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Conselho Científico

Qual é o Potencial Pandémico dos Vírus Emergentes?

What is the Pandemic Potential of Emerging Viruses?

Paulo CRUZ PAIXÃO✉[1]
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Palavras-chave: Doenças Transmissíveis Emergentes; Pandemia
Keywords: Communicable Diseases, Emerging; Pandemics

As pandemias fazem parte da nossa História, sendo o seu impacto muitas vezes superior ao de qualquer outro evento nocivo para a Humanidade, como as guerras ou as catástrofes naturais. A pandemia de gripe em 1918-19, com pelo menos 50 milhões de mortes num espaço de tempo relativamente curto, a peste e a varíola, com números difíceis de estimar, mas seguramente catastróficos para a nossa espécie, são dos exemplos mais citados quando queremos fazer a abordagem histórica do tema.[1]

Depois da pandemia causada pelo vírus da gripe H1N1 em 2009-2010, que causou grande alarme inicial, mas acabou por ter um impacto relativamente baixo,[2] a ideia que prevaleceu nas populações foi de que esta questão das pandemias era bastante empolada pelos especialistas e pelas autoridades de saúde internacionais e nacionais. Por outro lado, cresceu a convicção de que os desafios futuros passam pelas doenças crónicas e que o papel das doenças infeciosas será cada vez mais residual, o que parece justificar o ceticismo com que grande parte da população encarou o início da presente pandemia. No entanto, a COVID-19 veio expor uma cruel realidade, a de que nossa ciência ainda é limitada para lidar convenientemente com algumas das maiores ameaças à Humanidade, sejam elas vulcões, tufões ou pandemias virais. Contudo, a ciência também tem as suas vitórias, e certamente que a maioria de nós concordará que a vacinação para a COVID-19 foi/é disso um grande exemplo.

Mas será que o que aprendemos até agora com a COVID-19 poderá ser útil numa pandemia futura? Vamos de novo recorrer à história: o que têm de comum as grandes pandemias do passado e a do presente – as da peste, varíola, gripe e, claro, da COVID-19? A resposta é inequívoca: a transmissão respiratória (por gotículas e aerossóis). E se é verdade que a peste bubónica é transmitida por pulgas, a peste pneumónica terá provavelmente sido a responsável pela rápida disseminação da peste em muitas das zonas atingidas.[3] Não incluiremos aqui a infeção VIH/SIDA, causadora de uma pandemia importantíssima mas com uma evolução lenta, fora do contexto destas pandemias de atingimento rápido da população mundial.[4]

A transmissão respiratória é, como a presente pandemia o tem demonstrado, muito difícil de evitar, implicando medidas tão rigorosas como os confinamentos a que assistimos recentemente.[5] Se olharmos para as outras formas de transmissão, rapidamente percebemos que, por muito importantes que possam ser a nível local ou mesmo regional, dificilmente poderão originar uma situação pandémica global.

Vejamos a transmissão fecal-oral, por exemplo no caso da cólera: ainda hoje origina surtos importantíssimos em certas zonas do globo mas o saneamento básico consegue, nos países onde se encontra disponível, controlar os avanços causados pelo *Vibrio cholerae*.[6]

Por outro lado, a transmissão sexual, pode também efetivamente originar pandemias, mas como já referimos anteriormente a propósito da infeção VIH/SIDA, não tem capacidade de o fazer de uma forma rápida.[7]

Já a transmissão pelo contato direto com doentes infetados, como acontece com a infeção pelo Ébola, pode ser difícil de controlar, sobretudo em determinados contextos sociais e económicos. Contudo, a implementação de medidas rigorosas acabará por ser bem sucedida antes que adquira caráter pandémico, tal como se tem verificado nos diferentes surtos epidémicos causados por este vírus.[8]

Quanto a um outro agente emergente, o vírus Nipah, que esporadicamente é noticiado como causador de surtos em certas regiões do mundo, o seu potencial pandémico pode ser limitado pela transmissão predominante através de contato com animais infetados, sobretudo porcos e morcegos, não sendo a transmissão inter-humana muito eficaz. No entanto, deverá ser uma situação para acompanhar no futuro.[9]

Mas afinal onde estarão as origens das próximas pandemias? Pelo que já foi dito, e com base na experiência do passado, os grandes candidatos ao título serão, claro, os vírus respiratórios. Na nossa opinião, estes últimos serão seguidos, muito provavelmente, pelos arbovírus (*arthropod-borne virus*), vírus transmitidos por mosquitos. A lista deste tipo de ameaças é longa, umas mais mediáticas do que outras, e inclui os vírus do dengue, zika, chikungunya, o vírus da encefalite japonesa e o vírus do Nilo Ocidental. As alterações climáticas estão a facilitar a disseminação

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de espécies de mosquitos transmissoras destes vírus, pelo que bastará vermos a evolução na Europa do *Aedes albopictus* (mosquito que pode transmitir, entre outras, os vírus do dengue ou chikungunya) nos últimos anos, ou o que aconteceu com o vírus do Nilo Ocidental nos Estados Unidos da América, para percebermos que esta ameaça é real e que dentro de um prazo relativamente curto poderemos ter epidemias por estes vírus em zonas onde anteriormente nunca suspeitaríamos que isso pudesse acontecer.[10]

Terminamos com a questão inicial: será a transmissão respiratória inter-humana de vírus a forma catalisadora de uma futura pandemia? De que vírus respiratórios estamos a falar? Os vírus da gripe (intencionalmente no plural) são sempre fortes candidatos, podendo a ameaça surgir sob várias formas. Uma delas, aquela que mais receio tem suscitado, seria uma pandemia de um vírus causador de gripe aviária capaz de atravessar a barreira de espécies. Esta questão pode ser analisada sob duas perspetivas diferentes: por um lado, a má notícia é que estes vírus já existem: falamos do famoso H5N1, mas existem outros, com menor notoriedade e já capazes de infetar diretamente o homem, em geral com taxas de mortalidade muito mais elevadas que a COVID-19 (a taxa de mortalidade para o H5N1 está acima dos 50%).[11] Por outro lado, a boa notícia é que, até agora, a transmissão inter-humana não se efetuou de uma forma eficaz. Por fim, não devemos também descartar outros vírus da gripe, como por exemplo algumas variantes originárias dos suínos, que poderão mais facilmente fazer o trajeto inter-espécies e originar uma epidemia de larga escala.[12]

E os coronavírus? Relembremos que mesmo antes da COVID-19 os coronavírus já tinham suscitado algum alarme, quer com o SARS-CoV-1, que como sabemos foi rapidamente dominado, quer com o MERS-CoV, associado ao Médio Oriente e aos camelos dromedários - e se esta curiosa associação com os camelos até nos pode fazer sorrir, a mortalidade descrita de 30% e a possibilidade de transmissão inter-humana nada têm de divertido. Felizmente, a monitorização desta situação tem revelado que embora a transmissão inter-humana exista, não se tem revelado muito eficaz.[13] Contudo, o próprio SARS-CoV-2, através da sua capacidade de adaptação ao ser humano e de alteração genética, poderá constituir uma ameaça futura, sob forma de alguma variante mais transmissível e/ou mais resistente à resposta imunitária pós-vacinação, não esquecendo que no seu reservatório natural (morcegos), existem ainda muitos outros 'primos' com potencial para nos afectar.[14]

Em suma, os vírus respiratórios, nomeadamente os da gripe e os coronavírus, estão, na nossa opinião, claramente na *pole position* para uma futura pandemia. Os arbovírus e, eventualmente, outros vírus emergentes, como o Nipah, deverão igualmente ser monitorizados nos anos vindouros apesar da menor probabilidade de causarem pandemias. Deverão preparar-se e divulgar-se planos de preparação pandémica que considerem estas diferentes possibilidades, com a brevidade possível, de forma a que se reaja de forma mais proactiva e imediata numa próxima situação semelhante.

CONFLITOS DE INTERESSE

O autor declara não ter conflitos de interesse relacionados com o presente trabalho.

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The Primary Care Research Landscape and its Relationship with Clinical Practice: A Scientometric Analysis

O Panorama da Investigação em Cuidados de Saúde Primários e a sua Relação com a Prática Clínica: Uma Análise Cientométrica

ARTIGO ORIGINAL

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ABSTRACT

Introduction: It is unclear if research published in primary care journals aligns with the broad spectrum of problems managed in primary care practice. The aim of this study was to analyse publication trends concerning the burden of medical conditions reported in primary care journals, and to compare these findings with the burden of problems seen in clinical practice, in order to identify research gaps.

Material and Methods: Scientometric tools were used to analyse 9956 articles of primary care journals indexed in MEDLINE. Through keyword analysis, a relations map was built. Literature review and a primary care database were used to identify active problems and reasons for visiting a family physician. Rankings and frequencies of research output and conditions were compared.

Results: Keyword analysis identified five clusters of publication trends: cardiovascular conditions and conditions related with unhealthy lifestyles; mental disorders; infections; oncology and health management. By comparing publications with clinical problems, the fields of orthopaedics, endocrinology/metabolism, gastroenterology/hepatology, dermatology, ophthalmology, and the respiratory system show the biggest gaps. Through the relations map, more concrete potential research topics were identified such as palliative care, chronic pain, insomnia, antibiotic prescribing, burnout, osteoporosis, osteoarthritis, and COVID-19.

Conclusion: The distribution of publications in primary care journals is distinct from the burden of problems faced in clinical practice and reasons for visiting a family physician. The use of scientometric tools to identify publication trends and their comparison with common problems could be a strategy to identify areas with research gaps in primary care.

Keywords: Bibliometrics; Database Management Systems; Primary Health Care; Publishing

RESUMO

Introdução: Desconhece-se se a investigação publicada na área dos cuidados de saúde primários está alinhada com os problemas geridos na prática clínica. Pretendemos analisar as tendências de publicação das revistas científicas de cuidados de saúde primários no que diz respeito a problemas médicos e comparar os resultados com a prevalência dos problemas na prática, para encontrar lacunas investigacionais.

Material e Métodos: Utilizando ferramentas cienciométricas, analisámos 9956 artigos de revistas de cuidados de saúde primários indexadas à MEDLINE. Através da análise de palavras-chave, construímos um mapa de relações. Identificámos os problemas prevalentes através da revisão da literatura e de uma base de dados dos Cuidados de Saúde Primários. Comparámos as áreas de investigação com problemas ativos e motivos de consulta quanto à frequência e *ranking*.

Resultados: Identificámos cinco grupos de tendências de publicação: doenças cardiovasculares/condições relacionadas com estilos de vida não saudáveis; patologia mental; infeções; oncologia; e gestão em saúde. Comparando publicações com problemas clínicos, as áreas de ortopedia, endocrinologia/metabolismo, gastrenterologia/hepatologia, dermatologia, oftalmologia e sistema respiratório apresentam as maiores lacunas. Através do mapa de relações, encontrámos potenciais áreas de investigação mais concretas, como cuidados paliativos, dor crónica, insónia, *burnout*, osteoporose, artrose, COVID-19.

Conclusão: A distribuição das publicações em revistas de Medicina Geral e Familiar diverge da proporção dos problemas e motivos de consulta. A identificação de tendências de publicação com ferramentas cienciométricas e a sua comparação com problemas comuns pode ser uma estratégia para reconhecer lacunas de investigação.

Palavras-chave: Bibliometria; Cuidados de Saúde Primários; Publicação; Redes de Comunicação de Computadores

INTRODUCTION

Primary health care covers a broad spectrum of conditions which reflect the prevalence of diseases in the general population.[1] The research activity in this field has increased noticeably over recent years, and the internet has made information widely available. With the increasing amount of evidence, clinicians must make an increasing effort to remain up to date.[2] Primary care journals can respond to physicians' needs by publishing evidence that covers recent advances on a broad range of common clinical topics. Some authors stress the importance of identifying research needs in clinical practice in order to improve the alignment between academia and clinical practice.[3-6] Therefore, research efforts can impact positively on the quality of care, by addressing knowledge gaps.

The need for evidence in primary care has been addressed in some studies to find gaps in research. Burgers *et al*[7] identified research questions for each ICPC-2 chapter through knowledge gaps in guidelines and input from stakeholders in the Netherlands. Muscat *et al*[8] analysed clinical questions submitted by GPs in Australia. A recent study analysed the grey literature concerning research studies in Portugal, to identify topics for a research agenda.[9] Finley *et*

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al looked at the most prevalent conditions in primary care, allowing the identification of priority areas in need of guidelines and medical training.[3] Furthermore, big data analysis of electronic health records in primary care databases has been proposed as a useful tool in healthcare management and research.[10,11] The update of these databases is continuous, which makes them very suitable for discovering and monitoring healthcare trends.[11]

Despite the information available on common conditions in primary care, either through clinical studies or primary care databases, there might be a gap between frequent problems managed in primary care and published primary care research. A single study[12] addressed this question in the Australian context, finding important discrepancies between literature and practice, but it is unclear if these findings are globally identical.

Scientometrics have been employed to perform empirical and quantitative analysis of a high volume of publications, to achieve an overview of the current status and trends in several research fields, which has proved useful in identifying research gaps.[13] The analysis of research landscapes might therefore be used to complement the search for researchgaps in primary care.

The first aim of this study was to identify and analyse publication and citation trends concerning medical conditions, in primary care journals, published between 2010 and 2020. Secondly, we wanted to compare publication trends with the most common medical problems in primary health care, in Portugal and globally, to detect areas with publication and/or research gaps, to address the needs of primary care physicians.

MATERIAL AND METHODS

Data source and search strategy

We chose the Web of Science (WoS) search engine to retrieve recent literature related to primary care practice, due to its wide coverage, as it includes the MEDLINE database, and for offering powerful analysis tools, compared to other search engines.[14,15]

We accessed WoS on the 15th October 2020 and, since we were interested in global primary care research activity, the following search approach was employed: in an 'advanced search' topic (a field which includes title, abstract and author keyword we selected ('primary care' OR 'family practice' OR 'family medicine' OR 'general practice'), document type (article OR review), time span (2010 - 2020), source titles (primary care related journals), MeSH qualifiers related with clinical issues thus excluding qualifiers related with organizational and administrative issues (e.g. 'organization administration', 'history', 'economics', 'legislation jurisprudence'), database (MEDLINE), language (all). WoS citation files for the selected period were downloaded as 'full record and cited references' and saved in a 'tab-delimited' file format. The identified articles, with the corresponding titles, keywords, author information, abstracts, and references, were stored in a TXT format and the content was classified into major disease categories. The references not related with medical conditions were excluded.

To describe the Portuguese reality and explore the potential of electronic health records in research, after approval by the Portuguese Data Protection Authority, we assessed the Portuguese Primary Health Care Identity Card (BI-CSP),[16] a health and clinical governance primary care database. We obtained and ranked data concerning active problems which was extracted from the problems list of users of primary health care centres of the Portuguese National Health Service. We categorized the data according to the International Classification of Primary Care 2nd Edition (ICPC-2).[17] We excluded the ICPC-2 code 'A98' for not being consistently considered a problem in the patient´s problems list.

Furthermore, to obtain data on reasons for medical appointments and acute conditions that generally are not listed in problem lists, and to obtain a globally more relevant view, we searched WoS, PubMed, and Google Scholar for publications describing the most common problems in primary care, so we could make broader comparisons.

In terms of ethical issues, the study was not submitted to an Ethics Committee, since no intervention was made (which would require previous approval), patient data is anonymised, the Portuguese Data Protection Authority approved the access to the data, and secondary use of health data for research purposes is allowed by Portuguese law if the information is anonymized. As far as informed consent for data collection is concerned, it is given on an opt-out basis by citizens.

Data analysis and presentation

With the information obtained from WoS concerning the included articles, we used the open-source software VOSviewer[18] to visualize the recent primary care research landscape. VOSviewer employs the visualisation of similarities (VOS) mapping technique, which can be used to create maps either based on a text corpus or based on networks such as citation networks. The VOSviewer network visualization option displays concepts based on their importance. The larger the label and the circle, the more important the concept is. The colour of the circle indicates the cluster to which the term belongs to. For each term that met the threshold, a relevance score was calculated, and based on this score, the most relevant terms were selected. In the present study, we analysed the co-occurrence of words using networking maps, based on the title and abstract fields.

Additionally, using the information extracted from WoS on the Publons publications tracking platform,[19] we created a ranking of research areas with a greater number of published papers covering primary care conditions. Concurrently, with the information extracted from the BI-CSP, we created a ranking of active clinical problems in Portugal. We also listed the ranking of general categories for reasons for consulting a family physician co - Reasons for Visits (RFV) from Finley *et al*,[3] a systematic review of 18 studies that included patient and physician reported reasons for visits as well as problems managed by physicians.

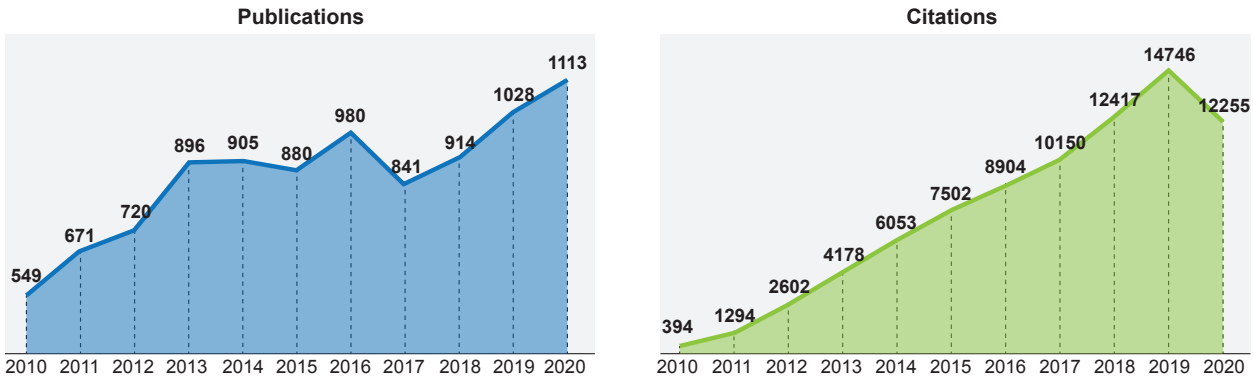

Figure 1 – Evolution of publications and citations in primary care journals

Then, the ranking of search findings was compared with both rankings, to assess whether the research effort in primary care is aligned with the occurrence of primary care issues.

RESULTS

Publications and citations

Our search of the primary care literature retrieved a total of 13 388 original articles from the MEDLINE database, of which 9956 fulfilled the inclusion criteria. Fig. 1 shows the development of the yearly number of publications and citations among primary care journals. Despite some fluctuations, it is possible to appreciate a positive trend in the research carried out in this field over the past decade.

English was the key language of the primary care literature with 9332 documents (93.73%), followed by Spanish (6.22%) and French (1.13%). The United Kingdom dominated the primary care literature with 4436 articles followed by the United States (2822), Australia (882), Canada (777), and Spain (633). According to Fig. 2, the most cited publications are from Europe (43.82%), followed by North America (35.89%), Asia (9.95%), Australia (8.42%), and South America (1.91%).

Research areas, authors, institutions, and journals

Excluding general scientific areas (e.g., health care sciences, Pharmacology, Health Economics), the most relevant clinical areas were Psychology (39.42%), General Internal Medicine (26.03%), Geriatrics (24.04%), Paediatrics (13.71%), and the cardiovascular system (9.71%). Paul Little from the University of Southampton (UK) was the most productive author in this field: with 59 papers, he contributed to 0.59% of total scientific publications of primary care literature. The Nuffield Department of Primary Care Health Sciences from the University of Oxford (UK) was the leading institution, with 101 publications (1.01%). The most productive authors and institutions were all found to be from developed countries. In Table 1 we identify the top 20 journals in terms of publications and Impact Factor. The British Journal of General Practice dominated the primary care literature and covered 13.30% of all documents, followed by BMC Family Practice (12.06%), Family Practice (7.99%), Canadian Family Physician (7.08%), and Family Medicine (6.34%).

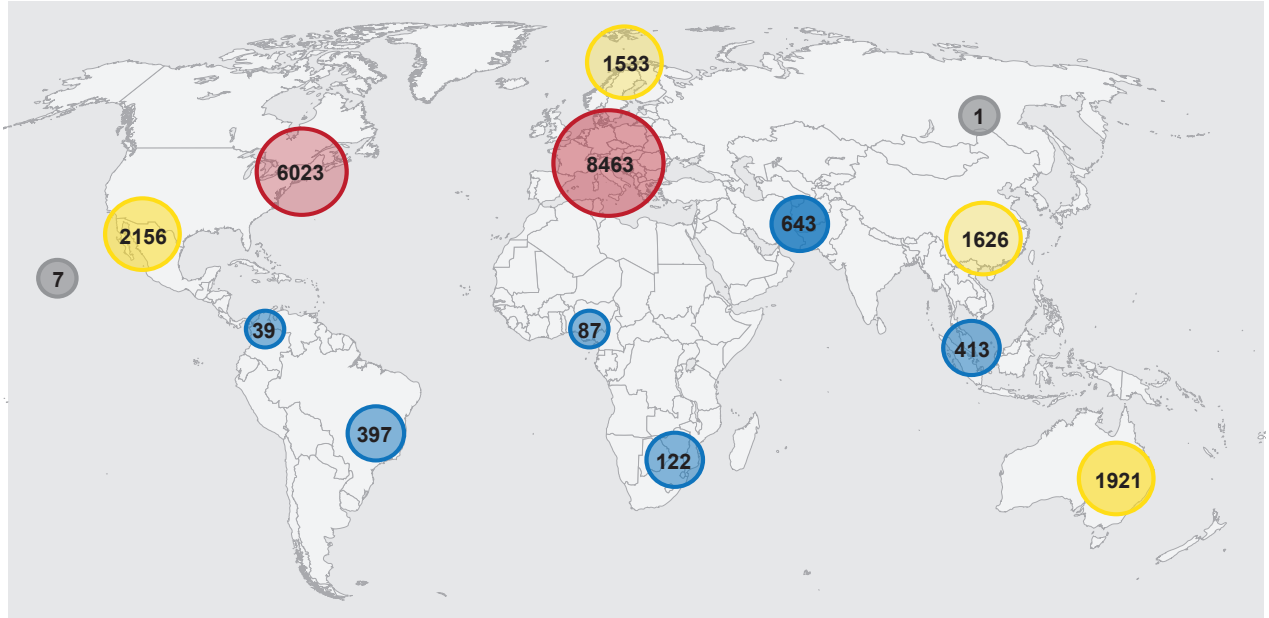

Figure 2 – Citation map regarding primary care publications

Table 1 – Top 20 journals in terms of publications for primary care and their impact factors

Source	Publications	% (n = 9956)	Impact factor
British Journal of General Practice	1324	13.299	2.634
BMC Family Practice	1201	12.063	2.550
Family Practice	795	7.985	2.024
Canadian Family Physician	705	7.081	1.538
Family Medicine	631	6.338	1.162
Australian Family Physician	576	5.785	0.690
Journal of the American Board of Family Medicine	506	5.082	2.429
Annals of Family Medicine	441	4.429	4.019
Atención Primaria	396	3.978	1.177
Education for Primary Care	395	3.967	0.726
Scandinavian Journal of Primary Health Care	354	3.556	2.329
Journal of Family Medicine and Primary Care	309	3.104	1.021
Primary Health Care Research & Development	290	2.913	1.072
Journal of Primary Care & Community Health	281	2.822	2.209
Semergen	245	2.461	0.376
American Family Physician	235	2.360	1.431
European Journal of General Practice	231	2.320	2.439
Journal of Family Practice	170	1.708	0.373
Australian Journal of General Practice	162	1.627	0.871
Journal of Primary Health Care	149	1.497	0.881

Scientometric network analysis

The WoS search result containing summaries and tittles was uploaded to the VOSviewer software, applying the 'binary counting' technique. For the identification of the main issues of published research, a word co-occurrence analysis was performed. First, 756 treasure words were excluded (common keywords without scientific relevance). Then, using a filter considering 65 as the minimal number of term occurrences, we created a keyword network infographic according to keyword frequency. In this way, we could identify not only the most frequently used terms in literature, but also identify their relations, forming clusters of topics. Fig. 3 displays the areas in which we found more density concerning this field of study. It also identifies the main clusters, as well as the areas with more existing research. The five most frequently used keywords were 'depression', 'communication', 'pain', 'diabetes' and 'infection'.

Table 2 displays in detail the clusters that are more cited within every group. Cluster one represents common health problems of modern society, mainly cardiovascular conditions, related unhealthy lifestyles, and associated diseases. Cluster two embodies mental disorders, showing a clear connection with socioeconomic problems. Cluster three illustrates the duality between infection prevention and control. Cluster four explores oncology topics, with a focus on early diagnosis. Cluster 5 focuses on health management and related issues like doctor-patient relationship, leadership, patient safety, and satisfaction to guarantee an improvement in the quality of services provided by healthcare institutions to the community. According to Table 2 and Fig. 3, we identified some decentralized topics, corresponding to areas without a significant amount of studies, such as 'palliative care, chronic pain, chronic illness, sleep (and insomnia), lifestyle change, children, prostate cancer, heart disease, antibiotic prescribing, burnout, quality improvement, breast cancer, vaccine, mental disorders, blood pressure control, osteoporosis, chronic disease management, osteoarthritis, doctor-patient relationship, primary care management and COVID', which represent potential areas for future research.

Comparing research with practice

Comparing the main scientific areas of the papers extracted from MEDLINE, with the coding of active problems in Portugal (June 2020), it is possible to notice that there are some discrepancies between the publication efforts of Primary Care journals and the most frequent active problems that health professionals face in the Portuguese context. A discrepancy can also be noted when in the internationally acknowledged RFV. In Table 3, we can visualize some gaps between the publication landscape and clinical conditions.

Considering the MEDLINE classification, the research areas with most publications are General Internal Medicine (27.10%), Cardiology (10.10%), Sociology (8.90%), Psychiatry (8.20%), and Neurosciences/neurology (7.80%). On the other hand, areas such as Ophthalmology (0.70%), Otorhinolaryngology (1.70%), Haematology (2.40%), Dermatology (2.70%), and Reproductive Biology (2.50%) are the areas with the least amount of publications.

By analysing the active problems in the Portuguese

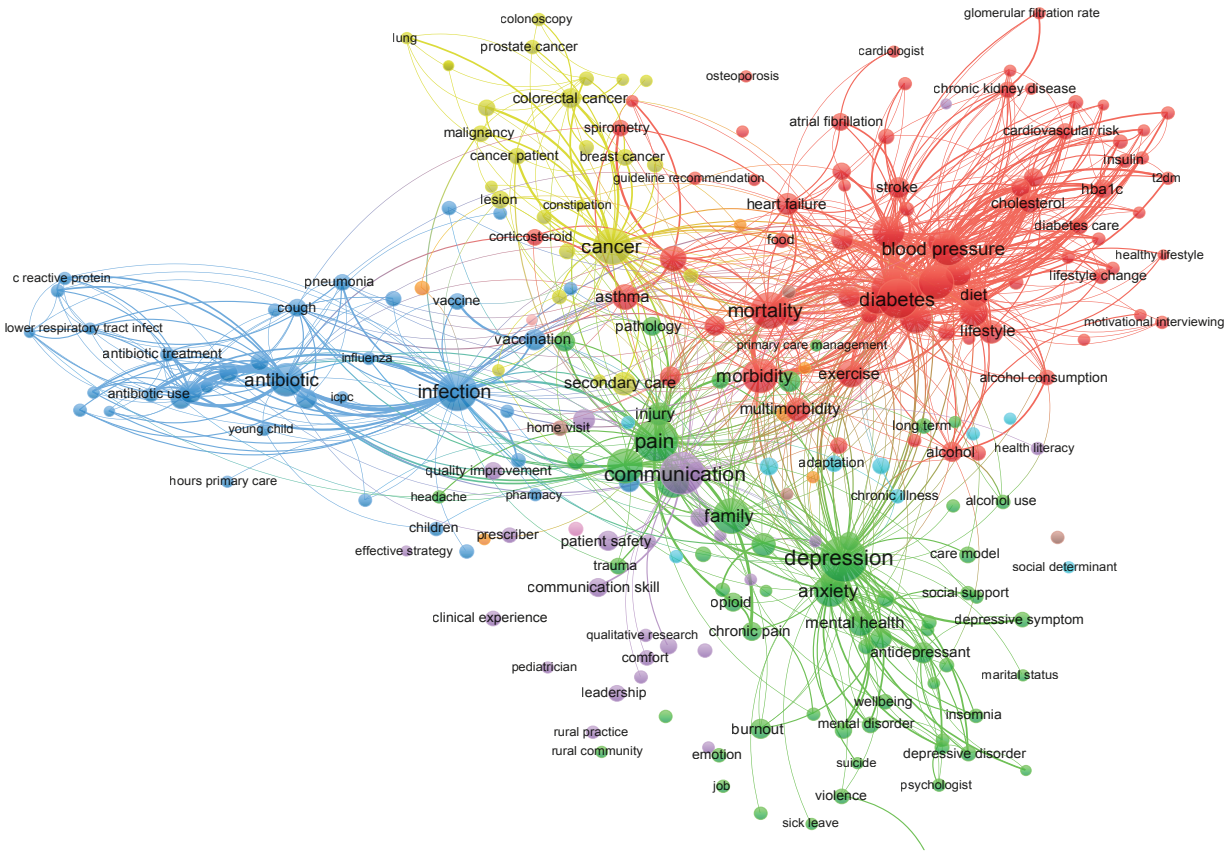

Figure 3 – Map of relations concerning primary care publications

context, we find a different ranking order. The most prevalent health issues (classified according to MEDLINE search areas) are related with orthopaedics (15.60%), endocrinology metabolism (12.90%), Cardiology (9.70%), respiratory system (9.40%), and Gastroenterology/hepatology (9.30%). On the other hand, clinical issues related with scientific areas such as Sociology (1.00%), Haematology (1.10%), male reproductive biology (1.50%), Otorhinolaryngology (2.10%), and Neurosciences/neurology (2.40%) have a lower frequency.

Therefore, by comparing the research efforts and the active problems in Portugal, which mainly correspond to chronic conditions, it is possible to identify the research areas where scientific publication in Primary Care journals is taking place with a higher proportion considering the needs that arise from clinical practice, namely in areas like Sociology (Δ = +8.00%) and Neurosciences/neurology. In contrast, a lower publication rate concerning areas with clinically higher demands is seen in areas such as Orthopaedics (Δ = -12.40%), Endocrinology metabolism (Δ = -6.40%), Gastroenterology hepatology (Δ = -5.50%), Dermatology (Δ=-3.50%), and Ophthalmology (Δ = -2.10%).

Finally, Table 3 also presents an RFV ranking obtained from the work developed by Finley *et al*.[3] Although the overlap between the classification from Finley *et al* and the MEDLINE search areas was not always possible, we also identify, qualitatively, some areas with lower publication output compared to their burden in terms of reasons for visit, with the respiratory, dermatology, and orthopaedic areas being the most relevant.

Furthermore, we observe an expected difference between the rankings of the active problems and the RFV, showing a higher prevalence of the areas of the respiratory system and nervous and sense organs in the RFV column, probably related to acute infections and Ear-Nose and Throat problems. In contrast, musculoskeletal problems are proportionally less common.

DISCUSSION

The present study identifies the leading countries, journals, and subjects, aside from relationships between prevalent topics among publications in Primary Care journals. There is growing scientific production in the field of primary care, showing a global interest in this field. The United Kingdom and the USA are the main contributors to scientific output, with Europe and North America being the regions with the highest number of citations. The fact that developed countries dominated the research landscape gives strength to our comparison with the Portuguese reality.

The keyword analysis identified 'depression', 'communication', 'pain', 'diabetes' and 'infection' to be the most frequent terms and found five clusters - 1st cardiovascular conditions and other conditions related with unhealthy lifestyles; 2nd mental disorders; 3rd infections; 4th oncology and

Table 2 – Most relevant clusters on primary care research

Cluster 1	Cluster 2	Cluster 3	Cluster 4
77 items	61 items	38 items	25 items
alcohol	addiction	antibiotic prescribing	cancer diagnosis
asthma	alcohol use	c reactive protein	cancer patient
cardiologist	antidepressant	acute cough	lung
cardiovascular disease	anxiety	antibiotic prescribing	colorectal cancer
cardiovascular risk	benzodiazepine	antibiotic resistance	colorectal cancer screening
cholesterol	burnout	antibiotic use	breast
chronic disease management	chronic pain	lower respiratory tract infection	prostate cancer
chronic kidney disease	comprehensive care	sore throat	colonoscopy
chronic obstructive pulmonary disease	dementia	respiratory tract infection	lung cancer
	depression	antibiotic	life care
coronary heart disease	emotion	acute otitis medium	malignancy
corticosteroid	employment	antibiotic treatment	breast cancer
demographic characteristics	family	upper respiratory tract infection	palliative care
diabetes	fatigue	urinary tract infection	cancer
diet	headache	cough	abdominal pain
exercise	illness	fever	constipation
food	injury	young child	specialist care
glomerular filtration rate	insomnia	pneumonia	clinical practice research
glucose	intimate partner violence	influenza	care excellence
healthy lifestyle	job	infection	early detection
heart disease	long term	aetiology	blood test
hospitalization	marital status	vaccine	secondary care
hypertension	mental disorder	infectious disease	early diagnosis
hypertensive patient	opioid	patient age	discrimination
insulin	osteoarthritis	vaccination	
LDL cholesterol	pain	quality indicator	Cluster 5
lifestyle	pathology	children	25 items
medication adherence	pharmacological treatment	chest pain	
morbidity	physical health	pharmacy	clinical experience
mortality	pregnancy	COVID	communication skill
motivational interviewing	psychiatrist	HIV	leadership
myocardial infarction	psychologist	urgency	doctor patient relationship
nutrition	rural community	childhood	effective strategy
obesity	sleep	hospitalisation	health information
osteoporosis	social support	primary care services	quality improvement
overweight	stigma		patient perception
patient record	stress		patient safety
physical activity	substance use		multidisciplinary team
preventive services	suicide		public health
smoker	trauma		health literacy
stroke	violence		patient satisfaction
systolic blood pressure			communication
tobacco			patients view

5th health management.

Furthermore, we identified and ranked the most common active problems in Portuguese primary care practice and compared their relative frequency with the relative frequency and ranking of the search topics. In order to cover the information about potential acute problems, we ranked the reasons for visit. Since no relative frequencies regarding this topic were available, no gap analysis was performed. Some difficulties arose concerning the correspondences between groups. The categories 'Cancer', 'Infectious/parasitic', 'Injury/poisoning', 'supplementary classification' had no direct match. We also considered the correspondence between the search topic 'General Medicine' and 'General and non-specific' imperfect and not representative of reality.

Nonetheless, whilst the use of different classification systems among the three data sources presented challenges in combining and comparing data, the findings seem consistent, in with some areas being under-represented in Primary Care journals and are probably not meeting the needs of primary care physicians. Concerning both, the active problems and the internationally acknowledged reasons for visit, the clinical areas of the Musculoskeletal System; Endocrine, Metabolic and Nutrition; Digestive and Respiratory Systems, and Skin were identified as having the largest discrepancies. Some of these areas might be covered by other journals and international guidelines, which is the case, for example, with diabetes, asthma, and chronic obstructive pulmonary disease.

Similar research gaps were described by other authors. Cooke *et al*[12] found that the research output of the journal

Table 3 – Comparison between the publication effort, the active problems, and the reasons for visit (RFV) in primary care

MEDLINE			ICPC-2				RFV ranking[3]
Search areas ranking	Records	%	Codification ranking	Records	%	Δ	
1. General Internal Medicine	2.591	27.1%	**17.** General and nonspecific (A)	4.546.760	7.6%	19.4%	**6.** General/unspecified
2. Cardiology	964	10.1%	**13.** Circulatory system (K)	5.785.898	9.7%	0.4%	**3.** Cardiovascular/circulatory
3. Sociology	854	8.9%	**16.** Social problems (Z)	578.246	1.0%	8.0%	**15.** Social problems
4. Psychiatry	787	8.2%	**9.** Psychological (P)	5.241.316	8.8%	-0.6%	**11.** Psychological
5. Neurosciences/neurology	742	7.8%	**15.** Nervous system (N)	1.451.782	2.4%	5.3%	**2.** Nervous system/sense organs
6. Respiratory system	740	7.7%	**6.** Respiratory system (R)	5.585.571	9.4%	-1.6%	**1.** Respiratory
7. Endocrinology metabolism	627	6.5%	**2.** Endocrine, metabolic and nutritional (T)	7.703.216	12.9%	-6.4%	**9.** Endocrine
8. Gastroenterology Hepatology	358	3.7%	**3.** Digestive system (D)	5.527.479	9.3%	-5.5%	**7.** Digestive
9. Obstetrics Gynaecology	334	3.5%	**11.** Pregnancy and family planning (W)	1.994.442	3.3%	0.1%	**12.** Pregnancy/perinatal
10. Urology/nephrology	314	3.3%	**12.** Urinary tract (U)	1.751.123	2.9%	0.3%	**8.** Genitourinary
11. Orthopaedics	304	3.2%	**1.** Musculoskeletal system (L)	9.302.969	15.6%	-12.4%	**5.** Musculoskeletal
12. Dermatology	261	2.7%	**4.** Skin (S)	3.683.137	6.2%	-3.5%	**4.** Skin/subcutaneous
13. Haematology	228	2.4%	**14.** Blood, hematopoietic and lymphatic (B)	640.508	1.1%	1.3%	**13.** Blood/ blood-forming organs
14. Reproductive Biology (female)	200	2.1%	**7.** Female genital system (X)	2.012.418	3.4%	-1.3%	n.a.
15. Otorhinolaryngology	162	1.7%	**10.** Ears (H)	1.234.553	2.1%	-0.4%	n.a.*
16. Ophthalmology	64	0.7%	**5.** Eyes (F)	1.649.603	2.8%	-2.1%	n.a.*
17. Reproductive Biology (male)	43	0.4%	**8.** Male genital tract (Y)	890.675	1.5%	-1.0%	n.a.

