praça,[2,3] mas a maioria da literatura assenta em relatos de casos isolados no mesmo contexto[4-7] ou acidentes com vacas selvagens na India.[8-10]

O mecanismo de trauma mais comum é o trauma penetrante por corno de touro[2] e as áreas anatómicas mais comummente afetadas são a região inguinal e os membros inferiores.[2,3] As lesões vasculares estão muitas vezes associadas aos traumatismos da região inguinal e coxa (cerca de 20%)[2] com necessidade de intervenção cirúrgica urgente em cerca de 30% dos casos.[3] As lesões vasculares constituem um fator prognóstico de gravidade e de mortalidade.[2]

Não é do conhecimento dos autores a existência de estudos descritivos destes incidentes em touradas à corda. O objetivo deste estudo foi caracterizar as lesões traumáticas tauromáquicas ocorridas nas touradas à corda de três ilhas dos Açores (Terceira, São Jorge e Graciosa) no que diz respeito à causa do incidente, mecanismo de trauma, área anatómica mais afetada e gravidade das lesões.

MÉTODOS

Desenho e população de estudo

Realizou-se um estudo transversal, com a colheita prospetiva de dados realizada de 1 de maio de 2018 a 31 de outubro de 2019.

Foram incluídos os doentes que consecutivamente recorreram ao serviço de urgência (SU) do Hospital de Santo Espírito da Ilha Terceira (HSEIT), provenientes das três ilhas dos Açores da área de abrangência do hospital de estudo (ilhas Terceira, São Jorge e Graciosa), por lesões traumáticas ocorridas em touradas à corda por trauma direto com o animal, ou quedas aquando da fuga do animal ou manuseio da corda. Foram excluídos doentes que recorreram ao SU do HSEIT por lesões ocorridas em touradas de praça ou bezerradas, ou lesões por touro fora do contexto festivo em estudo (tourada à corda).

Variáveis

Foram colhidos dados demográficos gerais dos doentes (idade, sexo, nacionalidade e residência), contexto festivo (tipo de evento e participação do doente enquanto pastor, capinha ou público geral), características da lesão (causa do traumatismo, mecanismo de lesão, área(s) anatómica(s) afetada(s) e gravidade das lesões), estado hemodinâmico na admissão hospitalar, tratamento(s) efetuado(s) no SU, necessidade de internamento hospitalar (respetivo departamento ou necessidade de transferência hospitalar) e mortalidade. Nos casos em que houve necessidade de internamento no HSEIT, foi feito o seguimento prospetivo com registo do número de dias de internamento, tratamentos efetuados, necessidade de cirurgia (urgente ou eletiva e procedimento efetuado). Nos casos em que foi necessária transferência hospitalar, foi registada a indicação/diagnóstico no momento da transferência. Nos doentes submetidos a cirurgia, foi feito o registo de morbimortalidade.

Definições

Relativamente ao contexto festivo, a participação do utente enquanto pastor refere-se aos profissionais responsáveis por manobrar a corda do touro controlando a sua mobilidade ao longo do arraial e enquanto capinha refere-se aos utentes que, nas touradas à corda, toureiam ou capeiam o animal. Foi feita esta distinção por representarem eventuais populações de risco para traumatismo tauromáquico pela proximidade que tem com animal durante estes eventos.

Em relação à causa do traumatismo, foi feita a colheita dos dados como causados por trauma direto com o animal, ou quedas aquando da fuga ou manuseio da corda. O mecanismo de lesão foi classificado com penetrante ou fechado.

A gravidade das lesões foi determinada pelo sistema anatómico *Injury Severity Score* (ISS), utilizando a escala *Abbreviated Injury Scale* (AIS)[11] para o seu cálculo. Trama *major* foi definido como ISS > 15.[12] Instabilidade hemodinâmica foi definida como tensão arterial sistólica (TAS) < 90 mmHg ou queda da TAS > 40 mmHg ou frequência cardíaca > 90 bpm ou alteração do estado de consciência.[13]

A morbimortalidade cirúrgica a 30 dias foi registada segundo a classificação de Clavien-Dindo.[14]

Tratamento dos dados

O estudo foi aprovado pela Comissão de Ética Hospitalar de acordo com a Declaração de Helsínquia. A colheita de dados foi feita pela equipa de internos de Cirurgia Geral, cirurgiões gerais e ortopedistas do HSEIT que observaram os doentes na admissão no SU.

Os dados foram colhidos para uma base de dados em formato Excel armazenada numa pasta da rede hospitalar, com acesso exclusivo aos intervenientes envolvidos na colheita de dados. Os dados registados não continham qualquer elemento identificativo do doente mantendo a confidencialidade e anonimato dos dados.

Análise estatística

A análise dos dados é descritiva e os cálculos foram realizados em SPSS. Os resultados referentes a variáveis quantitativas são apresentados como mediana e intervalo interquartil e os referentes a variáveis qualitativas são apresentados como frequências absolutas e relativas.

RESULTADOS

Em 2018 e 2019, 56 doentes foram admitidos no SU do HSEIT por traumatismos ocorridos em touradas à corda. Os dados demográficos gerais encontram-se sumarizados

na Tabela 1. A mediana de idades foi de 46 anos com intervalo interquartil de 30,25 anos, sendo 16,07% (9) dos doentes do sexo feminino.

Relativamente à causa do trauma, 66,07% (37) dos eventos ocorreram por trauma direto com animal enquanto os restantes 33,92% (19) resultaram de quedas aquando da fuga ou manuseio da corda. Ocorreu trauma fechado em 100% dos casos.

A Tabela 2 descreve as lesões ocorridas por área anatómica, somando-se 80 lesões nos 56 doentes observados

Tabela 1 – Dados demográficos gerais

Variável		N.º de doentes
Sexo		
(n = 56)	Feminino	9 (16,07%)
	Masculino	47 (83,93%)
Residência		
(n = 56)	Região Autónoma dos Açores	45 (80,36%)
	Portugal Continental e Região Autónoma da Madeira	2 (3,57%)
	País Estrangeiro	9 (16,07%)
Participação		
(n = 56)	Público-Geral	50 (89,28%)
	Pastor	3 (5,36%)
	Capinha	3 (5,36%)

Tabela 2 – Descrição das lesões por área anatómica. Em 'traumatismo *minor*' incluem-se dor ou lesões externas como pequenas lacerações, contusões, abrasões, hematomas ou queimaduras superficiais.

Área anatómica	N.º lesões na área anatómica	Diagnósticos	N.º
Cabeça e Pescoço	27 (33,75%)	Feridas e escoriações	19
		Traumatismo *minor*	6
		TCE associado a fratura	2
Tórax	16 (20,00%)	Feridas e escoriações	2
		Traumatismo *minor*	7
		Fratura de arcos costais	4
		Fratura da clavícula	3
Abdómen	2 (2,5%)	Feridas e escoriações	1
		Fratura esplénica	1
Coluna Vertebral	1 (1,25%)	Fratura de apófises transversas	1
Membro Superior	15 (18,75%)	Feridas e escoriações	4
		Traumatismo *minor*	2
		Luxação do ombro	1
		Fratura de troquiter	1
		Fratura do rádio	5
		Fratura de falanges	2
Membro inferior	19 (23,75%)	Feridas e escoriações	7
		Traumatismo *minor*	7
		Fratura do fémur	1
		Fratura da tíbia e perónio	2
		Fratura de metatarso	1
		Rotura de tendão de Aquiles	1
TOTAL:			80

TCE: traumatismo crânio encefálico

no SU. As áreas anatómicas mais afetadas foram, por ordem decrescente, a cabeça e pescoço (27; 33,75%), membros inferiores (19; 23,75%), tórax (16; 20%) e membros superiores (15; 18,75%). Vinte e dois doentes (39,28%) apresentaram lesões em mais do que uma área anatómica. Excluindo lesões externas e outros traumas das extremidades (lacerações, contusões, abrasões e queimaduras independentemente da localização na superfície corporal),[11] objetivou-se um predomínio de lesões do foro ortopédico – Tabela 2. Foram diagnosticadas 22 fraturas ósseas com predomínio de fraturas do rádio (5), fratura de arcos costais (4) e fratura da clavícula (3).

No que diz respeito à gravidade das lesões apresentadas, a mediana de ISS foi de 4 à admissão hospitalar e 10,5 nos doentes que necessitaram de internamento. Cinco doentes (8,92%) apresentaram trauma *major* (ISS > 15). Todos os traumas *major* resultaram de trauma direto com o animal e ocorreram em doentes do público geral. Oitenta por cento (4) dos traumas *major* ocorreram em doentes do sexo masculino. Dois doentes (3,6%) apresentaram instabilidade hemodinâmica à admissão no SU.

Em relação aos tratamentos realizados no SU: em 16 doentes foi realizado encerramento de feridas na sala de pequena cirurgia; em 12 doentes foi realizada desinfeção/desbridamento de feridas e outros cuidados de penso; 10 doentes realizaram terapêutica sintomática (inclui analgesia, fluidoterapia ou antieméticos); foram efetuadas 11 reduções de fraturas e/ou imobilizações na sala de trauma (cinco por fraturas do rádio e três por fratura de clavícula). Em apenas cinco (8,92%) doentes não foi realizado qualquer tratamento no SU. Seis doentes (10,71%) foram submetidos a intervenção cirúrgica urgente no bloco operatório (Tabela 3), sem registo de morbilidade e mortalidade pós-operatória.

Dez doentes (17,85%) necessitaram de internamento hospitalar com uma mediana de dias de internamento de sete dias (IIQ 4,5 dias). Quatro doentes foram internados no serviço de Cirurgia Geral, quatro no serviço de Ortopedia e Traumatologia e um no serviço de Neurologia. Um doente foi transferido para o serviço de Neurocirurgia de outro hospital local com diagnóstico de fratura complexa da calote craniana envolvendo buraco magno associada a hemorragia subaracnoídea, hematoma subdural e focos de contusão frontal e temporal. A lista dos motivos de internamento e tratamentos efetuados encontra-se descrita na Tabela 4. Três (30%) doentes necessitaram de internamento numa unidade de cuidados intensivos.

Não se registaram casos de mortalidade nos doentes admitidos e internados no HSEIT. Não existem dados relativamente aos tratamentos efetuados ou morbimortalidade do doente transferido para o serviço de Neurocirurgia do outro hospital local.

DISCUSSÃO

Em dois anos, ocorreram cerca de 460 touradas à corda na Região Autónoma dos Açores, tendo mais de 99% dos eventos ocorrido na ilha do hospital de estudo (ilha Terceira). Durante este período, registaram-se 56 admissões hospitalares cuja principal causa de traumatismo foi o trauma direto com o animal e o mecanismo de lesão foi o trauma fechado. As áreas anatómicas mais afetadas foram a cabeça e pescoço.

Ao atacar, o touro baixa a cabeça através da flexão do pescoço e, assim que alcança o alvo, estende o pescoço aplicando grande força no ponto de entrada dos cornos como consequência da grande massa e aceleração do animal.[2] À medida que o touro levanta o alvo do chão, faz um movimento circular com a cabeça, fazendo-o girar em torno do corno com todo o seu peso e causando dano tecidual extenso.[2] Por mecanismos relacionados com a altura da cabeça do animal e com a forma como ataca, a literatura descreve maior incidência de lesões penetrantes que ocorrem mais frequentemente nas coxas, virilha, períneo e abdómen.[2,3] No presente estudo, quer o mecanismo de lesão (trauma fechado) quer as áreas anatómicas mais afetadas (cabeça e pescoço) diferiram do descrito na literatura internacional. O facto de os animais terem os cornos protegidos nas touradas à corda pode constituir um dos motivos para o predomínio de traumatismos fechados que foi objetivado. Além disso, fatores relacionados com o contexto festivo, que ocorre nas ruas das freguesias locais com a participação da população geral, podem levar ao aumento do número de eventos relacionados as quedas que justifiquem as diferenças encontradas. Por último, é de realçar que este estudo não avaliou apenas lesões causadas por traumatismo com o corno do animal, pelo que era expectável

Tabela 3 – Intervenções cirúrgicas realizadas no bloco operatório, sob anestesia geral/sedação

Diagnóstico (n)	Procedimento	N.º de doentes
Fratura do baço (1)	Esplenectomia	1
Luxação do ombro (1)	Redução de luxações e/ou fraturas	4
Fratura da tíbia e perónio (2)		
Fratura do fémur (1)		
Rotura do tendão de Aquiles (1)	Tenorrafia	1
TOTAL:		6

Tabela 4 – Lista dos motivos de internamento e tratamentos efetuados

Enfermaria	Motivo de internamento	Tratamento efetuado	Internamento prévio UCI (em dias)	N.º dias internamento em enfermaria
Cirurgia Geral	Fratura de arcos costais	Terapêutica sintomática e vigilância	N/A	1
Cirurgia Geral	Fratura de arcos costais	Terapêutica sintomática e vigilância	N/A	10
Cirurgia Geral	Fratura de arcos costais complicada com pneumotórax	Drenagem torácica Terapêutica sintomática e vigilância	N/A	8
Cirurgia Geral	Fratura de arcos costais complicada com fratura do baço	Esplenectomia em BO Terapêutica sintomática e vigilância	1	5
Ortopedia e Traumatologia	Fratura do fémur	Redução em BO	N/A	6
Ortopedia e Traumatologia	Fratura da tíbia e perónio	Redução em BO	N/A	8
Ortopedia e Traumatologia	Fratura da tíbia e perónio	Redução em BO	N/A	5
Ortopedia e Traumatologia	Rotura do tendão de Aquiles	Tenorrafia em BO	N/A	1
Neurologia	Hemorragia subaracnoídea em fratura complexa da calote craniana	Terapêutica sintomática e vigilância	1	12
Neurocirurgia	Hemorragia subaracnoídea, pneumoencefalo, hematoma subdural, contusão cerebral e fratura complexa envolvendo o buraco magno	Sem dados*	Sem dados*	11

N/A: não aplicável; BO: bloco operatório.
* Os autores não tiveram acesso aos dados relativos ao tempo de internamento em UCI e tratamento efetuado ao doente transferido para o serviço de Neurocirurgia de outro hospital

um maior número de trauma contuso associado às quedas aquando da fuga do animal ou manuseio da corda.

Quanto à gravidade das lesões, apesar de se ter verificado um predomínio de traumatismos *minor* (mediana de ISS 4), o trauma *major* ocorreu em 8,92% dos doentes que recorreram ao SU. Foi colocada a hipótese de que os pastores e capinhas, pela maior proximidade que tem ao animal durante o controlo da corda e capeamento, pudessem constituir uma subpopulação de risco. No entanto, é de realçar que todos os traumas *major* ocorreram no público geral. Tendo em conta o elevado número de touradas à corda que ocorrem todos os anos e o facto de estes eventos fazerem parte das atrações turísticas da região, são necessários estudos com amostras superiores que permitam excluir ou confirmar esta relação e repensar a efetividade das medidas de segurança atualmente implementadas e alertas a dar à população.

Embora tenha demonstrado algumas limitações na predição de *outcomes* quando existem múltiplas fraturas nos membros inferiores ou em doentes com TCE,[15,16] o ISS constitui um bom indicador de gravidade.[17] Dos doentes hospitalizados, 40% apresentavam trauma *major* com uma mediana de ISS de 10.5 (IIQ 17.7). Mais ainda, dos doentes hospitalizados, 30% necessitaram de um período de internamento em unidades de Cuidados Intensivos (UCI) e 50% necessitaram de intervenção urgente no bloco operatório. Estes dados confirmam o enorme peso que estes doentes representam na utilização de recursos hospitalares, associada aos seus elevados custos. A acrescentar a estes custos e necessidade de disponibilidade de recursos, acrescem as evacuações aeromédicas realizadas para transporte dos doentes das ilhas de São Jorge e Graciosa para o HSEIT e do HSEIT para o outro hospital local, que não foram registados neste estudo, mas que representam limitações importantes relacionadas com a insularidade e que devem ser tidas em conta na abordagem destes doentes.

O hospital de estudo é o único que abrange as três ilhas da região autónoma dos Açores onde ocorrem a maior parte destes eventos. No entanto, os autores realçam as contingências relacionadas à insularidade que poderão estar a levar a uma subestimação do número de ocorrências relacionadas com estes eventos. Embora tenham sido registados incidentes de doentes das ilhas de São Jorge e Graciosa, coloca-se a hipótese de alguns incidentes *minor* terem sido tratados nas unidades básicas de urgência dos centros de saúde destas ilhas.

Este constitui, tanto quanto é do nosso conhecimento, o primeiro estudo descritivo das lesões traumáticas associadas a touradas à corda. Como tal, considera-se que este trabalho acrescenta valor ao conhecimento prévio e pode servir como ponto de partida para estudos futuros.

A amostra reduzida e o curto período de colheita de dados constituem limitações do presente estudo e impossibilitaram a significância estatística e consistência dos resultados apresentados, mas podem constituir um ponto de partida para a realização de outros estudos que pretendam caracterizar melhor estas lesões e suas correlações.

Para uma área de abrangência de cerca de 65 000 pessoas,[18] ocorreu uma tourada à corda para cada 283 habitantes. Dos 56 incidentes apresentados resultaram 80 lesões, 22 fraturas ósseas, 10 internamentos hospitalares, três internamentos em UCI e seis intervenções cirúrgicas em bloco operatório. Ao longo dos dois anos de estudo, por cada 100 touradas realizadas, resultaram 17 lesões traumáticas, 15 dias de internamento hospitalar em enfermaria, um internamento em UCI e 1,3 intervenções em bloco operatório. Embora estes dados devam ser interpretados com cautela devido à amostra pequena, constituem um alerta para o impacto destes eventos no que diz respeito aos custos económicos que acarretam, aos custos para a saúde da população local, às medidas de segurança atualmente implementadas e à disponibilidade dos meios necessários para tratar estes doentes.

CONCLUSÃO

A principal causa do traumatismo neste estudo foi o trauma direto com o animal. Verificou-se predomínio do trauma fechado e as áreas anatómicas mais afetadas foram a cabeça e pescoço. A taxa de internamento dos incidentes registados foi de cerca de 18% e taxa de traumatismo *major* foi de cerca de 8%. Cerca de 11% dos doentes foram submetidos a intervenção cirúrgica em bloco operatório.

