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Combating Vaccine Hesitancy Requires Knowledge of Misfortunes and Controversies

Combater a Hesitação Vacinal Requer Conhecimento de Infortúnios e Controvérsias

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Keywords: Vaccination; Vaccination Hesitancy; Vaccines
Palavras-chave: Hesitação Vacinal; Vacinação; Vacinas

The story of anti-vaccination: a *déja-vu*

Before the advent of safe vaccines, smallpox was a dreadful condition that occurred in epidemic waves with case-fatality rates around 30% (variola major).[1,2] In the 10th century, Chinese and Indian physicians rubbed the fluid from smallpox pustules into a scratch on the arm of healthy individuals. This process was called variolation: the inoculation with low doses of smallpox aimed to induce a mild infection that would lead to immunity against the disease. However, variolation could cause disease and even death (1% - 2%) and was also related to outbreaks.[2] In the 18th century, this practice spread throughout Europe, although many physicians considered it ineffective and were afraid to adopt it. The first movements of vaccine hesitancy appeared due to fear of the side effects of variolation (including possible death). More organized anti-vaccine sentiments were often based on religious antagonism, considering it a violation of divine providence.[1,3]

Variolation was replaced by the much safer vaccination process, which Jenner developed from 1796 to 1798, and self-published (*Variolae vaccinae*).[2,3] Between 1840 and 1853, pro-vaccination laws were enacted, for example, the English government made vaccination compulsory for children and the poor and determined fines and prison for heads of families refusing to vaccinate their offspring.[2,3] This situation generated a widespread antagonistic reaction from the population. While the main concern was the perceived infringement of individual freedom and the fear of establishing medical tyranny, social and economic aspects caused by the fines and imprisonment were also rife. All this led to the creation of the anti-vaccination league and in 1867 a new law was passed giving freedom to parents to take responsibility for not vaccinating their children (which is when the term 'conscientious objector' originated).[1-3]

Spectrum of vaccine hesitancy: from bizarre ideas to plausible economic concerns

Vaccine hesitancy is often detached from scientific reasoning and a rational risk assessment of efficacy and possible side effects. Many reasons, reminiscent of the historical anti-vaccination movements, are subjectively important concerns of a religious, social, cultural, or political nature; frequently guised as fear of persecution of minorities. In the shape of rumours, where central aspects are often factually incorrect, they may spread widely and rapidly.[4] One example is the fear of population control, such as alleged sterilization or intentional decimation with an infectious disease: the 'North', ex-colonizers *versus* African populations (i.e.: tetanus vaccination in Kenya) or Western civilization *versus* Muslims (i.e.: polio-vaccination in Pakistan).[4] Potentially more rational reasons of an economic nature may be important as the whole-cell pertussis vaccine scare during the 1970s in the United Kingdom (UK) may illustrate**.** Media reports abounded about an increase in alleged severe neurological sequela after vaccination, which epidemiological studies could not confirm. However, a large aspect of this was the perceived lack of social support to those potentially affected which led to a considerable drop in vaccination rates. The UK government passed the Vaccine Damage Payments Act, with a payment of £10 000 to those affected, to restore trust.[5]

The bumpy road of vaccine development: genuine misfortunes

Vaccines are arguably the biggest success story in medicine, with huge reductions in cases and associated mortality.[2] Healthcare workers (HCW) may often be unaware that the development was a bumpy road with several high-profile misfortunes or accidents (Table 1).[2,6,7] Undoubtedly, when comparing the dimension of these incidents with the overall beneficial public-health effects of these vaccines,

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Table 1 – Notable misfortunes and accidents in the history of vaccines

Designation/disease	Year	Comment/description
Lübeck disaster/Tuberculosis	1929 - 1933	BCG vaccine contaminated with *M. tuberculosis*: 173 developed disease and 72 died
Kolmer's Vaccine trial/Polio	1932	Poorly designed trial with 10 children developing polio and five deaths[a]
Cutter Incident/Polio	1955	120 000 doses contained live virus: 40 000 abortive polio cases, 250 paralytic polio cases, and 10 people died[b]
Simian virus 40/Polio	1955 - 1963	Polio vaccine contaminated with the SV40 (monkey virus) was potentially associated with an increased risk of cancer. Studies found no evidence for cancer in millions of vaccine recipients.
Swine Flu Vaccine/Influenza	1976	Slight increased risk of Guillain Barré syndrome (1 additional case/100 000)
Rotavirus Vaccine/Diarrhoea	1998 - 1999	RotaShield vaccine was associated with an increased risk of intussusception – withdrawn from the market[c]
H1N1 Flu Vaccine/Influenza	2009 - 2010	Pandemrix (monovalent H1N1 pandemic strain) was associated with an increased risk of narcolepsy in Europe (Finland/Sweden)

[a]: Brodie's trial at the same time with an inactivated vaccine also produced two polio cases and one death.
[b]: including secondary cases because of spread in families/community.
[c]: total number of cases observed in the US is very small; newer vaccines still carry a small risk of intussusception.
Based on information in references[2,6,7]

the administration of vaccines largely outweighs any damages caused, as the example of the polio vaccine illustrates particularly well (Table 1). Despite some misfortunes, like the polio cases and even deaths that occurred during the Cutter incident (Table 1), millions of cases of paralytic polio were prevented. Moreover, in the WHO African region, wild poliovirus is considered eliminated (Table 2). Nowadays, highly efficient security protocols are in place during vaccine development and administration to monitor for even rare adverse events and thus make vaccines safe.[6] However, HCW should be familiar with these misfortunes (and their dimensions) to be able to put them into perspective, which can allay the fears of vaccine-hesitant individuals who are aware of these incidents.

Controversies in vaccinology: measles and beyond

The measles vaccine also illustrates well the spectrum of arguments, from the ludicrous (scientifically disproved) to scientifically valid findings (even if controversial). Incorrect and fabricated results from 12 children published in *The Lancet* in 1998 by Wakefield and colleagues (retracted in 2010) caused the autism scare.[6,8] Yet, the association between measles vaccination and autism has been extensively refuted.[6] Similarly, no evidence was found that thiomersal, an ethylmercury preservative in vaccines is toxic (contrary to methylmercury which is toxic), or that thiomersal is associated with autism.[6] Unfortunately, the anti-vaccine movements are often enthralled by these myths, although the whole story, which includes vested financial interests and fraud, Wakefield being struck off the UK medical register, the making and contents of the movie "Vaxxed", or the involvement of celebrities, like Robert Kennedy Jr., seems more like something out of a blockbuster thriller.[4]

However, it is often ignored that, on a few occasions, vaccines and vaccination schemes may have been associated with poor outcomes, although the absolute effects were usually small, especially when compared to the overall beneficial effects the respective vaccine had (Table 2). For example, in Africa (Guinea-Bissau, Senegal, Zaire, Rwanda) the high dose Edmonton-Zagreb measles live vaccine was reported to have been associated with increased overall mortality in girls compared to the standard vaccine (1989 - 1992).[6,9] Although no satisfactory reason for the observation has been found yet, in 1992 the WHO suspended this recommended practice.[10] The administration of an inactivated measles vaccine to almost one million children during the 1960s resulted in short-lived protection, and worse, it led to atypical measles (a more severe form of the disease) and possibly some associated deaths.[6,9] A Danish group led extensive vaccination campaigns, focusing on measles, in post-independence Guinea-Bissau, which led to the creation of the Bandim research center. They reported that live vaccines (BCG, measles, etc.) seem to provide an additional non-specific, beneficial effect, and are associated with decreased mortality beyond the rate expected due to the decrease in the vaccine-targeted disease.[11] However, this was offset by their findings that the administration of inactivated vaccines only (especially diphtheria-pertussis-tetanus – but also others), seemed to be associated with increased childhood mortality, with a significant preponderance for girls.[11] It has also been observed that the administration of a live vaccine with or after administration of an inactivated vaccine seems to abolish this phenomenon.[11]

Combating vaccine hesitancy requires awareness of misfortunes and controversies

Certainly, vaccination is a crucial strategy to achieve better health outcomes for many infections. Even some

Table 2 – Conceivable factual origin of anti-vaccine arguments

Anti-vaccine argument	Possible factual origin[a]
Vaccines cause death/increase mortality	Misfortunes/accidents: Lübeck, Cutter[b]
	High titre measles vaccine in Africa was associated with increased risk of death[c]
	Increased risk of death after inactivated vaccines[c]
Vaccines cause the disease they should prevent	Oral polio-vaccine (OPV) strains, especially OPV 2, reverted (became pathogenic) and cause most polio cases in Africa now[d,e]
	Dengvaxia (dengue) vaccine may be associated with an increased risk of severe disease if there is no prior infection before the first vaccine dose (antibody-dependent enhancement)[d]
	Inactivated measles vaccine may cause atypical (more severe) measles[c]
	Varicella vaccine strain can become latent and cause herpes zoster (HZ), although HZ rates are lower in vaccinated than unvaccinated[d]
Vaccines cause (severe) side-effects/ disease	Increased risk of Guillain-Barré syndrome – swine flu vaccine 1976[b]
	Increased risk of narcolepsy after H1N1 pandemic flu vaccine in 2009[b]
	Increase in risk of intussusception after rotavirus vaccine[b]

[a]: it should be noted that most of the reported absolute risks are very small, especially when compared to the overall beneficial effects the respective vaccine has/had.
[b]: see Table 1 for a description.
[c]: see text for description and reference.
[d]: see references[2,6,7,9,10]
[e]: Wild poliovirus is considered eliminated in Africa since 2020 and sporadic cases are imported. WHO reports less than 1000 vaccine derived cases per year in 2020-2023.[12]

cancers, which represent a significant cause of morbidity and mortality worldwide, are now preventable through vaccination. While the minority (thought to be less than 10%) with extreme anti-vaccine views may not be swayed by these achievements or scientific arguments, most vaccine-hesitant people ('fence sitters') are usually open to discussion. Certainly, subjective concerns of a religious, cultural, or societal nature must be carefully respected to maintain the population's trust in HCW.

It should be noted that some common anti-vaccine arguments (Table 2) have hinged on a historically true incident or a factually correct misfortune, even if the dimension of any occurred damages or risks was very small when compared to all the beneficial effects of the respective vaccination. Considering that extensive literature suggests that humans often lack a solid understanding of the statistically correct dimension of risks, vaccine-hesitant people may lack the scientific literacy to realistically assess and understand the risk/benefit ratio and consequently be fearful, knowing that some anti-vaccine arguments might refer to some historically true incident or some factual controversy.

What could happen if HCW are not so aware of occurred misfortunes and current controversies? They may be more likely to rebuff vaccine doubters and reject any criticism as fake or untrue and provide 'generic information' that all vaccines are 100% safe, which may be perceived as patronizing and incorrect. This can easily erode the much-needed trust necessary to persuade vaccine-doubters to see the scientific evidence favouring vaccines for personal protection and as a public health good. As everything else in medicine, it is sound knowledge which allows one to respond best to vaccine-hesitancy, not only the capacity to debunk bizarre myths but especially the ability to explain the scientific facts (even the 'bad ones') in a convincing way.

AUTHOR CONTRIBUTIONS

VLPJ, EV: Conception and writing of the manuscript.

TH: Conception, writing, and critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

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Epidemiology of Psoriasis in Portugal: A Population-Based Study

Epidemiologia da Psoríase em Portugal: Um Estudo de Base Populacional

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ABSTRACT

Introduction: Psoriasis is a common, chronic, and inflammatory skin disorder with a high personal, social and economic burden and important implications for healthcare systems. The aim of this study was to provide an epidemiological characterization of individuals with psoriasis in Portugal.