Australian Family Physician and Guidelines were not aligned with the problems GPs most commonly face, with the topics hypertension, immunization, upper respiratory tract infection, depression, osteoarthritis and back pain showing relevant gaps. Burgers *et al*[7] created a research agenda through surveys among GPs and found similar research needs, with the highest number of research questions being related with the areas of musculoskeletal, psychological, skin, and general and unspecified ICPC-2 areas, and most of the research topics concerning common conditions. Muscat *et al*[8] coded clinical questions from GPs according to ICPC2, finding that the most frequently endorsed questions belonged to the endocrine/metabolic and nutritional chapter headings, followed by the general and unspecified, the digestive and the musculoskeletal chapters.

After analysing the map of relations (Fig. 3) and taking into consideration the ranking of active problems and reasons for a medical appointment, our study identified some potential topics for future research such as palliative care, chronic pain, motivational interviewing, lifestyle change, chronic disease management, quality improvement, sleep (and insomnia), antibiotic prescribing, burnout, breast cancer, vaccine, mental disorders, blood pressure control, osteoporosis, osteoarthritis, doctor-patient relationship, primary care management, COVID, among others.

To our knowledge, this is the first systematic mapping of the output of research topics in Primary Care journals.

The present study acknowledged potential research and publication gaps in Primary Care journals, identifying areas eligible for a higher number of publications as well as potential research topics. Although we acknowledge that primary care research might be published in journals from other fields and that physicians might access other sources of information, given the increasing amount of evidence, aggregating relevant information from the main primary care journals seems relevant to help clinicians stay up to date.

Considering that our findings overlap with findings from authors that explored research gaps, the use of scientometric analysis and comparison with common problems could be a strategy to recognize areas with research gaps in Primary care. The findings might also help to direct continuing medical education and help with guideline development.

*the author included ear and eye conditions in the general category 'nervous system'

[3] Finley CR, Chan DS, Garrison S, Korownyk C, Kolber M, Campbell S, et al. What are the most common conditions in primary care? Systematic review. Can Fam Physician. 2018;64:832-40.

Limitations and further research

This article presents the usual limitations of a scientometric study. The analysis was narrowed to studies and structured data collected from Web of Science regarding Journals indexed at MEDLINE. Therefore, only the articles published in those journals were analysed. Nevertheless, we consider that MEDLINE is the most accredited medical data base and provides an overview of the most relevant literature.[20]

Additionally, the search applied mainly big data tools, so an individualized assessment of each publication title and abstract was not done and only the title and abstract were considered, possibly missing some information, with the scientific quality of the studies not being considered. We also only analysed general fields and subtopics but could not identify specific research questions. The Dutch approach described by Burgers *et al.* and applied to single areas could be useful in defining concrete questions.

The data extracted from BI-CSP only contains information concerning the active problem lists, thus ignoring routine health care visits and preventive services as well as acute problems, that are not usually coded as problems on those lists. Furthermore, it only looks at the Portuguese reality; comparisons with primary care databases from other countries could prove useful. There could be a coding bias, favouring the coding of problems with associated health programs (diabetes and hypertension), as well as problems associated with pay for performance incentives (tobacco use; excessive weight, obesity). These problems could thus be overrepresented when compared to other codes that are frequently ignored, such as cataract or refractive error, despite its high prevalence in primary care. This approach also does not take into account a potential undercoding and underdiagnosis, although both may indicate a possible lack of knowledge and, by itself, a greater need for disclosure in the respective fields, thus not compromising the findings. We also recognise that primary care research can be published in journals from other fields and thus might have been excluded in this study.

CONCLUSION

While the number of publications in primary care journals has been increasing, the distribution of publications in Primary Care journals does not correspond to the problems faced in clinical practice, especially in the fields of musculoskeletal disease, dermatology, digestive and respiratory systems, and ophthalmology. The use of scientometric analysis to identify publication trends and its comparison with common problems could be a strategy to recognize areas with research gaps in Primary Care.

AUTHORS CONTRIBUTION

SA: Draft of the protocol, literature review, data processing, draft and review of the paper, approval of the final version.

PF: Conception of the methods, statistics section, data processing, draft and review of the paper, approval of the final version.

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 declare that they have no conflict of interest regarding this article.

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Chronic Urticaria in the Real-life Clinical Practice Setting in Portugal: Two-Year Results from the Non-Interventional Multicenter AWARE Study

Urticária Crónica na Prática Clínica de Vida Real em Portugal: Resultados de Dois Anos do Estudo Não Intervencional de Vida-Real AWARE

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ABSTRACT

Introduction: Information regarding chronic urticaria patients in the real-world setting is scarce. This analysis reports the two-year results of Portuguese patients included in the AWARE study.

Material and Methods: Non-interventional cohort study. Adult patients with a diagnosis of chronic urticaria with symptoms for at least two months, refractory to H1-antihistamines, consulting one of the 10 participating urticaria centers throughout Portugal, from the 31st October 2014 to 31st July 2015, have been included in the study. Clinical parameters, medicines taken for urticaria symptom relief, weekly urticaria activity score, and dermatology quality of life index have been collected throughout the two years of the study.

Results: Seventy-six patients were enrolled in the study. Results showed that the proportion of patients with omalizumab therapy almost duplicated after two years of the AWARE study, which was accompanied by the decrease of medical resources use and absenteeism. Moreover, urticaria severity and impact on quality of life both decreased after one year and continued to decrease at two years, although decreased severity was significant at both time points and quality of life was only significant at two years. At the end of two years, 79.0% of patients had their disease controlled compared to 29.3% at baseline ($p < 0.001$).

Conclusion: Chronic urticaria still has a significant impact on quality of life and therefore there is opportunity for further therapy optimization.

Keywords: Urticaria/classification; Urticaria/diagnosis; Urticaria/therapy

RESUMO

Introdução: A informação disponível sobre doentes com urticária crónica em contexto da prática clínica real é escassa. Esta análise reporta os resultados a dois anos dos doentes portugueses incluídos no estudo AWARE.

Material e Métodos: Estudo de coorte, observacional, prospetivo, de doentes adultos com diagnóstico de urticária crónica, com sintomas há pelo menos dois meses, refratários a antihístamínicos-H1 na dose aprovada, seguidos em 10 centros de urticária em Portugal, incluídos entre 31 de outubro de 2014 e 31 de julho de 2015. Ao longo dos dois anos do estudo AWARE foram avaliados parâmetros clínicos, medicação utilizada para alívio dos sintomas de urticária, o *Weekly Urticaria Activity Score* e o índice de qualidade de vida dermatológico.

Resultados: Foram incluídos setenta e seis doentes. Após dois anos do estudo AWARE, a percentagem de doentes sob terapia com omalizumab quase duplicou, sendo acompanhada por uma diminuição da utilização de recursos médicos e absenteísmo. A gravidade da urticária e o impacto na qualidade de vida diminuíram após um ano e continuaram a diminuir aos dois anos, embora o aumento da qualidade de vida apenas tenha atingido significado estatístico no segundo ano. A percentagem de doentes com patologia controlada aumentou de 29,3% no início do estudo para 79,0% ($p < 0,001$).

Conclusão: A urticária crónica tem impacto na qualidade de vida da população, mostrando que a terapêutica ainda poderá ser otimizada.

Palavras-chave: Urticaria/classificação; Urticaria/diagnóstico; Urticaria/tratamento

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INTRODUCTION

Chronic urticaria (CU) is a group of skin diseases characterized by itchy wheals and/or angioedema for more than six weeks. CU is divided into spontaneous (CSU) or inducible (CIndU), the latter being triggered by specific stimuli such as heat, cold, sun exposure or pressure.[1] It is known that two or more different subtypes of urticaria can coexist in any given patient.[1] An urticaria wheal has a fleeting nature and the skin returns to its normal appearance usually within 30 minutes to 24 hours.[1]

The diagnosis of urticaria is clinical and established by the evaluation of the typical features of symptomatic wheals.[2] The recommendations for Portugal on the diagnosis and management of CSU have been published in 2016.[3] In these recommendations, omalizumab was proposed as third line therapy, and cyclosporine should only be used as off-label therapy in case of inadequate control with omalizumab.[3] The same approach was proposed later, in 2017, by the EAACI/GA²LEN/EDF/WAO guidelines, in the chronic urticaria treatment algorithm.[1]

At the time of the AWARE study, the current guidelines were the 2014 EAACI/GA²LEN which recommended daily use of approved doses of non-sedative H1-antihistamines (H1-AH) as standard of care for CU.[1,2,4-9] Moreover, the dosage of these drugs could be increased up to fourfold, as second line therapy, in case of lack of response,[1,2,4-7,10-12] followed by add-on therapy with omalizumab, cyclosporine or montelukast as third-line therapy, the latter two being off-label for urticaria.[2] The 2017 revision of the guidelines have changed the recommendation of third line therapy to include only omalizumab. Cyclosporine was moved to forth line therapy, and montelukast has been moved to 'others', due to insufficient scientific evidence.[1]

This change was a result of the effectiveness that omalizumab showed in the control of H1-AH refractory CU patients.[13-16] Symptom control is the consensual therapeutic goal[1,2,4,6,9,11] and the weekly urticaria activity score (UAS7) questionnaire is the preferred tool for evaluating disease activity.[1,2,4,5,10-12] Given its strong impact on patients' quality of life (QoL), it is highly recommended that CU is assessed using a QoL tool such as the dermatology quality of life index (DLQI).[9,10,17] Moreover, the impact of symptoms and QoL on direct and indirect costs involving medication, physician appointments, visits to the emergency room (ER), hospitalizations and absenteeism,[4] although acknowledged, remain largely unknown in the real-word setting.[18-23] The non-interventional AWARE study was designed in order to overcome this gap. AWARE was a global (36 countries), prospective study of CU patients refractory to standard doses of H1-AH therapy in the real-world setting, conducted in specialized urticaria centers, designed to evaluate the CU disease burden and impact on QoL in these patients, as well as which therapies and medical resources are used.[24]

In this paper, we report the final 2-year data from patients with CU included in the AWARE study in Portugal. Baseline characteristics of the Portuguese patients enrolled in this study have been previously reported.[24]

MATERIAL AND METHODS

Study design

The AWARE (A World-wide Antihistamine-Refractory chronic urticaria patient Evaluation) study was designed to evaluate the real-world disease burden of adult patients with a diagnosis of CU for at least two months who were refractory to the approved dose of at least one H1-AH. Patients were enrolled at specialist urticaria centers, and the used therapies, impact on QoL and work productivity of individual patients were also evaluated. The study was approved by the Ethics Committee of each participating center and conducted according to the tenets of the Declaration of Helsinki, as revised in 2013.

Setting and participants

The AWARE study was a worldwide non-interventional international multicenter study conducted in 36 countries. This paper pertains only to patients recruited from the 10 participating centers throughout Portugal, from 31st October 2014 to 31st July 2015. In this cohort study, all study variables were collected at baseline, one year and two years, during a follow-up period of two years. Diagnosis of urticaria was confirmed at enrollment according to the European Guidelines.[2]

Inclusion criteria included written informed consent of the patient to participate in the study; age 18 years and over; medically confirmed diagnosis of CU present for more than two months; refractoriness to treatment with standard doses of H1-AH. Anticipated difficulties of follow-up during at least two years and participation in any other clinical urticaria study were defined as exclusion criteria.[24]

Methods of assessment

All variables were collected on an electronic case report form (eCRF) specifically designed for the study. Patient reported outcomes (PROs) evaluated included UAS7 from the week before the consultation[2,4,5,10-12] and DLQI[9,10,17] filled during the consultation, and scores were introduced on the eCRF. The UAS7 is a questionnaire that measures disease activity during seven days: UAS7 = 0 means urticaria-free, UAS7 = 1 - 6 means well controlled urticaria, UAS7 = 7 - 15 reflects mild urticaria, UAS7 = 16 - 27 reflects moderate urticaria and UAS7 = 28 - 42 corresponds to severe urticaria.[24] DLQI measures QoL in patients with chronic dermatologic diseases, including CU: DLQI between 0 - 1 indicates that the urticaria has no effect on patients' life; DLQI between 2 - 5 that it has a small effect on patients' life; DLQI between 6 - 10 that it has a moderate effect; DLQI between 11 - 20 that it has a very large effect; and DLQI between 21 - 30 indicates that urticaria has an extremely large effect on patients' life.[25,26] Neither UCT (urticaria control test) nor CuQ2oL were used because, at the time of the study, they were not validated for the Portuguese population.[3,27]

Quantitative variables

In addition to descriptive statistics, inference statistics

were performed for UAS7 and DLQI as continuous variables, in order to address their change from baseline to one and two years of the AWARE study. Inference statistics were also performed to evaluate the impact of CU on sick leave and in the use of medical resources at baseline, one year and two years.

Statistical methods

Continuous variables are presented as mean (95% confidence interval [95% CI]) and categorical variables as number (percentage). Between group analyses were performed using the Mann-Whitney U test when comparing two groups or the Kruskal-Wallis test with correction for multiplicity when comparing more than two groups. Within-group analyses were performed using the Friedman test or the Cochran's Q, both corrected for multiplicity, as appropriate. Correlations were assessed with the Spearman r test. Tests were considered significant at $\alpha = 0.05$ significance level (two-sided). The software used was SPSSv20.

RESULTS

Participants

Of the 5237 patients included worldwide in the AWARE study, the 76 patients enrolled and included in the Portuguese cohort were analyzed. Sixteen patients were lost to follow-up and thirty patients had all the data available. All tables and figures state the number of patients with data available for each analyzed variable. Missing data were considered to be missing completely at random (MCAR).

Demographic and clinical baseline characteristics

The demographic and clinical baseline characteristics of the AWARE study, reflecting the Portuguese population sample, have already been published.[24] Most patients had only CSU (63.2%), 13.2% had only some form of CIndU, and the remaining 23.6% showed both CSU + CIndU. The median age of the study cohort was 46.5 years and 76.3% of the patients were women. Only 29.3% of patients had well-controlled urticaria at enrollment, measured by UAS7.

Angioedema

Angioedema, present in 39.5%[24] of patients at baseline, was significantly decreased after one and two years to 10.7% and 12.2% ($p < 0.001$), respectively, with no difference between year one and year two.

Proportion of patients with omalizumab therapy

Non-sedative H1-AH were used by 85.5% of patients at baseline and 76.8% and 73.5% at one and two years, respectively. The proportion of patients under cyclosporin was 4.6% at baseline[24] and at year one and two no patients were under this therapy. Corticosteroid therapy was used by

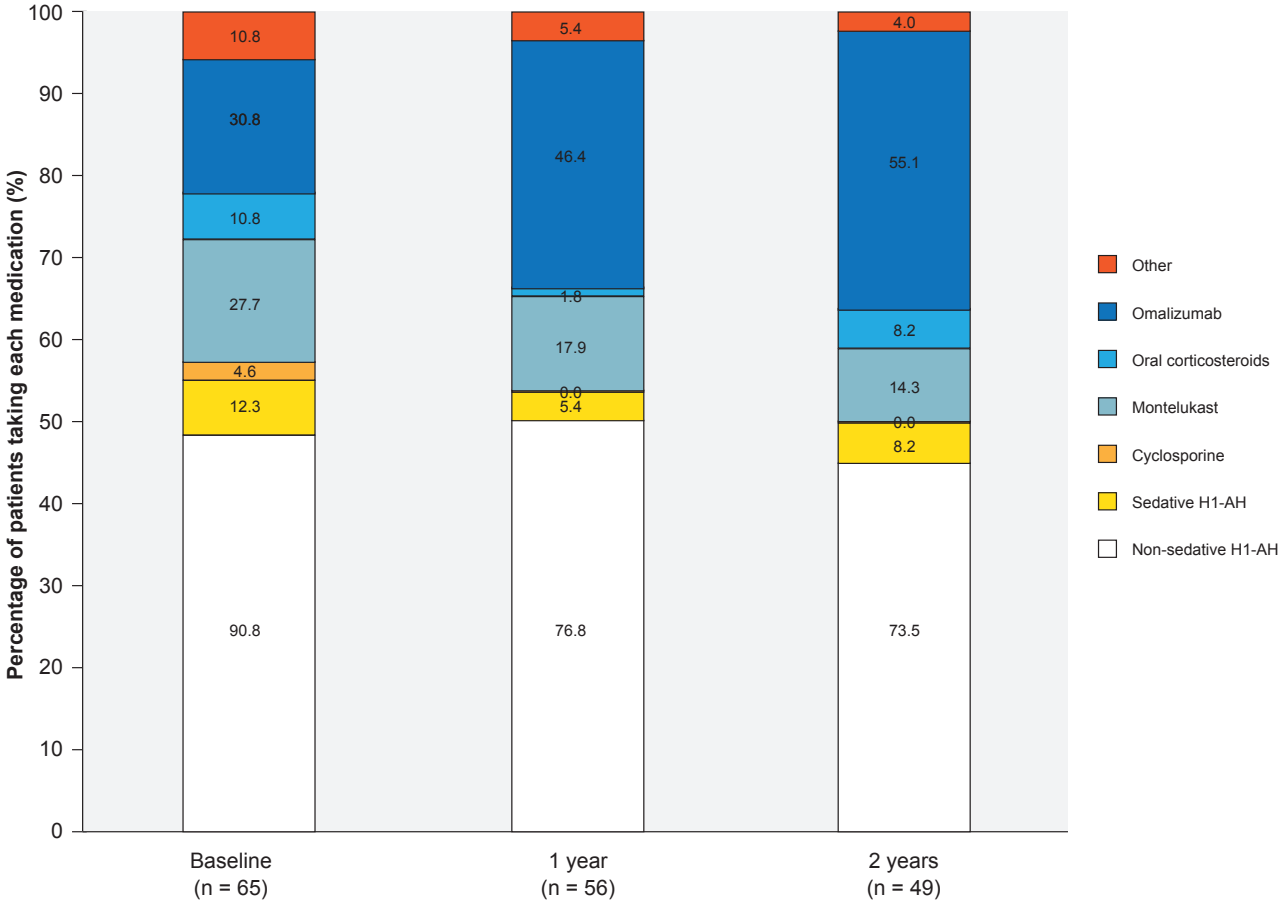

Figure 1 – Medication at baseline, one year and two years
H1-AH = H1: antihistamines

approximately 11% of patients at baseline and 1.8% and 8.2% at one and two years, respectively. Around 24% of patients were treated with montelukast at baseline, and 17.9% and 14.3% at year one and two, respectively. Throughout the study the proportion of patients under omalizumab almost duplicated from baseline (30.8%) to year two (55.1%) – Fig. 1.

Medical resources use and absenteeism

Medical resources and absenteeism are indirect measures of urticaria control. At the beginning of the AWARE study, 25% of patients had experienced at least one episode of sick leave due to urticaria, and around 70% had used medical resources, such as visits to the ER, primary care, other specialized care including dermatology and allergology medical appointments and, in more severe cases, hospitalization – Table 1. Over the two years of this study, there was a significant decrease of all used resources from baseline to years one and two ($p < 0.001$), except hospitalizations. Although not reaching statistical significance, the proportion of hospitalizations changed from 5.3% at baseline to 0.0% at years one and two. The proportion of patients with no sick leaves and that used no medical resources reached 100% at year one and two, respectively ($p < 0.001$). There were no significant changes between year one to year two.

Urticaria disease activity

Urticaria disease activity and the impact in QoL were measured through two patient reported outcomes (PROs): UAS7 and DLQI, respectively. Fig. 2 shows that UAS7 decreased after year one and further decreased at year two. Of notice, the decrease in year two is statistically significant when compared to baseline and to year one. UAS7 did not correlate with the number of years of urticaria diagnosis nor was it associated with the presence of angioedema.

Concerning DLQI, and although there was a decrease from baseline to year one, this was not statistically significant, only reaching significance at year two when compared to baseline (Fig. 3). At the end of the second year, 79.0% of patients had well controlled urticaria, which represented a significant improvement when compared to baseline ($p < 0.001$).

DISCUSSION

Although CU is a relatively common condition, there is a lack of studies evaluating patient care of urticaria patients in a real-world setting. This study presents the two-year results from the 76 patients of the AWARE Portuguese cohort, in a real-world context, and reflects the resources allocated during follow-up and treatment of CU patients.

Current urticaria guidelines recommend that complete symptom control should be the aim of CU treatment.[1] In this study, the main therapies used were non-sedative H1-AH, with a variation from 85.5% at baseline to 76.8% and 73.5% at year one and two, respectively. Omalizumab is recommended for the treatment of CSU in patients who remain symptomatic despite H1-AH therapy.[1] In the Portuguese cohort, the proportion of patients treated with omalizumab at baseline was 28.9% and almost duplicated at year two to 55.1%. The proportion of patients under omalizumab at baseline was similar to the proportion reported in the AWARE German cohort (21.4%).[28] However, it seems to be higher in our cohort at year two: 55.1% *vs* 31.4%.[29] This could reflect the fact that the AWARE study in Portugal recruited CU patients referred to specialized urticaria centers, who probably had more severe forms of CU.

Regarding corticosteroid therapy, and according to current recommendations, a short course of corticosteroids can be prescribed as relief therapy, regardless of the line of therapy the patient is receiving. Since urticaria is not a stable condition, oscillating between exacerbations and remissions, often without apparent triggering factors, the proportion of patients on this therapy at baseline, one year and two years may reflect the different exacerbation or remission phase the patient was experiencing when the visit occurred.

Although the current standard therapy with standard doses of H1-AH is still the mainstay of treatment for CSU, it only leads to an absence of symptoms in less than 50% of patients, and even increasing the dose still leaves approximately 30% of patients symptomatic. Omalizumab has been a major breakthrough in the care of these patients.[30]

The most important factors contributing to the impact of CU in QoL and psychological distress are the severe pruritus and the unpredictability of the disease episodes,[31] as well as the presence of angioedema and concomitant

Table 1 – Use of medical resources and sick leave at baseline, one year and two years

Variable	Baseline (n = 76)	1 year (n = 56)	2 years (n = 49)	*p*-value
Sick leave	19 (25.0)	0 (0.0)	0 (0.0)	**< 0.001**
Utilization of medical resources				
None	29 (38.2)	52 (92.9)	49 (100.0)	**< 0.001**
ER	40 (52.6)	2 (3.6)	0 (0.0)	**< 0.001**
Primary care	38 (50.0)	1 (1.8)	0 (0.0)	**< 0.001**
Hospitalization	4 (5.3)	0 (0.0)	0 (0.0)	0.102
Other specialized care	34 (44.7)	1 (1.8)	0 (0.0)	**< 0.001**

All values presented as n (%). *p* values refer to the difference from one year or two years *versus* baseline using the Cochran's Q test. There were no significant differences from year one to year two.
ER: emergency room

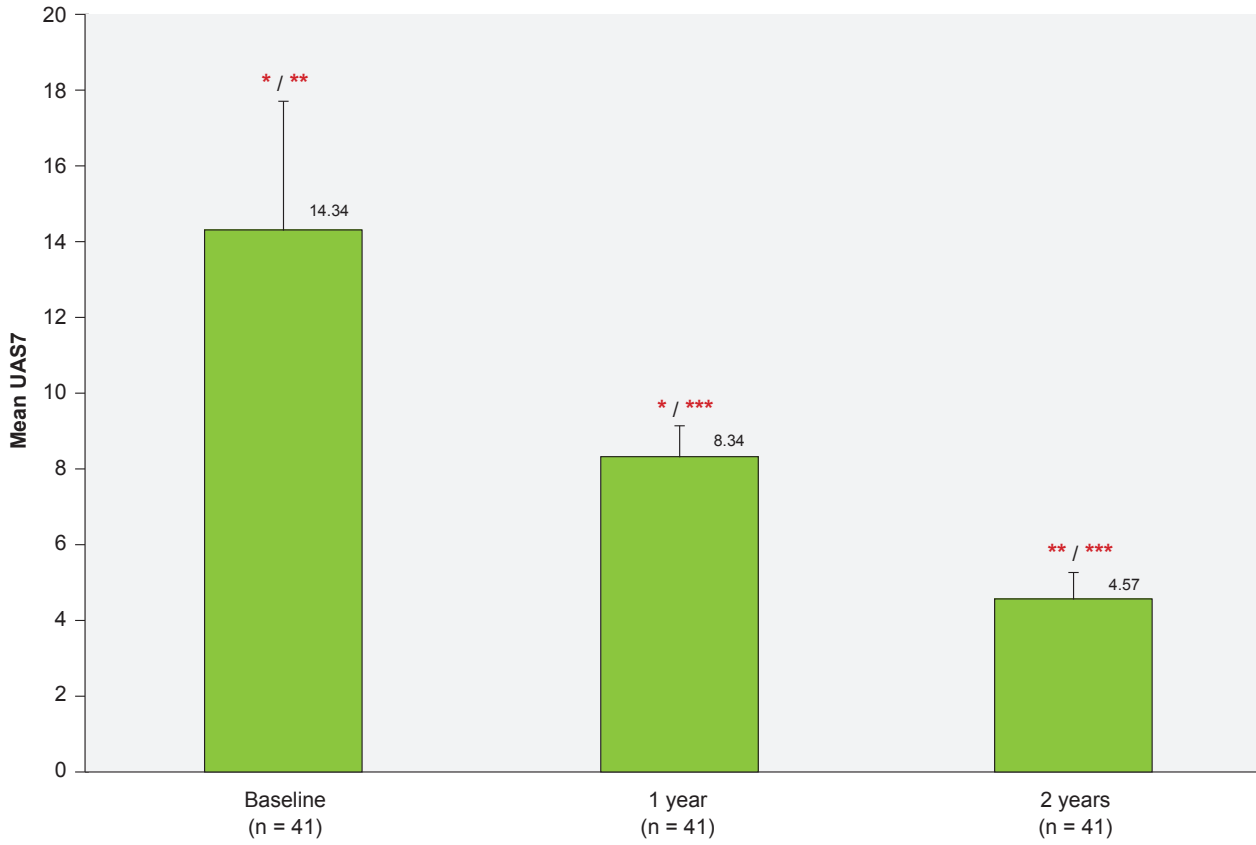

Figure 2 – UAS7 score at baseline, one year and two years

Bars represent means, error bars represent 95% CI. **p* = 0.001 baseline *versus* one year; ***p* < 0.001 baseline *versus* two years; ****p* < 0.001, one year *versus* two years. *P*-values obtained from the Friedman test with correction for multiplicity.

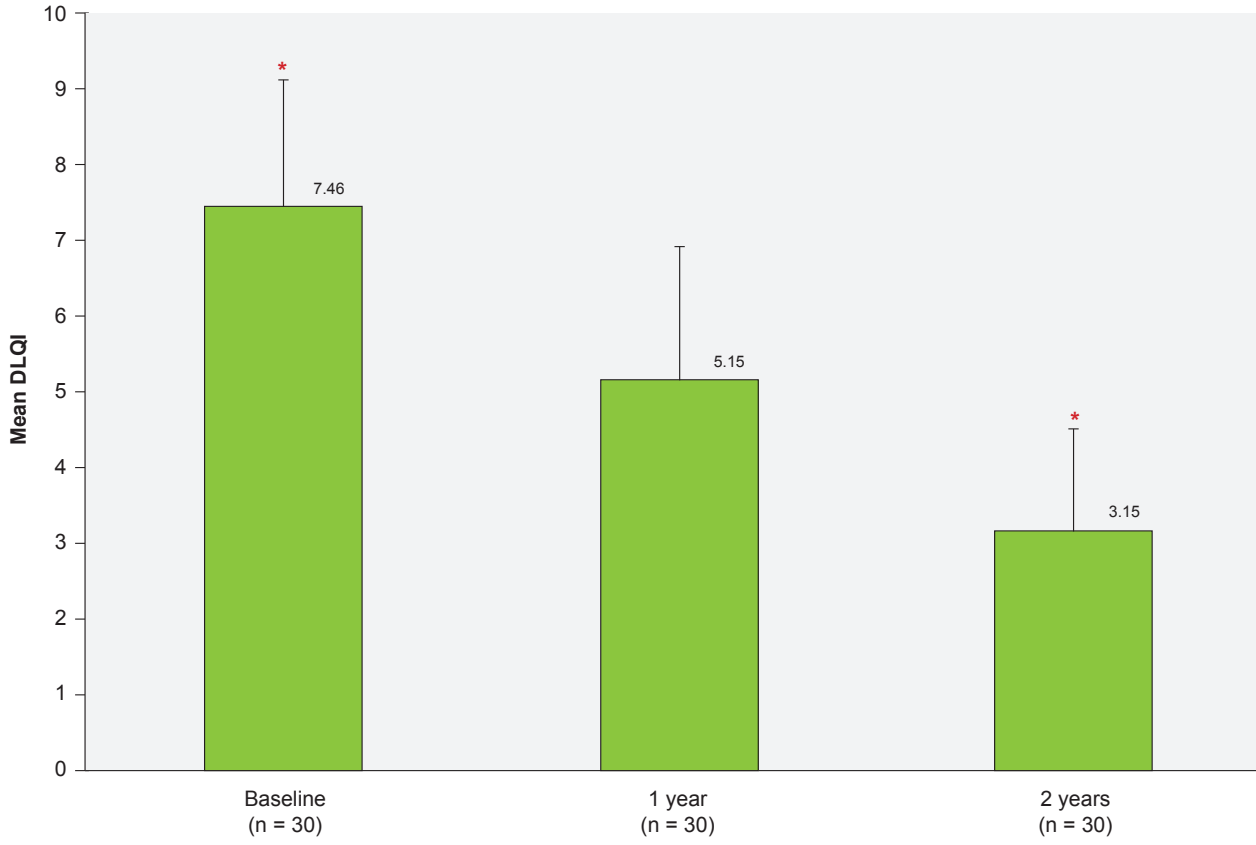

Figure 3 – DLQI total score at baseline, one year and two years.

Bars represent means, error bars represent 95% CI. **p* = 0.001, baseline *versus* two years

P-values obtained from the Friedman test with correction for multiplicity.

CIndU. Therefore, the impact of CU in the life of patients goes beyond the effects on the skin. The baseline results from the AWARE study in Portugal showed that CU had a very large impact in work activities, since 25% of patients experienced at least one episode of sick leave due to CU.[24] This proportion was similar to the one reported in the AWARE study in other countries such as Sweden, Norway, Denmark[32] and Germany.[33] The severity of the disease has been associated with sick leave, which has personal, social and economic implications.[19] Moreover, these studies also showed that CU patients were frequent users of medical resources,[24,32,33] an important aspect in CU, given it reflects direct and indirect costs associated with the condition.[34]

Our results show that the number of patients that have not used medical resources, including ER visits, primary care, and other specialized care, decreased from baseline to year one and reached 100% at year two ($p < 0.001$ compared to baseline at both time points). This decrease in medical resources use may reflect the control of CU and has an impact in both direct and indirect costs associated with the disease. Indirect costs, including wage loss due to medical appointments and to sick leave, and lack of productivity due to sick leave, are the second component of the total costs of CU, second to direct costs with medication.[35] Our results revealed that over the study period, no patients lost work-days due to CU at years one and two, except to attend medical consultations or for administrations of omalizumab, but not due to disease severity. This fact highlights the importance of disease control since year one, not only regarding symptoms but also in terms of the impact on personal and professional life.

The severity of CU was assessed by UAS7. UAS7 is based on the objective assessment of disease activity self-reported by the patient, which makes this score particularly valuable.[3] Moreover, as the urticaria activity can change in a short period of time, this score allows for the patient to quantify it every day during seven days.[14] The mean UAS7 at baseline was 14.34, corresponding to 'mild disease'; however, it is in the upper limit. The decrease to 8.34 at year one was significant ($p = 0.001$), although it remained in the 'mild disease' category. At year two the mean UAS7 further decreased to the level of 'well controlled disease', statistically different from baseline and year one ($p < 0.001$). These results are in line with other AWARE reports that have shown a decrease in total mean UAS7 score in CSU patients from baseline to year two, suggesting an improvement in disease control,[29,36,37] and reaching the level of 'well controlled disease' at year two.[29,37]

DLQI measures the impact of skin disease in the patients' QoL, ranging from no impact to most severe impact with a recall period of seven days.[3] In this study, the impact of CU on QoL was 'moderate' at baseline (mean DLQI 7.46) and changed to 'small effect' at year one (5.15) and year two (3.15). Although the decrease was significant only at year two ($p = 0.001$ *vs* baseline), it never reached 'no effect'. Our results at baseline and year one are in accordance with the AWARE study in Germany, with a median of DLQI of 8.3 at baseline and 4.1 at year one.[28]

The analysis of the variations in UAS7 and DLQI may lead us to speculate that since the decrease in symptoms occurred at year one and the significant differences in QoL were only apparent at year two, the perception of the effect on QoL occurs later than the perception of symptom improvement. Only when patients have the 'disease controlled', they recognize that CU has a 'small effect' on their QoL. Once more, this strengthens how much CU impacts the patients' QoL.

It is known that spontaneous remission of CU occurs in some patients and severity has been associated with the duration of the disease.[38] A study showed that symptoms disappeared spontaneously after one year, in 47.4% of patients in whom the cause of urticaria had not been identified.[39] In our study, there was no correlation between the duration of the disease and UAS7, probably reflecting the fact that patients with long-term CU refractory to H1-AH are not able to achieve spontaneous remission. Moreover, and although the burden of disease has been reported to be particularly high in patients with CSU and associated angioedema,[23] in our study, disease severity was not associated with the presence of angioedema ($p = 0.390$) or with the presence of CIndU ($p = 0.128$). Also, duration of CSU was not associated with the presence of angioedema ($p = 0.335$). However, the proportion of patients with angioedema significantly decreased from baseline to years one and two.

Taken together, all results showed a better disease control, evident at year one and confirmed at year two, through the improvement of the different analyzed variables. Based on these results, we could hypothesize that 1) referral to a specialist center for urticaria treatment is important and 2) the type of therapy is relevant. All our patients were followed-up in specialist urticaria centers and a high proportion had their urticaria signs and symptoms better controlled with an impact on QoL. We may speculate that one of the reasons for this is the number of patients under omalizumab therapy. Indeed, recent studies[14,15] have shown that omalizumab is a highly effective therapy in patients refractory to H1-AH therapy.

Three important key factors for this success are careful analysis of patient history,[31] reliability on therapy escalation, namely up-dosing of H1-AH, and omalizumab prescribing.[28] The impact on QoL should be emphasized in the choice of treatment in patients with CU refractory to H1-AH.[1]

An important message to highlight based on these results is the fact that if the patient is controlled in specialist centers, it is of paramount importance to alert primary care physicians regarding the referral of uncontrolled patients to specialist care.[40]

One limitation of the AWARE study is that it recruited CU patients referred to specialist urticaria centers from public primary care services, due to being refractory to at least the approved H1-antihistamine dose. If patients were not previously diagnosed with CU in the primary care setting, they would not be included. The non-interventional, observational

study design, depending on the information provided by the physician, is another limitation of this study.

CONCLUSION

The AWARE study was a real-world study that evaluated the impact of CU in patients refractory to H1-AH therapy. At the beginning of the study, a significant proportion of patients did not have the disease controlled with impact on quality of life and work productivity. At the end of two years, a significant proportion of patients had their disease controlled, an improvement on QoL, evaluated through DLQI, and a decrease of the use of medical resources. Therefore, the AWARE study allowed Portuguese physicians to recognize the importance of symptom control in CU, minimizing the resources involved in the management of this condition. Nevertheless, the mean DLQI at year two demonstrated that CU still has an effect in the QoL of Portuguese patients and therefore optimization of therapy can be further improved.

AUTHORS CONTRIBUTION

Both authors had equal contributions for the conception, design, draft, critical review and final approval of the paper.

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PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

Célia Costa declares having received honoraria as a speaker and/or medical advisor from Novartis, Menarini, AstraZeneca, Sanofi and LETIPharma outside the scope of this paper. João Gaspar Marques declares having received honoraria (lecture fees or medical consulting) from Astrazeneca, Bial, Laboratórios Vitória, Menarini, Mundipharma, Novartis, Procter&Gamble, Sanofi, Tecnifar and Teva, as well as research grants from Astrazeneca and Laboratórios Vitória. José Ferreira declares having received honoraria (lecture fees, medical consulting fees or research grants) from Astrazeneca, Bial, Laboratórios Vitória, Menarini, Novartis, Sanofi, Tecnifar, GSK, LETIPharma and Roxall. Gabriela Marques Pinto declares having received honoraria (lecture fees, medical consulting fees or advisory boards fees) from Leo Farmacêutica Portugal, Pfizer, Novartis, Lilly, Janssen and Abbvie. Sara Prates and Virgínia Sousa declare they have no conflicts of interests. Remaining authors are missing conflicts of interests disclosure.

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O Internato de Formação Especializada em Neurocirurgia: Qual o Atual Panorama Nacional?

Neurosurgical Residency in Portugal: What is the National Panorama?

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RESUMO

Introdução: Em Portugal, o número de médicos internos em Neurocirurgia tem vindo a aumentar progressivamente ao longo dos anos, contudo esta evolução não tem sido acompanhada de estudos que permitam compreender o estado atual da formação. Foi objetivo deste estudo caracterizar e quantificar a satisfação na formação especializada em Neurocirurgia, em Portugal, no ano de 2019.

Material e Métodos: Estudo quantitativo, observacional e transversal baseado num questionário original enviado eletronicamente aos internos e recém-especialistas de Neurocirurgia entre outubro e dezembro de 2019. Incluiu-se perguntas sobre características e satisfação em termos de formação teórica, prática, entre outras.