CONTRIBUTO DOS AUTORES

BV: Desenho do estudo; redação do protocolo de estudo; colheita, análise e interpretação dos dados; redação do artigo e aprovação da versão final

VT, AV: Desenho de estudo; revisão do protocolo de estudo; colheita e interpretação de dados; revisão crítica do manuscrito

DS, DM, FP, JS, LM, LP, MV, OR, SV, RB, TO, AM: Desenho do estudo, colheita de dados e aprovação final manuscrito

ASo: Desenho do estudo; colheita, análise e interpretação de dados; revisão crítica do manuscrito

ASi, DG: Desenho do estudo, colheita de dados e revisão crítica do manuscrito

IB: Análise e interpretação dos dados e revisão crítica do manuscrito

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFIDENCIALIDADE DOS DADOS

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

CONFLITOS DE INTERESSE

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

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ACTA MÉDICA PORTUGUESA
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Circulating Blood B and T Lymphocytes and Severity of Acute Pancreatitis: A Systematic Review Protocol

Linfócitos B e T no Sangue Periférico e a Gravidade da Pancreatite Aguda: Protocolo de Revisão Sistemática

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ABSTRACT

Introduction: Acute pancreatitis is an acute inflammatory process of the pancreas with a high prevalence rate and varying degrees of severity that can be potentially life threatening. Much is still unknown about which mechanisms determine the course and severity of acute pancreatitis. The primary objective of this review is to identify the potential association between circulating B and T lymphocytes and the severity of acute pancreatitis. Subgroup analyses will be done according to the severity classification of the Revised Atlanta Classification System as well as according to the distinction between B lymphocytes and T lymphocytes and the severity of acute pancreatitis.

Methods: A systematic search will be performed in Medline, Web of Science, EMBASE, Cochrane Central Register of Controlled trials and ClinicalTrials.gov. Three authors will independently do the selection process as well as data extraction that will be recorded into a flow diagram following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P). The pathophysiology of acute pancreatitis is still not fully understood and its evolution is sometimes unpredictable. In this context, through this systematic review, the research team intends to determine what has been described about the role of serum lymphocytes in determining the severity of acute pancreatitis, by identifying a potential indicator of the severity of this acute disease.

Keywords: B-Lymphocytes; Pancreatitis; Systematic Review; T-Lymphocytes

RESUMO

Introdução: A pancreatite aguda é uma doença inflamatória do pâncreas de elevada prevalência que pode evoluir com vários graus de gravidade e ser fatal. Muitos dos mecanismos que determinam a evolução e gravidade da pancreatite aguda ainda são desconhecidos. O objetivo principal desta revisão é identificar a potencial associação entre os níveis no sangue periférico dos linfócitos T e B e a gravidade da pancreatite aguda. Proceder-se-á também à análise por subgrupos de gravidade de acordo com os níveis de gravidade definidos pelo *Revised Atlanta Classification System* bem como a sua distinção de linfócitos T e linfócitos B.

Métodos: Será feita uma revisão sistemática na Medline, Web of Science, EMBASE, Cochrane Central Register of Controlled Trials e ClinicalTrails.gov. Três revisores farão de forma independente a seleção dos estudos bem como a extração de dados que serão registados em diagrama proposto pelo *Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols* (PRISMA-P). A pancreatite aguda é uma patologia com fisiopatologia ainda não totalmente esclarecida e evolução por vezes imprevisível. Neste contexto, através desta revisão sistemática a equipa de investigação pretende determinar o que há descrito sobre o papel dos linfócitos séricos na determinação da gravidade da pancreatite aguda, identificando um potencial indicador de gravidade desta doença aguda.

Palavras-chave: Linfócitos B; Linfócitos T; Pancreatite; Revisão Sistemática

INTRODUCTION

Acute pancreatitis is an inflammatory disease of the pancreas with an unpredictable course. This is one of the reasons why it is a leading cause of hospitalization from gastrointestinal diseases in Europe and the United States.[1,2] Acute pancreatitis can lead to significant morbidity as well as pancreatic insufficiency and long-term illness.[3]

We now know that injured acinar cells of the pancreas release chemokines leading to infiltration of immune cells, mainly neutrophils, with worsening tissue injury of the pancreas and systemic inflammation later on.[4] Neutrophils activate trypsinogen in acinar cells. These cells amplify the inflammatory cascade, generating many chemokines and cytokines including interleukins 1 and 6 (IL-1 and IL-6), and intercellular adhesion molecule 1 (ICAM-1) to promote pancreatic and extra-pancreatic multiorgan injury.[5] Disease severity depends on whether the inflammatory response resolves or expands.[6]

Predicting the severity of this disease as well as knowing its critical mechanisms is essential to better monitor and develop future treatments for patients who need the most, reducing morbidity and mortality of patients with acute pancreatitis. Several risk prediction scores, individual biomarkers and radiological scoring systems have been developed to predict outcomes. The Revised Atlanta Classification System, from 2012, defining the clinical diagnosis, computed tomography (CT) manifestations, and the disease course of acute pancreatitis is the most widely used in clinical practice.[7] This classification, evaluating additional local or systemic complications as well as the presence and duration of organ failure, divides acute pancreatitis into mild

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acute, moderately severe acute, and severe acute pancreatitis. However, this classification is only made when acute pancreatitis is already evolving and frequently when some of its complications are well established.

Other frequently used scores in clinical practice include calculation of body mass index and the APACHE II score and serum C-reactive protein. A few scoring systems including clinical and laboratory criteria have also been devised like the Bedside Index of Severity in Acute Pancreatitis (BISAP), and Ranson's criteria.[8] However, most of these scoring systems require 24 hours to predict severity, and several parameters are not easily available on admission. Therefore, early prediction of acute severity is still needed.[9]

As mentioned, acute pancreatitis is a disease characterized by local and systemic inflammation and the severity of this disease is associated with the systemic inflammatory response syndrome (SIRS).[10] The activation of the innate immune system has been well described in acute pancreatitis and it is known that the cascade of inflammation follows including the activation of the adaptative immune system.[5] Compensatory anti-inflammatory responses occur, shown by increases in regulatory T cells in lymphoid tissue, although this may turn out to be responsible for dysregulation instead of balance restoration and persistent inflammation or immunosuppression may prevail.[3]

Several studies have tried to relate the severity of acute pancreatitis and the different components of the innate immune system including c-reactive protein, cytokines but also lymphocytes.[11-14] These studies include the determination of blood B and T cells during the first week of hospitalization of patients with acute pancreatitis. It is known B and T cells play critical roles in the pathogenesis and severity of acute pancreatitis although their exact role has not yet been elucidated.[15,18] The neutrophil-to-lymphocyte ratio has also been indicated as a possible early marker of acute pancreatitis severity[16] mainly because this parameter has been shown to have significant correlation with systemic inflammation reaction in some autoimmune diseases.[17] However, and because broad-spectrum antibiotics, which are essential medicines in the treatment of severe acute pancreatitis, can affect neutrophil count by reducing inflammation, the neutrophil-to-lymphocyte ratio must be used with caution in determining the severity of acute pancreatitis in some clinical settings.[18]

So, by simply collecting a blood sample and evaluating the lymphocyte count, clinicians might have a useful tool for predicting the severity of acute pancreatitis.

The main objective of this work is to systematically review and summarize the current knowledge on the potential association between circulating B lymphocytes and T lymphocytes and relate it to the severity of acute pancreatitis.

Secondary objectives will include the exploration of the blood levels of B lymphocytes and T lymphocytes separately with the severity of acute pancreatitis using the Revised Atlanta Classification System.[7]

Therefore, this systematic review will focus on the role of these cells in helping to determine the severity of acute pancreatitis.

METHODS AND ANALYSIS

The study protocol has been pre-registered on PROSPERO (registration number CRD42023383303).

Eligibility criteria

This study will identify randomized controlled trials (RCT), cohort studies (prospective or retrospective) and case control studies that relate blood B lymphocytes and T lymphocytes to the severity of acute pancreatitis. We will exclude cross-sectional studies, case series and case reports.

We will include articles reported in the English language.

Studies on the adult human population (18 years and older).

No restriction regarding publication will be set. Therefore, studies will be included from inception to January 31, 2022 (Table 1).

Intervention exposure

Inclusion criteria: Human adults, hospitalized with the diagnosis of acute pancreatitis with blood collection to determine lymphocyte levels.

The diagnosis of acute pancreatitis will require the presence of two of the following three criteria: acute onset of persistent, severe epigastric pain often radiating to the back; elevation in serum lipase or amylase to three times or greater than the upper limit of normal; and characteristic findings of acute pancreatitis on imaging (contrast-enhanced computed tomography, magnetic resonance imaging, or transabdominal ultrasonography).

The severity of acute pancreatitis will be defined according to the classification of severity applied by the Revised Atlanta Classification System (mild acute pancreatitis, moderately severe acute pancreatitis and severe acute pancreatitis) and/or the following scoring systems: systemic inflammatory response syndrome (SIRS) score (≤ 2: mild pancreatitis[19]), the Acute Physiology and Chronic Health Examination (APACHE) II score (determined in the first 24 hours of admission score < 8 mild pancreatitis; score > 8 severe pancreatitis[20]), the Bedside Index of Severity in Acute Pancreatitis score (determined in the first 24 hours of admission BISAP: ≥ 3 severe pancreatitis[21]), Ranson's criteria (0 - 3 points: mild pancreatitis; ≥ 3 points: severe pancreatitis[22]), and the Computed Tomography severity index (score ≥ 6: severe pancreatitis[23]).

Table 1 – PICOST criteria for the inclusion of studies into the systematic review and meta-analysis

Criteria	Description
Participants	Adult human population (> 18 years old)
Exposure	Hospitalized patients with acute pancreatitis
Comparator	Not applicable
Primary outcome	Relate the change in peripheral blood lymphocytes and the severity of acute pancreatitis
Secondary outcome	Relate severity scores of acute pancreatitis with B lymphocytes and T lymphocytes separately
Study Design	Randomized controlled trials (RCT), cohort studies (prospective or retrospective), cross-sectional studies and case control studies
Timing	From inception to January 31, 2022

Exclusion criteria: < 18 years old, non-human, non-hospitalized.

Information sources and search strategy

We will conduct a comprehensive computerized literature search strategy to find the studies to be included in this systematic review. Published and unpublished studies will be searched in the following databases: PubMed/Medline, Web of Science, EMBASE and Cochrane Central Register of Controlled trials. The electronic database search will be supplemented by searching other electronic platforms such as ClinicalTrials.gov for ongoing or unpublished clinical trials.

If any relevant unpublished trial is found, the respective author will be contacted to obtain the necessary information and if the author does not respond or is not willing to share the required information, the trial will be excluded.

The search will include the following key words and all their variants, according to each database and its special requirements: “acute pancreatitis”, “severity”,” lymphocyte”, “B cell”, “T cell”, “immune cell’. Boolean operators like ‘OR’ or ‘AND’ will also be used (Table 2).

The reference list of the included articles will be searched to find eligible studies.

Study selection and data extraction

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[24] will be followed in this systematic review.

Two reviewers will, independently and blind to each other, conduct the selection process. All records identified in the search stage will be screened by title/abstract and those not matching the criteria will be discarded. The remaining studies will be full-text reviewed and included or excluded according to the inclusion and exclusion criteria. If any disagreement arises between the reviewers, this will be solved by consensus or a third one if necessary.

The selection process as well as data extraction will be recorded into a flow diagram (Fig. 1).

Missing data will be requested from study authors. The excluded studies and the reasons for exclusion will be registered.

Data extraction will be done by two independent reviewers. Data extraction will include features of the study, patient characteristics, study methodology, times of measurement and outcomes. Discrepancies between the reviewers will be identified and solved by consensus or a third one if necessary.

Data management

Published studies will be imported to the Mendeley citation software where duplicates will be managed and discarded. Titles as well as abstracts of all records will be evaluated.

Risk of bias assessment

To minimize bias in the methodological quality of all studies included in this systematic review, the studies will

Table 2 – Search strategy for PubMed

Query	Search
1	“pancreatitis” (MeSH terms) OR “pancreatitis” OR “acute pancreatitis” (MeSH terms) OR “acute pancreatitis”
2	“severity” (MeSH terms) OR “severity” OR “severe” (MeSH terms) OR “severe”
3	“lymphocyte” (MeSH terms) OR “lymphocyte” OR “immune” (MeSH terms) OR “immune” OR “immune cell” (MeSH terms) OR “immune cell”
4	“T cell” (MeSH terms) OR “T cell” OR “CD4” (MeSH terms) OR “CD4” OR “CD8” (MeSH terms) OR “CD8”
5	“B cell” (MeSH terms) OR “B cell”
6	1 AND 2 AND 3 AND 4 AND 5

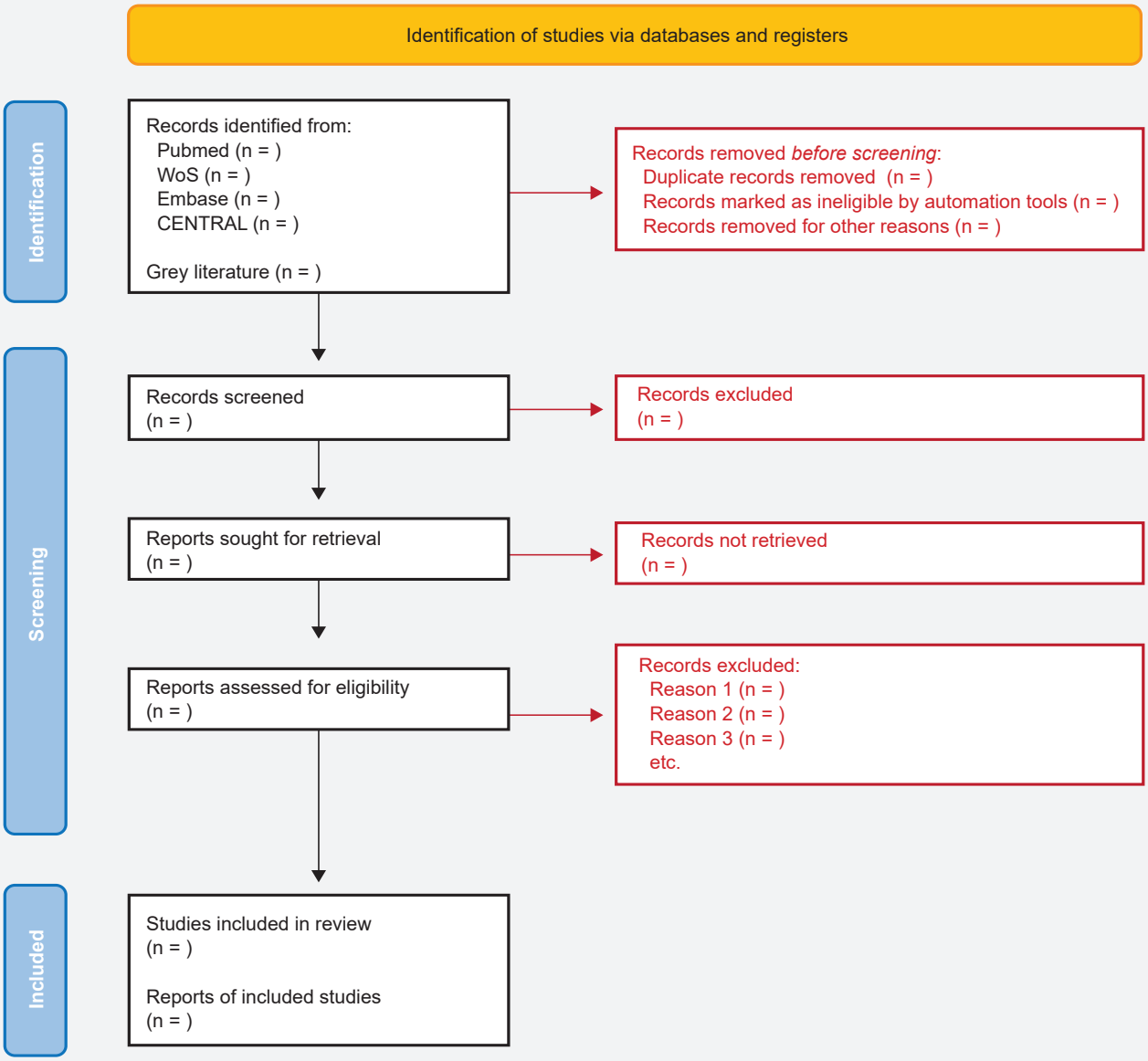

Figure 1 – PRISMA flow diagram of screening process

be categorized according to their quality by two independent reviewers (blind to each other) and disagreements will be solved by discussion or by a third reviewer. The Cochrane Collaboration Tool will be used for the assessment of bias of RCTs. For non-randomized trials the Newcastle-Ottawa Scale (NOS) will be used to assess quality. This is a reliable and valid tool to assess case-control and cohort studies.

Data synthesis

Data from eligible studies will be systematically presented. It will be of interest in this review: patient characteristics, time of blood collection for lymphocyte levels in hospitalized patients with acute pancreatitis (first 24 hours of hospitalization, 48 hours, 72 hours and during the first week), patient outcomes and determination of the severity of acute pancreatitis. The GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) will be used to assess the certainty of the evidence.

Due to the expected heterogeneity of the populations included in the studies, as well as heterogeneity in the timepoints chosen for blood collection and for the different scores of severity, we do not intend to perform a meta-analysis of the collected data. Therefore, the results of the

review will be reported in a table and a narrative synthesis of the findings will be provided with the previously mentioned data.

The three reviewers that will be involved in the selection process, methodological evaluation of the studies and data extraction and synthesis will be the same during the entire process of the systematic review/meta-analysis.

DISCUSSION

Acute pancreatitis is an acute inflammatory process of the pancreas that has a high prevalence rate and varying degrees of severity that can be potentially life threatening. Although there have been significant advances in the understanding of the pathophysiology of acute pancreatitis, much is still unknown about which mechanisms determine its course and severity.[25]

As previously mentioned, The Revised Atlanta Classification of acute pancreatitis is the most widely accepted classification of the severity of acute pancreatitis. Around 70% of patients have mild acute pancreatitis with an uncomplicated course and early discharge from hospital but around 20% - 25% have a moderately severe acute pancreatitis with prolonged hospitalization and around 10% develop severe acute pancreatitis with a significant risk of morbidity and death.[7]

Simpler tools, including risk prediction scores, and preferably easily obtainable biomarkers to predict the severity early in the course of acute pancreatitis are needed. Predicting the severity of this disease as well as knowing its critical mechanisms is essential to better monitor and develop future treatments for patients who need them the most, which may help reduce morbidity and mortality.

