AMP

ACTA MÉDICA PORTUGUESA

A Revista Científica da Ordem dos Médicos

ACTA MED PORT. ISSN 0870-399X e-ISSN 1646-0758

4 | 23

Número 4
Série II
Lisboa

Volume 36
Abril 2023
Publicação Mensal

FICHA TÉCNICA

AMP ACTA MÉDICA PORTUGUESA

A Revista Científica da Ordem dos Médicos

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Sede do Editor / Redação: Av. Almirante Gago Coutinho, 151. 1749-084 Lisboa, Portugal. Tel: +351 21 151 71 00 E-mail: secretariado@actamedicaportuguesa.com

ISSN:0870-399X | e-ISSN: 1646-0758

Assinaturas: Nacional: 300 Euros; Internacional: 350 Euros

AMP36(4) - Abril de 2023

Registo: Inscrito na Entidade Reguladora para a Comunicação Social com o Nº 106 369

Depósito legal: 20 957/88

Estatuto Editorial: http://www.actamedicaportuguesa.com/estatuto-editorial

Conselho Científico

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What is the Future of Preprint Peer Review?

Qual é o Futuro da Revisão por Pares de Preprints?

Richard SEVER✉[1], Thiago CARVALHO[2]
Acta Med Port 2023 Apr;36(4):225-226 ▪ https://doi.org/10.20344/amp.19675

Keywords: Peer Review; Preprints as Topic
Palavras-chave: Pré-Publicações como Assunto; Revisão por Pares

Sharing research manuscripts as 'preprints' that have not been formally peer reviewed is increasingly common in the biomedical sciences. Authors can upload their manuscripts to preprint servers such as bioRxiv (pronounced "bio-archive") and medRxiv (pronounced "med-archive"), and these are posted online for anyone to read within two to three days after screening for appropriateness (the servers do not perform peer review but typically check that papers are actually science and do not contain dangerous or inappropriate material). Manuscripts posted as preprints are usually then submitted to journals for traditional peer review and publication, but this is not required. bioRxiv, launched in 2013,[1] focuses on basic science. medRxiv, launched in 2019, focuses on clinical research.[2] To date the two servers have posted approximately 220 000 preprints, and they became critical tools for rapid dissemination of COVID-19 research during the pandemic.

The primary goal of preprint servers is to speed up science by allowing rapid dissemination of research many months before it is available in journals. Preprints also provide an opportunity for authors to get feedback on draft manuscripts before submitting to a journal for formal evaluation. In addition, they offer a mechanism for sharing certain findings that have traditionally been difficult to publish in journals, such as replication studies and negative results. The decoupling of dissemination and evaluation by preprints has another important consequence though: it enables the emergence of journal-independent peer review mechanisms that complement or serve as an alternative to traditional journal peer review.

There are various informal mechanisms for readers to provide feedback on preprints. Preprints are frequently discussed on social media, with hundreds of thousands of mentions on Twitter that can include long threads of in-depth expert analysis. Many servers also include on-site comments. On bioRxiv and medRxiv, only around 5% to 8% of papers receive on-site comments. But while many of these are simply brief responses and requests for clarification, there are some extensive discussions of papers that resemble formal peer reviews, and people reviewing papers for journals occasionally post their reviews as comments if the submission has also been posted as a preprint. The critique of research manuscripts on social media is transparent and inclusive, but some authors have expressed concerns that the process is vulnerable to the kind of hype and conflict magnification that is a frequent feature of these platforms.

It will be interesting to see how this informal peer feedback evolves. It is important to emphasize that, in contrast to journal peer review, it is usually unsolicited and entirely independent of the author. The ability to provide unsolicited feedback is of particular benefit to early career researchers (ECRs), who are less likely to participate in journal peer review. Initiatives like PreReview seek to bring the type of 'journal club' research institutions and university departments often run to preprints.[3] Preprint peer review provides an opportunity to train ECRs in peer review, as well as a way for them to demonstrate their critical skills to potential employers both inside and outside academia.[4]

Unsolicited peer review is of course not editorially curated. Thus, it presents a good opportunity to reflect on the role of editors. Not only do editors solicit reviewers; they must also solicit the 'appropriate' reviewers. For manuscripts of clinical interest, this means weighing the need for specific medical *versus* research expertise, as well as engaging reviewers that can review the quantitative data analysis employed. Editors also police conflicts of interest to ensure the integrity of the peer review process.

It is therefore significant that a decoupled publishing ecosystem means that formal complements and alternatives to peer review can emerge. Portable peer review is an idea that has been discussed for many years in publishing circles, but preprints now allow it to be realized. Review Commons is an initiative recently launched by EMBO and ASAPbio, a preprint advocacy group.[5] It functions as a journal-independent peer review service to which authors submit preprints and obtain peer reviews that they can then present to journals to consider. The process is overseen by professional editors at EMBO Press, and 17 journals have

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Recebido/*Received*: 25/01/2023 - **Aceite/*Accepted*:** 30/01/2023 - **Publicado *Online*/*Published Online*:** 07/03/2023 - **Publicado/*Published*:** 03/04/2023

agreed to consider peer reviews of preprints that Review Commons has solicited (authors are also free to submit their manuscripts and the Review Commons reviews to journals outside the consortium). Peer Community In (PCI) is a similar initiative,[6] comprising a series of communities that peer review preprints authors have submitted. Currently 16 PCI communities exist, covering areas from infectious disease to paleontology. Authors can take the peer reviews PCI communities arrange to journals that are considering their papers or alternatively submit to a dedicated journal run by PCI.

Another organization that is blurring the lines between preprint review and journals is eLife. eLife is an open access journal funded by the Howard Hughes Medical Institute (HHMI), the Wellcome Trust, and the Max Planck Society. It has required all authors to post preprints since 2020 but recently took the bold step of re-defining itself as a peer review service: eLife no longer accepts or rejects papers it considers; it simply peer reviews them and posts the reports online alongside the preprint.[7] PLOS Biology has also experimented with preprint peer review by asking editors to consider both formal peer reviews and unsolicited comments on bioRxiv preprints they are considering for publication.

Preprint peer review thus encompasses a spectrum of activities from informal commenting to new services that can augment or potentially displace journals in the research ecosystem. Perhaps most significantly it prompts us to consider what peer review is and what it should be. Journal peer review is currently mostly concentrated among a small fraction of senior scientists who are overloaded and not representative of the global potential reviewer pool. ECRs are not often involved, nor are scientists from the Global South. Preprint peer review provides an opportunity to involve a more diverse sample of the scientific community. Increasing the representation of researchers from marginalized groups and the Global South in the review of clinical research could boost fields like neglected tropical diseases and socio-economic determinants of health. And since decoupled review is not exclusive or restricted to a single point in time, it could provide the basis for a new, more multi-dimensional approach to the evaluation of scientific research.

A key question is how preprint peer review should operate in the clinical sphere. Journals do more than simply organize peer review, and the additional editorial checks they perform are particularly important for clinical studies. The medRxiv preprint server requires authors to make various ethics declarations, provide clinical trial IDs, and name the oversight body that approved any human subject research. But things like patient consent need to be verified for interventional studies, especially if identifiable images of research participants (which medRxiv will not post) are published. Who should perform these in a more decoupled ecosystem? Clinical research also presents a more fundamental challenge to the preprint system: from their origins in physics to their adoption by the life sciences, preprints have been posted on the tacit assumption that they would be read primarily by researchers, who could critically evaluate their content. Manuscripts of medical interest, however, may bring in a much more diverse readership, from physicians with no research training, to patient groups and investors. Clinical journals and new initiatives seeking to bring experiments in preprint review to medical publishing will need to consider this if the approach is to be successful.

AUTHOR CONTRIBUTIONS

Both authors made equal contributions in conceiving and writing the manuscript.

COMPETING INTERESTS

RS: Payments were made to Cold Spring Harbor Laboratory in the form of grants from the Chan Zuckerberg Initiative; received direct payment for writing from Springer Nature; has a Director role at Life Science Alliance.

TC: Received payments related to grants or contracts from the Champalimaud Foundation and EMBO and payments or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from EMBO, Springer Nature, Instituto Gulbenkian de Ciência, Sanofi Portugal, the American Association for Cancer Research and The Financial Times.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
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Pandemia, Saúde e Proteção: O Que nos Diz o Health at a Glance 2022?

Pandemic, Health and Protection: What Does the Health at a Glance Report 2022 Tell Us?

Pedro PITA BARROS✉[1]
Acta Med Port 2023 Apr;36(4):227-228 ▪ https://doi.org/10.20344/amp.19770

Palavras-chave: COVID-19; Indicadores Básicos de Saúde; Indicadores de Qualidade em Cuidados de Saúde; Organização de Cooperação e Desenvolvimento Económico; Pandemia; Portugal
Keywords: COVID-19; Health Status Indicators; Pandemics; Organisation for Economic Co-Operation and Development; Portugal; Quality Indicators, Health Care.

O relatório anual *Health at a Glance 2022*,[1] publicado em colaboração pela Organização para a Cooperação e Desenvolvimento Económico (OCDE) e a Comissão Europeia, apresenta uma visão sobre os sistemas de saúde europeus, nas suas diferenças e nas suas semelhanças de problemas e soluções.

Na sequência de relatórios de outros anos, também em 2022, referente a 2021 e anos anteriores, é apresentado um conjunto extenso de informação, cobrindo diversos aspetos do funcionamento dos sistemas de saúde, como o estado de saúde da população e sua evolução recente, os cuidados de saúde prestados, os comportamentos da população mais diretamente relacionados com riscos e benefícios para a saúde de cada um (consumo de tabaco e de álcool, exercício físico, alimentação).

Há nos hábitos individuais e na saúde uma evolução lenta e prolongada no tempo. A alteração dos comportamentos da população é lenta (e difícil de influenciar), pelo que não surpreende que em 2021 se tenham mantido os grandes traços gerais dos anos anteriores: redução de consumos de tabaco e de álcool e insuficiente atividade física regular. A falta de exercício físico acentuou-se durante o período da pandemia, por força das medidas adotadas (com confinamentos e encerramento de escolas), sendo uma evolução negativa que deverá merecer mais atenção pública.

Nos indicadores de saúde, devido à pandemia, a esperança de vida à nascença interrompeu o seu crescimento em todos os países nos anos de 2020 e 2021 (face a 2019), não sendo Portugal uma exceção a esta caracterização geral. Apesar disso, Portugal não sofreu tanto como outros países, ficando numa situação intermédia da mortalidade por COVID-19 (similar a Espanha, França e Bélgica, pior do que o Norte da Europa, melhor do que a Europa de Leste). Os anos da pandemia serão uma situação extraordinária. em termos estatísticos, pelo que será importante esperar pela retoma da normalidade do sistema de saúde nos próximos anos antes de retirar grandes conclusões sobre a evolução das principais causas de morte prematura. Infelizmente, não há informação para Portugal quanto à presença de condições crónicas múltiplas na população idosa e quanto às limitações na sua vida diária. Esta informação é retirada do *SHARE - Survey of Health, Ageing and Retirement in Europe (Wave 8)*.[2] No entanto, embora Portugal faça oficialmente parte da rede, não se tem conseguido assegurar financiamento e interesse suficientes para que o inquérito seja realizado em Portugal com a regularidade com que tem sido realizado nos outros países europeus participantes.

Em termos de despesas em cuidados de saúde, mantém-se a tradicional situação de a despesa *per capita* em Portugal ser relativamente baixa em valores absolutos, sendo que, em proporção do PIB, está no *top* 10 dentro da União Europeia. Contudo, a despesa em saúde só é relevante em comparações internacionais se o país for um claro caso divergente dos restantes, o que não sucede. Estando em linha com muitos outros países, a análise relevante é saber se são obtidos resultados adequados para a despesa realizada.

No financiamento da despesa em saúde, o elemento mais relevante é se há, ou não há, proteção contra despesas inesperadas de saúde. Ou seja, qual a dimensão dos pagamentos diretos (*out-of-pocket*). Nesse âmbito, Portugal tem um volume elevado no contexto europeu. É uma deficiência, antiga, do sistema de saúde português. Os pagamentos diretos são despesas financiadas pelas famílias, logo são despesas privadas. Parte é devida a pagamentos que o Serviço Nacional de Saúde (SNS) exige às famílias (taxas moderadoras, comparticipação na aquisição de medicamentos, etc) e parte é procura direta das famílias junto de prestadores privados de cuidados de saúde. Os seguros de saúde privados são responsáveis por pagar uma pequena parte dessa despesa privada.

Sendo a elevada proporção a pagamentos diretos uma

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Recebido/*Received*: 10/02/2023 - **Aceite/*Accepted*:** 02/03/2023 - **Publicado/*Published*:** 03/04/2023

fragilidade da cobertura do sistema de saúde português, é relevante conhecer melhor a sua constituição. Embora o relatório não forneça esse detalhe, tradicionalmente a despesa com medicamentos tem um peso elevado na despesa direta das famílias, sobretudo para as de menores rendimentos. Portugal é um dos países em que a despesa com medicamentos dispensados em farmácias é mais fortemente financiada por pagamentos diretos (44%), o que sugere a necessidade de atenção futura a ser dada à proteção financeira no uso do medicamento. Dados os preços relativamente baixos de muitos medicamentos usados pela população portuguesa, e face ao decréscimo dos preços de muitos medicamentos dispensados em ambulatório na última década, a revisão do sistema de comparticipações do SNS será um ponto de partida para melhorar esta situação.

Relativamente à qualidade dos cuidados prestados, em indicadores como o tempo dedicado ao doente numa consulta, o envolvimento do doente no processo de decisão de a prestação de explicações claras pelo médico, o relatório apresenta uma boa imagem do sistema português (dados de 2020).

O relatório dedica uma pequena referência à integração de cuidados, referindo três elementos: reforço da governação da prestação ou cuidados de saúde, desenvolvimento de sistemas de informação que assegurem interoperabilidade (ou seja, que a informação seja facilmente transmitida) e alinhamento de incentivos financeiros (leia-se, modos de pagamento aos prestadores de cuidados de saúde). Não há a insistência no que parece ser a preferência portuguesa na solução única de integração vertical numa mesma organização. Unidades locais de saúde e sistemas locais de saúde não são condição necessária e não são condição suficiente para ter-se integração de cuidados, embora sejam compatíveis com esse objetivo de cuidados integrados.

Nas barreiras de acesso a cuidados de saúde, as necessidades não satisfeitas em Portugal surgem sobretudo em medicina dentária, com enorme diferença entre grupos associada ao rendimento familiar.

Em termos de cobertura (proteção financeira), por definição Portugal tem 100% da população coberta pelo Serviço Nacional de Saúde, sendo ainda apresentada informação sobre a população que tem seguro de saúde privado, que pode ser complementar (cobrir as despesas que o SNS não cobre), suplementar (aumentar a cobertura que é dada pelo SNS, pagando parte do que fica à responsabilidade do cidadão) ou duplicativo da cobertura pública (pagando em alternativa ao SNS). Para Portugal, estes valores indicam que 31,32% da população tem cobertura de seguro duplicativo (isto é, cobrindo essencialmente o mesmo tipo de cuidados de saúde que o SNS). Contudo, não esclarece que esta cobertura de seguro privado de saúde financia menos de 5% da despesa total em saúde [segundo a Conta Satélite da Saúde, Instituto Nacional de Estatística (INE)], e não é por isso comparável com 22% de cobertura suplementar da Finlândia ou 30% de cobertura complementar da Alemanha. São tipos distintos de seguro de saúde privado.

Os pagamentos diretos em Portugal estão muito associados a cuidados de ambulatório (consultas e exames de diagnóstico e terapeuta) e a medicamentos, mas a distribuição por classes de rendimento é muito distinta entre elas, elemento não capturado pelos dados reportados no relatório, mas que resulta da análise dos inquéritos às despesas das famílias (produzidos pelo INE).

A falta de proteção financeira aliada a baixos rendimentos da população leva a que haja um valor expressivo, nos 20% da população de menores rendimentos, de situações em que as despesas privadas em saúde levam o rendimento líquido remanescente do agregado familiar para baixo de uma linha de pobreza, ou acentuam essa situação (o que se designa por despesas catastróficas em cuidados de saúde, indicador apresentado no documento).

Igualmente importante para as atuais discussões em Portugal é a evolução da remuneração dos médicos, com uma evolução real negativa (em termos de poder de compra) de 2010 a 2020, situação que só ocorreu em outros quatro países (Países Baixos, Bélgica, Eslovénia e Reino Unido). Relativamente aos enfermeiros, apesar da sua escassez relativa em Portugal, é dos países com mais baixa remuneração (em poder de compra).

Globalmente, o *Health at Glance 2022* permite colocar em perspetiva os elementos bons e os elementos a melhorar do sistema de saúde português, e do SNS como sua componente central. Em relação a problemas antigos, seja na organização e prestação de cuidados de saúde seja no financiamento das despesas realizadas, a pandemia trouxe novos problemas, na saúde da população e no acesso desta a cuidados de saúde adequados. Cabe-nos agora a responsabilidade de lhes dar solução.

CONFLITOS DE INTERESSE

PB recebeu apoio da Fundação “la Caixa” para a investigação na Nova SBE.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

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ACTA MÉDICA PORTUGUESA
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Resective Epilepsy Surgery and Respective Histopathological Diagnoses: A Retrospective Cohort Study

Cirurgia de Epilepsia Ressectiva e Respetivos Diagnósticos Histopatológicos: Estudo de Coorte Retrospectivo

Joana JESUS-RIBEIRO✉[1,2,3], Olinda REBELO[4], Conceição BENTO[5,6], Cristina PEREIRA[6,7,8], Conceição ROBALO[6,7], Manuel RITO[9], Ricardo PEREIRA[6,9], José Augusto COSTA[6,9], Joana BARBOSA MELO[2,3,10], António FREIRE[8,11], Isabel SANTANA[8,12], Francisco SALES[5,6]

Acta Med Port 2023 Apr;36(4):229-235 ▪ https://doi.org/10.20344/amp.18712

ABSTRACT

Introduction: Over recent decades, brain resection for drug-resistant epilepsy has proven to be a valuable treatment option. The histopathological classification was of paramount value for patient management. The aims of this study were to characterize our resective epilepsy surgical series including the histopathological diagnoses and to understand the differences in clinical practice between two different periods of our epilepsy surgical programme.

Material and Methods: We performed a retrospective cohort study, including patients with drug-resistant epilepsy that underwent resective surgery between 1997 and 2021 in the Coimbra University Hospital Centre. Histopathological diagnoses were classified into seven major conventional categories. For comparison purposes, the cohort was divided into two consecutive periods of 12 years.

Results: A total of 259 patients were included, from which 228 (88%) were adults at the time of surgery. The median disease duration prior to surgery was 14 (interquartile range 23) years. Fifty-five (21%) patients performed pre-surgical invasive work-up. The temporal lobe was the most frequently operated region (73%). Major and minor post-surgical complications were identified in 21 (8%) patients. A reduction in the number of antiepileptic drugs was possible in 96 (37%) patients after surgery. The most common histopathological diagnosis was hippocampal sclerosis, but among children it was long-term epilepsy associated tumour. Long-term epilepsy associated tumours, hippocampal sclerosis and vascular malformations had the best post-operative outcomes. Malformations of cortical development and glial scars had the worst outcomes. Regarding differences between the two periods, the absolute number of operated patients increased (119 *versus* 140), and the age at surgery was higher in the second period (p = 0.04). The number of malformations of cortical development increased (p = 0.01), but the number of other tumours (p = 0.01) and specimens with no lesion (p = 0.03) decreased in the same period.

Conclusion: This study is in line with contemporaneous research, reinforcing the previous knowledge on the underlying structural aetiologies, clinical practice, and surgical outcomes over more than two decades of experience. Our data provide realistic expectations about epilepsy surgery and highlight the need for further improvements in diagnosis and treatment paradigm for people with chronic epilepsy.

Keywords: Epilepsy/pathology; Epilepsy/surgery; Neurosurgical Procedures

RESUMO

Introdução: Nas últimas décadas, a cirurgia ressectiva demonstrou ser uma opção valiosa no tratamento da epilepsia farmacorresistente. A classificação histopatológica foi de grande importância na orientação do doente. Os objetivos deste estudo foram caracterizar a nossa série de cirurgia de epilepsia ressectiva incluindo os diagnósticos histopatológicos, e compreender as diferenças na prática clínica entre dois períodos diferentes do programa de cirurgia da epilepsia.

Material e Métodos: Realizou-se um estudo de coorte retrospetivo, incluindo doentes com epilepsia farmacorresistente submetidos a cirurgia ressectiva entre 1997 e 2021 no Centro Hospitalar e Universitário de Coimbra. Os diagnósticos histopatológicos foram classificados em sete categorias. Para análise comparativa, a coorte foi dividida em dois períodos consecutivos de 12 anos.

Resultados: Um total de 259 doentes foram incluídos, sendo 228 (88%) adultos aquando da cirurgia. A mediana da duração da doença antes da cirurgia foi de 14 (amplitude interquartil 23) anos. Cinquenta e cinco (21%) doentes realizaram investigação invasiva pré-cirúrgica. O lobo temporal foi a região mais frequentemente operada (73%). Complicações pós-cirúrgicas *major* e *minor* foram identificadas em 21 (8%) doentes. Uma redução no número de antiepiléticos foi observada em 96 (37%) doentes após a cirurgia. O diagnóstico histopatológico mais comum foi a esclerose do hipocampo, mas nas crianças foi o tumor associado a epilepsia de longa duração. Tumores associados a epilepsia de longa duração, esclerose do hipocampo e malformações vasculares tiveram os melhores resultados pós-operatórios. Malformações do desenvolvimento cortical e cicatrizes gliais tiveram os piores resultados. Relativamente às diferenças entre os dois períodos, o número absoluto de doentes operados aumentou (119 *versus* 140), e a idade aquando da cirurgia foi maior no segundo período (p = 0,04). O número de malformações do desenvolvimento cortical aumentou

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Recebido/*Received*: 14/06/2022 - **Aceite/*Accepted*:** 30/08/2022 - **Publicado *Online*/*Published Online*:** 15/09/2022 - **Publicado/*Published*:** 03/04/2023

(p = 0,01), mas o número de outros tumores (p = 0,01) e amostras sem lesão (p = 0,03) diminuiu no mesmo período.
Conclusão: Este estudo está de acordo com a literatura atual, reforçando o conhecimento prévio sobre as etiologias estruturais, prática clínica e resultados cirúrgicos ao longo de mais de duas décadas de experiência. Os dados analisados fornecem expectativas realistas sobre a cirurgia de epilepsia e destacam a necessidade de melhorias no paradigma de diagnóstico e tratamento destes doentes.
Palavras-chave: Epilepsia/cirurgia; Epilepsia/patologia; Procedimentos Neurocirúrgicos

INTRODUCTION

Resective epilepsy surgery was first introduced in the late 19th century, but the modern approach including electroencephalogram (EEG) was developed in the 1940s.[1,2] Currently, resective epilepsy surgery is an established treatment option for carefully selected drug-resistant focal epilepsies in children and adults, supported by an ever-growing number of surgical series,[3-6] and a few randomized controlled trials.[7-9] Epilepsy surgery has also proved its value in other domains, namely quality of life and productivity.[10,11] Based on the reported results, an early referral to tertiary centres that offer comprehensive evaluation, and surgery, if indicated, has been recommended.[3,12]

Recent progress in the pathologic diagnosis and classification of epileptogenic brain lesions was helpful for clinical correlation, outcome stratification, and patient management.[13] Histopathological diagnosis is an important prognostic factor for outcome of epilepsy surgery.[14] The European Epilepsy Brain Bank (EEBB) was established in 2006 under the direction of the Framework Program of the European Union to standardize histopathological reporting of specimens obtained from epilepsy surgery.[15] International recommendation for a comprehensive neuropathologic workup of epilepsy surgery brain tissue[13] and consensus classifications of specimens obtained during epilepsy surgery[16-18] contributed to an improvement in diagnosis reliability.

Over the last few decades, there have been advances in epilepsy knowledge and the practice of epilepsy surgery has been developed and refined.[5,19-21] Previous large studies have analysed the trends in presurgical evaluation and surgical treatment of epilepsy over time, conveying all the experience regarding clinical data, invasive brain recordings, surgical techniques, etiological groups, and outcomes.[3,4,22,23]

With this study, our first goal was to perform a clinical characterization of patients that underwent resective surgical treatment for drug-resistant focal epilepsy at a reference centre in our country, including the respective histopathological findings. Secondly, we analysed the differences in clinical practice between two different periods of our epilepsy surgical programme. Our study provides relevant data on epilepsy surgery practice over more than 20 years of experience, which may contribute to the understanding of how clinical trends evolved over time and also to the improvement of epilepsy care.

MATERIAL AND METHODS

We performed a retrospective cohort and single-centre study. Patients with a diagnosis of drug-resistant epilepsy, according to the consensus proposal by the *ad hoc* Task Force of the International League Against Epilepsy (ILAE) Commission on Therapeutic Strategies,[24] that underwent resective epilepsy surgery in the Coimbra University Hospital Centre in the period between 1997 and 2021, were included. Before surgery, all patients performed pre-surgical evaluation in the Epilepsy and Sleep Monitoring Unit, with a detailed non-invasive workup and invasive study when necessary. The histopathological diagnoses were executed by an experienced neuropathologist based on light-microscopic inspection of paraffin-embedded tissue stained with haematoxylin and eosin, and additional histochemical stains or immunohistochemical techniques when indicated, according to international reccomendations.[13] A histopathological diagnosis of hippocampal sclerosis was assumed as a segmental neuronal cell loss in anatomical sectors of the *cornu ammonis* of the hippocampus, as specified in the consensus classification of the ILAE.[16] Brain tumours were classified according to the 2021 World Health Organization (WHO) classification of tumours of the central nervous system.[25] Focal cortical dysplasia was defined based on the consensus classification system of the ILAE.[17] Histopathological diagnoses were classified into seven major conventional categories [hippocampal sclerosis (HS), malformation of cortical development (MCD), long-term epilepsy associated tumour (LEAT), other non-LEAT tumours (OT), vascular malformation (VM), glial scar (GS), and no lesion].

We included both adults and children (defined as patients whose age was under 18 years of age) with available histopathological diagnoses. A minimal dataset of clinical variables was collected from clinical records, encompassing gender, patient's age at the onset of epilepsy, patient's age at the time of surgery, duration of epilepsy before surgery (with dates rounded to whole year numbers), location of the lesion [frontal, temporal, parietal, occipital, multilobar (including hemispheric)], side of lesion, year of surgery, type of surgery, post-surgical complications, histopathological diagnosis, and post-operative outcomes (evaluated by Engel Classification[26]) at one year (n = 257) and three years (n = 229) after surgery. For patients that underwent more than one resection, we only included clinical data and histopathological diagnoses from the last surgical procedure.

Descriptive statistics for categorical variables were presented as total number (with corresponding percentage). For quantitative variables, the normality assumption was formally evaluated by the Kolmogorov–Smirnov test or Shapiro-Wilk test, depending on sample size. Variables with normal distribution were described using means [and standard deviations (SD)], whereas non-normally distributed variables were reported using medians [and interquartile ranges (IQR)]. Comparisons between groups were performed with the independent samples t-test, for normally distributed continuous variables, and the Mann-Whitney U test, for non-normally distributed continuous variables. To assess the association between categorical variables the chi-square test was employed. Regarding effect sizes, Cohen's d was applied for independent samples *t*-test and odds-ratio (OR) for chi-square test. For Mann-Whitney U test, effect size (r) was calculated dividing the z value for the square root of observation number. The descriptive analysis and hypothesis testing were performed using IBM SPSS® Statistics software (version 25).

This study was approved by the Ethics Committee of the local institution. It followed the principles of the Declaration of Helsinki 2013, national legislation for clinical research and good clinical practice norms (ICH-GCP).

RESULTS

Total cohort

A total of 259 patients underwent resective surgery. At the time of surgery, 228 (88%) patients were adults and 31 (12%) were children. Demographic and clinical data are summarized in Table 1. The median number of antiepileptic drugs (AEDs) tried prior surgery was three (IQR 2). Fifty-five (21%) patients performed pre-surgical invasive work-up. The operated region was the temporal lobe in 189 (73%) of the patients. Anterior temporal lobectomy with amygdalohippocampectomy (ATL-AH) was the most frequently performed surgery, in 119 (46%) patients, followed by lesionectomy in 115 (44%) patients. Among the 40 (15%) patients who had two or more surgical resections, OT (25%) and MCD (23%) were the most common conditions. Post-surgical complications were identified in 21 (8%) patients, including major and minor neurological complications in 6% [focal deficits (visual field defects or motor deficit), neuropsychiatric disturbances, memory deficit] and neurosurgical complications in 2% (intracranial haemorrhage, intracranial infection, cerebrospinal fluid leak). The percentage of patients free from seizures dropped from 156 (61%) at one year after surgery to 123 (54%) at three years. A reduction in the number of AEDs was observed in 96 (37%) patients after surgery. In patients with Engel class IA, discontinuation of AEDs was possible in 30 (24%) at latest follow-up.

Histopathological findings

HS was the most common histopathological finding, occurring in 94 (36%) of the surgical specimens. A second histopathological change (dual pathology) was found in four of these patients. Early seizure onset occurred in this group, with a median age of seven (IQR 14) years. The mean duration of epilepsy before surgery in patients with HS was 28 (SD 13) years, the highest among histological categories. At one year following surgical treatment, 60 (67%) patients were completely seizure-free (Engel's class IA). At three years after surgery, 46 (57%) patients achieved Engel's class IA.

LEATs were the second most common histopathological diagnosis in the cohort, representing 56 (22%) of all specimens, and the most common category considering resective surgery in the paediatric age (n = 15, 48%). Ganglioglioma (GG) was identified in 27 (48%) patients, and dysembryoplastic neuroepithelial tumours (DNT) were diagnosed in 23 (41%) patients. Other entities in the LEAT group were pilocytic astrocytoma, angiocentric glioma, between others.

Table 1 – Clinical data of all patients and according to histopathological categories

	Female no. (%)	**Age at onset** (years)	**Age at surgery** (years)	**Disease duration** (years)	**One-year post-operative outcome*** no. (%)	**Three-years post-operative outcome*** no. (%)
All patients	134/259 (52)	14 (IQR 20)	34 (SD 14)	14 (IQR 23)	156/257 (61)	123/229 (54)
HS	59/90 (66)	7 (IQR 14)	39 (SD 11)	28 (SD 13)	60/89 (67)	46/81 (57)
LEAT	22/56 (39)	17 (SD 11)	27 (SD 13)	7 (IQR 11)	41/56 (73)	34/47 (72)
OT	11/34 (32)	32 (SD 17)	37 (SD 15)	3 (IQR 5)	19/34 (56)	16/30 (53)
MCD	18/27 (67)	14 (IQR 22)	28 (SD 14)	10 (IQR 18)	10/26 (38)	8/24 (33)
VM	9/19 (47)	32 (SD 16)	38 (SD 13)	3 (IQR 9)	12/19 (63)	10/16 (63)
GS	3/9 (33)	10 (IQR 15)	36 (SD 16)	19 (SD 15)	1/9 (11)	1/9 (11)
No lesion	10/20 (50)	14 (IQR 11)	32 (SD 12)	16 (SD 10)	10/20 (50)	8/20 (40)

HS: hippocampal sclerosis; MCD: malformation of cortical development; LEAT: long-term epilepsy associated tumour; OT: other tumours; VM: vascular malformation; GS: glial scar
* Engel class IA: completely seizure-free since surgery (equivalent to category 1 in the ILAE classification system[31])

These tumours were located mainly on temporal lobe (n = 43; 77%), followed by frontal lobe (n = 9; 16%). One year after surgery, 41 (73%) patients with LEATs were seizure-free, representing the best postsurgical outcome. Other low-grade non-LEAT tumours were also present in our surgical series (n = 34; 13%), with astrocytoma and oligodendroglioma being the most frequent, with equal frequency (n = 13; 38%). These patients presented one of the shortest disease durations, with a median of three (IQR 5) years before surgery. The rate of seizure freedom at one year and three years after surgery was 56% and 53%, respectively.

MCD were found in only 27 (10%) patients of the whole cohort but represented the second most common category among children (n = 6, 19%). Focal cortical dysplasia (FCD) type II was the most common subtype of malformation, accounting for 16 (59%) cases. Other entities in the MCD category were FCD type I, FCD-not otherwise specified, and hemimegaloencephaly. These malformations were most often located in the frontal lobe 13 (48%). Both one-year and three-year postsurgical timepoints presented a low percentage of patients achieving Engel's class IA, 38% and 33% respectively. The outcome was similar considering only FCD type II (38% at one year, and 31% at three years).

VM were identified in 19 (7%) of all specimens. The cavernous angiomas were the most frequent type of VM (n = 16, 84%). The mean age at seizure onset was 32 (SD 16) years, being one of the categories with older patients at disease onset. A favourable post-operative outcome at one year and three years was registered in 63% of the patients. The least frequent category was GS (n = 9; 4%), which presented mainly an extra-temporal topography (56%). The percentage of patients with seizure freedom after surgery was the lowest (11%) of the cohort, representing the histological entity with the worst post-surgical outcome. No specific lesion could be identified or characterized by means of microscopic inspection in 20 (8%) of patients. This included findings of nonspecific reactive gliosis as the only histopathologic abnormality in the neocortex, white matter, or hippocampus. Freedom from seizures one year after surgery occurred in 50% of patients in this category.

Differences in epilepsy surgery between epochs

For comparison purposes, we divided this retrospective cohort into two consecutive time periods of 12 years (1997 to 2009 *versus* 2010 to 2021) and compared the two epochs (Table 2). The absolute number of operated patients increased, from 119 to 140. The age at seizure onset and disease duration before surgery did not present statistically significant differences between the two periods. However, the mean age at surgery was significantly higher in the second period (t = -2.08, p = 0.04). Regarding invasive work-up, the number of subdural grids/strips was similar in both epochs, but the number of stereo-EEG increased in the latter (although not statistically significant). Surgeries involving the temporal lobe were the most frequent in both periods, but extratemporal surgeries were carried out more frequently over the more recent period. Between 1997 and 2009, the most frequent type of surgery was ATL-AH (n = 57, 48%), and between 2010 and 2021 it was lesionectomy (n = 67, 48%). The rate of post-surgical complications remained stable. The number of MCD that underwent resective surgery significantly increased in recent years (χ^2 = 6.83, p = 0.01). On the other hand, the OT group (χ^2 = 7.42, p = 0.01) and the no lesion group (χ^2 = 5.05, p = 0.03) significantly decreased in the same period. There were no significant differences in surgical outcomes between the two periods.

DISCUSSION

We presented a resective surgery cohort from an active tertiary centre that provides epilepsy surgery to a mixed population of paediatric and adult patients. The presurgical clinical features of our patients with drug-resistant focal epilepsy requiring surgery were in line with previous studies,[4,14,15,27] and did not differ significantly between the two time periods, except for a trend towards an increasing age at surgery. Moreover, the delay from epilepsy onset to surgery exceeded more than 10 years on average (excluding the categories of brain tumours and VM) and remained identical in the different periods. These clinical parameters are relevant for prognosis, since young age at surgery and short duration of epilepsy were associated with more favourable outcomes.[14,28] The gap between evidence and practice with an early underuse of epilepsy surgery has been discussed and several reasons have been presented: epilepsy is a dynamic condition and patients may experience temporary seizure remission with new drugs; difficult access to health care resources; misconceptions about epilepsy surgery leading to under-referral to tertiary centres; overestimation of surgical risks or underestimation of seizure related mortality and morbidity; and depletion of eligible candidates with increasing focus on more complex cases.[1,3,29] The proportion of invasive EEG procedures remained identical, but the proportion of stereotactic studies increased in the most recent epoch. Although surgeries targeting the temporal lobe were the most frequent in both periods, ATL-AH was more prevalent in the former and lesionectomy in the latter. The rate of post-surgical complications was in the range of those previously reported[3,30] and remained stable over time.

Neuropathologic assessment of epilepsy surgery specimens allowed the confirmation of the underlying causes. Unsurprisingly, HS was the most common histopathological diagnosis among adults, a finding consistent with results of current studies.[4,15,27] LEAT was the most common diagnosis among children, which was different from other surgical

Table 2 – Comparison of clinical data between two epochs (1997 - 2009 *versus* 2010 - 2021) of resective epilepsy surgery

	1997 - 2009 (n = 119)	**2010 - 2021** (n = 140)	**Test values**	***p***	**Effect size**
Female no. (%)	61 (51)	73 (52)	χ^2 = 0.02	0.89	OR = 0.97
Children no. (%)	15 (13)	16 (11)	χ^2 = 0.08	0.77	OR = 1.12
Age at onset (years)	12 (IQR 19)	15 (IQR 24)	U = 6534,00	0.22	r = -0.08
Age at surgery (years)	33 (SD 12)	36 (SD 14)	*t* = -2.08	**0.04**	d = -0.26
Disease duration (years)	14 (IQR 20)	14 (IQR 25)	U = 7149,50	0.93	r = -0.01
Invasive workup and surgery					
Subtype icEEG no. (%) Δ	22 (19)	33 (24)	χ^2 = 0.99	0.32	OR = 1.36
Subdural no.	20	23	-	-	-
Depth no.	2	10	-	-	-
Surgery location - Temporal no. (%)	90 (76)	99 (71)	χ^2 = 0.79	0.38	OR = 0.78
Surgery location - Extra-temporal no. (%)	29 (24)	41(29)			
Post-surgical complications no. (%)	10 (8)	11 (8)	χ^2 = 0.02	0.89	OR = 0.94
Histopathological categories					
HS no. (%)	41 (34)	49 (35)	χ^2 = 0.01	0.93	OR = 1.02
LEAT no. (%)	23 (19)	33 (24)	χ^2 = 0.68	0.41	OR = 1.29
OT no. (%)	23 (19)	11 (8)	χ^2 = 7.42	**0.01**	OR = 0.36
MCD no. (%)	6 (5)	21 (15)	χ^2 = 6.83	**0.01**	OR = 3.32
VM no. (%)	8 (7)	11 (8)	χ^2 = 0.12	0.73	OR = 1.18
GS no. (%)	3 (3)	6 (4)	χ^2 = 0.60	0.44	OR = 1.73
No lesion no. (%)	14 (12)	6 (4)	χ^2 = 5.05	**0.03**	OR = 0.34
Post-operative outcome*					
One-year no. (%)	73/119 (61)	83/138 (60)	χ^2 = 0.04	0.84	OR = 0.95
Three-years no. (%)	67/118 (57)	56/111 (50)	χ^2 = 0.92	0.34	OR = 0.78

icEEG: intracranial EEG; HS: hippocampal sclerosis; MCD: malformation of cortical development; LEAT: long-term epilepsy associated tumour; OT: other tumours; VM: vascular malformation; GS: glial scar
* Engel class IA.
Δ: Considering only patients that posteriorly underwent resective surgery
Bold values indicate statistical significance at the 0.05 level

series, in which FCD was more frequent.[15,27] FCDs have been reported as being increasingly frequent in series of patients who underwent epilepsy surgery.[3,4,15] Our results supported these studies with a significant increase in the number of surgeries for MCD in the more recent years, probably due to the complexity of these patients. In contrast, the number of OT cases decreased, perhaps because patients with these tumours started to be referred to a specialized team dedicated to the treatment of brain tumours rather than an epilepsy team. No lesion specimens also decreased between epochs, likely related to an improvement in surgical and histological techniques.