Resultados: Obtiveram-se 37 respostas em médicos com cerca de 29,0 (± 4,0) anos, 78,4% homens e 54,1% provenientes de centros do Centro/Sul/Ilhas. Do total de respostas obtidas, 51,4% vieram de internos dos três primeiros anos. Quanto à formação teórica, evidenciou-se insatisfação em relação às reuniões de morbimortalidade (59,5%), existência de sessões/laboratório anatómico (89,2%), participação no ensino graduado (64,9%) e em investigação (64,9%). Quanto à formação prática, a insatisfação evidencia-se apenas em relação à consulta externa (56,8%). A primeira intervenção cirúrgica tende a ser realizada no primeiro mês de internato, no primeiro ano. Por ordem crescente, a primeira cirurgia é de trauma craniano (5,09 ± 4,59 meses), patologia de liquor (5,95 ± 4,3 meses), nervos periféricos (6,0 ± 7,0 meses), craniotomia (6,59 ± 3,88 meses) e patologia lombar (11,41 ± 1,5 meses). A cirurgia pediátrica é a última a ser iniciada (19,36 ± 20,0 meses). Parece existir satisfação geral com a avaliação anual (59,5%) mas não com a final (37,8%).

Conclusão: Este estudo cumpriu o objetivo principal de ser um ponto de partida na caracterização dos centros neurocirúrgicos portugueses e da satisfação no internato de formação especializada em Neurocirurgia.

Palavras-chave: Educação de Pós-Graduação em Medicina; Internato e Residência Neurocirurgia/educação; Portugal

ABSTRACT

Introduction: In Portugal, the number of neurosurgery residents has been rising steadily. However, there are no robust studies assesing the level of satisfaction and quality of the current training programs. The aim of this study was to describe and quantify the level of satisfaction about Neurosurgery residency in 2019, in Portugal.

Material and Methods: Quantitative observational cross-sectional study based on an original questionnaire about the level of satisfaction of neurosurgical training in Portugal in 2019, sent electronically to residents and young consultants between October and December 2019.

Results: A total of 37 responses were obtained from physicians aged around 29.0 (± 4.0) years old, of which 78.4% were men and 54.1% from centers in the center/south of the country/islands. Overall, 51.4% of the answers came from first three years' residents. As for the theoretical training, there was dissatisfaction with the morbidity and mortality meetings (59.5%), existence of sessions/anatomical lab (89.2%), participation in medical education (64.9%) and in research (64.9%). As for practical training, there was dissatisfaction only towards outpatient clinics (56.8%). There is a tendency for the first surgery to occur in the first month of residency and, in ascending order, firstly a cranial trauma surgery (5.09 ± 4.59 months), then for cerebrospinal fluid diseases (5.95 ± 4.3 months), peripheral nerves (6.0 ± 7.0 months), craniotomy (6.59 ± 3.88 months) and lumbar spine diseases (11.41 ± 1.5 months). Pediatric surgery was the last type of surgery to begin (19.36 ± 20.0 months). There seems to be a generalized satisfaction with the annual (59.5%) but not with the final examination (37.8%).

Conclusion: This study has succeed at being a better description of the Portuguese neurosurgical centers and of the level of satisfaction about neurosurgical training in Portugal.

Keywords: Education, Medical, Graduate; Internship and Residency; Neurosurgery/education; Portugal

INTRODUÇÃO

Em Portugal, o número de médicos internos e especialistas em Neurocirurgia tem aumentado progressivamente ao longo dos anos, à semelhança do que tem acontecido com outras especialidades, na tentativa de compensação da crescente formação pré-graduada, ainda que de forma ligeira e aparentemente controlada.[1] Apesar do Ministério da Saúde procurar por vezes enquadrar os recursos médicos existentes com as necessidades populacionais,[1] não existem estudos que visem caracterizar o internato médico de Neurocirurgia propriamente dito, a sua qualidade e a satisfação com o mesmo, à semelhança de outros países.[2–5]

O internato de formação especializada em Portugal

Segundo os últimos dados do Ministério da Saúde, desde 2014 criaram-se nove a 12 centros de formação especializada em Neurocirurgia, alguns deles com idoneidade parcial (cinco em 12), contudo nem sempre com possibilidade de vaga todos os anos.[1] Cada centro tende a

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receber entre um a dois internos, de acordo com o que é pedido pelo serviço/centro hospitalar, avaliado como capaz pelo Colégio de Especialidade de Neurocirurgia da Ordem dos Médicos e pelo Conselho Nacional do Internato Médico (CNIM), e por último decidido pelo Ministério da Saúde (ACSS – Administração Central do Sistema de Saúde, IP), de acordo com os recursos gerais do mesmo. Estima-se que existam anualmente cerca de 50 médicos internos de neurocirurgia em Portugal.[1]

Em 2019, o internato médico de Neurocirurgia seguia a Portaria número 146/98 de 9 de março, onde é referido um programa de formação com a duração de seis anos (72 meses).[6] Esta legislação viria a ser revogada pela Portaria nº 393/2019 de 6 de Novembro, não sendo aplicável na integra a quem respondeu a este inquérito. Durante estes anos, o médico interno tem objetivos de desempenho a nível cirúrgico (números mínimos de intervenções por grupo de patologia), objetivos de conhecimento (capacidade de diagnosticar e tratar) e de produção científica (comunicações e publicações). O programa termina com orientações para uma avaliação anual com duas componentes: desempenho (capacidade de execução técnica, interesse pela valorização profissional, responsabilidade profissional e relações humanas de trabalho) e conhecimento (contínua, complementada por uma prova de apreciação e discussão de um relatório anual de atividades produzido pelo médico interno).

O programa de formação é da responsabilidade do Colégio de Especialidade de Neurocirurgia da Ordem dos Médicos, que procura alinhá-lo com as normas europeias e, assim, garantir uma uniformização e melhoria contínua da qualidade assistencial.[1]

Para serem reconhecidos formalmente como centros de formação de médicos internos em Neurocirurgia, segundo o Colégio da Especialidade de Neurocirurgia, os serviços devem ter um número de casos e variedade de patologias suficiente para proporcionar uma formação adequada, um mínimo de quatro orientadores de formação, 30 camas no serviço e a 10 camas de Cuidados Intensivos por milhão de habitantes da área de influência direta.[1,7,8] É ainda exigido que estes serviços estejam equipados com microscópio, apoio de neuro-navegação, aspirador ultrassónico, endoscópio, motores como craniótomo e brocas de desbaste ósseo, intensificador de imagem, possibilidade de utilização de monitorização eletrofisiológica intraoperatória e acesso a bloco de ambulatório.[1,8] Outro requisito fundamental é a existência de urgência de 24 horas com capacidade de contribuir com determinados números (dados em tabela valores mínimos e ótimos) de cirurgias para o currículo ao interno no final da sua formação.[1,8] Nestes serviços deverão ainda existir pelo menos duas salas cirúrgicas preparadas para Neurocirurgia, com anestesistas formados em neuroanestesia e disponíveis 24 horas por dia.[1,8] O programa de formação deve integrar um estágio de Neurocirurgia Pediátrica e um estágio de Neurocirurgia Funcional, realizados no local de formação do médico interno ou noutro local com idoneidade reconhecida pela Ordem dos Médicos.[1,8] Apesar de todas estas recomendações, existe a perceção de que nem todos os serviços estão equipados de forma igual e de que existem eventuais assimetrias na formação do médico interno.

Enquadramento e formulação do estudo

Em Portugal, os estudos sobre a formação especializada em Neurocirurgia são escassos, impedindo a identificação das referidas dissemelhanças formativas existentes a nível nacional e internacional, nomeadamente quanto ao número de horas de trabalho, ao género dos médicos internos, à publicação de artigos e à carreira académica.[10–18]

É opinião dos autores que a satisfação dos médicos internos pode ser influenciada por vários fatores previamente identificados em estudos internacionais, como características e organização dos serviços, carga horária, distribuição de tarefas e oportunidades formativas (teóricas e práticas) disponibilizadas.

Em termos de constituição e organização dos serviços, acredita-se que esta satisfação poderá eventualmente variar de acordo com o número de internos em cada um, podendo ser maior no serviço de urgência (SU) (onde não se verificam tantos períodos de urgência), mas menor no bloco (por menos oportunidades). Um maior número de médicos com doutoramento poderá estar possivelmente associado a maior produção científica do serviço, o que poderá contribuir para uma maior satisfação dos médicos internos.

A realização de sessões clínicas ou *journal clubs*, eventualmente por permitirem uma revisão de temas importantes e atualização de conhecimento, poderá ser uma mais-valia e motivo de satisfação com em termos de formação teórica, assim como as reuniões multidisciplinares, que dependem da existência de determinadas subespecialidades num serviço, reuniões de morbilidade e mortalidade, sessões anatómicas e acesso a laboratório de anatomia. A colaboração no ensino graduado de Medicina, através de aulas ou do acompanhamento de teses de mestrado (ou outros documentos de produção científica como comunicações ou publicações) poderá estar associada a uma maior satisfação, eventualmente por permitir um contacto constante com informação atualizada. Esta satisfação também parece estar associada à realização de estudos de investigação no local de colocação, e à formação externa, incluindo cursos ou estágios nacionais e internacionais.

Quanto à formação prática, pensa-se que o desempenho e a satisfação dos médicos internos poderão estar associados a uma melhor organização do serviço, carga horária, distribuição de tarefas, ao apoio assistencial e ao número de doentes observados no serviço de Urgência, na enfermaria e nas consultas. Mais importante ainda, ao se tratar de uma especialidade cirúrgica, pensa-se que as oportunidades no bloco poderão ser uma das componentes mais relevantes e contribuidoras para a satisfação na formação prática e, quiçá, do Internato no geral.

Parece existir uma grande variabilidade entre países europeus quanto a aspetos práticos e teóricos da formação em Neurocirurgia, apesar da tentativa de

harmonização dos programas nas últimas duas décadas através da criação de normas europeias.[8,9] Segundo Stienen *et al*, os médicos internos portugueses são dos mais satisfeitos quanto à realização de *journal clubs,* ao início de prática cirúrgica precoce e ao contacto com um grande número de patologias. No entanto, esta satisfação encontra-se abaixo da média europeia quanto ao número de reuniões neurorradiológicas.[9]

Assim, a realização de um inquérito semelhante ao realizado ao nível europeu[9] poderia ser uma ferramenta útil quer para o Colégio de Neurocirurgia da Ordem dos Médicos, os diretores do internato médico, os orientadores de formação, a Sociedade Portuguesa de Neurocirurgia e os diretores de serviço hospitalares, permitindo identificar aspetos com potencial de melhoria em Portugal.

Objetivos finais

Este estudo pretende caracterizar a formação especializada no internato médico de Neurocirurgia em Portugal, assim como a satisfação dos atuais internos ou recém-especialistas, em 2019, no que diz respeito à formação teórica, prática e à sua avaliação. Num segundo momento, este estudo pretende também determinar uma possível associação entre a satisfação e os fatores estudados.

MATERIAL E MÉTODOS

Estudo quantitativo, observacional e transversal baseado num questionário original enviado eletronicamente aos internos e recém-especialistas de Neurocirurgia entre outubro e dezembro de 2019**.**

Questionário

O questionário utilizado foi elaborado em língua portuguesa, constituído por questões com resposta única e múltipla (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15110/Apendice_01.pdf). Trata-se de um trabalho original, tendo algumas perguntas sido adaptadas do mencionado artigo de MN Stienen, publicado na *Acta Neurochirurgica* com a autorização da EANS.[9]

O conjunto de perguntas encontra-se dividido nas categorias como 'Formação teórica', 'Formação prática', 'Avaliação do internato', 'Números cirúrgicos' e 'Questões (gerais) finais'. As perguntas de escolha múltipla que caracterizam a satisfação dos médicos internos seguiram uma escala de Likert de cinco pontos variando de 'Muito satisfeito' a 'Muito insatisfeito!' e uma opção 'Não existe / Não se adapta'.

O questionário foi colocado na plataforma Google Forms e o *link* para o mesmo divulgado através de correio eletrónico. O seu preenchimento foi voluntário e anónimo, tendo ficado disponível online por sete semanas, entre 21 de outubro e 9 de dezembro de 2019.

Aprovação ética

Para este tipo de estudo, o consentimento foi considerado tacitamente dado no preenchimento do questionário, pois a página de rosto contém informações sobre o estudo e o consentimento informado.

O protocolo de pesquisa foi submetido e aprovado pelo Comité de Ética do Centro Hospitalar de Lisboa Ocidental (CHLO), após parecer favorável e autorização do Conselho de Administração.

Análise estatística

Realizou-se análise descritiva através do cálculo de medidas de localização central (média/mediana) e de dispersão (desvio-padrão/amplitude interquartil) para as variáveis quantitativas contínuas, conforme apropriado. Para as variáveis qualitativas, foram calculadas frequências absoluta e relativa (percentagem). Para estudar a associação entre diversas variáveis foi utilizado o teste de qui-quadrado (ou o teste de Fisher, quando as frequências esperadas fossem inferiores a 5) para variáveis categóricas, e testes *t* de Student/ANOVA ou Mann-Whitney-U/Kruskal Wallis para variáveis contínuas, conforme apropriado. O nível de significância estatística utilizado foi de 5% (p = 0,05). O pacote estatístico utilizado foi o IBM SPSS Statistics versão 21.

Em alguns casos, para facilitar a análise e maior compreensão dos resultados, a escala de cinco categorias foi dicotomizada para satisfeito/satisfied, que inclui de 'Muito satisfeito' (*Very satisfied*), 'Satisfeito' (*Satisfied*) e 'Indiferente' (*Indifferent*); e não satisfeito/non-satisfied, que inclui 'Insatisfeito' (*Dissatisfied*), 'Muito insatisfeito' (*Very dissatisfied*) e 'Não existe / Não se adapta' (*Does not exist / does not adapt*).

RESULTADOS

Caracterização básica

Houve um total de 37 respostas e todas foram incluídos no estudo. A Tabela 1 mostra a caracterização básica dos participantes, incluindo parâmetros demográficos. A maioria das respostas vieram de internos do primeiro, terceiro e quinto ano. De modo a proteger o anonimato, foi decidido apenas identificar a origem dos internos por dois grupos – Norte e Centro/Sul/Ilhas.

Segundo a Tabela 1, a maioria dos centros de formação tende a ter cerca de sete internos e 13 especialistas, havendo um número muito reduzido de especialistas doutorados.

Formação teórica: caracterização

A Tabela 2 mostra a existência (ou não) e o tipo de reuniões multidisciplinares revelada pelos participantes. A reunião de tumores primários e secundários do sistema nervoso central (SNC) parece ser a mais frequentemente encontrada (86,1%) nos centros portugueses, seguida da de epilepsia (58,3%), estimulação cerebral profunda (DBS) (44,4%) e Neurovascular (38,9%).

Formação teórica: satisfação

A Fig. 1 mostra a distribuição da satisfação com sessões clínicas (incluindo *journal clubs*), reuniões multidisciplinares, reuniões de morbimortalidade, sessões de Anatomia e acesso a um Laboratório de Anatomia,

Tabela 1 – Caracterização da amostra

Variável		Resultados (n = 37)
Idade (anos)	Mediana (IQR)	29 (± 4,0)
Sexo masculino	n (%)	29 (78,4)
Região		
Norte	n (%)	17 (45,9)
Centro, Sul e Ilhas	n (%)	20 (54,1)
Ano de Internato		
1.º ano	n (%)	8 (21,6)
2.º ano	n (%)	4 (10,8)
3.º ano	n (%)	7 (18,9)
4.º ano	n (%)	4 (10,8)
5.º ano	n (%)	8 (21,6)
6.º ano	n (%)	4 (10,8)
Recém-especialista	n (%)	2 (5,4)
Caracterização dos serviços		
N.º de Internos	Mediana (IQR)	7 (± 3,0)
N.º de Especialistas	Média (DP)	13 (± 4,0)
N.º de Especialistas com doutoramento	Mediana (IQR)	1 (± 3,0)
Neurocirurgia como primeira escolha		
Sim	n (%)	32 (86,5)
Carga horária semanal referida		
Total	Mediana (IQR)	70 (± 20,0)
Bloco	Mediana (IQR)	20 (± 9,0)
Enfermaria	Mediana (IQR)	15 (± 14,0)
Urgência	Mediana (IQR)	24 (± 4,0)
Consulta	Mediana (IQR)	5 (± 2,0)
Estudo	Mediana (IQR)	4 (± 6,0)

Tabela 2 – Caracterização da existência de reuniões multidisciplinares segundo a amostra

Reuniões multidisciplinares		Resultados (n = 37)
Epilepsia	n (%)	21 (58,3)
DBS	n (%)	16 (44,4)
Dor crónica	n (%)	5 (13,9)
Lesões selares e paraselares	n (%)	18 (50,0)
Tumores primários e/ou secundários do SNC	n (%)	31 (86,1)
Coluna	n (%)	8 (22,2)
Patologia neurovascular	n (%)	14 (38,9)
Otoneurocirurgia ou base do crânio	n (%)	0 (0)
Neurociências	n (%)	27 (75,0)

contribuição para a formação médica pós-graduada, possibilidade de investigação clínica e saídas do serviço para cursos e/ou rotações (estágios). De uma maneira geral, os participantes não ficaram satisfeitos com as reuniões de morbimortalidade (59,5%), a existência (ou melhor, a inexistência) de sessões / laboratório anatómico (89,2%), a contribuição para a formação médica pós-graduada (64,9%) nem com a possibilidade de fazer investigação clínica (64,9%).

Formação teórica: análise estatística extra e breve discussão

O grau de satisfação geral com as reuniões multidisciplinares parece estar relacionado com a frequência com que ocorrem nos centros portugueses e, portanto, particularmente com a de Epilepsia (p = 0,001 teste não

paramétrico), DBS (p = 0,006 teste não paramétrico) e tumores do SNC (p = 0,062 teste não paramétrico).

A taxa de satisfação (cuja escala de cinco categorias foi dicotomizada para satisfeito/*satisfied* e não satisfeito/*non-satisfied*) com as reuniões de morbimortalidade parece estar associada ao ano de internato (p = 0,0036 teste

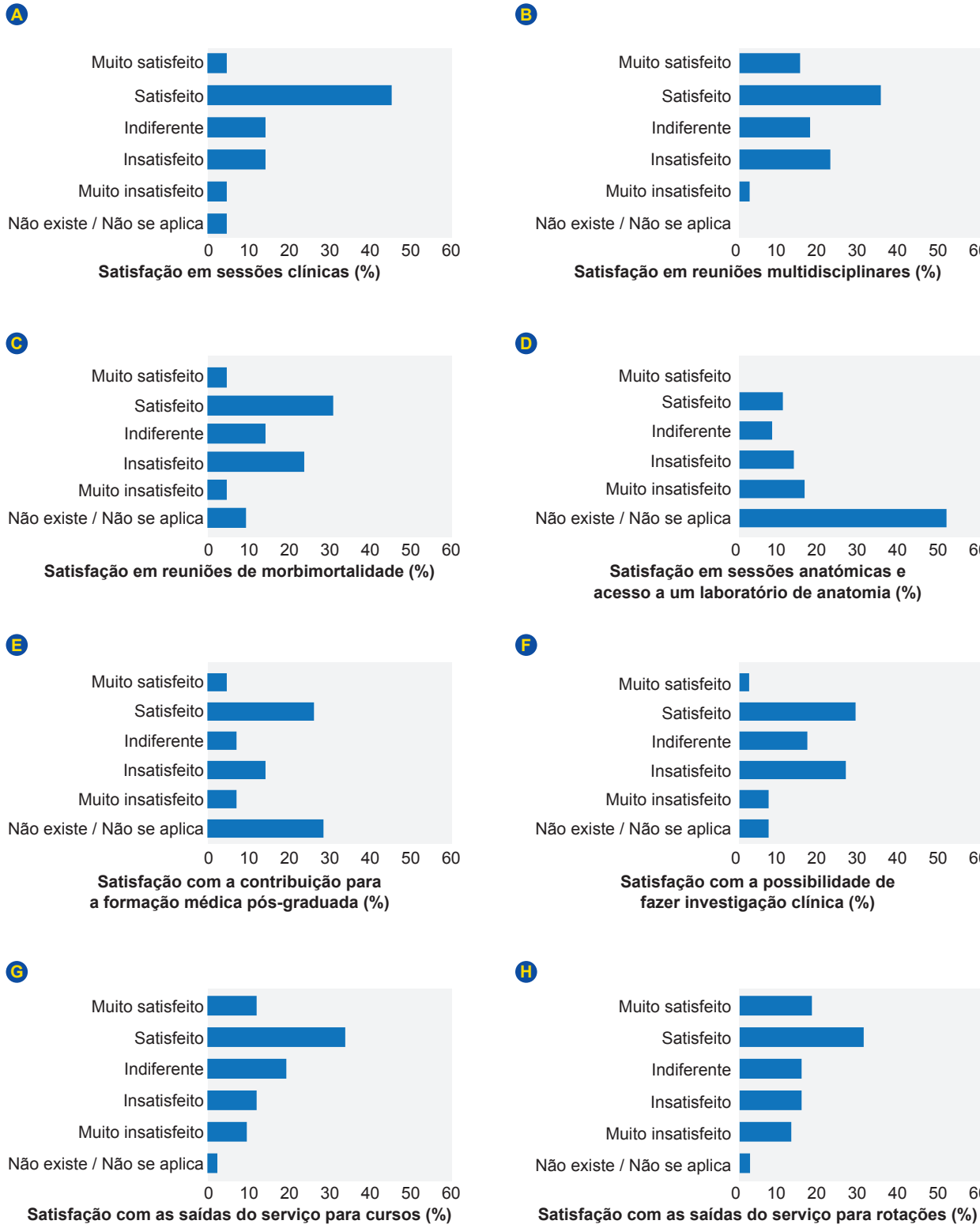

Figura 1 – Histograma do nível de satisfação com sessões clínicas (incluindo *journal clubs*) (A), reuniões multidisciplinares (B), reuniões de morbimortalidade (C), sessões anatómicas e acesso a um laboratório de Anatomia (D), contribuição para a formação médica pós-graduada (E), possibilidade de fazer investigação clínica (F) e saídas do serviço para cursos (G) e rotações (H). No eixo x foram colocadas as percentagens relativamente a graus de satisfação e no y os graus em escala de Likert de cinco pontos variando de "Muito satisfeito", "Satisfeito", "Indiferente", "Insatisfeito" e "Muito insatisfeito" e uma opção "Não existe / Não se adapta".

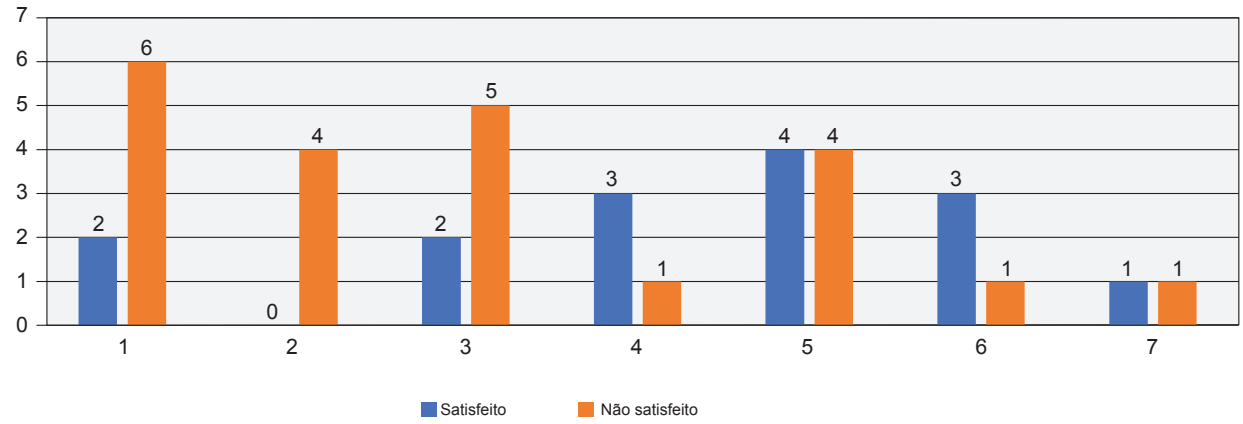

Figura 2 – Satisfação com as reuniões de Morbimortalidade em relação ao ano de internato. No eixo x apresenta-se o ano de internato, sendo o 7 correspondente ao ser recém-especialista. Cada ano mostra o número de internos satisfeitos e não satisfeitos.

não paramétrico) (Fig. 2), o que significa que os internos mais velhos parecem apreciar melhor este tipo de sessões. Além disso, o número de especialistas (p = 0,017 teste não paramétrico) e o número de médicos com doutoramento (p = 0,009 teste não paramétrico) mostraram também uma associação positiva com esta satisfação.

O maior grau de insatisfação expresso em relação às reuniões de morbimortalidade (59,5% *vs* 40,5%), parece estar associado à sua inexistência em alguns centros. Relativamente à sua periodicidade, observa-se uma proporção contrária, com maior satisfação para reuniões com a periodicidade semanal (70% de satisfação) e trimestral (71,4% de satisfação).

A satisfação com a possibilidade de fazer investigação parece estar associada ao número de horas dispensado (e provavelmente possível) por cada interno para estudo (p = 0,008 teste não paramétrico).

O número de horas de permanência no serviço de Urgência, isto é, a realização de maior número de urgências, parece ter uma associação inversa na satisfação face à possibilidade de realização de cursos (p = 0,049 teste não paramétrico) e rotações (p = 0,036 teste não paramétrico).

Formação prática: caracterização

A caracterização da prática clínica está descrita na Tabela 1. Quanto à carga semanal do interno, esta corresponde a cerca de 70 horas e inclui 24 horas de urgência (não descriminando se juntas ou separadas em dois blocos de 12 horas), e horas no bloco operatório (BO) (que constitui, naturalmente, a maior incidência de horas, à exceção das realizadas em urgência).

Formação prática: satisfação

Em relação à formação prática, parece haver maior insatisfação apenas em relação às consultas (56,8%) (ver Tabela 3).

Formação prática: análise estatística extra e breve discussão

Foi realizada análise estatística (com testes não paramétricos) para verificar a associação entre a satisfação e eventuais influenciadores (variáveis contínuas), tais como número de turnos de urgência e de horas de urgência, para a secção da satisfação geral no SU; número de visitas à enfermaria, número de doentes observados/dia, camas, número de horas na enfermaria, número de internos e especialistas (que contem para a distribuição dos doentes), para a secção de enfermaria; número de períodos de consulta, número de doentes observados e número de horas em consulta, para a secção de consulta; número de horas no BO (em cirurgia) e número de internos e especialistas (que operem), para a satisfação geral da secção do BO bem como para a satisfação na participação no BO e ainda para a autonomia progressiva neste.

No caso da consulta, a satisfação geral (ou melhor, a insatisfação) como escala Likert inicial (não dicotomizada), parece estar associada à satisfação quanto ao número de períodos de consultas (p = 0,002), número de doentes observados (p = 0,016) e número de horas de consulta (p = 0,008).

Dados cirúrgicos: caracterização

A Tabela 4 mostra o momento aproximado do internato (em meses) em que cada interno realizou a primeira cirurgia, por tipo de procedimento cirúrgico.

Tabela 3 – Caracterização da satisfação em relação às componentes da prática clínica

	Satisfeito n (%)	**Não-satisfeito** n (%)
Serviço de urgência (SU)	26 (70,3)	11 (29,7)
Enfermaria	25 (67,6)	12 (32,4)
Consultas	16 (43,2)	21 (56,8)
Bloco operatório (BO)	32 (86,5)	5 (13,5)

Tabela 4 – Momento da realização de primeira cirurgia, por procedimento cirúrgico, ao longo da formação especializada do internato médico

Variável	Medida de dispersão	Resultado (mês do internato)	Intervalo (min. - max.) (mês do internato)	Respostas consideradas n (%)
Geral	Mediana (IQR)	1,00 (± 1,00)	0 - 6	36 (97,3%)
Coluna lombar	Média (DP)	11,41 (± 1,50)	2 - 24	32 (86,5%)
Coluna cervical	Mediana (IQR)	13,00 (± 13,00)	2 - 30	29 (78,4%)
Patologia de LCR	Média (DP)	5,95 (± 4,30)	0 - 16	33 (89,2%)
Craniotomia	Média (DP)	6,59 (± 3,88)	0 - 12	35 (94,6%)
Traumatismo craniano	Média (DP)	5,09 (± 4,59)	0 - 16	33 (89,2%)
Patologia oncológica craniana	Média (DP)	16,70 (± 8,15)	3 - 36	29 (89,2%)
Nervos periféricos	Mediana (IQR)	6,00 (± 7,00)	1 - 24	34 (91,9%)
Pediátrica	Média (DP)	19,36 (± 20,00)	3 - 48	24 (64,9%)

Há uma tendência para que a primeira intervenção cirúrgica seja realizada no primeiro mês de internato e, no primeiro ano, em ordem crescente, a primeira cirurgia trauma craniano (5,09 ± 4,59 meses), posteriormente a de patologia de líquor (5,95 ± 4,3 meses), nervos periféricos (6 ± 7 meses), craniotomia (6,59 ± 3,88) e patologia lombar (11,41 ± 1,5 meses). A cirurgia pediátrica é o último grupo de patologias a ser iniciada (19,36 ± 20 meses) e a que apresenta maior inconsistência.

É interessante realçar que existe um intervalo importante de respostas na nossa amostra, e que encontrámos diferenças estatisticamente significativas quando comparámos as respostas de internos dos centros do Norte *versus* Centro / Sul / Ilhas, em relação à primeira cirurgia lombar (p = 0,047), craniotomia (p = 0,020), e especialmente para oncologia (tumores cerebrais) (p = 0,007) e cirurgia de nervos periféricos (p = 0,001), como as demais com o teste U de Mann-Whitney), parecendo sugerir que os internos dos centros do Norte iniciam esse tipo de cirurgias mais tarde (Tabela 5). Numa tentativa de identificar que outras variáveis contribuíram para o *timing* da primeira cirurgia, o ano de internato atual (primeiro ao terceiro ano *versus* quarto, até ao especialista recente) parece ter alguma importância, já que se identificou, por exemplo, que as cirurgias de nervos periféricos se têm vindo a iniciar mais tarde nos anos recentes (p = 0,049, teste U de Mann-Whitney), enquanto que o género do interno, na nossa amostra, não demonstrou ter qualquer impacto.

Dados cirúrgicos: satisfação e análise estatística extra

Em relação à satisfação com a participação no BO, esta parece estar bastante relacionada com os tempos da primeira cirurgia da patologia das vias de líquor ou líquido cefalorraquidiano (LCR) (p = 0,017 Teste de Kruskal-Wallis) e da cirurgia de trauma encefálico (p = 0,011 segundo o teste de Kruskal-Wallis). Para a autonomia progressiva no BO, parece que existe associação apenas com a patologia do LCR, entendendo-se que os que iniciam este tipo de cirurgias mais tarde são os mais insatisfeitos (p = 0,027 segundo o teste de Kruskal-Wallis).

Avaliação

Parece haver satisfação geral com o exame anual (59,5%), mas não com o final (37,8%). Os resultados posteriores podem sofrer um viés pelo fato de a maioria dos participantes ainda não ter passado por esta avaliação final.

De acordo com as diretrizes nacionais, o exame anual

Tabela 5 – Momento da realização de primeira cirurgia, por procedimento cirúrgico, ao longo da formação especializada do internato médico, no Norte *versus* Centro / Sul / Ilhas.

Variável	Medida de dispersão	Resultado (mês do internato) **Norte**	Medida de dispersão	Resultado (mês do internato) **Centro / Sul / Ilhas**
Geral	Mediana (IQR)	1,00 (± 0,0)	Média (DP)	1,5 (± 1,1)
Coluna lombar	Mediana (IQR)	12,50 (± 4,0)	Mediana (IQR)	7,0 (± 15,0)
Coluna cervical	Média (DP)	16,75 (± 5,8)	Mediana (IQR)	11,0 (± 22,0)
Patologia de LCR	Média (DP)	3,84 (± 4,7)	Média (DP)	4,9 (± 3,8)
Craniotomia	Mediana (IQR)	8,00 (± 7,0)	Média (DP)	4,9 (± 6,3)
Traumatismo craniano	Média (DP)	5,58 (± 5,2)	Média (DP)	4,5 (± 3,9)
Patologia oncológica craniana	Mediana (IQR)	18,00 (± 8,0)	Média (DP)	12,2 (± 7,3)
Nervos periféricos	Média (DP)	10,66 (± 7,0)	Média (DP)	4,0 (± 1,8)
Pediátrica	Mediana (IQR)	22,00 (± 17,0)	Média (DP)	17,2 (± 15,2)

deve ser dividido em três partes. Segundo as respostas do questionário, este parece conter parte teórica em 89,2% das instituições, parte prática em 83,8% e avaliação curricular em 94,6% dos casos. É de notar novo viés aqui, pelo facto de haver alguns internos de primeiro ano que poderão ter respondido sem ainda ter passado por este exame.

Outras questões

O trabalho em equipa com rotação (59,5%) ao longo do internato parece ser o modo de trabalho/organização mais comum nos centros de formação, com satisfações nas várias componentes práticas. As restantes modalidades presentes são numa equipa fixa ao longo do internato (13,5%), apenas/sobretudo com o orientador de formação (2,7%) e nenhuma das anteriores (24,3%).

A Tabela 6 mostra as subespecialidades marcadamente presentes nos centros da nossa amostra. Quando questionados sobre a satisfação quanto à possibilidade em se dedicar a uma determinada subespecialidade neurocirúrgica, 48,6% dos internos estão satisfeitos, porém 51,4% não (com um número importante de casos indiferentes ou não existentes / não se aplica).

Em 81,1% dos casos, o questionando afirmou deliberadamente que gostaria de ser contratado como Especialista no mesmo hospital onde está a ser - ou foi - treinado.

DISCUSSÃO

Em geral, o nosso estudo aponta para uma certa tendência de insatisfação quanto à formação teórica, mas de satisfação quanto à formação prática (principalmente cirúrgica) dos internos portugueses.

Quanto à formação teórica, a insatisfação incide especialmente nas sessões anatómicas/acesso a laboratório anatómico (89,2%), que não existem na maioria dos centros de formação, e na participação na formação médica (64,9%) e em investigação clínica (64,9%), já que, apesar da maior dos centros de formação se situarem em hospitais universitários, ligados a uma faculdade de medicina, não existe propriamente um estágio ou rotação neurocirúrgica na maioria das nossas faculdades de medicina portuguesas. Além disso, o recurso a internos para assegurar as urgências dificulta muito a possibilidade de realização de mais investigação científica, de deslocações quer a nível nacional quer a nível internacional para um curso ou estágio, oportunidades educativas extremamente importantes e gratificantes para quase todos internos. Mesmo assim existe, pelo menos durante o último ano de internato, o hábito de permitir que o interno se concentre numa área/subespecialidade, neurocirúrgica de preferência, ou que em que identifica menor conhecimento, dentro ou fora do seu Serviço. Portugal parece estar bastante atrasado relativamente a outros países no cenário da investigação e publicação científica, provavelmente em resultado de menor tradição e de falta de condições essenciais como recursos financeiros, infraestruturas, tempo e disponibilidade para tal. Contudo, esta questão não foi claramente identificada, nomeadamente a relação com publicações e estudos a decorrer em cada centro, dado a especificidade e a extensão já longa do questionário.

Tabela 6 – Caracterização das áreas específicas existentes nos serviços da nossa amostra

Áreas específicas		Resultados (n = 37)
Coluna	n (%)	31 (83,8)
Patologia neurovascular	n (%)	34 (91,9)
Oncologia	n (%)	29 (78,4)
Trauma craniano	n (%)	28 (75,7)
DBS	n (%)	25 (67,6)
Dor	n (%)	20 (54,1)
Epilepsia	n (%)	23 (62,2)
Lesões selares	n (%)	31 (83,8)
Base do crânio	n (%)	26 (70,3)
Pediatria	n (%)	24 (64,9)

A nossa amostra corrobora a média de mais de 60 horas de trabalho demonstrada por Stienen em 2016, o que nos coloca no topo dos países europeus com mais horas de trabalho.[15]

Quanto à formação prática, parece existir maior insatisfação apenas em relação às consultas (56,8%), que se encontra aparentemente associado ao descontentamento face ao número continuamente crescente de doentes encaminhados para consulta neurocirúrgica - número de períodos de consulta (p = 0,002), número de pacientes (p = 0,016) e número de horas em consultas (p = 0,008), que ultrapassam sempre a capacidade de resposta dos hospitais.

Estes resultados estão de acordo com o inquérito da EANS que demonstrou que os internos portugueses estão entre os mais satisfeitos no que diz respeito à organização dos *journal clubs*, ao início da prática cirúrgica e ao contacto com um grande número de patologias.

Apesar da intenção inicial ser avaliar números cirúrgicos propriamente ditos, percebeu-se nos questionários-teste que estes tipos de questões levariam mais tempo a ser respondidas, o que prejudicaria a adesão ao questionário, já em si bastante longo. Assim, decidiu-se avaliar a atividade cirúrgica com base no momento (*timing*) da primeira cirurgia. Os resultados parecem bastante justos e correspondentes ao esperado, até o facto da primeira cirurgia em neurocirurgia pediátrica ser mais tardia, pela sua especificidade, e bastante variável, provavelmente por não ser uma subespecialidade presente em todos os centros, o que obriga muitas vezes os internos a fazerem uma rotação fora. Além disso, não existem muitos casos pediátricos hoje em dia, pelo que a sua maioria são encaminhados para os centros de referência, para que estes também não percam habilidade ou conhecimento sobre o assunto. É interessante perceber que existe ainda um importante intervalo no que diz respeito aos momentos da primeira cirurgia na nossa amostra: quando comparamos os centros do Norte *versus* os do Centro / Sul / Ilhas, verifica-se que os internos dos centros do Norte tendem a iniciar mais tarde determinado tipo de cirurgias. A pergunta que devemos fazer é se

o problema reside em políticas e/ou tradições dos diferentes serviços, na disponibilidade de patologias/casos ou na necessidade de um número mínimo de cirurgias mais adequado.

Limitações

Este estudo apresenta várias limitações.

Apesar da reduzida amostra deste estudo, se pensarmos que anualmente existem cerca de 50 internos e eventualmente 9 a 11 recém-especialistas, 37 respostas correspondem a cerca de 61% a 63% de colaboração desta população-alvo, o que não parece ser um fraco resultado para um questionário longo e potencialmente controverso.