Methods: A large observational, cross-sectional, nationwide, population-based survey study developed by the Portuguese Psoriasis Group of the Portuguese Society of Dermatology and Venereology (GPP-SPDV). A structured questionnaire was designed and applied by experienced interviewers to a random, representative sample of Portuguese individuals with psoriasis and/or psoriatic arthritis. Patients were considered to have psoriasis if they replied positively to one of the following questions: "Does any physician have ever diagnosed you with psoriasis?" or "Do you have a skin disorder characterized by scaling, reddish skin lesions located in the elbows/knees/scalp?".

Results: A total of 6381 individuals were interviewed, of which 283 met the criteria for psoriasis, corresponding to a prevalence rate of 4.4% (95% CI 3.95 – 4.98). Out of the participants that met psoriasis criteria, 24% had suggestive signs/symptoms but did not have a clinical diagnosis established and were not being monitored by a physician. Although more than 70% of participants had active disease (scaling, erythema, or pruritus) and one third had joint symptoms, only 12% were on systemic treatment. Fifty percent of participants with psoriasis (n = 139) had relevant comorbidities (most frequently depression/anxiety and cardiometabolic diseases). Sixteen percent of participants with psoriasis (n = 46) reported that psoriasis interfered with their daily activities (median impact of 5 in a 0 – 10 scale) and 12% mentioned the disease had an impact in their sexual life (median impact of 5 in a 0 – 10 scale).

Conclusion: The results of this study suggest that the prevalence rate of psoriasis is likely to be high in Portugal, and several gaps exist at different levels of healthcare delivery to these patients, from diagnosis to treatment. This study provides important data for the future planning of interventions targeting the improvement of psoriasis care in Portugal.

Keywords: Arthritis, Psoriatic/epidemiology; Portugal; Psoriasis/epidemiology; Surveys and Questionnaires

RESUMO

Introdução: A psoríase é uma doença inflamatória crónica da pele com um elevado impacto ao nível pessoal, social e também económico nos sistemas de saúde. Este estudo foi desenhado com o objetivo de providenciar uma caracterização epidemiológica da população de doentes com psoríase em Portugal.

Métodos: Estudo observacional, transversal, nacional, de base populacional desenvolvido pelo Grupo Português de Psoríase da Sociedade Portuguesa de Dermatologia e Venereologia (GPP-SPDV). Para o efeito, desenhou-se um questionário que foi posteriormente aplicado por entrevistadores experientes a uma amostra aleatória e representativa dos indivíduos portugueses com psoríase e/ou artrite psoriática. Os critérios para diagnóstico de psoríase neste estudo incluíram a resposta positiva a pelo menos uma das seguintes questões: "Já foi diagnosticado com psoríase por algum médico?" ou "Tem alguma doença da pele que curse com lesões descamativas avermelhadas localizadas nos cotovelos/joelhos/escalpe?".

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Resultados: Foi realizado um total de 6381 entrevistas. Destas, 283 corresponderam a indivíduos com psoríase de acordo com critérios pré-estabelecidos, correspondendo a uma prevalência de 4,4% (IC 95% 3,95 – 4,98). Dos participantes que cumpriram os critérios para psoríase, 24% tinham sinais ou sintomas sugestivos, mas não tinham diagnóstico clínico estabelecido ou acompanhamento médico. Apesar de mais de 70% dos participantes terem doença ativa (descamação, eritema ou prurido) e um terço ter sintomas articulares, apenas 12% estavam a receber tratamento sistémico e menos de um terço estavam a ser acompanhados por um médico. Cinquenta porcento dos participantes (n = 139) referiram comorbilidades relevantes (sendo as mais frequentes depressão/ansiedade e doenças cardio-metabólicas). Sessenta por cento dos participantes com psoríase (n = 46) admitiram que a psoríase interferia com as suas atividades de vida diária (impacto mediano de 5 numa escala de 0 – 10), sendo que 12% referiram ainda um impacto na vida sexual (impacto mediano de 5 numa escala de 0 – 10).
Conclusão: Os resultados do estudo sugerem que a prevalência da psoríase parece ser elevada em Portugal, existindo atualmente várias lacunas no que concerne à prestação de cuidados de saúde a estes doentes, desde o diagnóstico ao tratamento. Este estudo providencia informação importante para o planeamento de estratégias interventivas que visem melhorar os cuidados de saúde aos doentes com psoríase.
Palavras-chave: Artrite Psoriática/epidemiologia; Inquéritos e Questionários; Portugal; Psoríase/epidemiologia

INTRODUCTION

Psoriasis is a common chronic inflammatory skin disorder that affects 0.51% to 11.43% of the population.[1] Visible lesions, skin symptoms and consequent discomfort trigger a negative cascade that markedly decreases the quality of life of patients. When compared with other chronic disorders (including cancer, ischemic heart disease and congestive heart failure), only depression and chronic lung disease were shown to impair psychological quality of life more than psoriasis.[2] The disease burden is further increased by the frequently associated comorbidities, such as metabolic syndrome and cardiovascular disease. Due to the importance of the psoriasis burden, the World Health Organization (WHO) raised awareness of this disease in the 67th World Health Assembly, in 2014. In its Global Report, WHO recognized psoriasis as a "chronic, noncommunicable, painful, disfiguring, and disabling disease for which there is no cure".[3] The high burden of psoriasis was also highlighted, resulting from the "inaccurate or delayed diagnosis, a lack of access to care, and therapeutic options which are limited in their ability to achieve patient satisfaction".[3]

The etiology of psoriasis is thought to be multifactorial, involving a combination of genetic, immunological and environmental factors.[4,5] Its prevalence is known to vary according to the geographic location and cultural environment, and there is currently an unmet need to better characterize the epidemiology of psoriasis on a country-basis.[1] To our knowledge, only one small study in Portugal that was published in 2000 has made an attempt to estimate the prevalence of psoriasis, but no further characterization of this population was performed.[6] Over the last decade, advances concerning the pathophysiology of the disease and the development of highly effective biologic drugs revolutionized the natural history and management of psoriasis.[7] However, a considerable proportion of patients remains undertreated.[8] Most of this data is unknown to the Portuguese psoriatic population. Therefore, the proper characterization of the Portuguese population with psoriasis is essential so that better nationwide strategies and protocols that can address the current needs in healthcare regarding this frequent dermatosis can be developed.

This study protocol was designed to obtain an epidemiological characterization of psoriasis in Portugal by recruiting and studying a random, representative sample and applying a specifically developed questionnaire. The aim of this study was to describe the prevalence of psoriasis, as well as the clinical characteristics, impact in quality of life, comorbidities, and treatment patterns of patients with psoriasis.

METHODS

This was a nationwide, epidemiological, observational, cross-sectional study that was designed to characterize the Portuguese population with psoriasis and/or psoriatic arthritis and to estimate the prevalence of psoriasis in Portugal. The Institute of Public Health of the University of Porto approved the protocol, and all participants gave their oral consent before participation. The study was performed in accordance with the tenets of the Declaration of Helsinki.

The study protocol consisted of a structured phone questionnaire with a limited duration of 20 minutes and was applied between May 2021 and November 2021. The questionnaire included six main sections: section I: focusing on the demographic characterization of the overall sample; section II: focusing on the demographic characterization of the subsample with psoriasis; section III: focusing on the social habits, medications, and co-morbidities of participants with psoriasis; section IV: focusing on the clinical characteristics and burden of psoriasis; section V: focusing on the treatment of psoriasis; section VI: focusing on psoriatic arthritis.

Patients were considered to have psoriasis if they replied positively to one of the following questions: "Has any physician ever diagnosed you with psoriasis?" or "Do you have a skin disorder characterized by scaling, reddish skin lesions located in the elbows/knees/scalp?". Psoriatic arthritis was defined as a positive answer by patients with psoriasis to one of the following questions: "Have you been diagnosed with psoriatic arthritis?" or "Are you attending rheumatology

appointments due to joint problems?" or "Have you ever had a swollen painful joint in the hands, feet, wrists, ankles or knees?".

The sample was collected by a random selection of telephone numbers from distinct geographic regions of Portugal with the aim of achieving a distribution matching that of the Portuguese population. Using this strategy, we warranted a random sampling representative of the target population. Our methods and strategy were in line with other similar previous studies.[8] A total of 80 000 phone numbers were set as the target sample size using the aforementioned method. We estimated extracting 40% of valid numbers, and a positive participation response rate of 50%, corresponding to a total of 16 000 participants. Considering that the estimated prevalence of psoriasis is 2.5%, we set a target sample size of 400 individuals aiming for an effect size of 16%, a power of 90% and a significance level of 0.05%. All phone calls were tried for a predefined number of attempts and time schedules. The inclusion criteria consisted of individuals who were residents in Portugal at the time of the study (regardless of the nationality). The exclusion criteria included: individuals living in nursing homes/prisons or other similar institutions and individuals with communication barriers (cognitive or neurological disease, deafness). We also excluded phone numbers attributed to enterprises/institutions. All information was collected and managed by experienced professionals in interviewing and health data collection.

In order to ensure the representativity of the sample, its demographic characteristics were compared to those from the Portuguese population using data provided by the National Statistics Institute (Instituto Nacional de Estatística, INE).

Statistical Analysis

For the comparison of proportions, the Pearson's chi-squared test if its assumptions are met, otherwise Fisher's exact test. In the case of comparison of two proportions, continuity correction was performed. Descriptive statistics were presented as total number (n) and percentage for categorical variables and as mean and standard deviation (SD) or median and first/third quartiles (Q1, Q3 respectively). The pooled prevalence of psoriasis was presented with the respective 95% confidence intervals (95% CI). Statistical analyses were performed with R, Version 4.2.1 with a significant level value of 0.05.

RESULTS

A total of 6381 individuals were interviewed by phone call and of those, 283 met the criteria for psoriasis. The main results of the questionnaire by section are presented below.

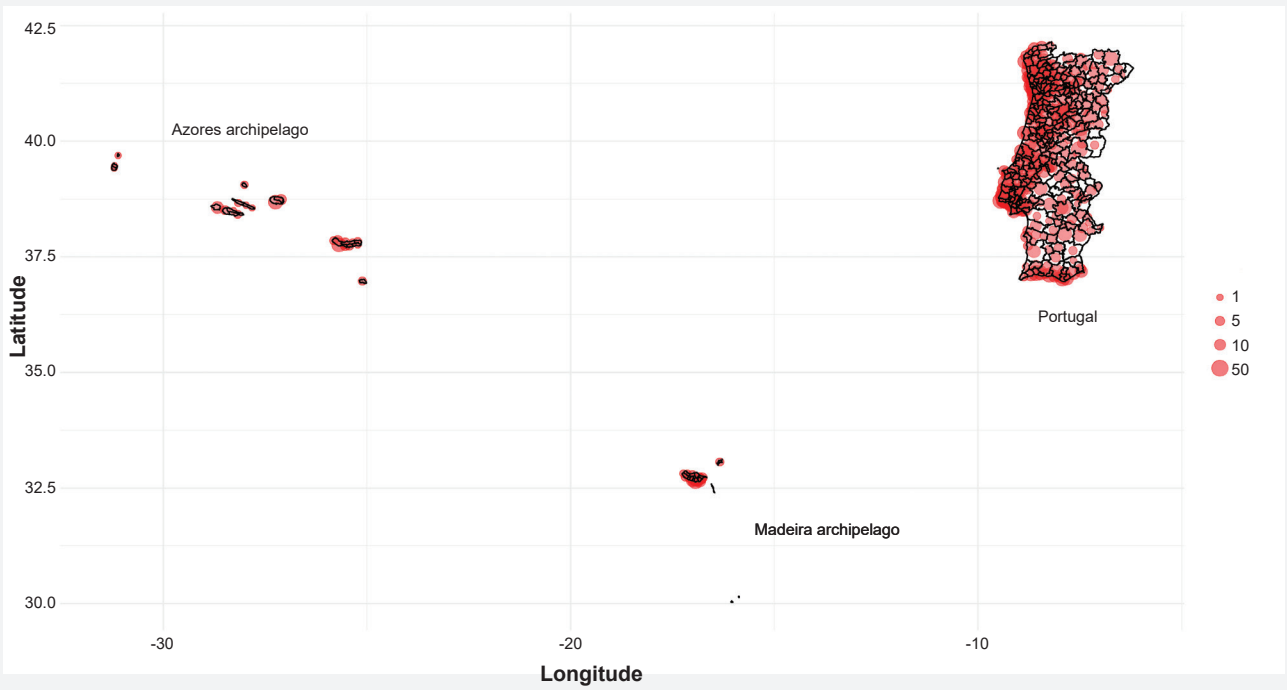

Figure 1 – Geographic representativity of the sample (n = 6381). The figure represents the geographic distribution of the sample by latitude (y axis) and longitude (x axis). The red circles on the left represent the sample size. Most of the sample corresponded to Portugal (latitude ranging 36º to 42º, longitude ranging from -6º to -9º). The islands of Madeira (cluster with latitude 32º - 33º) and Azores (cluster with longitude 25º - 31º) are also represented in the sample.