Overall, our postsurgical seizure control rates considering all patients and histological subgroups were in accordance with other data reported,[4,15,21] except for MCD and GS which were lower in our study. These patients usually represent more challenging cases, with a predominant extra-temporal location and longer epilepsy duration, which is known to negatively influence outcomes.[6,14,21] As previously reported,[14,21] the diagnoses of LEATs, HS and VM had the best post-operative outcomes. Interestingly, HS had a good post-surgical outcome despite the longer disease duration. Longer duration of epilepsy was associated with reduced chance of favourable outcomes for all lesions, except for HS.[14] The rationale behind this absence of an effect of duration for patients with HS was not clear.[14] The number of unclassifiable tissue samples was in agreement with other studies,[15] and it does not imply that the resected tissue was functionally normal, since 50% of these patients were seizure-free 12 months after surgery. This was probably related to the inconsistent nature of neurosurgical sampling.[15] No significant difference in the surgical outcomes was detected in the two periods of follow-up. However, there are discrepant results in the literature, with studies reassuring that epilepsy surgery functions in a stable manner on longitudinal evaluation,[4] and others showing improved

postsurgical outcomes in more recent years.[3,5] Our frequency of medication withdrawal after surgery for patients in Engel class IA was similar to previously published intervals.[1,6,21]

Our study has some limitations. First, it is a single-centre study, thus being likely influenced by local policies, available equipment, and referral bias. There was no standardized protocol of patient selection for presurgical evaluation, as in probably most centres. Its retrospective design, with potential imprecisions in data from the 1990s, is another limitation. Also, a few patients were lost to follow-up and some of the most recently operated patients have not yet reached the defined outcome evaluation times, leading to missing values in our dataset.

CONCLUSION

This study presented an important descriptive and basic inferential statistical analysis of a resective epilepsy surgery cohort, consolidating the previous knowledge on the underlying structural causes, clinical practice, and surgical outcomes over more than two decades of experience. There is still a considerable delay between epilepsy onset and surgery, and the age at surgery increased in the most recent years. Neuropathologic assessment is essential to confirm the aetiology of the epilepsy and the seven histopathological categories presented different post-surgical outcomes. Our data provide realistic expectations about epilepsy surgery and highlight the need for further improvements in the diagnosis and treatment paradigm, leading to a more harmonized approach in epilepsy care.

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

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

AnsT-19: Development and Validation of a Scale to Assess the Anxiety of Family Physicians during Teleconsultation

AnsT-19: Desenvolvimento e Validação de uma Escala de Avaliação da Ansiedade dos Médicos de Família em Teleconsulta

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Acta Med Port 2023 Apr;36(4):236-245 ▪ https://doi.org/10.20344/amp.18175

ABSTRACT

Introduction: Following the outbreak of the disease caused by the novel coronavirus it was necessary to increase the non-face-to-face care activity through alternative means such as teleconsultation in primary health care. The adjustment to a type of remote consultation could have generated anxiety among family physicians. The main aim of the present study was to develop and validate a scale to assess the anxiety of family physicians during teleconsultation.

Material and Methods: Observational, cross-sectional study involving a sample of family physicians working in Portugal. An online survey that evaluated anxiety in teleconsultation was developed.

Results: A total of 359 valid responses were included in an exploratory factor analysis, after determining the number of factors to retain. A four-factor structure was detected with loadings ranging overall, from 0.44 to 0.98. Correlations between factors ranged from 0.42 to 0.58. Exploratory factor analysis results varied between good and very good fit, with chi-square/df result = 2.448, root mean square error of approximation (RMSEA) = 0.062 [90% CI = (0.053, 0.073)], root mean square of the residuals (RMSR) = 0.030 and Tucker Lewis index (TLI) = 0.931. Composite reliability was higher than 0.7 for all factors and average variance extracted was close or above 0.5 for the extracted factors, confirming convergent validity. McDonald's omega (ω) = 0.95 suggested the presence of a second-order factor, and thus a global measure for assessing anxiety during teleconsultation. Concurrent validity results were good, with correlations ranging from r = -0.277 to r = -0.393 with General Self-Efficacy scale (GSE) and r = 0.302 to r = 0.547 with Depression Anxiety Stress scales (DASS). Moderate correlations found between DASS and the dimensions of AnsT-19 suggest that AnsT-19 is capturing anxiety from the teleconsultation point of view. AnsT-19 factors and total score were significantly associated with gender, experience as a family doctor, psychotropic medication during the pandemic period and pre-pandemic experience of teleconsultation, indicating good construct validity. The limitations of the study are related to the convenience process, the use of an online survey and self-reported measurements.

Conclusion: AnsT-19 is a valid instrument to assess the anxiety of family physicians during teleconsultation.

Keywords: Anxiety; Physicians, Family; Portugal; Remote Consultation; Surveys and Questionnaires

RESUMO

Introdução: A doença provocada pelo novo coronavírus, aumentou a atividade de atendimento não presencial através de teleconsulta nos cuidados de saúde primários, o que pode ter sido motivo de ansiedade nos médicos de família. O principal objetivo da presente investigação foi desenvolver e validar uma escala de avaliação da ansiedade dos médicos de família durante a realização de teleconsulta.

Material e Métodos: Estudo observacional, transversal, de carácter descritivo. Foi aplicado um questionário *online* para avaliar a ansiedade de médicos de família em Portugal durante a realização de teleconsulta.

Resultados: Foi conduzida uma análise fatorial exploratória com inclusão de 359 respostas válidas depois de determinado o número de fatores a reter. Foi detetada uma estrutura fatorial de quatro fatores, com cargas fatoriais a variar entre 0,44 e 0,98. As correlações entre fatores variaram entre 0,42 e 0,58. Os resultados da análise fatorial exploratória indicaram um ajustamento bom ou muito bom, com o teste qui-quadrado/gl = 2,448, raiz do erro médio quadrático de aproximação (RMSEA) = 0,062 [90% IC = (0,053, 0,073)], raiz do erro médio quadrático residual padronizado (RMSR) = 0,030 e índice Tucker Lewis (TLI) = 0,931. A fiabilidade compósita foi superior a 0,7 em todos os fatores extraídos e a variância média extraída próxima ou superior a 0,5, confirmando validade convergente. O ómega de McDonald (ω) = 0,95 sugeriu a presença de um fator de segunda ordem, e assim uma medida global de ansiedade na teleconsulta. A validade concorrente foi considerada adequada, com correlações entre r = -0,277 e r = -0,393 para com a *General Self-Efficacy scale* (GSE) e entre r = 0,302 e r = 0,547 para com a *Depression Anxiety Stress scales* (DASS). As correlações moderadas encontradas entre a DASS e as dimensões da AnsT-19 sugerem que a AnsT-19 está a captar a ansiedade sob o ponto de vista da teleconsulta. Os fatores da AnsT-19, bem como o *score* total associaram-se com o género, experiência como médico de família, medicação psicotrópica durante o período pandémico e experiência pré-pandémica de teleconsulta, indicando boa validade de construto. As limitações do estudo estão relacionadas com o processo de amostragem por conveniência e recurso a um questionário *online* de auto-reporte.

Conclusão: O AnsT-19 é um instrumento válido para avaliar a ansiedade dos médicos de família durante a realização de teleconsulta.

Palavras-chave: Ansiedade; Consulta Remota; Inquéritos e Questionários; Médicos de Família; Portugal

INTRODUCTION

Following the outbreak of the disease caused by the new coronavirus, COVID-19, which led to a pandemic being declared on the 11th March 2020,[1] the Portuguese health-care system underwent considerable changes. As far as primary health care (PHC) was concerned, it was essential to increase the non-face-to-face care activity, through alternative means, such as telemedicine (TM).[2-4]

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Recebido/*Received*: 27/02/2022 - **Aceite/*Accepted*:** 24/10/2022 - **Publicado *Online*/*Published Online*:** 20/01/2023 - **Publicado/*Published*:** 03/04/2023

Telemedicine tools [teleconsultations (TC) and telemonitoring] support the remote provision of healthcare through the use of information and communication technologies.[5] Telemedicine, within the scope of carrying out remote consultations, includes follow-up models ranging from telephone consultations (CT) to video consultations (VC).[6,7]

The application of TC provides conditions to increase accessibility to consultations, minimizes the difficulty and increases equity in access to secondary care, thus reducing associated costs. It allows patients to remain in their homes as they receive care or manage their recovery/stable chronic diseases.[8] Although the importance of TC in providing care in the context of the COVID-19 pandemic is not debatable, this type of consultation raises concerns among physicians who perform it.[9,10] One of the most critical decisions that physicians must make in TC is the decision whether to carry out a subsequent face-to-face consultation. Other concerns are the absence of visual cues or lack of verbal communication on the CT and the inability to confirm the suspected diagnosis with physical examination.[9,10] The awareness of the risk of failing to diagnose a potentially serious situation is also a major concern in TC, which sustains many of the fears in carrying them out.[9]

The deployment of TC in PHC has experienced exponential growth, precipitated by the challenges of confinement and social distancing, imposed by the COVID-19 pandemic.[2,6,7] Physicians with experience in TC have less difficulty carrying out the physical examination and feel more confident and satisfied with the TC, but most family physicians had little or no experience in carrying out remote consultations before the pandemic.[11,12]

The adjustment to a type of remote consultation, without the proximity of the user (a fundamental pillar of the doctor-patient relationship), in the middle of the pandemic (which causes an overload of work for healthcare professionals, to which the individual is not used to), can cause anxiety, which is an emotional state of heightened pressure, commonly characterized by physical symptoms.[3,13-15] Anxiety related symptoms refer to functions of the cognitive, affective, behavioural and physiological systems, which generally act simultaneously.[14] Hou *et al* investigated the gender differences associated with anxiety in situations of emotional stress.[16] The authors concluded that biologically and socially, women are more susceptible to having higher levels of anxiety. Similar results were found in physicians.[17,18] Higher levels of anxiety are related to short-term memory impairment and higher levels of distractibility during consultations.[19-21]

It seems that perceived self-efficacy (the belief or confidence that a person holds in his or her own ability to perform a particular task or solve a problem) predicts anxiety and behavior eviction.[22,23] According to Bandura's Social Cognitive Theory, in high social cognitive states, higher levels of self-efficacy correspond to lower levels of anxiety and greater capacity for coping, and this was later corroborated by other authors.[22]

TC has become a vital piece in patient healthcare during the COVID-19 pandemic. This pandemic period represents the starting point for the acceptance of TC use as routine healthcare delivery, leading to important opportunities for progress.[24] Teleconsultation is essential for healthcare, not only during the pandemic but also afterwards.[25] The medical profession can generate high levels of anxiety, thus increasing the odds of medical errors.[21,26] Therefore, it is important to identify factors that can increase the risk of developing anxiety among doctors. The available anxiety scales do not focus on TC as the process from which anxiety builds up, but rather on a more general approach. The aim of this study was to evaluate the anxiety in TC through the development and validation of a scale to assess the anxiety of family physicians during TC.

MATERIAL AND METHODS

We performed an observational, cross-sectional study. Our study involved a convenience sample of all family physicians (specialists and residents) working in mainland Portugal in Primary Health Care units and Local Health units (LHUs). The study protocol was approved by the Ethics Committee of Administração Regional de Saúde do Norte, I.P..

We created an online survey (developed by Google Docs Survey® technology), from September to November 2020, and sent it to the institutional email account of the coordinators of Primary Health Care units and Local Health units in Portugal. The survey data collection was performed between the 23rd July and the 6th August 2021. The participation was completely voluntary.

The survey consisted of 48 questions, 12 of which in the first section to evaluate sociodemographic characteristics (age, gender, workplace, years of work as a family doctor, years of work in the current workplace, frequency of use of telemedicine tools before and during the pandemic, use of psychotropic drugs before and the during the pandemic) and 36 questions, in the second section, concerning assessment of anxiety during the teleconsultation and general self-efficacy.

The second section was divided in three parts: assessment of anxiety in the teleconsultation, assessment of the respondent's anxiety using a validated scale [anxiety scale (AS) part of the Depression Anxiety Stress scale (DASS)] and assessment of the respondent's self-efficacy using a validated scale for the Portuguese population [General Self-Efficacy scale (GSE), adapted from the GSE, developed by Ralf Schwarzer and Matthias Jerusalem].[27-29]

The assessment of anxiety in the teleconsultation consists of 19 items, evaluated by the Likert scale, and integrates symptoms of the cognitive, affective, behavioural, and physiological systems. This question was developed based on a literature review and probed views of 13 family physicians, with between seven and 41 years of professional experience, about TC.

The AS part of DASS is a seven-item self-reported questionnaire that evaluates anxiety during the previous week on a 4-point scale (0: "It didn't apply to me"; 1: "It applied to me a few times"; 2: "It applied to me many times"; 3: "It applied to me most of the time"). The total score is calculated by the sum of the scores of the seven items. A higher score corresponds to a more negative anxiety state.

The GSE aims to assess the general feeling of personal competence to deal with stressful situations, and it's composed of 10 questions. For each item, the inquired person must assign a level of agreement, using a 4-point scale (1: "Not at all true"; 2: "Hardly true"; 3: "Moderately true" and 4: "Exactly true").

Statistical analysis

Statistical analyses were performed with R 4.4.1. The packages used included [psych] and [GPArotation]. For descriptive statistics we used frequencies (n) and percentages (%).

The decision regarding the number of factors to extract was based on the Kaiser-criterion (*eigenvalue* > 1), parallel analyses and very simple structure (VSS). Exploratory factor analysis (EFA) was used to determine the factorial structure of the AnsT-19 scale. Loadings were obtained with oblimin rotation, admissible when factors are expected to be correlated. Loading's criterion was higher than 0.45 and total explained variance was acceptable if higher than 50%. EFA fit was assessed following the recommendations of Hu and Bentler[30] with chi-square/degrees of freedom, acceptable when lower than 3, the root mean square error of approximation (RMSEA), acceptable when lower than 0.07 the root mean square of the residuals (RMSR) acceptable for lower than 0.05 and the Tucker Lewis index of factoring reliability (TLI), acceptable when higher than 0.9. Convergent validity was assessed with average variance extracted (AVE), acceptable when higher than 0.5 and composite reliability (CR) acceptable when higher than 0.7.[31] McDonald's omega (ω) was calculated to assess the feasibility of a second order model, considering as acceptable results of ω > 0.8.

Pearson correlations were calculated to assess concurrent validity. *T*-tests and ANOVAs were used to assess construct validity. For independent variables "gender" (male/female), "current consumption of psychotropic medication" (yes/no) and "pre-pandemic experience of teleconsultation"

Table 1 – Sample characteristics

	n	%
Sex		
Female	272	75.8%
Male	87	24.2%
Age		
≤ 30 years	66	18.4%
30 - 35 years	106	29.5%
36 - 45 years	93	25.9%
46 - 55 years	37	10.3%
≥ 56 years	57	15.9%
Place of work		
Unidade de Saúde Familiar (USF)	283	78.8%
Unidade de Cuidados de Saúde Personalizados (UCSP)	68	18.9%
Unidade Local de Saúde (ULS)	8	2.2%
Experience as a family doctor		
≤ 4 years	86	24.0%
5 - 10 years	122	34.0%
11 - 20 years	74	20.6%
21 - 30 years	28	7.8%
≥ 31 years	49	13.6%
Experience working at the same place		
≤ 4 years	182	50.7%
5 - 10 years	84	23.4%
11 - 20 years	60	16.7%
21 - 30 years	11	3.1%
≥ 31 years	22	6.1%
Pre-pandemic psychotropic medication		
No	317	88.3%
Yes	37	10.3%
Do not want to answer	5	1.4%
Previous psychotropic medication		
No	248	69.1%
Yes	105	29.2%
Do not want to answer	6	1.7%
Pre-pandemic teleconsultation experience		
No	308	85.8%
Yes	51	14.2%
Teleconsultation in the last week		
No	40	11.1%
Yes	319	88.9%
Teleconsultation using voice devices (e.g. telephone)		
Never	0	0.0%
Rarely	0	0.0%
Ocasionally	4	1.1%
Frequently	60	16.7%
Always	295	82.2%
Teleconsultation using video + voice devices (e.g. computer/tablet)		
Never	339	94.4%
Rarely	15	4.2%
Ocasionally	5	1.4%
Frequently	0	0.0%
Always	0	0.0%

(yes/no) *t*-tests were used to assess the statistical significance and Cohen's d to measure the effect size. For independent variable "experience as a family doctor", ANOVA tests were used to assess statistical significance and eta squared (η^2) to measure the effect size.

Significance was considered for $p < 0.05$.

RESULTS

A total of 381 family physicians answered the questionnaire, from which 22 were excluded because they had not performed TC during the pandemic. The total number of valid responses was 359 (94.2%). Most family physicians were females (75.8%) and worked at LHUs. Table 1 shows other sample characteristics.

First, we present the results regarding the assessment of the psychometric properties of AnsT-19.

Exploratory factor analysis (EFA) was performed to propose a factorial structure for AnsT-19. The number of factors to retain was determined by comparing results gathered from three different approaches: the Kaiser criterion, that includes all factors with eigenvalue greater than 1, parallel analysis, that uses random simulated data to compare with the eigenvalues of the original data and very simple structure (VSS) in which all loadings lower than the maximum loading (of an item to a factor) are suppressed to zero, forcing a particular factor model to become more interpretable and clearly distinguished.

Kaiser-criterion results suggested a three-factor extraction with *eigenvalues* of 8.64 (1st factor), 1.47 (2nd factor), 1.06 (3rd factor) and a potential 4th factor with *eigenvalue* equal to 0.96, parallel analysis suggested a two-factor solution and VSS a four-factor solution (Fig. 1).

Because the four-factor solution was theoretically more admissible and was supported both by the VSS analysis and the Kaiser criterion (*eigenvalue* of the 4th was very close from the criterion > 1) a four-factor model was selected as the best choice.

Figure 2 shows the structural diagram for AnsT-19, loadings and correlations obtained with EFA. Oblimin rotation was considered due to theoretical assumptions of moderate to strong correlations between factors. For details on each item see the questionnaire in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18175/15028).

AnsT-19 was divided into four different factors. The first factor was labelled "cognitive and emotional interference" (CEI), because it included the perceptions of medical doctors about the cognitive and emotional interferences of preparing, executing, and coping with technical difficulties of the teleconsultation. The second factor was labelled "distractibility" because it was related with difficulties of concentration and distractions during teleconsultation. The third factor was labelled "difficulties of physical exploration" (DFE) and it included items that evoked the challenges of not being able to perform the patient's physical examination. Finally, "changes in sleep pattern" (CSP) was related with difficulties of maintaining adequate levels of sleep and rest during the period in which teleconsultation was being performed.

Cognitive and emotional interference (CEI) loadings of its 12 items ranged from 0.44 to 0.81. Distractibility was composed of three items and loadings ranged from 0.56 to 0.98. Difficulties of physical examination (DFE) comprised a two items factor and loadings were 0.76 and 0.86. Finally, changes in sleep pattern (CSP), also a two-item factor, had loadings of 0.58 and 0.86. Correlations between factors ranged from 0.42 to 0.58. Overall, loadings and correlations were considered as good psychometric indicators for this structure solution.

Appropriate fit measures for EFA were calculated. The chi-square/degrees of freedom result was 2.448 (< 3). The root mean square error of approximation (RMSEA) was 0.062 (< 0.7) with 90% CI = [0.053, 0.073], the root mean square of the residuals (RMSR) was 0.030 (< 0.05) and the Tucker Lewis Index of factoring reliability (TLI) was 0.931 (>

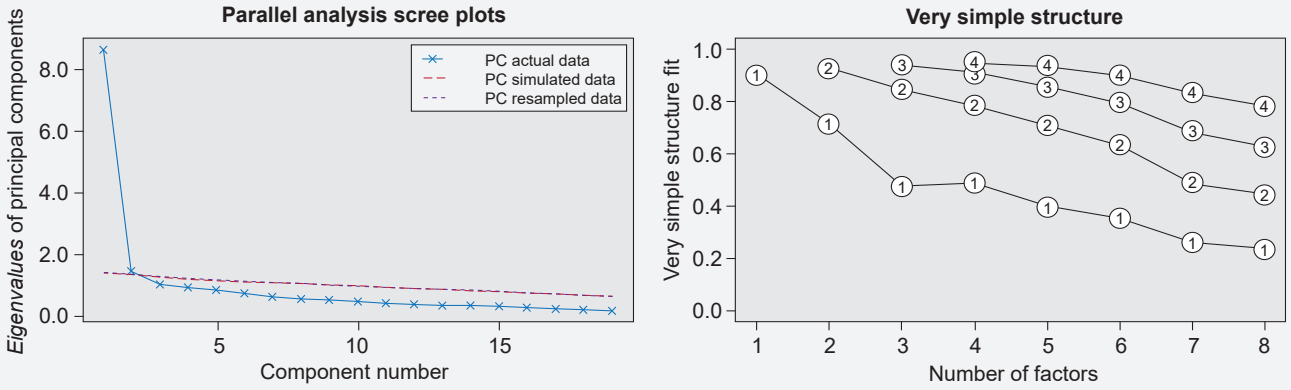

Figure 1 – Parallel analysis and VSS for factor extraction

0.9), all within the boundaries of good to very good fit.

Results of convergent validity showed composite reliability (CR) above 0.7 for all factors. Average variance extracted (AVE) was close or above 0.5 for the extracted factors. These results confirmed the existence of convergent validity for AnsT-19 (Table 2).

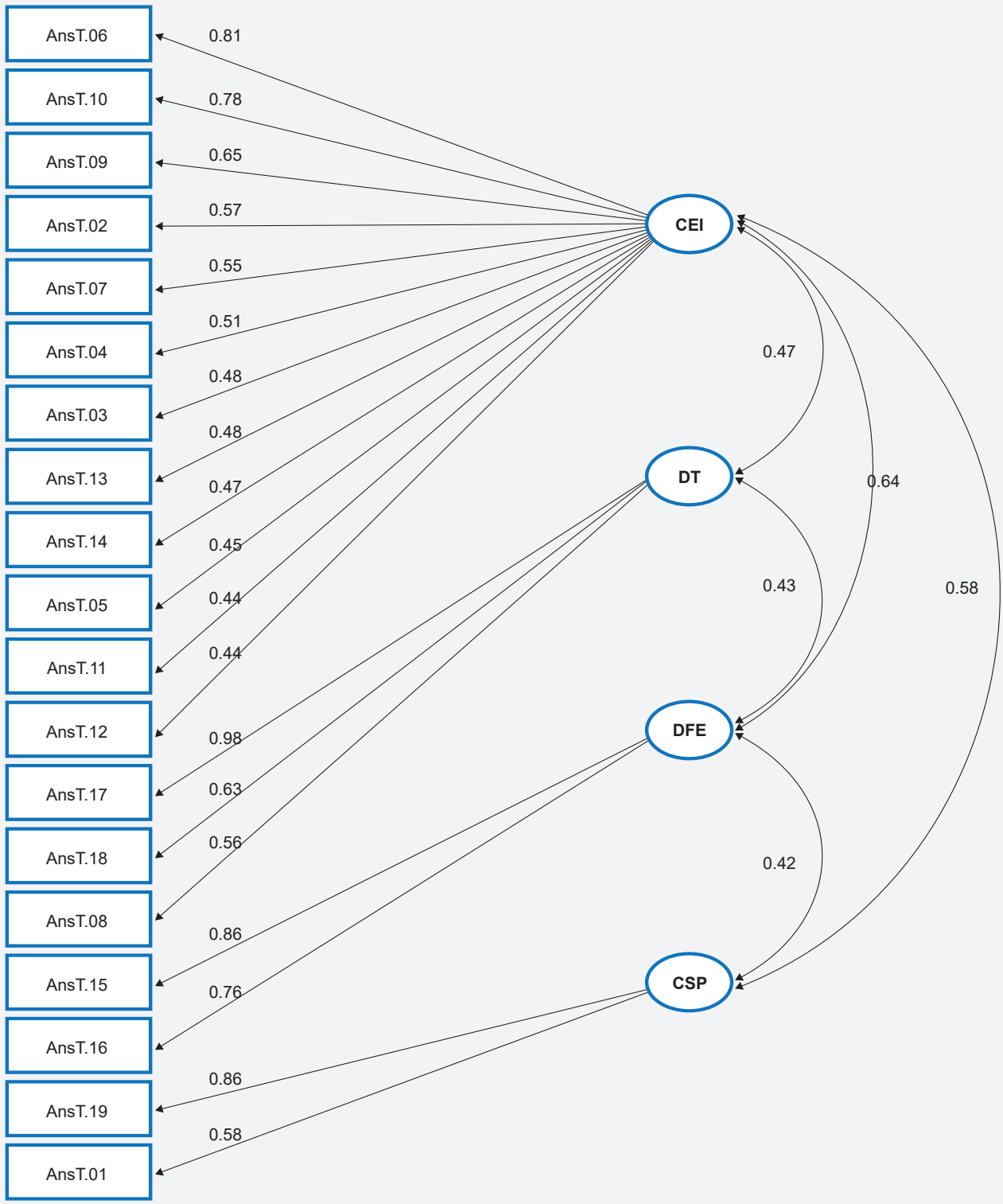

Figure 2 – Structural diagram for AnsT-19 obtained with EFA

Table 2 – Convergent validity

	Cumulative explained variance	Composite reliability	Average variance extracted
CEI	0.254	0.857	0.750
DT	0.363	0.909	0.457
DFE	0.477	0.853	0.660
CSP	0.561	0.747	0.597

Additionally, McDonald's omega (ω) was calculated to assess the feasibility of a second order model, considering the existence of a global factor labelled "anxiety in teleconsultation" (AnsT). McDonald's omega (ω) result of 0.95 (> 0.8) and loadings of each factor with the second-order factor AnsT were 0.968 for (CEI), 0.712, 0.793 (DFE) and 0.711 (CSP) suggested excellent feasibility for considering AnsT-19 as a global measure for assessing anxiety in teleconsultation.

As for the results of concurrent validity, each factor of AnsT-19 and the global measure of anxiety in teleconsultation (AnsT) were computed as observed variables by calculating the mean of their items.

Two other scales were included for this analysis. The GSE and the DASS, that in this study only included the dimension of anxiety. Reliability results for these two scales, assessed with Cronbach's alpha, were 0.895 and 0.882, respectively, suggesting very good reliability.

Table 3 shows that correlations between AnsT-19 factors and AnsT-19 global score (AnsT) with the measure of GSE were negative as expected, ranging from r = -0.277 to r = -0.393. Correlations between AnsT-19 factors and AnsT-19 global score (AnsT) with the anxiety dimension of DASS were positive, ranging from r = 0.302 to r = 0.547.

As for construct validity it was assessed by responding to four hypotheses: anxiety in TC is associated with gender (H1), anxiety in TC is associated with experience as a family doctor (H2), anxiety in TC is associated with psychotropic medication during the pandemic period (H3) and anxiety in TC is associated with pre-pandemic experience of teleconsultation (H4).

Fig. 3 shows the mean results of each factor and the corresponding *p*-value and effect size for the association with each independent variable.

Anxiety in TC was associated with the female gender, namely for cognitive and emotional interference (CEI), $p = 0.016$ (d = 0.30), difficulties of physical exploration (DFE), $p < 0.001$ (d = 0.42), changes in sleep pattern (CSP), $p = 0.003$ (d = 0.38) and the total score of anxiety in teleconsultation (AnsT), $p < 0.001$ (d = 0.35) (Fig. 3).

Anxiety in TC was associated with less experienced family physicians for factors of distractibility, $p < 0.001$ ($\eta^2 = 0.08$) and difficulties of physical examination (DFE), $p < 0.001$ ($\eta^2 = 0.07$). Associations were also found for cognitive and emotional interference (CEI), that peaks at 21 - 30 years of experience, and then drops for 30 years or more, $p < 0.001$ ($\eta^2 = 0.05$), changes in sleep pattern, that increase linearly until 21 - 30 years of experience and then decrease for the most experienced family physicians, $p < 0.001$ ($\eta^2 = 0.04$), and for the overall findings regarding anxiety in teleconsultation AnsT), revealing an equilibrium among all age groups until 21 - 30 years of experience, and then a lower result for the most experienced family physicians, $p < 0.001$ ($\eta^2 = 0.06$) (Fig. 3).

Associations with psychotropic medication during the pandemic period showed that there was an association between family physicians that took this type of medication and higher levels of cognitive and emotional interference (CEI), $p < 0.001$ (d = 0.49), distractibility, $p < 0.001$ (d = 0.24), difficulties of physical examination (DFE), $p <$

Table 3 – Pearson correlations of AnsT-19 with EAG and EADS anxiety

			Pearson correlations						
Measures	M	SD	1	2	3	4	5	6	7
1 CEI	2.18	0.70	1	0.608***	0.675***	0.580***	0.968***	-0.364***	0.542***
2 DT	2.35	0.84		1	0.519***	0.372***	0.732***	-0.316***	0.302***
3 DFE	2.75	0.98			1	0.429***	0.764***	-0.323***	0.332***
4 CSP	2.28	1.01				1	0.676***	-0.277***	0.524***
5 AnsT	2.28	0.68					1	-0.393***	0.547***
6 EAG	29.94	4.12						1	-0.407***
7 EADS anxiety	2.98	3.57							1

***: $p < 0.001$

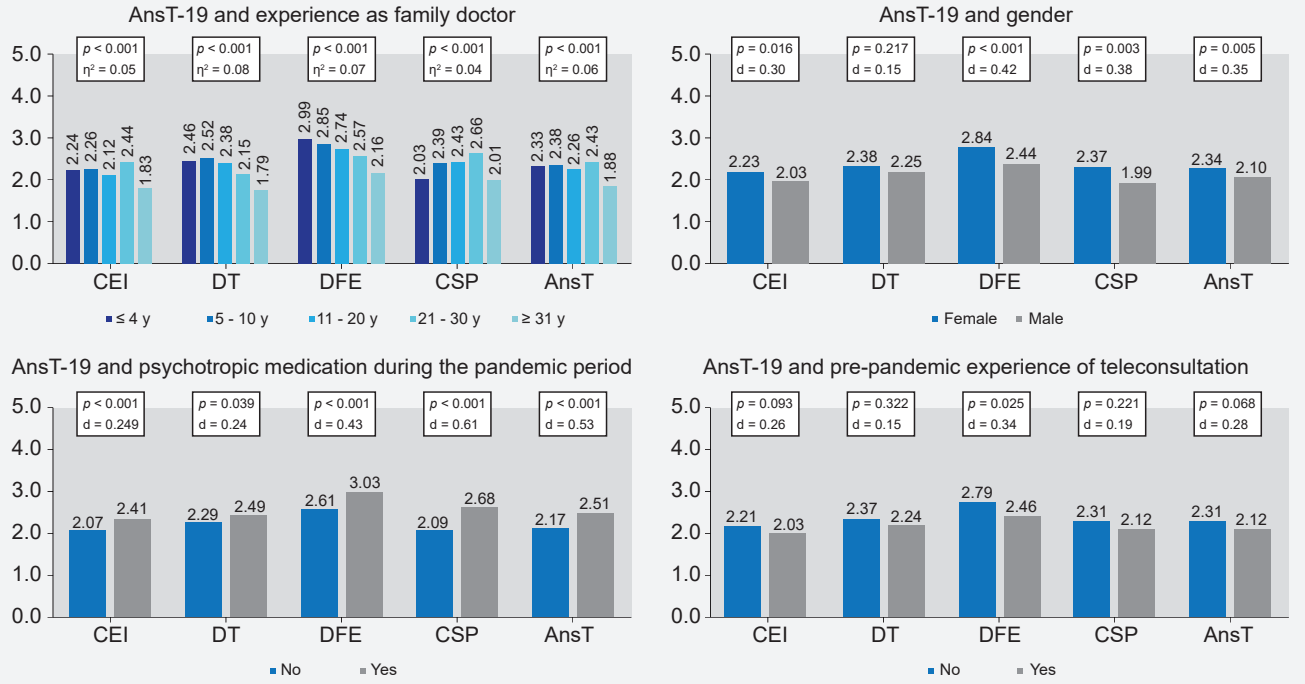

Figure 3 – AnsT-19 association with gender, experience as a family doctor, current psychotropic medication and pre-pandemic experience of teleconsultation

0.001 (d = 0.43), changes in sleep pattern (CSP), $p < 0.001$ (d = 0.61) and global anxiety in teleconsultation (AnsT), $p < 0.001$ (d = 0.53) (Fig. 3). We also checked for associations with pre-pandemic psychotropic medication, with no statistically significant results. Finally, associations with pre-pandemic experience in TC showed that family physicians with this type of experience were less prone to perceiving difficulties of physical exploration (DFE), $p = 0.025$ (d = 0.34); no differences were found for the other factors or for the total score (Fig. 3).

Considering the results obtained for hypothesis H1, H2, H3 and H4, AnsT-19 proved to be a discriminative measure, confirming construct validity.

DISCUSSION

Before the pandemic period most family physicians were not experienced in performing TC.[2,6,7] Our study corroborates this finding, with most family physicians having no experience in TC in the pre-pandemic period. During the pandemic period, the need to use TC increased very rapidly, and TC became an important tool in clinical practice. In our sample, 359 (94.2%) of the 381 doctors had performed TC in the previous week.

Adjusting to TC involves reducing the proximity to the patient, a basic pillar of the doctor-patient relationship, which can cause difficulties and anxiety.[3,15,32] The main purpose of the present study was to develop and validate a scale to assess the anxiety of family physicians in performing TC using a sample of family physicians from Portugal. In our sample, findings from EFA indicated that AnsT-19 was divided into four different factors: cognitive and emotional interference (CEI), distractibility, difficulties of physical examination (DFE), and changes in sleep pattern (CSP).

Cognitive processes influence the quality of the clinical decision-making process.[33] Hence, cognitive interference can have an impact in the decision making process, and ultimately influence clinical outcomes.[33] Moreover, clinical decisions are often made in contexts of emotionally challenging situations and require the ability to control emotions (own and others') and thus have an impact in the quality and safety of patient care.[34] Because cognitive processing can be influenced by emotions, especially when decisions involve conflict or anger, both emotion and cognition are engaged in clinical decision making and can influence clinical outcomes.[35,36] In this way, the first identified factor refers to the anxiety component associated with cognitive and emotional interference felt by family physicians in the context of TC.

The difficulty to ignore task-irrelevant stimuli, in other words, distractibility, causes longer medical appointments and increases diagnostic errors.[37] Distractibility and diagnostic errors are associated with having less clinical experience and increased degree of clinical complexity.[21] In the context of TC there are many distracting factors, such as patient environment, interruptions caused by calls, text messages, e-mails and app notifications associated with the use of smartphones. These sources of distraction increase the distractibility of physicians and potentially lead to patient care errors.[38] Therefore, the second identified factor concerns the anxiety component associated with distractibility of physicians during TC.

The inability to confirm a suspected diagnosis with physical examination is one of the main concerns about teleconsultation.[10] Visual messages and non-verbal

communication contribute more than 50% to an adequate clinical history, and facilitate physical examination.[10,39] The absence of a physical examination is a threat to patient safety as the probability of diagnostic errors is increased. The emphasis on history and eventually some point of care tests in TM without physical examination decreases the odds of reaching a clinical diagnosis.[40,41] Hence, the third identified factor was the anxiety component related with difficulties that physicians experienced regarding physical examination of patients during TC.

The COVID-19 epidemic increased the prevalence of psychological symptoms, such as anxiety, depression, fear, anger, and stress.[42] It is well established that stress is one of the major causes of sleep disturbances in doctors.[43,44] An increase of 23.6% in the prevalence of sleep disorders was reported in COVID-19 medical staff, a higher prevalence than in other community groups.[44] Therefore, the fourth and last factor identified refers to the anxiety component associated with changes in sleep pattern felt by family physicians in the context of TC.

Regarding concurrent validity, AnsT-19 factors and total score were positively correlated with the anxiety dimension of DASS and negatively associated with the measure of GSE suggesting good concurrent validity. Correlations of DASS with other anxiety measures have shown similar results, namely the Beck Anxiety inventory (BAI) and the State-Trait Anxiety inventory (STAI).[45,46] Correlations of GSE with other anxiety measures have also shown similar results, i.e. Hospital Anxiety and Depression scale (HADS) and slightly higher results with DASS in the study of Hussien.[20,47] Moderate correlations found between DASS and the dimensions of AnsT-19 lead us to believe that Anst-19 is capturing anxiety from the teleconsultation point of view. Therefore, AnsT-19 seems to have good concurrent validity which corroborates previous studies that showed that AnsT-19 is an instrument with good psychometric properties to assess anxiety in TC.

Construct validity was assessed by responding to four hypotheses. Regarding the association with gender (H1), female physicians had increased scores of anxiety in TC, namely for cognitive and emotional interference (CEI), difficulties of physical examination (DFE), changes in sleep pattern (CSP), and for the total score of anxiety in teleconsultation (AnsT). This result is consistent with previous studies in physicians namely McLean, Baptista *et al* and Pandey *et al*.[17-19]

Considering the experience as a family doctor (H2), our data showed that anxiety was higher in less experienced family physicians, as suggested by previous studies.[17,18,48] On the other hand, our results did not support the findings of the study by Demirgan *et al*[11] that suggested the anxiety level of physicians is not influenced by working experience. In our study, less experienced family physicians had higher scores of anxiety related with distractibility and difficulties of physical examination (DFE). Regarding cognitive and emotional interference (CEI), our results showed that this score reaches its highest within the 21 - 30 years of experience, decreasing afterwards. Similarly, anxiety in teleconsultation overall results (AnsT) had a lower result for the most experienced family physicians. These results can be justified by the increased workload of young doctors, that undergo strenuous medical training and to their lack of experience regarding the use of coping strategies.[17,18,48]

Associations with psychotropic medication (H3) showed that family physicians that took psychotropic medication during the pandemic period had higher levels of cognitive and emotional interference (CEI), distractibility, difficulties of physical examination (DFE), changes in sleep pattern (CSP), and global anxiety in teleconsultation (AnsT). No associations were found for psychotropic medication in the pre-pandemic period. Our results corroborate previous findings showing that essential workers faced higher rates of stress during the pandemic period and were more likely to increase the use of psychotropic medication.[49] To our knowledge our study was the first to demonstrate this association in the context of TC.

Finally, pre-pandemic experience of TC (H4) was associated with less perceived difficulties regarding physical examination (DFE). No differences were found for the other factors or for the total score. Previous research indicates that doctors with pre-pandemic experience in TC had a more positive perspective on TC.[11] Training in TC has been previously associated with higher confidence on performing a limited physical examination via telephone and with satisfaction towards TC.[12] Hence, our results and previous reports suggest that training in TC is an important tool to overcome assessment difficulties with physical examination.

AnsT-19 factors and total score associations with gender, experience as a family doctor, psychotropic medication, and pre-pandemic experience of TC support construct validity.

All fit measures were, at the very least, accomplishing the necessary criteria. In particular, McDonald's omega (ω) suggested the feasibility of a global measure of anxiety in TC. Every result obtained in this study suggested that AnsT-19 is a good instrument to assess anxiety in TC for family physicians.