Por se tratar da primeira vez que se elabora e realiza este tipo de inquérito no nosso país, os autores preferiram basear-se noutro já publicado,[9] adaptando-o à realidade portuguesa. Porém, de alguma forma, chegou-se a um ponto em que parecia haver dois tipos de estudo num só, ou dois tipos de perguntas e objetivos distintos – por um lado, caracterizar centros de formação e, por outro, analisar a satisfação com a formação neurocirúrgica - o que levou a um maior número de questões e necessidade de tempo para respondê-las. Esta situação poderá ter comprometido a participação da população-alvo, à partida com pouco tempo livre. A formulação do questionário e o reduzido tamanho da amostra tornaram quase impossível encontrar as associações que se desejavam, o que dificultou bastante a análise estatística. O trabalho apresenta vários vieses, tais como o facto de poder não ter chegado informaticamente a todos os elementos da população-alvo, poder ser sujeito a várias respostas por um mesmo indivíduo, incluir perguntas que poderão não se adaptar tão bem a todos os elementos da população-alvo (como as questões relativas aos tempos cirúrgicos e avaliações, entre outras) e poder sofrer de '*recall bias*', como por exemplo os internos mais novos poderem saber com maior exatidão determinados dados, nomeadamente quanto a *timings* cirúrgicos, dado estarem mais próximos desse momento. Apesar de sabermos que a qualidade da educação não está necessariamente relacionada com a satisfação, acreditamos que seja diretamente proporcional. Os autores reconhecem que a realização de estudos de qualidade passará primeiramente por definir critérios oficiais que ultrapassam a sua competência.

Ainda assim, consideramos ser útil apresentar este estudo, uma vez que poderá constituir um ponto de partida para estudos mais direcionados para determinadas questões, como por exemplo a identificação de associações entre o momento da primeira cirurgia e os números finais da cirurgia, o papel do tutor no internato, etc. e sobretudo, um alerta para a situação atual da formação em Neurocirurgia em Portugal, suspeitando-se que o crescente aumento do número de internos e recém-especialistas nos vários centros possa vir eventualmente a retirar currículo cirúrgico aos internos mais novos.

Em última instância, os autores esperam que este estudo possa servir como ponto de partida para outros estudos mais focados em determinadas áreas da formação, melhorias intra e inter-hospitalares e eventualmente para a elaboração do novo programa de formação do internato médico de Neurocirurgia.

CONCLUSÃO

De um modo geral, os internos portugueses parecem estar satisfeitos com a maioria dos sectores de formação propostos (algumas exceções estão relacionadas sobretudo com a indisponibilidade de alguma formação teórica e excesso de consultas).

Este estudo cumpriu o objetivo principal de ser um ponto de partida para a caracterização dos centros neurocirúrgicos portugueses e da satisfação no internato de formação especializada em Neurocirurgia. Esperamos que possa contribuir para a melhoria e uniformização do ensino da Neurocirurgia em Portugal.

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CONTRIBUTO DOS AUTORES

LND, PPL: Elaboração do estudo e redação do artigo.
CR: Conceção do trabalho, revisão crítica do estudo.
JC: Revisão crítica do estudo.

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.

CONFLITO DE INTERESSES

Os autores declaram não haver conflito de interesses.

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Knowledge and Patterns of Use of Emergency Oral Contraception among Portuguese Female Users of Healthcare Services

Nível de Conhecimento e Padrão de Utilização da Contraceção de Emergência entre as Mulheres Portuguesas Utilizadoras dos Cuidados de Saúde

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ABSTRACT

Introduction: The lack of knowledge about the existence, effectiveness, and supply of emergency contraception as well as access to it, its effective duration and the lack of recognition of the need for its use can prevent women from using it. The aim of this study was to ascertain the attitudes, experience, level of knowledge and information sources about emergency contraception of Portuguese female users of healthcare services.

Material and Methods: We conducted a multicentre, cross-sectional, observational study among 280 Portuguese women users of health care services through an original and anonymous questionnaire composed of 30 questions.

Results: The mean age of the women who replied to the questionnaire was 33.83 ± 8.76 years. Of the observed sample, 27.7% used EC, 50% of whom with no counselling. Despite 92.1% of women claiming knowledge about emergency contraception, only 31.2% of these answered 8 - 10 questions correctly (14 in total). The media were the most frequent source of information (63.4%). Most participants (67.5%) considered that emergency contraception is associated with severe adverse reactions. Furthermore, 76% did not know the time range of effectiveness after unprotected sexual intercourse. Youngest age (p = 0.038), higher education level (p < 0.001), increasing parity (p = 0.051) and previous use of emergency contraception (p = 0.011) were identified as the determinant sociodemographic factors for a higher level of knowledge about emergency contraception.

Conclusion: This study showed that female users of healthcare services were aware of the existence of emergency contraception, but they demonstrated a low level of knowledge about it, especially regarding the correct period of use, place of acquisition and safety issues.

Keywords: Attitude; Emergency Contraception; Health Education; Health Knowledge, Attitudes, Practice; Portugal; Sexual Health

RESUMO

Introdução: A falta de conhecimento sobre a existência, eficácia e fornecimento da contraceção de emergência, bem como a sua acessibilidade, prazo efetivo e a falta de reconhecimento da possibilidade da sua utilização podem impedir as mulheres de a utilizarem. O objetivo do estudo foi conhecer a experiência, atitudes, as fontes de informação e nível de conhecimento sobre a contraceção de emergência entre mulheres portuguesas utilizadoras dos cuidados de saúde.

Material e Métodos: Foi desenvolvido um estudo observacional, transversal e multicêntrico em 280 mulheres portuguesas utilizadoras dos cuidados de saúde, através da aplicação de um questionário original e anónimo constituido por 30 questões.

Resultados: A idade média das mulheres que responderam ao questionário situou-se nos 33,83 ± 8,76 anos. Da amostra em estudo, 27,7% referiram utilização prévia de contraceção de emergência, das quais 50% sem aconselhamento. Apesar de 92,1% afirmar conhecer esta opção, apenas 35,9% respondeu corretamente a entre oito a 10 questões de avaliação de conhecimento (total de 14). Os *media* constituiram a fonte de informação mais frequente (63,4%). A maioria das participantes (67,5%) considera que a contraceção de emergência está associada a efeitos adversos graves e 76% desconhece o intervalo de tempo de eficácia da contraceção de emergência após relações sexuais desprotegidas. A idade jovem (p = 0,038), maior nível de escolaridade (p < 0,001), o aumento da paridade (p = 0,051) e a utilização prévia de contraceção de emergência (p = 0,031) foram os fatores sociodemográficos associados a maior nível de conhecimento sobre a mesma.

Conclusão: O estudo demonstrou que apesar das utilizadoras dos cuidados de saúde de afirmarem ter conhecimento da existência da contraceção de emergência, revelaram baixo nível de conhecimento sobre este tipo de contraceção, particularmente em relação ao período correto de utilização, local de aquisição e questões de segurança.

Palavras-chave: Atitude; Conhecimentos, Atitudes e Prática em Saúde; Contraceção de Emergência; Educação em Saúde; Portugal; Saúde Sexual

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INTRODUCTION

In 2015, a study about contraception practices in Portugal including 4003 women showed that 94% of sexually active women regularly used contraception and 17% had used emergency contraception (EC) at least once.[1] Despite these figures, there is a high number of unwanted pregnancies. In 2017, 14 899 abortions at the woman's request were recorded; among Portugal's geographical areas, the central region was the region with the third highest incidence.[2] Since 2012, there has been a decreasing tendency[2] in unwanted pregnancies, but it is still a significant public health problem with high social impact.[3] These numbers may represent a gap in knowledge about contraception, in dissemination of information and access to or efficiency of family planning.

EC refers to any contraceptive method used after unprotected sexual intercourse to prevent an unwanted pregnancy.[3-5] Nowadays, three options are available in Portugal, in decreasing order in efficacy: the intrauterine copper device, ulipristal acetate and levonorgestrel.[5] In this country, EC is regulated through decree-law 12/2001[6] grants free access to EC in primary healthcare centres, family planning services, hospital gynaecology/obstetrics departments and youth care centres, with the Health National Service coordinating protocols and also in community pharmacies with no need for a medical prescription.

The effective use of regular contraception is the best prevention strategy for unwanted pregnancies. However, in case of unprotected intercourse, EC makes an effective contribution to increased family planning options and to decreasing unwanted pregnancies by 75% - 89%,[1] without also decreasing regular contraception use, according to scientific evidence.[3]

According to several studies, the lack of knowledge about the existence, efficacy and supply of EC as well as access to it, its effective deadline and the lack of recognition of the need for its use can prevent women from using it.[3,7,8] Increasing EC use in the case of unprotected intercourse will mainly depend on increasing awareness of it among both of the general public and healthcare professionals. Few studies[9,10] in Portugal have been carried out in recent decades which assess the level of knowledge about EC and also its method of use, particularly women of reproductive age.

We decided to undertake a study in the central region of Portugal to ascertain the attitudes, experience, level of knowledge and information sources about EC among female users of healthcare services. Our intention is to refine future strategies to improve access to and counselling on reproductive and sexual health, considering the specific needs of our population.

MATERIAL AND METHODS

This is a multicentre, cross-sectional, analytical, observational study, including sexually active Portuguese women between the ages of 18 - 49 years and who are users of family planning services in both primary or secondary health care in Portugal's central region. They all provided their informed consent to participate in the study. Women with cognitive deficit that could compromise understanding of the questionnaire were excluded.

Data was collected through a questionnaire composed of 30 questions; it was anonymous, self-administered and participants had the right not to answer. This questionnaire was adapted from others that had been previously published.[11,16] It was divided into five sections: sociodemographic characteristics (age, marital status, level of education, professional status, residential area, parity); contraceptive habits; EC education and sources of knowledge acquisition; profile of EC use or intended use if necessary; women's perspective on the need for improved EC information dissemination and means of doing so. The assessment of knowledge about EC was made using the questions shown in Table 1. Answers were categorized in "No", "Yes" and "Maybe". The final score was quantified by the frequency of correct answers from a total of fourteen questions.

All the data collected were registered on a database built with Excel® software, making sure participants remained anonymous. The study was conducted according to the principles of the Helsinki Declaration and was approved by the hospital ethics committee.

Statistical analysis was conducted through Statistical Package for the Social Sciences (SPSS®) software v.21.0. In descriptive analysis, categorical variables were presented as percentages and quantitative variables as mean and standard deviation. We used multiple linear regression to identify the sociodemographic characteristics that made an important contribution to the level of EC knowledge. A significance level of $p < 0.05$ and a confidence interval of 95% were considered.

RESULTS

Two hundred and eighty women with an average age of 33.83 ± 8.76 years were included. Of these, 19% were between 18 and 24 years old, 33.6% between 25 and 34 and 47.7% between 35 and 39 (Table 2). Most of them were married (57.4%), professionally active (73.7%) and had one or two children (54.6%) and 7.9% were students. Amongst the surveyed women, 42.5% of surveyed women had completed secondary level education and 37.5% had a university degree. As far as the place of residence is concerned, 54% of the women identified they lived in an urban area. Regular use of a contraceptive method was observed in 72.8% of women, of which combined oral contraception (COC) (61.3%) and intra-uterine devices (13.2%) were the most prevalent (Fig. 1).

Previous EC use was stated by 27.7% of women, of whom 50% with no previous counselling, 22.4% after counselling from their friends and 18.4% based on advice from healthcare professionals. EC had only been used once by 84.6% of the respondents, while 15.4% used it at least twice. The community pharmacy was the purchase location for 97%. Only 17.1% changed or started a regular

Table 1 – Response rate of the knowledge assessment questionnaire about the EC

Questions	Yes (%)	No (%)	Maybe (%)
Is EC the most adequate contraceptive method for occasional sexual intercourse?	11.2	70.4	18.4
Is EC the most adequate contraceptive method when there no fixed sexual partner?	8.8	80.0	11.2
Is EC an alternative contraception method that should be used only when all the others fail?	64.3	21.4	14.3
Is EC an abortive method?	23.1	57.9	19.0
Can EC be used as a routine contraceptive method?	0.8	94.4	4.8
In your understanding, does the EC's level of effectiveness depend on how early it is taken, meaning that it is more effective the sooner it is taken?	62.9	11.3	25.8
Is EC associated with serious adverse effects?	29.4	32.5	38.1
Does EC protect against sexually transmitted diseases?	0.0	94.4	5.6
Is EC harmful for future fertility?	23.0	35.7	41.3
Is EC available without medical prescription in pharmacies?	79.4	7.1	13.5
IS EC provided free of charge in health centres and hospitals?	27.0	25.4	47.6
Can a woman who cannot take birth control pill use EC?	18.4	41.6	40.0
After EC use, is it necessary to wait for the next period to start a method of contraception?	19.2	29.6	51.2
Until when should EC be used after unprotected sexual intercourse?	0 days: 19.4%		
	1 day: 30.8%		
	2 days: 24.4%		
	3 days: 18.6%		
	5 days: 5.4%		
	7 days: 1.4%		

contraceptive method after using EC.

Most women (92.1%) admitted knowing about EC, mostly from the media (63.4%), friends and family (43.1) and healthcare professionals (41.2%) (Fig. 2). Among these women who claimed to have prior knowledge, only 31.2% answered to 8 - 10 questions correctly and only 4.7% at least 11 questions (Fig. 3). Table 3 shows the response rates for every question. Most respondents (67.5%) considered that EC is or may be associated with serious adverse effects and compromises or may possibly compromise women's future fertility (64.3%). Only 27% knew that EC is provided free of charge in healthcare centres and hospitals. Furthermore, 76% did not know what the time range of EC effectiveness after unprotected sexual intercourse was (UPSI), and 50.2% considered that EC was only effective on the same day or the next day after UPSI. EC was considered an abortion method by 23%.

In the multiple linear regression analysis, the youngest age (p = 0.038), increasing parity (p = 0.051), higher educational level (p < 0.001) and prior EC use (p = 0.011) were identified as the determinant sociodemographic factors of a higher level of knowledge about EC (Table 3).

Among the previous users of EC, 73.7% stated that they would use it again in case of UPSI. In 15.8%, doubts remained, while 10.5% rejected using it again. In this group, only 17.1% started or changed their regular contraceptive method after EC use. In the group of previous non-users, 39.9% said they would use EC in case of UPSI, 36.4% remained in doubt and 23.7% rejected its use. In these two groups, the main reasons for not using EC were: fear of side effects in 51.9%, unfamiliarity in 11.9% and being against

Table 2 – Participants' sociodemographic characteristics

Characteristic	%
Age (years)	
18 - 24	19.0%
25 - 29	16.8%
30 - 34	16.8%
35 - 39	17.6%
40 - 49	30.1%
Marital status	
Single/ divorced	42.6%
Married/ cohabiting couples	57.4%
Level of education	
Primary and basic school (9 years)	20.0%
Secondary school (10 - 12 years)	42.5%
University (> 12 years)	37.5%
Professional situation	
Employed	73.7%
Unemployed	18.3%
Student	7.9%
Residential area	
Rural area	46.0%
Urban area	54.0%
Parity	
Nulliparous	37.7%
1 - 2	56.4%
> 2	5.9%

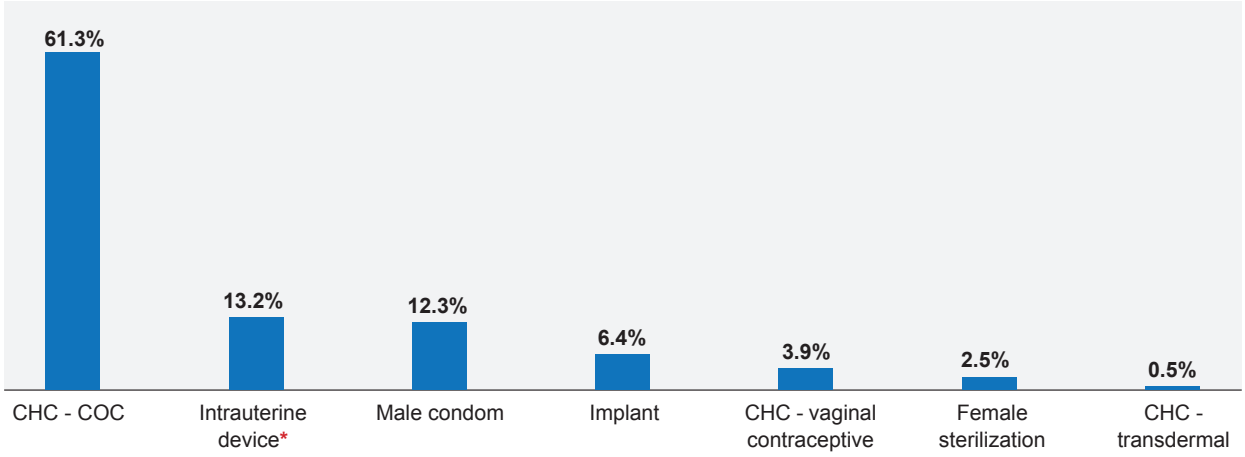

Figure 1 – Characterization of regular contraceptive practice
CHC: combined hormonal contraceptives; COC: combined oral contraceptive
* Intrauterine device includes copper-containing intrauterine device (Cu-IUD) and levonorgestrel-releasing IUDs (LNG-IUDs)

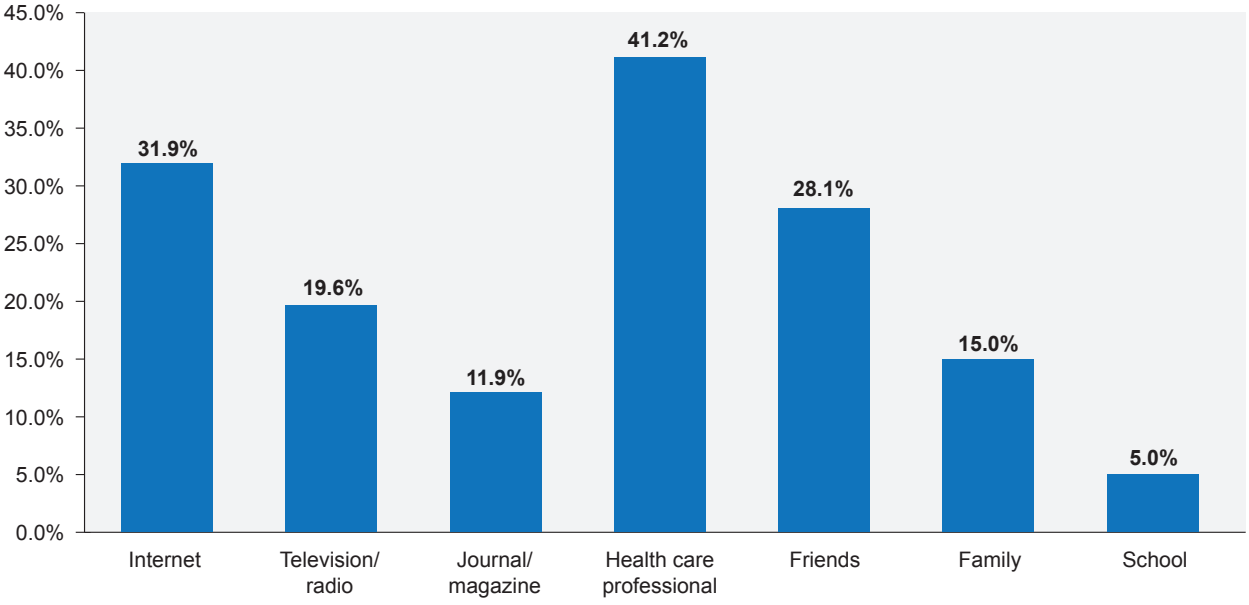

Figure 2 – Sources of information about EC

abortion in 7.1%. When asked about available EC information, 60.6% considered it to be insufficient and 83.9% needed more information, mainly through healthcare professionals (78.6%), internet (31.7%), school/university (26.6%) and television/radio (23.2%).

DISCUSSION

This study exposed a rate of previous EC use of 27.7%, higher than the 17% described in the study on the assessment of contraceptive practices in Portugal in 2015.[1] However, when comparing with a study carried out in five European countries (France, Germany, Italy, Spain and the United Kingdom) with 7170 women aged between 16 - 46 years, the incidence of previous EC use was similar (24%).[11]

The use of EC with no advice from anyone occurred in half of previous users. Use after counselling by healthcare professionals was lower than reported in the literature. Other studies show that, on the first use of EC, the rate of counselling from friends or community pharmacist was 53%[2] and 39% by healthcare professionals.[10] Community pharmacies were the most frequent place of purchase (97%), showing that it is easy to access EC. This is related to the fact that Portugal is one of the 56 countries in the world where EC is an over-the counter therapy.[4] This and the fact that it can be purchased in community pharmacies creates the possibility of anonymity and self-empowerment in its administration. This fact can also justify the low rate of women in this study who started or changed their regular contraceptive method after using EC (17.1%). Direct EC supply through community pharmacies does not allow for counselling on continuous and effective contraception, because pharmacists do not often provide that kind of advice.[3]

Regarding the level of knowledge about EC, 92.1% said they knew about it, like the 88% revealed in a previous

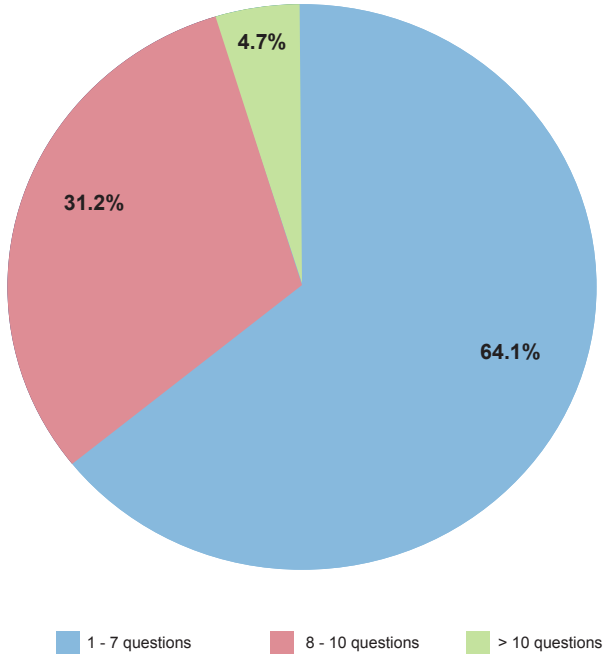

Figure 3 – Proportion of correct answers to the knowledge assessment questionnaire about EC (14 questions)

Portuguese study.[2] Similarly, Leon Han *et al,*[12] in a retrospective study involving 99 223 women aged 15 to 29 years, showed that 83% of women knew about EC in 2014.

The main source of information was the media (63.4%), followed by friends and family (43.1%) and then healthcare professionals (41.2%). Other studies have shown similar results. Rahman *et al*,[13] in a retrospective study composed of 1474 women of reproductive age, found that the main information sources were the media (77.1%), family and friends (33.8%) and healthcare professionals (30.4%). Bastineli *et al*[14] performed a retrospective study composed of 1773 women aged between 15 and 54 years old, who acquired information about EC through friends (41.6%) and the media (18.1%). In Portugal, there is no similar study involving adult female users of health care services. There is one, however, involving Portuguese teenage students, which reports the media as being the main source of information.[9]

The original questionnaire used to evaluate the actual knowledge of participants, despite not being validated, proved very useful in obtaining the intended goals. Although most women claim to know about emergency contraception, a minority revealed effective knowledge in the questionnaire. As these results show, while most women are aware of the existence of EC, the information they are getting is either incomplete or isn't being properly withheld when provided. Objectively, most consider that EC could possibly relate to serious adverse effects or could compromise future fertility and were unaware of the time range of its effectiveness after UPSI. Very few knew that EC is free of charge in primary healthcare centres and hospitals. From the authors' perspective, this low level of effective knowledge essentially limits the use of EC in the case of UPSI. These results were consistent with other studies[13,15] which illustrate the need to improve patient education, especially in terms of accessibility, safety and time range of effectiveness.

In this study, age, educational level, parity and previous EC use were the factors which were significantly associated with a higher level of knowledge, with educational level being the one with strongest impact, as reported by other studies.[13,15] This strong association revels that women who are more educated can have access to more sources of information and thus gain a higher level of knowledge and, ultimately, use.[4,16]

Most participants considered that it was important that availability of EC information should be improved, essentially through healthcare professionals instead of other sources. The same was found in another study,[11] with 80% revealing a need for more information, mainly by healthcare professionals. In this context, it seems important to reflect about the adequacy of information sources. The media, often the source of biased information, tends to override impartial and personalized information from healthcare professionals. Because of this, it seems important to the authors that healthcare professionals working in family planning services, particularly family doctors due to their greater proximity and trust, take every opportunity to give regular contraception counselling, including EC information, not only at the time of prescription.

For the authors, the fact that this evaluation study of the knowledge of female users of health care services about EC is one of the first conducted in Portugal, is seen as a

Table 3 – Multivariate linear regression analysis to determine sociodemographic factors independently associated with EC knowledge

Characteristic	β[a] (95% IC)	*p*
Age (years)	-0.04 (-0.08; -0.002)	**0.038**
Marital status[b]	-0.58 (-1.21; 0.06)	0.075
Parity	0.37 (-0.002; 0.74)	**0.051**
Level of education	1.16 (0.81; 1.52)	**< 0.001**
Professional situation	-0.01 (-0.51; 0.49)	0.965
Residential area	-0.10 (-0.59; 0.39)	0.687
Regular use of contraception	-0.22 (-0.75; 0.32)	0.427
Prior EC use	0.70 (0.16; 1.22)	**0.011**

[a] Possible rage: 0 – 14, increasing value: highest level of EC knowledge
[b] Values: 0 for single/divorced and 1 for married/cohabiting couples

strength. Similar Portuguese studies found focus specifically in an adolescent population. On the other hand, this study allowed improvement strategies for information dissemination to be created alongside the healthcare centres of our target population, like the creation and provision of information leaflets. In future studies it may be interesting to compare these results with some obtained from sexually active women who do not attend family planning services. On the other hand, assessing women's knowledge level regarding recognition of a pregnancy after UPSI would be interesting. The effective use of EC in UPSI depends not only on EC knowledge, but also on recognition of the need for its use, as some studies have shown.[3,15]

This study should be interpreted with the following limitations: first, this study only considered female users of health care services and should be expanded to cover women requesting EC in other places where the characteristics of EC users may be different; secondly, the self-reported data could be associated to recall bias.

CONCLUSION

Although Portugal is one of the countries where emergency contraception is accessible and available, this study showed that female users of healthcare services in Central Portugal were aware of the existence of emergency contraception, but they demonstrated a low level of knowledge about it, especially regarding the correct period of use, place of acquisition and safety issues.

AUTHORS CONTRIBUTION

AR: Draft of the paper.

BV, DT, MJA, JC, ML, AR: Recruitment of patients and data aquisition.

IA: Recruitment of patients.

MCA, ISS: Data aquisition, critical review of the paper.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Using Whole Genome Sequencing to Investigate a Mock-Outbreak of Carbapenem-Resistant Klebsiella pneumoniae in Real-Time

Sequenciação Total do Genoma Como Ferramenta Para Investigar em Tempo Real um Simulacro de Surto por Klebsiella pneumoniae Resistente aos Carbapenemos

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ABSTRACT

Introduction: Healthcare associated infections due to carbapenem-resistant *Klebsiella pneumoniae* (CRKP) are a major concern in Portuguese hospitals. Whole genome sequencing (WGS) can improve infection control, but this practice is not routinely used by hospital clinical laboratories in Portugal. We simulated the investigation of a CRKP outbreak based on WGS, with the aim of determining, in the minimum possible time, genetic relatedness between CRKP clinical and environmental isolates.

Material and Methods: Ten CRKP clinical isolates routinely obtained in the hospital laboratory were used. Forty environmental samples - from sinks and sink drains of ward rooms - were collected. Environmental samples were plated on selective media and presumptive CRKP colonies were isolated. Total DNA was extracted from all putative CRKP isolates and sequenced. Clonal relatedness was determined by multi-locus sequence typing and core genome single nucleotide polymorphism analysis; the presence of carbapenemase genes was evaluated.

Results: Clinical isolates were characterized in 48 hours: eight strains were confirmed as CRKP, of which six were of ST13 and carried bla_{KPC-3}. Environmental samples results were obtained in six days: eight CRKP were isolated from which five were of ST13 and carried bla_{KPC-3}. Clinical and environmental ST13 isolates were highly related: ten (of 11) isolates differed from each other in < 0.001% of 2 172 367 core nucleotides.

Conclusion: In Portugal, routine use of WGS to improve infection control could thrive through collaborative initiatives between hospitals and research institutes.

Keywords: Carbapenem-Resistant Enterobacteriaceae/genetics; Gene-Environment Interaction; Infection Control; Klebsiella Infections; Klebsiella pneumoniae/genetics; Whole Genome Sequencing

RESUMO

Introdução: As infeções associadas aos cuidados de saúde por *Klebsiella pneumoniae* resistente aos carbapenemos (CRKP) são uma preocupação nos hospitais portugueses. A sequenciação total do genoma [*whole genome sequencing* (WGS)] pode ajudar no controlo de infecção, mas esta prática não é comummente utilizada nos laboratórios clínicos hospitalares em Portugal. O objetivo deste estudo foi simular a investigação de um surto causado por CRKP, utilizando WGS. Pretendia-se testar a utilização desta técnica e determinar, no menor tempo possível, relações genéticas entre estirpes.

Material e Métodos: Foram analisados dez isolados clínicos de CRKP. Foram obtidas quarenta amostras ambientais que foram inoculadas em meio seletivo para isolamento de colónias sugestivas de CRKP e depois sequenciado o DNA total dos isolados presumptivamente identificados como CRKP A relação clonal entre as estirpes foi determinada por *multi-locus sequence typing* e análise de *single nucleotide polymorphisms* no genoma *core*. Foi determinada a presença de genes de carbapenemases.

Resultados: Os isolados clínicos foram caraterizados em 48 horas: oito isolados foram confirmados como CRKP. A maioria pertencia ao ST13 (n = 6) e possuía o gene bla_{KPC-3}. As amostras ambientais foram caraterizadas em seis dias: foram isoladas oito CRKP, das quais cinco eram ST13 e continham o gene bla_{KPC-3}. Os isolados ST13 clínicos e ambientais eram muito semelhantes entre si: dez dos 11 isolados diferiam entre si em menos de 0,001% dos 2 172 367 nucleótidos *core* analisados.

Conclusão: Em Portugal, o uso desta técnica em controlo de infecção pode ser implementado através de colaborações entre hospitais e institutos de investigação.

Palavras-chave: Controle de Infecções; Enterobacteriáceas Resistentes a Carbapenémicos/genética; Infecções por Klebsiella; Interação Gene-Ambiente; Klebsiella pneumoniae/genética; Sequenciamento Completo do Genoma

INTRODUCTION

Klebsiella pneumoniae is a Gram-negative *Enterobacteriaceae* and a major cause of healthcare associated infections. Carbapenem-resistant *K. pneumoniae* (CRKP), in particular, is ranked by the World Health Organization in the Global Priority Pathogens List of Antibiotic-resistant Bacteria as a critical pathogen.[1] Data from the European

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Antimicrobial Resistance Surveillance Network (EARS-Net) documented an increasing trend of infections caused by CRKP in 2014 – 2018 in seven European countries including Portugal. Of concern, it was estimated that, in 2018, the rates of CRKP infections in Portugal reached 11.7% of all *K. pneumoniae*, exceeding the average prevalence for Europe (7.5%).[2–4]

Transmission of pathogens within the hospital setting is often associated with patient-to-patient and patient-to-staff-to-patient contacts.[5,6] In addition, environmental reservoirs can also play an important role.[7,8] Sinks and sink drains, for example, have been identified as reservoirs of several bacteria,[9–12] including carbapenemase-producing *Enterobacteriaceae*.[13,14] These findings highlight the importance of screening the hospital environment when investigating the origin and transmission routes of pathogens causing healthcare associated infections.

ONEIDA (An OMICS Network to Prevent and Control Infectious Diseases and Antimicrobial Resistance) is a regional project that aims to be a resource for the benefit of healthcare institutions in the Lisbon area. One of its goals is to collaborate with hospitals to integrate real-time bacterial genotyping, based on whole genome sequencing (WGS), as a tool to improve infection control strategies. While WGS of bacterial pathogens is routinely used to prevent and trace outbreaks in some hospitals worldwide,[15–18] to our best knowledge, such approach is lacking in Portugal.

Here, we describe a pilot study carried out under the framework of ONEIDA that aimed to simulate the investigation of a CRKP outbreak in a Portuguese hospital using WGS.

MATERIAL AND METHODS

Clinical strains

Ten CRKP isolates collected in a hospital clinical laboratory were provided in pure cultures for the simulacrum of the outbreak.

Environmental samples

Forty samples were collected from sinks and sink drains of the wards where the CRKP-infected patients were admitted. These were collected using swabs (FloqSwabs, Copan), which were immediately placed into tubes containing 1 mL of trypticase soy broth with 15% glycerol. Tubes were placed on ice and transported to the research laboratory within six hours of sampling. In the research laboratory, 50 µL of each sample were streaked on each side of a chromID® CARBA SMART (BioMérieux), chromogenic selective plate which enables: (i) presumptive identification of *Klebsiella, Enterobacter, Serratia*, and *Citrobacter* (KESC) based on ß-glucosidase production and (ii) the selective growth of carbapenemase producing *Enterobacteriaceae* (CPE), including *K. pneumoniae* carbapenemase (KPC) and metallo-carbapenemase producers (on the CARB medium side), or OXA-48-type producers (on the OXA medium side). Plates were incubated in aerobic conditions for 18 - 24 hours at 35°C. For each plate, up to ten isolated colonies suggestive of CRKP were picked and streaked onto the CARB medium side of CARBA SMART plates in order to obtain pure cultures. For each sample only one pure culture was selected for further characterization.

DNA extraction and whole genome sequencing

Total DNA was extracted using the MagNA Pure Compact (Roche) automated system. Briefly, for each pure culture, one to three colonies were eluted into 1 mL of PBS solution; 200 µL were transferred into a sample tube containing 200 µL of lysis buffer (Roche) and 0.18 µg of RNase A (Merck) and incubated for 20 min at 37ºC. This mix was then used for total bacterial DNA extraction using the MagNA Pure Compact Nucleic Acid Isolation Kit (Roche), according to the manufacturer's instructions. DNA quality was assessed through determination of A_{260}/A_{280} and A_{260}/A_{230} ratios using Nanodrop. DNA quantification was performed using the dsDNA High Sensitivity Qubit kit (ThermoFisher), according to the manufacturer's instructions. Isolates were sequenced using the Illumina NextSeq 500 platform (Illumina) to an expected coverage of 100-fold using pair-ended (PE) with 150 bp per read.

Quality control and genome assembly

Quality control of raw reads and genome assembly was done using INNUca pipeline v3.1 (https://github.com/B-UMMI/INNUca) under default parameters.

Taxonomic identification, multilocus sequence typing (MLST), core genome tree construction and detection of carbapenemase genes

Bacterial species, genotyping through MLST, core genome tree construction, and the presence of carbapenemase genes were determined using Pathogenwatch (https://pathogen.watch/). Core-single nucleotide polymorphisms (SNPs) were defined based on 1972 genes and 2 172 367 nucleotides, and based on these, a phylogenetic tree was constructed, and a difference matrix was obtained.

Ethics

The study was conducted in accordance with the European Statements for Good Clinical Practice and the declaration of Helsinki of the World Health Medical Association and is integrated in ONEIDA project that was approved by the board of the participating hospital. All samples were numerically coded at the time of sample collection and processed anonymously thereafter.

RESULTS

For this pilot study, ten clinical isolates identified by the hospital microbiology laboratory as CRKP were received in pure culture and 40 unprocessed environmental samples were received in frozen tubes containing the original swab submerged in liquid medium.

The total DNA of the ten clinical isolates was extracted, whole genome sequenced, and results were analyzed and communicated to the hospital within 48 hours (Fig. 1).