The determination of blood lymphocytes, particularly of T cells, has been pointed out as a simple way of determining its severity early in the course of acute pancreatitis and as a future target for the treatment of acute pancreatitis.[26,27] Peripheral blood lymphocyte depletion in acute pancreatitis may result from both excessive apoptosis and migration to the site of inflammation.[28]

Clinical trials have already been conducted such as high-volume hemofiltration treatment in patients with severe acute pancreatitis aimed at ameliorating immune function by removing inflammatory mediators such as TGF-beta1, IL-10, IL-6, and IL-17 and by doing so reducing the imbalance between two groups of T cells, the Th17 and T regulatory cells.[29]

Other clinical trials have included corticosteroids because there is a significant inflammatory response. However, because of patient heterogeneity, the lack of immunological outcomes and the fact that definitions of the severity of acute pancreatitis and treatment protocols are still variable, the findings from these studies are largely exploratory.[30]

Therefore, a better understanding of the role of the cells of the adaptative immune system in this disease might have a huge impact on the outcomes and future treatments of patients with acute pancreatitis not only by trying to increase their number in peripheral blood but also by improving the function of some of the subpopulations of B cells and T cells that are recruited to the inflamed pancreas which most likely are responsible for the production of cytokines and interferons and consequently for the perpetuation of local and systemic inflammation.

To our knowledge, no systematic review outlining the current understanding of blood lymphocytes and severity of acute pancreatitis has been attempted, making our study the first to do so. We expect high heterogeneity between studies concerning the classification of the severity of acute pancreatitis as there is no consensus on which score, or biomarker, is best in predicting acute pancreatitis severity. This is what we believe to be the main limitation of this review.

This report describes the systematic review protocol that will be used to determine the association between peripheral blood B and T lymphocytes and the severity of acute pancreatitis. The results of this study may help to understand the pathophysiology of acute pancreatitis and the role of blood lymphocytes in this disease as well as to identify a new easily applicable and accessible biomarker predictive of the severity of acute pancreatitis.

AUTHOR CONTRIBUTIONS

FM: Study conception and design, drafting of the manuscript.

MN, LMB: Study conception and approval of the final version of the manuscript.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Kaplan-Meier Survival Analysis: Practical Insights for Clinicians

Análise de Sobrevida de Kaplan-Meier: Fundamentos Práticos para Clínicos

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ABSTRACT

This article aims to provide a guide that will help healthcare professionals and clinical researchers from all fields that deal with Kaplan-Meier curves. Survival analysis methods are among the most frequently used in the medical sciences and in clinical research. Overall survival, progression free survival, time to recurrence, or any other clinically relevant parameter represented by a Kaplan-Meier curve will be discussed. We will present a practical and straightforward interpretation of these curves, setting aside intricate mathematical considerations. Our focus will be on essential concepts that interface with biological sciences and medicine in order to guarantee proficiency in one of the most popular yet frequently misunderstood methods in clinical research. Being familiar with these concepts is not only essential for designing new clinical studies but also for critically assessing and interpreting published data.
Keywords: Kaplan-Meier Estimate; Survival Analysis

RESUMO

Este artigo tem como objetivo funcionar como um guia que ajudará profissionais de saúde e investigadores clínicos de todas as áreas que lidam com curvas de sobrevida. Os métodos de análise de sobrevida estão entre os mais usados nas ciências médicas e na investigação clínica. Serão discutidos os conceitos de sobrevida global, sobrevida livre de progressão, tempo de recidiva e todos os parâmetros de interesse clínico que possam ser representados por curvas de Kaplan-Meier, com uma interpretação prática e direta dessas curvas. Deixaremos de lado todas as considerações no campo da matemática. Referiremos apenas conceitos essenciais que interagem com as ciências biológicas e a medicina, de forma a garantir a proficiência de um dos métodos mais populares e frequentemente incompreendidos na investigação clínica. Estar familiarizado com esses conceitos é essencial não apenas para projetar novos estudos clínicos, mas também para avaliar e interpretar estudos publicados de forma crítica.
Palavras-chave: Análise de Sobrevivência; Estimativa de Kaplan-Meier

INTRODUCTION

Survival analysis provides an essential tool for understanding results in clinical research. It is of the utmost importance to know how to interpret these methods, as well as to be aware of alternatives and their limitations.

This paper was specifically designed to elucidate the basic principles of the analysis, interpretation, design, and execution of the most widespread and standard method in survival analysis, according to the typical needs arising in clinical practice. It does not explain alternative and more accurate methods adapted to specific scenarios. Also, it does not address multivariable regression analysis.

The core of survival analysis is time and how the factors under study may affect the time until the event, rather than the event itself. Although the term 'survival' intuitively makes us think of the event as death, it may be any other outcome. A straightforward example is given by José de la Mata *et al*[1] when they analyzed the time to "treatment termination because of toxicity and lack of response"; Zhang *et al*, while studying the association of levels of metalloproteinase-7 and the risk of renal survival and fibrosis, defined one of the endpoints as the time between the diagnosis of nephropathy and the event which was defined as a 50% decline in glomerular filtration rate[2]; Conden *et al* studied the influence of type D personality and the time to the event of recurrent myocardial infarction.[3]

Kaplan-Meier curves

Kaplan-Meier (KM) curves are the most traditional method to show survival data. Its success is due to the amount of information that can be obtained from one single chart. Fig. 1 depicts an example of a KM curve. The horizontal x-line measures time, while the vertical y-axis refers to the survival rate. Using this figure as an example, in the beginning, 100% of the study sample did not experience the event. The first step-down means that the first event occurred at four months. Each step-down represents one or more events. The line immediately after the step-down represents the proportion of patients who did not experience the event after that time. In contrast, the line immediately before the step-down represents the proportion of patients who did not experience the event until that time. The vertical difference between both lines represents the number of events that

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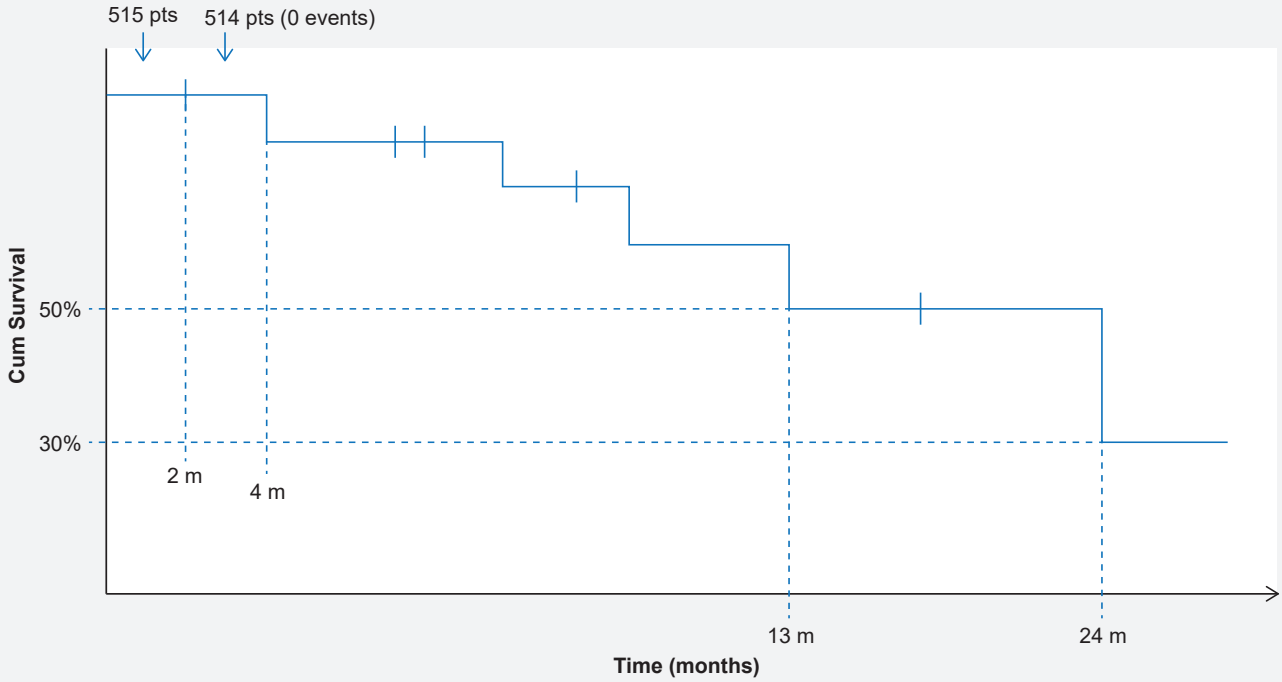

Figura 1 – Example of a Kaplan-Meier curve

occurred at that time point. The vertical step-down is as high as the number of events. However, the number of right-censored patients up to that time-point (the number of patients who were lost to follow-up without experiencing an event in the last time interval) will also increase the step-down.

In survival analysis, we usually refer to the median survival time (and not the average time): a median survival time of 13 months means that at 13 months after treatment (or any other variable), 50% of all subjects have experienced the event.

In Fig. 1, survival at two years is 30%. Two-year survival, five-year survival, or survival at any specific time point corresponds to the proportion of patients who, after two years, five years, or X years of follow-up, have not experienced the event. This is computed by dividing the number of patients who did not experience the event after the analyzed time by the number of patients included.

The vertical lines (|) in the figure indicate censoring, i.e., at any given time, a patient leaves the study without experiencing an event. In other words, censoring represents patients who exit the study, either due to being lost to follow-up or reaching the end of the study time period without having experienced the event under investigation. Censoring in a study occurs when there is incomplete information regarding the event in a given participant. Right censoring happens specifically when a subject leaves the study before experiencing the event. In such cases, we do not know whether the patient experienced the event or when the event occurred. However, we do know that during the period in which a given patient was included, no event occurred. That incomplete information is of utmost importance for the study. This is the case of lost-to-follow-up (or when the study time ends without any event occurring) and is referred to as type I right censoring. On the other hand, type II right censoring refers to studies that ended when a predefined number of individuals have experienced the event.

Left censoring is observed when the subject is already at risk for the event being studied before the study initiation, a scenario that is unusual in most clinical studies.

Interval censoring, on the other hand, occurs when there is no information regarding the occurrence of the event for a given patient during a specific time period of the study. This situation is also not commonly observed in 'standard' clinical studies.[4]

After censoring, the proportion of patients with no event is lower (censored subjects leave the study), although the number of events is the same.

Still in Fig. 1, 515 patients were included and reached two months with no event. However, only 514 patients remained after two months without an event. The patient represented by the vertical line was a 'dropout' at that time, but no event had occurred.

Comparing different groups and different outcomes with Kaplan-Meier curves

Lee EC *et al* studied the time until death for all causes and the time until recurrence.[5] The authors could draw a KM curve regarding time to recurrence according to T-stage, N-stage, gender, and other variables. However, no information could be collected regarding the influence of all variables together since KM is not a multivariable analysis.

Each variable must be a categorical/ordinal variable: it is possible to compare T1 *vs* T2 *vs* T3; N0 *vs* N+; male *vs* female. However, it is not possible to study continuous variables such as age, unless the continuous variable can be grouped in classes.

Figure 2A shows KM curves, which can be read as time to event according to a given variable, where the variable is represented as group 1 and 2. Immediately, the reader assumes that group 1 has a better prognosis with a time to event lower than group 2 and, consequently, a higher survival at any given time point. However, to infer population results based on data from a sample (statistical inference), a hypothesis test has to be performed. The hypothesis test will determine if the result is statistically significant.

This may be a misinterpretation because to know if that difference is statistically significant, a statistical test must be performed. The most widely used test is the log-rank test, although there are others for specific situations. The log-rank test compares the difference between the real-life observed curves with a hypothetic expected curve where all the events would be equally distributed between groups. The larger the difference between the observed and expected curves, the higher the likelihood of the different curves being statistically different. The log-rank test is the most powerful rank test when considering the proportional hazard model.

This model assumes that the effect of exposure on the hazard rate remains constant over time. In simpler terms, it implies that the risk of death, recurrence, or any other event remains the same after one week of the treatment (or other intervention) or after one year. This is the opposite of accelerated models, where the risk of an event is higher or lower over time. For instance, in accelerated models, the risk of death or cancer after one week of quitting smoking is higher than the risk of death or cancer after two years. Whenever the hazard rate remains constant over time, it is called a proportional hazards model, and the log-rank test is the appropriate statistical method.

The Gehan-Breslow (Wilcoxon) test assigns more weight to early time events, making it particularly useful when studying early differences in two or more survival curves (Fig. 2A). While the log-rank test provides an outline between observed survival times in both groups and how they deviate from the expected values, the Gehan-Breslow-Wilcoxon test is based on the number of participants at risk in both groups at a given time. That is why it assigns greater

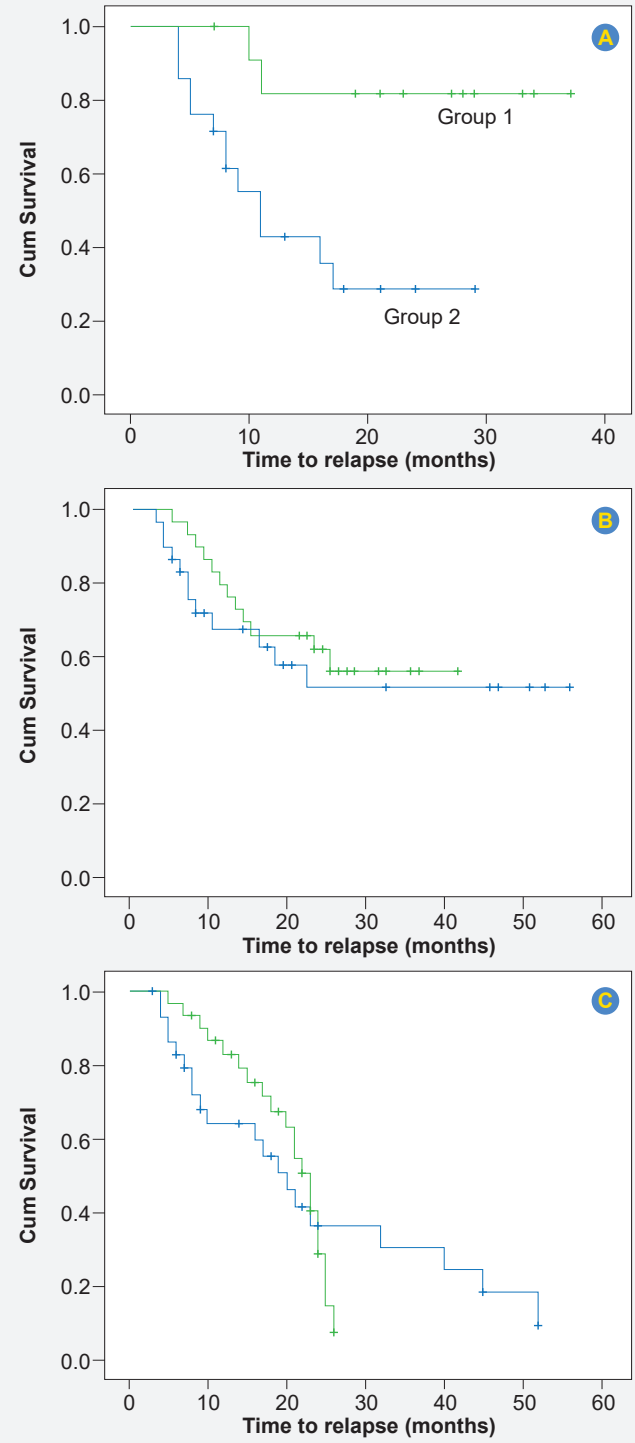

Figura 2 – Examples of a Kaplan-Meier curves comparing two groups of patients/subjects

weight to early differences. For example, it is often applied in certain types of cancer studies where death or recurrence tends to occur within the first or second years, even when patients are followed up to 10 or more years. However, this test is more sensitive to early censoring.

When two or more survival curves cross each other (Fig. 2B), it indicates a change in the hazard rate over time, implying non-proportional hazards. In such cases, Tarone-Ware, Peto-Peto, and Fleming-Harrington family tests may be performed. However, addressing these cases poses statistical challenges, and there is no correct answer regarding the most powerful test to apply. Most widely available software packages offer a variety of tests specifically tailored to each of these situations.

In clinical research, a 95% confidence level is usually the standard. This means there is a 95% probability that the 'true' value of the population falls within that range. If we were to repeat the experiment 100 times under the same conditions, in approximately 95 of those instances, the true value of the population would fall within the assumed confidence interval. It is important to note that the width of the confidence interval decreases as the sample size increases; it is inversely proportional to the square root of the sample size).[6]

Verifying Kaplan-Meier assumptions

Statistical models aim to represent reality and to make predictions as accurately as possible. To do so, statistical models need to rely on certain principles (assumptions). By violating the assumptions, we are withdrawing predictive acuity from these models. To obtain valid conclusions from these graphs, it is necessary to keep in mind the following principles:

1 – Independent samples: groups are based on random selection (the selection of one patient does not influence another patient's selection);
2 – Censoring is independent of the outcome and independent of the study group – the chance of a subject 'drop out' before the event should be the same in each group;
3 – If a subject is included today, the probability of having the event in the next year must be the same for a subject that will be included in the following months;
4 – An event can occur at any given time. However, in clinical sciences, most of the time we can only know that the event occurred between two time points. For example, a KM curve from a sample where patients are followed-up through 18 months with scheduled visits every six months has much less information than the same sample followed-up through 56 months with scheduled visits every three months.

The previously mentioned assumptions are intimately associated with methodology, data collection, and database design and not so much with statistical issues. Even though most of the times it is impossible to absolutely verify all the assumptions, the way we measure their impact on our results is very important for external validity and reproducibility of an experiment.

How to collect data to compute KM curves

It is somewhat intuitive to compute survival analysis statistics and KM curves with most of the available statistical packages. However, this relies on data collection and database design.

For each patient/subject it is necessary to clearly state:

1 – Follow-up period (when a patient enters the study and when the patient leaves the study);
2 – The reason for the patient leaving the study (whether it is due to an event or censoring).

How to present descriptive data in survival analysis

a) Study time follow-up;
b) Median follow-up time (FUP) for the whole sample and for study groups: typically used to ascertain how long the subjects were under study. This concept is relevant since in survival analysis each patient may enter and leave the study at different times. A median FUP time of 52 weeks means that 50% of the patients/subjects were studied for at least (or for no more than) 52 weeks;
c) Sample size for the whole sample and for study groups;
d) Number and proportion of events in a given time for the whole sample and for each group. This is usually expressed as two-year survival, five-year survival, etc.;
e) Median survival time (explained above).