The limitations of the study are related to the convenience process that reduces generalisability. Including doctors from other specialties besides family physicians and repeating the study in a post-pandemic period could reveal additional anxiety responses to TC.

Being a cross-sectional study, it was not possible to

establish causality between variables, namely between the use of psychotropic drugs and anxiety related to consultation. The use of an online survey for data-collection and self-reported measurements can have an impact on obtaining the true scores of the assessed variables.

The results in this scale would always need to be compared with anxiety results in face-to-face consultations during the peak pandemic periods to allow for any type of comparison of face-to-face *versus* TC.

Future studies should also compare AnsT-19 and other COVID-19 related anxiety measures (e.g., Taylora, Landryb, Paluszekb, Fergusc, McKayd and Asmundsonb).[50]

In terms of clinical implications, the detection of high anxiety levels among family doctors during TC can contribute to the reduction of the sources of anxiety assessed with AnsT-19, namely technical difficulties, reduction of distractibility, reduction of physical examination and sleeping disorders. This is, to the best of our knowledge, the first assessment of anxiety in family physicians during TC in Portugal.

CONCLUSION

AnsT-19 is valid instrument to assess the anxiety of family physicians during teleconsultation. The development of a validated scale for the evaluation of family physicians' anxiety in performing teleconsultation (AnsT-19) can help identify anxiety in physicians both during the pandemic period and in the post-pandemic period, and it could become an important resource in planning teleconsultations.

AUTHOR CONTRIBUTIONS

ACB: Writing of the manuscript, conception of questionnaires, data collection, final review.

AIC: Writing of the manuscript, conception of questionnaires, data collection.

SG: Writing of the manuscript, conception of questionnaires.

RD: Conception of questionnaires, final review.

EM: Writing of the manuscript, statistical analysis.

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.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Preoperative Location of Parathyroid Adenomas in Primary Hyperparathyroidism: The Role of Cervical Doppler Ultrasound

Localização Pré-operatória de Adenomas da Paratiroide no Hiperparatiroidismo Primário: O Papel da Ecografia Cervical com Doppler

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Acta Med Port 2023 Apr;36(4):246-253 ▪ https://doi.org/10.20344/amp.18735

ABSTRACT

Introduction: Parathyroid adenoma is the most frequent cause of primary hyperparathyroidism. In recent years, the preoperative location of parathyroid adenomas allowed minimally invasive surgical techniques that have become preferred over the traditional bilateral neck exploration. The more recent guidelines on this subject highlight the role of nuclear medicine imaging tests. The aim of this study was to review the current role of Doppler ultrasound (US) in assessing the preoperative location of parathyroid adenomas in patients with primary hyperparathyroidism.

Material and Methods: Retrospective study based on data from patients with primary hyperparathyroidism that underwent parathyroidectomy between January 2013 and January 2022 at the Centro Hospitalar Universitário Lisboa Central. Statistical analysis was performed with IBM SPSS Statistics, version 26.0.0.0®.

Results: Parathyroidectomy was performed in 171 patients (77.8% females) with primary hyperparathyroidism. Cervical Doppler ultrasound was the most performed test (64.3%, n = 110) for preoperative location and detected a suspicious lesion in 98 patients (89.1%). The preoperative location of the parathyroid adenomas was assessed through the Doppler ultrasound and was compared with the surgical reports and histological findings; a correct identification was made in 76 patients (77.6%). Doppler ultrasound slightly underestimated the mean adenoma size (18.1 ± 7.7 mm preoperative *versus* 22 ± 8.4 mm postoperative). Calcium, parathyroid hormone levels, adenoma size and concomitant presence of thyroid nodules did not affect the accuracy of Doppler ultrasound.

Conclusion: Doppler ultrasound showed high diagnostic accuracy even in patients with nodular thyroid disease regardless of calcium and parathyroid hormone levels and adenoma size. Furthermore, its safety, affordability and availability should favor its use as first line test in primary hyperparathyroidism to assess the preoperative location of parathyroid adenomas.

Keywords: Hyperparathyroidism, Primary; Parathyroid Neoplasms/diagnostic imaging; Ultrasonography, Doppler

RESUMO

Introdução: O adenoma da paratiroide é a causa mais frequente de hiperparatiroidismo primário. Nos últimos anos, a localização pré-operatória de adenomas da paratiroide tem permitido técnicas cirúrgicas minimamente invasivas que se tornaram preferíveis à exploração cervical bilateral tradicional. As recomendações internacionais mais recentes relativamente a este tópico têm dado ênfase aos exames de imagem de medicina nuclear. Neste estudo, os autores revêem o papel atual da ecografia cervical com Doppler na localização pré-operatória de adenomas da paratiroide em doentes com hiperparatiroidismo primário.

Material e Métodos: Estudo retrospetivo de doentes com hiperparatiroidismo primário submetidos a paratiroidectomia entre janeiro de 2013 e 2022 no Centro Hospitalar Universitário Lisboa Central. Análise estatística realizada com IBM SPSS Statistics, versão 26.0.0.0®.

Resultados: Foram identificados 171 doentes com hiperparatiroidismo primário submetidos a paratiroidectomia (77,8% sexo feminino). A ecografia cervical com Doppler foi o exame mais solicitado para localização pré-operatória de adenomas da paratiroide (64,3%, n = 110) e detetou a lesão em 98 doentes (89,1%). A análise comparativa da localização pré-operatória do adenoma da paratiroide baseada na ecografia cervical com Doppler com os achados cirúrgicos e histológicos demonstrou identificação correta do adenoma em 76 doentes (77,6%). A ecografia cervical com Doppler subestimou ligeiramente a dimensão dos adenomas (18,1 ± 7,7 mm pré-operatório *versus* 22 ± 8,4 mm pós-operatório). Os níveis de cálcio, paratormona, a dimensão do adenoma e a presença concomitante de nódulos tiroideus não afetou a eficácia diagnóstica da ecografia cervical com Doppler.

Conclusão: A ecografia cervical com Doppler demonstrou elevada precisão diagnóstica independentemente da presença concomitante de nódulos tiroideus, dos níveis de cálcio e paratormona e da dimensão dos adenomas da paratiroide. A sua disponibilidade, segurança e custo aliado à capacidade diagnóstica demonstrada devem favorecer o seu uso como primeira linha na localização pré-operatória de adenomas da paratiroide no hiperparatiroidismo primário.

Palavras-chave: Neoplasias da Paratiroide/diagnóstico por imagem; Hiperparatiroidismo Primário; Ultrassonografia Doppler

INTRODUCTION

Primary hyperparathyroidism (PHPT) is one of the most common endocrine disorders. More asymptomatic patients are being diagnosed due to a greater use of routine screening tests. Incidence estimates for PHPT vary from 0.4 to 82 cases per 100 000.[1] Solitary parathyroid adenoma is the cause of PHPT in about 80% of patients. The remaining

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Recebido/*Received*: 18/06/2022 - **Aceite/*Accepted*:** 05/08/2022 - **Publicado *Online*/*Published Online*:** 14/10/2022 - **Publicado/*Published*:** 03/04/2023

causes are multiple adenomas, hyperplasia and, rarely, carcinoma.[2] In recent years, minimally invasive surgical techniques have challenged the traditional bilateral neck exploration. They are believed to offer distinct advantages such as shorter operative time and reduced complication rate (early postoperative hypocalcemia and injury to the adjacent tissues).[3] There are different imaging techniques for preoperative location of parathyroid adenomas. Ultrasonography (US) and ^{99m}TC-sestamibi scintigraphy are the dominant imaging techniques, followed by contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI). The most recent guidelines on this subject highlight the use of nuclear medicine imaging techniques to get the best sensitivity and specificity.[4]

Ultrasonography is an available non-invasive and cost-effective imaging method. The advances in equipment such as enhanced contrast resolution, increased dynamic range and color power Doppler have increased its accuracy.[5] Parathyroid adenomas are usually oval or bean-shaped and, in the large majority, homogeneously hypoechoic on gray-scale imaging because of its marked and compact cellularity. Color and power Doppler imaging is a very helpful tool to confirm a suspicious parathyroid adenoma. Different parenchymal flow patterns of parathyroid adenomas have been reported, including no flow, central vascularity, peripheral vascularity (ring) with a large polar feeding vessel and combined central and peripheral vascularity.[6,7]

The aim of this retrospective study was to review the current role of Doppler US in assessing the preoperative location of parathyroid adenomas in patients with PHPT.

MATERIAL AND METHODS

Study population

The authors reviewed data from patients with PHPT that underwent parathyroidectomy between January 2013 and January 2022 at the Centro Hospitalar Universitário Lisboa Central and had a histological result of adenoma. Surgical criteria were based on the 2014 Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism.[8] At least one of the following criteria should be present: serum calcium > 1.0 mg/dL upper limit of normal; bone mineral density by dual-energy X-ray absorptiometry (DEXA) with a T-score < -2.5 at lumbar spine, total hip, femoral neck, or distal one-third radius; vertebral fracture; creatinine clearance < 60 mL/min; 24-h urine for calcium > 400 mg; presence of nephrolithiasis or nephrocalcinosis or age < 50 years-old. Patients with parathyroid carcinoma and hereditary PHPT including multiple endocrine neoplasia type 1 and 2A, familial isolated hyperparathyroidism and hyperparathyroidism-jaw tumor syndrome were not included. Patients with history of a previous neck surgery and/or chronic kidney disease stage 3 or higher were also excluded. A study cohort of 171 patients was obtained. Parathyroidectomy was performed by high-volume surgeons in all cases. Doppler US was performed by the same radiologist in 108 patients (98.1%). No patient underwent parathyroid hormone (PTH) washout on the lesions detected by Doppler US.

Study variables

Data on the following parameters were collected: age, gender, preoperative serum calcium, phosphate, intact parathyroid hormone and 25-hydroxyvitamin D. The performed tests and preoperative location findings, surgical findings and histopathological results were also collected. The results of the imaging studies were compared with the intraoperative and histological findings.

Statistical analysis

Measurement data on normal distribution were expressed as mean ± standard deviation. The correlations between continuous variables were evaluated using the Spearman test. The χ^2 test was used to compare the nominal variables between the groups. The analyses were completed using IBM SPSS Statistics, version 26.0.0.0® (IBM Corporation, Armonk, NY, USA). All *p*-values were two-tailed, and statistical significance was set at $p < 0.05$.

The study was approved by the local Ethics Committee and informed consent was waived.

RESULTS

From January 2013 to January 2022, 171 patients (133 female and 38 male) with PHPT underwent parathyroidectomy. The baseline characteristics of the patients are reported in Table 1. Most patients required one or two tests to detect the enlarged parathyroid(s). The frequency of each performed test is reported in Fig. 1.

The Doppler US found a suspicious lesion in 98 patients (89.1%): left superior (n = 11), right superior (n = 9), left inferior (n = 32), right inferior (n = 43), and multiple locations (n = 3). The preoperative location of the parathyroid adenomas was assessed through both the Doppler US and the surgical reports and histological findings (Fig. 1). Doppler US was able to correctly locate parathyroid lesion in all cases of left superior parathyroid adenomas (11/11), 88.9% (8/9) of right superior adenomas, 81.3% (26/32) of left inferior adenomas, 65.1% (28/43) of right inferior adenomas and 100% (3/3) of multiple adenomas. Overall, a correct identification was made in 77.6% of cases (76/98). Considering the laterality, Doppler US correctly located 86.5% (n = 45) of lesions on the right side and 100% (n = 43) on the left side.

No correlation was found between the accuracy of cervical Doppler US and calcium levels ($p = 0.339$) or PTH levels ($p = 0.804$) at diagnosis. Adenoma size did not interfere with

Table 1 – Baseline characteristics

		Range	Reference range
Patients	n = 171		
Female	n = 133 (77.8%)		
Male	n = 38 (22.2%)		
Mean age at HPTP diagnosis (years-old)	64.4 ± 13	22 – 89	
Dual energy X-ray absorptiometry (DEXA)	n = 131 (76.6%)		
Renal Ultrasound	n = 121 (70.8%)		
Mean serum calcium at HPTP diagnosis (mg/dL)	11.5 ± 1	9.9 – 18	8.6 – 10.3
Mean serum phosphorus at HPTP diagnosis (mg/dL)	2.5 ± 0.6	0.6 – 4.3	0.6 – 4.3
Mean serum intact PTH (pg/mL)	286.1 ± 400.3	50.3 – 4738	10 – 52
Mean 25-hydroxivitamin D level (ng/mL)	18.1 ± 10.5	4.2 – 59.6	25 – 80
Concomitant nodular thyroid disease	n = 116 (67.8%)		
Number of performed tests preoperatively:			
1 test	n = 59 (34.5%)		
2 tests	n = 61 (35.7%)		
3 tests	n = 45 (26.3%)		
4 tests	n = 6 (3.5%)		

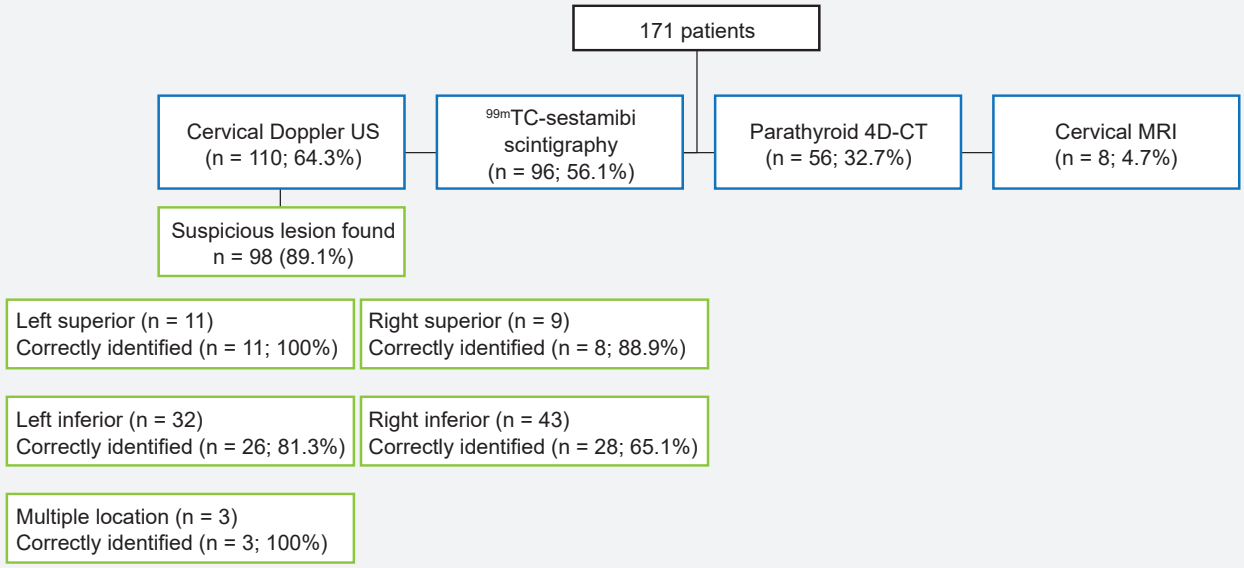

Figure 1 – Tests performed for preoperative location in the cohort of patients with primary hyperparathyroidism. Findings of cervical doppler ultrasound (compared with surgical and histological reports).

Doppler US accuracy (p = 0.832).

The impact of simultaneous nodular thyroid disease with the accuracy of Doppler US was also evaluated. Multinodular goiter was present in 116 patients (67.8%). Doppler US was performed in 60 patients with simultaneous nodular thyroid disease. Diagnostic accuracy was not affected by the presence of thyroid nodules (p = 0.419).

Doppler US was performed by the same radiologist in almost all cases (108/110; 98.1%). The mean adenoma size with this technique was 18.1 ± 7.7 mm (ranged 5 to 37 mm). Postoperative mean adenoma size was 22 ± 8.4 mm (ranged 7 to 48 mm).

In 12 patients, Doppler US did not find any parathyroid lesion. In those cases, ^{99m}TC-sestamibi scintigraphy was

performed in nine patients and correctly located the lesion in eight of them (88.9%) finding an ectopic location (mediastinal) in three (33.3%). Parathyroid 4D-CT was also performed in nine patients and detected the lesion in six (66.7%). Cervical MRI was performed in one patient with correct identification of parathyroid lesion. Bilateral neck exploration was needed in four patients. Those four patients had negative results with Doppler US, ^{99m}TC-sestamibi scintigraphy and parathyroid 4D-CT.

The median follow-up time after surgery was 5.4 ± 2.1 years. Cure was achieved in 108 of 110 patients (98.1%) that performed Doppler US for preoperative location of enlarged parathyroids and was sustained during the follow-up time. Two patients had persistent hypercalcemia after surgery, defined by hypercalcemia within six months following surgery.

DISCUSSION

Although an experienced surgeon remains the best option to detect parathyroid lesions, it is widely accepted that preoperative location reduces the operative time and complication rate.[9]

A variety of imaging techniques have been employed with different accuracy rates. No universally accepted algorithm exists to assess the preoperative location of parathyroid lesions and different tests have various advantages and disadvantages depending on the clinical scenario.[10]

Ultrasonography has improved in recent years. The enhanced gray-scale contrast resolution and color power Doppler increased the sensitivity for the detection of parathyroid adenomas.[5,11,12] It allows the investigation of the vascularization pattern of tumors and the distinction between parathyroid lesion and fibrotic areas, lymph nodes or other parts of the thyroid gland. A meta-analysis performed by Ruda *et al* encompassing 54 studies done between 1995 and 2003 using ultrasonography to assess the preoperative location in primary hyperparathyroidism estimated the ultrasonographic sensitivity for the detection of adenoma at 79%.[13]

^{99m}TC-sestamibi scintigraphy has been extensively used in the setting of PHPT and studies report a sensitivity range of 44% - 88%.[14] The advantages include relative operator-independent effectiveness and improved detection of ectopic or far posterior lesions that US is prone to miss. However, and according to the literature, approximately 20% of sestamibi scans are false negative or inconclusive despite biochemical evidence of PHPT.[15-18] Recently, the use of SPECT/CT allowed better identification of parathyroid lesions providing anatomical and functional information that led to a high sensitivity and specificity.[19]

4D-CT is more commonly used as a problem-solving tool for inconclusive or discordant first line imaging outcomes which introduces potential bias in most studies that assess its performance. The reported sensitivity when used as the initial imaging study ranges from 62% to 92%.[10,20] An advantage of 4D-CT is the ability to identify parathyroid lesion that were avascular on color Doppler but that will still enhance after contrast injection. The main advantage of MRI is its potential performance that is comparable to 4D-CT without radiation exposure. However, in comparison with 4D-CT, it is less available, more expensive and time consuming. The reported sensitivity ranges from 64% to 93%.[10,21]

Our study with 110 patients that performed Doppler US confirms the validity of this imaging technique to assess the preoperative location of parathyroid adenomas in PHPT. Almost all patients (98.1%) underwent Doppler US by the same radiologist which reduces inter-operator variability. Overall Doppler US recognized the correct side of parathyroid adenomas in the neck (100% for left adenomas and 86.5% for right adenomas). The reliability for predicting superior or inferior location was lower (52.8%). This could be explained mainly by the fact that adenomas have a longitudinal expansion which makes it difficult for the radiologist to classify as a superior or inferior lesion. Our study demonstrates that the main mistake occurs when the radiologist locates the lesion on the inferior pole. As shown in Table 2,

Table 2 – Comparative results of parathyroid lesion location with Doppler US *versus* surgical/histological findings

Suspected location (Doppler US)	**Histologically confirmed location of the lesion**				
	Superior right (n = 17)	**Superior left** (n = 19)	**Inferior right** (n = 28)	**Inferior left** (n = 31)	**Multiple** (n = 3)
Superior right (n = 9)	8	1	0	0	0
Superior left (n = 11)	0	11	0	0	0
Inferior right (n = 43)	9	1	28	5	0
Inferior left (n = 32)	0	6	0	26	0
Multiple (n = 3)	0	0	0	0	3

six of the 32 adenomas located in the inferior left pole were actually in the upper pole and the same happened to nine of the 43 adenomas initially identified in the inferior right pole. Nevertheless, cervical Doppler US was effective in correctly identifying laterality which still allows minimally invasive surgical techniques and a unilateral neck exploration in nearly all patients.

A brief note should be done to the patient that presented with a high PTH (4738 pg/mL) due to a suspicious parathyroid carcinoma – the histology slides of this patient were reviewed, and the diagnosis of a massive 4.5 cm parathyroid adenoma was confirmed (Bcl2+; Ki67 < 1%).

Multiglandular disease is responsible for 10% to 15% of primary hyperparathyroidism. In this study there were three patients with multiglandular disease. These patients had preoperative cervical Doppler US suggesting two parathyroid adenomas. Despite this preoperative location the surgeon performed a conventional bilateral neck exploration in all these cases. The surgery and histological report confirmed the ultrasound findings, and all patients are cured. The few patients with multiglandular disease in this sample does not allow conclusions to be drawn. In patients with suspicious multiglandular disease all parathyroid glands should be exposed and examined with an intraoperative determination of the extent of parathyroidectomy.

Contrary to expectations, the adenoma size did not interfere with Doppler US accuracy. This is probably explained by the fact that most adenomas were large enough to be detected by Doppler US (18.1 ± 7.7mm). The experienced radiologist that performed almost all the tests could also explain the good rate of detection.

In our study we calculated an overall sensitivity of 89.1% and an accuracy of 77.6% for Doppler US which is slight lower than what is described in the literature.[5,6,22] This could be explained by the fact that some superior lesions were identified by the radiologist as being inferior and vice versa. When considering only the ability to locate the right side of the neck, we calculated an overall sensitivity of 92.6%. Furthermore, we did not find any statistically significant differences in the accuracy of Doppler US between patients with and without nodular thyroid disease. Calcium levels, PTH levels at diagnosis and adenoma size also did not affect the cervical Doppler US accuracy. Doppler US slightly underestimated the mean adenoma size (18.1 ± 7.7 mm preoperative *vs* 22 ± 8.4 mm postoperative), but a moderate to strong correlation was observed between preoperative and postoperative adenoma size (r_s = 0.558, p < 0.001).

Parathyroid tissue generally consists of chief cells, but it may contain oncocytic cells, transitional cells, and clear cells. Previous studies have reported some associations between the ultrasound pattern and the histological subtype of the parathyroid adenoma. The typical parathyroid adenoma is usually hypoechoic and well-defined with homogenous echotexture as a result of a uniform arrangement of

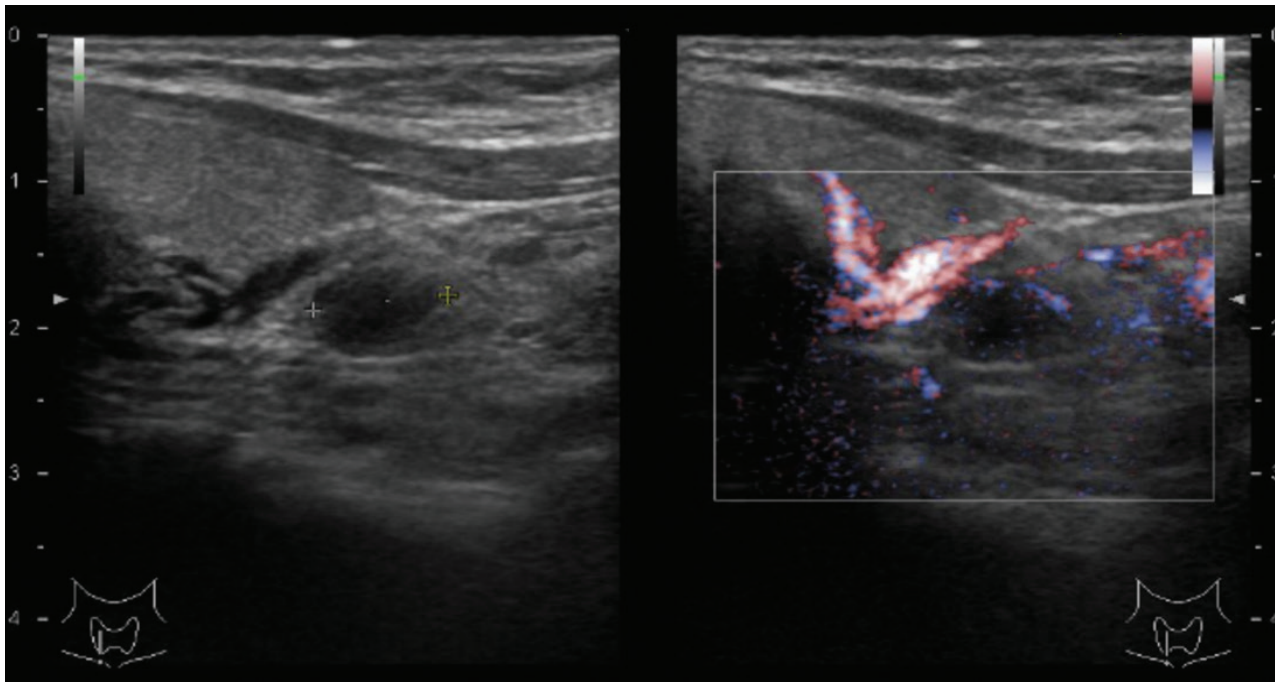

Figure 2 – A parathyroid adenoma was identified adjacent to the lower pole of the right thyroid lobe. The left image shows a solid lesion with 8.9 mm, rounded and well-circumscribed, hypoechoic with respect to the thyroid tissue. On the right image with Doppler technique a feeding artery is identified that enters the adenoma through one of its poles and is distributed towards the periphery (vascular arch pattern).

the parathormone-producing chief cells (Fig. 2). Connective and fat tissue usually have an hyperechogenic pattern. Due to the presence of fibrous bands and cellular atypia in atypical parathyroid adenomas, the finding of a parathyroid adenoma with greater hyperechogenic area may indicate an atypical lesion and therefore clinical follow-up can be performed more closely.[22] In our study, the histological composition of parathyroid adenomas lacks in histological reports. However, in the future, it would be interesting to compare the ultrasound pattern and the histological subtype of the parathyroid adenoma in a prospective study.

In 12 patients of this study, no lesion was found with Doppler US. ^{99m}TC-sestamibi scintigraphy and 4D-CT was performed in nine of them, being diagnosed in 88.9% (n = 8) and 66.7% (n = 6), respectively. In four patients, no parathyroid lesion was found with these imaging modalities.

While it is relatively consensual that Doppler ultrasound should be used as a first line test for parathyroid imaging due to its safety, availability, accuracy and ability to assess for concomitant thyroid disease,[23] there is no consensus on which should be the second line test.

The 2016 Guidelines for Definitive Management of Primary Hyperparathyroidism of The American Association of Endocrine Surgeons recommend that patients who are candidates for parathyroidectomy should be referred to an expert clinician to decide which imaging studies should be performed based on their knowledge of regional imaging capabilities. They recommend cervical ultrasonography performed by an experienced radiologist as the first line test and suggest adding ^{99m}TC-sestamibi or 4D-CT to get the most cost-effective strategy.[25] The advantage of radionuclide parathyroid imaging over US lies in the identification of ectopic glands, as well as in easier recognition of posteriorly located upper glands.[4]

However, more recent practice guidelines for parathyroid imaging of the European Association of Nuclear Medicine recommend combining ^{99m}TC-sestamibi SPECT/CT with cervical ultrasound performed by an experienced sonographer as a first-line strategy. PET/CT with ^{18}F-labeled choline analogues has shown better results but data from large cohorts and on cost-effectiveness are not currently available.[25] It may be considered a potential alternative first-line method whenever possible as it appears to be an effective technique even in patients with negative/equivocal standard imaging findings. 4D-CT may be useful in case other imaging studies are negative or inconclusive, in patients with distorted neck anatomy, or after futile surgery. It has similar diagnostic accuracy compared with ^{99m}TC-sestamibi SPECT but a higher radiation exposure. ^{18}F-labeled choline analogue PET may be combined with 4D-CT in complicated cases (e.g., re-operated patients) to enhance the sensitivity and predictive positive value compared with either technique alone. MRI may be also used after negative/inconclusive first-line imaging or in pregnant patients. Invasive diagnostic procedures remain as last resort.[4]

A similar recommendation was made by the last consensus of the European Society of Endocrinology Education Program of Parathyroid Disorders (PARAT 2021). To detect multiglandular disease and/or small lesions, the preoperative localization procedures that are more sensitive are 18F-fluorocholine PET/CT, with or without enhanced arterial imaging, and 4D-CT.[27]

In our study, there were only few patients with no detected parathyroid lesion on Doppler ultrasound. Based on our results and on its safety, availability, and low cost, we still agree that color Doppler ultrasound should be the first line test to assess the preoperative location of parathyroid adenomas.

Among the strengths of this study are the homogeneity of the cohort and the reduced inter-operator variability. To the best of our knowledge, this is the first study on preoperative location of parathyroid adenomas from a nationally representative cohort of patients.

The limitations of the study include the relatively small sample size compared with other similar studies. The ultrasound detection of parathyroid hyperparathyroidism is largely dependent on radiologist experience. The strength we focused on having one experienced radiologist performing almost all tests, could also be considered a limitation to apply this technique in other centers and highlights the need to have an experienced radiologist dedicated to performing parathyroid US. Another limitation is related to the retrospective nature of the study. The clinic's preoperative location approach to primary hyperparathyroidism was not the same in all patients. Even though most patients performed Doppler US as a first line test, the second-line test was different among the ones that had no suspicious lesion identified on Doppler US. This fact limits our conclusion about which test should be performed next in the cases where Doppler US does not find any lesion. Given this limitation, future research to focus on the best clinical approach would be interesting. In our center, Doppler US is now being performed as the first-line test in all patients and 4D-CT as the second line test. The present findings should be further confirmed in a prospective study.

CONCLUSION

Doppler US showed an overall sensitivity of 89.1%. When regarding the location on the correct side of the neck we found a sensitivity of 92.6%. It was also valuable to evaluate the thyroid preoperatively and even in patients with nodular thyroid disease, the accuracy of Doppler US was not affected. Its widespread availability, low cost, lack of radiation exposure and high sensitivity may justify its use

as a first line test in most situations for preoperative location of parathyroid adenomas in PHPT.

AUTHOR CONTRIBUTIONS

SA: Conception of the study; Data collection, analysis, and interpretation; Drafting of the manuscript.

TR: Conception of the study; Data collection, analysis, and interpretation; Revision of the results and approval of the final version of the manuscript.

AP: Data analysis and interpretation; Revision of the results and approval of the final version of the manuscript.

NC, JMC, PT, JSN: Revision of the results and approval of the final version of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

The Impact of the Enhanced Recovery After Surgery (ERAS) Protocol on Colorectal Surgery in a Portuguese Tertiary Hospital

Impacto da Aplicação do Programa ERAS na Cirurgia Colorrectal de um Centro Hospitalar Terciário

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Acta Med Port 2023 Apr;36(4):254-263 ▪ https://doi.org/10.20344/amp.18284

ABSTRACT

Introduction: The benefits of the multimodal Enhanced Recovery After Surgery® (ERAS) program have been described all over the world. The adoption of several perioperative strategies translates into an improvement in the quality of the healthcare provided. The aim of this study was to report the results of the implementation of the ERAS® program for colorectal surgery in a tertiary hospital.

Material and Methods: In this single-center observational study, 534 patients who underwent colorectal surgery between December 2018 and May 2021 were included. Two groups were considered: before and after the implementation of the ERAS® program. The primary outcome measure was 30-day morbidity. The length of hospital stay, readmission rate, reintervention and mortality among the two groups were also evaluated.

Results: The pre-ERAS group included 102 patients and the ERAS group included 432 patients. There was a statistically significant reduction in morbidity at 30 days (37.3% *vs* 26.5%, $p < 0.05$), length of stay (7 days *vs* 5 days, $p < 0.001$) and readmission rate (12.9% *vs* 6%, $p < 0.05$) after the implementation of the ERAS program.

Conclusion: The ERAS® protocol for colorectal surgery was successfully and safely implemented in our hospital, contributing to an improvement in perioperative care provided to patients.

Keywords: Anesthesia; Colorectal Surgery/methods; Enhanced Recovery After Surgery; Perioperative Care/methods

RESUMO

Introdução: Os benefícios do programa multimodal *Enhanced Recovery After Surgery*® (ERAS) têm sido descritos em todo o mundo. A adoção de várias estratégias peri-operatórias traduz-se numa melhoria dos cuidados de saúde prestados com ganhos para o doente e para a instituição. O objetivo deste estudo foi reportar os resultados da implementação do programa ERAS® na cirurgia colorretal num hospital terciário.

Material e Métodos: Neste estudo unicêntrico observacional foram incluídos 534 doentes submetidos a cirurgia colorretal entre dezembro 2018 e maio de 2021. Foram criados dois grupos: antes e depois da implementação do programa ERAS® com o objetivo primário de comparar a morbilidade aos 30 dias. Foi também avaliado o tempo de internamento, a taxa de reinternamento, reintervenção e a mortalidade entre os grupos.

Resultados: O grupo pré-ERAS era constituído por 102 doentes e o grupo ERAS por 432 doentes. Verificou-se uma redução significativa na morbilidade aos 30 dias (37,3% *vs* 26,5%, $p < 0,05$), no tempo de internamento (7 dias *vs* 5 dias, $p < 0,001$) e na taxa de readmissão (12,9% *vs* 6%, $p < 0,05$) após a implementação do programa.

Conclusão: O protocolo ERAS® na cirurgia colorretal foi implementado com sucesso e segurança no nosso hospital, contribuindo para uma melhoria dos cuidados peri-operatórios prestados aos doentes.

Palavras-chave: Anestesia; Cirurgia Colorretal/métodos; Cuidados Perioperatórios; Recuperação Pós-Cirúrgica Melhorada

INTRODUCTION

Enhanced Recovery After Surgery® (ERAS) represents a paradigm shift in surgical patient care and can result in substantial benefits in both clinical outcomes and cost-effectiveness through optimization of the perioperative period.[1]

The ERAS colorectal program, established in 2010, aims to improve recovery after surgery through a multidisciplinary framework and multimodal treatments based on interventions in the preoperative, intraoperative and postoperative scenario.[2] For patients to receive a holistic evaluation, they need to be assessed preoperatively by a surgeon, an anesthesiologist, a nurse skilled in the preoperative preparation of patients, a physiatrist, a nutritionist and a social worker. This ensures the early identification and effective clinical management of 'higher-risk' patients and reduces variation in practice.[3] In the intraoperative phase, in addition to minimally invasive procedures and goal directed fluid therapy, patients have an evidence-based and procedure-specific analgesic regimens, which included regional analgesia.[4,5] In the postoperative scenario, the key protocol elements are

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Recebido/*Received*: 21/03/2022 - **Aceite/*Accepted*:** 23/08/2022 - **Publicado *Online*/*Published Online*:** 04/10/2022 - **Publicado/*Published*:** 03/04/2023

early feeding, early mobilization and opioid-sparing analgesia.

Different meta-analysis demonstrated that minor and major postoperative complications after major abdominal surgery increased mortality, decreased health related quality of life and increased healthcare expenditure.[6] For a range of surgical disciplines, there is evidence highlighting the effect of the ERAS program in improving preoperative well-being and patient outcomes, namely decreased length of stay, 30-day morbidity and readmissions.[7]

The ERAS program for colorectal surgery was implemented at our institution with the aim of reducing morbidity and length of stay and reducing healthcare expenditure. The aim of this study was to report the impact of this program's implementation in our institution.

MATERIAL AND METHODS

This study was reported according to the STROBE checklist. Institutional approval was obtained for the conduct of the study as an audit of practice.

Patient selection

In this cohort study, patients undergoing colorectal surgery at a single Portuguese center between December 2018 and May 2021 were prospectively included in an electronic database. All consecutive adult patients (aged over 18) undergoing colorectal surgery were included regardless of the surgical approach [open, laparoscopic, single incision laparoscopic surgery (SILS)] or surgery for malignant disease. Data collected included demographic and clinical data: age, body mass index (BMI), gender, history of smoking, diabetes or other comorbidities, Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity risk (P-POSSUM), American Society of Anesthesiologist (ASA) physical status, diagnosis, disease location and use of neoadjuvant treatment; preoperative, intraoperative and postoperative variables related with compliance; and surgical outcomes such as surgical type and approach, creation of stoma and duration of surgery. Emergency surgeries were excluded.

Patients in the post implementation ERAS program (ERAS group) were compared with 102 consecutive patients undergoing traditional care, before the implementation of ERAS (pre-ERAS group), between December 2018 and May 2021.

The primary outcome measure was any 30-day morbidity, which was classified *a priori* according to the Clavien-Dindo (CD) system specific to abdominal surgery.[8] Minor morbidity was defined as the occurrence of a CD grade I or II complication, and major morbidity was defined as the occurrence of a grade III or IV complication. Postoperative length of stay (LOS) was considered a secondary outcome measure. Other secondary outcome measures included 30-day readmission, reintervention, and 30-day mortality.

Enhanced recovery after surgery

All patients in the pre-ERAS group followed the institution's generic protocol which included pre-operative tests, skin preparation, bowel preparation, multidrug resistant organisms screening as per national guidelines, bowel preparation, venous and antibiotic prophylaxis. No intra-operative or postoperative strategies were formally adopted in this group.

In the ERAS group, the patients followed a standardized protocol divided into preoperative, intraoperative, and postoperative phases (Fig. 1).

Preoperative phase

All patients were admitted to hospital on the day before their surgery, maintained oral diet and started a therapeutic regimen according to patient comorbidities and surgical intervention. Although the ERAS society recommends against the use of mechanical bowel preparation (MBP), our protocol included MBP in combination with oral antibiotics for all patients. Up to two hours before induction of anesthesia, patients were given complex carbohydrate drinks if not contraindicated and routine administration of preanesthetic sedative medication was not given.

Perioperative phase

Prophylactic antibiotics were given within 60 minutes prior to induction. Minimally invasive surgery was used whenever possible. Abdominal trunk blocks such as the transversus abdominis plane (TAP) block were performed in laparoscopic surgery and rectus sheath block in open surgery. Intravenous non-steroidal anti-inflammatory drugs and paracetamol were used as adjuncts to pain relief.

Balanced crystalloid solution and vasopressors were administered when needed to avoid intraoperative hypoperfusion. Normothermia was maintained through active warming devices and venous thromboembolism prophylaxis included pharmacologic and nonpharmacologic measures. Urinary catheters were placed but routinely removed within 24 to 72 hours and if intra-abdominal drains were used, they were removed as soon as possible.

Postoperative phase

On the day of the surgery, patients started drinking water and liquids and were seated for the first time two to four hours after surgery. Intravenous fluids were stopped on the first postoperative day. Solid oral intake was introduced 48 to 72 hours after surgery.