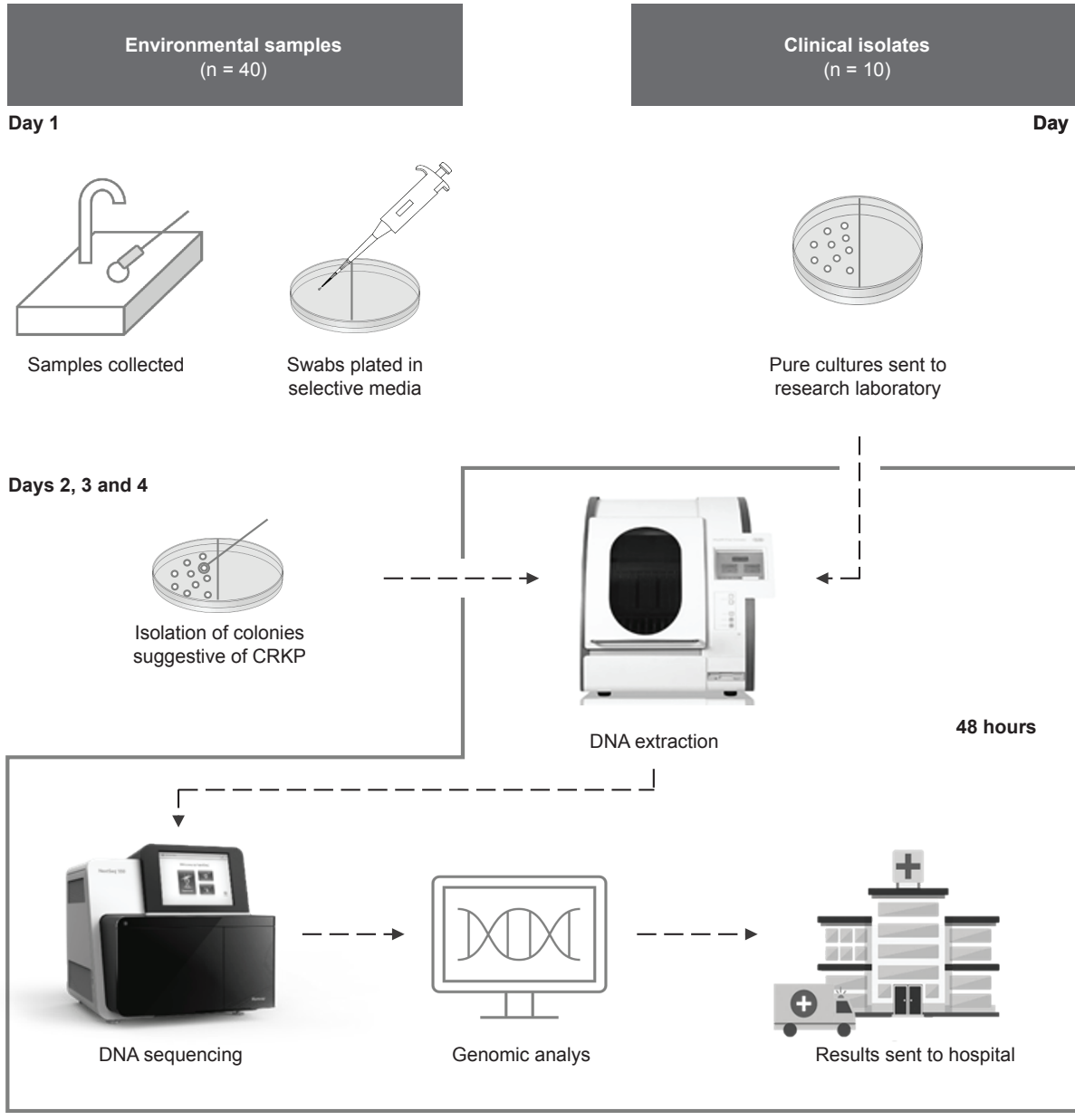

Figure 1 – Timeline of the investigation of a mock-outbreak
CRKP: carbapenem-resistant *Klebsiella pneumoniae*

This included confirmation of species, evaluation of genetic relatedness among strains, and detection of carbapenem resistance determinants.

The results confirmed that eight clinical isolates were CRKP as indicated by the hospital. Two isolates, however, were *Klebsiella aerogenes*. MLST of the eight CRKP identified three clones: ST13 (n = 6), ST14 (n = 1) and ST111 (n = 1). All isolates of ST13 harbored the bla_{KPC-3} gene. Isolates of ST14 and ST111 harbored the $bla_{OXA-181}$ gene (Table 1).

Environmental samples took longer to process as culture and isolation of presumptive CRKP had first to be done. This took four extra days compared to the clinical isolates. In total, sample collection, culture isolation, DNA extraction, sequencing, analysis and communication of results took six days (Fig. 1).

Among the 40 environmental samples, nineteen (three from sinks and 16 from sink drains) yielded colonies compatible with KESC in the selective media. Pure cultures of the 19 colonies were grown, DNA was extracted and whole genome sequencing was carried out (Fig. 1). The nucleotide raw reads of one isolate did not pass quality control (OND468) and were not analyzed. Among the remaining eighteen isolates, eight were confirmed as CRKP and ten belonged to other species: *Enterobacter kobei* (n = 5), *Aeromonas hydrophila* (n = 1), *Citrobacter freundii* (n = 1), *Klebsiella oxytoca* (n = 1), *Raoultella ornithinolytica* (n = 1) and *Serratia marcescens* (n = 1). The medium coverage obtained after assembly of the eighteen isolates was 54-fold.

Six of the eight of CRKP environmental isolates were recovered from sink drains. MLST identified three clones: ST13 (n = 5), ST323 (n = 2) and ST147 (n = 1). All environmental CRKP isolates harbored the bla_{KPC3} gene.

Table 1 – Characteristics of clinical isolates

Sample ID	WGS results		
	Species	ST	Carbapenemase genes
OND451	*Klebsiella pneumoniae*	13	bla_{KPC-3}
OND452	*Klebsiella pneumoniae*	111	$bla_{OXA-181}$
OND453	*Klebsiella aerogenes*	-	-
OND454	*Klebsiella pneumoniae*	14	$bla_{OXA-181}$
OND455	*Klebsiella pneumoniae*	13	bla_{KPC-3}
OND456	*Klebsiella pneumoniae*	13	bla_{KPC-3}
OND457	*Klebsiella pneumoniae*	13	bla_{KPC-3}
OND458	*Klebsiella pneumoniae*	13	bla_{KPC-3}
OND459	*Klebsiella aerogenes*	-	-
OND460	*Klebsiella pneumoniae*	13	bla_{KPC-3}

ST: sequence type

Table 2 – Characteristics of environmental samples with colonies suggestive of CRKP

Stample ID	Isolation site	Colonies suggestive of CRKP?	WGS results		
			Species	ST	Carbapenemase genes
OND462	sink drain	yes	*Klebsiella oxytoca*	nd	nd
OND463	sink drain	yes	*Enterobacter kobei*	nd	nd
OND466	sink drain	yes	*Klebsiella pneumoniae*	13	bla_{KPC-3}
OND467	sink	yes	*Enterobacter kobei*	nd	nd
OND470	sink drain	yes	*Enterobacter kobei*	nd	nd
OND472	sink drain	yes	*Aeromonas hydrophila*	nd	nd
OND474	sink drain	yes	*Raoultella ornithinolytica*	nd	nd
OND482	sink drain	yes	*Klebsiella pneumoniae*	147	bla_{KPC-3}; bla_{GES-5}
OND484	sink drain	yes	*Enterobacter kobei*	nd	nd
OND486	sink drain	yes	*Serratia marcescens*	nd	nd
OND488	sink drain	yes	*Citrobacter freundii*	nd	nd
OND490	sink drain	yes	*Klebsiella pneumoniae*	13	bla_{KPC-3}
OND493	sink	yes	*Klebsiella pneumoniae*	323	bla_{KPC-3}
OND494	sink drain	yes	*Klebsiella pneumoniae*	323	bla_{KPC-3}
OND495	sink	yes	*Klebsiella pneumoniae*	13	bla_{KPC-3}
OND496	sink drain	yes	*Enterobacter kobei*	nd	nd
OND498	sink drain	yes	*Klebsiella pneumoniae*	13	bla_{KPC-3}
OND500	sink drain	yes	*Klebsiella pneumoniae*	13	bla_{KPC-3}

ST: sequence type; CRKP: carbapenem-resistant *Klebsiella pneumoniae*; nd: not determined

The ST147 isolate also harbored the bla_{GES-5} gene (Table 2).

Core genome SNP clustering of all CRKP isolates

A core genome distance-based neighbor-joining tree based on core SNP data was constructed for all CRKP isolates – eight clinical and eight environmental – and the results are summarized in Fig. 2. This analysis was particularly important to evaluate whether isolates sharing the same sequence type were closely related (*i.e.,* differed in a very small number of core nucleotides) and thus cross-transmission might have occurred very recently in time. Alternatively, isolates sharing the same sequence type but differing in several core nucleotides might reflect dissemination of an endemic clone.

Comparison of the 11 isolates (six clinical, five environmental) of ST13, revealed that ten differed from each other in 0-19 nucleotides and, of these, eight had less than six nucleotide differences between them. Notably, isolates OND458 (clinical) and OND498 (environmental) had no nucleotide differences between them. On the other hand, one isolate (OND490) differed in 124 nucleotides or more from all the other ST13 isolates (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15174/Appendix_01.pdf).

DISCUSSION

We simulated the investigation of a CRKP outbreak in a Portuguese hospital, using approaches based on WGS.

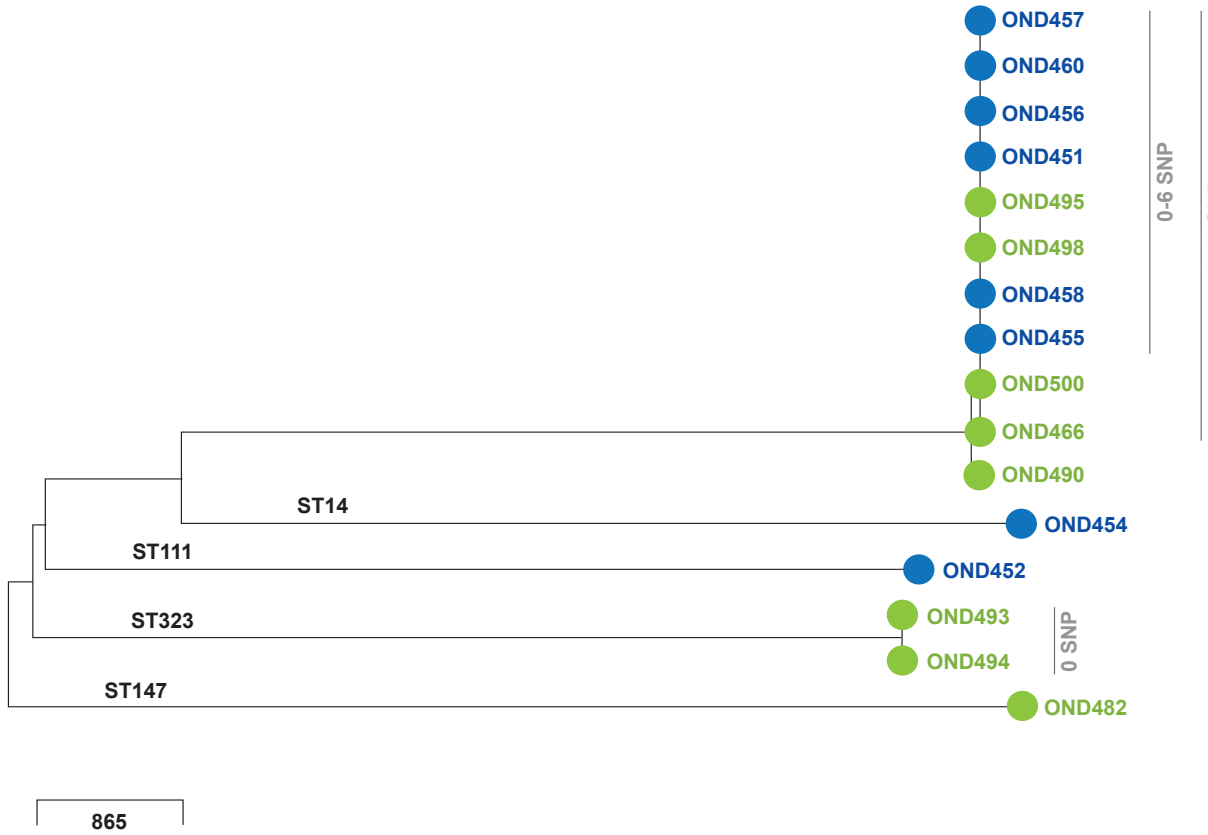

Figure 2 – Core genome distance-based neighbor-joining tree based on core-SNP data of all carbapenem-resistant *Klebsiella pneumoniae* isolated
Blue, clinical isolates; green, environmental isolates; ST: sequence type; SNP: core-single nucleotide polymorphism

Our specific goals were to determine, in the minimum possible time, (i) whether environmental samples contained CRKP and (ii) the genetic relatedness between CRKP clinical and environmental isolates.

The results regarding similarity of clinical isolates were communicated to the hospital within 48 hours. The results regarding the presence of CRKP in environmental samples and its similarity to other CRKP were obtained within six days. Both results were thus obtained within a reasonable time needed for an infection control team to understand how to best tackle a sudden increase of healthcare associated infections due to CRKP.

This study has a major limitation. Only one colony per environmental sample was studied, preventing eventual identification of additional CRKP from these type of samples.

On the other hand, our results support the use of WGS as a high-resolution effective tool to investigate healthcare associated infections and track routes of dissemination in real-time. We advocate that, in Portugal, routine use of such approaches could thrive through collaborative initiatives between hospitals and research institutes. Although the costs associated with WGS of bacterial pathogens are considered high to be used on a routine basis in Portugal for hospital surveillance, they allow for rapid decision-making and implementation of targeted infection control measures. Such actions are crucial to prevent hospital-acquired infections and offset the health and economic costs associated with it. To increase immediate cost-effectiveness, in future studies, the use of matrix assisted laser desorption ionization - time of flight, (MALDITOF) which is available in several hospital laboratories), should be considered for the confirmation of species assignment before DNA extraction and WGS.

This pilot study demonstrated the ability to investigate an outbreak in real time through WGS. The results further indicate that concomitant environmental sampling is informative to determine transmission routes, allowing for rapid decision-making. Collaborative partnerships between hospitals and research institutes should be fostered to accelerate introduction of WGS as an effective tool to support infection control teams.

CONCLUSION

This pilot study highlights the importance of collaborative partnerships between hospitals and research institutes to accelerate and/or introduce effective tools to support healthcare workers in infection control.

AUTHORS CONTRIBUTION

ASS: Conception of the study; environment sample collection; analysis of the results; draft and critical review of the manuscript.

TT: Conception of the study; sample processing; analysis of the results; draft and critical review of the manuscript.

NAF: Conception of the study; sample processing; analysis of the results; critical review of the manuscript.

SPL, JC: Sample processing; critical review of the manuscript.

SB: Conception of the study; environment sample collection; critical review of the manuscript.

MS, CP, RBL: Conception of the study; critical review of the manuscript.

MM: Conception of the study; analysis of the results; critical review of the manuscript.

RSL: Conception of the study; analysis of the results; draft and critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors report no conflicts of interest.

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Hemorragia Peri-Intraventricular Grave em Prematuros: Impacto na Mortalidade e no Neurodesenvolvimento aos 24 Meses

Survival and Neurodevelopmental Outcomes of Premature Infants with Severe Peri-Intraventricular Hemorrhage at 24 Months of Age

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RESUMO

Introdução: A hemorragia peri-intraventricular grave tem sido associada a maior mortalidade e sequelas do neurodesenvolvimento. Mantém-se controverso o impacto da hemorragia peri-intraventricular isolada, sem lesão da substância branca. O objetivo deste trabalho foi avaliar a influência da hemorragia peri-intraventricular grave, associada ou não a leucomalácia peri-ventricular quística, na mortalidade e no neurodesenvolvimento aos 24 meses.

Material e Métodos: Estudo de coorte retrospetiva que incluiu os recém-nascidos com hemorragia peri-intraventricular grave, internados numa maternidade de apoio perinatal diferenciado, entre 2006 e 2015, e dois controlos com a mesma idade gestacional, internados logo a seguir ao caso, sem hemorragia peri-intraventricular. A avaliação do neurodesenvolvimento, aos 24 meses, foi realizada em 99 crianças, com recurso à escala *The Schedule of Growing Skills Scale II* em 52 e à escala de desenvolvimento mental de *Ruth Griffiths* em 47 crianças. Considerou-se défice grave do neurodesenvolvimento: paralisia cerebral, atraso do desenvolvimento psicomotor, surdez com necessidade de prótese auditiva ou cegueira.

Resultados: Foram incluídos 41 recém-nascidos com hemorragia peri-intraventricular grave e 82 controlos. Ocorreram 23 óbitos, 16 (39,0%) nas hemorragias peri-intraventricular graves e sete (8,5%) nos controlos (OR 7,6; IC 95% 2,6 - 20,4; $p < 0,001$). Verificou-se défice grave do neurodesenvolvimento em sete (30,4%) no grupo de hemorragia peri-intraventricular grave e um (1,3%) no grupo de controlos (OR 32; IC 95% 3,7 - 281; $p < 0,001$). Na análise individualizada, a mortalidade foi superior quer nas hemorragia peri-intraventricular grau III com leucomalácia peri-ventricular quística associada (OR 4,4 IC 95% 1,3 - 14,2; $p = 0,015$), quer na hemorragia peri-intraventricular grau IV (OR 12; IC 95% 3,5 - 41,2; $p < 0,001$), em relação aos controlos. Verificaram-se também diferenças no défice grave do neurodesenvolvimento em relação aos controlos (1,3%) na hemorragia peri-intraventricular grau III com leucomalácia peri-ventricular quística associada (75,0%, $p < 0,001$) e na hemorragia peri-intraventricular grau IV (50,0%, $p < 0,001$).

Conclusão: Os recém-nascidos com hemorragia peri-intraventricular de grau IV ou grau III com leucomalácia peri-ventricular quística associaram-se a maior mortalidade e sequelas graves do neurodesenvolvimento.

Palavras-chave: Cérebro/diagnóstico por imagem; Deficiências do Desenvolvimento/diagnóstico por imagem; Hemorragia Cerebral Intraventricular; Recém-Nascido de Muito Baixo Peso

ABSTRACT

Introduction: Severe peri-intraventricular haemorrhage has been associated with higher mortality and neurodevelopmental impairment. The impact of peri-intraventricular haemorrhage alone (without white matter injury) remains controversial. The aim of this study was to evaluate the influence of severe peri-intraventricular haemorrhage, associated or not with cystic peri-ventricular leukomalacia, on mortality and neurodevelopment at 24 months.

Material and Methods: Retrospective cohort study, that included newborns with severe peri-intraventricular haemorrhage admitted to a maternity hospital with differentiated perinatal support between 2006 and 2015, and two controls with the same gestational age, without peri-intraventricular haemorrhage, who were admitted immediately after the case. Neurodevelopmental assessment, at 24 months, was performed in 99 children, using the Schedule of Growing Skills II scale in 52 and the Ruth Griffiths mental development scale in 47 children. Severe neurodevelopmental deficit was diagnosed in the following conditions: cerebral palsy, delayed psychomotor development, deafness requiring hearing aids and blindness.

Results: The study included 41 cases and 82 controls. Out of these, 23 died, 16 (39.0%) in the group of severe peri-intraventricular haemorrhage and seven (8.5%) in the control group (OR 7.6, 95% CI 2.6 - 20.4, $p < 0.001$). Severe neurodevelopmental deficit was diagnosed in seven (30.4%) in the severe peri-intraventricular haemorrhage group and one (1.3%) in the control group (OR 32; 95% CI 3.7 - 281, $p < 0.001$). Individualized analysis showed that mortality was higher in peri-intraventricular haemorrhage grade III with associated cystic peri-ventricular leukomalacia (OR 4.4 95% CI 1.3 - 14.2, $p = 0.015$) and in peri-intraventricular haemorrhage IV (OR 12; 95% CI 3.5 - 41.2, $p < 0.001$), when compared to controls. Differences were also noticed regarding severe neurodevelopmental deficit when compared with controls (1.3%) in grade III peri-intraventricular haemorrhage with associated cystic peri-ventricular leukomalacia, (75.0%, $p < 0.001$) and grade IV peri-intraventricular haemorrhage (50.0%, $p < 0.001$).

Conclusion: Preterm newborns with peri-intraventricular haemorrhage grade IV or grade III with cystic peri-ventricular leukomalacia, had a higher risk of mortality and severe neurodevelopmental impairment.

Keywords: Brain/diagnostic imaging; Cerebral Intraventricular Hemorrhage; Cranial Ultrasound; Developmental Disabilities/diagnostic imaging; Infant, Very Low Birth Weight

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INTRODUÇÃO

Nas últimas duas décadas, assistiu-se a uma melhoria dos cuidados perinatais, atribuída ao uso generalizado de corticoides pré-natais, à utilização de surfactante exógeno e à transferência *in utero* para centros de referência, com consequente aumento da sobrevida nos recém-nascidos (RN) pré-termo (RNPT), mesmo em idades gestacionais no limiar da viabilidade.[1-4] Contudo, apesar do aumento da sobrevida, a morbilidade neonatal permanece elevada, existindo um risco acrescido de complicações clínicas com repercussão no neurodesenvolvimento a curto e longo prazo, como é o caso da hemorragia peri-intraventricular (HPIV).[3-10]

A HPIV normalmente tem início na matriz germinativa sub-ependimária, onde se originam as futuras células neuronais e da glia, nos cérebros imaturos.[10] A matriz germinativa caracteriza-se por apresentar elevada atividade metabólica, com parede endotelial nesta área ainda muito frágil e imatura. Estas vulnerabilidades associam-se à imaturidade de autorregulação cerebral, o que contribui para uma maior suscetibilidade à ocorrência de hemorragia.[7,10]

A ecografia transfontanelar é a técnica de neuro-imagem mais frequentemente utilizada para diagnosticar a HPIV, dado ter elevada sensibilidade, estar prontamente disponível nas unidades de cuidados intensivos neonatais e ser isenta de radiação.[11]

A classificação de Papile *et al* tem sido classicamente usada para avaliar a gravidade da hemorragia.[12] Apesar de estudos recentes sugerirem a utilização de outros sistemas de classificação mais precisos,[13] a classificação de Papile é ainda amplamente usada na orientação, decisão terapêutica e aconselhamento.[14] A HPIV grave associa-se a maior mortalidade e alterações do neurodesenvolvimento, que incluem a paralisia cerebral (PC), défice intelectual e alterações neurossensoriais.[5,7,9,10,15-17] Não obstante, a literatura continua a ser limitada, com metodologias muito heterogéneas e amostras reduzidas devido à elevada mortalidade, mantendo-se controverso se é a HPIV em si a responsável pelas sequelas ou se estas são devidas à lesão da substância branca, que muitas vezes existe associada. Alguns estudos selecionam os doentes pelo peso de nascimento (PN), enquanto outros baseiam-se na idade gestacional (IG), e poucos são os estudos que fazem ajuste para os possíveis fatores confundidores.[8,14,16] Os pais de RNPT com esta morbilidade questionam os neonatologistas, na fase aguda da doença, não só acerca da sobrevida, mas também sobre a possibilidade de sequelas graves, e daí a importância de uma melhor definição deste prognóstico.

O objetivo deste trabalho foi avaliar a mortalidade e o neurodesenvolvimento aos 24 meses de idade dos RNPT com HPIV grave, com ajuste para os cofactores que possam influenciar os resultados, e procurar avaliar individualmente o impacto da HPIV grau IV e do grau III, com ou sem atingimento da substância branca.

MATERIAL E MÉTODOS

Estudo de coorte retrospetiva, realizado numa população de RNPT internados na Unidade de Cuidados intensivos da Maternidade Bissaya Barreto – Centro Hospitalar e Universitário de Coimbra. Foram selecionados retrospetivamente os RN com HPIV grave, com idade gestacional inferior a 34 semanas, internados entre janeiro de 2006 e dezembro de 2015 na Unidade de Cuidados Intensivos Neonatais. Foram igualmente selecionados dois controlos com a mesma IG, sem HPIV, internados imediatamente após os RN com HPIV grave e registados na base de dados própria da Unidade (onde são registados todos os RN internados). A seleção dos RN e a análise dos dados clínico-demográficos maternos, perinatais e do neurodesenvolvimento, foram obtidos a partir do registo da referida base de dados da Unidade, assim como dos registos da consulta disponíveis na plataforma electrónica SClínico Hospitalar (SClínico).

Os RN sem registo no SClínico da avaliação do neurodesenvolvimento foram excluídos do estudo. A existência de malformações congénitas *major* foi considerada também fator de exclusão.

O diagnóstico foi realizado, como é prática na Unidade, através da avaliação seriada com ecografia cerebral, por dois neonatologistas com formação específica e experientes, seguindo o protocolo do consenso nacional.[18]

Foi definida HPIV grave, como a ocorrência de HPIV de graus III e IV, de acordo com classificação de Papile,[12] correspondendo a HPIV grau III a hemorragia ocupando mais de 50% do ventrículo lateral, levando habitualmente à dilatação, e o grau IV indica HPIV associada a enfarte hemorrágico na substância branca ipsilateral.

Nos dois grupos foram analisados os dados clinico-demográficos maternos, perinatais e a morbilidade neonatal.

Os RN cujo PN foi inferior ao percentil 3 para a IG, segundo as curvas de Fenton, foram considerados leves para a idade gestacional (LIG).[20]

A persistência do canal arterial foi avaliada por ecocardiograma de forma sistemática, de acordo com protocolo ou mediante suspeita clínica.[21] Definiu-se sépsis, quando o RN apresentava clínica compatível, associada a parâmetros laboratoriais positivos (contagem de leucócitos superior a 30 000/mm^3 ou inferior a 5000/mm^3 e proteína C reativa superior a 2 mg/dL), com ou sem hemocultura positiva.[22] A enterocolite necrosante foi classificada segundo o sistema modificado de Bell.[23] A displasia broncopulmonar foi definida pela necessidade de oxigenoterapia às 36 semanas de idade pós-menstrual.[24] A retinopatia da prematuridade foi classificada de acordo com a classificação internacional.[25] Avaliou-se a presença de leucomalácia peri-ventricular quística (LPVQ) segundo a classificação de De Vries *et al*.[26]

Todas as crianças que nasceram com IG inferior a 32 semanas ou com PN inferior a 1500 gramas foram seguidas numa consulta de follow-up neurológico da nossa Maternidade e os dados registados no SClínico. Para a avaliação do neurodesenvolvimento psicomotor, aos 24 meses, recorreu-se à escala *The Schedule of Growing Skills Scale II* (SGS-II), nos primeiros seis anos do estudo (52 crianças) e à escala de desenvolvimento mental de Ruth

Griffiths (RG), realizada nos últimos quatro anos do estudo (47 crianças), procedimento atual na nossa Unidade.[27,28] Estas escalas foram realizadas por uma técnica com formação adequada para a sua aplicação, sem conhecimento da presença ou ausência de HPIV, que as realiza de forma sistemática a todas as crianças de risco neurológico seguidas na consulta. A primeira (SGS-II) é um teste de rastreio, que avalia nove áreas de competências e fornece um perfil de desenvolvimento; quando duas ou mais áreas se encontram desfasadas em mais do que um intervalo de idades da folha de perfil o resultado é sugestivo de atraso significativo do desenvolvimento. A escala de desenvolvimento mental de RG avalia seis áreas de competências, sendo os resultados obtidos apresentados como quocientes (das várias subescalas e global) e por idades mentais. Os quocientes das subescalas podem ser convertidos em percentis permitindo expressar o desempenho da criança relativamente à população em geral. Optou-se neste estudo por utilizar o quociente de desenvolvimento global que traduz o resultado das várias subáreas avaliadas.

Foi considerado atraso de desenvolvimento psicomotor quando no teste de RG a criança obteve um quociente de desenvolvimento (QD) global igual ou inferior a 70, ou quando no teste SGS-II o perfil era sugestivo de atraso significativo do desenvolvimento.

O diagnóstico de PC foi estabelecido de acordo com a classificação internacional e pelo sistema de classificação da função motora global.[29,30] As crianças com alguma alteração motora foram avaliadas e seguidas por equipa multidisciplinar que inclui neuropediatra. Foi aceite ausência de PC perante a inexistência de algum grau de perturbação motora aos 24 meses.

A acuidade auditiva e visual foi avaliada de um modo sistemático em consultas da especialidade.

Considerou-se défice/alteração grave do neurodesenvolvimento, quando estava presente pelo menos uma das seguintes alterações: atraso do desenvolvimento psicomotor, PC, surdez neurossensorial com necessidade de prótese auditiva ou cegueira.

Avaliou-se inicialmente o impacto da HPIV grave no neurodesenvolvimento e posteriormente a repercussão, isoladamente, da HPIV de grau IV e a da HPIV grau III com ou sem LPVQ.

Para a análise estatística recorreu-se ao SPSS versão 20. Foi feita a análise univariada pelo teste *t-student para* amostras independentes, para variáveis quantitativas e teste do qui-quadrado/Fisher para variáveis categóricas; foram calculados os *odds ratio* (OR) e respetivo intervalo de confiança *a* 95% (IC 95%). Nas variáveis com significado estatístico, que poderiam contribuir para alterações do neurodesenvolvimento, realizou-se o ajustamento pela regressão logística. Foi considerado um valor de $p < 0,05$ para indicar diferenças com significado estatístico.

Dado que se tratou de um estudo retrospectivo e com a análise dos dados anónima, não foi considerada essencial a aprovação pela Comissão de Ética. No entanto todos os procedimentos foram realizados 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.

RESULTADOS

No período de estudo foram internados 1004 RN com IG inferior a 34 semanas, tendo ocorrido 127 (13%) casos de HPIV, 41 de HPIV grave (4%): 24 de grau III (2,4%) e 17 de grau IV (1,7%).

No mesmo período, houve 538 RN de muito baixo peso. A incidência de HPIV nestes grupos foram 114/538 (21%) e da HPIV grave 38/538 (7%).

Foram avaliados 129 RN, sendo excluídos seis por ausência de registo de avaliação do neurodesenvolvimento no SClínico, e incluídos no estudo 123 RN, sendo 41 RN com HPIV grave e 82 controlos (Fig. 1).

A média da IG foi de 27 semanas, nos dois grupos, e a média do PN foi de 1077g nos RN com HPIV grave e 991g nos controlos (Tabela 1).

Comparando os RN com HPIV grave com os controlos em relação às características perinatais, verificou-se que os primeiros pertencem mais ao género masculino (73,2% *vs* 45,1%, $p = 0,003$), tiveram uma utilização de corticóides pré-natais significativamente inferior (70,7% *vs* 92,5%, $p = 0,003$), nasceram mais fora (*outborn*) da instituição (31,7% *vs* 9,8%, $p = 0,002$) e tiveram maior taxa de reanimação com necessidade de ventilação por pressão positiva e posterior intubação endotraqueal e ventilação mecânica (75,6% *vs* 48,8%, $p = 0,005$). Os fatores de morbilidade neonatal que mostraram diferenças significativas foram a hipotensão (36,6% *vs* 12,2%, $p = 0,002$) e a sépsis neonatal (53,7% *vs* 28,0%, $p = 0,005$), respetivamente nos RN com HPIV grave em relação aos controlos. Foram incluídos no modelo de regressão logística as seguintes variáveis, que podem influenciar o neurodesenvolvimento: corticoides pré-natais, género, *outborn*, sépsis e hipotensão. Os corticoides pré-natais revelaram efeito protetor e apenas se mantiveram como fatores de risco independentes o género masculino, a sépsis neonatal e a hipotensão (Tabela 1).

Ocorreu LPVQ em 11 casos de HPIV grave (26,8%): cinco (29,4%) HPIV grau IV e seis (25,0%) HPIV grau III (Tabela 1). Ocorreram 23 óbitos, 16 (39,0%) nas HPIV graves e sete (8,5%) nos controlos (OR 7,6; IC95% 2,6 - 20,4; $p < 0,001$).

Foram encontrados 11 casos de hidrocefalia, por dilatação pós-hemorrágica, dos quais sete foram submetidos a intervenção cirúrgica para drenagem e quatro não necessitaram de qualquer intervenção. Nos RN que necessitaram de alguma intervenção (reservatório ventricular ou derivação ventrículo peritoneal) ocorreu défice grave do neurodesenvolvimento em quatro, contrariamente aos RN sem necessidade de intervenção, onde não verificaram alterações graves do neurodesenvolvimento. Contudo estas diferenças não se revelaram estatisticamente significativas (Tabela 2).

Obteve-se o resultado do *follow-up* aos 24 meses em 99 crianças (99% dos sobreviventes).

A avaliação do neurodesenvolvimento encontra-se representada na Tabela 3. A HPIV grave associou-se mais a défice grave do neurodesenvolvimento do que os controlos, respetivamente 30,4% *vs* 1,3%, (p < 0,001). Verificou-se maior percentagem de atraso global do DPM, em relação aos controlos, respetivamente 12,5% *vs* 1,3% (p = 0,043) e ocorreu PC em seis crianças, todas no grupo das HPIV graves (p < 0,001). A classificação da função motora global foi de grau I-II em quatro crianças e grau III-IV em duas. Foi diagnosticado apenas um caso de surdez com necessidade de prótese auditiva num controlo e não se registou nenhum caso de cegueira.

A análise individualizada das HPIV graves revelou que a taxa de óbitos foi significativamente superior, quer no grau III (OR 4,4; IC 95% 1,3 - 14,2; p = 0,015), quer no grau IV (OR 12; IC 95% 3,5 - 41,2; p < 0,001), em relação aos controlos (Tabela 4).

Os resultados do neurodesenvolvimento das crianças com HPIV grau IV e grau III, associado ou não a lesão da substância branca, encontram-se na Tabela 4.

Óbito ou défice grave do neurodesenvolvimento foram significativamente superiores nos RN com HPIV grau IV ou com HPIV grau III com LPVQ associada, em relação aos controlos, contrariamente à HPIV grau III sem LPVQ, que não mostrou diferenças no neurodesenvolvimento.

DISCUSSÃO

A taxa global de HPIV e da HPIV grave nos RN de muito baixo peso foi de 21% e 7% respetivamente, sobreponível à da literatura.[1,3,17,31,32]

Dadas as características do estudo, emparelhado pela IG, foi possível avaliar outros potenciais fatores de risco para HPIV. Identificou-se como fator de risco, após regressão logística, o género masculino, a ausência de corticoterapia pré-natal, a sépsis neonatal e a hipotensão com necessidade de inotrópicos, tal como referido na literatura.[10,17]

O mecanismo pelo qual os corticoides antenatais têm um efeito protetor na redução do risco de HPIV pode dever-se a uma ação multifatorial: a aceleração da maturidade pulmonar, com consequente diminuição dos distúrbios

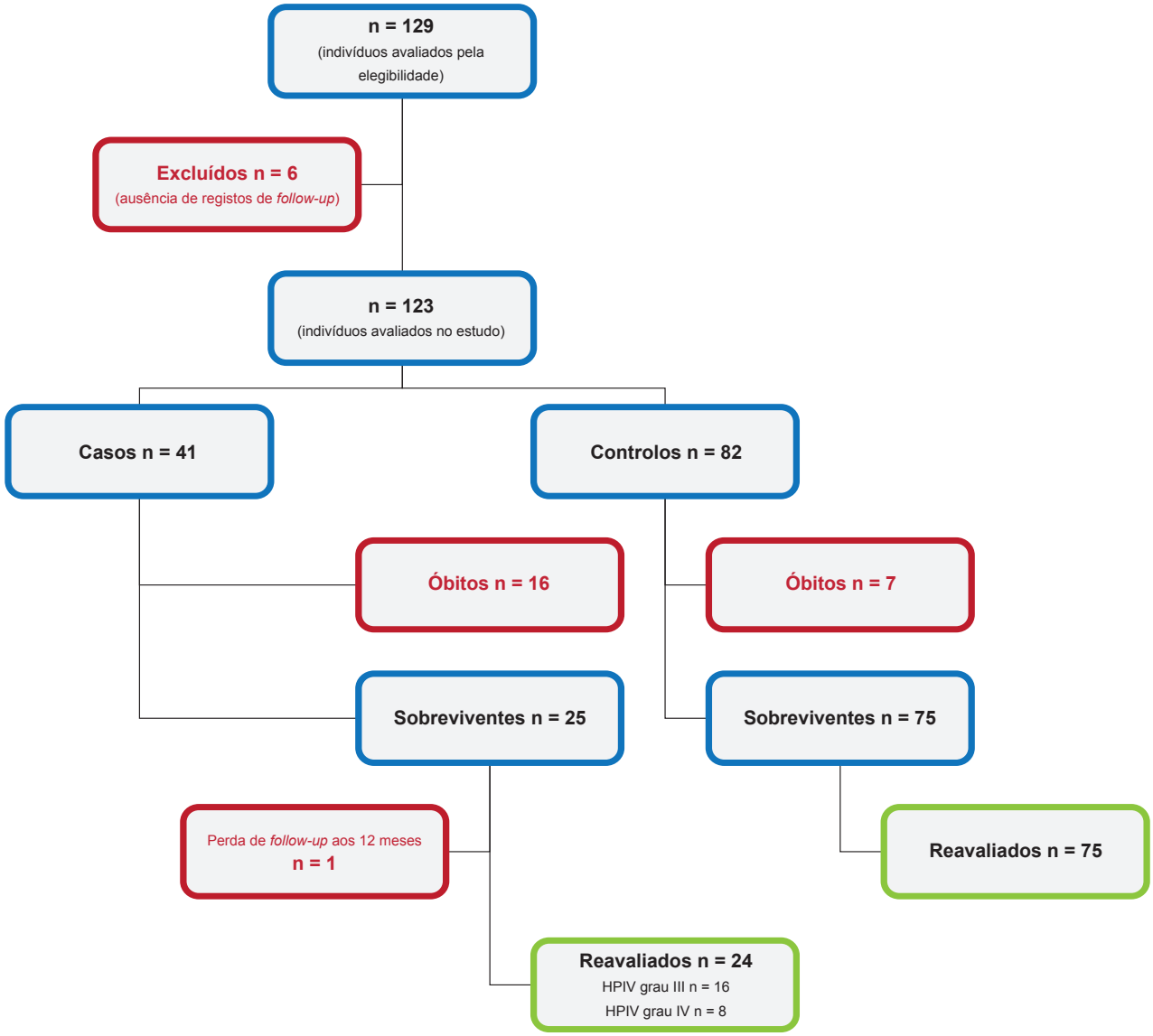

Figura 1 – Fluxograma dos recém-nascidos incluídos no estudo

Tabela 1 – Características clínicas e demográficas dos recém-nascidos com hemorragia peri-intraventricular grave e dos respetivos controlos

Total (n = 123)	RN com HPIV grau III-IV (n = 41)	Grupo Controlo (n = 82)	*p*	OR (IC 95%)	ORa (IC 95%)
Características maternas					
Idade materna (anos) [média (dp)]	29,2 (4,9)	31,2 (5.5)	0,056*	-	-
Primípara n (%)	22 (53,7)	48 (58,5)	0,61£	-	-
Corioamnionite n (%)	5 (12,2)	8 (9,80)	0,758†	-	-
Pré-eclâmpsia/HTA n (%)	7 (17,1)	17 (20,7)	0,63†	-	-
Nível educacional			0,3†		
Básica n (%)	8 (24,3)	15 (19,2)		-	-
Secundária n (%)	11 (33,3)	37 (47,4)		-	-
Universitária n (%)	14 (42,4)	26 (33,3)		-	-
Características perinatais					
Parto - cesariana n (%)	23 (56,1)	45 (54,95)	0,80£	-	-
Corticoides pré-natais n (%)	29 (70,7)	75 (91,5)	**0,003£**	0.22 (0,1 - 0,6)	**0,26 (0,1 - 0,9)**
Índice Apgar < 7 ao 5 min n (%)	9 (23,1)	8 (10,0)	0,056†	-	-
Reanimação profunda (TET) n (%)	31 (75,6)	40 (48,8)	**0,005£**	3.2 (1,4 - 7,6)	-
Características neonatais					
Masculino n (%)	30 (73,2)	37 (45,1)	**0,003£**	3.3 (1,4 - 7,5)	**4.7 (1,6 - 13,9)**
IG, semanas [média (dp)]	27,3 (2,2)	27,4 (2,1)	> 0,99*	-	-
PN, gramas [média (dp)]	1077 (315)	991(306)	0,257*	-	
Outborn n (%)	13 (31,7)	8 (9,8)	**0,002†**	4,2 (1,6 - 11,4)	-
LIG n (%)	4 (9,8)	15 (18,3)	0,218†	-	-
Gemelaridade n (%)	8 (20,0)	21 (25,6)	0,45†		
DMH n (%)	24 (58,5)	47 (57,5)	0,89£	-	-
Sépsis tardia n (%)	16 (39,0)	16 (19,8)	**0,022**£	2,6 (1,1 - 5,9)	**2,8 (1,03 - 7,9)**
DBP n (%)	3 (7,3)	6 (7,9)	0,90†		
PCA tratado n (%)	11 (26,8)	13 (16,0)	0,15£	-	-
Hipotensão n (%)	15 (36,6)	10 (12,2)	**0,002£**	4,1 (1,6 - 10,3)	**8,3 (1,8 - 37,6)**
ENC n (%)	6 (14,6)	8 (9,9)	0.54†	-	
ROP ≥ grau 3 n (%)	0	1 (1,3)	0,46†	-	-
CRIB > 5 n (%)	19 (46,3)	23 (28,0)	**0,044£**	2,2 (1,1 - 4,8)	-
LPVQ n (%)	11(26,8)	0	**< 0,0001†**		

CRIB: *clinical risk index for babies*; dp: desvio padrão; DBP: displasia broncopulmonar; DMH: doença de membrana hialina; ENC: enterocolite necrosante; HPIV: hemorragia peri-intraventricular; HTA: hipertensão arterial; IC: intervalo de confiança; IG: idade gestacional, LIG: leve para idade gestacional; LPVQ: leucomalácea periventricular quística; OR: *odds ratio*; PCA; persistência canal arterial; PN: peso de nascimento; RN: recém-nascido; ROP: retinopatia da prematuridade; TET: tubo endotraqueal; £: qui-quadrado; †: teste de Fisher; * t-*Student* para amostras independentes, com nível de significância $p < 0,05$; ORa: *odds ratio* ajustado.