Section I: Demographic characterization of the total sample

The geographical characterization of the sample is presented in Fig. 1. The sample homogenously represented the territory of Portugal, including the archipelagos of Madeira and Azores, with no significant differences for age, gender or education level when compared with the population data for Portugal provided by the National Statistics Institute [Appendix 1, Table 1 (https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19048/15021)]. Fifty-two percent (n = 3284) of participants were female and the majority (71%, n = 4494) were aged between 25 and 64 years-old, following a distribution that is representative of the Portuguese population [Appendix 1, Table 1 (https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19048/15021)]. Most of the sample (61%, n = 2333) had at least 10 years of education.

Section II: Subsample of patients with psoriasis

A total of 283 participants met the criteria for psoriasis, corresponding to a prevalence rate of 4.4% (95% CI 3.95 - 4.98). From those, 133 (47%) were female and 196 (69%) were over 40 years old. Out of the 283 participants who met the criteria for psoriasis, 216 (76%) had been diagnosed by a physician: in 57% (n = 160) the diagnosis was performed by a dermatologist, in 11% (n = 30) by a family physician, and in 1% of cases (n = 4) by a rheumatologist. The remaining 67 participants (24%) met the selected criteria for psoriasis, although without a previous clinical diagnosis of psoriasis.

Section III: Habits, medications, and comorbidities in patients with psoriasis

More than half of the patients with psoriasis (n = 164, 59%) were/had been smokers and the majority (n = 249, 89%) were consumers of alcoholic beverages (no quantitative data was collected) (Table 1). In addition, more than 80% (n = 229) had a sedentary lifestyle and about 60% (n = 163) were overweight or obese (Table 1).

Fifty percent of participants with psoriasis (n = 139) had relevant comorbidities, requiring regular medical follow-up, and were taking regular medication (n = 148, 52%) (Table 1). The most frequent comorbidities were depression/anxiety (n = 35, 18%), and cardiometabolic diseases [hypertension (n = 20, 10%), dyslipidemia (n = 20, 10%), diabetes (n = 12, 6%) and cardiovascular disease (n = 6, 3%) (Table 1). Of note, 5.5% of participants had an oncologic disease (cured or active).

Section IV: Clinical characteristics and burden of the disease

The mean age at which the first signs and symptoms appeared was 29.7 (16.9) years-old, but the diagnosis of psoriasis was made at a mean age of 32.6 (16.6) years, with no sex-related differences found (p = 0.68). Most participants (n = 170, 62%) had no family history of psoriasis.

Although nearly 80% had visited a dermatologist at least once in their lifetime (n = 227, 82%), only 32% (n = 90) were currently being monitored by a physician at the time of the study, which in most cases was a dermatologist (n = 61, 68%) (Table 2). From the 90 patients regularly monitored, 39 patients (43%) had appointments twice a year or more. Although only a minority of 1.5% of the patients (n = 4) had ever been hospitalized due to psoriasis, 17% (n = 47) had to seek an urgent appointment at least once.

For those patients with active disease, the most common locations were the scalp (59%) followed by elbows (50%), trunk (31%), knees (27%), face (25%), genitals (18%), nails (15%), and palms and soles (9%). The most frequently reported signs and symptoms at the time of the study were scaling (n = 173, 80%), erythema (n = 161, 73%) and pruritus (n = 158, 73%), and the most bothersome signs/symptoms were pruritus (n = 146, 66%), followed by scaling (n = 112, 50%) (Table 3). Of note, 31% mentioned joint pain as the most bothersome symptom (Table 3).

Sixteen percent of participants with psoriasis (n = 46) reported that the disease interfered with their daily activities and 12% (n = 32) reported an impact in their sexuality (median impact of 5 in a 0 - 10 scale). At least 7% (n = 18) admitted that psoriasis interfered with the career choice, and 4% (n = 12) had been on leave because of the disease (Table 3). Nearly 7% (n = 20) also admitted that psoriasis affected the way they took care of their children, and the majority (n = 165, 61%) admitted fearing that their children may develop the disease (Table 3). For those patients with active psoriasis lesions, the median global impact of psoriasis in daily life (in a 0 - 10 scale) was 5 (Table 4).

Section V: Psoriasis treatment

Data on psoriasis treatment is presented in Table 5. Most participants with psoriasis had never received systemic treatment, neither oral (n = 176, 70%) nor injectable (n = 253, 95.8%). At the time of the interview, most patients were applying topical treatments (n = 194, 71%), while 12.1% were being treated with systemic therapy (only 3.3% were receiving biologic therapy). Regarding treatment satisfaction, the most satisfied patients were those receiving injectable drugs (median satisfaction of 9 in a 0 - 10 scale). The factors that were mostly valued by patients in a treatment strategy included complete resolution of lesions (n = 143, 64%), fastest onset of action (n = 142, 65%), pruritus relief (n = 109, 50%), quality of life improvement (n = 97, 45%) and treatment safety (n = 87, 41%).

Section VI: Psoriatic arthritis

A total of 120 participants (42%) with psoriasis met the selected criteria for psoriatic arthritis although only 8% (n = 22) mentioned they had the diagnosis confirmed by a physician. For those patients who met our criteria for psoriatic arthritis, the majority mentioned the joint manifestations appeared after skin involvement (60%, n = 72) and only a minority were being monitored by a rheumatologist (n = 8, 3%). Nearly 25% (n = 31) admitted their joint pain was not controlled. Detailed data is presented in Table 2 of the Appendix 1 (https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19048/15021).

DISCUSSION

This study presented an epidemiological characterization of a representative sample of Portuguese individuals with psoriasis. A total of 283 participants met the criteria for psoriasis – 76% of the patients were previously diagnosed by a clinician, corresponding to a prevalence rate of 4.4% (95% CI 3.95 - 4.98). As such, we can estimate that about 440 000 individuals may have psoriasis in Portugal, and this represents a huge burden for healthcare systems and calls for appropriate screening strategies. The published prevalence rate of psoriasis ranges between 0.51% to 11.43% worldwide, varying with the geographical region, and the broad interval highlights the absence of high-quality real world epidemiological data.[1,9] Prior to our work, only one small study estimated the prevalence rate of psoriasis in Portugal in 2000, and the estimate found was slightly lower: 1.9%.[6] However, this study was based on a small sample from a restricted geographic location and no further characterization of this population was performed. The increased prevalence rate that we found may also reflect the recent improvements in the knowledge and diagnosis of the disease as well as the effect of disease awareness campaigns.

Importantly, this study suggests that psoriasis may be underdiagnosed in Portugal. Although most participants with psoriasis (n = 216, 76%) had been diagnosed by a physician – we found a gap of three years between the appearance of the first symptoms and the time of clinical diagnosis, a delay that we know that can impact the natural history of the disease.[4] Nearly a quarter of patients (n = 67, 24%) reported that they had lesions compatible with psoriasis, but no official clinical diagnosis. Both public awareness and screening strategies are needed to address the current challenges of early recognition and management of psoriasis in Portugal. Concerning this matter, a recently published study[10] analyzed the unmet needs in the diagnosis and management of psoriasis in Spain from a different range of perspectives. The authors of that study raised awareness about the importance of not only addressing the clinical effectiveness of new treatments, but most importantly, to focus on patient-related challenges (including educational strategies) in the decision-making process, in clinical communication and at a social level. It is therefore essential to establish multidisciplinary and multidimensional strategies when approaching psoriasis.[11-13]

We also found that psoriasis was undertreated in our Portuguese sample, which is in accordance with the published literature.[14] Although an accurate evaluation of severity of the disease was not performed in our study, we know from the literature that 20% to 30% of the population with psoriasis has moderate-to-severe disease, requiring systemic therapy.[14] In our population, more than 70% of participants had active disease and nearly one third had joint pain. From those with active disease, 73% (n = 158) of patients reported such an important symptom as pruritus. However, only 12% of participants were on systemic treatment and less than one third were being monitored by a physician. In addition, an important proportion of patients reported skin lesions in highly impactful and difficult-to-treat areas such as the scalp (59%), nails (15%), palms and soles (9%), or sensitive areas such as the face (25%) and genitals (18%) – similar proportions compared to the worldwide literature.[15,16] These findings reinforce the extent of undertreatment in our population, since current guidelines recommend systemic therapy for patients with psoriasis affecting body areas where it is difficult to apply topical treatment such as the scalp, nails or palms and soles – leading to lower adherence to treatment and worse control of the disease – and sensitive regions such as face and genitals due to the high impact of the disease in patient quality of life.[17]

Regarding the treatment strategy, our population with psoriasis valued the complete resolution of skin lesions (64%), fastest onset of action (65%) and relief of pruritus (50%) the most. Interestingly, these factors were even more valued than improvement of quality of life (45%) or treatment safety (41%). These findings suggest that our population with psoriasis seeks highly effective and fast-acting therapeutic options, such as the biological agents that we now have in the armamentarium of psoriasis management and that should be considered in each patient when other options fail.

More than half of participants with psoriasis in our study had comorbidities requiring clinical monitoring. The most frequent one was depression/anxiety, and our rate (18%) is in line with the literature that estimates that depression affects between 9% - 55% of patients with psoriasis.[18] Depression in these patients is thought to be multifactorial. In fact, several factors play a role in the psychological burden of the disease, including the stigma that these patients feel due to the appearance of their disease, as well as uncontrolled symptoms – in our

sample, mainly pruritus (66.1%) – that impact daily activities, or the fear of transmitting the disease to their children.[19] Evidence also suggests that the chronic pro-inflammatory state can play a role and explain the increased rates of anxiety and depression in patients with psoriasis.[18,20] The high burden of the disease results in an enormous impact of psoriasis on the quality of life of patients,[2] and this is clear in our sample: participants admitted psoriasis interfered with daily activities (16%), with sexual life (12%), with family life (7% admitted the disease affected the way they took care of their child), and with their career (4% were on sick leave due to their disease). Nearly 61% of the patients with psoriasis had a constant fear that their children would also develop psoriasis. The psychosocial impact of psoriasis in undeniable, and it has been shown to severely debilitate patients in several dimensions since the onset of the first symptoms.[21] Patients with psoriasis are at risk for absenteeism and their sexual life is also negatively affected by the disease, as patients may experience feelings of embarrassment and shame due to their condition.[22] The psychological and social impact of psoriasis is a very important aspect in patient counselling, and providers should be aware of this – not only through the assessment of traditional measures such as Dermatology Life Quality Index (DLQI), but also through the evaluation of highly impactful symptoms such as pruritus, skin pain or burning sensation –, as the patients' understanding of the illness may be limited and support lacking.