A standardized analgesic regimen was used consisting of acetaminophen and non-steroidal anti-inflammatory

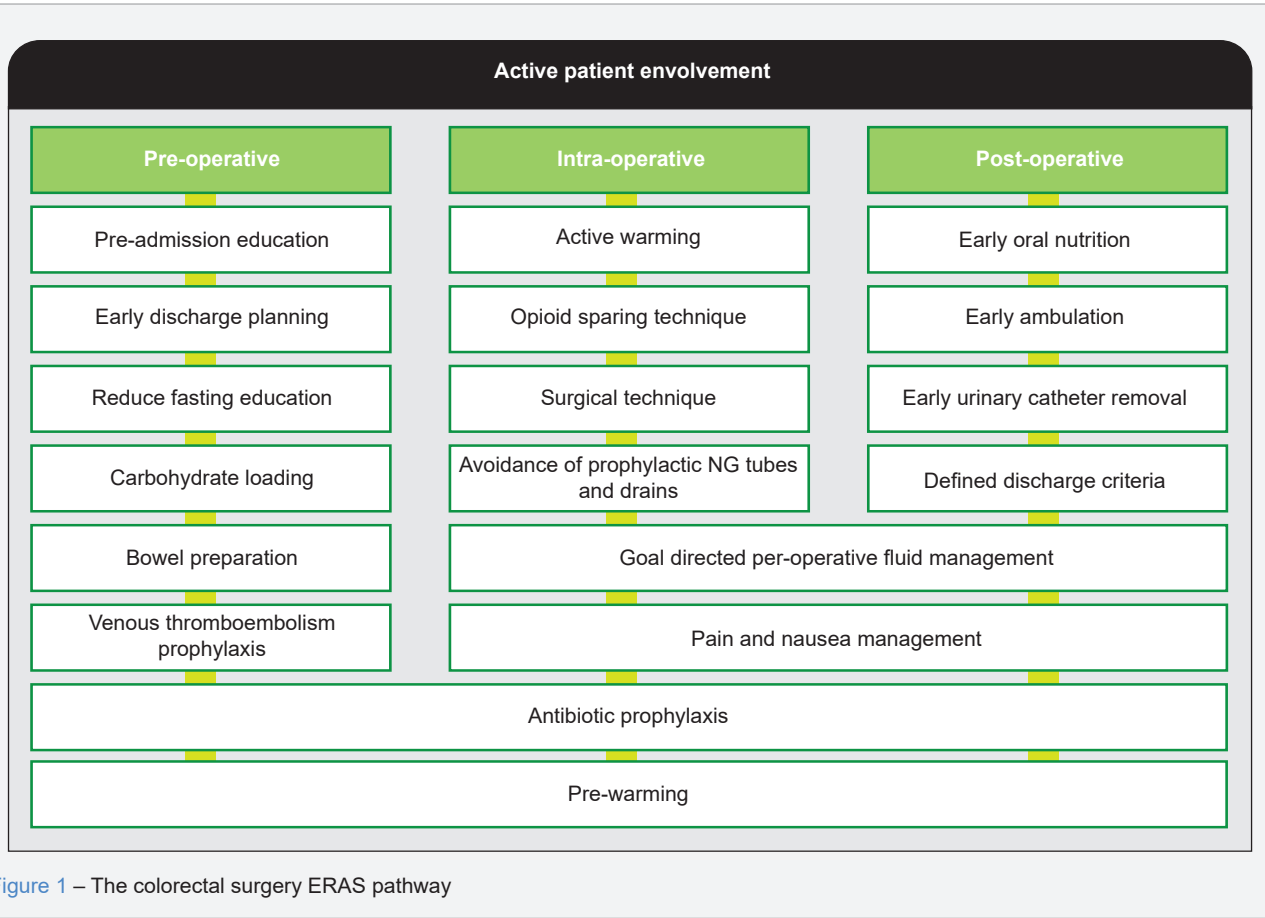

Figure 1 – The colorectal surgery ERAS pathway

drugs. Opiates were avoided when possible and epidural blockades, when used, were continued until postoperative day two. Ileus was defined as a transient cessation of bowel motility after surgery.[9] A multimodal approach to prevent postoperative ileus, nausea and vomiting was used. This included the use of antiemetic agents (metoclopramide), peripherally acting l-opioid receptor antagonists and bisacodyl.[2] Wound infection diagnosis was made according to CDC definitions.[10]

Statistical methods

Continuous variables were expressed as median and interquartile range, and normality was assessed with the Kolmogorov-Smirnov test. Categoric variables were expressed as count and percentages. The group of patients that underwent surgery after the protocol implementation (ERAS group) was compared with a conventional care control group (pre-ERAS group). The analysis between groups was conducted using the Mann–Whitney U test for continuous variables that were not normally distributed. Categorical variables were compared with the Pearson's chi-square test or Fisher exact test as appropriate. Univariate analysis was also performed to identify significant variables for predictors of morbidity at 30 days. A *p*-value of less than 0.05 was considered statistically significant. Bivariate analysis followed by binary regression analysis were used to identify predictors of morbidity and in-hospital mortality.

RESULTS

A total of 534 consecutive patients (102 cases in the pre-ERAS 432 cases in the ERAS group) were included during the study period. Table 1 shows patient demographics, comorbidities and procedural characteristics in the pre-ERAS and ERAS program.

Clinical characteristics

The median age was 66 years (IQR 57.0 – 78.0) in the pre-ERAS group and 68 years (IQR 57.0 – 77.0) in the ERAS group. Most patients had cancer (76.0% in the pre-ERAS group and 72.0% in the ERAS group) The median body mass index (BMI) was 26.4 kg/m2 (IQR 24.2 – 29.7) in the pre-ERAS group and 26.2 kg/m2 (IQR 23.4 – 29.2) in the ERAS group (both overweight). Alcohol consumption was significant higher in the pre-ERAS group (*p*-value < 0.001).

Regarding comorbidities, patients in the ERAS group

Table 1 – Clinicopathological characteristics of patients.

	Pre-ERAS (n = 102)	**ERAS** (n = 432)	***p*-value**
Age, years – median (IQR)	66 (57.0 – 78.0)	68 (57.0 – 77.0)	0.912
BMI, kg/m^2 – median (IQR)	26.4 (24.2 – 29.7)	26.2 (23.4 – 29.2)	0.498
Gender, n (%)			0.276
Female	31 (30.4)	156 (36.1)	
Male	71 (69.6)	276 (63.9)	
Smoker, n (%)	7 (8.6)	48 (11.1)	0.510
Alcohol use, n (%)	12 (15.6)	9 (2.1)	**< 0.001**
Comorbidities, n (%)			
Cardiovascular	3 (2.9)	19 (4.4)	0.781
Diabetes	23 (22.5)	104 (24.2)	0.727
Pulmonary disease	2 (2.0)	7 (1.6)	0.684
Immunosuppressive treatment	4 (4.7)	16 (3.7)	0.758
P-POSSUM mortality risk, % (IQR)	3.5 (2.0 – 9.0)	12,0 (6.0 – 24.0)	**< 0.001**
ASA, n (%)			**< 0.001**
I	6 (8.8)	11 (2.6)	
II	39 (57.4)	211 (49.3)	
III	23 (33.8)	194 (45.3)	
IV	0 (0.0)	12 (2.8)	
Diagnosis, n (%)			0.423
Benign	24 (24.0)	118 (28.0)	
Malign	76 (76.0)	304 (72.0)	
Disease location, n (%)			0.104
Colon	63 (62.4)	294 (68.5)	
Rectum	34 (33.7)	130 (30.3)	
Colon and rectum	4 (4.0)	5 (1.2)	
Neoadjuvant radio-chemotherapy[1], n (%)	18 (18.0)	64 (14.8)	0.443

[1] Some missing values were found in the pre-ERAS and the ERAS groups

had a higher proportion of cardiac disease and diabetes, but without statistical significance. In terms of preanesthetic comorbidities, the ASA physical status classification system was used. Most patients in the ERAS group were ASA grade II (49.3%) or ASA grade III (45.3%). In the ERAS group, 12 patients (2.8%) were classified as ASA IV. In the pre-ERAS group, no patients were classified as ASA IV. There were no patients classified as ASA grade V.

Concerning P-POSSUM, the median level in the pre-ERAS group was 3.5% compared with 12% in the ERAS group.

There were no baseline statistically significant differences between groups in age, gender, BMI, and comorbidities but there was a statistically significant difference between P-POSSUM values and ASA score (Table 1).

Perioperative protocol and ERAS compliance

Compliance with individual items is shown in Table 2. As only a few ERAS program items were included in the pre-ERAS group, relatively low compliance wasfound for the variables pre-operative nutritional assessment, nutritional support with preoperative oral carbohydrate treatment (0%) and no/selective bowel preparation (21.6%).

Concerning the intraoperative phase, the use of nerve blocks and local anesthesia also increased (2.9% *vs* 62.6%, *p*-value < 0.001) and there was a statistically significant difference in the use of systemic opioids given. Regarding nausea and vomiting prophylaxis there was also a statistically significant difference (49% *vs* 71.8%, *p*-value < 0.001).

During the postoperative period there was a significant decrease in the median duration of intravenous fluid

Table 2 – Perioperative protocol and ERAS compliance

	Pre-ERAS (n = 102)	ERAS (n = 432)	*p*-value
Pre-operative			
No bowel preparation done, n (%)	22 (21.6)	78 (18.1)	0 413
Preoperative oral carbohydrate treatment, n (%)	0 (0)	336 (77.8)	**< 0.001**
No preoperative sedative medication, n (%)	69 (67.6)	428 (99.1)	**< 0 001**
Thrombosis prophylaxis, n (%)	99 (97.1)	432 (100)	**0 007**
Antibiotic prophylaxis, n (%)	54 (52.9)	247 (57.3)	0 424
Intra-operative			
No epidural or spinal used unless applicable[1], n (%)	96 (95)	411 (95.1)	1.000
Lumbar supplementary analgesia[1], n (%)	3 (3)	9 (2.1)	0.707
Nerve blocks or local anesthesia[1], n (%)	3 (2.9)	270 (62.6)	**< 0.001**
No long-acting systemic opioids given[1], n (%)	19 (76.0)	432 (100.0)[1]	**< 0.001**
PONV prophylaxis administered, n (%)	50 (49.0)	310 (71.8)	**< 0.001**
Forced-air heating cover used, n (%)	94 (93.1)	411 (96.5)	0.161
Total fluid volume, mL – median (IQR)	1250 (762.5 – 2237.5)	1400 (1000 – 1900)	0.256
Post-operative			
No NG tube used postoperatively, n (%)	49 (48)	410 (94.9)	**< 0.001**
Stimulation of gut motility[2], n (%)	7 (7.9)	375 (93.3)	**< 0.001**
Balanced fluids day 0, ml – median (IQR)	2315 (437.5 – 3603.8)	2160 (1641.75 – 2800.00)	0.930
Duration of IV fluid infusion, nights – median (IQR)	6 (4 – 7)	1 (1 – 1)	**< 0.001**
Oral intake on day 0, mL – median (IQR)	0 (0)	200 (200 – 300)	**< 0.001**
Mobilization at all on day of surgery	0 (0)	312 (73.2)	**< 0.001**

[1] Some missing values were found in the pre-ERAS and the ERAS groups
[2] Intravenous or oral laxatives as bisacodyl

therapy in the ERAS group (six days versus one day, *p*-value < 0.001) as well as an increase in the median volume of oral fluids intake on the day of surgery (0 mL *vs* 200 mL, *p*-value < 0.001). This group also had a statistically significant increase in stimulation of gut mobility, avoidance of nasogastric tubes as well as earlier mobilization (*p*-value < 0.001).

Surgical outcomes

Procedural characteristics are represented in Table 3. There were more colon procedures in the ERAS group and the most common procedures were right hemicolectomy (27.6%), rectal anterior resection (20.9%) and sigmoidectomy (19.1%). No difference was found in operative time between the two groups (180 *vs* 180 min, *p*-value 0.818).

Surgical approach changed after ERAS program implementation (*p*-value < 0.001) with laparoscopic procedures becoming more common (43.1% *vs* 73.1%).

Morbidity and mortality

The primary outcome of this study was 30-day morbidity, which was classified *a priori* according to the Clavien-Dindo system specific to abdominal surgery. Summary of postoperative complications at30 days is listed in Table 4 for both groups.

According to the CD classification, there was a statistically significant difference in surgical complications (*p*-value 0.004) and the rate of overall complications was lower in patients included in the ERAS protocol (37.3% *vs* 26.5%, *p*-value 0.003) In the pre-ERAS group, 56.8% of patients had CD complications classified as grade I compared with 20.5% in the ERAS group. Only one case in the pre-ERAS group and three cases in the ERAS group resulted in death after the operation, and patients with other complications in both groups were discharged successfully after conservative treatment or surgical interventions. No statistically significant difference in mortality was observed between groups.

Table 3 – Procedural characteristics

	Pre-ERAS (n = 102)	ERAS (n = 432)	*p*-value
Surgery, n (%)			**0.009**
Right colectomy	24 (24.0)	119 (27.6)	
Left colectomy	4 (4.0)	26 (6.0)	
Sigmoidectomy	13 (13.0)	82 (19.1)	
Rectal anterior resection	26 (26.0)	90 (20.9)	
Abdominoperineal resection	7 (7.0)	27 (6.3)	
TAMIS	0 (0)	11 (2.6)	
Protocolectomy	3 (3.0)	4 (0.9)	
Total/ Subtotal colectomy	8 (8.0)	13 (3.0)	
Ostomy closure	14 (14.0)	48 (11.1)	
Protopexy	1 (1.0)	1 (0.2)	
Exploratory laparoscopy/laparotomy	0 (0)	9 (2.1)	
Stoma, n (%)			0.285
No	82 (81.2)	348 (80.9)	
Ileostomy	14 (13.9)	44 (10.2)	
Colostomy	5 (5.0)	38 (8.8)	
Surgical approach, n (%)			**< 0.001**
Open	46 (45.1)	76 (17.6)	
Laparoscopic	44 (43.1)	316 (73.1)	
SILS (single incision laparoscopic surgery)	0 (0)	7 (1.6)	
Through stoma	12 (11.8)	33 (7.6)	
Duration of surgery, minutes, median (IQR)	180 (125 – 250)	180 (120 – 240)	0.818

Surgical complications included surgical wound infection, intra-abdominal abscess, anastomotic dehiscence, and bleeding. The presence of ileus in the pre-ERAS group was not evaluated, so this variable was not included in surgical complications.

The median LOS in the pre-ERAS group was 7 (5 - 10,25) days compared with 5 days (4 - 9 days) in the ERAS group. The difference in median LOS between the two groups was statistically significant ($p < 0.001$). On the other hand, four patients (3.9%) in the traditional pathway and 24 (5.6%) in the ERAS group required reoperation. Causes for reoperations included hemorrhage, intestinal obstruction, anastomotic leak, and abscess.

The rate of 30-day readmissions was 12.9% (13 patients) in the pre-ERAS group and 6.0% (26 patients) in the ERAS group. The difference between the two groups was statistically significant ($p < 0.05$) (Table 5).

A regression was performed to adjust the results for possible confounding factors, as shown in Table 6.

Linear logistic regressions were adjusted considering P-POSSUM and ASA score as independent variables. The application of the ERAS program (category coded as “1” in the database) compared with pre-ERAS (refers to the independent variable, the category with “0” in the database) had a shorter average of 2.06 days ($10^{0,143}$) in the LOS.

A multivariate logistic regression model was performed to predict hospital readmission, which were not associated with P-POSSUM (OR -0.012, 95% CI 0.885 – 1.104, *p*-value 0.834) or ASA score (OR 0.478, 95% CI 0.877 – 2.966, *p*-value 0.124).

DISCUSSION

This retrospective review of a prospectively collected database has provided an insight into the preoperative, intraoperative, and postoperative factors including patient demographics, disease state, and ERAS compliance that may influence the outcomes achieved in a colorectal ERAS program. With key outcome and process data collection we were able to make a continuous improvement to the program.

The ERAS program has been introduced to optimize both physical and psychological well-being of patients prior

Table 4 – Postoperative outcomes in the Pre-ERAS and ERAS groups

Complications	**Pre-ERAS** (n = 102)	**ERAS** (n = 432)	***p*-value**
Overall, n (%)	38 (37.3)	114 (26.5)	**0.003**
Anesthetic, n (%)	0 (0.0)	4 (3.2)	1
Surgical, n (%)	12 (11.8)	41 (9.5)	0.494
Type of complication, n (%)			
Cardiovascular	1 (1)	17 (3.9)	0.220
Respiratory	4 (3.9)	37 (8.6)	0.113
Renal	1 (1)	24 (5.6)	0.064
Psychiatric	8 (7.8)	12 (2.8)	**0.036**
Tromboembolic complications	0 (0)	2 (0.5)	1
Ileus	NA	48 (11.1)	**NA**
Nausea and vomiting PONV,	18 (17.6)	14 (3.2)	**< 0.001**
Wound infection, n (%)	6 (8.1)	16 (4.2)	1
Dehiscence, n (%)	2 (2.0)	15 (3.5)	0.753
Intraabdominal abcess, n (%)	1 (1)	16 (3.7)	0.217
Clavien-Dindo			**0.004**
I	21 (56.8)	32 (20.5)	
II	10 (27.0)	76 (48.7)	
III	5 (13.5)	38 (24.3)	
IV	0 (0)	7 (4.5)	
V/ Mortality	1 (2.7)	3 (1.9)	

to colorectal surgery. This study was designed to report on the collective impact of ERAS implementation across the perioperative period. It has also specifically examined the impact of a multimodal approach on clinical and functional outcomes following colorectal surgery.

Compliance rates in each prehabilitation modality have been evaluated, to assess the potential effect on outcomes. The main findings of the study comprised a considerable reduction in the hospital LOS without an increase in the complications rate compared to our previous standards.

ERAS describes multimodal protocols designed to optimize patients perioperatively with the goal improving of postoperative recovery. The goal of ERAS protocols lies in reducing both intra- and postoperative adverse events, which have the potential to impair patients' perioperative well-being and to delay discharge.

The ERAS protocol includes administration of antibiotic prophylaxis and thromboprophylaxis, prevention of hypothermia and fluid imbalance, as well as operative measures that help decrease colorectal complications.[11-13] The most common complications reported in colorectal surgery are wound infection and ileus.[14] Ileus was the most frequent complication (11%) in the ERAS group. The incidence found in our study was not higher than that described in the literature (10% - 30%).[15] Moreover, and despite being associated with nausea/vomiting, pain and failure of oral food intake, there was no increase in these parameters in the ERAS group.[16] The ERAS® Society does not recommend bowel preparation as a routine on colorectal surgery, but it is still controversial depending on the location of the lesion and the surgical approach.[17] Some studies suggested that preparation is linked to adverse effects such as prolonged ileus and patient distress without any evidence of advantages and should not be used routinely.[18]

The analysis of some studies showed that the ERAS pathway was associated with a reduction of morbidity, particularly associated with a reduced number of surgical complications.[19-22] In our study, we found similar results to those previously reported in other studies.

Our study included a wide range of patients that are representative of daily practice. By analyzing the data, it is possible to infer that patients in the ERAS group were more complex than those in the control group, with more comorbidities and at greater cardiovascular risk. More patients in the ERAS group had cardiac disease, a known predictive factor for postoperative mortality according to the Lee Index, and higher ASA and P-POSSUM scores.[23] The ASA grade and the P-POSSUM score have been

Table 5 – Main outcomes in the Pre-ERAS and ERAS groups

	Pre-ERAS (n = 102)	ERAS (n = 432)	*p*-value
Length of stay, days median, (Q1 – Q3)	7 (5 – 10.25)	5 (4 – 9)	**< 0.001**
Readmission, n (%)	13 (12.9)	26 (6.0)	**0.018**
Reoperation, n (%)	4 (3.9)	24 (5.6)	0.505

Table 6 – Main simple and multiple linear regression model for length of stay[1]

	Non-adjusted model ß (95% CI)	*p*-value	Adjusted model ß (95% CI)	*p*-value
ERAS Protocol (yes)	-0.143 (-0.21 – 0.77)	**< 0.001**	-0.204 (-0.279 – 0.129)	**< 0.001**
P-POSSUM	-	-	0.021 (0.013 – 0.029)	**< 0.001**
ASA score[2] (mild)	-	-	0.001 (0 – 0.002)	0.091

[1] The authors performed a logarithmic transformation of LOS
[2] ASA score was treated as categorical one (ASA < 2 being recoded as 'healthy' and ASA < 2 as 'mild')

considered a useful adjunct to informed consent and for monitoring surgical performance. The hypothesis that preoperative morbidity defined by P-POSSUM and ASA score should have influenced the results was considered. For this reason, a linear and multiple logistic regression was performed according to the outcomes. We found that morbidity does not seem to affect the percentage of readmissions ($p > 0.05$). The P-POSSUM was recognized as a confounding factor but not the ASA score for LOS. The P-POSSUM is a wider and more inclusive scale, considering physiological and surgical factors, and is not directly associated with physiological status. For this reason, the authors considered that the ERAS programs are very beneficial in patients with comorbidities because they lead to optimization of all comorbidities. Probably the worst patients benefit more than healthier patients.

There were significant differences between the two groups in terms of overall complications and morbidity assessed by the CD classification. In terms of medical complications, there was a significant difference in psychiatric complications and PONV.

Postoperative delirium is increasingly recognized in surgical practice, particularly in the elderly population who have pre-existing cognitive dysfunction.[24] Preventive measures such as avoidance of prolonged fasting, deep anaesthesia, disturbance of the sleep–wake cycle or delirogenic medications like benzodiazepines can probably explain why psychiatric complications decreased.

The multimodal approach to PONV within the ERAS pathway contains the use of antiemetics. Other factors like the reduction of preoperative fasting, carbohydrate loading, adequate hydration and the use of regional anaesthetic techniques and the use of non-steroidal anti-inflammatory drugs (NSAIDs) as opioid-sparing strategies may influence the prevalence of PONV.[8]

In agreement with other studies, there was a significant decrease in the rate of medical but not of surgical complications.[25-27] The multidisciplinary team was the key for these results. While surgeons were focused on disease, surgery planning, improvement of technical and laparoscopic skills and treatment, anesthesiologists and other professionals prepared patients to surgical aggression. They focused on medical optimization, reduced the level of anxiety and tried to achieve a better compliance with the ERAS protocol.

In the present study, minimally invasive surgery was performed more frequently in the ERAS program (p-value < 0.001). Meta-analysis and international databases showed that laparoscopic colorectal resection has several advantages, such as a substantial reduction of the total LOS and the number of complications.[28,29] The laparoscopic learning curve is usually related with a higher complications rate, but our colorectal team increased the number of laparoscopic procedures without impairment of surgical time, comorbidities, and reoperation rate.[30] Moreover, the ERAS program being a 'multimodal prehabilitation' had an additive effect by improving patient safety after discharge.[27]

In our study, everything helped patients to recover faster. The absence of urinary catheters and surgical drains facilitated early mobilization. Patients were also encouraged to promptly resume independent drinking and eating, and the standard practice has been modified to abolish routine use of post-operative nasogastric tubes. The anesthetic technique allowed early mobility on postoperative day one. A multimodal opioid-sparing analgesic scheme was implemented: the use of peripheral nerve blocks or local anesthesia increased from 2.9% to 66.5%. Peripheral abdominal

wall block was the most commonly used analgesic technique in laparoscopic procedures. Anesthesiologists performed it using ultrasound and surgeons performed it under direct laparoscopic visualization.

There is currently no consensus on the optimal analgesic package for patients who undergo laparoscopic colorectal surgery within enhanced recovery programs, although some authors defend that the sparing of opioids in abdominal surgery leads to a decreased rate of postoperative ileus.[31,32]

Some reports show that the short- and long-term prognoses are closely related with ERAS program compliance.[33] In this study, it has been shown that compliance rates were higher in the ERAS group (Table 2), which perhaps influenced the earlier discharge favorably, the LOS and readmissions in a tertiary hospital. There was a statistically significant decrease in LOS from a median of seven to five days for all elective colorectal patients. This shorter LOS in the ERAS group may have been associated with a quicker return to normal daily activities and decreased use of healthcare services, an important consideration in the current era of cost-containment in healthcare. This shorter length of stay was not associated with a higher percentage of readmissions, which reflects the safety of this program.

Study limitations

All colorectal patients in our institution are on an ERAS pathway regardless of procedure, comorbidities or surgical approach, and our study reports consecutive patients admitted under our care over a two-year period. A randomized controlled trial would have been ideal but there would have been considerable contamination between control and study groups managed in the same institution, on the same ward, by the same team.

We also identified a lack of information about primary and secondary outcomes before the implementation of the ERAS protocol.

We were unable to analyze how comorbidities interacted with the efficacy of our protocol in either group.

We have not introduced a measure of patient satisfaction at our institution. Patient generated data on quality of life or functional status would contextualize the actual benefit of ERAS according to the patient.

CONCLUSION

The integration of this protocol produced favorable results in our hospital. Due to protocols and the coordination between different specialties, it was possible to perform high complexity surgeries safely in patients with more comorbidities and higher mortality risk.

The ERAS pathway revealed positive results regarding the reduction of complications, LOS and readmissions, emphasized ERAS principles as reduction of surgical stress, maintenance of physiological functions and optimized recovery. The implementation of the ERAS protocol allowed patients with comorbidities and a higher perioperative risk to have surgery safely.

The authors believe that the homogenization of practices across all surgical departments has made it possible to obtain optimal compliance and to assess its real impact on outcomes in patients undergoing colorectal surgery.

With an optimal organizational model and multi-disciplinary surgical care, patients are treated effectively and efficiently. Traditional care pathways are abandoned, and the adoption of new strategies and concepts allows a quicker postoperative recovery and shortens hospitalization days.

ACKNOWLEDGEMENTS

The authors would like to thank the colorectal and ERAS team of Centro Hospitalar e Universitário de Coimbra.

AUTHOR CONTRIBUTIONS

CL e MVG: Design of the work, data acquisition and processing, statistical work and drafting of the paper, approval of the final version of the manuscript.

MR, AA, LIS, JGT: Critical review of the manuscript and approval of the final version of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Prescrição de Benzodiazepinas e outros Sedativos na Administração Regional de Saúde de Lisboa e Vale do Tejo de 2013 a 2020: Um Estudo Retrospetivo

Prescribing Trends of Benzodiazepine and other Sedatives in the Lisbon and Tagus Valley Regional Health Administration between 2013 and 2020: A Retrospective Study

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Acta Med Port 2023 Apr;36(4):264-274 ▪ https://doi.org/10.20344/amp.18680

RESUMO

Introdução: Portugal é o país da Organização para a Cooperação e Desenvolvimento Económico com maior consumo de ansiolíticos, hipnóticos e sedativos, sendo uma proporção significativa constituída por benzodiazepinas ou análogos, associados a efeitos de tolerância e dependência. Por este motivo, em alternativa às benzodiazepinas para tratamento da insónia, algumas publicações identificam outros fármacos com efeito hipnótico, como antidepressivos, anti-histamínicos, antipsicóticos ou anticonvulsivantes. Assim, torna-se necessário compreender a evolução do consumo destes medicamentos, pelo que foi objetivo deste estudo avaliar a evolução da dispensa de benzodiazepinas, outros fármacos ansiolíticos, hipnóticos ou sedativos não benzodiazepínicos, fármacos com potencial uso *off-label* na insónia e os resultados de indicadores dos Cuidados de Saúde Primários neste âmbito na região de Lisboa e Vale do Tejo.

Material e Métodos: Realizou-se um estudo em base de dados, censitário e retrospetivo, no período de 2013 até 2020, avaliando-se a evolução das variáveis total de doses diárias definidas, doses diárias definidas por 1000 habitantes por dia (DHD) e dos indicadores relevantes. Os dados foram extraídos da plataforma SIARS da Administração Regional de Saúde de Lisboa e Vale do Tejo.

Resultados: Verificou-se uma diminuição da dispensa de benzodiazepinas (de 57,44 para 51,77 DHD) mas o aumento da dispensa de não benzodiazepinas e de fármacos com potencial uso *off-label* (de 6,56 para 8,56 DHD e de 14,70 para 25,92 DHD, respetivamente). O zolpidem foi o mais dispensado entre os fármacos não benzodiazepínicos, acompanhando a tendência crescente de dispensa (de 4,86 para 6,96 DHD). Do conjunto de fármacos com potencial para uso *off-label* verificaram-se aumentos da dispensa para a trazodona (de 3,81 para 7,92 DHD), mirtazapina (de 3,52 para 6,48 DHD), pregabalina (de 3,15 para 4,87 DHD), quetiapina (de 2,68 para 4,59 DHD) e gabapentina (de 1,32 para 1,90 DHD), mas mais significativo ou apenas verificado nas formulações com dosagem mais baixa. A mediana dos resultados do indicador "proporção de idosos sem prescrição de sedativos, ansiolíticos e hipnóticos" em 2015 foi de 81,0, tendo em 2020 aumentado para 84,9. A mediana do indicador "proporção de utentes sem prescrição prolongada de ansiolíticos, sedativos e hipnóticos" em 2019 foi de 93,6 e aumentou para 94,3 em 2020.

Conclusão: Globalmente, verificou-se uma redução da dispensa de benzodiazepinas prescritas na Região de Lisboa e Vale do Tejo. Parece existir uma alteração do padrão de prescrição no tratamento da insónia. São necessários estudos mais robustos para confirmar esta observação.

Palavras-chave: Benzodiazepinas; Hipnóticos e Sedativos; Padrões de Prática Médica/tendências; Portugal; Uso de Medicamentos/tendências; Uso Off-Label

ABSTRACT

Introduction: Among the Organization for Economic Co-operation and Development members, Portugal has the highest reported consumption of anxiolytics, hypnotics, and sedatives, of which a large proportion are benzodiazepines or related drugs. These are known to cause tolerance and dependence. Other drugs with hypnotic effect, such as antidepressants, antihistamines, antipsychotics, or anticonvulsants have been identified by some reports as alternatives to benzodiazepines for the treatment of insomnia. In this regard, the aim of this study was to characterize the consumption of benzodiazepines, non-benzodiazepine anxiolytic, hypnotic or sedative effect drugs and other drugs with the potential to be used off-label to treat insomnia, and the results concerning benzodiazepine consumption related indicators in the primary health care setting in the Lisbon and Tagus Valley region.

Material and Methods: From 2013 to 2020, a census, descriptive and retrospective study was conducted. The evolution of the variables total defined daily doses, defined daily doses per 1000 inhabitants per day (DHD) and relevant indicators were characterized. Data were extracted from the SIARS platform used in the Lisbon and Tagus Valley regional Health Administration.

Results: There was a decrease in the consumption of benzodiazepines (from 57.44 to 63.11 DHD) and an increase of non-benzodiazepines and of drugs with potential off-label use (from 6.56 to 8.56 DHD and from 14.70 to 25.95 DHD, respectively). Among non-benzodiazepines, zolpidem was the most consumed drug, also showing an increasing trend (from 4.86 to 6.96 DHD). For the group of drugs with off-label use potential, there was an increased consumption of trazodone (from 3.81 to 7.92 DHD), mirtazapine (from 3.52 to 6.48 DHD), pregabalin (from 3.15 to 4.87 DHD), quetiapine (from 2.68 to 4.59 DHD) and gabapentin (from 1.32 to 1.90 DHD), which was only the case (or, at least, more significantly) for the lower dose formulations. The median

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Recebido/*Received*: 06/06/2022 - **Aceite/*Accepted*:** 13/09/2022 - **Publicado/*Published*:** 03/04/2023

of results of the Primary Health Care setting indicator "proportion of elderly patients without prescription of sedatives, anxiolytics, and hypnotics", was 81.0 in 2015 and increased to 84.9 in 2020. For the indicator "proportion of patients without prolonged prescription of sedatives, anxiolytics, and hypnotics", the median was 93.6 in 2019 and 94.3 in 2020.
Conclusion: There was, overall, a decreasing trend in the dispensing of benzodiazepines in the Lisbon and Tagus Valley Region. Even though this data suggests a change in the therapeutic pattern for insomnia, more robust studies are needed to confirm this observation.
Keywords: Benzodiazepines; Drug Utilization/trends; Hypnotics and Sedatives; Off-Label Use; Portugal; Practice Patterns, Physicians/trends

INTRODUÇÃO

As benzodiazepinas (BZD) são um grupo de fármacos depressores do sistema nervoso central (SNC) com efeito ansiolítico e hipnótico. Pelo seu perfil de eficácia e segurança têm sido amplamente utilizadas para tratar estados de ansiedade ou insónia.[1,2]

No entanto, as BZD não são isentas de riscos. No caso dos idosos, por alterações farmacocinéticas associadas ao envelhecimento (e.g., aumento da semivida) existe maior propensão para a ocorrência de efeitos indesejáveis, como sonolência, ataxia, confusão mental, alterações de raciocínio, amnesia anterógrada, aumento do risco de quedas e diminuição das funções cognitivas.[1,3] As BZD estão também associadas a fenómenos de tolerância e dependência, que ocorrem de forma transversal em todos os grupos etários.[1,2]

O tratamento com BZD deve ser de curta duração, não só pelos efeitos indesejáveis descritos, mas também porque a dependência e tolerância podem ocorrer apenas algumas semanas após início do tratamento.[1,4] Os sintomas de privação variam em intensidade, desde ligeiros (pesadelos, insónia, ansiedade) a severos (alterações da perceção, psicose, hiperpirexia, convulsões que podem ameaçar a vida).[1,2]

Em linha com o descrito anteriormente, as recomendações nacionais em vigor para o tratamento sintomático da ansiedade e insónia, atualizadas em 2015, advogam o uso de BZD e análogos no tratamento dos casos moderados a graves durante quatro a 12 semanas, incluindo o período de desmame. Em caso de falência terapêutica com esta primeira abordagem em contexto de Cuidados de Saúde Primários (CSP), recomenda-se o encaminhamento para uma consulta de psiquiatria.[4]

Em 2016, Portugal era o país da Organização para a Cooperação e Desenvolvimento Económico (OCDE) com maior consumo reportado de ansiolíticos, hipnóticos e sedativos (N05B-*Anxiolytics* e N05C-*Hypnotics and Sedatives*, segundo a classificação ATC 2017 – *Anatomical Therapeutical Chemical*), somando 114 doses diárias definidas por 1000 habitantes/dia (DHD). Em relação às benzodiazepinas (BZD) e análogos (N05BA-*Benzodiazepine derivatives*, N05CD-*Benzodiazepine derivatives* e N05CF-*Benzodiazepine related drugs*, ATC 2017), a utilização portuguesa em 2015 situava-se em 80 DHD, valor bastante superior às 50, 22 e 12 DHD utilizadas pela Finlândia, Dinamarca e Holanda, respetivamente. Contrariamente ao observado nestes países, em Portugal mais de 85% das BZD eram de ação ansiolítica, tendendo o seu consumo a aumentar com a idade e a ser superior no sexo feminino.[5] No entanto, do ponto de vista farmacológico, não existe uma clara distinção entre BZD hipnóticas ou ansiolíticas, visto que a maior parte das BZD ansiolíticas induzem o sono se tomadas à noite e a maior parte das BZD ansiolíticas causam sedação se tomadas durante o dia.[1] Ainda em 2016, avaliando as diferentes administrações regionais de saúde portuguesas, temos que as DHD de BZD e análogos dispensados em farmácias comunitárias na Administração Regional de Saúde de Lisboa e Vale do Tejo (ARSLVT) foram de 63, valor inferior ao da Administração Regional de Saúde (ARS) Norte (94 DHD), ARS Centro (97 DHD) e ARS Alentejo (72 DHD), embora superior ao da ARS Algarve (49 DHD).[5]

Atenta a este problema, a Comissão de Farmácia e Terapêutica (CFT) da ARSLVT publicou em 2017 o boletim terapêutico "Utilização de Benzodiazepinas: Um Grave Problema de Saúde Pública". Além de recomendações gerais para o uso racional das BZD, este boletim fornecia orientações para auxiliar os médicos na sua descontinuação gradual, em caso de uso inadequado. A par deste boletim, foi publicado no sítio eletrónico da ARSLVT um folheto com informação destinada às pessoas que utilizam BZD e, posteriormente, divulgado em reuniões presenciais nos CSP. Esta abordagem dual visou reforçar as recomendações de boa prática na utilização deste grupo de fármacos e facilitar a adoção de estratégias para promover a sua descontinuação.[6]

Sendo as BZD uma das principais estratégias utilizadas para tratamento da insónia,[7–9] em sua alternativa e para esta indicação foi defendido em Portugal, em associação com a terapia cognitivo-comportamental, o uso de outros fármacos com efeito hipnótico, nomeadamente antidepressivos, como a trazodona (25 a 150 mg/dia), a mirtazapina (7,5 a 30 mg/dia) e a trimipramina (10 a 150 mg/dia), e anti-histamínicos, como a doxilamina (25 a 50 mg/dia) e a hidroxizina (37,5 a 75 mg/dia).[10] Outras classes farmacológicas com efeito hipnótico, como os antipsicóticos (quetiapina) e os anticonvulsivantes (gabapentina e pregabalina), são também apresentadas internacionalmente como de utilização *off-label* no tratamento da insónia, nomeadamente se associada a comorbilidades, principalmente psiquiátricas.[11–13] Assim, o estudo da evolução do consumo destes fármacos pode ser importante na interpretação da evolução

do consumo global das BZD.

Considerando a problemática pública da utilização das BZD e o facto de a maior parte da informação disponível estar agregada por região, sem distinção quanto ao local da prescrição e, geralmente, não estar associada ao estudo de potenciais alternativas farmacológicas às BZD nem ao estudo de indicadores de monitorização terapêutica existentes, torna-se importante avaliar a evolução: (1) da dispensa de BZD, (2) da dispensa de outros fármacos não benzodiazepínicos com efeito ansiolítico, hipnótico e/ou sedativo, (3) da dispensa de outros fármacos com potencial uso *off-label* na insónia e (4) dos indicadores dos CSP relacionados com a prescrição de BZD.

Procurou obter-se um conhecimento mais abrangente do problema exposto. Para o efeito, definiram-se como objetivos a caraterização do consumo de BZD e de um conjunto de outros fármacos com indicações semelhantes e/ou com potencial uso *off-label*, bem como a integração dos dados com indicadores de contratualização institucionais na área da prescrição. Desta forma, pretende-se fomentar na comunidade médica, científica e noutros intervenientes a discussão fundamentada sobre eventuais oportunidades de melhoria e futuras investigações.

MATERIAL E MÉTODOS

Realizou-se um estudo observacional, censitário e retrospetivo em base de dados, entre 2013 e 2020.

O racional subjacente à definição do período avaliado foi conhecer a tendência prévia às medidas implementadas pela CFT através do boletim terapêutico N.º 1/2017: "Utilização de Benzodiazepinas: Um Grave Problema de Saúde Pública". A acessibilidade aos dados também foi um fator tido em conta, principalmente no caso dos indicadores dos CSP.

Os dados da utilização de BZD e de outros fármacos não benzodiazepínicos com efeito ansiolítico, sedativo e/ou hipnótico foram retirados do Sistema de Informação da Administração Regional de Saúde (SIARS) de Lisboa e Vale do Tejo, onde se obteve informação sobre os medicamentos prescritos em toda a ARSLVT desde que faturados pelas farmácias comunitárias em qualquer região do país, de acordo com o Centro de Conferência de Faturas. A informação extraída compreendeu o número de embalagens de cada fármaco pela denominação comum internacional (DCI) de acordo com a dosagem, forma e apresentação disponíveis no mercado. Esta pesquisa foi efetuada de forma independente para todas as BZD pertencentes ao grupo farmacoterapêutico (GFT) "2.9.1. Ansiolíticos, sedativos e hipnóticos", para fármacos não BZD pertencentes ao mesmo GFT e para outros fármacos com efeito hipnótico, conforme identificados na introdução, considerados, pelos autores, como de potencial uso *off-label* caso não tivessem aprovada a insónia como indicação terapêutica. A lista por DCI pode ser consultada no Apêndice (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18680/15097). Os dados foram extraídos e organizados por ano e por setor de prescrição, simultaneamente para todos os anos do período em estudo. Foram feitas três extrações independentes desta forma, uma para cada grupo de fármacos a avaliar (BZD, não BZD e potencial para uso *off-label* na insónia).