This is the minimum standard set of descriptive data needed to present or read a study with survival analysis. As an example, we selected the work of Ryu *et al*[6]: the authors explain that 34 patients were treated for gastric cancer liver metastasis with three different techniques (n = 14, n = 13 and n = 7). They clearly show the median FUP time: 29.4 months (ranging between 2.2 and 170.4 months) and the one-year, three-year and five-year overall survival (84.4%, 38.6%, and 34.7% respectively). Also, censored patients are clearly presented with a dot in the KM curves (Fig. 3).

Most frequently used concepts in survival analysis

Overall survival

Overall survival (OS) measures the time between the diagnosis or treatment initiation of a disease (or other factor clearly defined as the beginning of the study period) and death (or other event) for all causes.

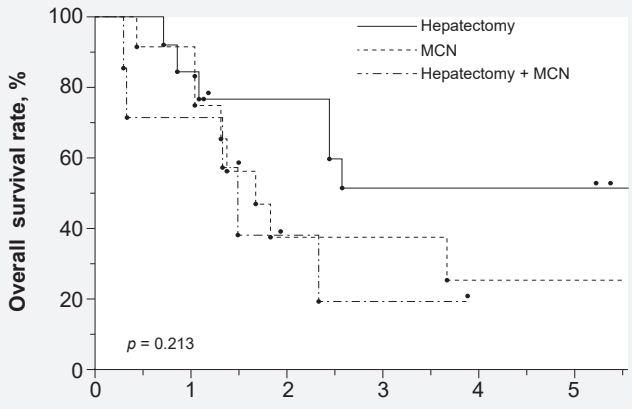

Figura 3 – Kaplan-Meier analysis of overall survival. Three groups, representing three different approaches to liver metastasis from gastric cancer are compared with long-rank statistic. Dots represent censured patients. Reproduced with permission from Tomoki Ryu.[7]

Progression free survival/recurrence free survival/ disease free survival/time to recurrence

Progression free survival (PFS) / Recurrence free survival (RFS)/ Time to recurrence (TTR) and disease-free survival (DFS) represent similar concepts, although arriving at a clear definition is challenging and not consensual.

The primary aim of these measures is to study the time interval between the diagnosis (or treatment) and diagnosis of recurrence. However, it is worth noting that some authors consider death as an event, while others consider it as right-censoring (similar to a loss to follow-up). Furthermore, determining whether recurrence was the cause of death or not can often be a complex task, introducing potential biases into the results.

Given the lack of a universally accepted definition, we strongly recommend that research methods clearly state whether death is considered an event or not, and how the cause of death is determined.

Providing this information allows readers to better understand the limitations and the direction and magnitude of potential associated biases.[8,9] Progression free survival is more frequently used than TTR and is more 'unfavorable' to the drug being studied: if a patient does not have a recurrence and dies, we assume that the patient dies because of the disease. In TTR, if the same patient dies, it would not be considered for the number of events (it would be censored), even if the death is most likely to be due to recurrence.

In Fig. 3 both patients would be included to assess OS (patient 1 at point B); both patients would be included to assess PFS (patient 1 at point A); and only patient 1 at point A would be included to assess TTR (patient 2 would be censored at time of death).

Hazard ratio

The hazard ratio (HR) refers to the ratio between the proportion of patients with the event with the condition/treatment under study and the proportion of patients with the event in the reference condition for a given period.

As an example, HR = 2 for lymph node metastasis (N1) to recurrence. This means that, for any given interval of time, the probability of having recurrence is twice as high for the N1 patients compared to N0 patients.

HR = (N1 with recurrence/N1 with no recurrence)/(N0 with recurrence/N0 with no recurrence) = 2.

Another example of the application of this concept is illustrated by Zhang *et al*: "Follow-up analyses revealed that increased serum MMP-7 levels were linked with a greater risk of poor renal outcome with a hazard ratio of 1.898 per doubling MMP-7 concentration".[2] Here, the reader would conclude that the proportion of patients with poor renal outcome is 1.898 times the proportion of patients with poor renal outcome with half of the MMP-7 concentration.

CONCLUSION

Clinicians should understand statistics well enough to conduct and evaluate studies which provide evidence-based data for clinical practice. Being familiar with these concepts is essential to critically assess and interpret published data.

This is an approach specifically designed to elucidate the basic principles in the analysis, interpretation, design, and execution of the most widespread and standard method in survival analysis, according to the typical needs of clinical practice. It does not explain alternative and more accurate methods adapted to specific scenarios. Also, it does not address multivariable regression analysis.

AUTHOR CONTRIBUTIONS

APG, RM: Literature review, writing of the manuscript.
BC: Writing and critical review of the manuscript.
VN, CC: Critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Linfocitose Policlonal Persistente de Células B (LPPB): Uma Entidade que Não É o que Parece

Persistent Polyclonal B-Cell Lymphocytosis (PPBL): An Entity That Is Not What it Seems

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RESUMO

A linfocitose policlonal persistente de células B é uma doença rara, caracterizada por linfocitose crónica policlonal, que ocorre mais frequentemente em mulheres fumadoras de meia-idade, que se apresentam assintomáticas ou com sintomas inespecíficos. A presença de linfócitos B binucleados é considerada a assinatura citomorfológica desta entidade. A imunofenotipagem comprova a sua origem policlonal, observando-se muitas vezes uma elevação da IgM sérica. É controverso se existe um risco aumentado de desenvolvimento de linfoma. A predisposição genética é também um fator de risco, além do tabagismo. Apesar da sua natureza policlonal, alterações genéticas recorrentes estão descritas. Na linfocitose policlonal persistente de células B a abordagem terapêutica consiste habitualmente numa vigilância regular, o que reforça a importância do seu reconhecimento. Os autores descrevem o caso de uma mulher de 46 anos, fumadora, com linfocitose crónica, IgM elevada e linfócitos binucleados. O diagnóstico diferencial com linfoma assumiu particular importância, considerando os sintomas constitucionais e esplenomegalia que apresentava.
Palavras-chave: Linfócitos B; Linfocitose; Linfocitose de Células B Policlonal Persistente

ABSTRACT

Persistent polyclonal B-cell lymphocytosis is a rare disease with chronic lymphocytosis of polyclonal origin, which is more frequent in mostly asymptomatic middle-aged female smokers. The hallmark of this entity is the presence of bilobed/binucleated B lymphocytes, which are polyclonal as demonstrated by immunophenotyping; an elevated IgM level is common. This disease shows, in most cases, an indolent course over many years and, although controversial, it may rarely convert to malignant lymphoma. In addition to smoking, a genetic predisposition for persistent polyclonal B-cell lymphocytosis is likely. Recurrent genetic aberrations have been described. The differential diagnosis includes non-Hodgkin's lymphoma and a clear distinction between both entities is of the utmost importance because treatment is generally not indicated in the former: instead, regular follow-up is recommended. The authors describe the case of a 46-year-old female smoker, who presented with chronic lymphocytosis, elevated IgM and circulating binucleated lymphocytes. Excluding lymphoma was important considering the unusual presentation with constitutional symptoms and splenomegaly.
Keywords: B-Lymphocytes; Lymphocytosis; Persistent Polyclonal B-Cell Lymphocytosis

INTRODUÇÃO

A linfocitose policlonal persistente de células B (LPPB) é uma entidade rara, inicialmente descrita em 1982,[1] que ocorre principalmente em mulheres fumadoras[2] e que se caracteriza por uma linfocitose policlonal com presença de linfócitos binucleados ou com núcleo bilobado em circulação, e por um aumento policlonal da IgM. A maioria dos doentes é assintomática, mas estão descritos casos associados a astenia significativa, a esplenomegalia, ou excecionalmente, hepatomegalia e/ou adenopatias.[3]

A linfocitose é habitualmente estável e persistente, embora o diagnóstico possa ser realizado em doentes sem linfocitose absoluta, se as características citomorfológicas associadas à apresentação clínica forem sugestivas. A particularidade dos linfócitos anormais serem tipicamente binucleados ou com núcleo bilobado é um dado fortemente sugestivo, e considerado como a assinatura citomorfológica desta entidade.

Existe frequentemente uma elevação policlonal da IgM sérica, sendo a imunofenotipagem importante na exclusão de uma neoplasia linfoproliferativa de células maduras. As células anormais parecem representar uma expansão de células B de memória, expressando IgM e IgD, conjuntamente com marcadores pan-B, sem restrição de cadeias kappa/lambda.

Existe ainda uma associação HLA em 90% dos casos (HLA-DR7),[4] com casos familiares descritos e sendo conhecida uma associação com instabilidade cromossómica e anomalias cromossómicas adquiridas, em particular do cromossoma 3.[5] Sabe-se que a evolução da LPPB é benigna em aproximadamente 90% dos casos.[3] Apesar de rara, a progressão e a emergência de uma subpopulação clonal predominante é possível, motivo pelo qual está recomendada uma vigilância a longo prazo.

CASO CLÍNICO

Doente do sexo feminino, de 46 anos, fumadora (30

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unidades maço/ano), referenciada à consulta de hematologia por linfocitose e cansaço. Referia sintomas constitucionais com dois anos de evolução, nomeadamente perda ponderal de 7 kg e astenia. Ao exame objetivo apresentava esplenomegalia, palpável 4 cm abaixo do arco costal esquerdo, sem outras alterações, nomeadamente adenopatias periféricas. Analiticamente, apresentava leucocitose e linfocitose de 10,4 x 10^9/L (vr 1,00 – 4,00 x 10^9/L), sem citopenias, LDH normal e elevação da IgM (812 mg/dL, vr 45 - 150 mg/dL); foram excluídas infeções a EBV, CMV e parvovírus B19 através da carga viral. Na morfologia do sangue periférico observavam-se linfócitos de tamanho médio com citoplasma moderadamente basófilo, binucleados ou com núcleo bilobado, por vezes com nucléolo visível (Fig. 1).

A imunofenotipagem do sangue periférico por citometria de fluxo mostrou uma expansão policlonal de células B maduras (relação kappa/lambda equilibrada). A biópsia de medula óssea revelou uma hiperplasia reativa do tecido hematopoiético e um infiltrado intra-sinusoidal de linfócitos B expressando CD20, IgD heterogéneo e negativos para CD11c e CD123. Estas células não apresentavam restrição na expressão das cadeias leves de imunoglobulina. A análise citogenética da medula óssea revelou um cariótipo normal. A conjugação destes dados, sobretudo as características citomorfológicas dos linfócitos em circulação, era compatível com o diagnóstico de linfocitose policlonal persistente de células B.

A doente encontra-se atualmente em vigilância na consulta de hematologia, sem intercorrências, com estabilidade do ponto de vista da linfocitose e com indicação para cessação tabágica.

DISCUSSÃO

A LPPB é uma entidade subdiagnosticada tendo em conta a sua evolução clínica indolente e benigna e, por vezes, a ausência de linfocitose absoluta. A maior casuística publicada até agora (Cornet *et al,* 2008)[3] descreve as características de 111 destes doentes e inclui 82% de mulheres, com 98% de fumadores. Para além do tabagismo, sabe-se que a infeção crónica a EBV (vírus Epstein-Barr) e a predisposição genética[6] são também fatores de risco para LPPB.

O caso descrito é pouco habitual pela repercussão importante no estado geral, com astenia associada a esplenomegalia, o que sublinha a importância do diagnóstico diferencial com os linfomas não-Hodgkin (LNH). Na referida série de doentes, apenas 2,7% desenvolveu um LNH (dois casos de linfoma B difuso de grandes células e um caso de linfoma da zona marginal) e adicionalmente quatro doentes foram diagnosticados com gamapatia monoclonal de significado indeterminado do tipo IgM. A grande maioria dos doentes (89%) teve uma evolução favorável, com um tempo médio de *follow-up* de 4,4 anos. No caso descrito foi possível chegar ao diagnóstico através da integração dos dados clínicos e laboratoriais, fundamentalmente o reconhecimento da citomorfologia muito específica desta entidade, permitindo orientar a marcha diagnóstica.

A medula óssea destes doentes demonstra por vezes uma distribuição intra-sinusoidal dos linfócitos B,[7] semelhante ao envolvimento por linfoma esplénico da zona marginal, mas estando ausentes os nódulos com centro germinativo e o padrão característico de zona marginal. Podem estar ainda presentes focos de células B ativadas, que são o elemento diferenciador de outros linfomas de células B pequenas. Adicionalmente, a dificuldade no diagnóstico diferencial com doença linfoproliferativa maligna pode aumentar porque a LPPB se associa frequentemente a anomalias cromossómicas e rearranjos múltiplos dos genes *BCL2/IGH*, tal como se observa em alguns LNH,[8,9] embora aqui o infiltrado de células B tenha um padrão de marcação de BCL2 intracitoplasmático e heterogéneo, ao contrário dos linfomas de células B pequenas.[6]

Não existe um tratamento padrão, mas a cessação tabágica e esplenectomia estão descritas como sendo eficazes na abordagem terapêutica em alguns destes doentes. Nos poucos casos descritos na literatura[10,11] com referência

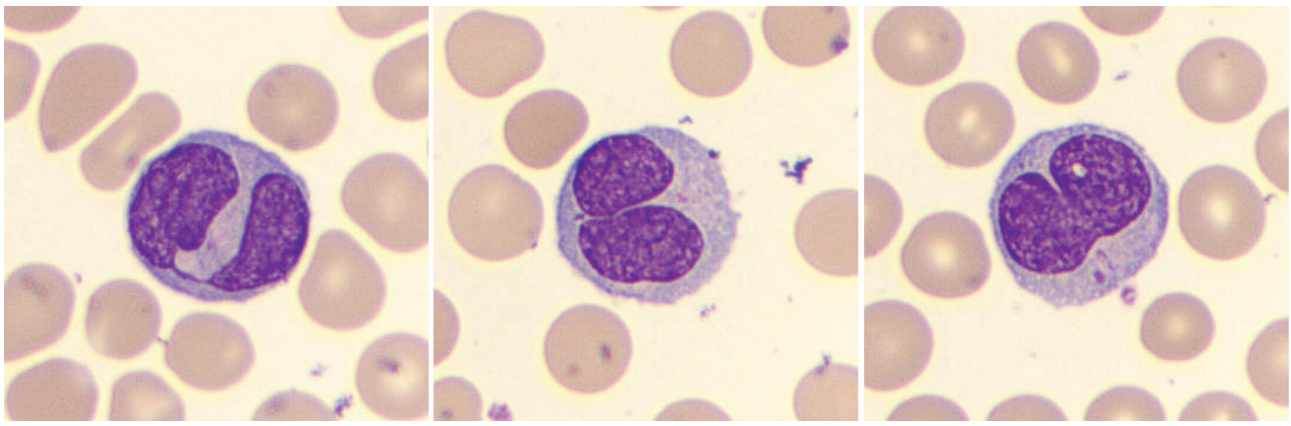

Figura 1 – Linfócitos bilobados/binucleados, característicos da LPPB. Coloração de May-Grunwald-Giemsa (10 x 100).

à citomorfologia e imunohistoquímica esplénicas, importa salientar que podem mimetizar o envolvimento por um linfoma de células B, sendo aqui fundamental a correlação com a citomorfologia do sangue periférico, estudos de clonalidade das células B por citometria de fluxo e o estudo de rearranjos dos genes das imunoglobulinas.

CONCLUSÃO

A LPPB é uma entidade rara, cuja possibilidade deve ser considerada na presença de linfócitos binucleados/bilobados no sangue periférico, o que permite orientar desde o início a marcha diagnóstica para excluir uma neoplasia de células linfóides maduras e a confirmação da LPPB.

Permanece por esclarecer se os doentes afetados têm um risco aumentado de desenvolver uma doença hemato-oncológica, nomeadamente uma neoplasia de células B maduras, a longo-médio prazo, pelo que a LPPB requer monitorização obrigatória. O curso clínico benigno desta entidade e a ausência de evolução para doença neoplásica na maioria dos casos salientam a necessidade do seu reconhecimento e diagnóstico correto desde o início, evitando-se assim um tratamento agressivo inútil e prejudicial para o doente.

CONTRIBUTO DOS AUTORES

AF: Redação do manuscrito.

ACF, DP: Revisão crítica, aprovação da versão final.

CS, MC: Revisão da literatura, revisão crítica e aprovação da versão final.

RB: Supervisão de todas as etapas da produção do manuscrito, análise de dados, revisão crítica, aprovação da versão final.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFIDENCIALIDADE DOS DADOS

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

CONSENTIMENTO DO DOENTE

Obtido.

CONFLITOS DE INTERESSE

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

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Mediastinal Enlargement in an 8-Year-Old Child: What Could Be Causing It?

Alargamento do Mediastino numa Criança de 8 Anos: Quais as Possíveis Causas?

Inês Isabel AIRES MARTINS✉[1], Bárbara COSTA CORREIA[2], Sofia Alexandra MORAIS PIMENTA[2], Ana Clara GOMES GRACIO DOS REIS[2]
Acta Med Port 2024 Apr;37(4):289-290 ▪ https://doi.org/10.20344/amp.20727

Keywords: Child; Mediastinal Cyst/diagnostic imaging
Palavras-chave: Criança; Quisto do Mediastino/diagnóstico por imagem

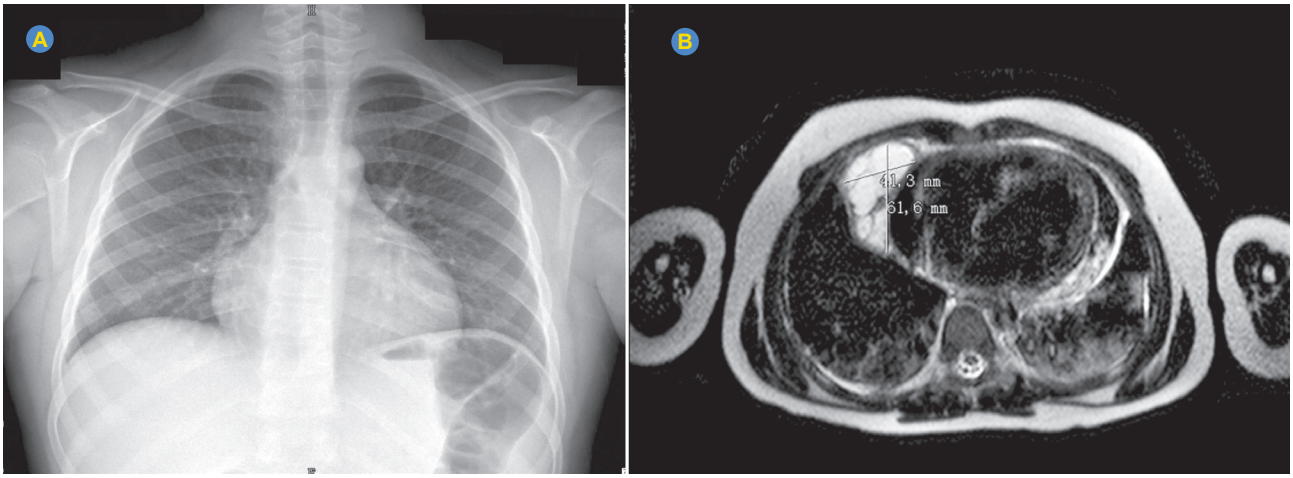

Figure 1 – Enlargement of the mediastinum in the chest radiography (A). MRI showing pericardial cyst in the right hemithorax, measuring 61.6 x 41.3 mm (B).