Cardiovascular risk factors were among the most frequent comorbidities (obesity, hypertension, diabetes, and dyslipidemia). This relationship has also been highlighted in the literature and the evidence linking psoriasis and cardiovascular diseases is strong.[23] The explanation for this association appears to involve a combination of a predisposing chronic inflammatory state and higher rates of unhealthy behavioral risk factors including smoking and alcohol use and a sedentary lifestyle, that were also found to be present in our sample – nearly 59% were/had been smokers, nearly 89% were consumers of alcoholic beverages, and nearly 58% were sedentary.[24-27] Obesity has also shown to be a key component of psoriasis[28] and in our sample more than half of the participants were overweight or obese. Adipose tissue is known to actively contribute to the proinflammatory state in psoriasis, thus potentiating the consequences of the disease.[29] Not only obesity is a risk factor for developing psoriasis, but it also aggravates an existing condition.[30] In addition, overweight may interfere with the medical management of the disease, reduce the efficacy of biological drugs, and further increases the cardiovascular burden that is already high in these patients.[30,31] The high prevalence rate of overweight/obesity in our sample also highlights the unmet need of addressing this modifiable risk factor in the Portuguese population. The long-term consequences of the association between psoriasis and cardiovascular risk factors are undeniable, with a recent cohort study demonstrating that patients with moderate-to-severe psoriasis have increased mortality that is mostly related with cardiovascular diseases.[32] Besides this strong association, no clear guidelines have been defined for screening cardiovascular disease in patients with psoriasis. In addition, the role of the new drugs in the natural history of psoriasis-associated cardiovascular disease also remains poorly understood. Specific programs and preventive strategies using multidisciplinary approaches should be considered in the future. It is also important to highlight the role of physical activity as potentially modifiable risk factor for psoriasis. In our sample, more than 80% (n = 229) of the individuals reported they had a sedentary lifestyle. Decreased levels of physical activity have been associated with psoriasis, for both psychological and physiological reasons.[33] The stigma of psoriasis may work as a psychological barrier in this population, leading to social avoidance, including sports and collective showers. In addition, as discussed, obesity and overweight are more prevalent in patients with psoriasis, which may therefore impact the physical performance of these patients. Importantly, the lack of physical activity may further aggravate the cardiovascular risk profile in these patients.[33] Therefore, patients with psoriasis should be encouraged to modify their sedentary habits, as this may further reduce the cardiovascular risk load, obesity, and act as a measure to promote generalized psychological wellbeing in this population.

Psoriasis is notably associated with psoriatic arthritis, a specific form of inflammatory arthritis usually characterized by asymmetry and seronegativity for rheumatoid factor.[5] In our sample, around 40% of participants with psoriasis met our criteria for suspected psoriatic arthritis that most commonly appeared after skin changes, and this is in line with the literature that points out that psoriatic arthritis is found in about 20% - 30% of the patients with the skin condition.[34] Importantly, only 8% had a formal clinical diagnosis, which could mean that there is an unmet need for addressing psoriatic arthritis in patients with psoriasis . One possible explanation for this last finding could be the low number of patients (3.2%) that were seeing rheumatologists due to joint problems. However, we should stress that several conditions may cause joint complaints in adults and older populations (more than 30% of participants had more than 55 years of age), leading to the fact that our proportion – nearly 40% – of patients with suspected psoriatic arthritis could be overestimated and required further evaluation and

investigation that could not be performed in a 20-minute phone questionnaire. Another limitation is the fact that in our questionnaire we did not consider axial complaints for the diagnosis of psoriatic arthritis. Axial psoriatic arthritis is an important condition that is difficult to diagnose and should not be forgotten in daily practice by all clinicians seeing patients with psoriasis. As the burden of psoriatic arthritis has important implications for healthcare policies and treatment implementation, it is essential to raise awareness to this problem among all physicians that manage psoriasis so that the prevalence of undiagnosed disease can be reduced.[35]

Our results can also be compared to those of the Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) that included several participants from different countries – Portugal was not included, but several European countries such as Spain, France, United Kingdom, Italy, or Germany were.[36] The prevalence rate of patients with psoriasis ranged from 1.4% (Spain) to 3.3% (Canada). In European countries, just like in our sample, 22.3% to 52.1% had scalp psoriasis - it was the most common location of skin lesions in the United Kingdom, France and Germany, and the second most common in Spain and Italy. Regarding psoriasis in sensitive areas, and like our population, 4.5% - 10.6% of patients in European countries had genital psoriasis, while 5.9% - 21.5% had facial skin lesions. Pruritus was the most bothersome symptom (31% - 41%, compared to 66% in our population). The analysis of data from European countries also highlighted the importance of underdiagnosis of psoriatic arthritis in their populations: 36% of patients that did not have a diagnosis of psoriatic arthritis reported joint pain, and 30% of patients had more than four joints affected. Undertreatment was also highlighted in the results and discussion of the study: particularly in Spain and similarly to our study population, the vast majority (nearly 84%) were receiving no systemic treatment.

Although the importance of our study is clear, it has potential limitations that should be considered. Firstly, it is based on data from responders to a questionnaire and this study design has inherent biases, including the respondents' inaccurate recall and interpretation of questions, as well as nonresponse. Secondly, our results should not be extrapolated to other cultural environments with, for instance, medical facilities and systems that are different from those in Portugal. Thirdly, the survey lacked a control group. Fourthly, our study did not include any traditional measure of quality of life, such as the Dermatology Life Quality Index (DLQI), due to the limited time for the phone questionnaire. Finally, our definitions were partially based on the positive answer to a clinical scenario and not on an objective evaluation of patients, which may have over/under-diagnosed both psoriasis and psoriatic arthritis and limited our capacity to assess the severity of the disease. We also have to highlight that we did not reach our initial target sample size (283 of 400). However, this size allowed us to achieve the same power, significance level and an effect size of 0.19 or larger, which is not meaningfully different from our initial aim. Besides the potential limitations, the main strengths of our study are its design that was planned to avoid selection bias and provide a representative sample of the Portuguese population, thus providing data that is essential for future intervention strategies in this population.

CONCLUSION

This cross-sectional population-based study provides important data for the future planning of interventions aiming to improve the management of psoriasis patients in Portugal. The pooled prevalence rate of psoriasis in our study was 4.4%, and the survey results suggest that several gaps exist in the diagnosis, management, and treatment of these patients: our sample of patients were likely underdiagnosed and undertreated, with insufficient management of their clinical condition. This is a high-risk population due to the associated comorbidities and implications in terms of quality of life and healthcare burden. Further nationwide strategies are important to address the current challenges, and to disseminate the best healthcare possible to psoriasis patients in Portugal.

AUTHOR CONTRIBUTIONS

All authors contributed to the literature research, study conception and design, data collection, analysis and interpretation, drafting of the article, version review, critical review of the article's content and 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

TT has received consultancy and/or speaker's honoraria from and/or participated in clinical trials sponsored by AbbVie, Amgen, Almirall, Amgen, Arena Pharmaceuticals, Biocad, Biogen, Boehringer Ingelheim, Bristol Myers Squibb,

Celgene, Fresenius-Kabi, Janssen, LEO Pharma, Eli Lilly, MSD, Mylan, Novartis, Pfizer, Samsung-Bioepis, Sanofi-Genzyme, Sandoz and UCB.

FMB has received consultancy and/or speaker's honoraria from Janssen.

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PMB has received honoraria for acting as a consultant and/or as a speaker for AbbVie, Janssen, Novartis, LEO Pharma, Almirall, Sanofi, Viatris, Lilly, L'Oréal and Cantabria Labs. He has also worked as a principal investigator in clinical trials supported by Pfizer, AbbVie, Sanofi and Novartis.

MJPL has received consultancy and/or speaker's honoraria from and/or participated in clinical trials sponsored by AbbVie, Almirall, Boehringer Ingelheim, Janssen, LEO Pharma, Eli Lilly, Mylan, Novartis, Pfizer, Sanofi-Genzyme, Viatris.

GMP has received consultancy and/or speaker's honoraria from and/or participated in clinical trials sponsored by AbbVie, Almirall, Janssen, LEO Pharma, Lilly, Novartis.

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Fatores de Risco para Alta Prorrogada por Motivos Sociais: Um Estudo Retrospectivo

Risk Factors for Delayed Discharge due to Social Factors: A Retrospective Study

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RESUMO

Introdução: Os hospitais deparam-se com uma percentagem das suas camas ocupadas por doentes cuja alta hospitalar está limitada não pela alta clínica, mas por outros fatores. Cria-se a necessidade da identificação precoce dos indivíduos que estão em risco de uma alta prorrogada por motivos sociais (internamentos sociais - IS), de forma a reduzir gastos e a acrescentar valor que se traduza em saúde dos utentes. O objetivo deste estudo foi identificar os fatores de risco demográficos e clínicos que condicionam risco de internamento social.

Métodos: Foram analisados 582 internamentos referentes a um serviço de Medicina Interna de hospital terciário nos anos de 2018 e 2019, e consideradas as características demográficas e comorbidades clínicas dos doentes. Foi feita uma regressão logística binominal ajustada ao sexo, idade e internamento clínico prolongado, para identificação de potenciais fatores de risco associados a alta prorrogada.

Resultados: Foram incluídos neste estudo um total de 473 doentes admitido no serviço no período de dois anos em estudo. Noventa e quatro (19%) doentes tiveram a sua alta prorrogada, dos quais 64 (68%) eram do sexo feminino. As principais características estatisticamente significativas associadas a maior risco de prorrogação da alta foram o sexo feminino (OR 2,84, 95% IC 1,65 – 4,90, *p-value* < 0,05), o internamento clínico prolongado (OR 2,64, 95% IC 1,60 – 4,937, *p-value* < 0,05) e a diabetes *mellitus* (OR 1,87, 95% IC 1,08 – 3,23, *p-value* < 0,05); para além destes, a presença de insuficiência cardíaca (OR 0,52, 95% IC 0,27 – 0,99, *p-value* < 0,05) e de doença renal crónica (OR 0,34, 95% IC 0,14 – 0,86, *p-value* < 0,05) associaram-se a um risco inferior de prorrogação de alta.

Conclusão: O sexo feminino, os internamentos clínicos prolongados e diabetes *mellitus* associaram-se a um maior risco de internamento social, enquanto a insuficiência cardíaca e a doença renal crónica se associaram a um risco inferior de IS. Estes achados servem de base de construção para um futuro estudo multicêntrico para criação de uma regra de predição clínica para estratificação do risco de internamento social na população portuguesa.

Palavras-chave: Alta do Doente; Custos Hospitalares; Factores de Risco; Medicina Interna; Portugal; Tempo de Internamento; Vulnerabilidade Social

ABSTRACT

Introduction: The hospital setting faces a rate of bed occupation by patients whose discharge is limited by other factors apart from clinical needs. This urges the need for an early identification of the patients at risk of delayed discharge due to social factors in order to reduce expenses and to add value that converts itself into the patient health. The aim of this study was to identify the demographic and clinical factors that may be associated with delayed discharge.

Methods: Demographic and clinical comorbidity data on 582 patients of an internal medicine ward from a tertiary hospital center during the years 2018 and 2019 was analyzed. A binomial logistic regression model was used, adjusted for sex, age, and length of clinical stay, in order to identify potential risk factors associated with delayed discharge.

Results: A total of 473 patients admitted in the internal medicine ward throughout the two years of study were included. Ninety-four (19%) of these patients had their discharge delayed beyond their clinical needs; sixty-four (68%) of these were females. The most representative age was between 75 - 89 years old (45.7%). The characteristics that significantly differed between both non-delayed and delayed discharge were female sex (OR 2.84, 95% CI 1.65 – 4.90, *p*-value < 0.05), prolonged clinical stay (OR 2.64, 95% CI 1.60 – 4.937, *p*-value < 0.05) and diabetes mellitus (OR 1.87, 95% CI 1.08 – 3.23, *p*-value < 0.05). Besides these, the presence of heart failure (OR 0.52, 95% CI 0.27 – 0.99, *p*-value < 0.05) and chronic kidney disease (OR 0.34, 95% CI 0.14 – 0.86, *p*-value < 0.05) were associated with a lower risk of delayed discharge.