Tabela 2 – Neurodesenvolvimento das crianças com diagnóstico de hidrocefalia

	RN com hidrocefalia com derivação n = 7	RN com hidrocefalia sem derivação n = 4	*p*
ADPM moderado a grave n (%)	2 (28,6)	0	0,49†
Paralisia cerebral n (%)	4 (42,9)	0	0,23†
Défice neurossensorial n (%)	0	0	
Défice grave n (%)	5 (57,0)	0	0,19†

ADPM: atraso de desenvolvimento psicomotor; RN: recém-nascido; †: teste de Fisher, com nível de significância $p < 0,05$

Tabela 3 – Neurodesenvolvimento das crianças com hemorragia peri-intraventricular grave aos 24 meses

	RN com HPIV III-IV n = 24	Grupo controlo n = 75	*p*	OR (IC 95%)
ADPM moderado a grave n (%)	3 (12,5)	1 (1,3)	0,043†	10,5 (1,1 - 106)
Paralisia cerebral n (%)	6 (25,0)	0	0,001†	
Défice neurosensorial n (%)	0	1 (1,3)	0,56†	
Défice grave n (%)	7 (30,4)	1 (1,3)	0,001†	32 (3,7 - 281)
Défice grave/morte (*) n (%)	23 (57,5)	8 (9,8)	< 0,001†	12,5 (4,7 - 32,7)

ADPM: atraso de desenvolvimento psicomotor; IC: intervalo de confiança; OR: *odds ratio*; RN: recém-nascido (*) Taxas relacionadas com o N total, que inclui óbitos; † teste de Fisher com nível de significância $p < 0,05$

respiratórios, promovendo assim maior estabilidade no fluxo sanguíneo cerebral, e a estimulação da maturação da microvasculatura da matriz germinativa, são algumas das razões apontadas.[33]

Como descrito noutros estudos, o género masculino revelou-se um fator de risco para HPIV.[34] Esta associação tem sido atribuída a melhor maturação neurovascular e aos mecanismos de regulação cerebral no género feminino. Os estrogénios foram associados a redução da lesão cerebral *in vivo* e *in vitro*, e a progesterona mostrou proteção contra lesões isquémicas ou traumáticas em modelos animais.[35-37]

A sépsis é um factor de risco reconhecido para HPIV devido a libertação de citoquinas vasoactivas cerebrais,[38,39] tendo sido identificada como fator de risco independente neste estudo. As citoquinas libertadas podem causar alterações hemodinâmicas no endotélio vascular da matriz germinativa,[10] e a instabilidade hemodinâmica, acidose metabólica e distúrbios de coagulação, num contexto de sépsis, podem levar à lesão do endotélio vascular, já por si imaturo e frágil, da matriz germinativa.

A hipotensão, ao provocar diminuição do fluxo cerebral, pode lesar os capilares da matriz germinativa por reperfusão, tendo esta associação sido reportada não só neste trabalho, como também noutros estudos,[39] como fator de risco para HPIV.

Segundo a maioria dos autores, os RN com dilatação ventricular pós-hemorrágica associam-se a pior prognóstico.[7,40,41] A necessidade de intervenção por dilatação ventricular tem mais sequelas do que os RN cuja dilatação estabilizou sem necessidade de cirurgia.[7,42] No presente estudo, embora a percentagem de défice grave do neurodesenvolvimento fosse maior no grupo que necessitou de intervenção, não se evidenciou diferença estatisticamente significativa, provavelmente relacionado com o número reduzido de casos.

Este estudo demonstrou que os RN com HPIV grave tiveram pior prognóstico, maior mortalidade/défice grave do neurodesenvolvimento, (57,5% *vs* 9,8%, $p < 0,001$) em relação aos controlos. A elevada mortalidade dos RN com HPIV de grau IV (52,9%) esteve de acordo com a referida noutros estudos.[9,15,16,31]

Os sobreviventes com HPIV grave tiveram mais sequelas graves do neurodesenvolvimento, nomeadamente maior taxa de PC e de atraso do desenvolvimento psicomotor (DPM). Estes resultados estão de acordo com o referido por outros autores,[14] contudo, a alta taxa de mortalidade, transversal a todos os estudos, dificulta a realização de estudos de neurodesenvolvimento, pelo limitado número de sobreviventes.

A maioria dos estudos avaliam as hemorragias graves em conjunto, e por vezes, ainda, com lesões parenquimatosas associadas,[31] o que limita o conhecimento sobre o real impacto das hemorragias grau III e IV isoladamente no prognóstico a curto e longo prazo.

A avaliação isolada da HPIV grau IV e grau III, com ou sem lesão parenquimatosa, mostrou que os RN com HPIV de grau III sem LPVQ não apresentavam diferença significativa, quer na PC, quer no desenvolvimento psicomotor, tal como demonstrado por O´shea *et al*,[8] que refere que os défices associados à HPIV poderão refletir a associação

Tabela 4 – Neurodesenvolvimento das crianças com Hemorragia peri-intraventricular grau III e IV

	Controlos n = 75	HPIV grau III sem LPVQ n = 12	HPIV grau III sem LPVQ *vs* Controlos (*p*)	HPIV grau III com LPVQ n = 4	HPIV grau III com LPVQ *vs* Controlos (*p*)	HPIV grau IV n = 8	HPIV IV *vs* Controlos (*p*)
ADPM moderado a grave n (%)	1 (1,3)	0	0,7†	1 (25,0)	0,09†	2 (25,0)	0,023†
Paralisia cerebral n (%)	0	0	➢ 0,99†	3 (75,0)	< 0,001†	3 (37,5)	0,001†
Défice neurosensorial n (%)	1 (1,3)	0	0,7†	0	0,7†	0	0,7†
Défice grave n (%)	1 (1,3)	0	0,8†	3 (75,0)	< 0,001†	4 (50,0)	< 0,001†
Défice grave/morte (*) n (%)	8 (9,5)	5 (29,4)	0,052†	5 (83,3)	< 0,001†	13 (76,5)	< 0,001†

ADPM: atraso de desenvolvimento psicomotor; HPIV: hemorragia peri-intraventricular; LPVQ: leucomalácia peri-ventricular quística; OR: *odds ratio*; (*)Taxas relacionadas com o n total, que incluí óbitos; †, teste de Fisher com nível de significância $p < 0,05$

desta com lesão da substância branca.

Cerca de 80% dos RN com HPIV de grau IV faleceram ou tiveram défice grave. Três dos oito RN que sobreviveram tiveram PC (37,5%), resultados semelhantes à literatura. O atraso de DPM ocorreu em (2/8) 25% dos RN. O pequeno número de sobreviventes com HPIV de grau IV é uma limitação do nosso estudo, contudo é uma dificuldade atual referida pela maior parte dos autores.[43]

Uma limitação deste estudo diz respeito ao facto de se tratar de uma análise retrospectiva. Contudo, o registo rigoroso dos RN numa base de dados da Unidade e a avaliação sistemática destas crianças em consulta, permite reduzir algumas dificuldades, habitualmente relacionadas com este tipo de estudo, tal como as frequentes falhas de informação. A avaliação do neurodesenvolvimento, numa idade precoce (24 meses) e a utilização, numa proporção significativa de casos, do teste de SGS-II (teste de rastreio), constituem outra limitação. Contudo, a ausência neste teste de alterações significativas aos 24 meses colocará como pouco provável a presença de sequelas graves. Neste estudo, poucos casos realizaram ressonância magnética (RM), a qual pode detetar lesões da substância branca e do cerebelo não objetiváveis na ecografia, o que é outra limitação a considerar.

É ponto forte deste estudo a seleção de RN com HPIV grave e controlos emparelhados pela IG. É conhecido o efeito da prematuridade na ocorrência de alterações do neurodesenvolvimento e este tipo de emparelhamento terá permitido avaliar melhor o efeito atribuído à hemorragia. Outro ponto forte a realçar refere-se à avaliação isolada da repercussão no neurodesenvolvimento dos vários tipos de HPIV grave (grau III com e sem LPVQ e grau IV). A avaliação do impacto das hemorragias grau III (com ou sem lesão da substância branca) e grau IV, separadamente, permite dar um contributo para uma melhor informação a dar aos pais, apesar de um possível subdiagnóstico das lesões difusas parenquimatosas, apenas diagnosticáveis pela RM.

Nas unidades de Cuidados Intensivos Neonatais, a definição do prognóstico dos grandes prematuros com HPIV grave é muito complexa, o que constitui uma grande preocupação quer dos profissionais de saúde, quer dos pais.[44,45] Saber se o filho vai sobreviver ou se vai andar autonomamente e ter uma vida normal são as questões mais imediatas de todos os pais, às quais é difícil responder, sobretudo quando os RN associam vários fatores de risco para alterações do neurodesenvolvimento. Os resultados deste estudo representam a realidade de uma unidade de Cuidados Intensivos Neonatais, podendo contribuir para o conhecimento desta problemática, noutras unidades nacionais semelhantes.

CONCLUSÃO

O presente estudo revelou maior mortalidade e sequelas graves do neurodesenvolvimento nas crianças com HPIV de grau IV ou grau III com LPVQ, podendo assim dar algum contributo para a informação que os neonatologistas e outros técnicos possam dar os pais de RN com esta

patologia, na fase aguda da doença.

Salienta-se, a importância da realização de um estudo multicêntrico, prospetivo e de seguimento a longo prazo destas crianças, para a avaliação do real impacto das HPIV graves, com e sem envolvimento parenquimatoso, no seu neurodesenvolvimento.

CONTRIBUTO DOS AUTORES

JA, SP: Contribuição intelectual, análise de dados, participação na escrita do manuscrito.

DF: Contribuição intelectual, revisão do manuscrito.

CR, AT: Contribuição intelectual, participação na escrita 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 actualizada 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 terem fontes de financiamento nem conflitos de interesse.

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Uterine Compression Sutures in Controlling Postpartum Haemorrhage: A Narrative Review

Suturas Uterinas de Compressão no Controlo da Hemorragia Pós-Parto: Uma Revisão Narrativa

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ABSTRACT

Introduction: Postpartum haemorrhage is still the main cause of maternal morbidity and mortality. Many treatments are available, but they may threaten fertility potential. As a uterine sparing procedure, we aimed to review uterine compression sutures in order to better understand when they should represent an appropriate option.

Material and Methods: A comprehensive search in MEDLINE and PubMed databases including the terms 'postpartum haemorrhage' and 'uterine compression sutures' was performed. Results were revised and articles reviewing or presenting case reports of uterine compression sutures to treat postpartum haemorrhage were included.

Results: The first description of uterine compression sutures to control postpartum haemorrhage was published in 1997, by B-Lynch *et al*. After this publication, many others have reported successful management of postpartum haemorrhage with different suturing techniques. Most of them describe success rates above 75% and the possibility of fertility preservation, with cases of uneventful pregnancy after uterine compression sutures already published. Complications associated with each technique are rare.

Conclusion: Uterine compression sutures are effective, safe and simple to perform in an emergent situation and preserve fertility potential in cases of postpartum haemorrhage.

Keywords: Hysterectomy; Obstetric Labour Complications; Postpartum Hemorrhage; Sutures

RESUMO

Introdução: A hemorragia pós-parto é a principal causa de morbimortalidade materna. Apesar dos tratamentos disponíveis, o potencial fértil da mulher pode ser colocado em causa. As suturas uterinas de compressão representam uma terapêutica conservadora do útero. Assim, revimos os tipos de suturas uterinas de compressão para compreender quando devem ser uma opção terapêutica.

Material e Métodos: Foi realizada pesquisa na MEDLINE e PubMed com os termos 'postpartum haemorrhage' e 'uterine compression sutures' separados e em conjunto. Os resultados foram revistos e os artigos de revisão ou descrevendo casos clínicos de suturas uterinas de compressão foram selecionados.

Resultados: Em 1997, B-Lynch *et al* descreveu pela primeira vez as suturas uterinas de compressão para tratamento da hemorragia pós-parto. Desde aí, publicações de diferentes tipos de suturas uterinas de compressão, com registo de casos bem-sucedidos, têm sido publicadas. A maioria reporta taxas de sucesso acima de 75%, com preservação da fertilidade, existindo vários casos de bom desfecho obstétrico posteriormente descritos. As complicações associadas são raras.

Conclusão: Em situações de hemorragia pós-parto, as suturas uterinas de compressão são eficazes, seguras e simples de realizar, preservando o potencial reprodutivo.

Palavras-chave: Complicações do Trabalho de Parto; Hemorragia Pós-Parto; Histerectomia; Suturas

INTRODUCTION

Postpartum haemorrhage is an obstetrical emergency and the major cause of maternal morbidity and mortality.[1–4] It is challenging: it can occur during the first twenty-four hours until twelve weeks after delivery, and estimating blood loss is difficult, as bleeding is not always visible.[2,5] However, its recognition is vital as it requires immediate action.[4,6–9] Uterine atony is the most frequent cause, despite prophylactic measures during the third stage of labour.[8] Other causes are vaginal or uterine trauma, retained placental fragments or coagulopathies.[1,3] Medical treatment is the first approach, but in many situations other interventions are needed, namely when the haemorrhage is severe, requires blood transfusion or causes haemodynamic instability.[4,6,9–14] A surgical approach to uterine atony depends on its cause and may ultimately lead to hysterectomy. Conservative techniques are first attempted to control postpartum haemorrhage and avoid hysterectomy: balloon tamponade, uterine compression sutures, uterine artery ligation, hypogastric artery ligation, and selective radiological arterial embolization.[6,14–16] Despite many pros and cons of these techniques, Doumouchtsis *et al*[6] points that so far there is no evidence to suggest that any method is better than another.

Nevertheless, uterine compression sutures (UCS) are a conservative option and their results in controlling postpartum haemorrhage are encouraging given efficacy and potential to preserve fertility.[6,9–11,13,14,17] Since the first cases presented by B-Lynch *et al,*[18] many others have published results on uterine compression sutures' efficacy in

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postpartum haemorrhage due to uterine atony. These reports describe different suture techniques that may be used to treat uterine atony or haemorrhage due to placenta praevia or accreta.[16,18–31]

Given the importance of uterine compression sutures to preserve fertility potential, we aimed to present the different types of sutures, how they are performed, their complications and impact on fertility. Our final goal was to understand when and how these techniques should be chosen over more interventional surgical procedures and which one is more suitable for each situation.

MATERIAL AND METHODS

We have performed a comprehensive search in the MEDLINE and PubMed databases including articles published between 1997 and June 2018, with the terms 'uterine compression sutures' and 'postpartum haemorrhage' combined. Results included 126 articles whose abstracts were analysed by two authors (Fig. 1). Articles reviewing postpartum atony treatments (including UCS), presenting series of cases or case reports of UCS and/or techniques of UCS, and those presenting results or reviews of uterine compression sutures' results and follow-up were included. In case of disagreement between authors, a third opinion was sought. In some cases, in order to better understand and strengthen the evidence, articles referenced in the selected articles were also included in the final review.

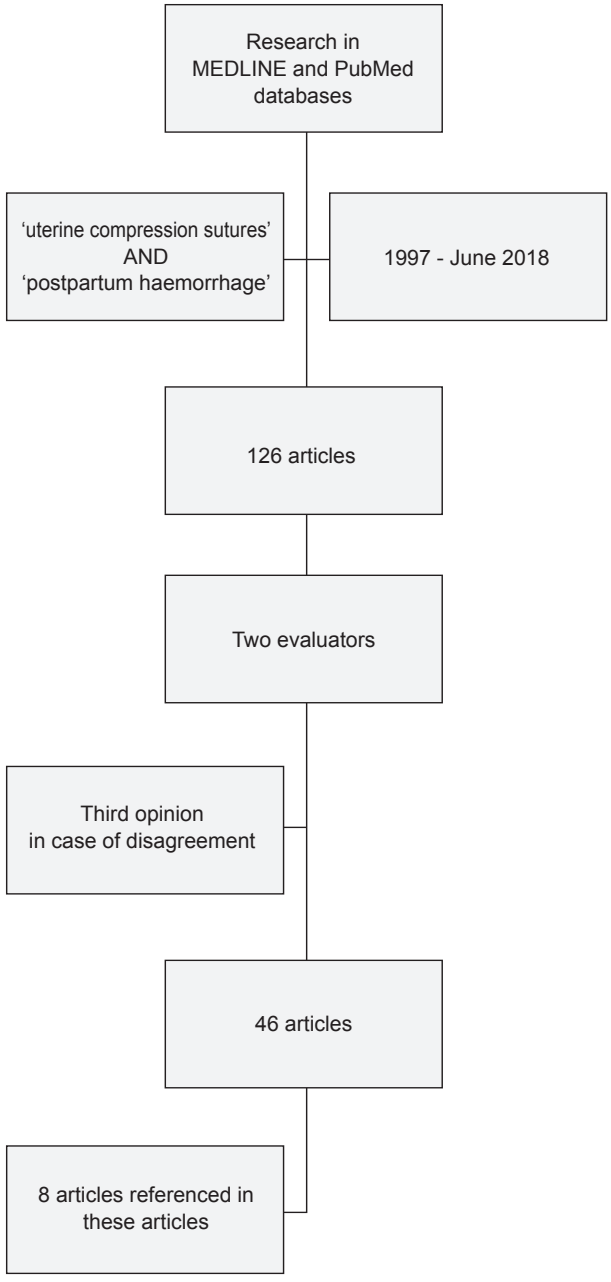

Figure 1 – Simplified article selection flowchart

RESULTS

Types of uterine compression sutures

B-Lynch *et al*[18] were the first to report five women who were successfully treated with uterine sutures after life-threatening postpartum haemorrhage. Regardless of whether the delivery was vaginal or by caesarean section, a Pfannenstiel incision of the abdomen and a lower segment incision of the uterus are needed. The uterus must be exteriorised to assess the bleeding cause, and if uterine atony is the most likely diagnosis, bimanual uterine compression should be performed to verify the technique's potential success.[18,25] The suture begins below the right inferior limit of the uterine incision, inserting the needle through the anterior uterine wall. The needle is exteriorized again in the anterior uterine wall above the superior border of the incision. The thread then goes to the uterine posterior wall, passing above the fundus, and then the needle is inserted through the posterior wall in a point corresponding to the thread's anterior exit. Afterwards, the needle should be inserted a few centimetres laterally to the entry point, and the thread is then passed longitudinally through the fundus to the anterior wall. The needle is then inserted above the left superior margin of the uterine incision through the uterus wall and exits on the inferior margin (parallel to the first stitches). An assistant should compress the uterus while the surgeon pulls the thread firmly and applies a strong knot (Fig. 2). Finally, the uterine incision should be closed.[18,25] B-Lynch *et al*[18] also advocate UCS in cases of placenta praevia, performing an independent figure-eight suture anteriorly, posteriorly, or both, prior to the application of their suturing technique.

Most of the techniques reported after B-Lynch's work present subtle variations. Bhal *et al*[26] have described two sutures which start by inserting the needle below the uterine section and passing it through the uterine wall until it reaches the posterior side of the uterus. Then, the thread passes above the uterine fundus exteriorly until the anterior side of the uterus, where the needle is inserted above the uterine section and crosses the anterior wall, exiting below the section in a point superior to the initial inserting needle spot. The procedure was repeated on the other side, and two knots were tied in the anterior-inferior margin of the lower uterine segment.[26] Nelson and Birch,[32] bearing in mind the risk of lateral thread slipping above the fundus during

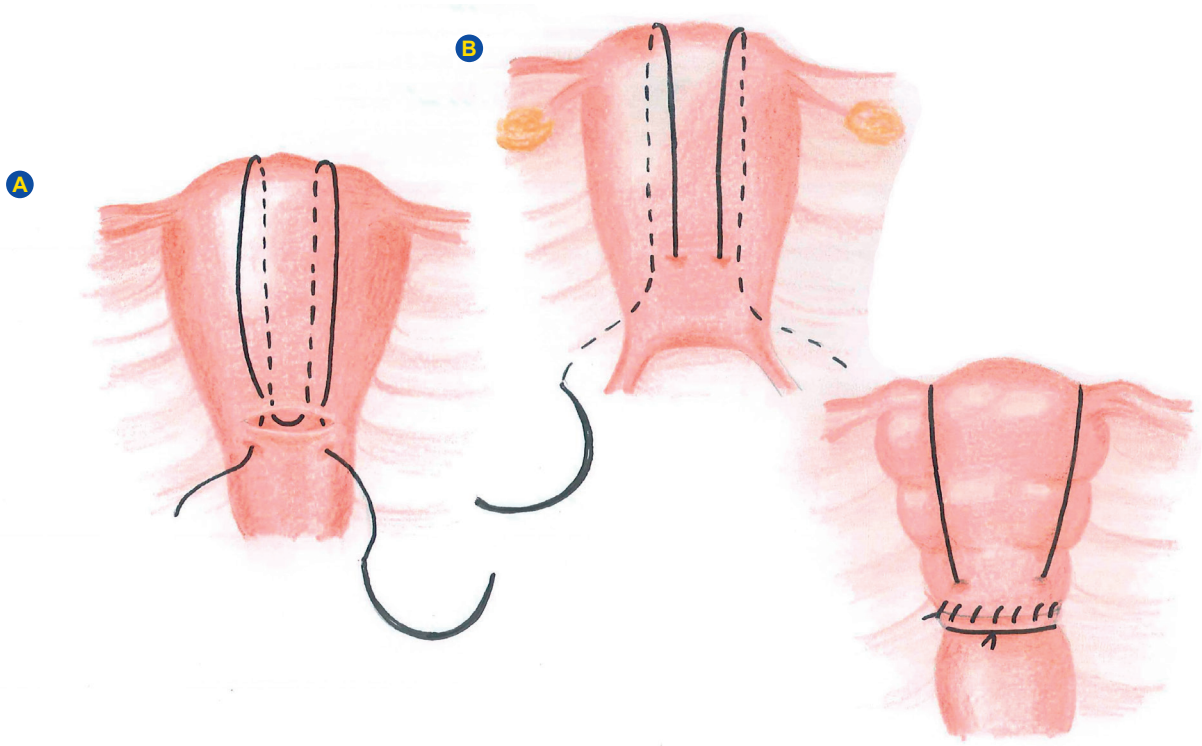

Figure 2 – B-Lynch suture.[54] (A) Anterior view of the uterus before performing the knot, showing how the thread passes through the uterine wall; (B) Posterior aspect of the uterus before performing the knot; (C) Anterior view of the compressed uterus after performing the knot and the suture of the hysterotomy.
Dashed lines represent the suture on the posterior aspect of the uterus.

uterine involution, have proposed a suture initiated like in the technique by B-Lynch, but when the needle comes out anteriorly above the hysterotomy site, the thread is not passed above the uterine fundus. Instead, the needle is introduced through the uterine fundus until its posterior aspect. Then, the thread runs along the posterior wall and the needle is inserted again in the lower segment of the uterus through the uterine cavity until the anterior wall, exiting below the uterine incision (Fig. 3A). The same steps are repeated on the other side, and knots are tied tightly on the anterior aspect of the uterus.[32] Marasinghe *et al*[31,33] have also claimed to avoid the sutures slip off the uterine fundus, using two sutures beginning anteriorly below the uterine section. The needle is passed through the uterine cavity until its posterior side, where the thread is passed over the fundus until the anterior wall; there, the needle is inserted below the fundus, passing the uterine cavity until its posterior wall; the thread is then passed over the fundus, reaching the anterior aspect, where a tight knot is performed (Fig. 3B). The procedure is repeated on the other side.[31,33]

More recently, the use of a double B-Lynch suture was described as successful in 14 cases where only one suture was unable to control haemorrhage. Authors performed the original B-Lynch technique and the second suture 0.5 cm from the lateral side of it.[34] Another modification of the technique was performed in 19 women in whom Mansoura-VV sutures were applied. They use two longitudinal sutures that pass through the uterine cavity below the hysterotomy incision (one left and one right). The knots are tied in the uterine fundus as the thread is divided in two, creating a V-shaped

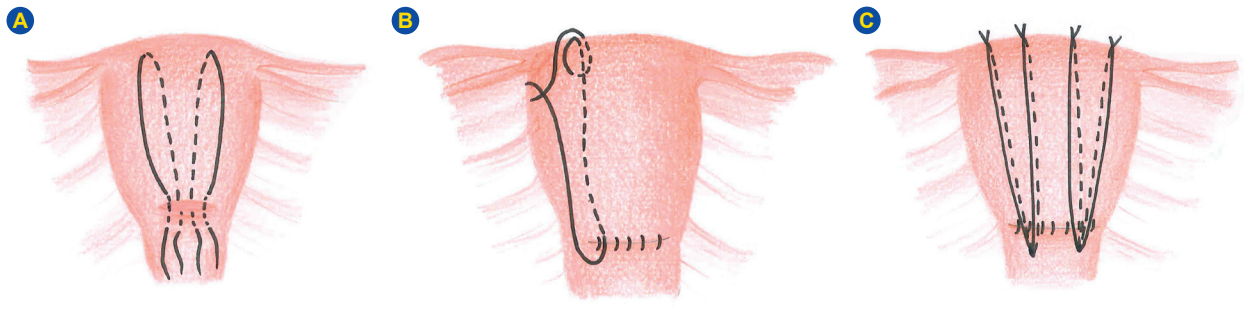

Figure 3 – Longitudinal sutures variations. (A) Nelson and Birch's description of uterine compression sutures.[32]; (B) Marasinghe *et al* technique to avoid thread slipping over the uterine fundus.[33]; (C) Mansoura VV-suture.[21,35]
Dashed lines represent the suture on the posterior aspect of the uterus.

suture (Fig. 3C).[21,35] El-Sokkary *et al*[22] have published another variation: it begins on the anterior aspect of the uterus below the hysterotomy, but the thread, after exiting above the hysterotomy, crosses the uterine fundus on the contralateral side and is inserted in the posterior wall on that same side. On the posterior aspect of the uterus the suture is performed as B-Lynch description but on the anterior wall the thread crosses again creating an X-shaped suture.[22]

The association of B-Lynch suture with other postpartum haemorrhage control techniques have also been described. Nelson and O'Brien[29] have reported five cases in which B-Lynch's compression sutures were performed but were not successful, so they've applied an intrauterine Bakri balloon – 'uterine sandwich technique'. According to the authors, after placing the balloon, the hysterotomy incision is closed and the balloon is filled with normal saline while observing the uterine response to tamponade.[29] Similar descriptions also support the success of these combined strategies.[36–38]

Cho *et al*[19] have published their experience in controlling postpartum haemorrhage due to uterine atony, but also abnormal placentation, after caesarean delivery. This technique uses multiple square sutures to get anterior and posterior uterine walls closer so that no space is left between them and haemorrhage is controlled. It is performed in the bleeding area, where the anterior wall is punctured until the posterior aspect of the uterus. There, 2-3 cm laterally, the uterine wall is punctured again until the anterior wall, where 2-3 cm below or above a new point of the wall is punctured until the posterior side. Again, the needle is inserted until the anterior aspect of the uterus so that a square/rectangle is formed after the knot. This suture is repeated four to five times from the uterine fundus until its lower segment in cases of uterine atony. If placenta accreta is the bleeding cause, two to three areas in it are selected, and the square suture is performed; in cases of placenta praevia, the sites with heavier bleeding are selected, and sutures are performed.[19] Two years after Cho's publication, Hayman and colleagues[24] have described a technique in which two to four longitudinal compression sutures are placed from the anterior to the posterior uterine wall (Fig. 4). A straight needle enters the anterior wall below the uterine incision until the posterior wall, and a knot is made on the uterine fundus. This procedure can be performed on the other side so that two or more longitudinal sutures wrap the uterus and control haemorrhage. If an incision was not performed, the needle is inserted in the place where it should be. Hayman *et al*[24] also highlight the possibility of a transverse suture near the cervix when haemorrhage originates at that level, namely, in cases of placenta praevia: the needle passes through the anterior wall approximately 3 cm below the inferior caesarean section and 2 cm from the lateral border; on the posterior wall, the needle should then be inserted 1 cm medially on the same exit level passing through the uterine walls until the anterior one; the same procedure is repeated on the contralateral side.[24]

Ouahba *et al*[28] have published a technique with four sutures to control postpartum haemorrhage in a series of 20 cases of uterine atony. The procedure consists of four uterine sutures inserted from the anterior to posterior wall; the needle is again inserted until the anterior wall approximately 8 cm from the initial point, and a tight double knot is tied on the anterior aspect of the uterus. Two of the sutures are transverse (one in the middle of the fundus and one in the lower segment) and two are oblique and placed 2-3 cm medial from the uterine horns.[28] Hackethal *et al*[30] have also described a technique where the suture enters the uterine cavity from the anterior to the posterior wall. The needle passes 2 to 4 cm from the initial point through the uterine cavity until it reaches the anterior aspect of the uterus, where a double knot is performed, resulting in a U-transverse suture. The number of sutures used depends on the uterine size and the persistence of the bleeding.[30]

Being different from the ones already described, Pereira's suture includes longitudinal and transverse sutures around the uterus that do not cross the uterine wall, being inserted only superficially in the serous membrane and the subserous myometrium (Fig. 5).[27] Two to three transverse sutures should be performed first, starting from the superior one: it starts anteriorly by inserting the needle in the subserous myometrium and passing it through the broad ligament to the posterior side of the uterus; then, some bites of the subserous myometrium should be taken, and the

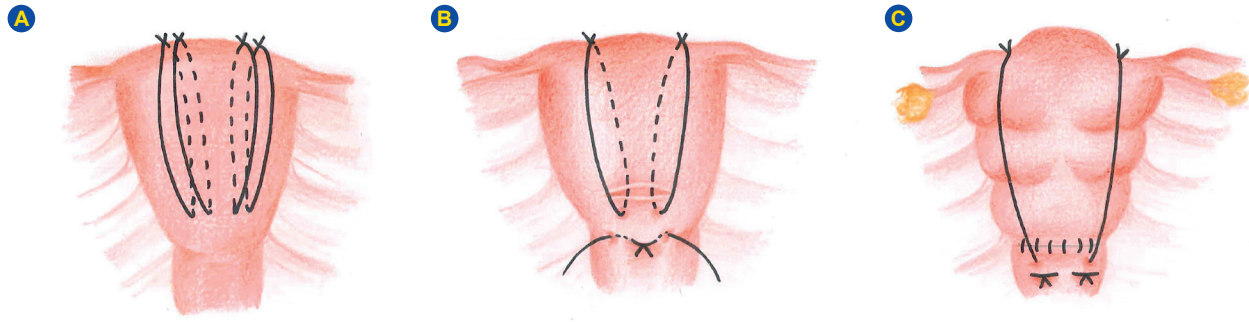

Figure 4 – Scheme of Hayman's *et al*[24] suture technique. (A) Anterior aspect of the uterus after a vaginal delivery, when no hysterotomy was needed.[24]; (B) and (C) Anterior aspect of the uterine wall illustrating the transverse sutures also described by Hayman *et al*[24]; (B) Aspect before the suture of the uterine incision; (C) Final aspect after performing the knots of both transverse sutures and closure of the hysterotomy.
Dashed lines represent the suture on the posterior aspect of the uterus.

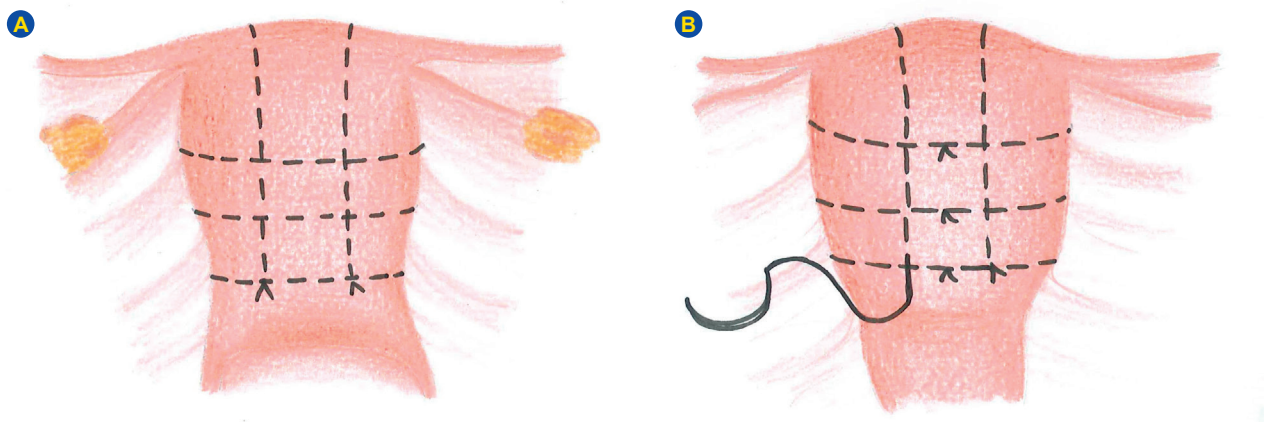

Figure 5 – Pereira's suture[27]. (A) Posterior view; (B) Anterior view.

needle crosses the broad ligament again to the anterior wall, where the knot is performed. The number of bites depends on uterine size and tension that is perceived as necessary to compress the uterus. The most inferior transverse suture is used as an anchor to the knots of the longitudinal sutures, which should start on the posterior wall. After performing a knot to the lowest transverse suture, several bites of the subserous myometrium are taken until the anterior side of the uterus, where it should end. This procedure can then be repeated two to three times.[27] A modification of Pereira's technique has been recently described in two patients: longitudinal sutures were performed according to B-Lynch's technique, but additional transverse sutures included superficial bites involving only the serous membrane and the subserous myometrium like those used by Pereira.[23]

Effectiveness of the different techniques

Kayem *et al*[17] reported the efficacy of UCS after reviewing 199 deliveries which required UCS in the United Kingdom between September 2007 and March 2009. The most frequent technique chosen was the B-Lynch suture, and a modified version of it was the second most frequent option. The overall failure rate was 25%, and in these cases, a hysterectomy was necessary; the rate of failure did not differ significantly according to the suturing method. A higher risk of hysterectomy was observed when there was a prolonged delay of 2 to 6 hours between delivery and UCS, and when there was a vaginal delivery, maternal age was 35 years or older or when the woman was multiparous.[17]

A systematic review in 2007[6] analysed the success rates of conservative techniques to control postpartum haemorrhage, and a success rate of 91.7% for UCS was estimated. It was noted that there was no statistically significant difference in success rates between conservative procedures, and therefore, the authors advised clinicians to use the least invasive, easiest and quickest approach, namely, balloon tamponade.[6] These results have been recently corroborated by a Çetin *et al*[39] when comparing Hayman suture and Bakri balloon tamponade.

Ghezzi *et al*[40] reported eleven cases of massive postpartum haemorrhage in which ten were successfully controlled with UCS, and only one patient ultimately required a hysterectomy. More recent articles reviewed comparative studies and case series and estimated a success rate of UCS of 71% to 75%.[14,41] Variations of B-Lynch suture have also been reported as effective or even more effective than the original technique.[22,34,35]

Although a randomized control trial comparing the different types of UCS' effectiveness is lacking, the results published so far point to a success rate between 36% and 98% (the majority of them above 75%).[14,34,35,38] The technique chosen may not be the only contributor to different results. The time between the beginning of the haemorrhage, its diagnosis, previous medical treatment and the time by which the UCS are applied may be vital to success.[14,34,35,38]

Complications related to uterine compression sutures

From the beginning, the importance of ensuring that compression of the uterus controls active haemorrhage before performing the suture has been outlined.[18,25] Otherwise, the uterine suture may not be effective.