Para cada um dos grupos farmacológicos assim definidos estimou-se, anualmente:

- O total de doses diárias definidas por ano (DDD [atributo definido pela Organização Mundial de Saúde (OMS) que pode ser definido como a dose média de manutenção diária de um determinado fármaco usado na sua indicação principal em adultos];
- A DHD (número de DDD por dia em 1000 habitantes), que pode ser interpretada como a proporção da população que diariamente recebe tratamento com um dado medicamento, assumindo uma posologia correta;
- O resultado dos indicadores dos CSP, de acordo com as definições do Bilhete de Identidade dos Indicadores dos Cuidados de Saúde Primários (BI-CSP) da ACSS[14,15]:
  - Proporção de utentes com idade igual ou superior a 65 anos, sem prescrição prolongada de ansiolíticos, nem de sedativos, nem de hipnóticos, no período em análise (código SIARS: 2013.297.01 FX)[15];
  - Proporção de utentes sem prescrição prolongada de ansiolíticos, nem de sedativos, nem de hipnóticos, ajustada para uma população padrão (código SIARS: 2018.409.01 FX)[14].

Quanto aos fármacos sem DDD definida pela OMS foi feita a estimativa da dose média diária, de acordo com as indicações descritas em RCM, para os que apresentaram dispensas no período em análise [Apêndice 2 (Apêndice 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18680/15098), a fim de calcular o total de DDD. As fórmulas de cálculo do total de DDD e DHD prescritos podem ser consultados no Apêndice 3 (Apêndice 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18680/15099).

Tendo em conta o tipo de dados extraídos/acessíveis, a população avaliada, no que diz respeito à prescrição, consistiu em todos os utentes com cuidados de saúde na ARSLVT, no setor público ou privado. A determinação da população está, assim, diretamente relacionada com os dados acessíveis na base de dados. Ou seja, como os dados disponíveis eram os dos fármacos faturados, para um determinado período, sem associação ao utente individual,

a população em estudo é, obrigatoriamente, constituída por todos os utentes com possibilidade de terem uma prescrição efetuada na ARSLVT durante o mesmo período. Sempre que necessário, foi utilizada a estimativa da população residente na área de abrangência da ARSLVT (segundo o Instituto Nacional de Estatística) como valor aproximado de indivíduos da população, para cada ano.

Quanto aos indicadores dos CSP a população é diferente, sendo constituída por todos os utentes inscritos nos agrupamentos de centros de saúde (ACES) da ARSLVT a cada ano.

Os dados foram exportados e trabalhados no sistema Microsoft Excel 365®. A limpeza de dados baseou-se principalmente na extração do conteúdo numérico nos parâmetros "dosagem" (que representa a dose de fármaco por comprimido ou a concentração em caso de soluções) e "apresentação" (que representa a quantidade de comprimidos ou a quantidade e capacidade de recipientes em caso de soluções). Para este fim foram utilizadas fórmulas do sistema informático, recorrendo-se posteriormente a uma inspeção visual dos dados para garantir a fidelidade dos mesmos. Não foram utilizadas ligações de dados entre diferentes bases de dados. A avaliação estatística foi meramente descritiva.

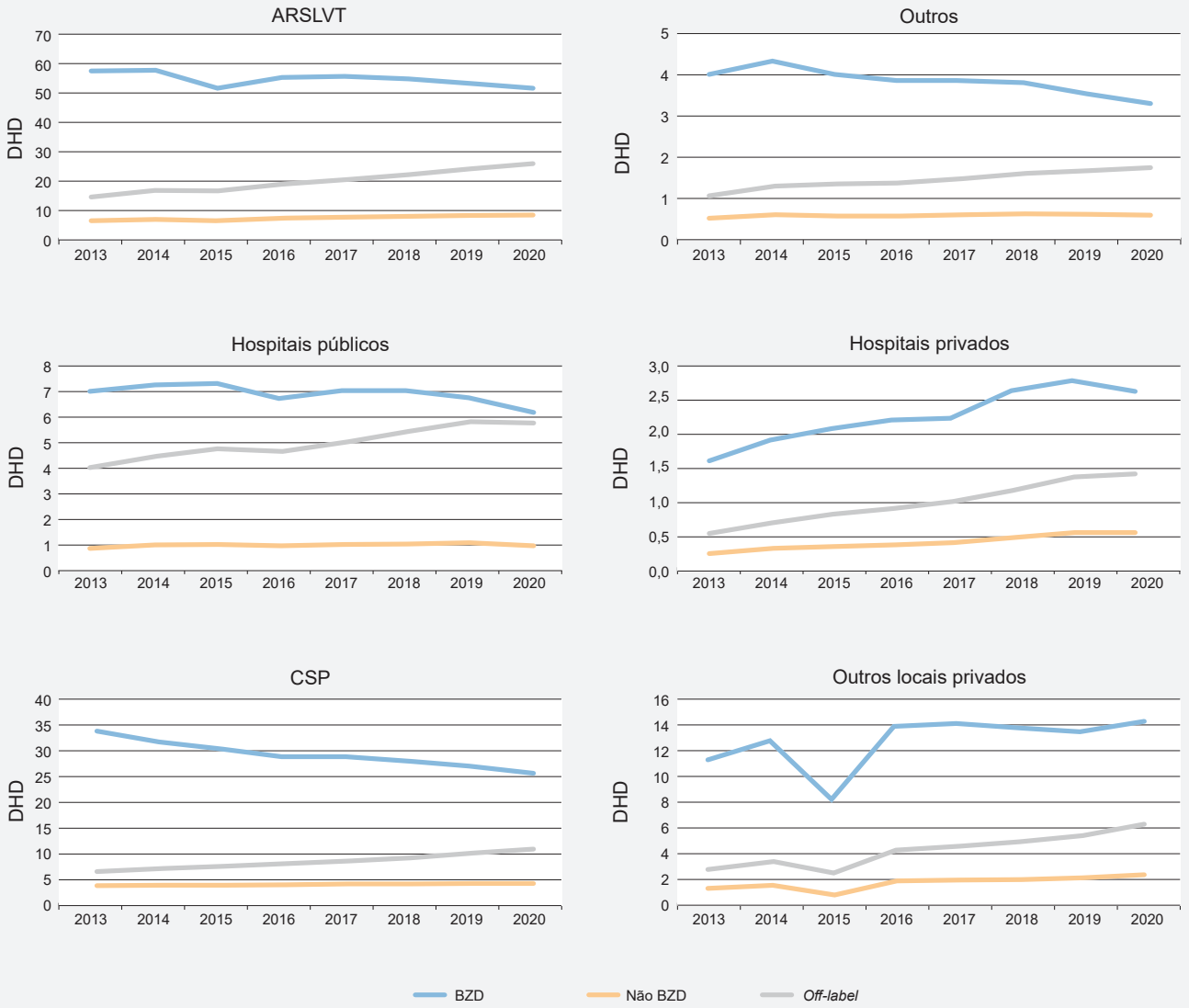

Figura 1 – Evolução da dispensa dos três grupos farmacoterapêuticos no período em análise, por local de prescrição.
CSP, Cuidados de Saúde Primários; Outros Locais Privados, clínicas e consultórios privados; Outros, associações (mutualistas, por exemplo), setor social, serviços médicos de empresas, centros de respostas integradas (CRI), centros de vacinação internacional, serviços prisionais, etc.; DHD, número de doses diárias recomendadas de determinado medicamento dispensadas por dia e por 1000 habitantes.

Considerações éticas

Tendo em conta o caráter censitário e a impossibilidade de ligar os dados obtidos a qualquer utente de forma individual, considera-se cumprido o pressuposto de proteção e confidencialidade dos dados pessoais. Da mesma forma, não se aplica, neste contexto, a necessidade de consentimento informado. O protocolo do presente estudo foi avaliado e aprovado pela Comissão de Ética para a Saúde da Administração Regional de Saúde de Lisboa e Vale do Tejo (ARSLVT), pelo parecer 091/CES/INV/2020.

RESULTADOS

Em 2013, foram prescritas na ARSLVT e dispensadas em farmácias comunitárias 76,2 milhões de DDD de BZD, 8,7 milhões de DDD de não BZD e 19,5 milhões de DDD de fármacos de potencial uso *off-label*. Em 2020 prescreveram-se menos 6,6 milhões de DDD de BZD, mais 2,8 milhões de DDD de não BZD e mais 15,3 milhões de DDD de fármacos de potencial uso *off-label*.

Estes valores traduzem-se, para 2013, em 57,44 DDD por 1000 habitantes da ARSLVT por dia (DHD) de BZD, 6,56 DHD de não BZD e 14,70 DHD de fármacos de potencial uso *off-label*. Em 2020 foram dispensadas menos 5,67 DHD de BZD, mais 2,00 DHD de não BZD e mais 11,21 DHD de fármacos com potencial uso *off-label*.

A tendência de redução da dispensa das BZD e de aumento dos não BZD e dos fármacos com potencial uso *off-label* é transversal a quase todos os setores de prescrição.

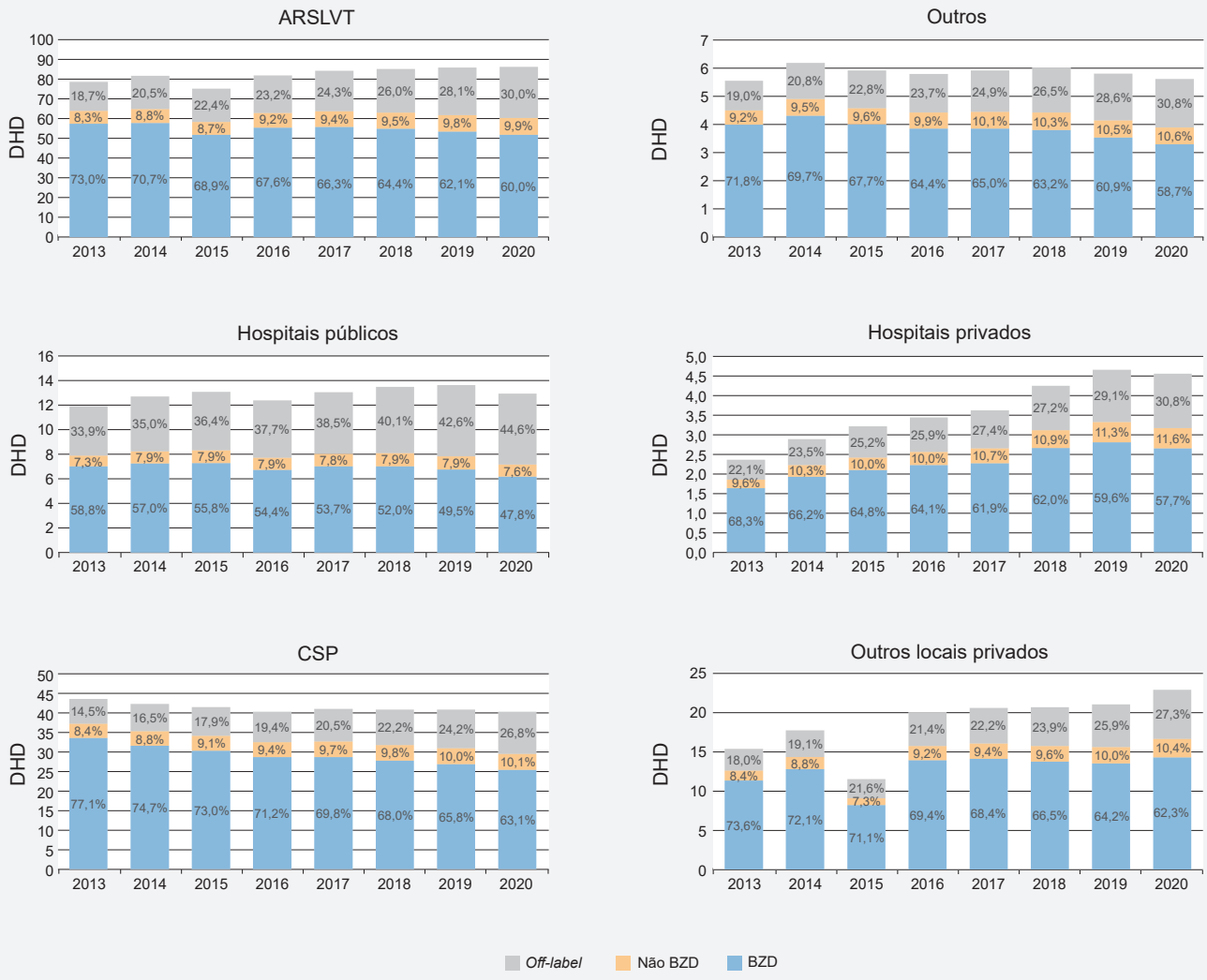

Figura 2 – Evolução da dispensa do total dos três grupos farmacoterapêuticos e respetiva proporção no período em análise, por local de prescrição. A legenda dos dados representa a percentagem de cada grupo de fármacos no ano correspondente.
CSP, Cuidados de Saúde Primários; Outros Locais Privados, clínicas e consultórios privados; Outros, associações (mutualistas, por exemplo), setor social, serviços médicos de empresas, centros de respostas integradas (CRI), centros de vacinação internacional, serviços prisionais, etc.; DHD, número de doses diárias recomendadas de determinado medicamento dispensadas por dia e por 1000 habitantes.

No conjunto das clínicas privadas (que inclui instituições de solidariedade social), pequenos prescritores privados e similares, daqui em diante referidos como 'outros locais privados', assim como nos hospitais privados, isso não se verifica, pois também as BZD parecem mostrar uma tendência crescente (Fig. 1). No entanto, no conjunto destes três grupos de fármacos, a proporção de BZD tem vindo a diminuir, independentemente do setor de prescrição. Por outro lado, verifica-se o aumento relativo dos fármacos de potencial uso *off-label*, de tal forma que, para a ARSLVT, apesar do decréscimo absoluto na DHD das BZD, se constata um aumento na DHD conjunta dos três grupos de fármacos (BZD, não BZD e de potencial uso *off-label)* (Fig. 2).

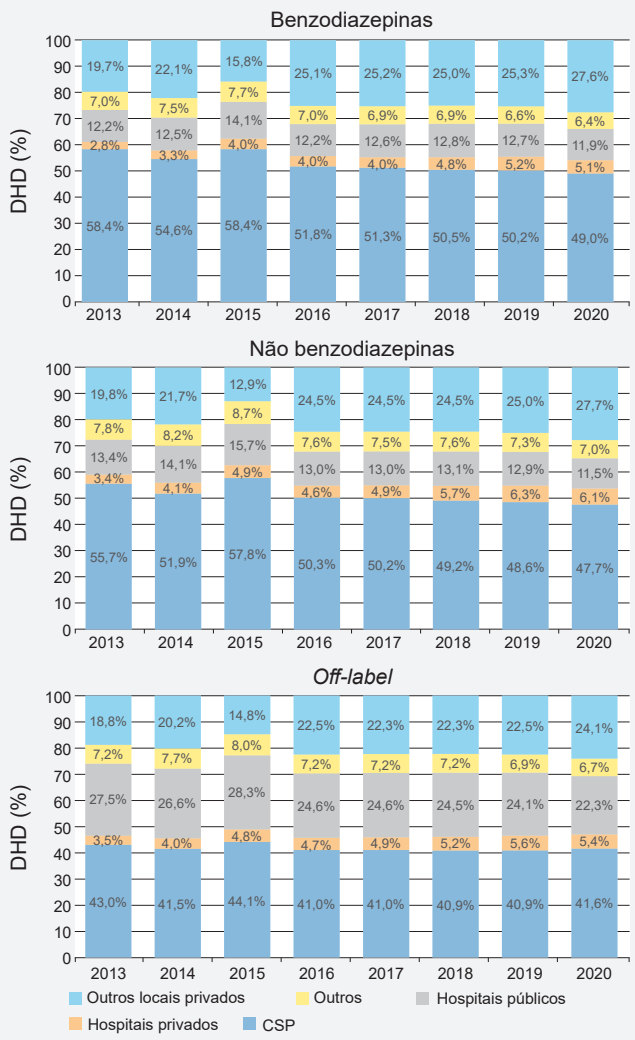

Figura 3 – Evolução da proporção da origem das receitas levantadas para cada grupo de fármacos, no período em análise.
CSP, Cuidados de Saúde Primários; Outros Locais Privados, clínicas e consultórios privados; Outros, associações (mutualistas, por exemplo), setor social, serviços médicos de empresas, centros de respostas integradas (CRI), centros de vacinação internacional, serviços prisionais, etc.; DHD, número de doses diárias recomendadas de determinado medicamento dispensadas por dia e por 1000 habitantes.

Os CSP apresentam-se como o principal sector responsável pelas DHD nos três grupos de fármacos, mas numa proporção que tem vindo a diminuir de forma pouco expressiva no grupo das BZD e Não BZD. Os hospitais públicos têm registado a terceira maior porção de DHD de BZD e não BZD, depois do sector de outros locais privados. Quanto aos fármacos de potencial uso *off-label*, os hospitais públicos representaram a segunda maior porção de DHD, mas a sua preponderância foi diminuindo ao longo dos anos, até que, em 2020, o conjunto de outros locais privados assumiu a segunda posição. Constata-se que os sectores de hospitais privados e outros locais privados têm vindo a ganhar expressão na proporção de DHD consumidas nos três grupos de fármacos analisados (Fig. 3).

Quanto aos fármacos não BZD, o zolpidem, em 2013, representava 4,86 DHD, 5,18 em 2014 e 4,84 em 2015, ano em que iniciou crescimento sustentado, de forma a apresentar em 2020 6,69 DHD, cerca de 87% do total das DHD deste grupo de fármacos nesse ano. Este crescimento foi sensivelmente uniforme nos diferentes sectores de prescrição. A hidroxizina (comprimidos de 25 mg), desde 2013 até 2020, apresentou um valor máximo de 1,56 DHD em 2014 e mínimo de 1,06 DHD em 2020, verificando-se um decréscimo sustentado desde 2016. Esta diminuição foi mais acentuada nos sectores CSP e hospitais públicos. De forma menos expressiva, sem tradução significativa em DHD, a buspirona tem também registado um aumento progressivo. De 2013 a 2015 as dispensas em DDD variaram entre 572 570 (2014) e 502 617 (2015), tendo a partir dai registado um aumento progressivo até às 733 537 em 2020. Esta tendência foi relativamente semelhante entre os diferentes locais de prescrição.

No conjunto dos fármacos com potencial uso *off-label*, para o período em análise, apenas a trimipramina não apresentou evolução positiva das DHD (0,21 em 2013 e mínimo de 0,16 em 2020, máximo de 0,21 em 2014). Em 2020, o fármaco mais prevalente foi a trazodona com 7,92 DHD (mínimo de 3,81 em 2013, máximo em 2020). Seguiu-se a mirtazapina com 6,48 DHD (mínimo de 3,52 em 2013, máximo em 2020), a pregabalina com 4,87 DHD (mínimo de 3,15 em 2013, máximo em 2020), a quetiapina com 4,59 DHD (mínimo de 2,68 em 2013, máximo em 2020) e, por fim, a gabapentina com 1,90 DHD (mínimo de 1,32 em 2013, máximo em 2020). Dos últimos cinco fármacos, o comportamento crescente não se verificou da mesma forma para todas as doses (Fig. 4).

A análise dos indicadores dos CSP foi realizada desde 2015 para a "Proporção de utentes com idade igual ou superior a 65 anos, sem prescrição prolongada de ansiolíticos, nem de sedativos, nem de hipnóticos" e desde 2019 para a "Proporção de utentes sem prescrição prolongada de ansiolíticos, nem de sedativos, nem de hipnóticos,

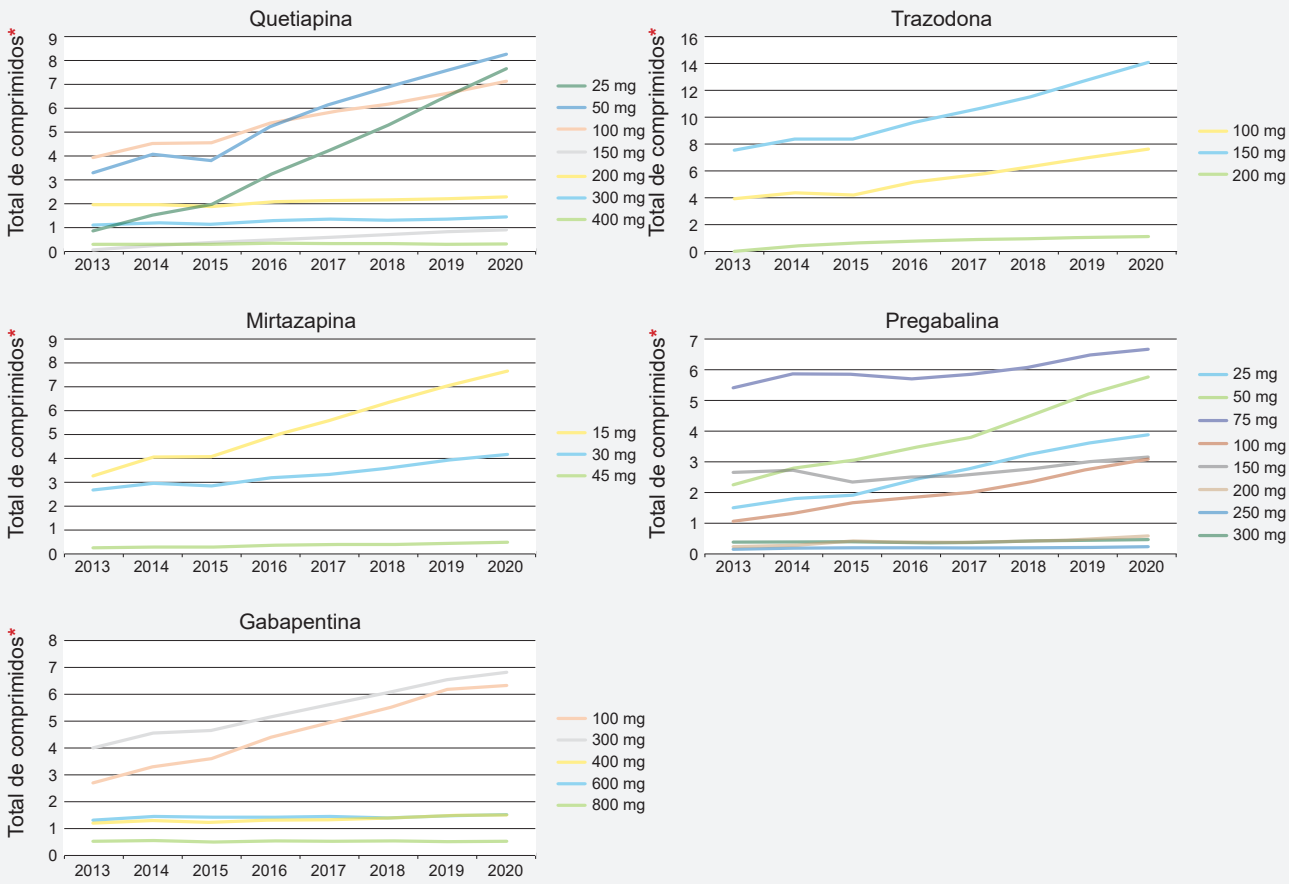

Figura 4 – Evolução do número total de comprimidos dispensados por dose, para cada fármaco de potencial uso *off-label* que registou aumento em DHD durante o período em análise, de acordo com as receitas emitidas na ARSLVT independetemente do local de prescrição

*: milhões

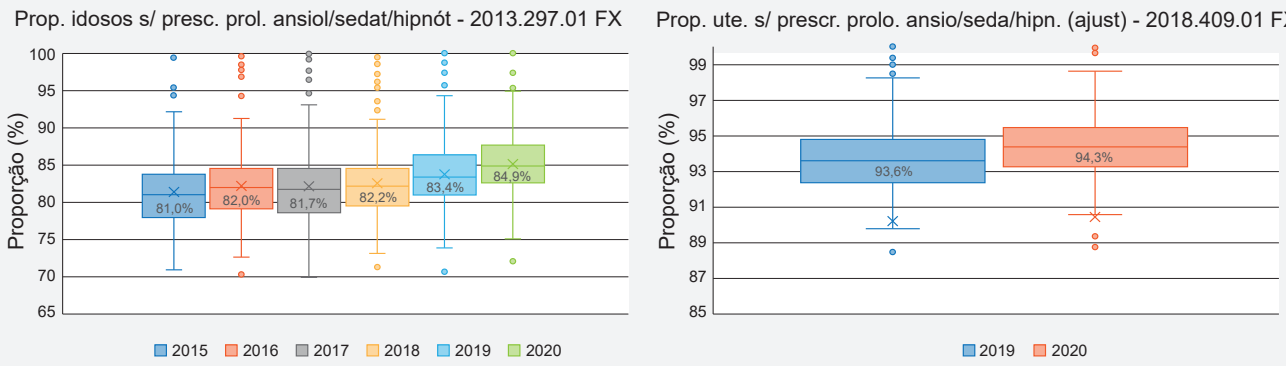

Figura 5 – Evolução da distribuição dos resultados dos indicadores relavantes dos Cuidados de Saúde Primários, para cada ano com resultados disponiveis. Apresentam-se os diagramas de "Caixas e Bigodes" que representam a distribuição dos resultados de todas as unidades funcionais em cada ano. O número dentro da caixa é a legenda do valor mediano (representado pelo traço que divide a caixa). A média é representada pelo "X" (não legendado).

ajustada para uma população padrão", por serem os únicos anos com resultados disponíveis. Verificou-se uma melhoria progressiva durante os períodos analisados (Fig. 5).

DISCUSSÃO

De uma forma global, na ARSLVT verificou-se a diminuição na dispensa de BZD desde 2013 a 2020. No entanto, esta diminuição não foi uniforme entre os diferentes setores de prescrição de onde se originaram as receitas dispensadas nas farmácias. Com efeito, a tendência no setor privado foi, globalmente, de crescimento ou estabilização. O principal potenciador da redução que se verifica para a ARS, pelo maior volume de utentes, mas provavelmente também pela magnitude do decréscimo, foi o setor dos CSP.

Quanto aos fármacos não BZD, em números absolutos, a tendência foi de crescimento ligeiro, de forma mais ou menos transversal a todos os setores de prescrição. O agente preponderante para este aumento foi o zolpidem, apesar de nas recomendações nacionais ser enquadrado da mesma forma que as BZD[4] e não existir evidência clara de ter um perfil de segurança e eficácia diferente das mesmas (provavelmente mais seguro que BZD de longa duração de ação, mas possivelmente menos eficaz no tratamento da insónia a curto prazo que as BZD de ação curta ou intermédia), com a particularidade de ser uma substância menos estudada.[16,17]

Já para os fármacos de potencial uso *off-label* o crescimento verificado é mais significativo e aconteceu de forma transversal a todos os setores de prescrição. O aumento conjugado da dispensa dos fármacos não BZD e de potencial uso *off-label* foi de tal ordem que apenas no setor dos CSP se verificou um decréscimo de 3,25 DHD ao longo do período em análise quando avaliados os três grupos de fármacos em conjunto. No global da ARSLVT, verificou-se um aumento de cerca de 7,55 DHD, maioritariamente impulsionado pelo setor privado.

Os dados apresentados podem sugerir um desvio do padrão de prescrição, passando-se da utilização de BZD para a utilização de zolpidem, de buspirona (embora com muito menor expressão) e fármacos com potencial para uso *off-label* na insónia, como serão alguns antidepressivos, gabapentinóides ou antipsicóticos.[10–13] No entanto, importa ressalvar que, como não se conhece qual o motivo clínico para a prescrição, é difícil assumir o seu uso em substituição ou como alternativa às BZD. Mesmo que tenham sido usados no contexto de insónia, esta pode ser secundária a patologias para as quais estes fármacos podem ter indicação aprovada, como é o caso da ansiedade ou da depressão. Ainda assim, vem reforçar esta hipótese o facto de, entre os fármacos de potencial uso *off-label*, as dosagens que registam aumentos mais significativos não parecerem ser compatíveis com a DDD definida pela OMS, valor que se baseia na dose diária que, em média, é necessária como manutenção terapêutica na indicação principal do medicamento.[18] Usando como exemplo a quetiapina, cuja DDD é 400 mg, o número de comprimidos de 25 mg dispensados nas farmácias comunitárias, no período em análise, aumentou 911% (de 838 466 em 2013 para 7 638 686 em 2020), o que parece ser desproporcional, uma vez que esta dosagem, de acordo com a monografia do fármaco,[19] será maioritariamente utilizada na titulação do tratamento até à dose mínima eficaz nas indicações aprovadas. Assim, seria expectável que a sua utilização em número de comprimidos fosse marginal, o que não se tem vindo a verificar. Este aumento, aparentemente desproporcional, nas formulações de menor dosagem também se verifica para outros grupos farmacológicos de potencial uso *off-label* avaliados. No entanto, tendo em conta especificidades da utilização desses mesmos fármacos, a interpretação desse facto deverá ser cuidadosa. Tanto quanto é do nosso conhecimento, não se encontram publicados estudos internacionais que permitam a comparação destes dados com os de outros países.

Os dados da OCDE mostram que em Portugal o consumo de fármacos hipnóticos e sedativos (ATC N05C, que inclui BZD de efeito hipnótico, derivados das BZD, derivados da melatonina, entre outros) tem vindo a diminuir (18,3 DHD em 2013 para 16,3 DHD em 2020), tendência que se verifica pelo menos desde o ano 2000.[20,21] Em 2019, entre os países com dados disponíveis, era o 12.º país com maiores consumos (máximo de 65,9 DHD e mínimo de 0). Quanto aos fármacos ansiolíticos (ATC N05B, que inclui BZD de efeito ansiolítico, a hidroxizina, a buspirona, entre outros) a tendência para Portugal também é decrescente (97,7 DHD em 2013 e 84,8 DHD em 2020).[21] Esta observação referente aos últimos sete anos pode corresponder a um período de inversão de tendência, que se verifica crescente em avaliações temporalmente mais alargadas (de 2000 a 2018).[20] Ainda assim, para este grupo de fármacos, desde 2013 que Portugal se apresenta, de forma destacada, como o principal consumidor dentro da OCDE, sendo o segundo lugar ocupado pela Espanha, que por sua vez tem registado uma tendência crescente no consumo destes agentes (52,3 DHD em 2013 para 57,9 DHD em 2020).

Em 2019, o país com menor consumo foi a Turquia, com 2 DHD. Globalmente, entre os vários elementos da OCDE, a tendência quanto ao consumo destes grupos de fármacos não parece ser uniforme, assim como também se regista uma variação muito significativa no volume consumido. Deve ser referido, no entanto, que a forma de aferição dos dados não é igual entre os vários países, realçando o facto de em alguns (como é o caso de Portugal)

não ser contabilizada utilização hospitalar.[21] Apesar de não diretamente comparável tendo em conta a utilização de diferentes classificações farmacológicas, os dados obtidos no presente estudo quanto à evolução da dispensa global de ansiolíticos, hipnóticos e sedativos (GFT 2.9.1.) na ARSLVT, que decresceu de 64,0 DHD em 2013 para 60,3 DHD em 2020, estão em linha com os apresentados para Portugal pela OCDE (ATC N05C e N05B). No entanto, o consumo a nível médio nacional parece ser significativamente maior ao que se verifica nesta região. Avaliando apenas as BZD e análogos, na ARS Norte, entre 2015 e 2018 e para os CSP, o número de DHD manteve-se sensivelmente estável, aproximando-se das 58.[22] Quantificando todos os setores de prescrição (exceto utilização hospitalar), este valor aumentou para as 94 DHD no ano de 2016. Nesse ano, também a ARS Centro (97 DHD) e ARS Alentejo (72 DHD) apresentaram dispensas superiores à ARSLVT. A ARS Algarve foi a que apresentou valores inferiores (49 DHD).[5] Assim, a diferença de volume dispensado que parece existir entre a ARSLVT e a média nacional pode justificar-se pela não uniformidade do consumo destas substâncias entre as várias administrações de saúde do país.

Os indicadores dos CSP têm apresentado uma evolução favorável, denotando uma proporção de utentes sem prescrição prolongada de ansiolíticos, sedativos e hipnóticos progressivamente maior. Isto é compatível com os dados verificados neste trabalho relativamente aos CSP. Deve ser, no entanto, referido que os fármacos com potencial uso *off-label* em avaliação não são de qualquer forma contabilizados nestes indicadores.[14,15] Isto significa que não são sensíveis na monitorização de terapêuticas potencialmente desadequadas caso se esteja a verificar a transferência de terapêuticas prolongadas com BZD para o uso de fármacos *off-label*, nomeadamente para tratamento da insónia.

Eventualmente por meio de possíveis constrangimentos no acesso aos cuidados de saúde[23] ou de influência do confinamento na saúde mental,[23,24] da observação dos dados é difícil inferir a existência de impacto da pandemia de COVID-19, decretada em 2020 pela OMS, nas dispensas avaliadas durante esse ano.

As observações comentadas nos parágrafos anteriores revestem-se de importância prática pois suportam a necessidade de inclusão de medidas não farmacológicas nos planos terapêuticos, sendo estas consideradas primeira linha quer na ansiedade quer na insónia.[13,25–27] Para além disso, poem em evidência a necessidade de monitorizar o consumo de fármacos de forma abrangente, principalmente como ferramenta de avaliação do impacto de recomendações clínicas na prática terapêutica; sugerem que o impacto das recomendações clínicas não é uniforme pelos diferentes setores de prescrição, deixando em aberto a possibilidade de intervenções diferenciadas por sector e, por fim, devem motivar a discussão e investigação no sentido de esclarecer a adequação do uso dos fármacos de potencial uso *off-label* na insónia aqui avaliados, uma vez que recomendações internacionais elaboradas sistematicamente não suportam, com algumas exceções, a sua utilização.[13,25,26] Uma avaliação semelhante à descrita neste trabalho em outras regiões do país pode revestir-se de relevância para a comunidade científica e para a saúde pública.

Do ponto de vista metodológico, foi possível obter os dados dos medicamentos faturados que tinham sido prescritos na ARSLVT, mas não foi possível associar essa prescrição ao utente específico. Desta forma, os dados foram trabalhados de forma censitária. Foram avaliadas as prescrições efetivamente dispensadas, ultrapassando os potenciais problemas relacionados com prescrições duplicadas não adquiridas pelos utentes ou com validade expirada, que podem originar novas prescrições. Assim, entendemos que considerar para análise as prescrições feitas na ARSLVT faturadas em qualquer ARS do país será uma forma relativamente fiável de aferir as práticas quer de prescrição quer de consumo na região administrativa de Lisboa e Vale do Tejo. No entanto, há que ter em conta que esta abordagem pode subestimar os hábitos de prescrição e sobrestimar os hábitos de consumo. Por outro lado, não são contabilizadas as dispensas sem receita médica ou a obtenção destes fármacos de forma ilícita, o que pode levar, por sua vez, à subestimação do consumo. Tanto quanto é do nosso conhecimento, não existem estimativas portuguesas sobre este tipo de acesso.

No entanto, existem limitações que importam discutir. Em primeiro lugar, os dados obtidos através do SIARS não foram validados por nenhum estudo, tanto quanto é do nosso conhecimento. Porém, tratando-se de uma plataforma e base de dados institucional, julgamos que a informação obtida seja fiável.

Outra limitação direta da base de dados acessível é não constar na análise o consumo proveniente de farmácias hospitalares, pelo que os resultados referentes aos hospitais públicos e privados poderão estar subestimados. Outro problema que limita a interpretação dos resultados é desconhecer-se a indicação pela qual foram prescritos os fármacos de potencial uso *off-label*.

O facto da população utilizada para o cálculo dos indicadores dos CSP ser diferente daquela de onde se afere o volume de prescrição dos fármacos ansiolíticos e/ou hipnóticos, apesar de especularmos que de forma pouco significativa, impossibilita a comparação direta dos dois resultados. Acresce que a população usada no cálculo de DHD traduz a estimativa anual do INE para a população residente na área geográfica de abrangência da ARSLVT. No entanto, a população real do estudo são os utentes que têm os seus cuidados médicos nesta mesma região. Ou

seja, podem estar incluídos utentes que residem fora da área geográfica de interesse, mas têm cuidados médicos na mesma e podem estar excluídos utentes que residem na área geográfica de interesse, mas têm cuidados médicos prestados em centros fora da abrangência da ARSLVT. A fonte de dados não permite aferir este número, pelo que se utilizou a fonte teoricamente mais aproximada.

Como não é possível associar o fármaco ao utente específico, existe a possibilidade de um mesmo utente estar a fazer múltiplos dos fármacos estudados, o que não é acautelado pelas medidas usadas neste estudo. Da mesma forma, não é possível associar as prescrições a um determinado diagnóstico, o que reforça o caráter meramente exploratório deste estudo.

Existe a possibilidade de as doses utilizadas no tratamento da insónia com fármacos *off-label* ser inferior à DDD definida pela OMS.[10] Isto faz com que o valor de DHD ou o total de DDD de um determinado fármaco não seja muito sensível para aferir alterações no padrão de prescrição de doses mais baixas (geralmente apenas utilizadas no período de titulação até às doses mais altas, de manutenção). Assim, o aumento das DHD nos fármacos de potencial uso *off-label* podem não traduzir a real magnitude do seu uso, caso estejam efetivamente a ser utilizados para tratar insónia com dosagens inferiores ao preconizado para a indicação principal.

O clonazepam, também uma BZD, pertence ao grupo farmacoterapêutico "2.6 – Antiepiléticos e anticonvulsivantes" motivo pelo qual não foi selecionado para avaliação, de acordo com a metodologia aplicada neste estudo. No entanto, teria sido interessante avaliar a evolução da dispensa desde fármaco no grupo de potencial uso *off-label* na insónia, por ser uma BZD e, como tal, a sonolência ser um dos seus efeitos secundários comuns.[28] Para além deste, outros fármacos poderiam ter sido estudados no grupo de potencial utilização *off-label* na insónia, como o antidepressivo amitriptilina ou outros anti-psicóticos.[13] Os que acabaram por ser avaliados foram selecionados ou por estarem referidos numa recomendação nacional[10] ou por parecerem relevantes no contexto nacional, pela experiência clínica dos autores.

Por fim, o caráter observacional deste estudo não permite chegar a conclusões definitivas quanto a uma eventual alteração do padrão terapêutico na insónia, sendo apenas gerador de hipóteses. Estas deverão ser avaliadas e, se confirmadas, ter o seu impacto aferido com estudos robustos.