Conclusion: Female sex, a prolonged clinical stay and diabetes mellitus were associated with a higher risk of delayed discharge, while heart failure and chronic kidney disease were associated with a reduced risk. These findings create a basis for a possible future multicentre study aimed at creating a clinical prediction rule to stratify the risk of delayed hospital discharge in the Portuguese population.

Keywords: Hospital Costs; Internal Medicine; Length of Stay; Patient Discharge; Portugal; Risk Factors; Social Vulnerability

INTRODUÇÃO

Os hospitais deparam-se com uma percentagem não-negligenciável das suas camas ocupadas por doentes cuja situação clínica já não justifica o internamento, mas que, por diferentes motivos, necessitam de um prolongamento da sua estadia. Estes internamentos são coloquialmente denominados de internamentos sociais (IS) – internamentos em que a alta hospitalar é prorrogada para além da alta clínica. Os dados do Barómetro de Internamentos Sociais de 2017 - 2019, apresentado pela Associação Portuguesa de Administradores Hospitalares, demonstram que estes números podem alcançar cerca de 4% a 6% do total das camas e uma duração média de internamento de 60 a 90 dias. Estes dados podem ser extrapolados para um gasto nacional anual acima de €83M.[1,2]

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O prolongamento do internamento além da necessidade clínica conduz a um aumento das complicações potencialmente evitáveis como infeções nosocomiais, agravamento do estado de dependência e da saúde mental dos doentes.[3–6] Para além do impacto individual, esta ocupação de camas tem também impacto nos internamentos eletivos pois a manutenção de taxas de ocupação acima do recomendado condiciona adiamento da atividade programada, com aumento dos custos, listas de espera e a consequente degradação dos cuidados de saúde disponíveis para o doente.[4]

Apesar de se tratar de um problema complexo, as causas apontadas focam-se no foro organizacional e social, como a falta de resposta da Rede Nacional de Cuidados Continuados Integrados (RNCCI) e incapacidades familiares, sejam estas últimas do foro socioeconómico ou de adaptação à dinâmica necessária à reintegração do doente.[4,7,8] No entanto, apesar da relevância do problema, os dados quantitativos sobre as várias dimensões deste fenómeno a nível nacional são escassos, dificultando uma atuação direcionada.

Giraldo *et al* e Gaughan *et al* levantam a hipótese de que, para além dos fatores acima mencionados – externos à instituição hospitalar –, o próprio sistema interno e ineficiências processuais poderão contribuir, nomeadamente no atraso da execução dos planos de alta, erros médicos, falta de recursos humanos qualificados, etc.[4,6]

Em 1978, Schrager *et al* concluiu que a identificação precoce e a sinalização de novos doentes idosos nas primeiras 48 horas permitia uma antecipação da alta hospitalar em cinco dias, comparativamente aos doentes sem uma avaliação social.[9] Estes achados demonstram que a necessidade de uma intervenção precoce, e a redução da ocupação hospitalar sem motivo é um tema importante debatido há décadas. No entanto, para possibilitar uma intervenção efetiva, é necessário caracterizar o processo e os doentes em risco, e promover decisões baseadas em dados e factos. Esta é uma necessidade não apenas identificada, mas desejada pelos hospitais, sendo crucial a caracterização e identificação dos fatores demográficos e clínicos.[5,10]

Este estudo retrospetivo observacional observou 582 indivíduos internados numa enfermaria de Medicina Interna de um hospital terciário português, de forma a avaliar a hipótese de associação entre determinados fatores clínicos, demográficos e um maior risco de IS. A identificação de fatores de risco clínico sustentará a atuação precoce aquando do internamento de doentes cujo perfil de risco seja coincidente com os achados do estudo, potenciando a estratificação de prioridades na preparação da alta e fundamentando os protocolos adequados para o apoio ao utente e a sua transferência para a comunidade. O objetivo principal deste estudo foi determinar as características clínicas e demográficas que, nesta população, possam ser possíveis fatores de risco para IS, e o objetivo secundário foi calcular o custo estimado dos dias perdidos em camas ocupadas por internamentos sociais.

MÉTODOS

Tipo de estudo

Este estudo é um estudo de coorte retrospetivo.

Avaliação da Comissão de Ética

O protocolo e desenho deste estudo foram aprovados pela Comissão de Ética do Centro Hospitalar Universitário de Lisboa Central, seguindo as normas estabelecidas pelo Regulamento Geral da Proteção de Dados (RGPD) (EU)2016/679, de 27 de abril de 2016. O Investigador Principal foi responsável pelo tratamento da informação, tendo em conta os princípios da minimização dos dados e a sua anonimização.

Amostra

Tamanho da amostra

Através da fórmula de Fleiss,[11] para um rácio de 5:1 internamentos clínicos para internamentos sociais, previsto com base na situação da enfermaria sob avaliação durante os anos precedentes - para se obter um nível de confiança de 90% e uma potência de 80%, estimando um *odds ratio* de 1,50, seria necessária uma amostra total mínima de 548 doentes – o que, baseado em dados prévios, corresponderia a dois anos de internamentos nesta enfermaria.

Seleção de doentes

Foram selecionadas pessoas internadas numa enfermaria de Medicina Interna de um centro hospitalar terciário de Lisboa em 2018 e 2019, com idade superior ou igual a 18 anos. Foram excluídos os doentes falecidos durante o internamento ou transferidos para outras enfermarias, outros hospitais ou em altas contra parecer médico.

Recolha de dados

Os dados foram colhidos no momento da alta do serviço, sendo recolhidas as informações demográficas (idade, sexo) assim como a presença de comorbilidades clínicas que permitissem calcular o índice de comorbilidade de Charlson (ICC) – um índice de classificação de comorbilidade para predição de mortalidade a curto e a longo prazo que utiliza uma quantificação cumulativa da carga de doença a partir do conjunto específico de diagnósticos secundários[12] – hipertensão arterial (HTA), diabetes *mellitus* 2 (DM), doença hepática crónica (DHC), doença renal crónica (DRC), insuficiência cardíaca (IC), historial de enfarte agudo do miocárdio (EAM), doença pulmonar obstrutiva crónica (DPOC), historial de doença cerebrovascular (DCV),

demência, úlceras pépticas, doença arterial periférica (DAP), doenças do tecido conjuntivo (DTC) e malignidade. Os itens hemiplegia e infeção por vírus da imunodeficiência humana fazem parte da escala, mas não foram discriminados nos resultados – o primeiro por ser uma sequela e não uma patologia por si só, o segundo por preocupações por parte do Comité de Ética do Centro Hospitalar. Estes diagnósticos englobaram doenças já previamente diagnosticadas e patologias diagnosticadas durante o internamento.

Foram ainda colhidas informações sobre o internamento, nomeadamente as datas de internamento, alta clínica, alta hospitalar, e eventual proveniência de cuidados paliativos.

Conceitos-chave

Disponível para consulta na Tabela 1.

Análise estatística

Todas as análises foram feitas com recurso ao *software Statistical Package for Social Science*® versão 26 (IBM® SPSS, Inc, Chicago).

Foi escolhida uma abordagem estatística não paramétrica devido às características da amostra. As medidas descritivas são apresentadas como mediana e distância interquartil (DIQ); as variáveis categóricas são apresentadas como número e percentagem da amostra (%). As variáveis contínuas foram comparadas com recurso ao teste de Mann-Whitney-Wilcoxon. O teste qui-quadrado (χ^2) ou o teste exato de Fisher foram usados para comparar variáveis categóricas sempre que apropriado. De modo a avaliar comorbilidades médicas como preditores de IS, foi realizada regressão logística binomial, ajustada ao sexo, escalão etário e internamento clínico prolongado (potenciais preditores não relacionados com comorbilidades – o isolamento social é mais comum nos idosos, particularmente do sexo feminino, e longos períodos de internamento condicionam perda de autonomia) nos grupos de doentes com e sem IS. Realizou-se regressão logística binomial nos mesmos grupos para avaliar o índice de comorbilidades de Charlson como fator preditor de IS, com ajuste ao sexo, escalão etário e internamento clínico prolongado.

Os dados deste estudo estavam completos, não se verificando informação em falta, logo, o tratamento estatístico de dados perdidos não se aplica.

Todos os intervalos de confiança (ICs) relatados foram intervalos bilaterais de 95% e o nível de significância para todos os testes (*p-value*) definido foi de 0,05.

RESULTADOS

Descrição dos doentes com IS e sem IS

A identificação inicial incluiu um total de 582 doentes. Após aplicação dos critérios de exclusão (doentes falecidos ou transferidos para outro hospital), foram considerados como amostra os restantes doentes (473), divididos por grupos “Com IS” e “Sem IS” (Fig. 1).

Do total de 473 doentes elegíveis, 94 (19,87%) foram objeto de internamento social (Fig. 1, Tabela 2). O sexo mais prevalente na amostra com IS foi o feminino (68%). A mediana de idades total foi de 78 anos, com uma diferença estatisticamente significativa entre grupos, com o grupo com IS com uma mediana de 81 anos, comparativamente aos 77 anos do grupo sem IS.

A mediana de dias em IS foi de 4,50 dias (DIQ 1 - 11), sendo que a prorrogação mais prolongada correspondeu a 91 dias. O número total de dias em IS é de 944 dias, o que corresponde a 20,03% do número total de dias de internamento para todos os doentes analisados.

O internamento clínico prolongado ocorreu em 41% dos doentes sem IS, com uma mediana de sete dias de internamento, comparativamente a uma percentagem de 62% dos doentes com IS, nos quais houve uma mediana de 10 dias.

Verificou-se heterogeneidade intergrupos com diferença estatisticamente significativa em fatores como o sexo, a idade e o número de dias em internamento clínico prolongado, bem como na percentagem de internamentos clínicos prolongados. Relativamente às comorbilidades médicas, não houve uma diferença estatisticamente significativa.