The cases described by Nelson and O'Brien,[29] which involved the uterine sandwich technique, were all successful in controlling postpartum haemorrhage, but the authors outlined one patient who developed endomyometritis and another with postpartum oliguria. The risk of endometritis has also been reported by Suzuki *et al*[42] when evaluating perioperative complications of UCS in their hospital.

As the thread is passed through the uterine cavity in Hayman's and Cho's procedure, there is at least, a theoretical risk of blood trapping within it.[25,43] Cho's suture could also interfere with physiologic uterine involution, and it was already reported to be associated with pyometra and uterine cavity synechiae.[25,43–45] Also, a higher risk of uterine ischaemia and necrosis seemed to be associated with UCS combined with vessel ligation, so long-term follow up in these women is advisable.[16,46,47] Pereira's technique does not involve suturing the anterior and posterior wall together, and the needle only enters the subserous myometrium without penetrating the uterine cavity. Therefore, the aforementioned risks are overcome and the risk of infection is reduced.[27,43] Given the small size of the bites, it is believed that the risk of bowel or omentum trapping in the suture is low. This is a minimal risk even with other techniques due to

the applied compression and the fact that suturing materials are absorbed in a few weeks.[43]

Given the absence of larger trials and the reporting biases regarding complications, it is important to bear in mind a possible higher risk of complications than what is reported in literature.

Results for future fertility and pregnancy outcome

Data regarding menstrual cycles and fertility post-UCS are scarce since follow-up is mostly short and only a few cases of long follow-ups have been reported. A 2013 review[48] about fertility rates and pregnancy outcomes after postpartum haemorrhage treated with UCS estimated a fertility rate ranging from 10% to 100%, noting lower performance with B-Lynch's and Hayman's modified procedures. Authors have explained this wide range with the information described in case reports, case series or even studies performed by surgeons who first described the techniques. Despite these important biases, they stated that the majority of pregnancies were mostly uneventful, but the most frequent mode of delivery was an elective caesarean section. It seems safer and ensures the quick management of postpartum haemorrhage complications since recurrence is not negligible.[48]

These results are comparable to those obtained by Doumouchtsis *et al*.[49] By analysing six studies assessing menstrual and fertility data after UCS, they estimated that more than 90% of women resumed normal menstruation. Between women who revealed a desire for a subsequent pregnancy, approximately 85% achieved conception. They noted that this desire may have been inadequately reported and that many women did not want another pregnancy after a life-threatening event.[49] Another review in 2013[50] evaluated the outcomes of subsequent pregnancies after UCS – Hayman's suture and the multiple square suture technique – at their hospital. They compared 42 women treated with UCS with 139 untreated women during their previous delivery by caesarean section. They concluded that all women treated with UCS who got pregnant conceived naturally and that pregnancy outcomes were similar (namely prematurity rates, estimated blood loss and rate of UCS in subsequent deliveries). It is important to point out that pelvic adhesions in a subsequent caesarean delivery were more prevalent in women who were treated with UCS. Despite the relevant number of women evaluated, this study only compared outcomes in pregnant women and did not assess the potential effect of UCS on fertility.[50]

Cowan *et al*[51] compared adverse outcomes in subsequent pregnancies in women with postpartum haemorrhage treated with a B-Lynch suture *versus* women treated with

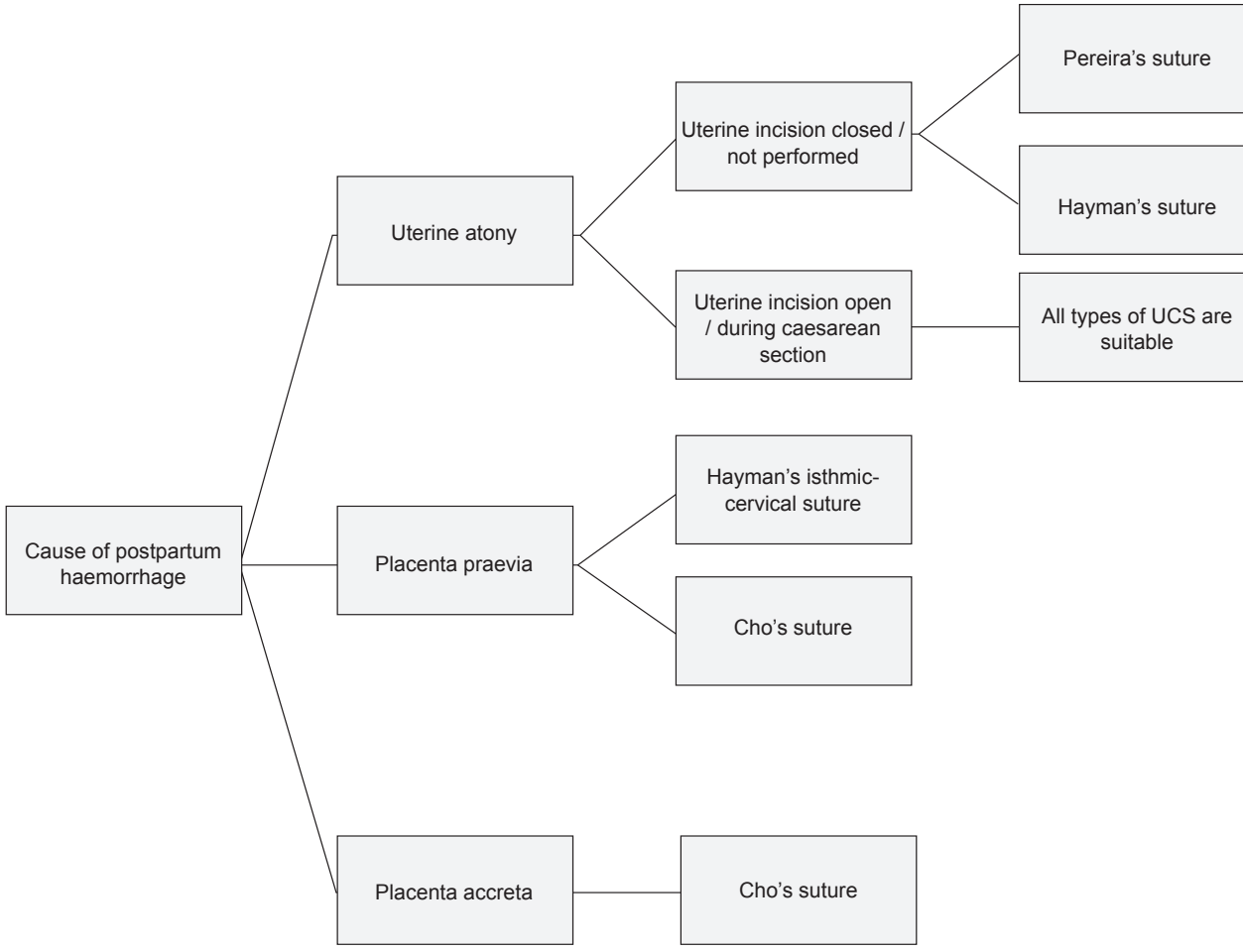

Figure 6 – Simplified flowchart on how to choose a uterine compression suture technique

another method (artery ligation and uterine artery embolization). They found no significant difference between groups, and they also found no association between the use of B-Lynch compression sutures and adverse outcomes in future pregnancies.[51] Recent series of cases also support the possibility of successful pregnancy after UCS.[34]

The overall conclusion from small reports to bigger reviews is that most women resumed normal menses and that those women who desired another pregnancy were able to conceive naturally with comparable outcomes to other women who did not undergo UCS on their previous caesarean delivery.

DISCUSSION

The choice of an optimal uterine suture technique

Although it exists, the evidence supporting UCS has poor quality, which has been a main conclusion of many studies. Nevertheless, almost every article and recent review about the conservative management of postpartum haemorrhage agrees with the relevant success rate of UCS and the simplicity of performing them under an emergent situation, even by obstetricians with less training.[9,12,16,20,25,26,28,32,34,40,43,48–50]

Despite many similarities, these techniques have some specific characteristics that can make them more suitable in some situations. When choosing a UCS, at first, it is important to determine whether the uterine incision is already closed or was not performed (cases of postpartum haemorrhage after vaginal delivery in which a laparotomy was considered necessary). In these situations, Pereira's or Hayman's sutures are possible options[24,27](Fig. 6).

Equally important is the perceived cause of haemorrhage, since all UCS may be applied in cases of uterine atony, which implies the exclusion of other causes of postpartum haemorrhage. On the other hand, Hayman's technique[24] includes a possible isthmic-cervical suture to control haemorrhage due to placenta praevia and Cho's suture[19] can also control postpartum haemorrhage due not only to placenta praevia but also placenta accreta (Fig. 6).

Ultimately, the surgeon's experience and knowledge about each technique will define the best approach since there are no randomized or controlled trials to compare the different types of UCS. It's also important to note that the option of a UCS should be considered as soon as possible when pharmacological measures fail to control postpartum haemorrhage and a surgical option is considered.[6,7,10,12–14,16,20,41,43,50,52,53]

CONCLUSION

Uterine compression sutures are a conservative treatment option to control postpartum haemorrhage that should be used when first line medical treatment isn't enough. They can be performed either after vaginal and operative delivery, do not require interventional radiology support and may be performed shortly after the onset of haemorrhage. The main reasons favouring this conservative surgical technique are its effectiveness but also its simplicity, while preserving women's fertility potential. The data published so far suggests that, after UCS almost all women resumed normal menses and could conceive spontaneously. Subsequent pregnancies tended to be uneventful. Also, complications described after UCS were rare.

Since there are no randomized control trials comparing UCS with other surgical conservative procedures or even comparing different types of sutures, critical judgement is vital. Nevertheless, the UCS success rates and its simplicity should lead to its inclusion in PPH treatment protocols before more complicated or aggressive surgical approaches like hysterectomy. It is vital to teach UCS in order to prepare every obstetrician to know when and how to perform each technique.

AUTHORS CONTRIBUTION

MLC: Research, data analysis, draft of the paper and critical review.

JB: Research, data analysis and critical review of the paper.

MJM: Critical review of the paper and design of the original images.

LGM: Concept of the work and critical review of the paper.

COMPETING INTERESTS

The authors report no competing interests.

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A Rare Cause of Hemoperitoneum in Pregnancy

Uma Forma Rara de Hemoperitoneu na Gravidez

CASO CLÍNICO

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ABSTRACT

Spontaneous hemoperitoneum in pregnancy is a rare complication resulting in high maternal and fetal morbidity and mortality. The authors describe the case of a pregnant woman presenting at 32 weeks of gestation with abdominal pain and free abdominal fluid on ultrasound. Laparotomy revealed a hemoperitoneum resulting from a suspected ruptured varices on the uterine posterior surface. A live newborn was delivered by cesarean-section, and hemorrhage was controlled with sutures and compression. Clinicians should be aware of this diagnosis when a pregnant woman presents with abdominal pain, anemia or hypovolemic shock. Early intervention will avoid poor outcomes for both the mother and the fetus.

Keywords: Hemoperitoneum/diagnosis; Hemoperitoneum/etiology; Hemoperitoneum/surgery; Pregnancy; Pregnancy Complications/diagnosis; Varicose Veins/complications

RESUMO

O hemoperitoneu espontâneo na gravidez é uma complicação rara, associado a morbimortalidade materna e fetal elevadas. Os autores descrevem o caso clínico de uma grávida que, às 32 semanas de gestação, recorreu ao serviço de urgência por dor abdominal, apresentando líquido livre na ecografia abdominal. Na laparotomia identificou-se um hemoperitoneu com aparente origem num vaso varicoso da face posterior do útero. Fez-se cesariana, resultando um nado-vivo. A hemorragia foi controlada com pontos hemostáticos e compressão. Os médicos devem considerar este diagnóstico perante uma grávida com queixas de dor abdominal, anemia aguda ou sinais de choque hipovolémico. Uma intervenção precoce prevenirá maus desfechos maternos e fetais.

Palavras-chave: Complicações na Gravidez/diagnóstico; Gravidez; Hemoperitoneu/cirurgia; Hemoperitoneu/diagnóstico; Hemoperitoneu/etiologia; Varizes/complicações

INTRODUCTION

The term 'spontaneous hemoperitoneum in pregnancy' (SHiP) describes a condition where significant bleeding occurs inside the abdominal cavity with no apparent cause during pregnancy or puerperium.[1] Hereby, we describe a clinical case of SHiP during the third trimester of pregnancy.

CASE REPORT

A thirty-five-year-old woman, primigravida, was admitted at 32 weeks of pregnancy with acute persistent abdominal pain in the lower quadrants, nausea and vomiting.

On admission, her vital signs were stable and body temperature was normal. The gynecological examination was unremarkable. On abdominal examination, she referred pain on palpation of the left iliac fossa and both abdominal flanks. An ultrasound scan revealed a live fetus, with both normal body movements and amniotic fluid; the placenta was posterior, distant from the internal *os*. The second trimester blood tests showed a hemoglobin level of 12.5 g/dL. A new red blood cell count was performed, revealing a hemoglobin level of 9.6 g/dL, high leucocyte count (17.9 x 10^9/L) and C-reactive protein of 5 mg/L. Analgesia was instituted but there was no reduction in pain intensity.

On re-evaluation, the patient mentioned shoulder pain, which changed with lateral decubitus. An abdominal ultrasound examination allowed the detection of abdominal free fluid with no obvious organ injury (Fig. 1).

Corticosteroids were administered in order to induce fetal lung maturation.

A multidisciplinary evaluation with a general surgeon concluded that an acute appendicitis could not be excluded, so an urgent appendicectomy was decided due to acute abdomen, in the context of a suspected perforated appendicitis.

The opening of the parietal peritoneum revealed hemoperitoneum with a moderate amount of blood and clots. On inspection, the appendix was normal and prophylactic appendicectomy was undertaken. Subsequently, a low transverse incision was performed, showing a reddish-purple uterine surface, suggestive of a uterine wall hematoma (Fig. 2). A low incision was then made in the uterus, revealing normal amniotic fluid and a 1950 g newborn was delivered. The Apgar score was 1/5/7 at 1', 5', 10', respectively. The fetal umbilical cord artery pH was 7.345. The placenta was normal, complete and there was no evidence of abruption. The uterine cavity was also normal. On posterior uterine wall inspection, the presence of a hematoma surrounding the inferior uterine segment was observed, extending to the left uterine horn, broad ligament and ipsilateral round ligament, with small bleeding spots associated with varicose veins (Fig. 3). The hemorrhage was controlled with hemostatic sutures on the posterior uterine wall, over the varicose veins, and moderate compression with a surgical dressing

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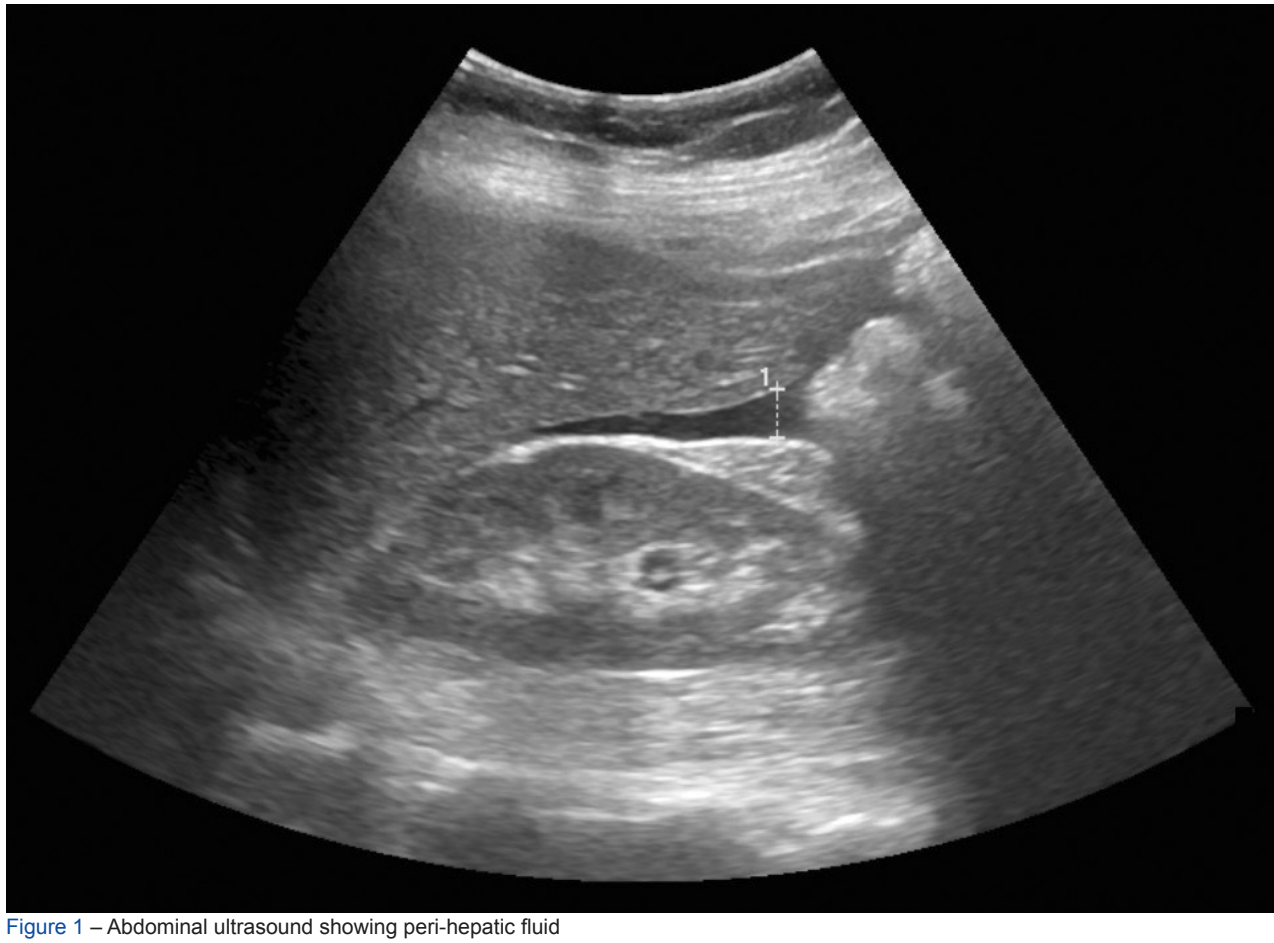

Figure 1 – Abdominal ultrasound showing peri-hepatic fluid

and tranexamic acid. A hemostatic powder was also used. The arterial blood gas test during surgery showed a maternal hemoglobin level of 6.6 g/dL and she received both erythrocyte (2) and plasma (1) transfusions. The patient was then transferred to the Intermediate Care Unit, where she remained for three days, for monitoring and recovery from anemia. During the post-operative period there were complications due to the presence of remnant blood clots in the abdominal cavity, which caused some abdominal discomfort and increased inflammatory markers (leukocytosis

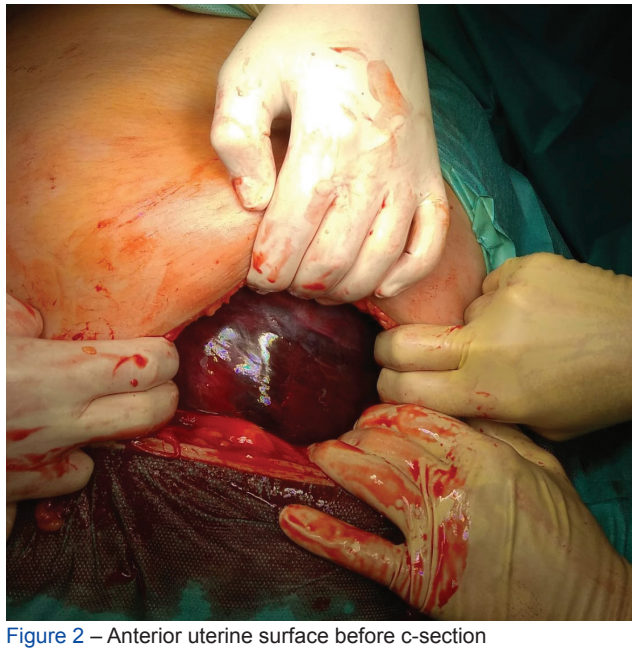

Figure 2 – Anterior uterine surface before c-section

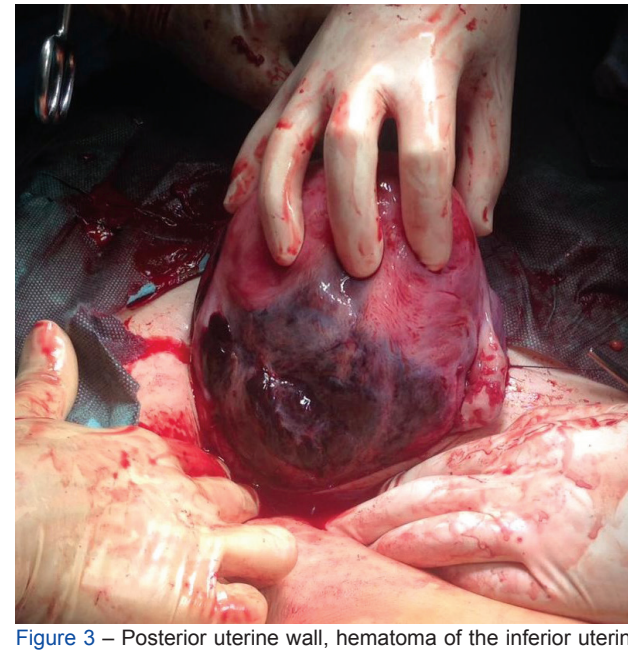

Figure 3 – Posterior uterine wall, hematoma of the inferior uterine segment, extending to the left uterine horn

and C-reactive protein). These were successfully treated with antibiotics (cephazolin and metronidazole) and analgesia. The patient was discharged 10 days after the surgery.

DISCUSSION

Hemoperitoneum during pregnancy is a rare complication. Initially, maternal mortality was reported to be 49% - 56%, having decreased recently to 0% - 4% as result of improved advanced life support, anesthetic and operative techniques.[2-5] However, perinatal mortality remained at 31% - 36%.[4,6] The prevalence of spontaneous hemoperitoneum in pregnancy (SHiP) before labor is 61% (the majority occurring during the third trimester of pregnancy),[5] 18% during labor and 21% occur during the puerperium.[2]

The etiology of this condition is poorly understood. It is known that endometriosis is present in 55.9% of cases.[5] Other suggested etiological factors include increased venous pressure in the utero-ovarian circulation during muscular activity or straining which could lead to the rupture of uterine vessels.[7] There are reports of rupture of uterine vessels, uterine artery, utero-ovarian vessels, uterine varices or uterine artery aneurysm.[7,8] High maternal blood pressure and atherosclerosis may also contribute to this complication.[2]

The most frequent clinical presentation is acute or subacute abdominal or flank pain (94.9%) with signs of hypovolemic shock (47.5%) and/or decreased level of hemoglobin (62.7%) without visible bleeding. Signs of fetal distress occur in 40.7% of cases.[5]

The diagnosis is difficult to establish prior to laparotomy.[2] Radiological tests such as abdominal ultrasonography and computed tomography scan[9] may identify free peritoneal fluid in 62.7% of cases and, of these, 89.2% are detected on ultrasonography.[5]

The differential diagnosis includes ectopic pregnancy, placental abruption with uterine rupture, abdominal pregnancy, ruptured appendix, HELLP syndrome, liver or spleen rupture, hepatocellular adenoma, uterine arteriovenous malformation, uterine hemangioma or even the rupture of a perivascular epithelioid cell neoplasm.[2,5,7,10-13]

In the described clinical case, the patient presented with acute abdominal pain without evident signs of bleeding in the third trimester of gestation and there were no signs of fetal distress. The investigation was focused on a possible non-obstetrical cause for the abdominal pain. The potential diagnosis of ruptured appendicitis resulted from the patient complaints of abdominal pain, nausea and vomiting, signs of rebound tenderness, free fluid and leukocytosis. The patient was always hemodynamically stable.

Treatment for this condition requires immediate surgery to prevent maternal hypovolemic shock. Lier *et al*,[5] on its review, raised the possibility of a wait-and-see approach in cases of SHiP in the absence of maternal hypovolemic shock or fetal distress. However, this approach was criticized by Markou and Fysekidis,[14] which argued that it is not possible to find out what the etiology of hemoperitoneum was or to predict its severity and evolution without an exploratory laparotomy. The fetal prognosis depends on gestational age and good hemodynamic maternal conditions. Lier *et al*[5] described an intervention rate of 94.9%: 69.6% for maternal reasons, 3.6% for fetal distress and 26.8% for both. During surgery, the bleeding site must be identified: it usually originates from the posterior surface of the uterus or the utero-ovarian vessels in the parametrium. Thereafter, hemostasis should be undertaken. Bleeding can be controlled following hemostatic sutures and/or compression.[9] Exceptionally, a hysterectomy or oophorectomy may be required.

Lim *et al*[9] reviewed eight case reports of SHiP. In his series, all cases occurred during the third trimester of pregnancy and post-delivery spontaneous hemoperitoneum was described in one of them. The most frequent clinical presentation was hemodynamic shock and severe abdominal pain. In many of these cases, an emergent cesarean-section was performed due to suspected scar or uterine rupture, abruption, or non-reassuring fetal status. The diagnosis was confirmed intra-operatively in all cases, which were successfully managed with hemostatic sutures and compression. Hysterectomy was performed only in one patient. Maternal mortality was not reported, but there was a case of perinatal death in one multiple pregnancy. Aziz *et al*[2] described the case of a 20 weeks pregnant woman presenting with hypovolemic shock resulting from massive bleeding. This was originated from a ruptured uterine vessel and associated with a left adnexal mass and decidualized endometriosis, with subsequent fetal death.

Mzarin *et al*[1] have also reported a case of a 46-year-old woman at 26 weeks of pregnancy presenting with acute abdominal pain and hypovolemic shock. Free fluid was observed on ultrasound and a laparotomy was performed due to a suspected ruptured uterus. A massive hemoperitoneum with nine liters of blood was observed. The mother received treatment, but the fetus did not survive.

In this case report, as described in the literature, the diagnosis only became clear intraoperatively. The rapid intervention allowed a good outcome for both the mother and the fetus, although the former had to receive blood transfusions for anemia.

Hemoperitoneum in pregnancy is a serious complication, associated with both maternal and fetal poor outcomes. It is not a preventable complication, and it is therefore essential that clinicians are aware of this clinical entity in order to enable early diagnosis and treatment, which lead to improved maternal and neonatal outcomes.

AUTHORS CONTRIBUTION

AE: Conception of the study, draft of the manuscript.

CCG: Data acquisition and interpretation, draft of the manuscript.

RM: Data acquisition, critical review and approval of the final version of the paper.

AF: Critical review and approval of the final version of the paper.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

INFORMED CONSENT

Patient informed consent was obtained.

COMPETING INTERESTS

The authors declare that there are no competing interests.

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Sebaceous Carcinoma of the Vulva: An Unexpected Diagnosis and Literature Review

Carcinoma Sebáceo da Vulva: Um Diagnóstico Inesperado e Revisão da Literatura

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ABSTRACT

Sebaceous carcinoma of the vulva is a rare malignancy of the sebaceous glands, with potentially aggressive behaviour, that is usually found in the peri-ocular area. Nonetheless, there are sebaceous glands in the vulva and this diagnosis is especially rare, with only ten cases described in the literature. We report a case of 78-year-old female patient who presented with vulvar pruritus, previously treated with topical steroid and antifungal treatments, without improvement. The vulvar examination showed a visible yellow papule, 12 x 10 mm on the right major labia, which was biopsied and the microscopic examination revealed an invasive sebaceous carcinoma of the vulva, with an *in situ* component. We performed an uneventful excisional biopsy, followed by a subsequent margin widening. Three months after the diagnosis, she presented with the first recurrence. Two and half years after the diagnosis, she recurred with a larger lesion (13 mm) in the upper half of small right lip, more than 10 mm away from the midline. In a multidisciplinary meeting it was decided that the patient should undergo partial right vulvectomy with homolateral inguino-femoral sentinel node biopsy (one negative node). There was no evidence of recurrence one-year post-surgery.

Keywords: Sebaceous Gland Neoplasms; Vulva; Vulvar Neoplasms

RESUMO

O carcinoma sebáceo da vulva é uma neoplasia maligna rara das glândulas sebáceas com comportamento potencialmente agressivo, mais comummente encontrada na área periocular. Este diagnóstico é particularmente raro nas glândulas sebáceas da vulva, com apenas dez casos previamente descritos na literatura. Relatamos o caso de uma paciente de 78 anos que se apresentou com prurido vulvar, anteriormente tratado com corticóides tópicos e antifúngicos, sem melhoria evidente. Ao exame objetivo apresentava uma pápula amarela visível, com cerca de 12 x 10 mm no grande lábio direito, que foi biopsada. O exame microscópico revelou um carcinoma sebáceo invasivo da vulva, com componente *in situ*. Posteriormente, foi realizada uma biópsia excisional, com alargamento de margens, sem intercorrências. Três meses após o diagnóstico, surgiu a primeira recidiva, pelo que foi realizada uma nova biópsia excisional. Dois anos e meio após o diagnóstico, a doente apresentava uma lesão com 13 mm, na metade superior do pequeno lábio direito, mais de 10 mm afastada da linha mediana. Em reunião multidisciplinar decidiu-se que deveria ser submetida a uma vulvectomia parcial direita, com pesquisa de gânglio sentinela inguino-femoral homolateral (um gânglio negativo). Um ano após a cirurgia, a doente encontra-se sem evidência de recorrência.

Palavras-chave: Neoplasias das Glândulas Sebáceas; Neoplasias Vulvares; Vulva

INTRODUCTION

Sebaceous carcinoma (SC) of the vulva is a rare malignancy of the sebaceous glands with potentially aggressive behaviour. Sebaceous carcinoma is most commonly found in the periocular area. Extra ocular vulvar SC is particularly rare, with ten cases described in the literature.[1] Due to limited data, little is known about the appropriate management and prognosis of vulvar SC. Reported risk factors for SC in general include advanced age, women of Asian or South Asian ethnicity, previous irradiation, genetic predisposition for Muir-Torre syndrome or possibly familial retinoblastoma.[2-4]

The most confusing aspect of vulvar SC is the myriad of clinical presentations, but it can be frequently described as yellow-tan nodules, with various sizes and ulcerated. We present a case of a recurrent vulvar SC.

CLINICAL CASE

A 78-year-old Caucasian woman, gravida 1 *para* 1, menopause at 45-years of age, presented to Instituto Português de Oncologia de Coimbra (IPOC) with chronic vulvar pruritus. She had been previously treated with topical steroids and antifungals, without improvement. She denied other symptoms such as pain, vaginal bleeding, ulceration, discharge or dysuria.

The patient had a previous history of significant hypertension, hypothyroidism, arthritis, type 2 diabetes and anxiety. She had no other relevant gynaecologic history and no family history of known malignancies.

At physical examination, she presented with a small yellow papule in the major right lip, 10 x 12 mm, with a reddish ridge. No inguinal adenopathies were noticeable. We performed a biopsy in which the histopathological examination showed a vulvar invasive SC with an intra-epithelial component. The genetic test for Muir-Torre syndrome and HPV were negative. Two months after the diagnosis she underwent an uneventfully excisional biopsy, with

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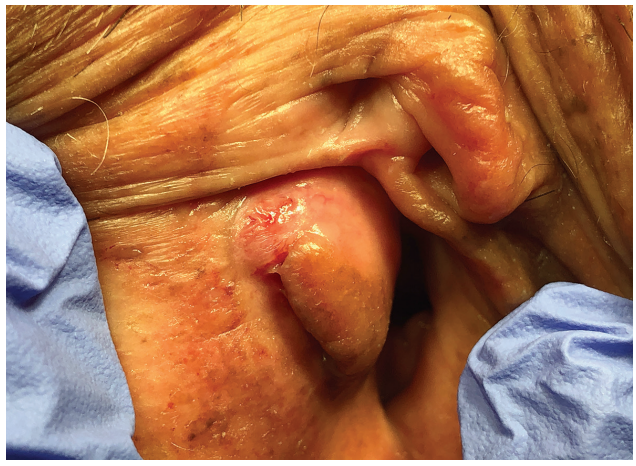

Figure 1 – Ulcerated nodule with approximately 10 mm in the small right lip

subsequent margin widening due to insufficient margins. She was discharged from the hospital disease-free. The patient was followed up on in an outpatient clinic, with no signs of persistent disease or relapse.

Three months after the initial diagnosis, she presented with newly onset pruritus and an ulcerated papule. The biopsy confirmed a local recurrence. She underwent another excisional biopsy and maintained regular outpatient follow-up.

Two and half years after the second surgery, she presented with an ulcerated nodule with approximately 13 mm in the upper half of small right lip, more than 10 mm away from the midline (Fig. 1). The biopsy confirmed another local recurrence of the initial diagnosis. A full body computed tomography scan showed no evidence of distant metastatic disease or any other malignant neoplasm.

After a multidisciplinary discussion with the presence of the patient, we performed a partial right vulvectomy with homolateral inguino-femoral sentinel node biopsy (one negative lymph node) (Fig. 2). Two weeks after the surgery, she presented with wound dehiscence in the groin area, which was re-sutured. The patient received no adjuvant therapy and one year after the last surgical intervention, she was healing well without signs of recurrence.

On histopathological examination, the first vulvar biopsy showed a well differentiated SC, characterized by a proliferation of neoplastic cells with sebaceous differentiation, showing multivesicular cytoplasmic clearing and nuclear scalloping (clearly different from simple cytoplasmic clearing) (Fig. 3A), with moderate nuclear pleomorphism and significant mitotic activity [10 mitoses / 10 high power field (HPF)]. The tumour grew in lobules of variable dimension, invading the dermis in an expansive pattern, some appearing to have a connection with the epidermis (Fig. 3B) and was considered grade I. Moreover, some of the neoplastic cells were present inside the epidermis, in small aggregates or with a pagetoid distribution, which was interpreted as an *in-situ* (intraepithelial) component (Fig. 3C). The neoplastic cell showed diffuse immunoreactivity for cytokeratin (CK) 7, CK 8/18, androgen receptor (AR) and Ber-Ep4; immunos-

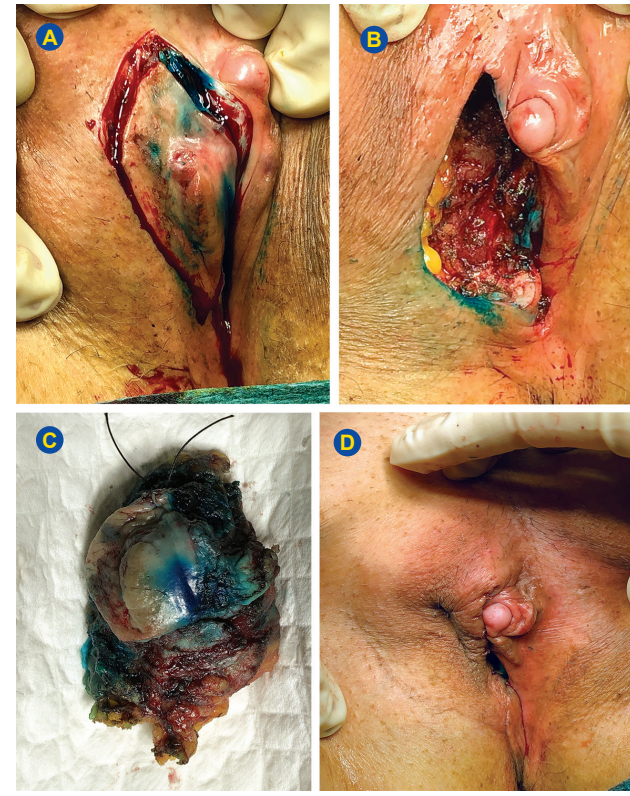

Figure 2 – A and B - partial right vulvectomy; C - surgical piece of right vulvectomy; D - surgical closure

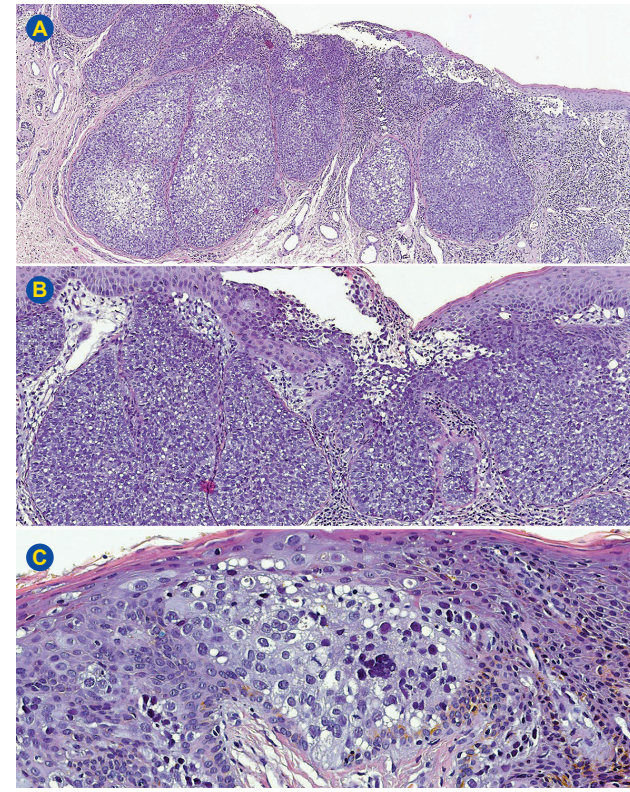

Figure 3 – First biopsy, microscopy: The tumor grew in lobules of variable dimension, invading the dermis in an expansive pattern (A), some appearing to have a connection to the epidermis (B). Some of the neoplastic cells were present inside the epidermis, in small aggregates or with a pagetoid distribution, which we interpreted as an *in-situ* (intraepithelial) component (C).