CONCLUSÃO

Verificou-se uma redução da dispensa de BZD na ARSLVT, mas esta tendência não foi uniforme entre os diferentes setores de prescrição. Globalmente, esta redução foi acompanhada de um aumento na prescrição de não BZD e outros fármacos com potencial uso *off-label*. Isto poderá traduzir uma alteração no padrão terapêutico e não a uma melhoria da qualidade da prescrição, nomeadamente no que diz respeito à insónia. Estudos mais robustos são necessários para confirmar esta hipótese e aferir potenciais impactos para a saúde que dela advenham. Os indicadores dos CSP quanto à prescrição prolongada de sedativos, ansiolíticos e hipnóticos apresentaram uma evolução favorável durante o período em análise.

CONTRIBUTO DOS AUTORES

SG: Desenho, pesquisa, colheita e tratamento de dados, reflexão crítica e redação do manuscrito.

PBG: Planeamento, pesquisa, reflexão crítica e revisão do manuscrito.

MPG, DC, NR, CM: Planeamento, reflexão crítica e revisão do manuscrito.

RA: Planeamento, pesquisa e tratamento de dados, reflexão crítica e revisão do manuscrito.

JC: Planeamento, reflexão crítica e revisão 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.

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

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Pneumonitis Associated with Fluoropolymer Waterproofing Agents: Case Report

Pneumonite Associada a Impermeabilizantes com Fluoropolímeros: Caso Clínico

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Acta Med Port 2023 Apr;36(4):275-277 ▪ https://doi.org/10.20344/amp.17786

ABSTRACT

Pneumonitis associated with fluoropolymer waterproofing agents, an entity with few reported cases, can result from occupational exposure. This condition has a rapid onset after exposure, usually resolves with supportive treatment but there could be chronic sequelae. The authors report the case of a 48-year-old male patient admitted to hospital with acute onset of dyspnea and chest pain after using an aerosolized fluoropolymer-containing waterproofing product. He presented tachypnea, leukocytosis, elevated C reactive protein, elevated serum lactate dehydrogenase and hypoxemic respiratory failure. Chest computed tomography revealed bilateral ground-glass opacities with peribronchovascular distribution. The patient was treated with oxygen and corticosteroid therapy, with clinical improvement. This chemical pneumonitis represents a diagnostic challenge since it implies a history of exposure to toxic agents and the pathophysiological mechanisms and safe exposure limits are still unknown.
Keywords: Fluorocarbon Polymers/poisoning; Inhalation Exposure/adverse effects; Occupational Diseases/chemically induced; Pneumonia/chemically induced

RESUMO

A pneumonite associada a impermeabilizantes com fluoropolímeros é uma entidade com poucos casos relatados e que pode resultar duma exposição ocupacional. Esta condição tem um início rápido após a exposição, que geralmente se resolve com tratamento de suporte, podendo resultar em sequelas crónicas. Os autores relatam o caso de um homem de 48 anos admitido no hospital com quadro agudo de dispneia e dor torácica após uso de impermeabilizante que continha fluoropolímeros em aerossol. Apresentava taquipneia, leucocitose, proteína C reativa elevada, níveis séricos de lactato desidrogenase elevados e insuficiência respiratória hipoxémica. A tomografia computadorizada do tórax revelou opacidades em vidro despolido bilaterais com distribuição peribroncovascular. O doente foi tratado com oxigenoterapia e corticoterapia com melhoria clínica. Esta pneumonite química representa um diagnóstico desafiante já que implica uma história de exposição a tóxicos, sendo que a fisiopatologia e os limites de segurança de exposição ainda são desconhecidos.
Palavras-chave: Doenças Ocupacionais/induzidas quimicamente; Exposição por Inalação/efeitos adversos; Pneumonia/induzida quimicamente; Polímeros de Fluorcarboneto/intoxicação

INTRODUCTION

Chemical pneumonitis can result from occupational exposure, either accidentally or by disregarding safety rules. Fluoropolymer-containing waterproofing agents are generally composed of a solvent, a propellant and a water repelling fluoropolymer,[1] i.e., a molecule consisting of carbon and fluorine that is an ultrafine and respirable particle. Fluoropolymers have been associated with outbreaks of respiratory diseases[2] and their mechanisms depend on the methods of application, as well as on personal and environmental factors.[1] Toxicity may also result from the solvent when it vaporizes and is inhaled and the hydrophobic agent remains on the surface.

Respiratory symptoms, leukocytosis, hypoxemia and radiological changes caused by this lung injury usually start minutes to a few hours after exposure.[1,3,4] Most cases have complete resolution in days under supportive treatment and supplemental oxygen.[3,4] However, there are reports of persistent symptoms and progression to fibrosis.[1,5]

CASE REPORT

We report the case of a 48-year-old male, light smoker (less than one pack/day) with no relevant previous medical history, that complained of progressively worsening dyspnea and chest pain which evolved over four hours, after using an aerosolized waterproofing product. He was a stone restoration technician with previous similar contacts with other formulations.

He applied a fluoropolymer-containing waterproofing product, *HS O,* a colorless volatile liquid. According to the manufacturer, the composition was 94% solvent with C9-C11 paraffinic hydrocarbon, 0.45% solution of 3-iodine-2-propnyl-butylcarbamate and 5.55% fluoroacrylate polymer with ethyl acetate. The product was applied with a trigger spray in an occupational setting with inadequate ventilation and inappropriate personal protective equipment. Based on technical information obtained from the manufacturer,[6] the product was developed to be applied by brush or roller, in order to avoid prolonged direct contact with the skin and inhalation and not to be used at temperatures above 35º C.

In the Emergency Department the patient presented tachypnea, leukocytosis (16.8 x 10^9/L), elevated C reactive protein (7.5 mg/dL) and elevated serum LDH (275 U/L).

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Recebido/*Received*: 28/12/2021 - **Aceite/*Accepted*:** 14/06/2022 - **Publicado *Online*/*Published Online*:** 22/07/2022 - **Publicado/*Published*:** 03/04/2023

There was no fever, no wheezing and the cardiovascular examination was normal. The arterial blood gases analysis showed hypoxemic respiratory failure (pH 7.45, pO2 46 mmHg, pCO2 32 mmHg, oxygen saturation 85.6%). A chest computed tomography (CT) revealed centrilobular emphysema and bilateral ground-glass opacities with predominant peribronchovascular distribution in the upper lobes and associated with centrilobular micronodules (Fig. 1).

After hospital admission, oxygen therapy and prednisolone (1 mg/kg/day) were prescribed. The patient underwent a bronchoscopy with bronchoalveolar lavage (BAL) of the middle lobe and microbiological and cytological (immunocytology) investigations were unremarkable. The cellular analyses of BAL fluid revealed a macrophage dominant cell pattern (277 cells/mm^3 with 3% lymphocytes, 2% neutrophils, 87% macrophages and CD4/CD8 ratio of 2.7). Transbronchial lung biopsies of the right lower lobe were indeterminate (normal respiratory epithelium).

Blood serological markers for autoimmunity, immunoglobulins, angiotensin converting enzyme levels and precipitins for birds and fungi were performed with normal results.

Eight days after admission, respiratory function tests revealed volumes, flow rates, resistance and carbon dioxide lung diffusion within normal parameters [FEV1 3.84 l (109% predicted), FVC 4.60 l (106%), FEV1/FVC 83%, TLC 6.61 l (99%), RV 1.95 l (94%), DLCO 9.3 mmol/min/kPa (94%)].

Both clinical and radiological evolution were excellent. The patient was discharged on the tenth day, with no residual symptoms and maintained corticosteroid therapy and smoking cessation at home.

The patient received follow-up in the Pulmonology department and smoking cessation out-patient clinic, remained asymptomatic. At one month, the ground-glass opacities and micronodules had resolved completely.

DISCUSSION

These findings were consistent with the diagnosis of fluorocarbon aerosol pneumonitis supported by the onset of respiratory symptoms. The hydrocarbon aspiration pneumonitis was ruled out by the pulmonary manifestations instead of known central nervous system or cardiac effects.

Acute lung injury after inhalation exposure to fluoropolymer has several manifestations. This case, induced by aerosol exposure, illustrates an entity with few cases reported in outbreaks. It differs from the known polymer fume fever in the less often reported systemic symptoms, the BAL cellular pattern and it does not involve heating the polymer.

In order to identify this pneumonitis, it is important to obtain a history of exposure to toxic agents, their formulation, as well as personal and environmental factors. Even though this patient had previous similar contacts with other formulations, he did not have the experience of using it with a trigger spray, nor did he have the proper professional training or the personal protective equipment to use.

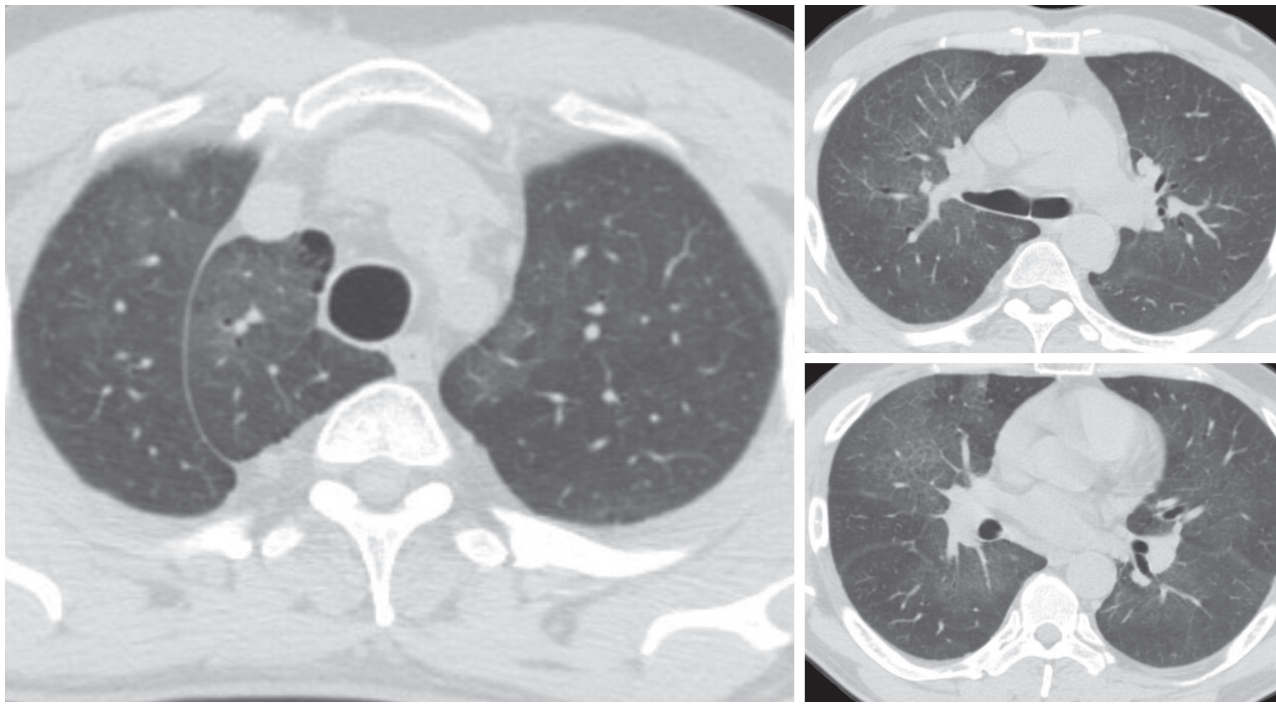

Figure 1 – Chest CT at the Emergency Department showing bilateral ground glass opacification with peribronchovascular distribution predominant in the upper lobe

National poison centers (like the Centro de Informação Antivenenos - CIAV) play a crucial role in the characterizationof the exposure and detection of these outbreaks. The pathophysiological mechanisms and safe exposure limits are unknown.

Workplace education should stimulate the use of these products according to the indications from the manufacturer and promote awareness of the potential hazards of fluorocarbons in order to prevent future toxic exposures.

AUTHOR CONTRIBUTIONS

JAB: Draft of the manuscript.

FF, AJF: 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 published in 2013.

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

All authors report no competing interests.

FUNDING SOURCES

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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ACTA MÉDICA PORTUGUESA
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Mesenteric Schwannoma, Intestinal Malrotation and Ileal Diverticulum: A Unique Association

Schwannoma Mesentérico, Má-rotação Intestinal e Divertículo Ileal: Uma Associação Única

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Acta Med Port 2023 Apr;36(4):278-282 ▪ https://doi.org/10.20344/amp.17544

ABSTRACT

Mesenteric schwannomas are rare benign tumors that arise in the mesentery. Ileal diverticula and intestinal malrotation in adults are rare findings, since they are usually asymptomatic. We present the case of an 86-year-old man, without any known previously known medical conditions, who was admitted in the emergency department with recurrent abdominal distension and intense pain. The radiological study suggested an intestinal malrotation. An exploratory laparotomy confirmed the intestinal malrotation with intermesenteric bands, as well as a mesenteric mass adjacent to an ileal diverticulum. Following a segmental enterectomy, the histology of the mass reported a mesenteric schwannoma. To the best of our knowledge, this is the first report of such association. We therefore present this report to showcase the diagnostic and therapeutical challenges in managing these conditions.
Keywords: Diverticulum; Intestinal Diseases; Neurilemmoma

RESUMO

Os *schwanomas* mesentéricos são tumores benignos raros com origem nas células de Schwann do mesentério. Divertículos ileais e má-rotação intestinal em adultos são também achados raros, por serem geralmente assintomáticos. Neste artigo apresentamos o caso de um homem de 86 anos, sem antecedentes conhecidos, que recorre à urgência por um quadro de dor abdominal e distensão. O estudo imagiológico sugeria uma má rotação intestinal, pelo que se realizou uma laparotomia exploradora, onde se verificaram várias bandas intermesentéricas, bem como uma massa mesentérica adjacente a um divertículo ileal. Foi realizada lise de bandas e uma enterectomia segmentar. A avaliação anatomo-patológica mostrou tratar-se de um *schwanoma* mesentérico. Tanto quanto é do nosso conhecimento, este é o primeiro relato de um caso com esta associação tripla, e tem como objetivo reforçar os desafios diagnósticos e terapêuticos na abordagem destas patologias.
Palavras-chave: Divertículo; Enteropatias; Neurilemoma

INTRODUCTION

Mesenteric schwannomas are rare benign tumors that arise from Schwann cells in neural sheaths in the mesentery, and are part of the family of benign peripheral nerve tumors.[1] Intestinal malrotations are disorders of the intestinal development and positioning, with a broad spectrum of anatomical presentations. The diagnosis in the elderly is rare and most commonly the presentation is either asymptomatic or with insidious symptoms.[2] Ileal diverticula are rare findings, seldom symptomatic, and are usually associated with dysmotility of the small bowel.[3] We present, to the best of our knowledge, the first report of an association of these three conditions.

CASE REPORT

An 86-year-old man, without previously known medical conditions, presented to the emergency department with recurrent diffuse abdominal distention and pain, loss of appetite and vomiting for two weeks. Bowel movements were present, and the feces were liquid, yellow, without blood, pus or mucus. No significant change in body weight was reported. The patient had been admitted due to the same symptoms four months before and had undergone conservative treatment with full recovery. At that time, the radiologic and endoscopic tests did not reveal any unusual findings. In our evaluation, there were no changes of inflammatory or other biochemical parameters. A CT scan was performed and suggested an atypical intestinal malrotation based on a whirlpool pattern (Fig. 1) with mild intestinal distention. Given the recurrence of symptoms and considering the CT findings, we decided to perform an exploratory laparotomy. We confirmed the existence of a mildly distended small bowel, due to a torsion caused by an atypical intestinal malrotation. This torsion was caused by anomalous intermesenteric bands (Fig. 2). Surprisingly, we also found a mesenteric mass of 3.5 x 4 x 3.6 cm, of elastic consistency, white colored, adjacent to an ileal loop (Figs. 3 and 4). We sectioned the intermesenteric bands and performed a segmental enterectomy, which included the mass. During this process, an ileal diverticulum was found within the sheaths of the mesentery, next to the mass (Fig. 4). Due to its covert position, the diverticulum was accidentally sectioned, without significant field contamination. The recovery was

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Recebido/*Received*: 07/12/2021 - **Aceite/*Accepted*:** 08/07/2022 - **Publicado *Online*/*Published Online*:** 01/08/2022 - **Publicado/*Published*:** 03/04/2023

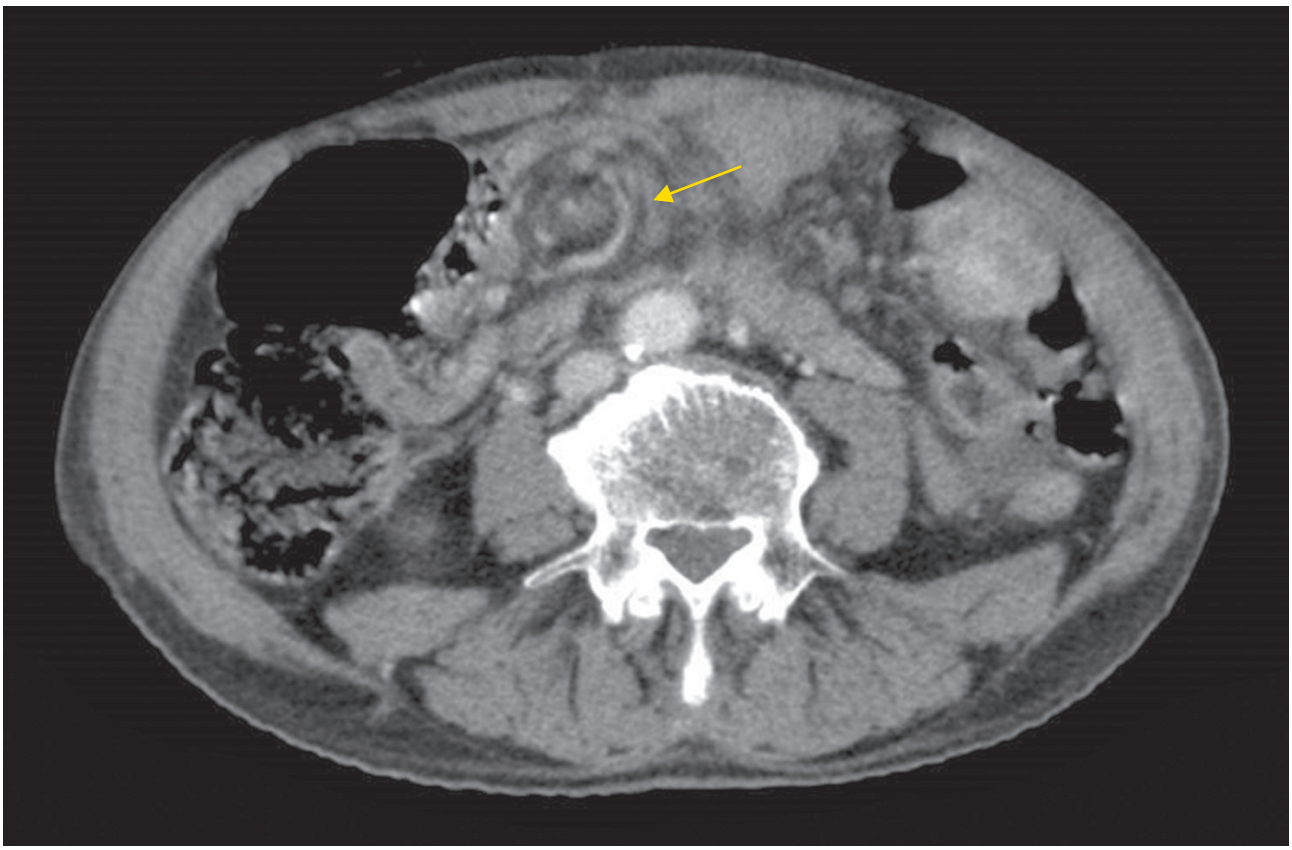

Figure 1 – Abdominal CT scan, axial. Arrow: whirlpool sign, suggestive of mesenteric torsion.

uneventful, and the patient was discharged five days after. The histology of the mass was reported as a mesenteric schwannoma. In the microscope it was possible to identify Antoni A areas, composed of Schwann cells, alternating with hypocellular Antoni B areas, with rare cells with a hyalinized stroma (Fig. 5A). Moreover, immunohistochemistry assays showed a strongly positive nuclear staining for S-100 (Fig. 5B). The patient has been followed up for two years. During this time, he remained asymptomatic and without complications following the surgical intervention.

DISCUSSION

Schwannomas are benign neoplasms that originate from Schwann cells and are part of the family of benign nerve sheath tumors, along with other neoplasms such as neurofibromas or perineurinomas.[1] The occurrence of mesenteric schwannomas is exceedingly rare. These tumors are usually slow-growing and therefore asymptomatic, even though they may cause recurrent abdominal pain or gastrointestinal occlusion due to organ compression.[4] Hence, schwannomas are usually incidentally discovered in imaging studies or during surgery. Since their radiological findings are non-specific and biopsy has low sensitivity, the definitive diagnosis is given by the pathological evaluation of the mass following surgical resection.[5] An incidental finding of mesenteric masses is unusual, with an estimated prevalence in the United States of 1/100 000. The most common mesenteric masses are cystic lymphangiomas, which account to nearly 50% of all cases of mesenteric masses, and the most frequent mesenteric solid masses are lymphomas, although other diagnoses are possible.[6] Given the possibility of malignancy, and to avoid complications associated with tumor growth, the resection of a mesenteric mass is thus indicated whenever discovered.

The case we present depicts a clinical scenario composed of vague but recurrent symptoms which can be attributed to the schwannoma, to the malrotation or to the combination of both conditions. An intestinal malrotation is an abnormality of the intestinal position and the fixation is secondary to an irregular intestinal embryological development.[7] A finding like this in adulthood is infrequent, with approximately 90% of the cases presenting in the first year of life.[2] The presentation of intestinal malrotations in adults is more frequently insidious, with chronic mild gastrointestinal symptoms such as recurrent abdominal pain, nausea, vomiting and constipation, but may be more evident with

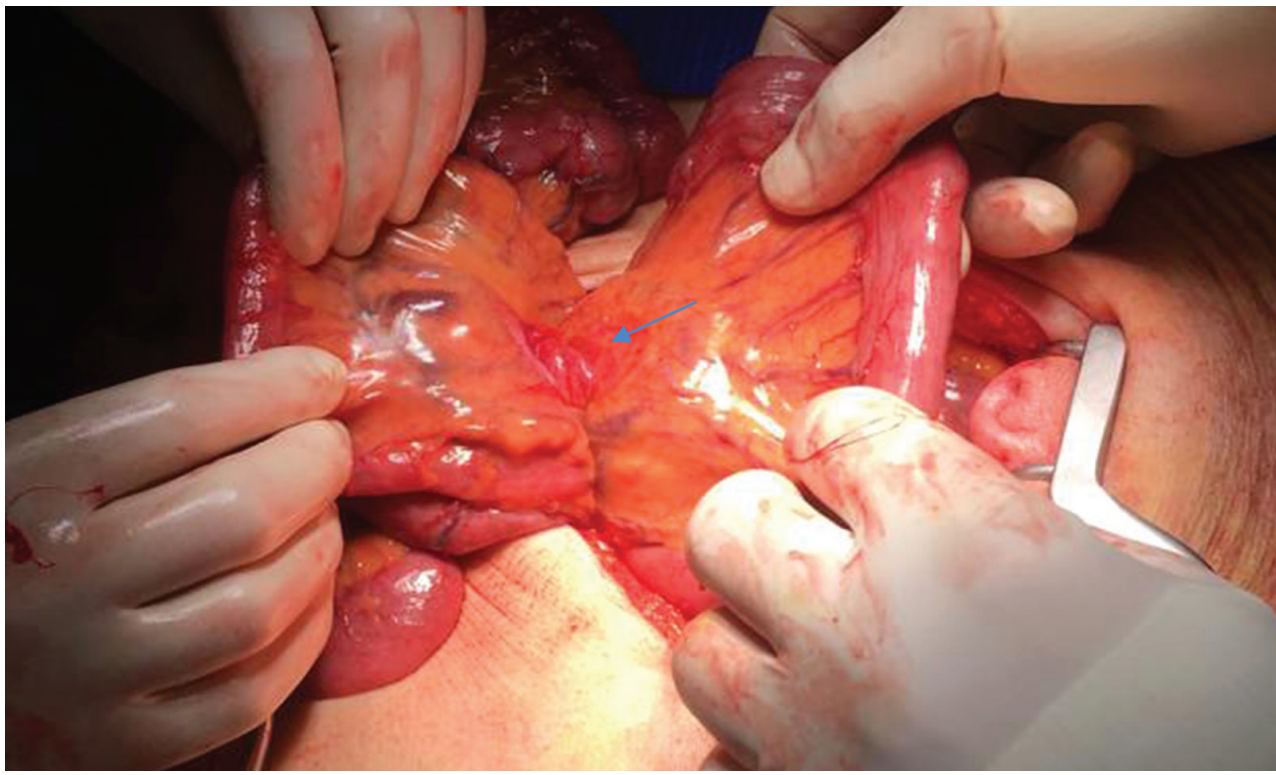

Figure 2 – Intraoperative finding. Arrow: intermesenteric band.

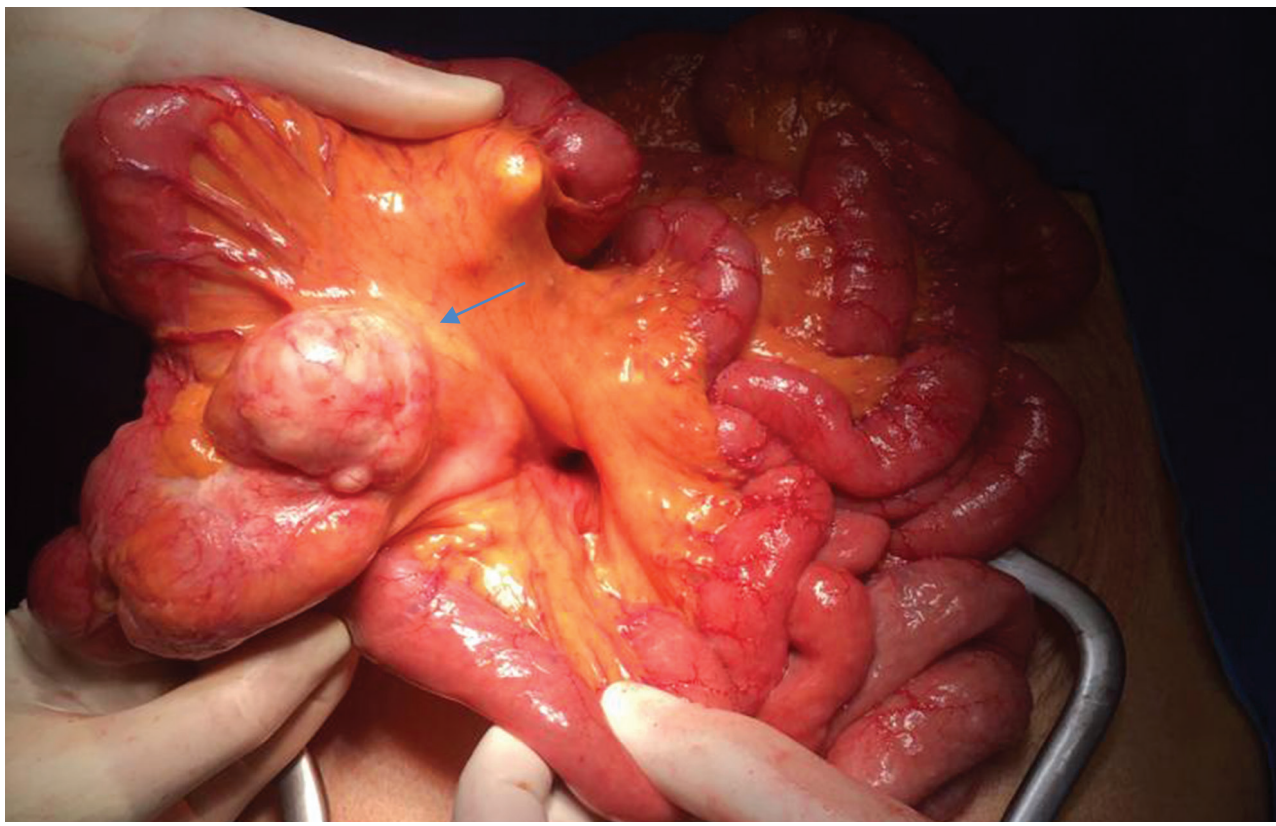

Figure 3 – Intraoperative finding. Arrow: mesenteric mass adjacent to an ileal loop.

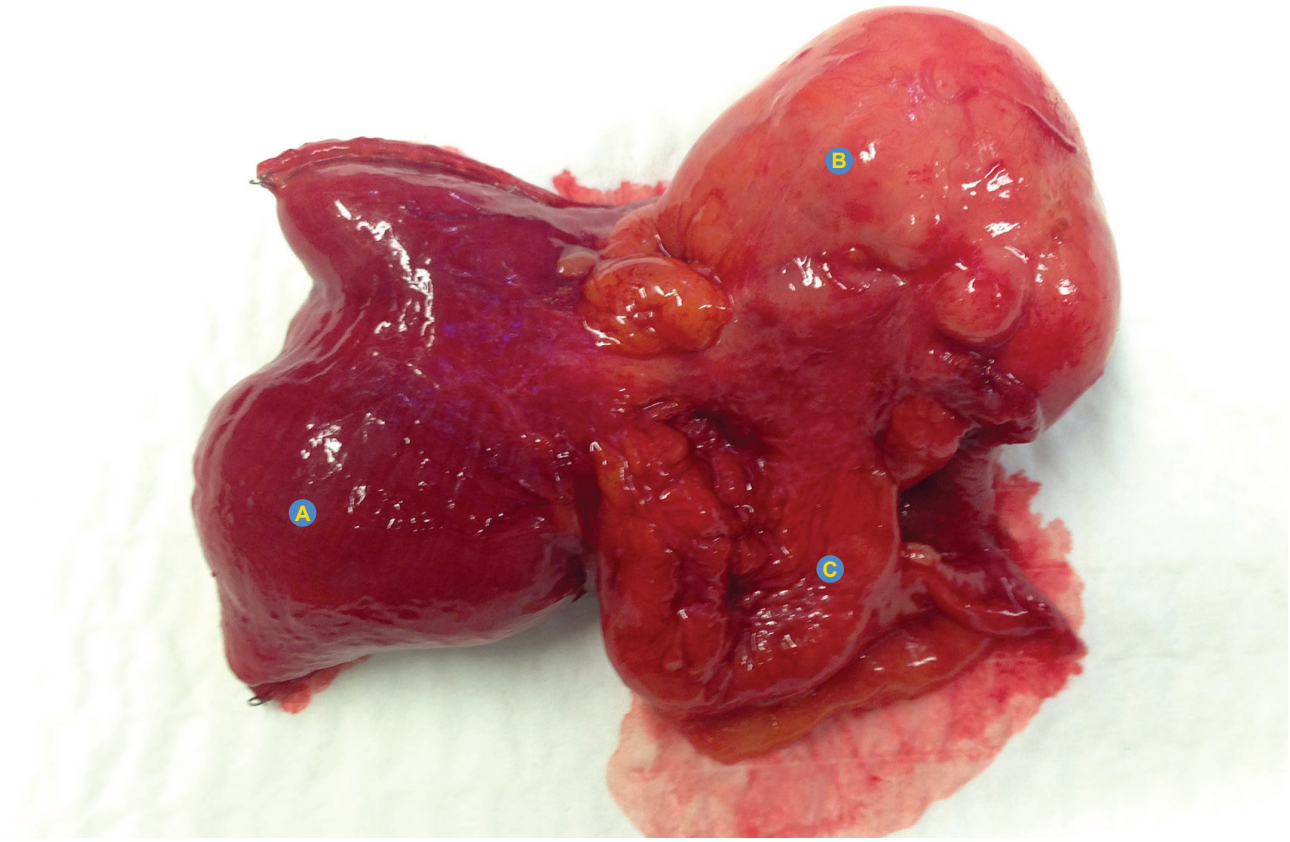

Figure 4 – Resection specimen (A) ileal loop; (B) mesenteric mass; (C) ileal diverticulum within the mesentery sheaths.

occlusive symptoms or in association with symptoms related to additional congenital defects.[8] The most common findings in the CT scan were already described elsewhere,[9] with a particular note on the possibility of finding the whirlpool sign.[10] This pattern, which our patient presented, depicts a twist of the mesentery, and must raise suspicion of an intestinal volvulus. The treatment of symptomatic intestinal malrotations is surgical.[11] Some studies suggest that asymptomatic patients can be treated conservatively, but this approach remains controversial.[12]

Our procedure was complicated by the section of an ileal diverticulum occurring within the mesenteric sheaths,

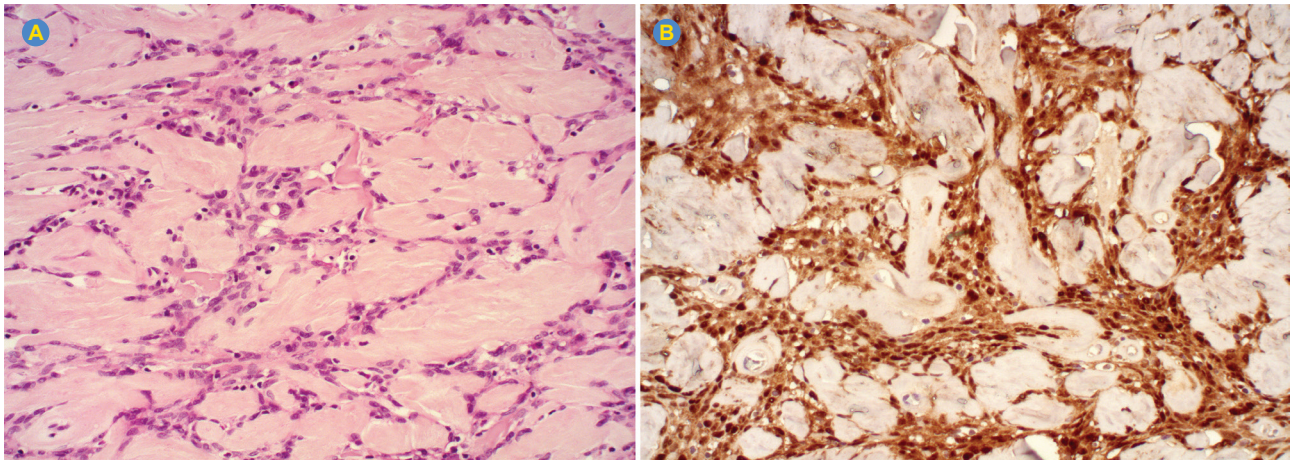

Figure 5 – Characteristic histological findings of schwannomas (200x, electronic microscope) (A) Antoni A and Antoni B areas; (B) Positive S100 nuclear protein immunohistochemistry staining.

next to the mass. Jejunoileal diverticula are rare, with reported incidence rates ranging from 0.3% to 1.3%, with a lower incidence in the ileum. They occur more commonly during the sixth and seventh decades of life.[13] Most acquired ileal diverticula are related with intestinal dysmotility and high intraluminal pressures, which cause an invagination through weakened smooth muscle regions next to penetrating mesenteric branches. These diverticula are frequently engulfed within the mesenteric sheaths, which explains why they are often overlooked during surgery.[3] In this case, it is possible that a local compressive effect by the mass altered the local intestinal motility, hence promoting the formation of a diverticulum.

To the best of our knowledge, this is the first report of an association of a mesenteric schwannoma, an intestinal malrotation and an ileal diverticulum. This case report draws attention to multiple aspects that the surgeon must bear in mind: there are cases in which non-specific symptoms without obvious clinical cues may be a sign of an underlying important condition; intestinal malrotation has to be a differential diagnosis of occlusion in the elderly, despite its low frequency; when approaching incidental mesenteric masses one must always consider the possibility of malignancy; consideration to disorders that are concomitant with intestinal diseases must be given, such as small bowel diverticula.

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 published in 2013.

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

All authors report no competing interests.

FUNDING SOURCES

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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A Pruritic Linear Eruption After an Arthropod Bite

Erupção Linear Pruriginosa Após Picada de Artrópode

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Acta Med Port 2023 Apr;36(4):283-284 ▪ https://doi.org/10.20344/amp.16988

Keywords: Insect Bites and Stings; Lymphangitis
Palavras-chave: Linfangite; Mordeduras e Picadas de Insetos

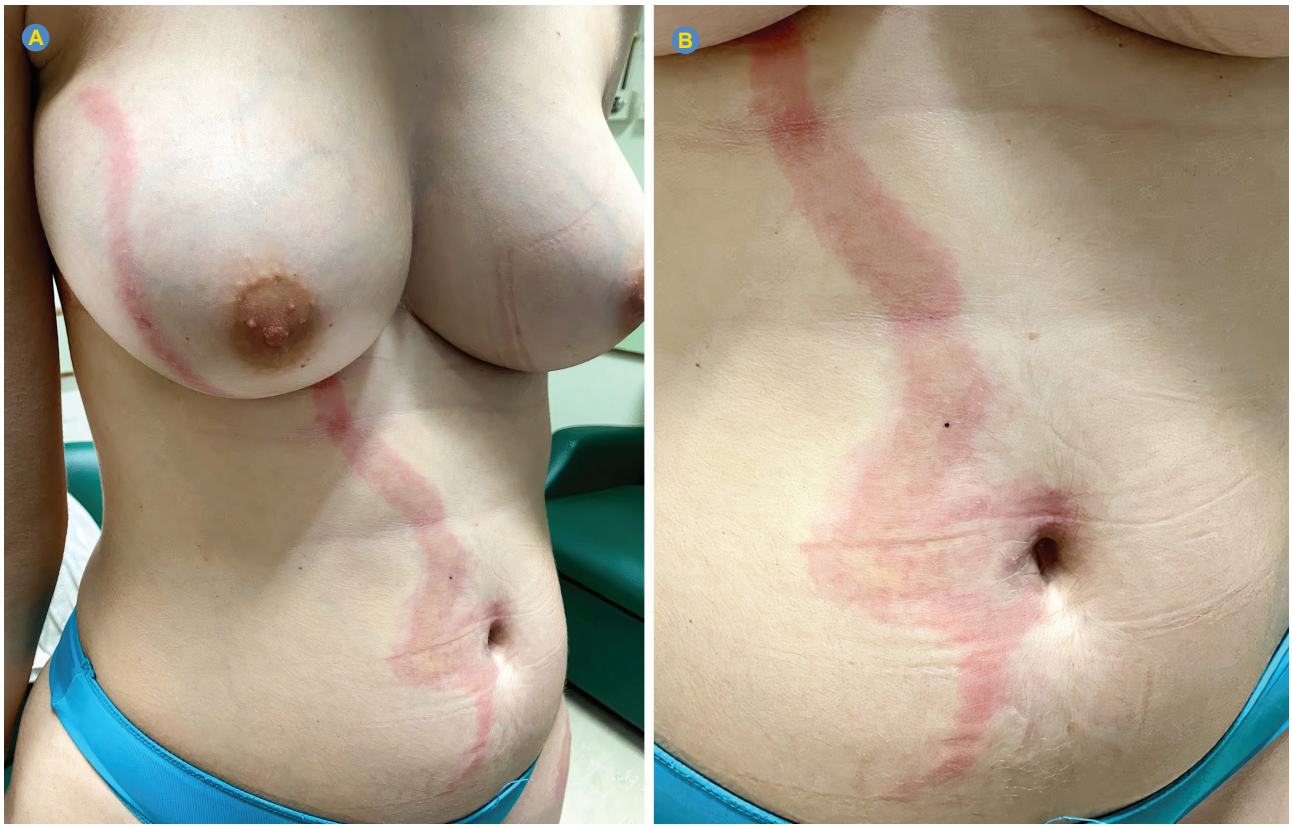

Figure 1 – (A) Linear erythematous streak from the lower abdomen to the right axilla; (B) A close-up of the area of the insect bite

A 25-year-old woman presented with a pruritic linear eruption on the anterior wall of the trunk that appeared 24 hours after a mosquito bite on the lower abdomen. On examination, one red streak starting from the area of the bite towards the right axillary fold was observed (Fig. 1). She denied any systemic symptoms and there were no palpable lymph nodes. Her medical history was unremarkable.