Preditores clínicos para IS

Uma regressão logística binomial ajustada à idade,

Tabela 1 – Conceitos-chave do estudo e sua definição

Conceito	Definição
Internamento clínico	Tempo de internamento cuja necessidade teve justificação clínica
Alta clínica	Fim da justificação clínica para o internamento
Internamento clínico prolongado	Internamento cuja duração foi superior a oito dias, tendo em conta o proposto pelo Ministério da Saúde da República Portuguesa, como a duração média de internamento de oito dias para uma enfermaria de Medicina Interna de hospital terciário[13]
Internamento social	Tempo de internamento após a alta clínica; estadia sem justificação clínica
Internamento hospitalar	Total da estadia hospitalar, inclui o internamento clínico e o IS
Alta hospitalar	Fim da permanência em meio hospitalar

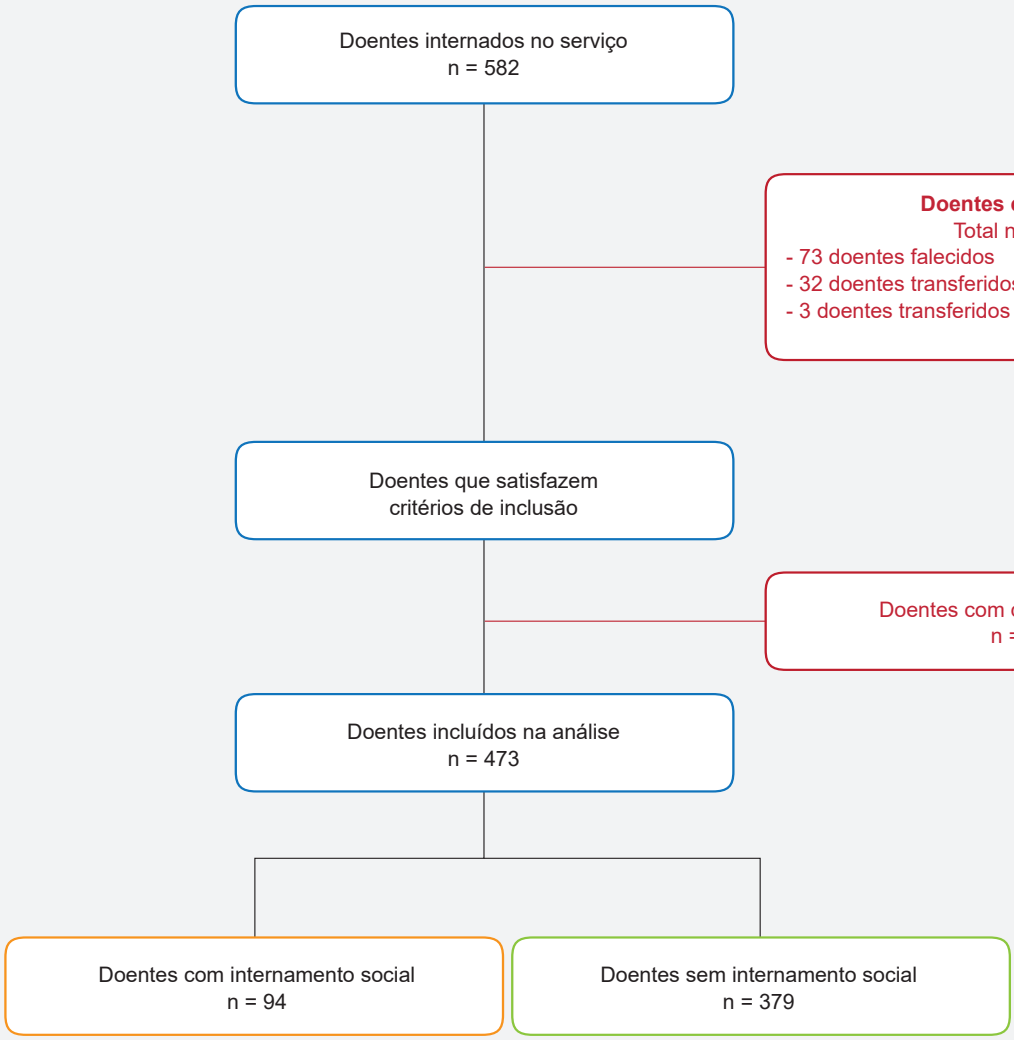

Figura 1 – Tratamento de dados analisados e aplicação dos critérios de inclusão

sexo e internamento clínico prolongado (Tabela 3) foi realizada para verificar os efeitos das diferentes comorbilidades médicas na probabilidade de os doentes terem uma alta prorrogada. O modelo de regressão logística foi estatisticamente significativo, $\chi^2(4) = 57{,}043$, $p < 0{,}0005$. O modelo explicou 18,0% (Nagelkerke R^2) da variância do protelar da alta e classificou corretamente 81,4% dos casos. A sensibilidade foi de 13,8%, a especificidade de 98,2%, o valor preditivo positivo de 65,0% e o valor preditivo negativo de 82,0%. A área sob a curva ROC foi de 0,734 (IC 95%, 0,679 a 0,790), que é um nível aceitável de discriminação de acordo com Hosmer *et al.*[14] Das variáveis preditoras, apenas três foram estatisticamente significativas: DM, IC e DRC.

Os doentes com diabetes tiveram 1,87 vezes mais *odds* do que os doentes com IC (0,52) ou DRC (0,34) de verem protelada a sua alta do internamento.

Foi realizada igualmente regressão logística binomial (Tabela 3), ajustada à idade, sexo, internamento clínico prolongado. O modelo de regressão logística foi estatisticamente significativo, $\chi^2(4) = 33{,}463$, $p < 0{,}0005$. O ICC não mostrou impacto estatisticamente significativo.

Impacto económico

O estudo reporta-se a dados de 2018 e 2019, numa época de gestão não afetada pela pandemia de 2020, o que possibilita a análise do impacto económico associado aos internamentos sociais.[1] Apesar de não ter sido incluído neste estudo o diagnóstico dos utentes admitidos, nem a sua codificação em grupos de diagnósticos homogéneos (GDH), a consulta do Relatório de Gestão e Exercício de Contas de 2019 da unidade hospitalar permite calcular

Tabela 2 – Caracterização descritiva da amostra total e por grupos

Caracterização geral		Amostra total (n = 473)	Sem IS (n = 379)	Com IS (n = 94)	*p-value*
Feminino, % (n)		50,9 (241)	**47,2 (179)**	**68,1 (64)**	**< 0,05**
Idade, anos (DIQ)		78 (64 – 85)	**77 (64 – 84)**	**81 (67 – 88)**	**< 0,05**
Escalão etário, % (n)	15 – 29	1,5 (7)	1,8 (7)	0	0,39
	30 – 44	5,3 (25)	5,5 (21)	4,3 (4)	
	45 – 59	12,1 (57)	12,9 (49)	8,5 (8)	
	60 – 74	22,8 (108)	22,7 (86)	23,4 (22)	
	75 – 89	45,7 (216)	45,6 (173)	45,7 (43)	
	> 89	12,7 (60)	11,3 (43)	18,1 (17)	
Tempo de internamento clínico, dias (DIQ)		8 (5 – 12)	**7 (5 – 11)**	**10 (6 – 15)**	**< 0,05**
Internamento clínico prolongado (> 8 dias), % (n)		31,5 (149)	**41,2 (90)**	**62,8 (59)**	**< 0,05**
Doentes em cuidados paliativos, % (n)		13,3 (63)	12,1 (46)	18,1 (17)	0,13
Comorbilidades					
HTA, % (n)		62,6 (296)	62,5 (237)	62,8 (59)	1,00
DM, % (n)		30,0 (142)	28,2 (107)	37,2 (35)	0,10
IC, % (n)		27,1 (128)	28,5 (108)	21,3 (20)	0,19
Demência, % (n)		21,6 (102)	20,1 (76)	27,7 (26)	0,12
Malignidade, % (n)		19,2 (91)	19,8 (75)	17,0 (16)	0,66
DCV, % (n)		18,6 (88)	16,9 (64)	25,5 (24)	0,07
DPOC, % (n)		15,2 (72)	14,2 (54)	19,1 (18)	0,26
DRC, % (n)		13,3 (63)	14,8 (56)	7,4 (7)	0,06
EAM prévio, % (n)		9,5 (45)	10,0 (38)	7,4 (7)	0,56
DHC, % (n)		8,7 (41)	9,2 (35)	6,4 (6)	0,54
DAP, % (n)		4,7 (22)	4,7 (18)	4,3 (4)	1,00
Úlcera péptica, % (n)		2,7 (13)	2,6 (10)	3,2 (3)	0,73
DTC, % (n)		2,5 (12)	2,4 (9)	3,2 (3)	0,71
ICC, pontos totais (DIQ)		5 (4 – 7)	5 (4 – 7)	6 (5 – 7)	0,11

HTA: hipertensão arterial; DM: diabetes *mellitus* 2; IC: insuficiência cardíaca; DCV: doença cérebro vascular; DPOC: doença pulmonar obstrutiva crónica; DRC: doença renal crónica; EAM prévio: Historial de enfarte agudo do miocárdio; DHC: doença hepática crónica; DAP: doença arterial periférica; DTC: doenças do tecido conjuntivo; ICC: Índice de Comorbilidade de Charlson.

uma média destes dados, assim como da demora média do internamento, esta última corroborada com acesso ao *website* do Serviço Nacional de Saúde.[15] Assim, o índice de *case mix* – o índice de complexidade resultante da produção hospitalar codificada em GDH – de internamento do Centro Hospitalar Universitário Central de Lisboa foi de 1,33 e a demora média foi de entre 7,9 a 8,8 dias (dependendo das fontes).[16,17] Com estes dados, sabendo que o preço base único de internamento contratualizado em 2019 era de €2285, temos um valor médio de €3039, resultando numa estimativa de €345 a €384 por dia de internamento.

No presente estudo foram contabilizados um total de 994 dias em IS, o que significa que em 994 dias houve camas ocupadas sem que houvesse uma justificação clínica para tal. De acordo com o contrato programa para 2019, e tendo em conta o histórico de produção e complexidade deste centro hospitalar, é estimado que o valor associado a esta ocupação atinja os €342 930, sendo este um valor consideravelmente subvalorizado. Importa ainda referir que existem no mesmo centro hospitalar sete enfermarias e que este estudo apenas incluiu uma em anos distintos, pelo que o valor real de despesa deverá ser proporcionalmente superior.

DISCUSSÃO

As principais características estatisticamente significativas associadas a um maior risco de prorrogação da alta foram o sexo feminino (OR 2,84, 95% IC 1,65 – 4,90, *p-value* < 0,05), o internamento clínico prolongado (OR 2,64, 95% IC 1,60 – 4,937, *p-value* < 0,05) e a diabetes *mellitus* (OR 1,87, 95% IC 1,08 – 3,23, *p-value* < 0,05). Para além destes, a presença de insuficiência cardíaca (OR 0,52, 95% IC 0,27 – 0,99, *p-value* < 0,05) e de doença renal crónica (OR 0,34, 95% IC 0,14 – 0,86, *p-value* < 0,05) associaram-se a um risco inferior de prorrogação de alta.

Para além dos condicionantes de caráter exclusivamente social, a prorrogação da alta hospitalar é condicionada por diversos fatores clínicos e organizacionais. Apesar dos condicionantes sociais serem os que inicialmente limitam o retorno ao domicílio ou a instituições de apoio social, o

Tabela 3 – Modelos (não ajustado e ajustado) de regressão logística de potenciais preditores de IS

Geral	***Odds ratio* para IS** (modelo não ajustado)	***p-value***	***Odds ratio* para IS** (modelo ajustado)	***p-value***
Feminino	2,38 (1,48 – 3,84)	< 0,05	**2,84 (1,65 – 4,90)**	**< 0,05**
Idade (intervalo)	-	0,55	-	0,89
Internamento prolongado	2,41 (1,51 – 3,84)	< 0,05	**2,64 (1,60 – 4,37)**	**< 0,05**
Cuidados Paliativos	1,60 (0,87 – 2,94)	0,31	1,68 (0,77 – 3,638)	0,19
Comorbilidades				
HTA	1,01 (0,63 – 1,61)	0,97	0,80 (0,46 – 1,41)	0,44
DM	1,51 (1,05 – 2,90)	0,09	**1,87 (1,08 – 3,23)**	**< 0,05**
IC	0,68 (0,39 – 1,17)	0,16	**0,52 (0,27 – 0,99)**	**< 0,05**
Demência	1,52 (0,90 – 2,56)	0,11	1,33 (0,71 – 0,99)	0,38
Malignidade	0,83 (0,46 – 1,50)	0,54	0,85 (0,40 – 1,78)	0,66
DCV	1,69 (0,99 – 2,88)	0,06	1,20 (0,64 – 2,25)	0,58
DPOC	1,43 (0,79 – 2,57)	0,24	1,95 (0,99 – 2,8)	0,05
DRC	0,46 (0,20 – 1,05)	0,07	**0,34 (0,14 – 0,86)**	**< 0,05**
EAM prévio	0,72 (0,31 – 1,67)	0,45	0,77 (0,35 – 2,21)	0,78
DHC	0,67 (0,27 – 1,64)	0,38	0,93 (0,34 – 2,49)	0,88
DAP	1,12 (0,37 – 3,40)	0,84	0,98 (0,29 – 3,31)	0,97
Úlcera péptica	1,21 (0,33 – 4,51)	0,77	2,24 (0,54 – 9,35)	0,27
DTC	1,36 (0,36 – 5,11)	0,39	1,56 (0,37 – 6,62)	0,55
ICC	1,05 (0,97 – 1,15)	0,22	1,03 (0,93 – 1,14)	0,57