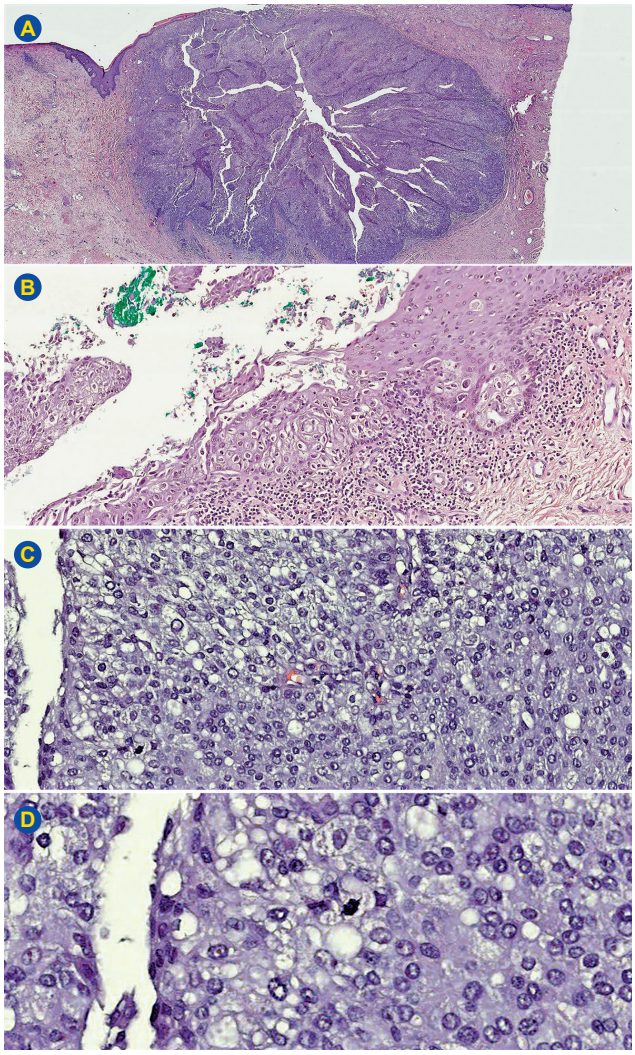

Figure 4 – Partial right vulvectomy, microscopy: a recidivated sebaceous carcinoma was observed, less differentiated than the previous excisions. It retained the same lobular growth pattern, with an expansive type of invasion (A); as before, focal *in-situ* growth was also observed (B). The neoplastic cells displayed evident nuclear pleomorphism and high mitotic activity with atypical mitosis; the cytoplasms were clear or granular, with cytoplasmic microvacuolization less common (C and D).

taining for epithelial membrane antigen (EMA) was focally positive, enhancing the cytoplasmic vacuolization of the tumour cells. The surgical margins appeared clear, but with a minimum distance to the neoplasm of only 0.3 mm.

Both the second incisional *biopsy* and the re-excision specimen, showed a SC with the same histopathological morphology as the first lesion, including the *in-situ* component. The surgical margins appeared clear once again, but with a minimum distance to the neoplasm of only 0.48 mm.

In terms of the right vulvectomy (Fig. 4), the histopathological examination of the surgical specimen showed a relapsed SC, less differentiated than the previous excisions (Fig. 3). It retained the same lobular growth pattern, with an expansive type of invasion (Fig. 4); as before, and focal *in-situ* growth was also observed. The neoplastic cells displayed evident nuclear pleomorphism and high mitotic activity with atypical mitosis (21 mitoses / 10 HPF); the cytoplasm was clear or granular, with cytoplasmic microvacuolation less common (Fig. 4). The immunohistochemical tests yielded similar results, with the neoplastic cells maintaining immunoreactivity for AR, EMA, Ber-Ep4 and CK8/18 (focal); however, CK7 was negative (Fig. 5).

DISCUSSION

Ten previous cases of vulvar SC have been published to date in the literature and were similarly treated with surgical excision. Nonetheless, some were treated also with radiotherapy and/or quimotherapy.[1] It is estimated that the presence of SC in the genitals is approximately 1.1% of all SC.[3] Extra ocular SC was once thought to be highly aggressive, but recent reports suggest similar prognosis for both ocular and extra ocular disease.[3,5] Apart from the different clinical characteristics and the types of surgical treatment of the previous cases, the overall prognosis is favourable, with only one patient deceased.[6] These neoplasms appear to have a 30% – 40% risk of local tumour recurrence, a 20% – 25% risk of distant metastases and a 10% – 20% risk of tumour-related mortality.[1]

The pathogenesis of extra ocular SC remains poorly understood. There are no cases of HPV infection and only two cases presented with a strong family history suggesting possible Muir-Torre syndrome (an autosomal dominant disorder, a subgroup of hereditary nonpolyposis colorectal cancer associated with some SC).[7,9] Therefore, it is important to have genetic counselling due to this known association, which was non-existent in our patient.

Unlike ocular SC, little is known about prognostic factors in vulvar SC. Older age, higher grade tumours and distant metastasis have been described as poor prognostic factors, but lymph node metastasis have not been described as an independent prognostic factor for SC of the head and neck.[2,10] Limited information is available in the literature regarding lymphovascular space invasion and depth of invasion, with only one previous case that reported distant metastasis with metastatic disease in the lung published.[6] There is variable and inconclusive information about the relationship between the tumour size and the positive node status.[7,8,11]

Of the ten cases previously described, five women underwent inguinal lymphadenectomy with three of them having positive lymph nodes[1,7]; such was not the case in our patient, who had a negative sentinel lymph node and therefore lymphadenectomy was not performed. The two patients described who had lymph node metastasis received adjuvant radiotherapy (RT), with only one having a recurrence of disease within the time frame of follow-up.[7,11] Our patient is the first one with negative lymph node metastasis, but with a recurrence of the disease. Due to the rarity of this disease, the optimal treatment still unknown. However, all authors find it reasonable to consider surgery to be the adequate initial intervention, with the goal aim being complete excision of the disease. In the largest series of SC (ocular and extra ocular),[3] only 5.3% of the patients received RT. It is

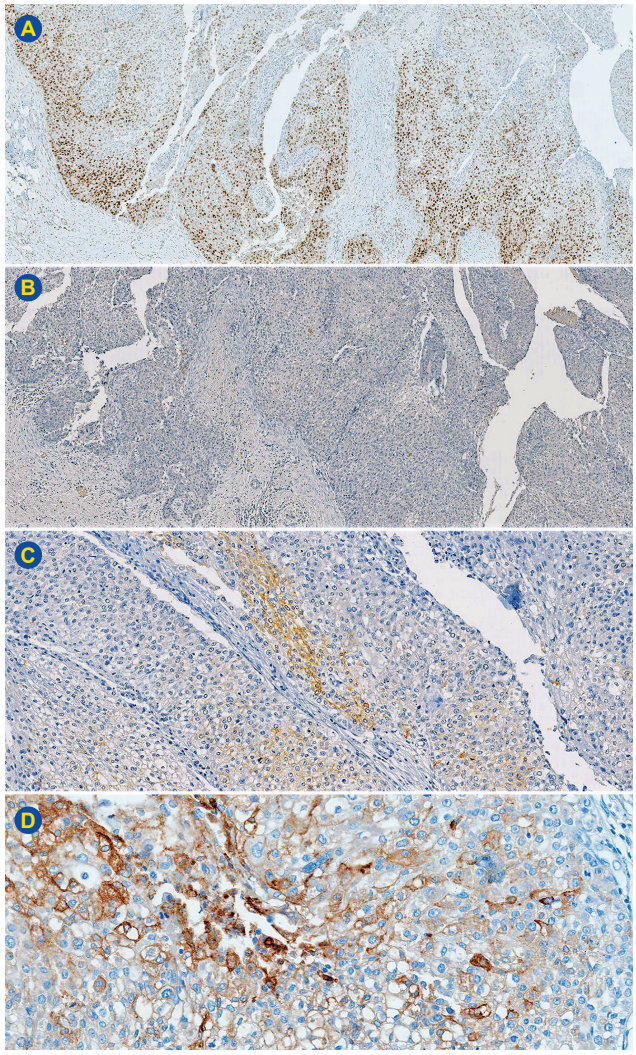

Figure 5 – Partial right vulvectomy, microscopy: the neoplastic cells maintained immunoreactivity for AR (A); however, CK7 was negative (B). CK8/18 was focally positive (C) and EMA was also positive, being harder to observe the microvacuolization of the cytoplasms (D), compared to the first biopsy.

reasonable to consider adjuvant therapy, such as RT, with positive lymph node metastasis; however, there is little information guiding this practice.

In summary, the vulva is a rare primary location for SC, which appears to have many clinicopathological differences when compared to the classic disease. As far as we know, our case is the first one with an intraepithelial/*in-situ* component. It is important to recognize and make the appropriate diagnosis of these rare tumours in order to better understand the natural history of this disease.

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AUTHORS CONTRIBUTION

ACC: Data acquisition and interpretation, draft of the manuscript, wrote the final version of the paper.

MIS: Data acquisition and interpretation, critical review and approval of the final version of the paper.

CA: Conception and analysis of anatomopathological information, critical review and approval of the final version of the paper.

RS: Data acquisition and interpretation, critical review and approval of the final version of the paper

PROTECTION OF HUMANS AND ANIMALS

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

PATIENT CONSENT

Obtained.

DATA CONFIDENTIALITY

The authors declare that they followed the protocols in use at their working center regarding patients' data publication. Patient consent obtained.

COMPETING INTERESTS

The authors declare that there are no competing interests.

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Malformação Linfática Microcística Simulando Condilomas Acuminados

Microcystic Lymphatic Malformation Mimicking Condylomata Acuminata

Diogo TEIXEIRA✉[1], Eduarda OSÓRIO FERREIRA[1], Artur CÉSAR[1]
Acta Med Port 2022 Jan;35(1):68-69 ▪ https://doi.org/10.20344/amp.14022

Palavras-chave: Adulto; Anomalias Linfáticas; Condilomas Acuminados; Escroto; Linfedema; Malformação Linfática Microcística; Pénis

Keywords: Adult; Condylomata Acuminata; Lymphatic Abnormalities; Lymphedema; Scrotum

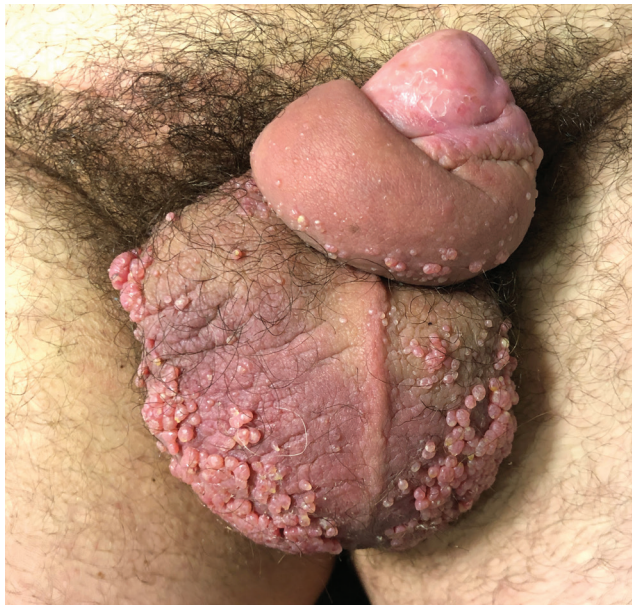

Figura 1 – Linfedema crónico marcado do pénis e do escroto, com múltiplas pápulas milimétricas, algumas agrupadas em placas de aspeto verrucoso, algumas cor de pele, outras translúcidas

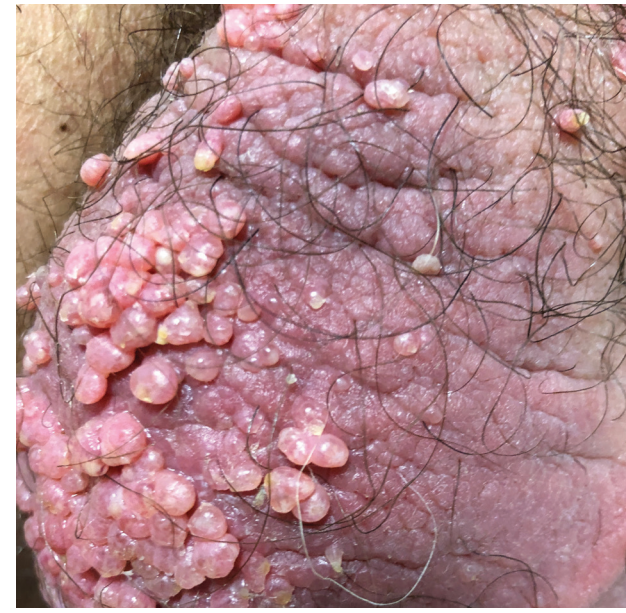

Figura 2 – Pormenor das lesões no escroto

Doente do sexo masculino de 49 anos, foi referenciado ao Serviço de Dermatologia por lesões no pénis e escroto, assintomáticas, de crescimento lento e com um ano de evolução, previamente diagnosticadas como condilomas. Apresentava também linfedema crónico da região genital, consequência do tratamento de um carcinoma do pénis submetido a circuncisão e linfadenectomia inguinal há 18 anos. Ao exame objetivo, observaram-se múltiplas pápulas agrupadas, algumas cor de pele, outras translúcidas, no escroto e pénis (Fig.s 1, 2). O diagnóstico clínico de malformação linfática microcística foi confirmado após a biópsia revelar ligeira acantose epidérmica e dilatação linfática marcada, com infiltrado polimórfico ligeiro a moderado, edema e fibrose. Uma vez que o diagnóstico de condilomas foi descartado, não foram rastreadas outras infeções sexualmente transmissíveis.

A malformação linfática microcística é uma malformação vascular. Pode ser congénita ou adquirida (nomeadamente secundária a linfedema), sendo raro o aparecimento em adultos.[1,2] Na região genital, as lesões podem ter um aspeto verrucoso, levando ao diagnóstico errado de condilomas.[1] O tratamento destas lesões é a excisão cirúrgica, sendo a recorrência frequente.[3,4] Neste caso, dada a localização e associação ao linfedema, optou-se pela atitude conservadora.

CONTRIBUTO DOS AUTORES

DT, EOF, AC: Todos os autores tiveram igual contributo na redação e revisão final do manuscrito.

PROTECÇÃO 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

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e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

CONFIDENCIALIDADE DOS DADOS

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

CONSENTIMENTO INFORMADO

Obtido.

CONFLITOS DE INTERESSE

Os autores declaram não ter qualquer conflito de interesse relativamente ao presente artigo.

FONTES DE FINANCIAMENTO

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Carta ao Editor Referente a "Saúde Mental nos Cuidados de Saúde Primários: Desafios e Oportunidades em Contexto de Pandemia"

Letter to the Editor Concerning "Mental Health in Primary Health Care: Challenges and Opportunities in the Context of a Pandemic"

Palavras-chave: COVID-19; Cuidados de Saúde Primários; Pandemia; Perturbações Mentais; Portugal; Saúde Mental; Serviços de Saúde Mental
Keywords: COVID-19; Mental Disorders; Mental Health; Mental Health Services; Pandemics; Portugal; Primary Health Care

Caro Editor,

No artigo "Saúde Mental nos Cuidados de Saúde Primários: Desafios e Oportunidades em Contexto de Pandemia",[1] publicado no número de outubro 2021 da Acta Médica Portuguesa, Albuquerque *et al* defendem que a pandemia de COVID-19 é uma oportunidade para monitorizar os cuidados de saúde mental prestados nos Cuidados de Saúde Primários (CSP) através de indicadores que eventualmente incluam a teleconsulta.[1] Por outro lado, os autores também referem que os indicadores não refletem a medicina centrada na pessoa,[1] tendo esta uma reconhecida importância tanto nos CSP como nos cuidados de saúde mental.[2] Deste modo, como médico de família, acredito que no período pós-COVID-19 se quisermos colocar a pessoa com doença mental no centro dos cuidados teremos que ir mais longe e não nos limitarmos apenas a integrar a saúde mental nos CSP e monitorizá-la.

A desestigmatização da doença mental, alavancada pela cobertura mediática do reconhecido sofrimento psicológico durante a pandemia de COVID-19, poderá ser o ponto de partida ideal para uma significativa transição coordenada para cuidados de saúde mental baseados na comunidade, com maior proximidade aos doentes (melhorando ao mesmo tempo os fluxos de doentes a nível hospitalar em contexto de pandemia) e reforço da complementaridade com os CSP, envolvendo, numa perspetiva integrada de cuidados, psicólogos, terapeutas ocupacionais, enfermeiros e psiquiatras, e também os doentes, as suas famílias e outras entidades da comunidade, como por exemplo as associações de doentes. O modelo centrado no hospital continua a ser assinalado como um ponto fraco de Portugal, segundo o documento de 2017 "Joint Action on Mental Health and Well-Being: Towards Community-Based and Socially Inclusive Mental Health Care"[3] da European Agency for Health and Consumers. A promoção da desinstitucionalização e da reabilitação destes doentes terá de passar necessariamente pela redução de outras fragilidades assinaladas em Portugal.[3] Será necessário um maior número de profissionais da área de saúde mental, uma melhor coordenação entre as diversas partes interessadas e a melhoria das redes sociais, o que no período pós-COVID-19 poderá traduzir-se por maior investimento na área social e uma efetiva integração ou gestão conjunta da assistência social e do sistema de saúde.[4]

É ainda prematuro prever como será a evolução da saúde em geral, e da saúde mental em particular, no período pós-COVID-19 em Portugal, que provavelmente também passará pela teleconsulta, como referido por Albuquerque *et al*.[1] Contudo, e independentemente do rumo de mudança, esta é uma oportunidade única para fomentar o diálogo entre todos os *stakeholders* com o objetivo de melhorar o futuro dos cuidados de saúde mental em proximidade.

CONFLITOS DE INTERESSE

O autor declara 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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Mental Health During a Pandemic: Additional Action is Required

Saúde Mental Durante uma Pandemia: É Necessária Ação Adicional

Keywords: COVID-19; Mental Health; Mental Health Services; Pandemics; Population Health Management
Palavras-chave: COVID-19; Gestão da Saúde da População; Pandemias; Saúde Mental; Serviços de Saúde Mental

Dear Editor,

We read with great interest the recent article entitled "Mental Health in Primary Health Care: Challenges and Opportunities in the Context of a Pandemic", by Albuquerque *et al*,[1] in which the authors describe guidelines for the management of mental health problems faced by coronavirus disease 2019 (COVID-19) patients. In light of the wide scope of this problem, combined with some gaps which we identified in the above paper, we wish to discuss some additional action which is required to address and advance the appropriate management of this public health concern.

Globally, the pandemic is far from under control. Given the worrying circulation of rapidly arising variants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) across the world,[2] coupled with the low rates of COVID-19 vaccination in many of them,[3] we would firstly like to emphasize the importance of implementing prevention and case management programs in the context of mental health problems faced by healthcare professionals working on the COVID-19 front lines. This is especially important since significant levels of stress, anxiety, and depression amongst healthcare workers have been widely reported in the literature.[4,5]

Moreover, in cases involving the hospitalization of critically ill patients (especially involving admission to intensive care, intubation and/or death) the provision of psychological screening and assistance to family members is essential, as many hospitals do not allow visits to COVID-19-positive patients, which places significant strain on the grieving process.[6] Activities to improve mood, create positive attitudes towards recovery, and encourage conversations about mental health, are some of the essential components of a program that could play a significant role in the holistic approach to patients who are mentally and physically recovering from this disease.

Finally, the emerging understanding of the high burden presented by patients with prolonged COVID-19 symptoms or 'long-COVID' (including those of a mental health nature),[7] should lead health authorities and governments to plan a vigorous expansion and implementation of structured mental healthcare services in order to effectively provide long-term care and support for these patients.[8] Fig. 1 shows the depiction of a model of a mental healthcare program, which summarizes our suggestions.

We thank Albuquerque *et al* for proposing effective policy changes, which, together with our suggestions, will hopefully create a more favorable structure for addressing the mental health issues of all those affected during long-term global pandemics.

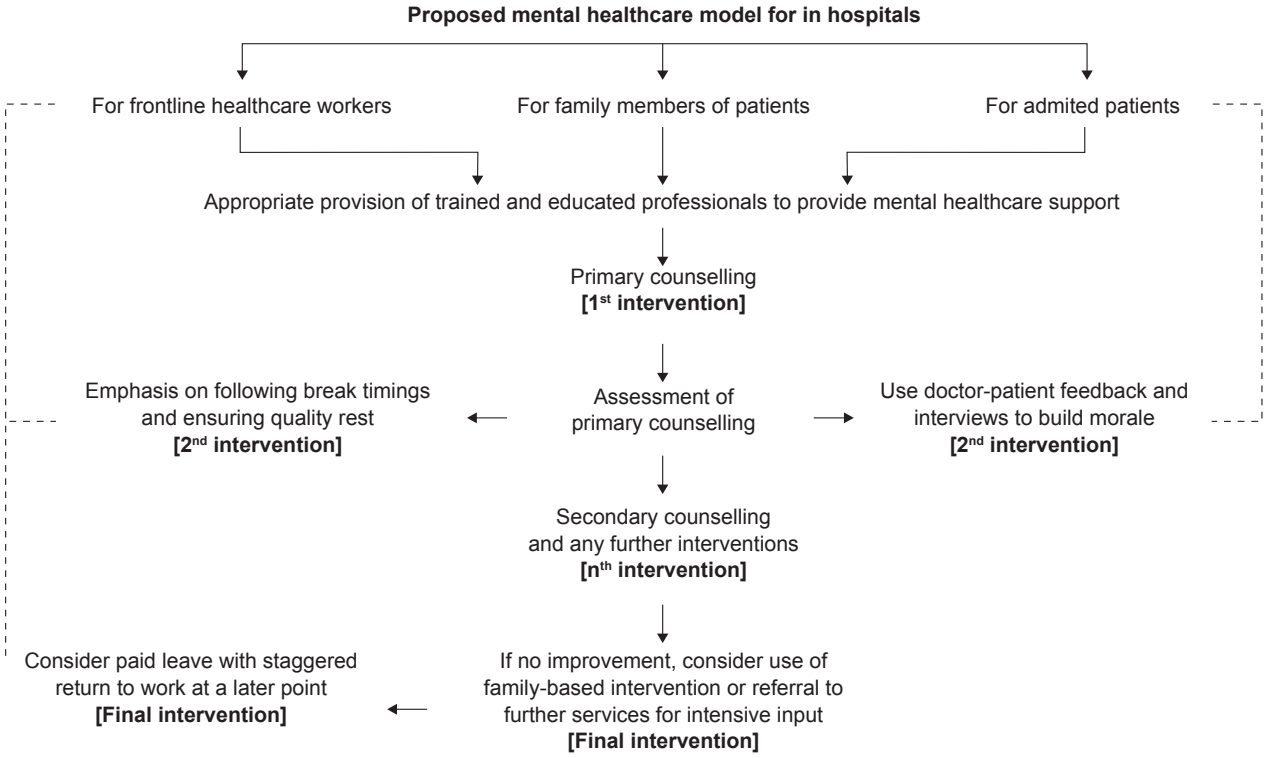

Figure 1 – Proposed model of a mental healthcare program for care of frontline healthcare workers and long-term inpatients

AUTHORS CONTRIBUTION

TF: Draft of the paper, critical review, and copyedit.

PAS: Draft of the paper, critical review.

MRTP: Conception of the work, draft of the paper, and supervision.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Letter to the Editor Concerning "Why is Palliative Care Training During the Portuguese Family Medicine Residency Program Not Mandatory?"

Carta ao Editor Relativa a "Porque é que a Formação em Cuidados Paliativos no Internato de Medicina Geral e Familiar em Portugal Não é Obrigatória?"

Keywords: Education, Medical; Internal Medicine; Internship and Residency; Palliative Care

Palavras-chave: Cuidados Paliativos; Educação Médica; Internato e Residência; Medicina Interna

Dear Editor,

The issue raised by Castro *et al*[1] in your latest issue is of utmost importance. The authors argue that palliative care (PC) training should, more than ever, become mandatory during the Family Medicine residency program. As the authors highlighted, an ever-ageing population in whom the management of multimorbidity is incredibly complex demands the redefinition of the goals of care.

In Portugal, Internal Medicine (IM) is likely to be the secondary care specialty which manages such patients more closely. Death and dying have moved from the community setting to hospitals, and internists care daily for terminally ill patients. In a recent study,[2] most patients (54%) admitted to a Portuguese IM ward had PC needs.

PC is not a mandatory rotation in the Portuguese IM residency program (PIMRP), but residents' demand for elective training in the field is increasing. In fact, several studies[3] in North America have shown that IM residents perceive a lack of preparedness in end-of-life training. Even though similar studies have not yet been conducted in Portugal, it is widely acknowledged (mostly informally) by residents and national organisations - namely the Portuguese Medical Association (Ordem dos Médicos) and the Portuguese Society of Internal Medicine - that improving PC training during the PIMRP is imperative. Several calls have been made,[3] but they tend to go unnoticed.

In 2016, the National Palliative Care Commission, on behalf of the Portuguese National Healthcare System, published the "Strategic Plan for Palliative Care Development".[4] In line with the recommendations of the European Association for Palliative Care, this government document proposes 'intermediate training level' for IM physicians. In 2019, the Portuguese College of Palliative Care reinforced this same recommendation. Contrary to popular belief, this

level of PC training requires proper education in technical skills such as end-of-life communication, symptom assessment, psychosocial and spiritual support, and bereavement care. However, the PIMRP does not formally train or evaluate the competence of residents on these topics. It tends to focus on curative medicine instead.

We advocate for mandatory PC training and the development of a PC curriculum with clear goals that are aligned with the competencies of IM residents and expected expertise. We need to adjust our training to our patients' needs. To defend this is to defend a more rigorous and humane medical practice!

We should not be shy in standing for PC. It is already the present and unarguably the future of healthcare. Therefore, we hereby urge decision makers to take the lead and raise the bar of IM training.

AUTHORS CONTRIBUTION

BP, MB, PCF: Lead authors, all contributed equally to the writing of the letter with overall responsibility and topic conception.

TNG, FR, IGN: Critical review of the paper with significant intellectual contribution

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

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Fortificação Alimentar com Vitamina D em Portugal

Food Fortification with Vitamin D in Portugal

Palavras-chave: Comida Fortificada; Política de Saúde; Raios Ultravioleta; Vitamina D
Keywords: Food, Fortified; Health Policy; Ultraviolet Rays; Vitamin D

Caro Editor

O Sol, quando nasce, é para todos! Esta expressão popular traduz a disponibilidade da radiação solar ultravioleta (RSUV) no ambiente sem custos associados e a liberdade de cada um poder usufruir dela. Sendo a concentração sérica de vitamina D um bom indicador da exposição ambiental à RSUV, em virtude de esta ser a sua principal fonte, a constatação da existência de uma "pandemia" de deficiência de vitamina D – um verdadeiro problema de Saúde Pública – comprova a necessidade de encarar a exposição ambiental insuficiente a RSUV como um fator de risco relevante.

Em Valência (latitude 39°; Espanha), na primavera e verão (março a setembro), cerca de 10 minutos de exposição solar entre as 11h30 e 12h30 com 25% da área corporal exposta (pele fototipo III) serão suficientes para alcançar as necessidades diárias de vitamina D; o tempo mínimo de exposição aumenta para cerca de 25 minutos pelas 09h00

ou 15h00.[1] Pelo contrário, nos meses de outono e inverno (outubro a fevereiro), não é praticável a síntese cutânea de vitamina D em níveis suficientes.[1]

Em Portugal, considerando os três estados de vitamina D reportados pela Direção-Geral da Saúde [deficiência (< 20 ng/mL), insuficiência (≥ 20; < 30 ng/mL) e suficiência (≥ 30 ng/mL)], apenas 3,6% dos adultos apresentam suficiência de vitamina D, o que levanta a necessidade urgente de um debate amplo e cientificamente robusto sobre as intervenções mais adequadas nos níveis individual e social.[2] Neste contexto, impõe-se a implementação de medidas políticas com impacto a nível populacional, entre as quais se destaca a fortificação alimentar com vitamina D – em alternativa a medidas como o fomento da ingestão de alimentos naturalmente ricos em vitamina D e a suplementação – sendo esta opção altamente custo-efetiva e recomendada pela Sociedade Europeia do Tecido Calcificado.[3]

A fortificação alimentar, voluntária ou obrigatória, já foi acolhida por outros países, sendo preferível considerar baixas doses num número alargado de alimentos (p.e. leite, manteiga, pão, cereais, cogumelos). A Finlândia implementou uma política promotora da fortificação alimentar voluntária e conseguiu aumentar a prevalência de suficiência de vitamina D de 4,1% em 2000 para 19,9% em 2011 (de 3,8% para 12,6% nos não consumidores de suplementos).[4]

O número de alimentos fortificados disponíveis para consumo no mercado português poderá ser maximizado no âmbito de uma política de fortificação alimentar com vitamina D.[5] Não estará na altura de colocar a fortificação alimentar com vitamina D na agenda política portuguesa?

CONTRIBUTO DOS AUTORES

MH: Revisão bibliográfica, redação do artigo, aprovação da versão final.

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Carta ao Editor Referente a "Linhas Orientadoras para Pensar, Desenvolver e Implementar a Comunicação em Saúde em Portugal"

Letter to the Editor Concerning "Guidelines to Think, Develop and Implement Health Communication in Portugal"

Palavras-chave: Comunicação em Saúde; Cuidados de Saúde Primários; Literacia em Saúde
Keywords: Health Communication; Health Literacy; Primary Health Care

Caro Editor,

Lemos com grande interesse o artigo "Linhas orientadoras para pensar, desenvolver e implementar a comunicação em saúde em Portugal",[1] publicado no número de outubro de 2021. Em uníssono com a nossa opinião, a literatura defende que a otimização da comunicação é fundamental como estratégia de apoio à gestão de equipas multidisciplinares e ao desenvolvimento de processos e redes de apoio institucional e comunitário. O contexto de pandemia promoveu a reflexão sobre a importância da comunicação e literacia em saúde na alteração de comportamentos e atitudes pela população.[2] A constante atualização da evidência e orientações desafiou a adaptabilidade dos profissionais na transmissão de informação aos utentes. O investimento na formação dos profissionais de saúde permitiria a sua capacitação em estratégias efetivas de comunicação, não só em campanhas de educação para a saúde da população, mas também no contacto individualizado, focado na centralidade do utente.

O seguimento longitudinal, próximo e centrado na pessoa, que caracteriza os Cuidados de Saúde Primários, representou para alguns utentes uma fonte confiável de informação durante a pandemia. Não devemos, porém, subestimar a infodemia relativa a outros problemas de saúde para além da COVID-19, um desafio crescente para os profissionais de saúde. Como referido por Santos *et al*,[3] não é suficiente ter acesso à informação, é necessário saber como utilizá-la. Intervir no aumento da literacia em saúde, formando a população na procura, triagem, interpretação e esclarecimento da informação recebida, é também responsabilidade da classe médica.

O abandono da atitude paternalista, a adoção de uma política de transparência e decisão partilhada, aliada à criação de estruturas como o Conselho da Comunidade, promovem a educação em saúde tendo por base meios de comunicação eficazes.

Ao longo do artigo são propostas linhas orientadoras baseadas no conhecimento empírico das autoras, dada a escassez de evidência científica sobre comunicação em saúde. Reforçamos a importância da investigação em comunicação adaptada à população portuguesa, auscultando tanto os profissionais de saúde, como a população com diferentes níveis de literacia. Numa perspetiva de melhoria contínua da qualidade, seria importante também investir em estratégias e indicadores de monitorização de comunicação, como da avaliação da satisfação dos intervenientes.

Comunicar é, sem dúvida, uma competência altamente diferenciada que o médico deve dominar. Teremos de conjugar esforços conjuntos para promover a investigação, a formação e a capacidade de comunicar.

CONTRIBUTO DOS AUTORES

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The Rise and Fall of SARS-CoV-2 Variants

A Ascensão e Queda das Variantes de SARS-CoV-2

Keywords: COVID-19; Portugal; Risk Assessment; SARS-CoV-2
Palavras-chave: COVID-19; Medição de Risco; Portugal; SARS-CoV-2

Dear Editor,

As the pandemic evolves, Portugal and countries worldwide are facing the threat of the emergence of new SARS-CoV-2 variants, which represent potential game-changers in this fight. One of the most recently detected variants was the Mu variant (B.1.621). It was classified on August 30 by the World Health Organization as a variant of interest for presenting mutations that are shared with some of the variants of concern and that suggest a potential property of immunological escape.[1] This lineage carries several Spike protein mutations, some common with other variants of concern, while others are new. Indeed, experimental studies demonstrated that the Mu variant could escape humoral immunity acquired from infection from previous strains or vaccines.[2] At that point, further studies were required to assess the biological and epidemiological roles of the substitution pattern found.

However, the scientific community's interest quickly faded in parallel with the favorable epidemiological evolution of the new variant. In terms of cases sequenced, the global prevalence rate has been increasing since January, peaked in mid-July and then declined, being consistently below 0.2% (spectrum). In Portugal, it was reported firstly at the end of May, and, until now, a total of 24 cases were sequenced; a decreasing trend was observed, representing 0% of sequenced cases since August.[3] Thus, the Mu threat seems to have been quelled. However, its emergence reminds us that the tracking of SARS-CoV-2 variants is crucial. The first Italian cluster of the SARS-CoV-2 B.1.621 lineage was associated with a traveler from Colombia, which underlines that surveillance of SARS-CoV-2 genomic evolution is essential to limit the spread of new lineages to different countries.[4]

At the moment, a new Delta sublineage (AY.4.2) is arising in England and was classified as 'variant under investigation' on October 22nd by the UK Health Security Agency.[5] It contains two mutations in the Spike protein, already found in other lineages and has been suggested that it might be 10% to 15% more transmissible than the original Delta variant.[5] The first cases emerged in late June and represent up to now less than 1% of cases sequenced worldwide.[3] In Portugal, nine cases were sequenced, and the respective epidemiological contexts are under investigation.[3] Further studies concerning the ability to escape immunity are needed.

As countries gradually resume pre-pandemic activities, risk assessments should continue to be conducted systematically, updating the global lists of variants to support priority setting for surveillance and research, and ultimately guide response strategies.

AUTHORS CONTRIBUTION

TPS: Conducted the research and wrote the first draft of the letter; approved the final draft of the manuscript.

AA, MP: Participated in the writing, reviewing and editing of the letter; approved the final draft of the manuscript.

RD: Conceived the idea and participated in the writing, reviewing and editing of the letter; approved the final draft of the manuscript.

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Letter to the Editor Regarding the Article "Rethinking the Choosing Wisely Portugal Recommendation on Breast Cancer Screening"

Carta ao Editor em Relação ao Artigo "Repensar a Recomendação Choosing Wisely Portugal sobre Rastreio do Cancro da Mama"

Keywords: Breast Neoplasms; Decision Making, Shared; Early Detection of Cancer; Mammography; Patient-Centered Care
Palavras-chave: Assistência Centrada no Paciente; Deteção Precoce de Cancro; Mamografia; Neoplasia da Mama; Tomada de Decisão Compartilhada

We would like to clarify that there is an article about the "Choosing Wisely Portugal" recommendation for Breast Cancer Screening[1] in this journal[2] where the best scientific evidence (including reviews, randomized studies, meta-analyses, etc.) underlying the recommendation basis was discussed. Choosing Wisely recommendations are usually brief, and therefore it is not possible to detail all the required information and references in one or two paragraphs. The American College of Radiology has also published patient-oriented summaries about this screening among their recommendations.[3]

The article by Silva *et al*[2] does not avoid the issue of possible overdiagnosis, as it justifies the low values (0% - 5%) in adequately adjusted studies.

The argument that delaying the start of screening or increasing its intervals has an effect on the already low overdiagnosis rate does not seem legitimate to us. There is recent evidence supporting the contrary,[4] where it was found that there is no effect on the frequency of overdiagnosis in 'less intensive' screenings. Instead, the prognosis is worse for women in whom breast cancer is detected later on.[5]

A sensitive and serious discussion about the risks and potential harms is needed when comparing the anxiety caused by a false positive result with the one of an often-mutilating invasive cancer. The first is brief and transient in most cases, while the latter is often way more distressing, particularly when we also consider the (chemo)therapeutic aspect. Evidence exists that transient anxiety does not dissuade women from continuing their screening in the following year,[6] nor does it diminish the importance given to it.[7]

It is important to mention that the American Society of Breast Surgeons also supports the recommendation to screen annually starting at age 40.[8] Between 81% to 87% of American clinicians recommend not to postpone screening to the age of 50. Moreover, 67% of them consider that screening should be continued after the age of 75.[9] To give even more strength to the recommendation, we agree that patients should be informed, and that is why the justification accompanying the recommendation mentions "shared decision (…) duly informed about the benefits and drawbacks",[1] which is in line with the "Choosing Wisely Canada" recommendation. In the European Union, radiological tests must be subjected to informed consent in agreement with the European Council Directive 2013/59/Euratom. Therefore, the task that the radiologist who is about to perform the test has of informing patients does not seem strange, difficult or inconvenient to this specialty, quite the contrary.

Therefore, we stress that the recommendation "Choosing Wisely Portugal" for Breast Cancer Screening[1] takes into account the shared decision and the balance between risks and benefits and it stands in the best interest of the woman/patient or any association representing them, such as the "Associação Portuguesa de Apoio à Mulher com Cancro da Mama", whose president is co-author of this letter and also supports the "Choosing Wisely Portugal" program. This program is tolerant, inclusive and has already given voice to similar recommendations before, also alerting to the less frequent, but no less important risks of "less can be more in the end" [see recommendations: "Choose not to postpone the referral for cryptorchidism (…)"[10] and "Choose not to postpone the measurement of total bilirubin (…) in a newborn"[11]].

AUTHORS CONTRIBUTION

SCN: First draft, conception, literature research.
AJ: Revision, conception.
PF: Revision, conception.
MA: Patient-centered critical review.
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