The anamnesis and the distinctive configuration of the lesion supported the diagnosis of insect bite-induced superficial lymphangitis. The patient was successfully treated with a one week course of oral antihistamines.

Superficial lymphangitis after an insect bite is an under-recognized entity,[1] in which acute lymphangitis presents without fever and lymphadenopathy.[1,2] To date, there are only a few cases reported.[1-5] The pathogenesis presupposes a toxic or hypersensitivity reaction to insect toxins,[3] which enter the lymphatic draining vessels and result in a linearly disposed inflammatory reaction of the overlying skin.

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Recebido/*Received*: 10/08/2021 - **Aceite/*Accepted*:** 11/11/2021 - **Publicado *Online*/*Published Online*:** 04/02/2022 - **Publicado/*Published*:** 03/04/2023

AUTHOR CONTRIBUTIONS

ASP: Literature research, draft of the paper.
RC: Data acquisition and interpretation.
JCC: Critical review of the manuscript.

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INFORMED CONSENT

Obtained.

COMPETING INTERESTS

All authors report no competing interests.

FUNDING SOURCES

The authors declare that there were no external sources of study for the performance of this article.

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ACTA MÉDICA PORTUGUESA
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Orientações de Consenso para a Abordagem dos Resultados Alterados nos Testes de Rastreio do Cancro do Colo do Útero pela SPCPTGI

Consensus Guidelines for the Management of Abnormal Cervical Cancer Screening Tests by the SPCPTGI

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Acta Med Port 2023 Apr;36(4):285-295 ▪ https://doi.org/10.20344/amp.18776

RESUMO

O cancro do colo do útero (CCU) é globalmente um dos tipos de cancro mais comum em mulheres. O rastreio do CCU é indispensável para a deteção e tratamento de lesões neoplásicas cervicais que possam evoluir para neoplasia, com o objectivo de reduzir a incidência deste cancro. Nos últimos anos, têm ocorrido alterações que visam o aumento da eficácia do rastreio. Nomeadamente, o uso de teste de deteção do vírus do papiloma humano como método de rastreio primário do CCU e a valorização da importância de adaptar a prática clínica em função do risco de desenvolvimento do CCU. Desta forma, são necessárias novas normas de atuação clínica, que contemplem esta mudança de paradigma. Assim, um grupo de especialistas analisou e discutiu a literatura mais recente, definindo recomendações e propondo normas de prática clínica que se focam na estratificação de risco, avaliação diagnóstica, e na conduta terapêutica e de seguimento de mulheres com resultados dos testes de rastreio alterados. Este trabalho tem como objetivo facilitar a prática clínica em resposta a resultados alterados nos testes e, consequentemente, melhorar a prevenção secundária do CCU.

Palavras-chave: Colposcopia; Lesões Escamosas Intraepiteliais; Neoplasias do Colo do Útero; Triagem; Vírus do Papiloma Humano

ABSTRACT

Cervical cancer is one of the most common types of cancer in women. Cervical cancer screening is needed for the detection and treatment of cervical neoplastic lesions that can evolve to neoplasia and to reduce the incidence of cervical cancer. Recently, changes were made to increase the efficiency of the screening process such as employing the human papilloma virus detection test as the gold standard for cervical cancer screening and acknowledging the importance of adapting clinical practice to consider the risk of developing this neoplasia. Considering this paradigm shift, new clinical practice guidelines are now needed. For this purpose, a group of experts analyzed and discussed the most recent literature, defining recommendations and proposing clinical practice guidelines that focus on risk stratification, diagnostic evaluation, and on the therapeutical approach and follow-up of women with altered screening results. The aim of this article is to guide clinical practice regarding actions to take in face of altered results of cervical cancer screening and, consequently, to improve the secondary prevention of this condition.

Keywords: Colposcopy; Human Papillomavirus; Screening; Squamous Intraepithelial Lesions; Uterine Cervical Neoplasms

INTRODUÇÃO

Globalmente, o cancro do colo do útero (CCU) é o quarto tipo de cancro mais comum nas mulheres.[1] Em Portugal, em 2020, foi determinada uma incidência e mortalidade padronizada para a idade de 10,7 e 3,2/100 000 mulheres-ano, respectivamente.[2]

A 17 de novembro de 2020, a Organização Mundial de Saúde lançou uma estratégia global para a eliminação do CCU, assente em três pilares (vacinação, rastreio e tratamento), com o objetivo de assegurar a vacinação completa de 90% das raparigas até aos 15 anos, o rastreio de 70% das mulheres entre os 30 e os 45 anos de idade, e o tratamento de 90% de mulheres diagnosticadas com lesões pré-invasivas ou cancro invasivo. O alcance destas metas resultaria numa redução na incidência de CCU de 2% em 2030, 42% em 2045 e 97% em 2120.[3]

Nos últimos anos, a evidência científica tem mostrado

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Recebido/*Received*: 28/06/2022 - **Aceite/*Accepted*:** 21/11/2022 - **Publicado *Online*/*Published Online*:** 23/01/2023 - **Publicado/*Published*:** 03/04/2023

que o rastreio primário com teste de deteção do vírus do papiloma humano (HPV) tem maior sensibilidade do que a citologia para detetar lesões pré-malignas e melhor desempenho na prevenção do CCU.

A colposcopia é fundamental para avaliar mulheres com testes de rastreio anormal (incluindo citologia e testes de HPV) ou para avaliar mulheres com colo do útero clinicamente suspeito. Mulheres com resultado positivo no rastreio do CCU (RCCU) correm o risco de ter uma lesão neoplásica cervical que, sem tratamento, pode evoluir para cancro. Da mesma forma, algumas lesões podem regredir espontaneamente, especialmente em mulheres jovens, e, portanto, o tratamento deve ser evitado. Assim, o principal desafio do RCCU é a distinção entre lesões sem potencial evolutivo e lesões pré-malignas.

Os critérios de referenciação para a colposcopia variam entre os diferentes programas de RCCU.

Este artigo pretende ser uma atualização do anterior Livro de Consenso Sobre Lesões Intraepiteliais do Colo do Útero, Vulva e Vagina, publicado em 2014 pela Secção Portuguesa de Colposcopia e Patologia do Trato Genital Inferior da Sociedade Portuguesa de Ginecologia (SPCPTGI-SPG).[4] Este documento foca-se na orientação de mulheres com provas de rastreio alteradas, não sendo abordadas a organização e a gestão do RCCU. Adicionalmente, este documento contempla a mudança de paradigma, que passou a valorizar a importância de individualizar a conduta clínica em função do risco e a introdução de um programa nacional de RCCU baseado no teste do HPV.

MATERIAL E MÉTODOS

Este trabalho baseou-se na literatura científica mais atual para definir recomendações e propor normas de atuação clínica perante as alterações ao teste de RCCU.

No dia 1 de julho de 2021 foi realizada uma pesquisa bibliográfica na base de dados PubMed, utilizando as palavras-chave "HPV", "colposcopy", "screening", "uterine cervical neoplasms" "treatment", "LSIL" (lesões escamosas intraepiteliais de baixo grau), "HSIL" (lesões escamosas intraepiteliais de alto grau), com os filtros "humans, female, age 19+" e restrita a artigos científicos com publicação nos 10 anos anteriores. Foram selecionados artigos em inglês e espanhol. Os artigos foram inicialmente avaliados através dos títulos e resumos, e aqueles considerados de interesse foram selecionados para avaliação posterior. Consultou-se também bibliografia referenciada nos artigos selecionados e recomendações internacionais.

Foram constituídos três grupos de trabalho: grupo 1 - estratificação do risco, grupo 2 - avaliação diagnóstica, e grupo 3 - condutas terapêuticas e de seguimento. Por fim, todos os elementos dos grupos elaboraram em conjunto o documento final que foi enviado a um grupo mais alargado de peritos e discutido na reunião nacional das unidades de colposcopia no dia 29 de janeiro de 2022. As unidades de colposcopia participantes encontram-se listadas no Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18776/15030). As divergências foram solucionadas por consenso. As recomendações foram classificadas tendo em conta o nível de evidência que suporta cada recomendação, segundo o sistema desenvolvido pela *Scottish Intercollegiate Guidelines Network* (SIGN), sendo a classificação A a mais elevada e a D a mais baixa.[5] A classificação será indicada pela respetiva letra (A - D) em frente a cada afirmação.

1. Conduta clínica baseada na avaliação do risco

A estratificação pelo risco baseia-se no reconhecimento de que: 1) a infeção persistente pelo HPV é necessária para o desenvolvimento de lesões pré-invasivas e cancro; 2) a lesão intraepitelial cervical de alto grau (HSIL/CIN 2 e CIN 3) é considerada a verdadeira lesão precursora do cancro do colo do útero; 3) as intervenções diagnósticas e terapêuticas devem ser recomendadas em função do risco de neoplasia intraepitelial cervical de alto grau ou superior (CIN 3+) imediato e a longo prazo, e não apenas baseadas na presença de doença.[6]

1.1. Colposcopia: orientação diagnóstica e terapêutica

1.1.1. Risco baixo

De acordo com os estudos ATHENA e ALTS, a coexistência de infeção por HPV não 16/18, anomalias citológicas *minor* e achados colposcópicos normais ou de grau 1 comporta um risco de CIN 2+ subjacente entre 1,00 e 2,27%. O risco de CIN 3+ situa-se entre 0,50 e 0,91%.[7,8]

As biópsias aleatórias ou não dirigidas, efetuadas numa zona de transformação (ZT) sem anomalias colposcópicas, não demonstraram utilidade nos casos de baixo risco de lesões ≥ HSIL/CIN 2.[9]

Recomendações:

- Biópsia dirigida às áreas anómalas à colposcopia (B);
- Vigilância sem biópsia se achados colposcópicos normais (B);
- Não realizar biópsias aleatórias (B);
- Se a ZT for de tipo 3 (i.e., com envolvimento endocervical sem junção escamocolunar completamente visível), considerar estudo do endocolo (B).

1.1.2. Risco elevado

A estratégia "ver e tratar" (excisão sem biópsia prévia) reduz os custos associados e a ansiedade das doentes, mas comporta o risco de sobretratamento.

Uma citologia que revele HSIL associa-se a um risco de CIN 2+ superior a 60% e de lesão invasiva de cerca de 2%,

que atinge 8% aos cinco anos em mulheres com mais de 30 anos. Nesta faixa etária, a coexistência de citologia HSIL e teste de HPV positivo determina um risco de CIN 3+ aos 5 anos de 50%. Mesmo nos casos incomuns de citologia HSIL com HPV negativo, o risco de CIN 3+ aos 5 anos foi calculado em 29%.[10]

Recomendações:

- Biópsias múltiplas de áreas aceto-brancas - entre duas e quatro, de acordo com a dimensão e a complexidade das lesões (B);
- Estudo endocervical se a classificação da citologia for de células glandulares atípicas (AGC) ou se a ZT for de tipo 3 (B).

1.2. Conduta perante as alterações nos testes de rastreio

1.2.1. Teste de HPV positivo e citologia negativa para lesão intraepitelial ou malignidade (NILM) (Fig. 1)

- Na presença dos genótipos 16/18 é sempre recomendada a colposcopia (B).
- Na presença de genótipos não 16/18, está recomendada a realização de co-teste (citologia em meio líquido concomitante com o teste de HPV) aos 12 meses (B):
  - HPV negativo e citologia NILM aos 12 meses: retorno ao rastreio (D);
  - HPV positivo e/ou se a citologia apresentar classificação de células escamosas atípicas de significado indeterminado ou mais grave (≥ ASC--US) aos 12 meses: referenciação para colposcopia (B).

1.2.2. Teste de HPV positivo com citologia classificada como ASC-US ou lesões escamosas intraepiteliais de baixo grau (LSIL) (Fig. 2)

- A colposcopia está recomendada em todas as mulheres com HPV positivo e citologia ASC-US ou LSIL (A).
- Perante achados colposcópicos anormais, deve ser efetuada uma biópsia dirigida (C).
- Se ZT tipo 3, deve ser realizado um estudo do endocolo (D).
- Se o resultado da colposcopia for normal ou se a biópsia revelar um diagnóstico < CIN 2, deve ser realizado co-teste aos 12 meses (D):
  - HPV negativo e citologia NILM aos 12 meses: rastreio aos três anos
  - HPV positivo e/ou citologia ≥ ASC-US aos 12 meses: colposcopia

1.2.3. Teste de HPV positivo e citologia com classificação de células escamosas atípicas não podendo excluir lesão escamosa intraepitelial de alto grau ou lesão escamosa intraepitelial de alto grau (ASC-H/HSIL)

- Em todos os casos está recomendada colposcopia com biópsia às lesões de maior gravidade colposcópica (B). Se ZT tipo 3, está recomendado o estudo do endocolo (D). No caso de não identificação de lesão, é obrigatória a realização de vaginoscopia (D).
- Nas situações de discordância cito-colpo-histológica é adequada qualquer das seguintes opções:
  - proceder à revisão daqueles exames e atuar em conformidade. Se permanecerem inalterados escolher uma das outras opções (D);
  - realizar a excisão da ZT com finalidade diagnóstica (B);
  - optar pela vigilância com teste de HPV aos 12 e 24 meses. Se os dois testes de HPV forem negativos, volta ao rastreio (D).

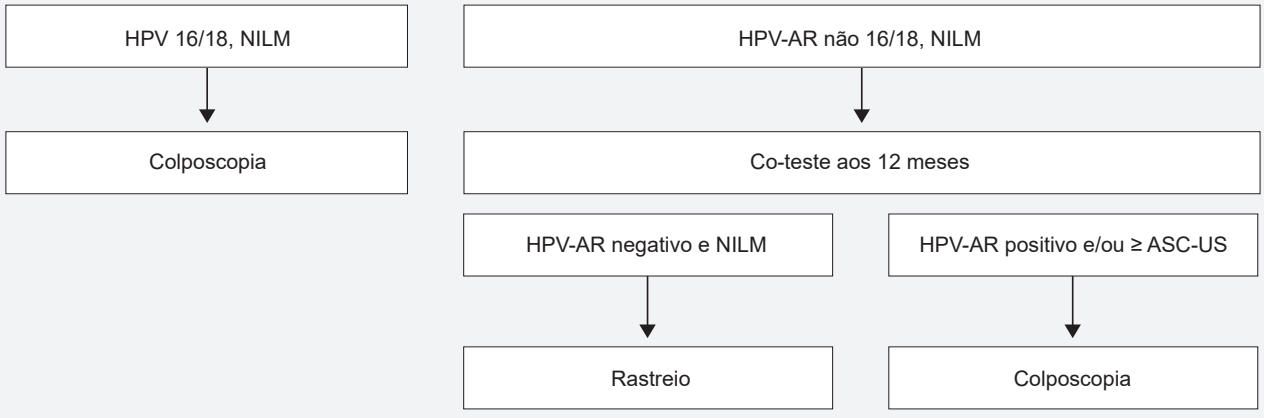

Figura 1 – Conduta perante teste de HPV positivo e citologia NILM
ASC-US: células escamosas atípicas de significado indeterminado; HPV: vírus do papiloma humano; HPV-AR: vírus do papiloma humano de alto risco; NILM: negativa para lesão intraepitelial ou malignidade.

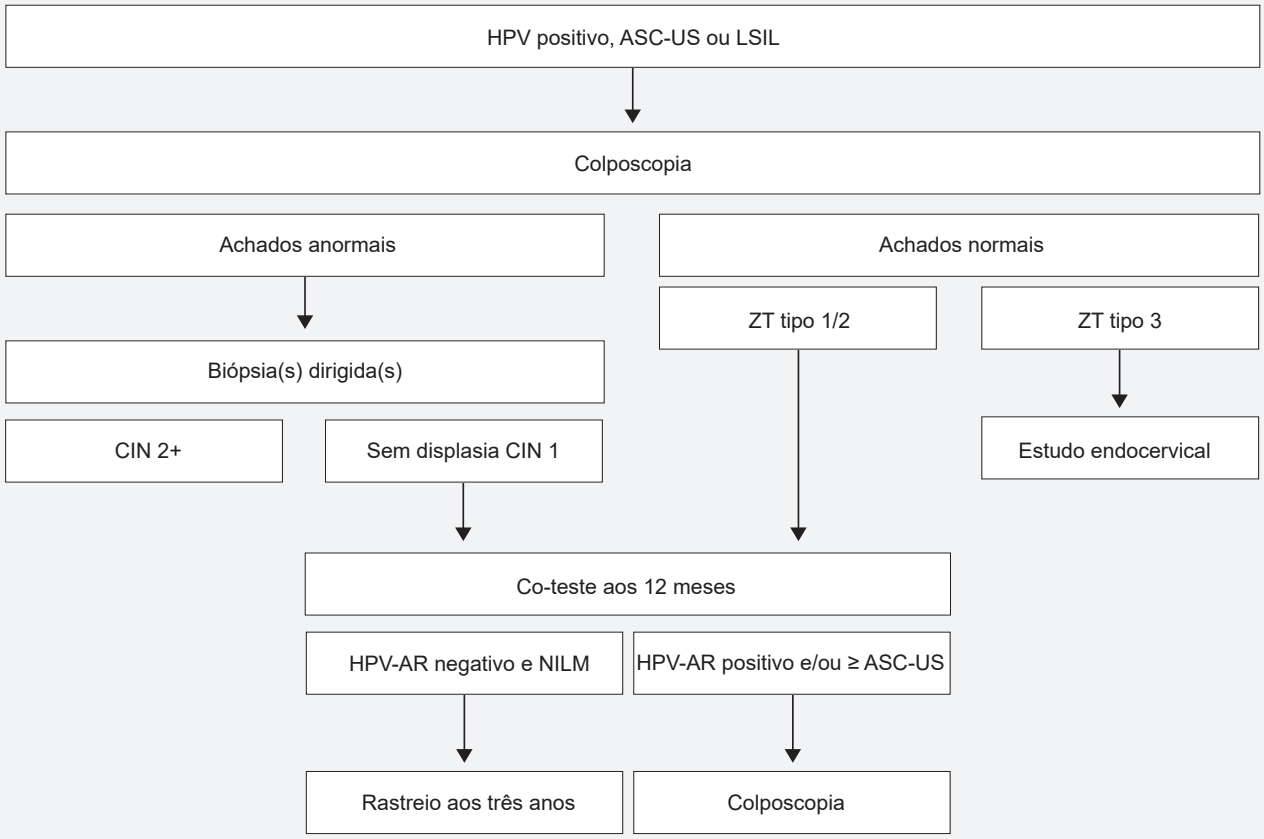

Figura 2 – Conduta perante teste de HPV positivo e citologia ASC-US/LSIL
ASC-US: células escamosas atípicas de significado indeterminado; CIN: neoplasia cervical intraepitelial; HPV: vírus do papiloma humano; HPV-AR: vírus do papiloma humano de alto risco; LSIL: lesões escamosas intraepiteliais de baixo grau; NILM: negativa para lesão intraepitelial ou malignidade; ZT: zona de transformação.

1.2.4. Teste de HPV positivo e citologia AGC/AIS

- A colposcopia e o estudo do canal cervical são recomendados para todas mulheres, de qualquer idade, com AGC e adenocarcinoma in situ (AIS; B).
- Em mulheres com mais de 35 anos, não grávidas, a ecografia ginecológica e o estudo do endométrio devem ser realizados (B).
- Em doentes não grávidas e com menos de 35 anos em risco, a amostra endometrial também é recomendada nas situações de hemorragia uterina anómala ou condições que sugiram anovulação crónica (B).
- É recomendada a avaliação inicial limitada à amostra endometrial e endocervical em doentes com células endometriais atípicas, sendo a colposcopia aceitável no momento da avaliação inicial (D).
- Para doentes com citologia que revelem células glandulares atípicas não específicas (AGC-NOS) ou células endocervicais atípicas não específicas, nas quais não se diagnosticou lesão, é recomendado um co-teste anual, nos dois anos seguintes. Caso os dois co-testes sejam negativos, recomenda-se a sua repetição aos três anos (B).
- Em mulheres com AGC ou células endocervicais atípicas favoráveis à neoplasia ou AIS, é recomendada colposcopia inicial para excluir doença invasiva. Na ausência de doença invasiva, é recomendado um procedimento excisional de diagnóstico, de forma a obter uma amostra intacta com margens interpretáveis. É preferível a obtenção de uma amostra endocervical acima do leito excisional (B).

1.2.5. Teste de HPV positivo e células endometriais benignas

- Em mulheres pré-menopáusicas assintomáticas, o aparecimento de células endometriais benignas, células do estroma endometrial ou histiócitos, não requer avaliação adicional (B).
- Para doentes pós-menopáusicas com células endometriais benignas, é recomendada a avaliação endometrial (B).

2. Tratamento

O objetivo do tratamento é a prevenção da possível progressão para cancro, evitando o sobretratamento, uma vez que as lesões podem regredir espontaneamente e o tratamento pode ter morbilidade associada.

A classificação LAST (*Lower Anogenital Squamous Terminology Standardization Project*) enfatiza que há dois estados biológicos causados pelo HPV: LSIL (infeção viral produtiva de partículas virais, de menor risco biológico) e HSIL (infeção HPV transformante ou neoplásica, de maior risco biológico).[11]

2.1. Abordagem perante LSIL/CIN 1

2.1.1. LSIL/CIN 1 ≥ 25 anos (Fig. 3)

a. Abordagem de LSIL/CIN 1 precedido de HPV positivo e/ou citologia LSIL/ASC-US/NILM.
   - Não está recomendado tratamento e deve ser feito seguimento aos 12 meses com co-teste; se negativo, tem alta para o rastreio (D).
   - Se LSIL/CIN 1 persistente por dois anos é indicado manter vigilância (B) mas é aceitável tratar (D).
   - Caso se opte por efetuar tratamento, se a junção escamocolunar (JEC) for totalmente visível e se existirem lesões totalmente visíveis, estão indicados tanto tratamentos excisionais como destrutivos (C). Os tratamentos excisionais têm a vantagem de fornecer diagnóstico histológico.

b. Abordagem de LSIL/CIN 1 precedido de citologia ASC-H, HSIL ou AGC.
   - Quando após citologia com classificação ASC-H ou HSIL não é identificado CIN 2+, é aceitável fazer revisão da citologia, histologia e achados colposcópicos. É obrigatória a avaliação adequada da vulva e vagina. No caso de a revisão resultar num diagnóstico diferente, a abordagem terapêutica deve seguir o protocolo específico (D).
   - Se citologia prévia está classificada como HSIL e o diagnóstico histológico é de LSIL ou inferior, é aceitável fazer uma excisão diagnóstica da ZT ou vigilância com co-teste e colposcopia em seis meses, desde que a JEC e o limite superior da lesão sejam totalmente visíveis e que o estudo

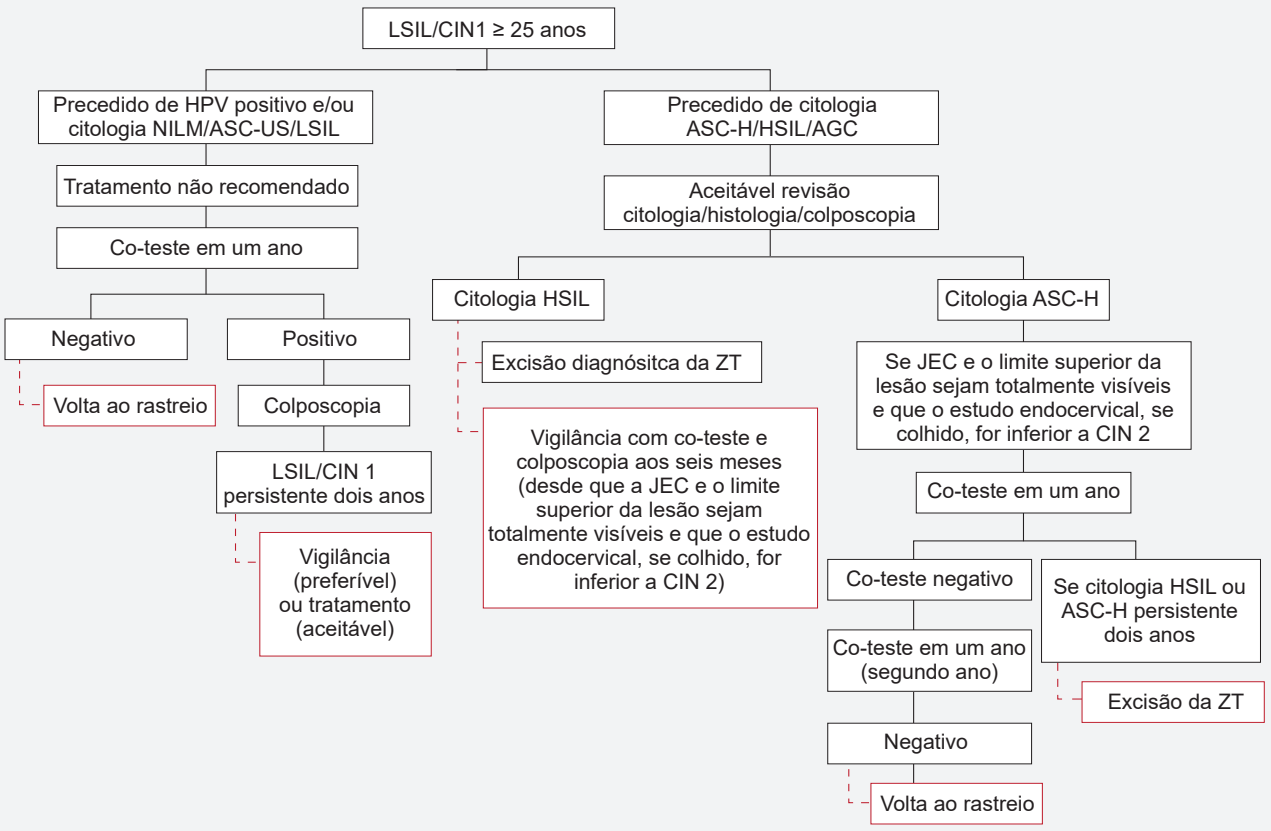

Figura 3 – Diagrama representativo da vigilância de lesões escamosas intraepiteliais baixo grau quando idade superior a 25 anos

AGC: células glandulares atípicas; ASC-H: células escamosas atípicas, não podendo excluir lesão escamosa intraepitelial de alto grau; ASC-US: células escamosas atípicas de significado indeterminado; CIN: neoplasia cervical intraepitelial; HSIL: lesões escamosas intraepiteliais de alto grau; JEC: junção escamocolunar; LSIL: lesões escamosas intraepiteliais de baixo grau; NILM: negativa para lesão intraepitelial ou malignidade; ZT: zona de transformação.

endocervical, se colhido, for inferior a CIN 2 (B).
- Se citologia prévia está classificada como ASC-H, não é recomendada a excisão diagnóstica da ZT; se a JEC e o limite superior da lesão estiverem totalmente visíveis e se o estudo endocervical, se colhido, for negativo, é recomendada observação em um ano com co-teste (B).
- Tanto para citologia prévia com classificação HSIL como ASC-H, caso se opte por vigilância, se no seguimento de um ano todos os testes estiverem negativos, deve repetir-se o co-teste dois anos depois da citologia original. Após dois anos consecutivos com exames negativos volta ao rastreio (D).
- No caso de, durante o período de vigilância, existir algum teste com resultado anormal, é recomendada a repetição da colposcopia (D).
- Está indicada a excisão diagnóstica da ZT se a citologia apresentar HSIL no primeiro ou no segundo ano de seguimento, e se a citologia apresentar ASC-H persistente por dois anos (D).

2.1.2. LSIL/CIN 1 < 25 anos (Fig. 4)

a. Abordagem de LSIL/CIN 1 precedido por citologia ASC-US/LSIL:
   - Se a biópsia confirmar a presença de LSIL/CIN 1 a citologia deverá ser repetida dentro de um ano (B):
     1. Se citologia NILM/ASC-US/LSIL: repetir a citologia dentro de um ano e se o resultado for negativo volta ao rastreio.
     2. Se citologia ASC-H/HSIL/AGC: deverá ser realizada uma colposcopia (B).

b. Abordagem de LSIL/CIN 1 precedido por citologia ASC-H ou HSIL:
   - A observação é recomendada e não estão recomendados procedimentos excisionais diagnósticos desde que a JEC e o limite superior da lesão se encontrem totalmente visíveis e que o estudo endocervical, se colhido, seja inferior a HSIL/CIN 2-3 (D).
     1. Se citologia HSIL recomenda-se colposcopia e citologia um e dois anos depois.
     2. Se citologia ASC-H recomenda-se citologia um e dois anos depois e colposcopia se a citologia ≥ ASC-US (D).

2.1.3. Abordagem de LSIL/CIN 1 na grávida

- O tratamento de mulheres grávidas com CIN 1 está contraindicado. A reavaliação deverá ocorrer seis semanas pós-parto de acordo com a alteração que precedeu o LSIL/CIN 1 (D).

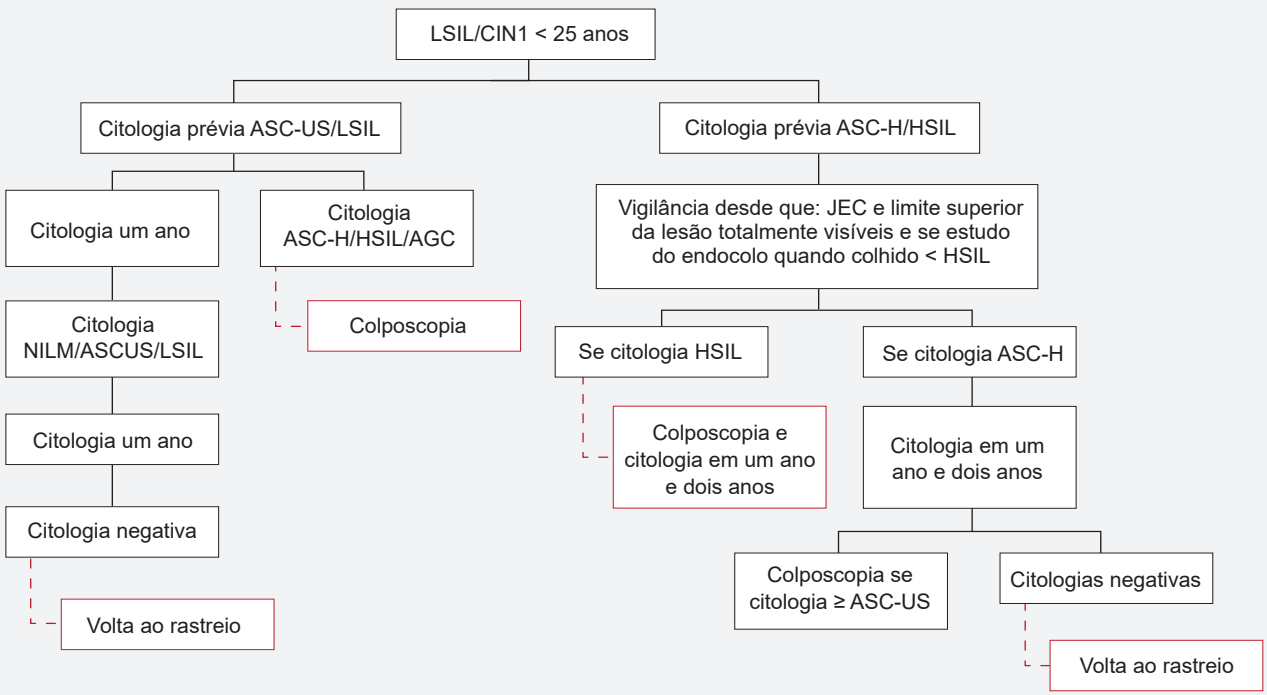

Figura 4 – Diagrama representativo da vigilância de lesões escamosas intraepiteliais baixo grau quando idade inferior a 25 anos
AGC: células glandulares atípicas; ASC-H: células escamosas atípicas, não podendo excluir lesão escamosa intraepitelial de alto grau; ASC-US: células escamosas atípicas de significado indeterminado; CIN: neoplasia cervical intraepitelial; HSIL: lesões escamosas intraepiteliais de alto grau; JEC: junção escamocolunar; LSIL: lesões escamosas intraepiteliais de baixo grau; NILM: negativa para lesão intraepitelial ou malignidade.

2.2. Abordagem perante HSIL

2.2.1. HSIL histológico em doentes ≥ 25 anos

a. HSIL histológico não especificado – e.g., reportado como HSIL ou HSIL/CIN 2,3
   - A CIN 3 é considerada precursora direta do cancro cervical. Se não puder ser excluída CIN 3, é preferível abordar a mulher como se esta esteja presente (D).
   - Em mulheres não grávidas com ≥ 25 anos, o tratamento excisional é preferido se o HSIL histológico não puder ser especificado (A).

b. HSIL histológico (HSIL/CIN 2 ou HSIL/CIN 3)
   - Em mulheres não grávidas com diagnóstico histológico HSIL/CIN 2, o tratamento é recomendado (B).
   - A observação é aceitável se:
     - as preocupações da mulher sobre potenciais desfechos obstétricos adversos após um procedimento excisional superam os receios sobre o cancro (B);
     - toda a JEC e lesão são visíveis na colposcopia e a avaliação do endocolo não demonstra CIN 2+ ou CIN não graduável (B).
   - A observação é inaceitável quando a JEC ou o limite superior da lesão não são completamente visualizados ou quando os resultados de uma amostra endocervical, se realizada, for CIN 2+ ou não graduável (nível de recomendação D).[6]
   - Para todas as mulheres não grávidas com um diagnóstico histológico de HSIL/CIN 3, o tratamento é recomendado e a observação inaceitável (B).
   - Quando considerado o tratamento, deve optar-se por um método excisional - excisão com ansa diatérmica, excisão LASER, excisão a frio (A).
   - Tratamentos não cirúrgicos, incluindo agentes tópicos (ex. ácido tricloroacético), vacinas terapêuticas e outros tratamentos biológicos, são inaceitáveis para o tratamento de HSIL histológico (CIN 2 ou CIN 3), fora do contexto de ensaios clínicos (D).
   - A histerectomia é inaceitável como terapêutica primária para tratamento de HSIL histológico (CIN 2, CIN 3 ou não qualificado; B).

2.2.2. Abordagem de CIN 2 em doentes preocupadas com o efeito potencial do tratamento em gravidezes futuras

- A observação é aceitável, desde que a JEC seja visível e não seja identificado CIN 2+ ou CIN não graduável em amostras endocervicais (D).
- Se HSIL histológico não puder ser especificado como CIN 2, o tratamento é preferível, mas a observação é aceitável (D).
- Para doentes com 25 anos ou mais, a observação inclui colposcopia e citologia a cada seis meses e teste de HPV anual até dois anos. Se durante a observação todas as avaliações demonstrarem menos de CIN 2 e menos de ASC-H em duas ocasiões sucessivas, espaçadas de seis meses, a observação subsequente deve ocorrer um ano após a segunda avaliação e usar o teste baseado em HPV. Se o resultado de três testes de seguimento anuais consecutivos for negativo, deve prosseguir-se com o acompanhamento a longo prazo (D).
- Se for observada CIN 2 durante um período de dois anos, o tratamento é recomendado (C).

2.2.3. HSIL histológico (CIN 2 ou CIN 3) em doentes com menos de 25 anos

- Se o diagnóstico histológico for HSIL/CIN 3, o tratamento é recomendado e a observação é inaceitável (B).
- Se o diagnóstico histológico for HSIL/CIN 2, a observação é preferida e o tratamento é aceitável (nível recomendação B).
- Se o diagnóstico for HSIL não especificado como CIN 2 ou CIN 3, a observação ou o tratamento são aceitáveis (D).
- Quando a observação é realizada:
  - deve consistir inicialmente em citologia e colposcopia aos seis e 12 meses (D);
  - se a classificação da citologia é inferior a ASC-H e a da histologia é inferior a CIN 2 aos seis e 12 meses, a avaliação subsequente deve ocorrer um ano após a segunda avaliação (D);
  - se o diagnóstico de CIN 2 ou HSIL não especificado persiste aos dois anos, o tratamento é recomendado (D).

2.2.4. Doentes grávidas

- CIN 2 ou 3 em que não há suspeita de doença invasiva:
  - preferencialmente observação sem tratamento, com realização de colposcopia e citologia (teste de HPV se idade apropriada) a cada 12 semanas durante a gravidez (B);
  - a biópsia pode ser repetida apenas se se observar agravamento colposcópico da lesão (B);
  - a curetagem endocervical (CEC) está contraindicada (D);
  - diferir a colposcopia até às seis semanas pós-parto é uma alternativa aceitável (B);

- ◦ O tratamento de CIN 2 ou 3 não é recomendado (C).

2.2.5. Doentes com problemas de adesão à vigilância

- Tratamento imediato ou expedito pode ser aplicado a doentes não grávidas com citologia de alto grau em que seja pouco provável que cumpram um plano de seguimento ou que não venham rapidamente à consulta após resultados citológicos anómalos (D).

3. Seguimento

3.1. Seguimento de mulheres tratadas por HSIL (Fig. 5)

- A vigilância é realizada preferencialmente com teste de HPV ou co-teste (A).

3.2. Vigilância a curto prazo após tratamento de HSIL

- O co-teste aos seis meses é preferível independentemente do estado da margem da peça de excisão (B).
- Se o teste de HPV for positivo, deverá ser efetuada colposcopia (B).
- O seguimento aos seis meses com colposcopia e estudo do canal é aceitável (D).
- Quando as margens são positivas para CIN 2+ ou o estudo do canal efetuada no momento da excisão da ZT mostrar CIN 2+ em doentes ≥ 25 anos que não estejam preocupadas com o efeito potencial do tratamento numa gravidez futura, a repetição da excisão ou a observação são aceitáveis (D).
  - ◦ Para a observação, é preferível o co-teste aos seis meses; também é aceitável efetuar uma colposcopia e estudo do canal aos seis meses (D).
  - ◦ Para doentes < 25 anos ou preocupadas com o efeito potencial do tratamento numa futura gravidez, a observação é recomendada (D)
- Se se desenvolver HSIL recorrente (CIN 2+) após tratamento excisional, apenas se recomenda a histerectomia, se não for possível a repetição da excisão (D).