An 8-year-old boy presented to the Emergency Department with a persistent cough and right-sided chest pain. Physical examination was normal. Imaging tests revealed mediastinal enlargement on chest radiography (Fig. 1A), a 62 mm cystic lesion in close proximity to the pericardium on computed tomography, and an echocardiogram showed a small pericardial effusion. The magnetic resonance imaging test then confirmed a 62 mm pericardial cyst (Fig. 1B). Blood tests including inflammation markers and cardiac biomarkers were normal. Further tests including immunologic assays and tuberculosis screening were unremarkable. Pericardial cysts have an incidence of 1 in 100 000, accounting for 6% of mediastinal masses.[1] They are usually congenital and asymptomatic, often incidentally detected during imaging.[1,2] Most are benign, prompting a conservative approach, but symptomatic or rapidly enlarging cysts may require surgery.[1,3] In this case, conservative management was chosen, and the patient remained stable after eight months of follow-up.

AUTHOR CONTRIBUTIONS

IIAM: Study design, literature search, data acquisition, writing of the manuscript.

BCC: Data acquisition, critical review of the manuscript.

SAMP, ACGGR: Critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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DATA CONFIDENTIALITY

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

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Carta ao Editor Referente a "Prevalência e Fatores Preditivos do Aleitamento Materno Exclusivo nos Primeiros Seis Meses de Vida"

Letter to the Editor Concerning "Prevalence and Predictive Factors of Exclusive Breastfeeding in the First Six Months of Life"

Palavras-chave: Aleitamento Materno/psicologia; Lactentes; Mães; Portugal
Keywords: Breast Feeding/psychology; Infants; Mothers; Portugal

Caro Editor,

No artigo "Prevalência e Fatores Preditivos do Aleitamento Materno Exclusivo nos Primeiros Seis Meses de Vida", publicado na Acta Médica Portuguesa em junho de 2023, Branco *et al* observaram que a taxa de aleitamento materno exclusivo (AME) foi de 74,2% à data de alta da maternidade, caindo para menos de metade aos seis meses (25,6%). Os autores compararam os resultados com um estudo semelhante de 1999, concluindo que, apesar de haver uma melhoria significativa da taxa de aleitamento materno aos três e seis meses, a prevalência de AME aos seis meses mantém-se semelhante (23%).[1]

Na minha perspetiva, o impacto de fatores socioculturais e emocionais na amamentação ainda não foi devidamente estudado. O aleitamento materno é usualmente abordado como algo objetivo, mantendo o foco principal no produto, o leite materno, e não no processo.[2] As mulheres veem a amamentação como uma experiência fortalecedora, surgindo sentimentos de culpa quando algo não corre segundo as expectativas moldadas pela sociedade.[2] Vários estudos indicam que as mulheres relatam fortes expectativas ou pressão para amamentar, principalmente por parte de profissionais de saúde e padrões culturais,[3,4] estando essa pressão associada a uma experiência de amamentação negativa e à diminuição da autoeficácia.[2]

A iniciativa 'Hospitais Amigos dos Bebés' foi lançada em Portugal em 1994.[5] Este programa contribuiu para uma renovação das práticas clínicas nas maternidades, fomentando o vínculo entre a mãe e o recém-nascido. No entanto, existe uma pressão subjacente para o sucesso pleno da amamentação, esquecendo a experiência subjetiva vivenciada pela mulher e pela família. É essencial que um 'hospital amigo dos bebés' seja indissociavelmente amigo da mãe e da família.

A promoção da amamentação deve ir ao encontro da realidade da mulher deste século, que procura a sua identidade, inserida num contexto familiar, social e laboral rico e dinâmico. A grávida é inundada por um excesso de informação, frequentemente alicerçada em mitos e veiculada através das redes sociais. Se esta não encontrar na sua equipa de saúde o espaço para partilhar dúvidas, poderá procurar conselhos junto de fontes inadequadas.

Branco *et al* reforçam a importância do AME.[1] A amamentação resulta em inúmeras vantagens para a mulher e o recém-nascido, devendo ser promovida, protegida e preservada, sendo essenciais estudos que identificam os fatores que a facilitam ou dificultam.

Futuros estudos que foquem as dimensões sociocultural e emocional que influenciam o aleitamento materno permitirão desenvolver estratégias complementares para a sua promoção, otimizando a prestação de cuidados de saúde a grávidas e puérperas.

CONFLITOS DE INTERESSE

A autora declara não ter conflitos de interesse relacionados com o presente trabalho.

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Cholecystocutaneous Fistula Secondary to Cholelithiasis: A Case Report

Fístula Colecistocutânea Secundária a Litíase Biliar: Um Caso Clínico

Keywords: Biliary Fistula/diagnostic imaging; Cholelithiasis/complications; Cutaneous Fistula/diagnostic imaging; Gallbladder Diseases/diagnosis
Palavras-chave: Colelitíase/complicações; Doenças da Vesícula Biliar/diagnóstico; Fístula Biliar/diagnóstico por imagem; Fístula Cutânea/diagnóstico por imagem

Dear Editor,

Cholecystocutaneous fistula is a rare but potentially serious complication of acute cholecystitis. It may arise as a result of untreated gallbladder inflammation or previous surgical interventions. Abnormal communication between the gallbladder and the skin leads to the drainage of bile to the skin surface, which increases the risk of infections and sepsis.[1-3]

We describe the case of a 58-year-old male patient referring intense and persistent abdominal pain in the right hypochondrium and flank, accompanied by a high fever that persisted for more than a week. He reported no other significant complaints or symptoms. The physical examination revealed pain on superficial palpation of the right hemiabdomen, which limited the evaluation. Due to this limitation, computed tomography (CT) was requested. The test revealed a fluid collection with approximately 300 mL of volume in the abdominal cavity in the location of the gallbladder and invading the abdominal wall (Fig. 1A). A subsequent magnetic resonance cholangiopancreatography (MRCP) was requested for a more precise assessment of the bile ducts, identifying an abscess in the gallbladder region in contact with the proximal portion of the cystic duct (Fig. 1B). Additionally, the presence of obstructive lithiasis was observed in the distal third of the cystic duct measuring 1.8 cm, compatible with infected cholecystitis (abscess) with fistulization to the abdominal wall. The treatment consisted of drainage of the abdominal collection guided by CT, in addition to the administration of appropriate antibiotic therapy to control the infection.

A cholecystocutaneous fistula can arise as a result of different underlying conditions. The most common cause is cholelithiasis, that is, the development of gallstones in the gallbladder. These stones can damage the gallbladder wall over time, leading to the development of an abnormal pathway between the gallbladder and the skin. Additionally, chronic inflammation of the gallbladder (cholecystitis) can also contribute to the development of this fistula.[4,5]

The accurate diagnosis of a cholecystocutaneous fistula is essential to determine the most appropriate treatment strategy. However, a detailed clinical history, physical examination, and imaging tests, such as ultrasound and CT, are essential. The presence of symptoms such as persistent abdominal pain, drainage of bile fluid through the skin, and fever are strongly suggestive of a fistula.[3]

Other causes include complications after gallbladder surgery such as cholecystectomy (gallbladder removal), abdominal trauma, infections, and inflammatory bowel disease. Patients with a history of biliary disease, previous abdominal surgeries, and recurrent infections may be at greater risk of developing this condition.[1,2]

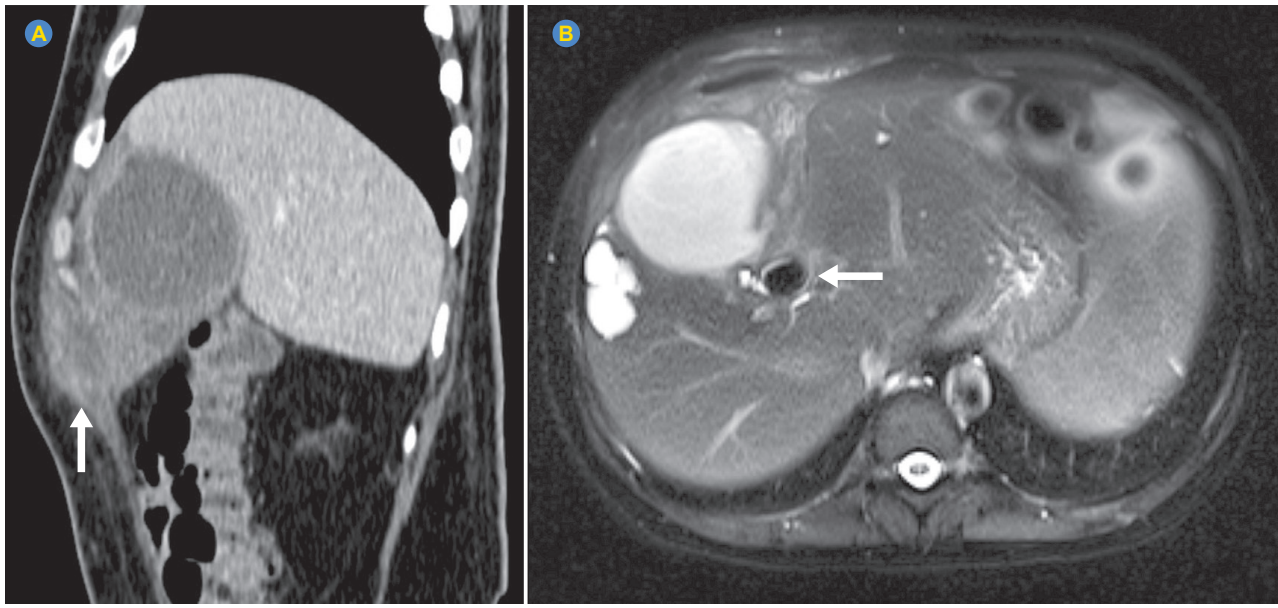

Figure 1 – CT scan with contrast in the portal phase in the axial view (A) demonstrating abscess in the abdominal cavity at the location of the gallbladder invading the abdominal wall (white arrow). MRCP in the T2 FAT SAT sequence in the axial view (B) showing abscess in the gallbladder region which is in contact with the proximal portion of the cystic duct, in addition to obstructive lithiasis in the distal third of the duct cystic (white arrow), compatible with infected cholecystitis with fistulization to the abdominal wall.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript and approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

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Eltrombopag Use in Children with Persistent and Chronic Primary Immune Thrombocytopenia in a Portuguese Pediatric Center

Uso de Eltrombopag em Crianças com Trombocitopenia Imune Primária Persistente e Crónica num Hospital Pediátrico Português

Keywords: Child; Purpura, Thrombocytopenic, Idiopathic/drug therapy; Receptors, Thrombopoietin; Thrombocytopenia/drug therapy
Palavras-chave: Criança; Púrpura Trombocitopénica Idiopática/tratamento farmacológico; Receptores de Trombopoetina; Trombocitopenia/tratamento farmacológico

Chronic immune thrombocytopenia (ITP) is often associated with limited activity and fear of bleeding which affect the patient's quality of life.[1] Eltrombopag is the only oral thrombopoietin receptor agonist approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use in pediatric patients older than one year with chronic ITP refractory to other treatments.[2]

We conducted a single-center retrospective study between January 2018 and December 2022, with the aim of evaluating the efficacy of eltrombopag in patients with persistent and chronic ITP. Due to the retrospective nature of the study and the confidentiality of patient data, informed consent was not obtained, and the study was not submitted to an ethics committee.

The response criteria were defined as complete response (CR) if the platelet count was > 50 × 10^9/L for more than six weeks without rescue therapy and partial response (PR), if the response lasted less than six weeks or required rescue therapy. Remission was defined as a platelet count > 100 × 10^9/L for more than six weeks without the need for rescue therapy.

Baseline demographic and clinical data are shown in Table 1.

A total of 13 patients with ITP were included, with a median baseline platelet count prior to initiation of eltrombopag of 10 × 10^9/L (IQR 6.5 x 10^9/L – 25 x 10^9/L). During treatment, most patients (11; 84.6%) achieved a platelet count higher than 50 × 10^9/L, with ten (76.9%) of them reaching this milestone between weeks two and six of treatment. Six patients (66.7%) achieved CR, including one (16.7%) in remission after 73 months of therapy. Three patients (23.1%), had a partial response to eltrombopag and four patients (30.8%) had no response as they never achieved a platelet count of 50 × 10^9/L. Rescue therapy was required during eltrombopag treatment in four patients (30.8%) – Table 2.

Concomitant treatment with corticosteroids/immunoglobulin were discontinued in three patients (42.9%).

Table 1 – Demographic and baseline clinical data of the 13 patients

Demographics (n = 13)	
Gender, n (%)	
Female	7 (53.8)
Male	6 (46.2)
Age at diagnosis, years, mean (SD)	7.4 (5.5)
Age at the start eltrombopag, years, mean (SD)	11.9 (4.7)
Second-line therapies prior to eltrombopag, n (%)	
Mycophenolate mofetil + Azathioprine	1 (7.7)
Mycophenolate mofetil + Rituximab	1 (7.7)
Splenectomy	-
Clinical characteristics, n (%)	
Epistaxis	4 (30.7)
Cutaneous (petechiae, ecchymosis)	12 (92.3)
Gingivorrhagia	3 (23.1)
Metrorrhagia	1 (7.7)
Laboratory features, median (IQR range)	
Baseline platelet count, x 10^9/L	10 (6.5 - 25)
ITP phase, n (%)	
Chronic	11 (84.6)
Persistent	2 (15.4)
Concomitant ITP medication use, n (%)	8 (61.5)
Low-dose corticosteroids	6 (75)
Azathioprine + low-dose corticosteroids	1 (7.7)
Immunoglobulin course	1 (7.7)

IQR: interquartil range; ITP: immune thrombocytopenia; SD: standard deviation

Table 2 – Treatment response and rescue therapy

Treatment response, n (%)	
Complete	6 (46.1%)
- in remission	1 (16.7%)
Partial	3 (23.1%)
Non-response	4 (30.8%)
Rescue therapy, n (%)	4 (30.8%)
iv. Immunoglobulin alone	2 (50%)
iv. immunoglobulin + corticosteroids	2 (50%)

One patient discontinued eltrombopag due to cholestatic hepatitis associated with bacteremia, which resolved after discontinuation of eltrombopag.

The current study is, to the best of our knowledge, the first Portuguese pediatric study on the use of eltrombopag in children under real-life conditions. The study demonstrated efficacy, tolerability, and safety as a treatment for persistent and chronic immune thrombocytopenia in children. More than 80% of patients had at least one platelet count > 50 x 10^9/L, and nearly 70% had a partial response, which is consistent with other published studies.[3-5]

Notably, a significant proportion of patients experienced a reduction in the use of concomitant therapies and an improvement in quality of life, which decreases the side effects of long-term corticosteroid use and the risks associated with intravenous therapy. Based on these findings, we recommend that eltrombopag be considered as a first-line therapy for pediatric patients with chronic ITP and persistent clinical manifestations, with corticosteroids or immunoglobulin being reserved for occasional hemorrhagic episodes.

AUTHOR CONTRIBUTIONS

CL: Data collection and interpretation, literature search, writing and critical review of the manuscript.

AC: Data collection and interpretation, critical review of the manuscript.

RM, SB: Critical review of the manuscript.

PK: Study design, critical review of the manuscript.

All authors approved the final version to be published

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COMPETING INTERESTS

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Small Bowel Obstruction Secondary to a Spontaneous Intramural Jejunal Hematoma

Oclusão Intestinal por Hematoma Intramural Espontâneo do Jejuno

Keywords: Anticoagulants/adverse effects; Hematoma/chemically induced; Intestinal Obstruction
Palavras-chave: Anticoagulantes/efeitos adversos; Hematoma/induzido quimicamente; Obstrução Intestinal

A 68-year-old man with no history of trauma or recent digestive tract procedures presented to the emergency department with a one-day history of abdominal pain and vomiting. The patient had undergone a mitral valve replacement one month before and was taking daily warfarin since then. He also had congestive heart failure and chronic obstructive pulmonary disease. On physical examination he was hemodynamically stable and presented a distended and globally tender abdomen. The blood workup revealed a hemoglobin level of 9.7 g/dL, an INR of 10 and increased inflammatory parameters. A plain abdominal film showed gas-fluid levels in the small bowel and the computed tomography (CT) scan suggested an intestinal obstruction due to an intramural jejunal hematoma with a moderate hemoperitoneum (Fig. 1). The elevated INR was reversed to a normal value with administration of prothrombin complex concentrate. During observation, the patient became hypotensive and tachycardic, accompanied by a drop of hemoglobin level to 7.8 g/dL, and therefore the team decided to abandon a conservative approach and perform an urgent laparotomy. We found a moderate hemoperitoneum and confirmed a small bowel occlusion due to a single circumferential intramural jejunal hematoma with signs of vascular compromise. This hematoma was 2.5 cm wide, 20 cm long and extended into the respective mesentery. Thereafter, we performed a segmental enterectomy (Fig. 2). Anti-coagulation was reintroduced on the third postoperative day with low molecular weight heparin. On the seventh postoperative day the patient was diagnosed with a hemorrhage of the anastomosis, which was managed conservatively. The subsequent evolution was eventless, and the histopathology report confirmed the diagnosis.

Small bowel obstruction in the setting of a spontaneous intramural jejunal hematoma is a rare condition and should be considered in patients taking oral anti-coagulants presenting with intestinal obstruction symptoms with no history of trauma. The diagnosis can be made by CT scan, which shows an intramural hyperdensity and circumferential thickening with luminal narrowing of a small bowel loop.[1] The treatment can be conservative or surgical, according to the patient's hemodynamic condition and the presence of signs of bowel ischemia or perforation.[2]

AUTHOR CONTRIBUTIONS

AAS: Design of the work, data acquisition, drafting of the manuscript.