HTA: hipertensão arterial; DM: diabetes *mellitus* 2; IC: insuficiência cardíaca; IS: internamento social; DCV: doença cérebro vascular; DPOC: doença pulmonar obstrutiva crónica; DRC: doença renal crónica; EAM prévio: Historial de enfarte agudo do miocárdio; DHC: doença hepática crónica; DAP: doença arterial periférica; DTC: doenças do tecido conjuntivo; ICC: Índice de Comorbilidade de Charlson.

estado de dependência e a complexidade das condições clínicas poderão ser os responsáveis pelo desajuste entre as necessidades do indivíduo e a capacidade de adaptação ao contexto do utente e da sua rede de suporte.[18]

O tempo em IS da nossa amostra foi inferior ao relatado na literatura, com diferentes autores em contextos distintos a relatar durações medianas de 13 a 16 dias.[5,6] A nossa amostra encontrou uma demografia de IS que corrobora os achados nacionais. No Barómetro de Internamentos Sociais de 2019, 58% dos internamentos sociais foram do sexo feminino e 44% apresentavam-se acima dos 80 anos.[1] A congruência dos dados não é uma surpresa, dado que a nossa amostra se integra na região de Lisboa e Vale do Tejo, sendo esta a região nacional que mais contribui em episódios e dias de IS (41% do total nacional).[1]

A situação reportada também se verifica a nível internacional. No Brunei, por exemplo, o sexo feminino representa perto dos dois terços dos internamentos sociais, mesmo quando as amostras apresentam idades inferiores às reportadas em Portugal.[19] Este resultado pode ser interpretado considerando questões independentes da idade, como o papel social da mulher ou a epidemiologia distinta.

No entanto, as justificações para a prevalência do sexo feminino e para a mediana superior de idades apresentada pelo grupo sujeito a IS. podem ser exploradas em conjunto. Do ponto de vista cultural e considerando uma diferença em 2019 da esperança média de vida em Portugal do homem (de 78,1 anos) comparativamente à mulher (83,7 anos), o sexo feminino encontra-se mais suscetível à viuvez, significando uma menor estrutura de apoio e capacidade de resposta em situações de dependência.[5,20]

A identificação de fatores de risco clínicos definida como objetivo deste estudo permite acrescentar uma componente da avaliação clínica à triagem e estratificação da necessidade de intervenção do Serviço Social de forma precoce para reduzir o IS. Estas relações foram pesquisadas por outros autores, com parte dos achados sobreponíveis aos deste estudo. Husaini *et al* encontrou fatores como a DM, HTA, obesidade, dislipidemia e falência respiratória hipoxémica, assim como o ICC, com uma diferença estatisticamente significativa comparativamente ao grupo sem alta prorrogada.[19] Bai *et al* identificou também a demência, DCV, para além da idade e a DM.[5] Assim, os achados demográficos e clínicos mais consistentes na literatura, e com representação no presente estudo, são os dados demográficos relativos ao sexo feminino assim como a presença da comorbilidade de DM.

No entanto, nenhuma das publicações consultadas encontrou fatores protetores do IS, em particular, justificação clínica, pelo que os argumentos relativos à DRC ou IC enquanto fatores protetores serão especulativos. A situação crónica de maior necessidade de acompanhamento médico que estas patologias originam, bem como a proximidade dos cuidados médicos e a necessidade de adequar a dinâmica familiar ao contexto do doente poderão ser parte da resposta. Por outro lado, há que atender ao perfil destes

doentes: Brunner-La Rocca *et al* identificou que estas duas comorbilidades estavam associadas a uma combinação, em média, de mais de três comorbilidades, e afetavam em maior percentagem os homens.[21]

Para além das características demográficas e comorbilidades conhecidas em cada doente, deve ainda ser considerado um fator que condiciona a variação do estado de dependência do utente: a duração do internamento clínico. Em Espanha, Giraldo *et al* concluiu que a duração mediana do internamento clínico é de 16 dias na população sujeita a IS, comparativamente à mediana de sete dias na população sem IS.[6] No Brunei, Husaini *et al* realizou uma pesquisa retrospetiva em doentes com internamentos sociais, tendo verificado a mesma tendência para internamentos clínicos mais longos.[19] Neste estudo, a duração do internamento clínico foi também um dos fatores de risco para internamentos sociais já que retiveram os doentes em internamentos superiores a oito dias.

Um doente que se mantém durante mais tempo em meio hospitalar encontra-se necessariamente fora da sua rotina, torna-se mais sedentário e recebe menor estímulo à função e autonomia.[22,23] Estes achados parecem ser independentes do grau de complexidade ou severidade do diagnóstico de entrada e da sua progressão clínica.[22,23] Esta é também a principal justificação para a crescente necessidade de incluir no plano de alta hospitalar a intervenção dos profissionais de reabilitação nestes doentes, o que se refletiria de forma positiva na sua independência e na redução de complicações secundárias, tais como quedas ou *delirium*.[24,25]

A prorrogação de uma alta hospitalar tem um impacto negativo não só no utente - num momento de particular vulnerabilidade e exposição a potenciais reinfeções e agravamento da sua condição de saúde e independência - mas também na gestão hospitalar, tanto logística como economicamente.[5,26]

Segundo o Barómetro Social de 2019, cerca de 4,7% dos doentes internados apresentavam-se em situação de alta prorrogada, atingindo uma média nacional de 98,4 dias de internamento. Estes dados permitiram extrapolar, na mesma edição, um custo associado à alta prorrogada anual para valores acima de 83 milhões de euros.[1]

Aos gastos associados à manutenção destes indivíduos em meio hospitalar acrescem os custos de oportunidade. Estes refletem a atividade programada não realizada que se traduz em custos diretos para os doentes, cujo acompanhamento médico se vê adiado, assim como para o hospital, impossibilitado de atingir as metas contratualizadas ou assegurar as melhores práticas.[17]

Relativamente ao não cumprimento do serviço contratualizado, o centro hospitalar executou apenas 95% da atividade codificada com GDH médico, sendo a percentagem relativa ao GDH cirúrgico ainda inferior (81,9%).[15] Estas diferenças não poderão ser atribuídas na totalidade à problemática das altas sociais, mas é no entanto um fator a contabilizar.

Por outro lado, as boas práticas clínicas são também afetadas, com uma taxa de ocupação de internamento de 89,4% em 2019 (consideravelmente superior à média da OCDE, de 76%). O valor da taxa de ocupação-alvo definido como boa prática não é um dado consensual[27]; no entanto, o National Institute for Health and Care Excellence recomendou em 2018 um objetivo de 85%, o que asseguraria um melhor fluxo de doentes e capacitaria os serviços para responder a crises sanitárias, permitindo internar cada doente no local mais adequado às suas necessidades.[27,28]

A otimização de todo o processo deverá ser uma preocupação contínua, com atenção a todas as suas componentes. Um exemplo da falência da abordagem unidimensional no serviço nacional de saúde do Reino Unido foi reportado por Gaughan *et al,* que procurou a relação económica entre a disponibilidade e os preços dos lares e a ocupação de camas com internamentos sociais. O resultado confirmou que os internamentos sociais respondiam inversamente a um aumento da disponibilidade de camas em lares, embora apenas com efeitos moderados.[7]

Não sendo uma problemática recente (os primeiros artigos datam de 1950), as soluções implementadas até à data revelam estar aquém do necessário, demonstrando-se que o reforço do suporte dos serviços sociais nos países desenvolvidos resulta apenas em ligeira diminuição do número de internamento sociais.[6,8]

Assim, importa voltar a olhar para os restantes motivos que resultam em IS. Segundo o Barómetro de IS de 2019, 18% dos internamentos resultavam da incapacidade de resposta das famílias, o que corresponde a 28% do total de dias em internamento social. Esta representa a segunda causa de internamento (a seguir à disponibilidade da Rede Nacional de Cuidados Continuados Integrados – RNCCI), sendo a principal responsável pelo número total de dias em IS.[1]

A avaliação das necessidades físicas e psicossociais do doente e do cuidador deve ser o mais precoce possível. Esta avaliação inclui o levantamento de serviços e equipamentos a mobilizar, devendo incluir a perspetiva da tríade composta pelo doente, cuidador e profissionais de saúde. Para tal, a comunicação com os cuidadores deve ser oportuna e apropriada, garantindo não apenas a transmissão da informação, mas também o entendimento por parte do recetor e a disponibilização de uma pessoa de contacto (no hospital ou na comunidade) para as questões que possam surgir após a alta hospitalar.[29] A efetividade da comunicação que permite este levantamento é um tema fulcral e que não deve ser descurado.

Os erros de comunicação são reconhecidos como uma das principais causas para o erro na Medicina, com alguns autores a encontrar esta justificação para cerca de 70% dos erros.[30]

Um dos obstáculos à alta, resultante dos défices de comunicação, prende-se com a preparação das entidades que irão receber os doentes, sejam esses informais (familiares e cuidadores) ou formais (instituições de apoio social).[31,32]

Uma revisão da literatura realizada pela Cochrane, em 2021, demonstrou uma ligeira redução na estadia hospitalar em resultado da planificação eficaz de altas em função das necessidades especificas dos doentes, apesar de não se poder afirmar que tal signifique ganhos em saúde ou nos custos associados.[3]

Outra barreira identificada no estudo de Okoniewska *et al* foi a necessidade de clareza na atribuição de tarefas e responsabilidades entre os elementos das equipas.[30] O papel das equipas de gestão de altas é convergente com as soluções propostas por Okoniewska *et al* que, para além de um plano de alta eficaz e proactivo, propõe a realização de reuniões diárias especialmente dedicadas à preparação da alta. Este deverá responder a seis perguntas: a duração esperada do internamento de cada doente; quais os doentes a terem alta imediata e quais os obstáculos para tal; para onde irá o doente; qual o plano médico para o dia; quais as necessidades médicas para a alta e qual o seguimento que o doente terá.[30] Desta forma, e graças à visão abrangente proporcionada pela literatura existente, percebemos que esta é de facto uma problemática complexa, com uma abordagem necessariamente multidimensional.

Apesar deste estudo permitir um enquadramento e levantamento contextual da realidade dos dados de doentes sujeitos a IS, deve ter-se em conta as suas limitações. O viés pode apresentar-se sob forma de registo inferior ao real de determinadas patologias tendencialmente subdiagnosticadas, sobretudo em população idosa, tais como a demência – levando-nos a ignorar potenciais fatores de risco importantes. Adicionalmente, a classificação das patologias foi realizada de forma binária, sem quantificação da sua severidade. O viés de seleção poderá ter ocorrido em resultado da realização de análise retrospetiva de uma amostra de conveniência, realizada a partir de uma base de dados que não foi originalmente desenhada para responder a esta questão específica de investigação, e que omitia dados sociais e económicos que poderiam (seguindo uma metodologia similar) reforçar o desenho do perfil socio-clinico-económico dos indivíduos que beneficiariam da intervenção precoce. Apesar do tamanho adequado da amostra, a avaliação de várias patologias torna esta estimativa mais imprecisa.

Com base nas limitações e aprendizagens proporcionadas por este estudo, e uma vez que a literatura existente é proveniente de diversos contextos a nível demográfico, epidemiológico, de estruturas sociais e sistemas de saúde, os autores propõem a realização de um estudo de resposta ao mesmo objetivo mas com a robustez de um projeto multicêntrico e com a colheita prospetiva dos dados demográficos, clínicos e sociais, permitindo a criação de uma regra de predição clínica, à semelhança do realizado por Bai *et al* mas adaptado à realidade portuguesa.[5]

CONCLUSÃO

O sexo feminino, os internamentos clínicos prolongados e a diabetes *mellitus* associaram-se a um maior risco de IS, enquanto a insuficiência cardíaca e a doença renal crónica se associaram a um risco inferior de IS.