3.3. Vigilância a longo prazo após tratamento de HSIL

- Após o co-teste aos seis meses, é preferível o co-teste anual até serem obtidos dois testes negativos consecutivos (B).
- Após o período de vigilância inicial, é recomendada a vigilância com co-teste em intervalos de três anos durante pelo menos 25 anos, mesmo para doentes com mais de 65 anos (B).
- Quando doentes com história de HSIL tratada atingem os 65 anos, se já completaram o período de vigilância inicial de 25 anos, é aceitável manterem uma avaliação cada três anos (HPV/co-teste) desde que a doente tenha um estado de saúde considerado razoavelmente bom (D).
- Caso o teste de HPV seja positivo ou haja alteração citológica > LSIL, deve ser feita referenciação para colposcopia com eventual biópsia dirigida (D).
- Se a avaliação colposcópica for negativa, as doentes devem fazer co-teste anual, até terem dois co-testes negativos consecutivos com um ano de diferença (B), passando a vigilância com co-teste de três em três anos.

4. Adenocarcinoma *in situ* (AIS)

Não existem recomendações ideais para mulheres tratadas conservadoramente.[6,12-15]

4.1. Tratamento

4.1.1. Mulher sem desejo gestacional, conforme resultado da excisão da ZT

- Margens endocervicais e estudo do canal negativos: histerectomia simples (D).
- Margens endocervicais ou estudo do canal cervical positivos: repetir excisão da ZT para obter margens negativas, com o objetivo de minimizar o risco de adenocarcinoma invasivo subjacente e tratamento definitivo subsequente com histerectomia (D). Na impossibilidade técnica de repetir a excisão da ZT: histerectomia simples (D).

4.1.2. Mulher com desejo gestacional, conforme resultado da excisão da ZT

- Margens e estudo endocervical negativos: vigilância com co-teste, colposcopia e estudo endocervical aos 6 meses (C).
- Margens endocervicais ou estudo endocervical positivos: nova excisão da ZT para obter margens negativas (C):
  - ◦ margens e estudo endocervical negativos após nova excisão: controlos mencionados acima (C);
  - ◦ margens ou estudo do canal endocervical positivos após nova excisão: nova excisão da ZT ou traquelectomia simples (remoção cirúrgica do colo do útero). Idealmente deve ser realizada uma biopsia intraoperatória da margem endocervical para garantir margens negativas. Se não for exequível ampliar a margem da traquelectomia deve ser proposta uma histerectomia (D).
- Após histerectomia: co-teste de três em três anos durante, pelo menos, 25 anos (D).

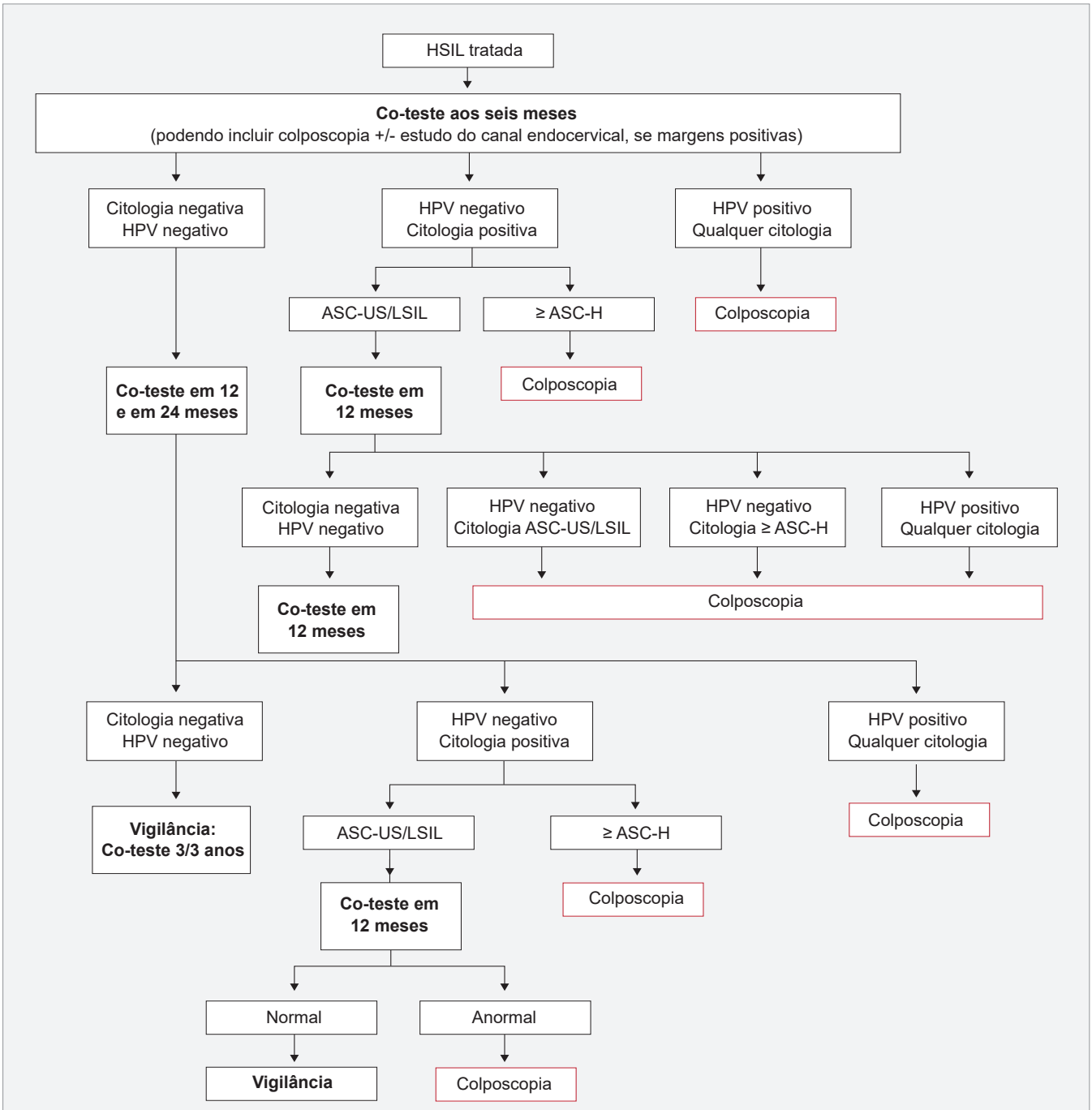

Figura 5 – Diagrama representativo da vigilância após tratamento de lesões escamosas intraepiteliais de alto grau

ASC-H: células escamosas atípicas, não podendo excluir lesão escamosa intraepitelial de alto grau; ASC-US: células escamosas atípicas de significado indeterminado; HPV: vírus do papiloma humano; HSIL: lesões escamosas intraepiteliais de alto grau; LSIL: lesões escamosas intraepiteliais de baixo grau.

4.2. Vigilância

4.2.1. Vigilância após tratamento cirúrgico de AIS

- Se após a histerectomia existir diagnóstico de adenocarcinoma invasivo as doentes devem ser tratadas de acordo com protocolo adequado (B).
- Na ausência de adenocarcinoma invasivo na peça operatória não existe um plano estabelecido de vigilância pelo que é admissível a realização de co-teste seis a 12 meses após a histerectomia com repetição anual se os resultados do co-teste forem negativos (D):
  - na presença de um resultado citológico anormal

deve ser realizada colposcopia da vagina, independentemente do resultado do teste de HPV (B);
- na presença de um resultado positivo das biópsias para displasia vaginal de alto grau (glandular ou escamosa), deve ser efetuado um procedimento destrutivo ou excisional (B);
- se os resultados da citologia vaginal forem normais, mas apresentar vírus do papiloma humano de alto risco (HPV-AR) positivo deve repetir o co-teste seis a 12 meses depois (B). Caso haja persistência de HPV-AR positivo, deverá realizar uma colposcopia e orientar o seguimento de acordo com os achados colposcópicos (B).

4.2.2. Vigilância após procedimento excisional de AIS

- Co-teste, colposcopia e estudo endocervical cada seis meses (D);
- Se os resultados forem consistentemente negativos durante três anos, o intervalo de vigilância pode passar a anual (B).
- Se a citologia ou o teste de HPV forem anormais durante o follow-up, avaliar através de colposcopia e CEC (B):
  - se os resultados da colposcopia e da CEC forem negativos as doentes devem retomar o protocolo de vigilância descrito acima;
  - se todos os controlos prévios forem negativos (incluindo o teste de HPV) é aceitável a vigilância com co-teste (acompanhamento > 25 anos) ou avaliar a possibilidade de histerectomia individualizada (D);
  - se durante a vigilância qualquer teste der um resultado positivo seguir as indicações do protocolo específico;
  - se AIS recorrente ou displasia escamosa de alto grau na biópsia guiada por colposcopia e/ou CEC, as doentes devem ser submetidas a re-excisão da ZT ou histerectomia (B).

5. Vacinação HPV em mulheres com ou tratadas por lesões escamosas intraepiteliais (SIL) ou CIN

- Administrar a vacina contra o HPV a mulheres tratadas por SIL/CIN (A), independentemente da persistência ou não do HPV após o tratamento.
- A vacina contra o HPV deve ser administrada num esquema de três doses (zero, dois e seis meses). Deve ser administrada o mais rapidamente possível após o diagnóstico, preferencialmente antes do tratamento (D).

AGRADECIMENTOS

Este artigo tem o apoio científico da Sociedade Portuguesa de Anatomia Patológica (SPAP) e da Associação Lusófona para o Estudo das Doenças Transmissíveis e Cancro (ACL-DTC). Os autores agradecem as sugestões construtivas e a revisão crítica do manuscrito realizadas por Pedro Vieira Baptista, Anabela Colaço, Teresa Rebelo, Elisa Paredes e Cátia Correia.

CONTRIBUTO DOS AUTORES

Todos os autores contribuíram para a conceção do trabalho, pesquisa bibliográfica, revisão crítica do manuscrito e todos aprovaram a versão final.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFLITOS DE INTERESSE

A Secção Portuguesa de Colposcopia e Patologia do Trato Genital Inferior da Sociedade Portuguesa de Ginecologia (SPCPTGI-SPG) recebeu apoio da Roche Diagnósticos, Portugal para serviços de *medical writing*, revisão e submissão deste artigo. Amélia Pedro é presidente da Comissão de Educação da Federação Europeia de Colposcopia, Amália Pacheco é membro da Sociedade Portuguesa da Contracepção, Rita Sousa é membro da Sociedade Portuguesa de Senologia, Daniel Pereira Silva prestou serviços de consultoria para Gedeon Richter e é presidente da assembleia geral da Federação das Sociedades Portuguesas de Obstetrícia e Ginecologia e José Fonseca Moutinho é vice-presidente da Sociedade Portuguesa de Ginecologia.

FONTES DE FINANCIAMENTO

O apoio de *medical writing*, revisão e submissão deste artigo foram financiados pela Roche Diagnósticos, Portugal.

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Mother-Baby Units: An Unmet Need for Mental Health Inpatient Care in Portugal?

Unidades Mãe-Bebé: Uma Necessidade por Suprir nos Serviços de Internamento de Saúde Mental em Portugal?

Keywords: Mental Disorders; Mother-Child Relations/psychology; Postnatal Care/psychology
Palavras-chave: Cuidado Pós-Natal/psicologia; Perturbações Mentais; Relações Mãe-Criança/psicologia

Dear Editor,

In the past few years, the mental health of women during the perinatal period has received increasing attention. The literature has shown that pregnancy and the postpartum period are associated with increased vulnerability to many psychiatric disorders, which affect 10% to 20% of women during this period.[1] Furthermore, mental illness in pregnant women and new mothers is associated with worse obstetric outcomes and can lead to long-lasting effects on their offspring's mental and physical health.[2] Therefore, the management of perinatal mental health is not only beneficial to the women receiving care, but may also work as a preventive intervention for the next generation.

Moreover, mental illness in the perinatal period is associated with substantial economic costs. It has been estimated that, in the United Kingdom (UK), the cost to the public sector of perinatal mental health problems is five times higher than the cost of improving services.[1] Designing services tailored to the specificities and needs of patients during the perinatal period has been a priority in many countries. In Portugal, however, studies on this subject and specialized teams are still sparse. While some hospitals offer Perinatal consultations, women are usually admitted to a general inpatient ward whenever inpatient care is necessary.

Mother and baby units (MBUs), currently considered the best practice in the UK, are acute inpatient mental health services where women diagnosed with severe perinatal psychiatric disorders can be admitted with their babies. In MBUs, specialized care is provided by a multidisciplinary team, which can include psychiatrists, psychotherapists, occupational therapists and nurses.[3] Their goal is to attend to women and babies' particular needs during this vulnerable period. For this purpose, besides providing medication, activities like breastfeeding support, parenting interventions, help with infant-care and mother-baby interventions are offered. The partner and the family are also involved in the recovery journey. According to a recent study on cost-effectiveness of MBUs, the rate of readmission appears to be similar but service satisfaction seems higher compared to generic wards.[4]

Although severe mental illness during the perinatal period is not common, its negative impact on a family can be devastating. MBUs offer specialized care which can improve the experience of inpatient care during this vulnerable period. On that account, we argue that MBUs could be an important addition to mental health care in Portugal. Cost-effectiveness studies applied to our population could help support its implementation.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

COMPETING INTERESTS

FFM has received payment or honoraria from Lundbeck Portugal for attending "Especialização avançada em Intervenção Familiar Sistémica" and support for attending the 28th International Symposium on Controversies in Psychiatry and "Growing Minds 2.0" from Angelini Pharma Portugal and BIAL, respectively.

SX has received support for attending "Congresso Nacional de Psiquiatria 2021" from Neuraxpharm.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Recebido/*Received*: 21/11/2022 - **Aceite/*Accepted*:** 30/01/2023 - **Publicado *Online*/*Published Online*:** 20/02/2023 - **Publicado/*Published*:** 03/04/2023

https://doi.org/10.20344/amp.19335

Non-Specific Pleuritis after Medical Thoracoscopy: A Prospective Study

Pleurite Não Específica após Toracoscopia Médica: Um Estudo Prospetivo

Keywords: Pleural Effusion; Pleurisy/etiology; Thoracoscopy
Palavras-chave: Derrame Pleural; Pleurisia/etiologia; Toracoscopia

More than 50 causes of pleural effusion are known and, although the majority are benign (85%), both malignant and unknown causes are common.[1,2]

If the cause of pleural effusion is not found after thoracocentesis, a pleural biopsy is indicated. Medical thoracoscopy (MT) is considered the gold-standard for the diagnostic investigation of a pleural effusion with the highest diagnostic yield. Nevertheless, there are some clinical situations where the diagnostic accuracy of a 'blind biopsy' is high, like tuberculosis.[3-5]

Non-specific-pleuritis (NSP) is an inflammatory pleuritis that cannot be attributed to a specific cause. Malignancy is reportedly found in about 5% to 25% of cases (mostly mesotheliomas).[2]

We carried out a prospective study which followed patients with NSP after medical thoracoscopy and the aim was to assess the incidence rate of pleural malignancy.

Prior to the MT, all patients had a detailed medical evaluation, radiological assessment, and pleural fluid analysis via percutaneous lung biopsy. With some occasional exceptions, only patients with lymphocytic exudative pleural effusions without a known cause were referred to the MT procedure. The pleural fluid was classified as transudative or exudative according to the Light´s criteria exudative if pleural total protein/serum total protein ratio > 0.5; pleural lactate dehydrogenase/serum lactate dehydrogenase ratio > 0.6 or pleural effusion lactate dehydrogenase level greater than two-thirds the upper limit of the laboratory's reference range of serum lactate dehydrogenase.)

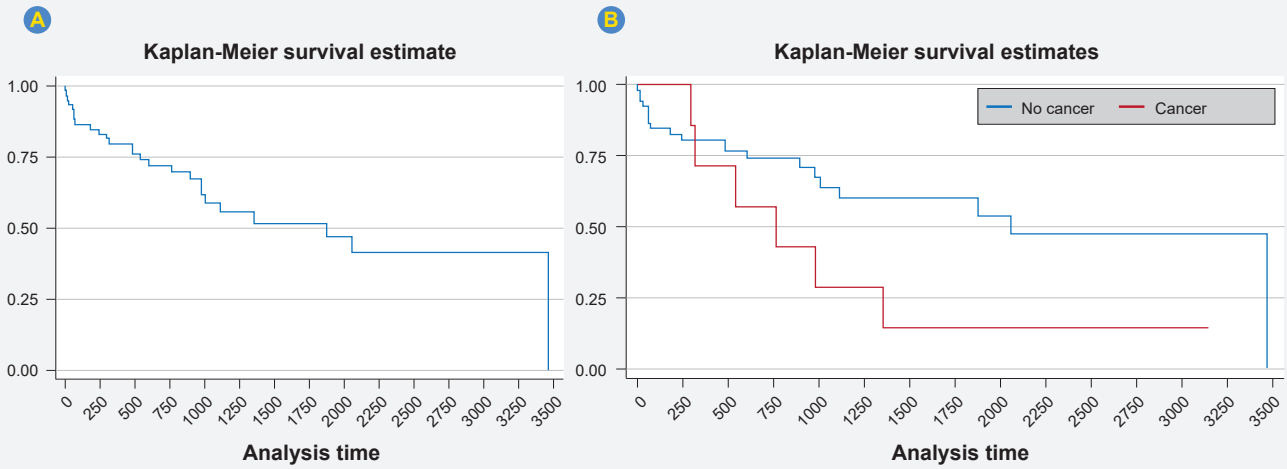
The data were properly anonymised and the study was carried out according to the principles of the declaration of Helsinki.

This study included the information extracted from electronic health records of patients that underwent medical thoracoscopy between 2011 and 2021 at a district hospital in Portugal. The patients were followed by a chest physician (appointments every three to six months after the diagnosis of NSP after MT) with regular chest X-rays or chest computed tomography to evaluate the relapse of the pleural effusion.

The end of follow-up was December 31, 2021 and patients were supervised until this deadline or until their death.

Data was analyzed using Stata® software, version 13 (StataCorp® LLC). Categorical variables are expressed as frequencies and percentages and continuous variables as means, standard deviations (SD), medians (Mdn/ Q2), quartiles (Q1, Q3), Skewness, and Kurtosis according to their distributions. Descriptive statistical methods were used for data analysis.

We plotted the Kaplan-Meier estimates (Fig. 1). The Kaplan-Meier estimator is a nonparametric estimate of the



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_t	Hazard ratio	Robust std. err.	Z	p > |z|	95% CI	
Malignancy	2.15	0.96	1.70	0.08	0.89	5.19
Age	1.03	0.01	2.02	0.04	1.00	1.06
Sex	1.18	0.45	0.44	0.66	0.55	2.52

Figure 1 – Survival analysis. (A) Kaplan-Meier survival-curve; (B) Kaplan-Meier survival-curve of patients with cancer and without cancer; (C) Hazard-ratios.

probability of survival past a given time or, of the probability of failing after that given time. We also used a Cox proportional hazards model, which is a semiparametric model, and which extended the survival analysis methods to assess the effect of several risk factors on survival time simultaneously.

During the 10-year-follow-up, a total of 238 MT were performed. The mean age was 69.0 years (SD ± 15.04) and most patients were male (54.6%).

The predominant diagnosis was pleural malignancy (47.9%), followed by NSP (24.8%).

Regarding the 59 cases of NSP, mean-age was 70.0 years (SD ± 14.41) with 64.4% males. This subset of patients had an average follow-up of 1003 days (SD ± 836.82; Q_1 = 465; Q_2 = 799; Q_3 = 1354; Skewness = 1.12; Kurtosis = 3.62).

During follow-up, 11.9% (n = 7) of patients with NSP (n = 59) received a diagnosis of malignant pleural effusion, while the cause of the pleural effusion in the other patients was non-malignant.

The average time-to-diagnosis was 773 days (SD ± 1037.06; Q_1 = 73; Q_2 = 323; Q_3 = 942; Skewness = 1.62; Kurtosis = 4.22). Diagnostic confirmation of two patients was achieved after video-assisted thoracoscopic surgery (VATS) and five patients with thoracocentesis. Histologically, most cancers were lung cancer (n = 2), gastrointestinal (n = 2), mesothelioma (n = 1), ovarian cancer (n = 1) and urothelial cancer (n = 1). At the end of the follow-up period, only one patient was still alive. Most patients were nonsmokers (71.4%).

The average time until death in patients initially with NSP that subsequently presented malignant pleural-effusion was 309 days (SD ± 197.79; Q_1 = 204; Q_2 = 267.50; Q_3 = 441; Skewness = 0.28; Kurtosis = 2.21).

Regarding survival analysis of patients with NSP, the Kaplan-Meier survival-curve in Fig. 1A showed that that the survival estimates rapidly declined until the 100th day. Then, it continued to decline at a slower pace until it reached 75% around the 500-day mark. After that, the chance of survival rapidly decreased until the 2000-day mark (below 50%).

In Fig. 1B, the estimate of survival was lower for patients with cancer and the difference between the probabilities became larger with time.

Regarding hazard-ratios in Fig. 1C, age was associated with an increased risk of death (p = 0.04). Each year of age increased the risk of death by 3% [HR = 1.03, 95% CI = (1.00; 1.07)] Moreover, malignant pleural effusion during follow-up was associated with an increased risk of death (p = 0.09). In these patients, the risk of dying increased by 115% [HR = 2.15; 95% CI = (0.56 to 2.52)].

In conclusion, most patients with NSP (n = 52; 88.1%) had benign pleural effusion (with 11.9% being diagnosed with malignancy). Age and malignant pleural effusion were associated with the risk of death during follow-up.

A watchful-waiting strategy in NSP-patients may be appropriate although the follow up regimen is not defined. We cannot recommend a defined follow-up period, but two years could be adequate since in our study most patients had the diagnosis before two years of follow-up (57.1%).

AUTHOR CONTRIBUTIONS

ES: Study design and conception, data collection, analysis and interpretation, writing of the manuscript.

PGF, GT, BR: Data interpretation, writing of the manuscript.

CS: Data interpretation and statistical analysis.

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

ES has received payment or honoraria from Boehringer for presentation of a clinical case; also received support for attending Congresso Nacional de Pneumologia.

PGF has received consulting fees from Boehringer Ingelheim Portugal, Lda; received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Boehringer Ingelheim Portugal, Lda and A. Menarini Portugal; and also received support for attending Congresso Nacional de Pneumologia

All other authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Recebido/*Received*: 09/08/2022 - **Aceite/*Accepted*:** 02/02/2023 - **Publicado *Online*/*Published Online*:** 09/03/2023 - **Publicado/*Published*:** 03/04/2023

https://doi.org/10.20344/amp.18945

Anemia da Doença Renal Crónica: Que Terapêuticas Estão Disponíveis?

Anemia of Chronic Kidney Disease: Which Therapeutics Are Available?

Palavras-chave: Anemia/tratamento farmacológico; Insuficiência Renal Crónica
Keywords: Anemia/drug therapy; Renal Insufficiency, Chronic

Na edição de outubro de 2022 da Acta Médica Portuguesa, foi publicado o artigo intitulado "Anemia da Doença Renal Crónica: O Estado da Arte".[1]

Trata-se de um útil artigo de revisão que aborda de forma clara e objetiva não só a fisiopatologia como também o diagnóstico e terapêutica da anemia da doença renal crónica (DRC). Contudo, face ao constante desenvolvimento de novas terapêuticas é necessário proceder a uma atualização. A 18 de agosto de 2021, o roxadustate, agente inibidor do *hypoxia-inducible factor* (HIF), foi aprovado pela European Medicines Agency e já está actualmente disponível em Portugal para tratamento da anemia na DRC. A inibição da hidroxilação da subunidade α da HIF induz a transcrição nuclear da eritropoietina, criando um ambiente de hipoxia e estimulando a produção de eritrócitos.[1] O roxadustate está disponível em farmácias comunitárias para prescrição por qualquer médico. Este fármaco ainda não foi aprovado pela Food and Drug Administration.[2] Adicionalmente, outros fármacos da mesma classe (ex.: daprodustat, vadadustat) estão ainda sob avaliação das entidades reguladoras relativamente à sua segurança e a potenciais benefícios adicionais.[3,4]

Apesar de o seu uso ainda não ser prática comum, é importante saber que está disponível para utilização e estarmos atentos a novos desenvolvimentos.[5]

CONTRIBUTO DOS AUTORES

Os autores colaboraram de igual modo na conceção do manuscrito.

CONFLITOS DE INTERESSE

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

FONTES DE FINANCIAMENTO

Este trabalho não recebeu qualquer tipo de suporte financeiro de nenhuma entidade no domínio público ou privado.

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Recebido/*Received*: 22/11/2022 - **Aceite/*Accepted*:** 07/02/2023 - **Publicado *Online*/*Published Online*:** 14/03/2023 - **Publicado/*Published*:** 03/04/2023

https://doi.org/10.20344/amp.19381

Spontaneous Monochorionic Quadramniotic Pregnancy: A Rare and Challenging Diagnosis

Gravidez Monocoriónica Quadriamniótica Espontânea: Um Diagnóstico Raro e Desafiante

Keywords: Amnion/diagnostic imaging; Chorion/diagnostic imaging; Pregnancy, Quadruplet; Twins, Monozygotic; Ultrasonography, Prenatal
Palavras-chave: Âmnio/diagnóstico por imagem; Córion/diagnóstico por imagem; Gémeos Monozigóticos; Gravidez de Quadrigémeos; Ultrassonografia Pré-Natal

Dear Editor,

Monochorionic quadruplet pregnancy is extremely rare, particularly if naturally conceived, with an estimated incidence of 1 in 15 million pregnancies.[1,2]

We present the case of a 40-year-old primiparous healthy pregnant woman that was referred to our department at 9 + 6 weeks for early-pregnancy assessment and a suspected spontaneous quadruplet gestation. The ultrasound investigation revealed a quadruplet pregnancy with a common placental mass and thin membranes approaching the placental surface in a T-shape, confirming a monochorionic quadramniotic pregnancy (Fig. 1). The crown-rump length was similar for all fetuses (fetus: A – 27.2 mm; B – 31.9 mm; C – 30.8 mm; D – 33.7 mm) and the placental insertion of the umbilical cord was velamentous (umbilical cord attaches to the chorioamniotic membranes surrounding the placenta instead of the central mass) in fetuses A and B and marginal in fetus C and D. After comprehensive counselling regarding the risks and complications of monochorionic quadruplets by a prenatal diagnosis multidisciplinary team, the parents decided to voluntarily interrupt the pregnancy, which is legally allowed in Portugal at the woman's request until ten weeks of gestation.

The risk of complications in quadruplet pregnancies is high and depends on the chorionicity (number of placentas in a multiple gestation). In multifetal pregnancies, monochorionicity is associated with higher morbidity and mortality rates, particularly in cases of twin-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence (TAPS) and selective intrauterine growth restriction, all complications of monochorionic pregnancies that may develop owing to placental vascular anastomoses and unequal placental sharing.[3] Although endoscopic laser ablation of these anastomoses has been considered an effective treatment in TTTS, this procedure could be particularly challenging in pregnancies with more than two fetuses that are at higher risk of complications, namely early preterm delivery and low birth weight.[1,3] Furthermore, maternal morbimortality is also higher in multiple gestations compared with singletons, in particular in monochorionic pregnancies and those with more than two fetuses, due to an increase of some life-threatening and potentially fatal complications such as hypertensive disorders, placental abruption or postpartum hemorrhage. In the literature, there are only four case reports on monochorionic quadruplets,[1–4] whose outcomes are detailed in Table 1.

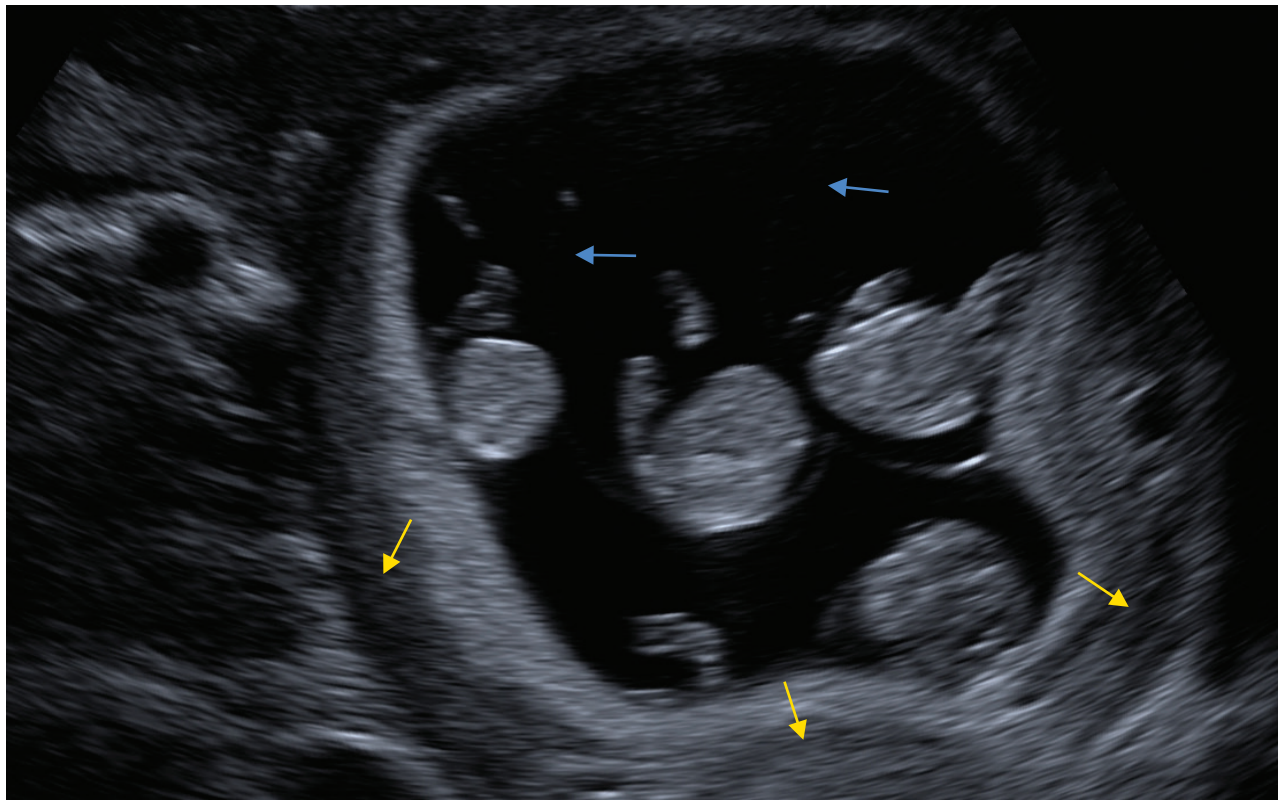

Figure 1 – Ultrasound imaging of a monochorionic quadramniotic pregnancy with a common placental mass (yellow arrows) and thin amniotic membranes (blue arrows)

Table 1 - Case reports in the literature on monochorionic quadruplets and its outcomes

Ref.	Age at diagnosis	TTTS	Laser treatment	Delivery	Postnatal outcomes
1.	-	TTTS between fetuses D (donor) and A (recipient) – Quintero stage IV. Diagnosis at 20 weeks.	Endoscopic laser ablation of 3 anastomoses at 20 weeks. Fetal demise of the recipient (A).	Spontaneous vaginal birth of 3 live neonates at 24 weeks (300 g, 650 g and 700 g).	Neonatal death of neonates D and B. Neonate C survived, presenting with complications related to prematurity and continuing to improve neurodevelopmentally.
2.	11 + 6 weeks	Polyhydramnios in the 4th fetus, suggesting the onset of TTTS at 28 weeks. Postnatal placental evaluation confirmed 3 intertwin AV anastomoses between the 3rd and 4th fetuses.	No	Elective CS of 4 live neonates (1050 g, 986 g, 1050 g and 1100 g) at 28 weeks.	Four healthy neonates were discharged from the hospital after 63 days in the NICU.
3.	12 + 6 weeks	Double TTTS (2 pairs: fetuses B and C and fetuses A and D) – Quintero stage II. Diagnosis at 19 weeks.	Endoscopic laser ablation of all visible anastomoses at 19 weeks.	Elective CS of 4 live neonates (1340 g, 1110 g, 1040 g and 1060 g) at 32 weeks.	Four healthy neonates were discharged from the hospital after 30 days in the NICU. No functional or developmental abnormalities were reported until the 2 years of corrected age.
4.	16 weeks	No	No	Elective CS due to preeclampsia at 31 weeks, with 4 live neonates (1440 g, 1361 g, 1380 g and 940 g).	All neonates were admitted to NICU with complications related to prematurity (ventilatory support and retinopathy of prematurity).

All monochorionic quadramniotic pregnancies were spontaneous.
TTTS: twin-twin transfusion syndrome; AV: arteriovenous; CS: cesarean section; NICU: neonatal intensive care unit

This article highlights a very rare and challenging clinical case, whose management was hindered by the advanced maternal age and the potential adverse outcomes related with monochorionic quadramniotic pregnancies. Moreover, early ultrasound assessment of chorionicity and amnionicity is strongly recommended to ensure a careful surveillance and avoid serious pregnancy complications, while allowing parents to promptly decide to terminate or continue the pregnancy, as demonstrated in this particular case.

AUTHOR CONTRIBUTIONS

DA: Conception and design of the manuscript and literature review.

MB: Image creation.

FM, ISS, MB: Patient management, critical review of the work, approval of the version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Recebido/*Received*: 02/11/2022 - **Aceite/Accepted:** 15/02/2023 - **Publicado/*Published*:** 03/04/2023

https://doi.org/10.20344/amp.19283

Exercise Intolerance Following COVID-19: What Is the Role of Dysfunctional Breathing?

Intolerância ao Exercício Após COVID-19: Qual o Papel da Respiração Disfuncional?

Keywords: COVID-19; Exercise Test; Exercise Tolerance; Post-Acute COVID-19 Syndrome; Respiration
Palavras-chave: COVID-19; Respiração; Síndrome Pós_COVID-19 Agudo; Teste de Esforço; Tolerância ao Exercício

Dear Editor,

Cardiopulmonary exercise testing (CPET) has been used to explore persisting symptoms post-COVID-19. Different pathophysiological patterns have been reported[1-3]: oxygen transport/delivery problems, dysfunctional breathing (erratic or inappropriate ventilation during exercise),[4] ventilatory limitation, gas exchange abnormality, chronotropic insufficiency (reduced ability to increase heart rate during exercise) and dysautonomia. To explain these findings, a number of mechanistic explanations have been proposed,[1,2] namely deconditioning, endothelial injury, enhanced chemoreflex sensitivity, respiratory centre dysfunction and mitochondrial dysregulation.

We analysed our case series from Glasgow (Gartnavel General Hospital and Glasgow Royal Infirmary), Scotland, of 46 adult incremental symptom-limited CPETs (the standard protocol in the unit) performed because of breathlessness post-COVID-19 that was not fully explained by pulmonary function tests, chest imaging or echocardiogram. The data in this study are anonymised and retrospectively collected from tests performed as part of the routine clinical care of patients. Consequently, ethics committee approval was not sought for this analysis.

The median (IQR) duration from COVID diagnosis to CPET was 14 (10) months. The mean (SD) age was 51.9 (12.8) years, 63% were women, mean (SD) BMI was 31.1 (6.2) kg/m^2 and 30.4% (n = 14) were smokers/ex-smokers. As for comorbidities, 13 patients had asthma, one had COPD, six had systemic hypertension, four had mild anaemia, three had type 2 diabetes, one had ischemic heart disease and seven had been prescribed heart rate-control medication. Twelve patients were hospitalized with one being admitted to the high-dependence or intensive care unit. Six patients had pulmonary embolism and three had a diagnosis of chronic thromboembolic pulmonary disease. The mean (SD) forced expiratory volume in 1 second (FEV_1) was 101% (17) and transfer factor for carbon monoxide (TLCO) was 82% (19), of the predicted value. Lung imaging was abnormal in five [minor non-specific reticular changes or ground glass (n = 3); expiratory air trapping (n = 1); and hemidiaphragm elevation (n = 1)] and the echocardiogram was abnormal in three out of 25 patients tested (mildly dilated right ventricle, mild left ventricular systolic dysfunction and bicuspid aortic valve).

Only 27 subjects (59%) performed a maximal test. The remaining patients stopped before clear physiological limitation. The mean (SD) peak oxygen uptake (VO_2) was 20.7 (6.7) mL/kg/min and 88.2% (20.1) of predicted, with 14 patients (30.4%) having a peak VO_2 below the lower limit of normal (LLN) and 80% showing functional limitation with VO_2 < 25 mL/kg/min. The commonest abnormalities seen were dysfunctional breathing/acute hyperventilation (54%), gas exchange abnormalities (52%; with dysfunctional breathing in 72% of these cases) and oxygen transport/delivery problems typically of mild degree and consistent with deconditioning (35%). Evidence of dysfunctional breathing was seen in 64% of those with a peak VO_2 < LLN. Dysfunctional breathing was identified subjectively from an abnormality in the biomechanical pattern of breathing in response of exercise during the test. The commonest abnormality was an abrupt rise in the respiratory exchange ratio (RER, the ratio between the metabolic production of carbon dioxide and the uptake of oxygen) (> 1.0) and ventilatory equivalents in the early part of the test which then fell again as the test proceeded. This was usually combined with an irregular pattern of tidal volume and respiratory rate when plotted against ventilation. There were no cases of ventilatory limitation and there was one case of postural tachycardia syndrome (which has also been reported[5] with other viruses).

Other than dysfunctional breathing, we did not find a COVID-19 specific CPET pattern of exercise intolerance that could not be explained by other conditions. In our view and as previously reported,[2-4] breathing dysregulation may represent a possible pathophysiological explanation for much of the physical limitation post-COVID-19.

ACKNOWLEDGMENTS

We acknowledge the respiratory physiology staff at

Gartnavel General Hospital and Glasgow Royal Infirmary who supervised the performance of the cardiopulmonary exercise tests.

AUTHOR CONTRIBUTIONS

CF: Conception of the original idea, data collection, literature search, statistical analysis, writing of the manuscript.

MJ: Conception of the original idea, data collection, critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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COMPETING INTERESTS

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FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Recebido/*Received*: 22/12/2022 - **Aceite/*Accepted*:** 16/02/2023 - **Publicado/*Published*:** 03/04/2023

https://doi.org/10.20344/amp.19526

Errata ao artigo "Linfoma Difuso de Grandes Células B com Invasão Cutânea Axilar num Doente com Infeção VIH", Publicado em Acta Med Port 2023 Mar;36(3):210-211.

Correction to the article "Diffuse Large B-Cell Lymphoma with Axillary Cutaneous Invasion in a HIV Positive Patient", Published on Acta Med Port 2023 Mar;36(3):210-211.

Na página 210, linhas 9 e 10 onde se lê (**a vermelho**):
"(...) confirming stage IV diffuse large B-cell lymphoma NOS, **type CCG** (...)"

Deverá ler-se (**a negrito**):
"(...) confirming stage IV diffuse large B-cell lymphoma NOS, **type GCB** (...)"

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https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16873

On page 210, lines 9 and 10, where it reads (**in red**):
"(...) confirming stage IV diffuse large B-cell lymphoma NOS, **type CCG** (...)"

It should read (**in bold**):
"(...) confirming stage IV diffuse large B-cell lymphoma NOS, **type GCB** (...)"

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https://doi.org/10.20344/amp.19888

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