CA, DS: Critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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DATA CONFIDENTIALITY

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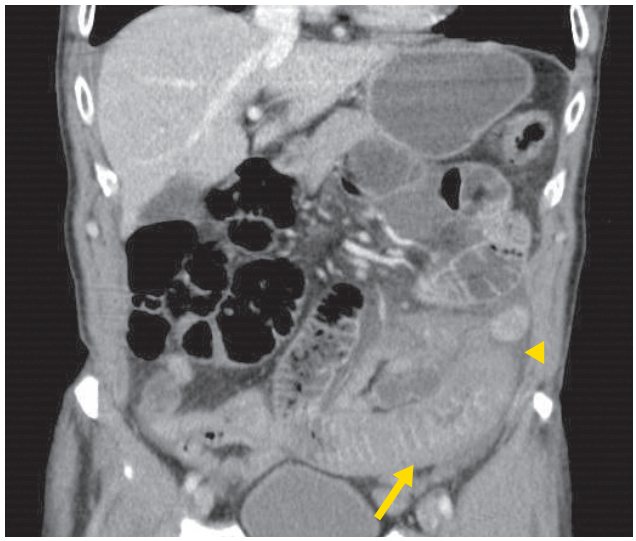

Figure 1 – Coronal abdominal computed tomography: intramural hyperdensity and circumferential thickening with luminal narrowing of a small bowel loop, suggestive of intramural jejunal hematoma (arrow), and hemoperitoneum (arrow head)

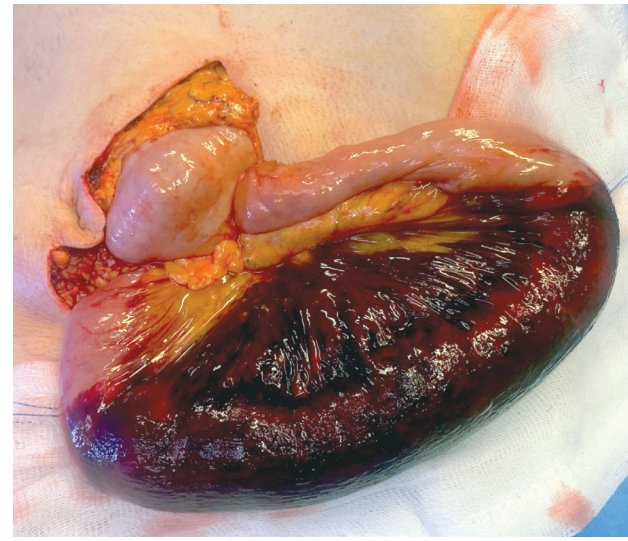

Figure 2 – Surgical findings showing a single, well delimited, 20 cm long circumferential intramural jejunal hematoma, extending into the respective mesentery

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

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A Importância das Escalas Validadas em Saúde para a Prática Clínica

The Relevance of Scales Measuring Health Outcomes in Clinical Practice

Palavras-chave: Avaliação de Resultados em Cuidados de Saúde; Clínica Geral; Inquéritos e Questionários; Reprodutibilidade de Resultados
Keywords: General Practice; Outcome Assessment, Health Care; Reproducibility of Results; Surveys and Questionnaires

Caro Editor

Foi com muito interesse que lemos o artigo "A Short Guide on How to Carry Out Validation of Scales Measuring Health Outcomes", que apresenta um guia prático para validar escalas usadas em contextos de saúde.[1] Este artigo, ao apresentar os principais aspetos a ter em consideração na validação de escalas que medem resultados em saúde, fez-nos refletir sobre a importância de ter estas escalas na prática clínica diária.

Para o médico de família, é essencial ter ferramentas objetivas e padronizadas na sua prática clínica. Quando aplicadas individualmente, as escalas permitem identificar ou priorizar problemas, apoiar a tomada de decisão clínica, monitorizar alterações no estado de saúde ou classificar a resposta aos tratamentos de forma sistemática ao longo do tempo, entre outros.[2] Permitem ainda identificar situações de melhoria ou agravamento que impliquem o ajuste do plano terapêutico.

De forma a aplicar instrumentos em diferentes contextos e culturas, torna-se necessário proceder a uma adaptação transcultural que, sendo um processo custoso e moroso, consiste numa opção com uma melhor relação custo-benefício.[3]

O seu uso melhora a continuidade e eficiência dos cuidados, otimiza o tempo do médico e o do utente, e garante uma maior personalização dos cuidados, além de melhorar a comunicação entre pares e dentro de equipas multidisciplinares.[4] Ao agilizar o processo de avaliação, as escalas de avaliação validadas podem contribuir para uma prestação de cuidados mais eficiente e eficaz, economizando tempo e recursos.

O uso de escalas validadas também é relevante para a investigação e elaboração de normas de orientação clínicas baseadas na evidência. Para isso há que garantir que a validação das escalas segue as orientações internacionais atuais para que seja produzida uma versão do instrumento com equivalência à versão original, permitindo a comparação entre populações separadas pela língua ou pela cultura.[3] A escala validada deve assim garantir fiabilidade, validade, poder de resposta, poder de interpretação e de aplicação.[5]

O uso de escalas validadas pelo médico de família, ao possibilitar uma avaliação consistente e confiável do estado de saúde do paciente, que pode ser replicada em múltiplos contextos de atendimento, é essencial para garantir a qualidade dos cuidados médicos prestados. Para concluir, a validação destas escalas nos cuidados de saúde primários é essencial, pois garante que sejam confiáveis, consistentes e que tenham precisão para uso clínico, proporcionando uma base sólida para a tomada de decisões e cuidados de qualidade para os pacientes.

CONTRIBUTO DOS AUTORES

As autoras declaram que contribuíram igualmente para este manuscrito.

CONFLITOS DE INTERESSE

As autoras declaram não ter conflitos de interesse relacionados com o presente trabalho.

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Analytic Re-Evaluation After Five-Year Gap between Blood Donations: A Useful Barrier?

Suspensão e Reavaliação Analítica Após Intervalo de Cinco Anos entre Dádivas de Sangue: Uma Barreira Útil?

Keywords: Blood Donation; Blood Donors; Time Factors
Palavras-chave: Doação de Sangue; Doadores de Sangue; Fatores de Tempo

In 1994, our blood bank, one of the largest in the country, established a criterion for suspending donors after a five-year gap between donations, with the obligation to perform analytic re-evaluation prior to the resumption of donations. This was proposed following the recommendations of an article reporting that lapsed donors were more likely to have high-risk behaviours and more frequently test positive for infectious agents.[1] Although all blood donations are routinely tested for infectious agents, this criterion was expected to reduce the risk of doing so during the serological window period. We aimed to describe the results of testing suspended donors for infectious agents.

We obtained data from all donors suspended as a result of this criterion between January 1, 2017, and December 31, 2021, as well as from subsequent donations. Information regarding lack of adherence to donation and serology of infectious agents (initial and subsequent) was obtained. The information used was from pre-existing and non-identifiable data therefore informed consent and ethics review board was waived.

During the study period, our blood bank had 93 594 donations of whole blood with 15 739 suspensions (for any reason). As a result of this specific criterion, 770 donors were suspended. Out of 749 donors who underwent testing for infectious agents, 737 results (98.4%) were negative and 12 (1.6%) were reactive (Table 1). Only three of them had clinical relevance – case 2 with infection by hepatitis B virus and cases 3 and 5 with a diagnosis of syphilis. All of them, if this deferral criterion had not been in use, would have been detected in the routine tests performed on all donations. No cases of seroconversion in post-suspension donation were detected.

On the other hand, this suspension criterion led to a total of 328 (42.6%) donors who did not donate blood ever again. This includes 21 donors who did not accept the initial serological study and 307 donors who underwent the serological study. They never returned to the blood bank for the resumption of donations, which may constitute an important handicap for the adherence rate.

The suspension criterion analysed in this sample did not apparently lead to increased transfusion safety. Since there were no cases of seroconversion, all reactive results would

Table 1 – Description of the reactive results of the serological studies

Case number	Results
#1	Reactive result in serological study of hepatitis C virus.
	No clinical significance. Disease not confirmed.
#2	Infection by hepatitis B virus.
	Clinical records consistent with diagnosis known for 24 years.
#3	Diagnosis of syphilis.
#4	Reactive result in serological study of human T-cell lymphotropic viruses.
	No clinical significance. Disease not confirmed.
#5	Diagnosis of syphilis.
#6	Reactive result in serological study of hepatitis B virus.
	No clinical significance. Disease not confirmed.
#7	Reactive result in serological study of hepatitis C virus.
	No clinical significance. Disease not confirmed.
#8	Reactive result in serological study of hepatitis C virus.
	No clinical significance. Disease not confirmed.
#9	Reactive result in serological study of hepatitis B virus.
	No clinical significance. Disease not confirmed.
#10	Reactive result in serological study of hepatitis B virus.
	No clinical significance. Disease not confirmed.
#11	Reactive result in serological study of hepatitis B virus.
	No clinical significance. Disease not confirmed.
#12	Reactive result in serological study of human T-cell lymphotropic viruses.
	No clinical significance. Disease not confirmed.

have also been detected in the routine study. Additionally, this was an important barrier to the adherence rate. While this criterion was defined based on published evidence, we consider that currently, for our blood bank, there is no benefit in maintaining it. These results highlight the importance of regularly reviewing suspension criteria.

AUTHOR CONTRIBUTIONS

IM: Data collection, drafting and critical review of the manuscript.

ST, RQ: Drafting and critical review of the manuscript.

CN, CK: Critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Mazabraud Syndrome: Clinical Review and Therapeutic Approach Regarding a Case Report

Síndrome de Mazabraud: Revisão Clínica e Abordagem Terapêutica de um Caso Clínico

Keywords: Fibrous Dysplasia of Bone/diagnostic imaging; Magnetic Resonance Imaging; Myxoma
Palavras-chave: Displasia Fibrosa Óssea/diagnóstico por imagem; Mixoma; Ressonância Magnética

Dear Editor,

Mazabraud syndrome is a rare condition, often undiagnosed, predominantly affecting women (68% of the cases) in their forties.[1] This syndrome is characterized by the association of intramuscular myxoma (IM) and benign soft tissue tumors. The latter are typically painless and slow-growing, primarily found in the leg muscles, especially the quadriceps, either solitary or multiple, with fibrous dysplasia (FD), defined as a benign fibro-osseous lesion that replaces healthy bone. There is no consensus regarding the incidence of monostotic (FD in one bone) and polyostotic (FD in several bones) forms.[1,2]

We describe the case of a 63-year-old woman who presented with tumors in the right thigh for the past five years that had been increasing in size and causing pain, as well as limiting the movement of her right lower limb. On physical examination, there were masses that were painless and had a hard consistency on her right thigh, there was limitation in the movement of her right lower limb and difficulty walking, which she reported had been worsening over the past few months. A magnetic resonance imaging (MRI) scan detected FD in the femur and multiple IMs (Fig. 1). A biopsy confirmed a diagnosis of Mazabraud syndrome.

Soft tissue IMs, which appear around the sixth decade

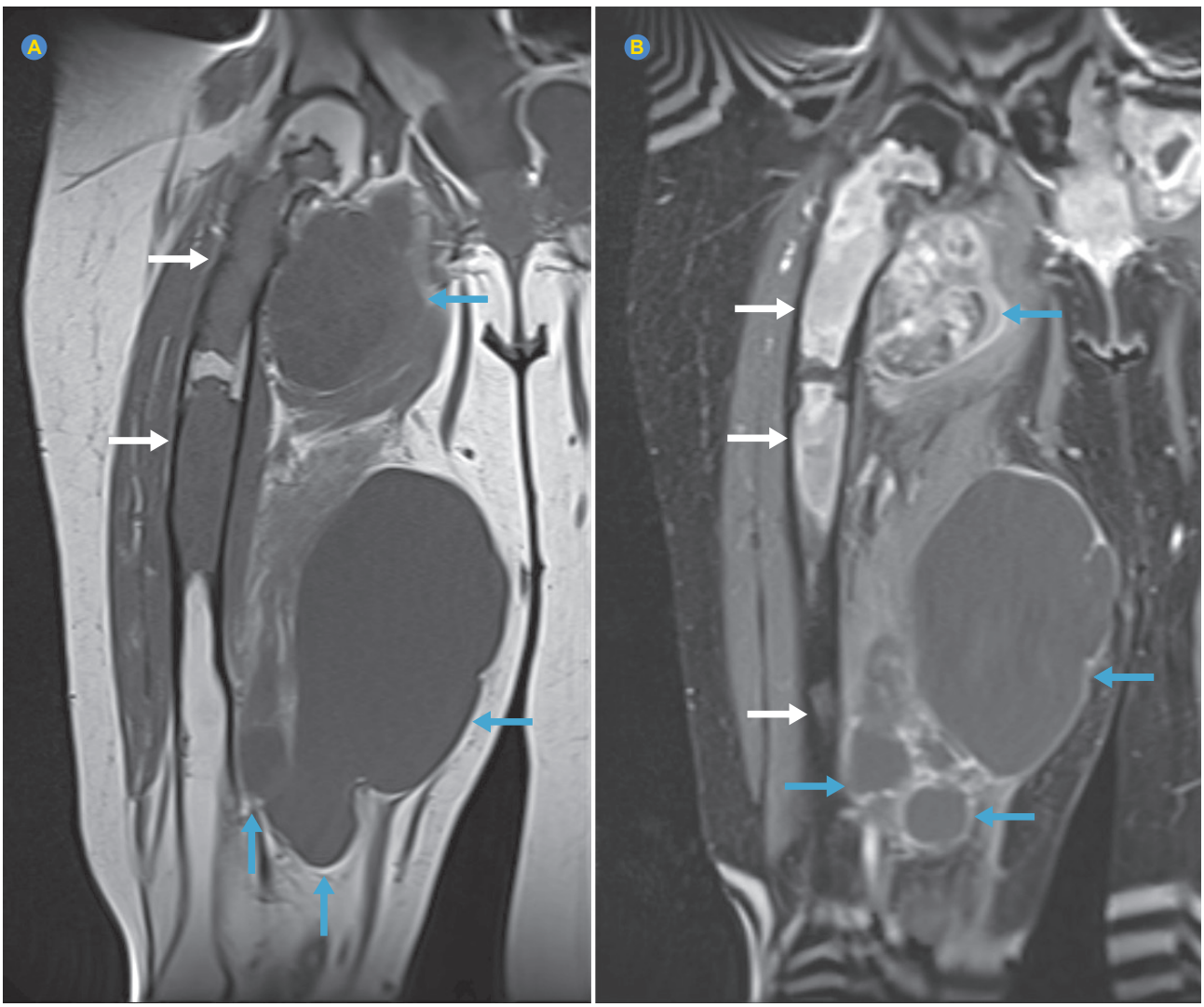

Figure 1 – T1 weighted-image MRI in coronal section (A); T1 FAT SAT DIXON with contrast weighted-image MRI in coronal section (B). MRI revealed extensive heterogeneity of the femur with an expansile appearance, significantly affecting its proximal portion, with heterogeneous contrast enhancement, in a 'cane-shaped' configuration, consistent with fibrous dysplasia (white arrows). Multiple lobulated intramuscular images with peripheral contrast enhancement and others with heterogeneous contrast enhancement, consistent with intramuscular myxomas (blue arrows).

of life and have a benign course, are considered soft tissue hamartomas with tumor-like growth.[3,4] Furthermore, it is important to note that the development of FD usually precedes the appearance of IMs by approximately 6.5 years. Sarcomas can develop in areas of FD, as they have a rare but clear potential for malignant transformation. The most common malignancies that can arise from FD are osteosarcoma (70%), followed by fibrosarcoma (20%), and chondrosarcoma (10%).[1,2]

Therapeutic management varies from clinical surveillance and imaging evaluation to orthopedic surgical intervention in symptomatic patients. Prolonged use of bone antiresorptive agents, like zoledronate, may be considered a viable alternative. These agents appear to reduce the volume of myxomas; however, they do not demonstrate significant effects on the regression of underlying FD.[5] Treatment options for Mazabraud syndrome include extensive excision of myxomas, particularly when painful or compressive symptoms are present. It should be emphasized that even after partial excision of myxomas, the possibility of local recurrence persists, underscoring the need for regular follow-up to detect local recurrences and the emergence of new lesions. The therapeutic approach to FD, in general, includes bisphosphonate therapy, with surgical intervention rarely being necessary. The concurrent presence of myxomas requires closer monitoring of FD lesions due to the potential risk of malignant transformation.[5]

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

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Vasospasmo Mamilar: Uma Causa Tratável de Mastalgia na Amamentação

Nipple Vasospasm: A Treatable Cause of Lactational Mastalgia

Palavras-chave: Aleitamento Materno; Doenças da Mama; Mastodinia; Mamilos
Keywords: Breast Diseases; Breast Feeding; Mastodynia; Nipples

O vasospasmo mamilar corresponde à diminuição do fluxo sanguíneo capilar como resultado da vasoconstrição excessiva, normalmente desencadeada pelo frio ou pelo stresse.[1] Está associado ao fenómeno de Raynaud, que ocorre em 3% a 5% da população, sendo quatro vezes mais frequente no sexo feminino e afeta 20% das mulheres em idade reprodutiva.[2,3] Também foi descrita a sua associação com outros fatores, como o uso de fármacos durante a gravidez, a cirurgia mamária e patologia autoimune.

Esta síndrome é reconhecida como um diagnóstico diferencial de dor mamária na amamentação.[4] O seu reconhecimento e tratamento precoces podem permitir o alívio sintomático e evitar erros de diagnóstico, tratamento inadequado e interrupção precoce da amamentação.[2]

Neste contexto, expomos um caso de uma primípara (índice obstétrico: 1001) de 34 anos previamente saudável, que recorre à consulta aberta 10 semanas após o parto, por dor mamilar intensa e intermitente desde o início da amamentação, sem melhoria após frenotomia do recém-nascido e ciclo de antifúngico tópico para candidíase mamilar. Referia dor mamária bilateral, que surgia com a mamada e persistia por cinco a 10 minutos, com irradiação axilar e parestesias associadas, sendo despoletada também pelo frio, com alteração sequencial da cor do mamilo – branco, arroxeado e vermelho – e diminuição da dor após retorno da coloração normal do mamilo. Não apresentava febre ou sinais inflamatórios associados. O leite materno não apresentava alterações de relevo. Ao exame objetivo da mama, apresentava palidez do mamilo com a exposição, sem alterações da pele, sinais de traumatismo, massas palpáveis ou sinais inflamatórios visíveis (Figs. 1 e 2).

Perante o quadro compatível com vasospasmo mamilar, foram propostas medidas não farmacológicas, como evitar a exposição ao frio, utilizar protetores de mamilo de algodão e evitar agentes vasoconstritores. Além disso, foi realizada prova terapêutica com nifedipina de libertação prolongada, toma diária de 30 mg por via oral, por um ciclo de duas semanas. Observou-se resolução completa dos sintomas, não tendo sido descritos efeitos secundários associados à medicação.

A proteção, promoção e apoio do aleitamento materno constitui uma prioridade da Organização Mundial da Saúde, estando recomendada a amamentação exclusiva nos primeiros seis meses de vida, seguida de amamentação complementar até pelo menos aos dois anos.[5]

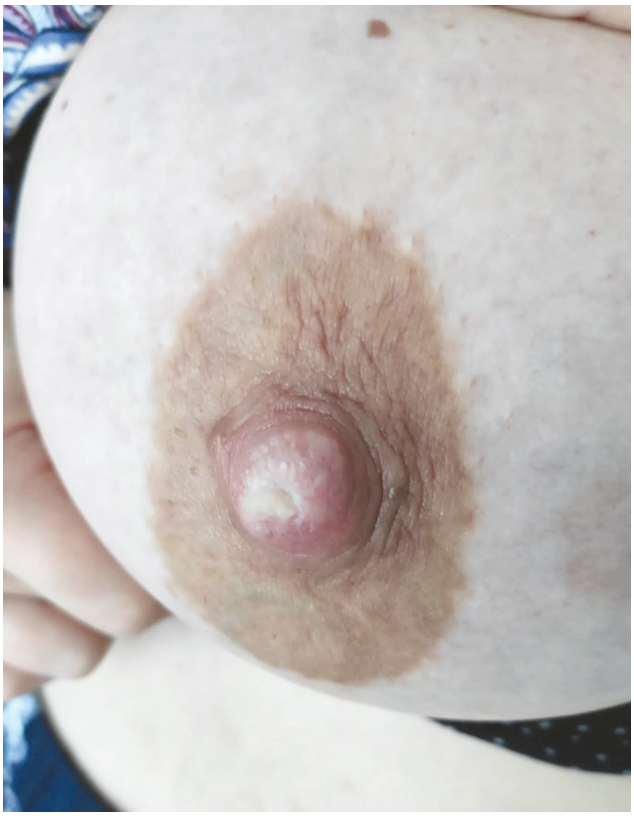

Figura 1 – Mamilo branco com a exposição ao frio – isquemia

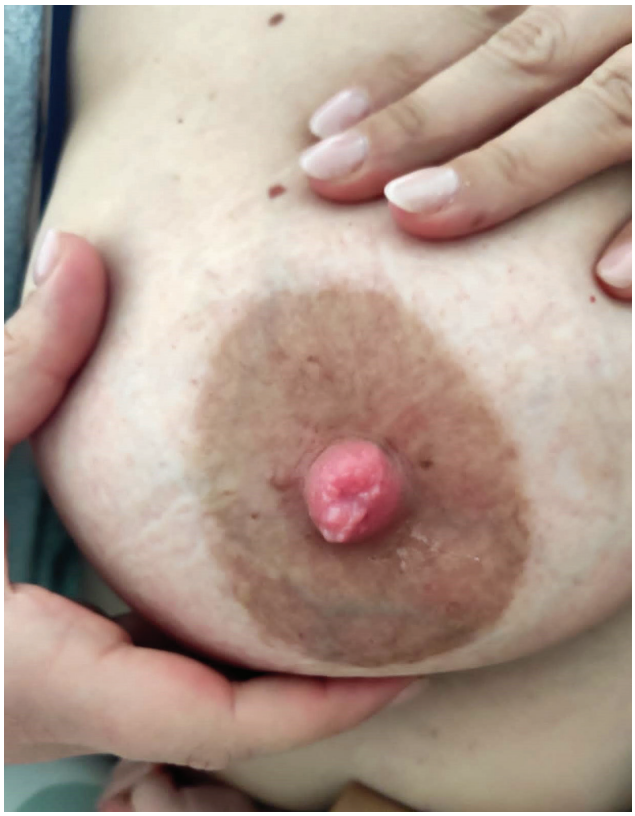

Figura 2 – Mamilo vermelho alguns minutos após a exposição ao frio – hiperemia reativa

Contudo, a mastalgia durante a amamentação é um dos principais fatores de risco para a suspensão do aleitamento materno.[4] Os cuidados de saúde primários, ao estabelecerem o primeiro contacto da puérpera com o sistema de saúde e ao promoverem os cuidados de pós-parto da mãe e do bebé, constituem um local privilegiado para a promoção da amamentação como prevenção da saúde materno-infantil, assim como no diagnóstico e acompanhamento das diferentes etiologias de dor na amamentação.

CONTRIBUTO DOS AUTORES

VDM: Revisão da literatura, elaboração e revisão crítica do manuscrito.

AO, LMG, MAS, ARO: Elaboração e revisão crítica do manuscrito.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFIDENCIALIDADE DOS DADOS

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

CONSENTIMENTO DO DOENTE

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Urgent Attention Needed for Mental Health Challenges Arising from Prolonged Grief During and in the Aftermath of COVID-19

Atenção Urgente Deve Ser Direcionada para os Desafios de Saúde Mental Emergentes do Luto Prolongado Durante e Após a COVID-19

Keywords: Attitude to Death; COVID-19; Grief; Mental Health; Portugal
Palavras-chave: Atitude Perante a Morte; COVID-19; Luto; Saúde Mental; Portugal

To the Editor,

The enduring impact of the COVID-19 pandemic on our society is notably reflected in the realms of grief and mental health. The repercussions of sudden deaths, decreased social support, job losses, and social isolation have given rise to prolonged grief disorder (PGD), which may significantly affect daily functioning for over six months after a loss.[1-3] This disorder was defined by Prigerson in 2009 as a continuous desire, concern with the departed, and deep emotional pain that produces significant functional impairment and lasts longer than six months following the loss.[3] Intense grief correlates with higher risks of chronic diseases, cancer, depression, anxiety, and suicidal thoughts,[4,5] along with poorer quality of life. Anxiety is a typical aspect of grieving,[6] and depression is linked to complicated grief.[7] Evidence indicates a prevalence rate of 66.5% of PGD in COVID-19 deaths,[8] highlighting the urgent need to address mental health challenges arising from the pandemic's impact on grief.

To delve into the specific impact of COVID-19 on individual grief experiences, we carried out a study focused on PGD among residents in Portugal and its correlation with anxiety and depression symptoms.

Employing a snowball sampling method and an online approach, data was collected between November 10, 2020, and February 10, 2021. From the total sample collected (n = 929), 166 reported that they had lost someone since the onset of the pandemic, thus representing our final sample. More information on the study methodology can be found elsewhere.[9] We used the Portuguese validated version of the PG-13 Prolonged Grief Disorder scale as an instrument to collect data on the experience of loss during the pandemic period[10] and for anxiety and depression symptoms we used the HADS scale.[11] PG-13 scores in this study were obtained by summing symptom items, excluding duration and functional impairment. Total scores ranged from 11 to 55, with a suggested clinical cutoff of ≥ 30.[3]

The study received approval from the Ethics Committee of Institute of Public Health of the University of Porto (CE20166). Participants were required to grant informed consent by accessing the questionnaire via the provided link. Given the online nature of the survey, participants were given the choice to either agree to take part in the study or decline (at the beginning of the questionnaire).

Most participants were female (66.9%), aged between 18 - 39 (59.6%), and had a higher education degree (70.5%). The types of losses varied: 30.7% losing a grandparent, 22.3% a friend, and 9.0% a parent. Participants described the emotional difficulty of their loss on a Likert scale, with 10.2% rating it as emotionally bearable, 12.7% as emotionally unbearable, and 24.7% as occasionally bearable.

The analysis of the PG-13 scale for 164 participants with complete data indicated a mean PGD symptom score of 20.89 (SD: 8.83). Of concern, 16.8% scored ≥ 30 (clinical cutoff for PGD), and from these, 15 (53.6%) fell into the definition of Prigerson *et al* (2009).[3] This means that 9.1% of the total potentially presented PGD symptoms.

Those who experienced loss, compared to those who did not, had a higher proportion of depression symptoms (10.2% *vs* 6.4%; $p = 0.030$) (Table 1). Notably, 8.4% of participants exhibited symptoms of both anxiety and depression. Among the 28 participants with a mean score ≥ 30 for PG symptoms, 21 had anxiety symptoms, and eight also exhibited depression symptoms.

Table 2 illustrates the link between demographic variables and anxiety and depression symptoms, and prevalence of PGD. Although not statistically significant, a lower education level was correlated with a higher level of PGD. Anxiety and moderate depression symptoms were significantly associated with PGD ($p < 0.001$). Moreover, those who reported "Emotionally unbearable" in relation with the loss also presented higher levels of PGD ($p < 0.001$), which

Table 1 – Prevalence of anxiety and depressive symptoms in participants that lost someone compared to the overall sample

Variable n (%)	Non-anxiety	Moderate anxiety	Anxiety symptoms	*p*-value	Effect size‡
Have lost someone					
No	384 (84.0)	171 (80.3)	195 (79.3)	0.233	0.056
Yes	73 (16.0)	42 (19.7)	51 (20.7)		
	Non-depression	**Moderate depression**	**Depression symptoms**		
Have lost someone					
No	541 (83.6)	121 (76.6)	48 (73.8)	**0.030**	0.090
Yes	106 (16.4)	37 (23.4)	17 (26.2)		

‡: effect size cut offs based on Rea *et al*[12] (0.00 and under 0.10 – negligible association; 0.10 and under 0.20 – weak association; 0.20 and under 0.40 – moderate association; 0.40 and under 0.60 – relatively strong association; 0.60 and under 0.80 – strong association and; 0.80 and under 1.00 – very strong association).
Bold values represent $p < 0.05$.

Table 2 – Relation between socio characteristics and anxiety and depressive symptoms in participants that present prolonged grief disorder (n = 164)

Variable n (%)	Non-prolonged grief disorder (n = 149)	Prolonged grief disorder (n = 15)	*p*-value	Effect size‡
Sex (n = 163)				
Male	50 (33.8)	4 (26.7)	0.577	0.044
Female	98 (66.2)	11 (73.3)		
Age group (n = 157)				
18 - 39 years	89 (62.7)	8 (53.3)	0.479	0.057
≥ 40 years	53 (37.3)	7 (46.7)		
Education level (n = 161)				
≤ 12 years	38 (26.0)	7 (46.7)	0.263*	0.136
Bachelor degree	48 (32.9)	3 (20.0)		
Master degree or superior	60 (41.1)	5 (33.3)		
Anxiety symptoms (n = 164)				
Non anxiety	71 (47.7)	1 (6.7)	***p* < 0.001***	0.381
Moderate anxiety	40 (26.8)	1 (6.7)		
Anxiety symptoms	38 (25.5)	13 (86.7)		
Depression symptoms (n = 158)				
Non depression	102 (70.3)	3 (23.1)	***p* < 0.001***	0.324
Moderate depression	32 (22.1)	5 (38.5)		
Depression symptoms	11 (7.6)	5 (38.5)		
How emotionally difficult was this loss for you? (n = 163)				
Emotionally bearable	16 (10.8)	0 (0)	***p* < 0.001***	0.579
Frequently bearable	19 (12.8)	0 (0)		
Sometimes bearable	36 (24.3)	1 (6.7)		
Occasionally bearable	40 (27.0)	1 (6.7)		
Rarely bearable	27 (18.2)	2 (13.3)		
Emotionally unbearable	10 (6.8)	11 (73.3)		

Note: From the total of 166 participants who had lost someone, 164 had complete information on the PG-13 scale and were considered for this analysis.
‡: Effect size measure cut offs (Cramer's V) based on Rea *et al*[12]
*: Fisher exact test
Bold values represent $p < 0.001$.

highlights the scale's sensitivity, particularly for those finding the loss emotionally unbearable.

In our study, 30.7% of bereaved participants reported anxiety symptoms and 10.2% reported depressive symptoms. Portugal, with the highest prevalence rate of psychiatric diseases in Europe (22.9%), underscores the urgency of our findings.[13] The prevalence rate of PGD, anxiety, and depression symptoms among bereaved individuals requires targeted interventions and support. In this study, 9.1% of bereaved participants could potentially be diagnosed with PGD based on the scale, surpassing rates in a recent meta-analysis (3.2%).[14] This aligns with studies suggesting traumatic loss tends to trigger PGD.[15,16] Our prevalence rate is lower than in Dutch patient samples (17.7% and 12.5%)[17,18] but higher than in Dutch citizens bereaved due to a plane crash (6.6%).[17] Moreover, pandemic research revealed higher prevalence (3.3% based on DSM-5-TR criteria) compared to the pre-pandemic period,[19] regardless of the diagnostic approach. Caution is needed in comparing results across studies due to variations in PGD assessment scales.

A key study limitation is the absence of clinical diagnoses for PGD, anxiety, or depression symptoms; the results stem solely from screening measures. Because of the cross-sectional design and lack of cause-of-death information, inferring COVID-19 causation was not possible. The predominantly female and relatively young age of participants may limit generalizability. The PG-13 scale underwent revision during our data collection period. Therefore, the updated criteria, published in February 2021 could not be considered in this analysis.

Post-pandemic, prioritizing mental health and bereavement support is crucial. Public health initiatives must ensure accessible services, acknowledging heightened risk among the bereaved. Transparent communication between families and caregivers is vital. Our study highlights a high prevalence rate of PGD, anxiety, and depression, urging immediate action to address the pandemic's mental health impact.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

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

DATA CONFIDENTIALITY

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

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Pantoprazole-Induced Liver Injury in the Setting of Diabetic Ketoacidosis

Lesão Hepática Induzida por Pantoprazol em Contexto de Cetoacidose Diabética

Keywords: Chemical and Drug Induced Liver Injury; Diabetic Ketoacidosis; Pantoprazole
Palavras-chave: Cetoacidose Diabética; Lesões Hepáticas Induzidas por Produtos Químicos e Medicamentos; Pantoprazol

Dear Editor

Critically ill patients are at higher risk of acquired liver injury, given the multiple coexisting potential causes of injury.[1] They are also at risk of stress ulcers, and prophylaxis with proton pump inhibitors (PPIs) is common in Intensive Care Units (ICUs).

A 54-year-old woman was admitted to the ICU due to diabetic ketoacidosis (DKA). On admission, she was hemodynamically stable, with a Glasgow Coma Scale score of 7 (E2V1M4). Her abdominal examination was normal, without palpable organomegalies, and her liver blood tests were within the normal range. She was intubated for airway protection and started on intravenous fluids, insulin perfusion, and prophylaxis with intravenous pantoprazole 40 mg/day.

A favorable clinical evolution allowed extubation on the second day and her DKA was resolved by the third day.

On the fifth day upon admission, her liver blood tests were markedly abnormal (AST 6189 U/L, ALT 2246 U/L, INR 1.64, total bilirubin 1.3 mg/dL, LDH 4948 U/L). She remained asymptomatic and did not develop hepatic encephalopathy. A careful review of the medical history, Doppler abdominal ultrasound, and viral serologies excluded acute alcoholic and viral hepatitis, vascular causes, and biliary obstruction. Her accumulated fluid balance was neutral in the previous 48 hours. Due to suspected drug-induced liver injury (DILI), pantoprazole was withdrawn, and her liver blood tests quickly recovered (four days after stopping pantoprazole: AST 44 U/L, ALT 430 U/L, INR 0.85, total bilirubin 0.5 mg/dL, LDH 207U/L).

Considering the positive response to withdrawing the potential causative drug, a liver biopsy was not performed.[2] Due to the lower likelihood, hyperacute presentation, and prompt resolution, other causes, such as autoimmune and metabolic hepatic diseases were not investigated. Hypoxic hepatitis had been ruled out, considering the sustained hemodynamic stability throughout the hospitalization.

Although globally very well tolerated, pantoprazole has rarely been reported to cause clinically apparent liver injury with an acute hepatocellular pattern,[3] like the presented case (where the ratio of serum activity of ALT to ALP was ≥ 5 - activity is expressed as a multiple of upper limit of normal). Although no liver biopsy was performed, the pattern of injury and elevation of LDH, after exclusion of hypoperfusion, is consistent with acute hepatic necrosis. Furthermore, according to the Roussel Uclaf Causality Assessment Method (RUCAM) scale,[4] this is a probable case of pantoprazole-associated DILI (RUCAM score 6).

Despite usual prompt resolution after withdrawal of the agent, as it was the case here, acute liver failure with PPIs has been reported. Besides, although there is no information on cross-reactivity among PPIs after pantoprazole hepatotoxicity,[5] caution should be taken in case the patient needs a PPI in the future.

Altogether, this case highlights the importance of a high degree of clinical suspicion for DILI, even with widely prescribed medications such as PPIs, particularly in the critical care setting.

AUTHOR CONTRIBUTIONS

RO: Data acquisition, literature search and writing of the manuscript.

MA: Literature search and critical review of the manuscript.

PL, AB: Critical review of the manuscript.

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DATA CONFIDENTIALITY

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

PATIENT CONSENT

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Congenital Central Hypoventilation Syndrome: The Singularity of A Successful Case

Síndrome de Hipoventilação Central Congénita: A Propósito de Um Caso de Sucesso

Keywords: Hypoventilation/congenital; Infant; Infant, Newborn; Sleep Apnea, Central/genetics
Palavras-chave: Apneia do Sono Tipo Central/congénita; Hipoventilação/congénita; Lactente; Recém-Nascido

Dear Editor,

Congenital central hypoventilation syndrome (CCHS) is a rare autosomal dominant genetic disease, with an estimated incidence of 1 per 148 000 – 200 000 live births,[1] caused by a mutation in the paired-like homeobox 2B (*PHOX2B*) gene encoding a transcription factor that is critical for the development of the autonomic nervous system. It is characterized by autonomic failure, with absence or decreased sensitivity to hypercapnia and hypoxemia, especially during sleep, causing hypoventilation and apneas. The diagnosis of CCHS should be made in the presence of sleep-related hypoventilation [especially in non-rapid eye movement (NREM) sleep] and *PHOX2B* mutation.[2] The longer polyalanine repeat expansion mutations (PARMs) typically present a classic phenotype, usually with the need for continuous ventilatory support and the onset of symptoms in the neonatal period. If accurate diagnosis and organ support are assured, CCHS is a chronic disease compatible with life, allowing patients to reach adulthood. Ventilatory support is the cornerstone of treatment.[3]

A 22-year-old woman was born from pre-term labor at 32 weeks, with generalized hypotonia, symptomatic central apneas, and ineffective ventilation, with the need for invasive mechanical ventilation (IMV) to be started during the neonatal period. There were no family members with similar manifestations. A CCHS diagnosis was established at two months, after the exclusion of other diseases, before *PHOX2B* genetic testing was available. Once diagnostic confirmation was possible, the presence of a PARM 20/27 was documented. The patient acquired an adequate ventilatory capacity during wakefulness at 10 months, and transition from IMV to non-invasive ventilation (NIV) was possible at 10 years. She reached adulthood with normal motor and cognitive development (Fig. 1). The parents were also tested and are not gene mutation carriers.

Invasive mechanical ventilation is the most frequent type of ventilatory support and is recommended until the ages of six to eight years through tracheostomy.[3] The use of NIV, especially if performed only during sleep, allows for an almost normal childhood and improved quality of life.[4] In this case, the acquisition of adequate ventilatory capacity during wakefulness is noteworthy. This is seldom described in the literature, mainly by the age of six to 12 months, being more frequent in patients with shorter PARMs.[2] Although the transition from IMV to NIV might impact the correction of alveolar hypoventilation, this case emphasizes that it is a safe and effective treatment, as demonstrated by the absence of polycythemia, pulmonary hypertension, *cor pulmonale*, or cognitive deficits. It is not clear whether neurological deficits are a primary manifestation of the disease or the result of untreated chronic hypoxemia.[5]

The authors emphasize the singularity of this case, in which the diagnosis was established in the pre-*PHOX2B* genetic testing era. It is also of note the ventilatory autonomy achieved during wakefulness at the age of 10 months in a patient with long PARM, and her normal motor and cognitive development.

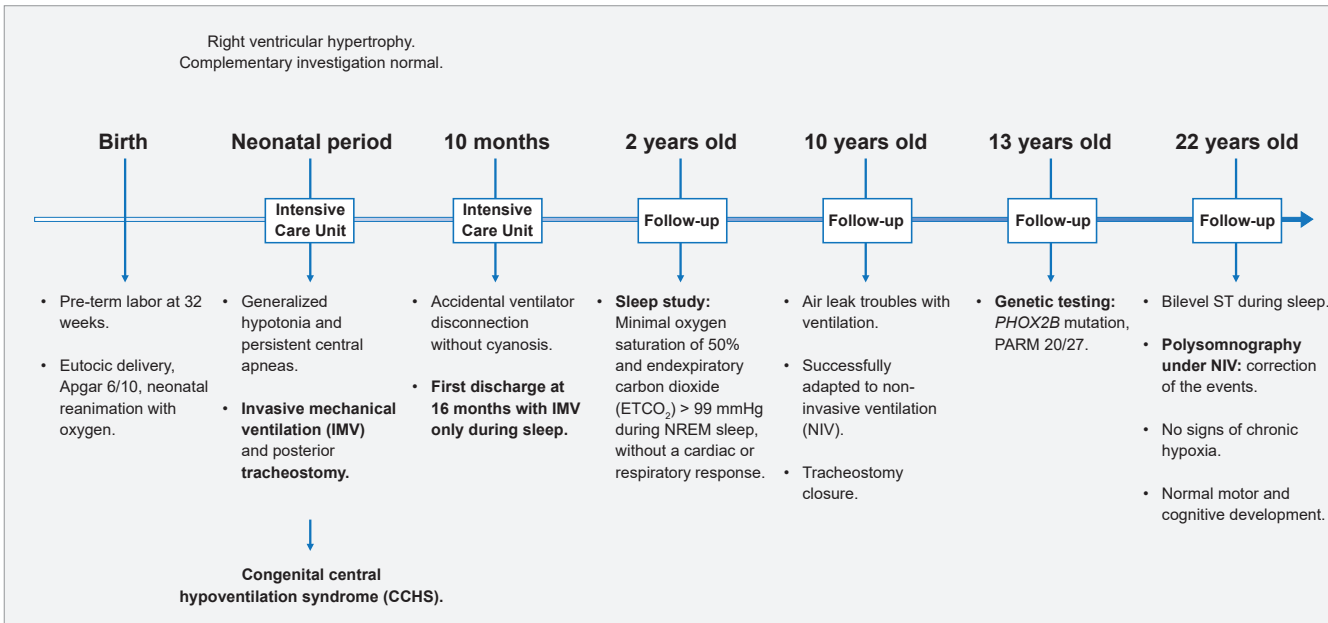

Figure 1 – Timeline highlighting the patient's clinical presentation and most relevant complementary exam findings

AUTHOR CONTRIBUTIONS

IB, IFP, DA: Literature review and writing of the manuscript.

MLP, SM: Writing and critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Scalp Eschar and Neck Lymphadenopathy Associated with Rickettsial Infection After a Tick Bite: A Case Report

Escara no Couro Cabeludo e Linfadenopatia Cervical Associada a Infeção por Rickettsia Após Picada de Carraça: Caso Clínico

Keywords: Lymphadenopathy; Rickettsia Infections; Scalp; Tick Bites/complications
Palavras-chave: Couro Cabeludo; Infecções por Rickettsia; Linfadenopatia; Picadas de carraças/complicações

The presence of a scalp eschar and neck lymphadenopathy (SENLAT) after a tick bite has been commonly associated with a rickettsial infection. This syndrome, firstly recognized in the 1980s in Slovakian and Hungarian patients became a new clinical entity, when, in 1997, the DNA of *Rickettsia slovaca* was detected in a French patient's eschar.[1,2] Due to the most pronounced sign of this disease – the neck enlarged lymph nodes – it was named tick-borne lymphadenopathy (TIBOLA).[2,3] Later, in Spain, some clinicians gave it another designation that includes the genus of the tick involved in the pathogen transmission: *Dermacentor*-borne necrosis erythema lymphadenopathy (DEBONEL).[4]

The etiological agent of TIBOLA/ DEBONEL, *R. slovaca*, was first isolated in 1968 from a *Dermacentor marginatus* tick in the former Czechoslovakia. Further, *R. slovaca* was also detected in ticks from countries across the Eurasian region. In Portugal, *R. slovaca* was first detected in 1995 in *D. marginatus* and, later, also in *D. reticulatus* ticks.[5] Some authors demonstrated that this syndrome can also be caused by other tick-borne pathogens such as *Borrelia burgdorferi*, *Bartonella henselae*, *Coxiella burnetii*, and *Francisella tularensis*, and proposed a new name SENLAT, which does not allude to a specific etiologic agent.[6]

We present a case report of SENLAT concerning an otherwise healthy 37-year-old woman who presented to the emergency department complaining of intense headache and reported removing a large tick from her scalp two days after the onset of symptoms (Fig. 1A). The patient reported a tick bite 10 days earlier, while spending holidays in the mountains of the central region of Portugal (Guarda). She had a necrotic eschar on the scalp surrounded by erythema and painful lymphadenopathies in the retroauricular and cervical regions (Fig. 1B), with no other systemic symptoms and an unremarkable laboratory evaluation. No reactive antibodies against spotted fever group rickettsiae were

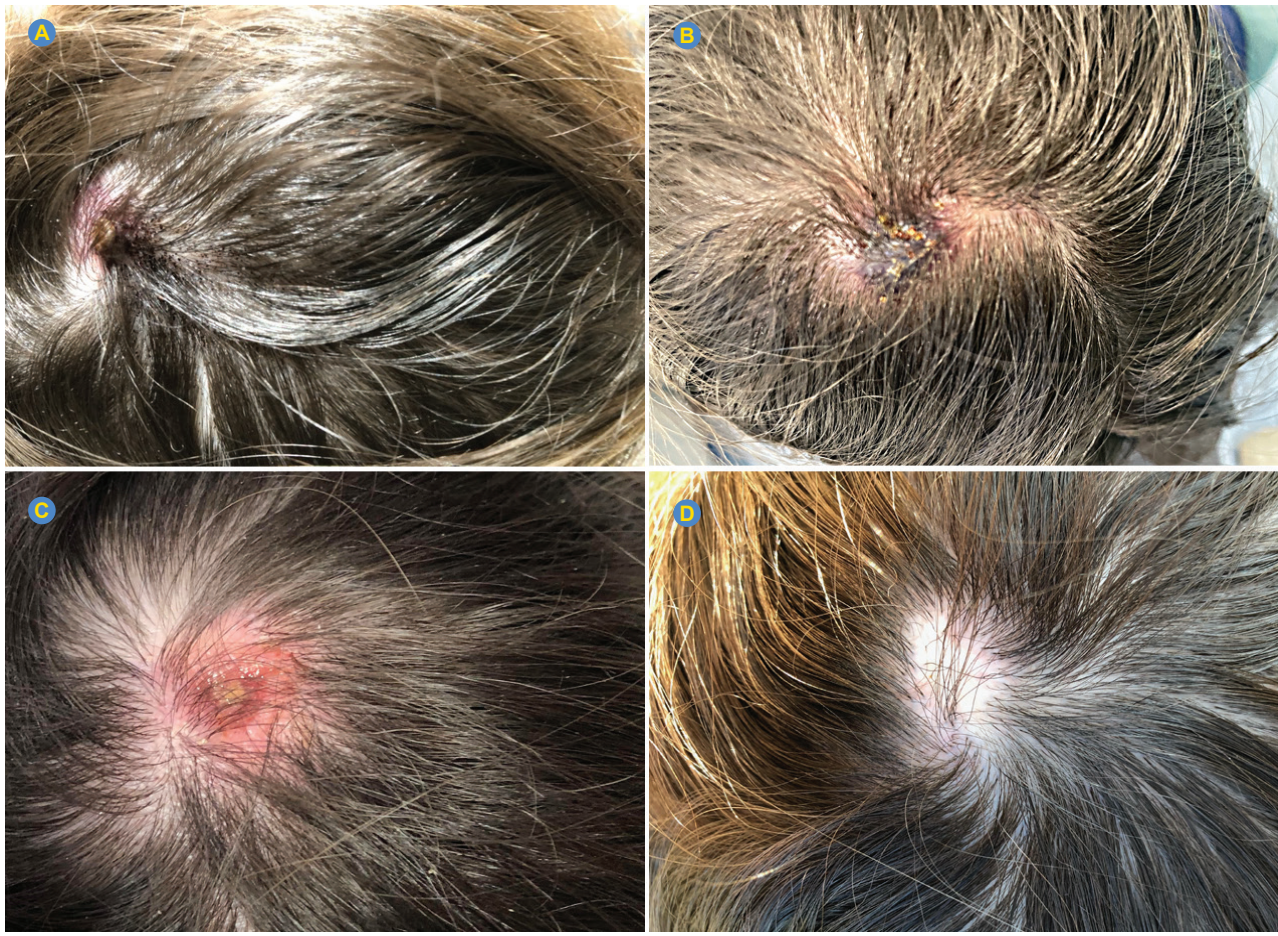

Figure 1 – Adult tick and black eschar on day six after tick bite (A); black eschar on day 10 after tick bite (before treatment) (B); scalp lesion on day 33 after tick bite (after treatment)(C); alopecia one year after tick bite (D).

Table 1 – Tick-borne rickettsioses in Portugal: main features

Disease	TIBOLA/ DEBONEL/ SENLAT	Mediterranean spotted fever	Lymphagitis associated rickettsiosis (LAR)	Rickettsia monacensis infection
Agents	***R. slovaca*; *R. raoultii***	***R. conorii***	***R. sibirica mongolitimonae***	***R. monacensis***
Vector	*Dermacentor marginatus*, *D. reticulatus*	*Rhipicephalus sanguineus*	*Rhipicephalus pusillus* (Portugal, Spain, France); *Hyalomma* spp.	*Ixodes ricinus*
Months of reported human cases	March to May and September to November	Majority of cases May-October (but can occur all year long)	Spring and Summer	Not defined (only one case)
Signs and symptoms				
Fever	Sometimes	Yes	Yes	Yes
Eschar (number and common location)	100% scalp	38% - 60% depends on *R. conorii* strain Location: limbs, trunk, neck	> 80% limbs, trunk and neck	~ 66%
Rash	Rare	Yes	Yes	Yes
Headache	Not reported	Yes	Not reported	Yes
Lymphadenopathy	Always	Sometimes	~50% cases	Sometimes
Lymphangitis	Not reported	Very rare	Yes	Not reported
Mortality rate	No fatal cases reported	3% - 7%	No fatal cases reported	No fatal cases reported
Preferred treatment	Doxycycline			

detected in serological assays at this time, using an indirect chemiluminescence immunoassay commercial kit. The patient was treated with oral doxycycline (100 mg twice a day for 14 days).

One week after the beginning of the treatment, there was total resolution of the symptoms. However, the necrotic eschar was still evident. At this time, a second blood sample was sent to the Portuguese Reference Laboratory for Rickettsioses for testing. No rickettsial DNA was detected in the blood. Serological testing using immunofluorescence assay slides demonstrated a reactive title of 64 for IgG (cut-off title IgG is 128). Eight months later, a third serum sample was collected, showing increased IgG antibodies with a title of 256. One year later, there was secondary alopecia on the affected site (Fig. 1D), that persisted since the black eschar disappeared which occurred one month after the tick bite (Fig. 1C).

This presentation, with no rash and no fever, is compatible with the typical mild illness of infections caused by *R. slovaca* and *R. raoultii*. It is important that physicians are aware of the main features of SENLAT to ensure a correct diagnosis and treatment and be able to make a differential diagnosis from other existing rickettsioses in Portugal with a poor prognosis, such as Mediterranean spotted fever (Table 1).

AUTHOR CONTRIBUTIONS

MAQF, MA, SEP: Data collection and writing of the manuscript.

ICC: Critical review of the manuscript.

RS: Literature review and writing of the manuscript.

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Errata ao Artigo "Doença de Hansen: Apresentação Incomum de uma Doença Antiga", Publicado em Acta Med Port 2024 Mar;37(3):215-219.

Correction to the Article "Hansen's Disease: An Unusual Manifestation of an Ancient Disease", Published on Acta Med Port 2024 Mar;37(3):215-219.

Na página 215, na linha de autoria onde se lê, (**a vermelho**):

Mário FERREIRA✉[1], Carlos GRIJÓ[2], Joana PAULO[1], Marta FONSECA[1], Zélia NEVES[1]

Deverá ler-se (**a negrito**):

Mário FERREIRA✉[1], **Carlos GRIJÓ**[2], **Joana PAULO**[1], **Marta FONSECA**[1], **Zélia NEVES**[1], **Rita BOUCEIRO MENDES**[3], **Pedro VASCONCELOS**[3]

Na mesma página 215, em rodapé (afiliação dos autores), onde se lê (**a vermelho**):

1. Medicina III. Hospital Fernando Fonseca. Amadora. Portugal.
2. Serviço de Medicina Interna. Centro Hospitalar Universitário de São João. Porto. Portugal.

Deverá ler-se (**a negrito**):

1. **Medicina III. Hospital Fernando Fonseca. Amadora. Portugal.**
2. **Serviço de Medicina Interna. Centro Hospitalar Universitário de São João. Porto. Portugal.**
3. **Serviço de Dermatologia. Hospital de Santa Maria. Centro Hospitalar Universitário Lisboa Norte. Lisboa. Portugal.**

Artigo publicado com erros:
https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20599

On page 215, list of authors, where it reads (**in red**):

Mário FERREIRA✉[1], Carlos GRIJÓ[2], Joana PAULO[1], Marta FONSECA[1], Zélia NEVES[1]

It should read (**in bold**):

Mário FERREIRA✉[1], **Carlos GRIJÓ**[2], **Joana PAULO**[1], **Marta FONSECA**[1], **Zélia NEVES**[1], **Rita BOUCEIRO MENDES**[3], **Pedro VASCONCELOS**[3]

On the same page 215, footer (authors affiliation), where it reads (**in red**):

1. Medicina III. Hospital Fernando Fonseca. Amadora. Portugal.
2. Serviço de Medicina Interna. Centro Hospitalar Universitário de São João. Porto. Portugal.

It should read (**in bold**):

1. **Medicina III. Hospital Fernando Fonseca. Amadora. Portugal.**
2. **Serviço de Medicina Interna. Centro Hospitalar Universitário de São João. Porto. Portugal.**
3. **Serviço de Dermatologia. Hospital de Santa Maria. Centro Hospitalar Universitário Lisboa Norte. Lisboa. Portugal.**

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https://doi.org/10.20344/amp.21460

Correction to the Article "Ophthalmology Census 2021: A Demographic Characterisation of Ophthalmologists in Portugal", Published on Acta Med Port (In Press), https://doi.org/10.20344/amp.20321.

Errata ao Artigo "Estudo Demográfico da População de Oftalmologistas em Portugal: Censo de Oftalmologia 2021", Publicado em Acta Med Port (In Press), https://doi.org/10.20344/amp.20321.

On page 5, 3rd paragraph, line 7, where it reads, (**in red**):
"(...) considering the international recommendation (**1**:10 000)[8]"
It should read (**in blue**):
"(...) considering the international recommendation (**0.5**:10 000)[8]"

Still on page 5, 5th paragraph, line 8, where it reads, (**in red**):
"(...) **in** the 40 - 50-year age group"
It should read (**in blue**):
"(...) **below** the 40 - 50-year age group"

On page 8, key of Table 1, line 5, where it reads, (**in red**):
"[1]: **PORTATA** 2021;"
It should read (**in blue**):
"[1]: **PORDATA** 2021;"

Article published with errors:
https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/20321

Na página 5, 3º parágrafo, linha 7, onde se lê, (**a vermelho**):
"(...) considering the international recommendation (**1**:10 000)[8]"
Deverá ler-se (**a azul**):
"(...) considering the international recommendation (**0.5**:10 000)[8]"

Ainda na página 5, 5º parágrafo, linha 8, onde se lê, (**a vermelho**):
"(...) **in** the 40 - 50-year age group"
Deverá ler-se (**a azul**):
"(...) **below** the 40 - 50-year age group"

Na página 8, legenda da Tabela 1, linha 5, onde se lê, (**a vermelho**):
"[1]: **PORTATA** 2021;"
Deverá ler-se (**a azul**):
"[1]: **PORDATA** 2021;"

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