As conclusões deste estudo estabelecem a base para a criação de um sistema de avaliação e priorização dos doentes em maior risco de prorrogação da alta, possibilitando uma intervenção precoce e a redução dos gastos financeiros, com uma visão baseada na criação de valor para o utente e permitindo uma abordagem à alta mais individualizada e com maior qualidade.

CONTRIBUTO DOS AUTORES

MM: Desenho do estudo, colheita de dados, elaboração do manuscrito, análise estatística, discussão de resultados.

AM, FM, MN, MS: Colheita de dados, revisão de conteúdo, discussão de resultados, aprovação final.

DC: Desenho do estudo, revisão bibliográfica, revisão de conteúdo, discussão de resultados, aprovação final.

HL: Desenho do estudo, revisão de conteúdo, aprovação final.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFIDENCIALIDADE DOS DADOS

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

CONFLITOS DE INTERESSE

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

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ACTA MÉDICA PORTUGUESA
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Lung Cancer Screening: Low-Dose Thoracic Computed Tomography Performed in a High-Risk Portuguese Population

Rastreio do Cancro do Pulmão: Tomografia Computadorizada Torácica de Baixa Dose Realizada numa População Portuguesa de Alto Risco

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ABSTRACT

Introduction: The Urgeiriça mines were once the main uranium producer in Portugal. The aim of this study was to estimate the benefit of low-dose chest computed tomography (LDCT) for lung cancer screening in former miners that were considered as being at high-risk.

Methods: A subgroup of former miners of the Uranium National Company exposed to uranium and with a smoking load greater than 20 pack-years, agreed to perform a LDCT. The Fleischner Society Guidelines were used to classify the nodules and establish follow-up.

Results: Initially, 265 former employees of the Uranium National Company were included. The mean time of employment was 15 (0 - 45) years. The non-smokers represented 50.9% and 30.2% were ever smokers; the remaining chose not to respond. One diagnosis of lung cancer was initially made. In the second phase, a subgroup of 66 former miner underwent a LDCT, 37 of whom presented pulmonary nodules. Most computed tomography (CT) scans revealed one single nodule (n = 13) and the mean size was 5 (1 - 16) mm. A suspicious 16 mm spiculated nodule was evaluated with PET/CT, and percutaneous and surgical biopsies, ultimately revealing a benign lesion.

Conclusion: The data highlights the importance of lung cancer screening in high-risk populations. This was, to the best of our knowledge, the first study performed in Portugal and can act as a bridge towards a wider implementation in the country.

Keywords: Early Detection of Cancer; Lung Neoplasms/diagnostic imaging; Tobacco/adverse effects; Tomography, X-Ray Computed; Uranium/adverse effects

RESUMO

Introdução: As minas da Urgeiriça foram, no passado, o principal produtor de urânio em Portugal. O objetivo deste estudo foi estimar o benefício da tomografia computorizada de baixa dose (TCBD) no rastreio do cancro do pulmão em ex-mineiros considerados como grupo de alto risco.

Métodos: Ex-mineiros da Companhia Nacional de Urânio com exposição a urânio e carga tabágica superior a 20 unidades maço ano, concordaram realizar uma TCBD. As recomendações da Sociedade Fleischner foram utilizadas na classificação dos nódulos e no estabelecimento do *follow-up*.

Resultados: Duzentos e sessenta e cinco ex-trabalhadores da Companhia Nacional de Urânio foram incluídos. O tempo médio de trabalho nas minas foi 15 (0 - 45) anos. Os não-fumadores representavam 50,9%, 30,2% referiram fumar ou ter fumado e os restantes não responderam. Foi diagnosticado inicialmente um caso de cancro do pulmão. Numa segunda fase, entre os 66 ex-mineiros rastreados foram identificados 37 com nódulos pulmonares, a maioria com nódulo único (n = 13) e tamanho médio de 5 (1 - 16) mm. Um nódulo espiculado de 16 mm foi avaliado por PET/TC, e por biópsia transtorácica e cirúrgica, revelando uma lesão benigna.

Conclusão: Os dados destacam a importância do rastreio em populações de alto risco. Este foi, tanto quanto é do nosso conhecimento, o primeiro estudo realizado em Portugal, e pode atuar como ponte para uma ampla implementação no país.

Palavras-chave: Deteção Precoce da Neoplasia; Neoplasias do Pulmão/diagnóstico por imagem; Tabaco/efeitos adversos; Tomografia Computorizada; Urânio/efeitos adversos

INTRODUCTION

In 1898, the discovery of radium by Marie Curie started a new chapter in nuclear physics and its application settled the foundation of radiotherapy and brachytherapy.[1] The Mines of Urgeiriça, explored by the British, began operations in 1913, and provided radium to Marie Curie's laboratory. In 1938, the discovery of nuclear fission later transformed Urgeiriça in the main uranium producer in Portugal.[2]

The most important uranium deposits in Portugal were located in the central region of the country, namely in the western part of the Iberian Massif, including the Central Corridor (Serra da Estrela, Lousã, S. Pedro de Açor, Gardunha), and extending further to Serras do Buçaco, Caramulo e Montemuro. There were several mines in these locations, such as Urgeiriça, Bica, Castelejo, Cunha Baixa, Quinta do Bispo and Pinhal de Soto.[3]

During the Second World War, the United States government became involved in Urgeiriça. Their aim was to control all the uranium that was available and therefore prevent the development of the atomic bomb by the Germans. The Portuguese-English agreement for uranium extraction in Urgeiriça ended in 1962, and afterwards uranium was no longer stockpiled in the context of the Cold War stocks and

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started to cater to Portugal's energetic needs.[2]

During the golden period (1962 - 1990), uranium was essential for those who explored it and for the workers who built their lives around this activity. In the following period, contestation regarding uranium mining began as a result of both the environmental impact of radioactivity and public and occupational health issues.[2]

The mining facilities were permanently closed in 2001. Former workers and their families faced an increased risk of lung cancer due to longstanding exposure to radioactive material.

Age and family history are known risk factors for lung cancer, although smoking has been established as the most significant since the 1960s.[4,5] Other carcinogens known to be risk factors include the exposure to asbestos, radon or uranium. The connection between lung disease and mining was recognized in European studies as early as the 16th century and subsequent reports confirmed those early observations and attributed pulmonary malignancies to high radiation levels found in the mines.[5-7]

Considering this, in 2007 the Portuguese Government approved a Health Intervention Programme addressed to the former employees of the Uranium National Company (UNC) and their families. Its coordination was regionally headed by the Department of Public Health and locally by the Public Health Units of Nelas municipallity.

In 2015, eight years after the program implementation, the Portuguese Society of Pulmonology was consulted on that matter. Considering scientific evidence published on the use of low-dose chest computed tomography (LDCT) for lung cancer screening (LCS) in high-risk groups, namely the Nacional Screening Lung Trial (NSLT)[8-11] and the Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym: NELSON study),[11-13] this test was included as a diagnostic tool in the Health Intervention Program.

This study reports the start of the first lung cancer screening initiative study performed in Portugal and its aim was to estimate the benefit of LDCT in a high-risk group.

METHODS

The first phase of the study included an initial medical assessment to the former employees of the UNC and occurred in Hospital of São Teotónio, in Viseu, between the 8th of November 2007 and the 16th of February 2009.

A questionnaire validated by the department of Public Health was delivered to all participants, allowing data collection. The initial evaluation included chest x-ray, electrocardiogram and abdominal ultrasound. Laboratory tests included complete blood count, prothrombin time and activated partial thromboplastin time, erythrocyte sedimentation rate, urea, creatinine, electrolytes, glucose, cholesterol and triglycerides, uric acid, electrophoretic proteinogram, lactate dehydrogenase, thyroid stimulating hormone, triiodothyronine (T3) and thyroxine (T4), thyroglobulin, alpha fetoprotein, beta 2 microglobulin, CA-125, CA 19-9, CA 15-3, carcinoembryonic antigen (CEA), neuron-specific enolase (NSE) and a urine test.

All participants underwent annual follow-up in primary health care.

In 2015, a selected subgroup of former employees, considered at increased risk of lung cancer, both by the presence of exposure to uranium (worked directly in mining) and a smoking load greater than 20 pack-years, was included in the second phase of the study. These participants agreed to perform a LDCT for LCS after providing informed consent.

A 64 slice Siemens® equipment with the following exposure parameters was used: mAs - 78 efet; Kv 100; Collimation - 0,6 mm; Pitch - 0,7; TR - 0,33 s; CTDI - 3,50 mGy; DLP – 102 mGy/cm - Effective dose: 1.5 mSy). Reconstruction with high resolution algorithm and lung window, as well as low resolution algorithm and mediastinal window was performed.

The software for measuring pulmonary nodules through volumetry was not available in the Radiology Department at the time of the study.

The CT scans performed were reported by the two radiologists who worked together in this study and were blinded to the patients' health record.

The variables considered for the study were age, gender, smoking load, co-morbidities, working time periods in the mines and the presence of lung nodules in LDCT, as well as their characteristics, namely their number, size, and growing pattern. The Fleischner Society Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images were used to classify the nodules and establish patient follow-up.[4]

The Lung-RADS classification is recommended by the American College of Radiology and is applied in low-dose CT lung cancer screening. It was officially released in 2014 after published data from several studies, namely the NLST and the European NELSON trial.[14] The Lung-RADS criteria increased the size threshold for a positive baseline screening result from a 4 mm greatest transverse diameter to a 6 mm transverse bi-dimensional average, and therefore substantially reduced the false positive rate of the previous NSLT criteria; however, sensitivity also decreased.[15]

The Lung-RADS Version 1.1 points out the estimated prevalence rate of nodules in the general population according to the score.[16] A Lung-RADS score of 1 or 2 corresponds to a negative screening.[14] The Score of 1 refers to the presence of no pulmonary nodules or benign nodules, namely nodules with specific calcifications such as complete, central, popcorn, concentric rings and fat containing nodules. A Lung-RADS score of 2 includes nodules with a

benign appearance that have a very low (< 1%) likelihood of becoming a clinically active cancer due to size or lack of growth.

This study was approved by the Portuguese Government and coordinated by the Department of Public Health. All selected former miners of the UNC had a considerable high-risk of lung cancer, both due to direct exposure to uranium (from working directly in mining) and a smoking load greater than 20 pack-years, which agreed with the scientific evidence published on the use of LDCT for LCS in high-risk groups, and therefore this study respected ethical criteria. The participants were told about the benefits and potential harms of the LDCT and gave consent to the treatment of their data/clinical information and were aware that their name would not be attached to it, thus ensuring anonymity; they also understood that their consent would not remove their rights to privacy.

RESULTS

The first phase of the study included 265 former employees of the UNC, with a mean age of 58 (32 – 92) years. Eighty-seven percent (n = 230) were male and the remaining 13% (n = 35) female.

Eighty-five-point seven percent (n = 227) answered they were non-smokers, 10.9% (n = 29) responded that were current smokers and 3.4% (n = 9) chose not to answer. In those with current smoking habits, the average smoking load was 17 pack-years. Thirty-point two percent (n = 80) were ever smokers and 50.9% (n = 135) never smoked. Fifty participants did not answer (Table 1).

The number of years of employment in the UNC was known in 95.5% (n = 253) of the participants, with a mean of 15 (0 - 45) years (Fig. 1). The professional categories described were mining, chemical treatment of uranium, motor-vehicle drivers, and administrative services.

Table 1 – Smoking status and medical conditions of the former employees of the Uranium National Company included in the first phase of the study

	n = 265	%
Smoking status		
Non-smokers	227	85.7
Current smokers	29	10.9
No answer	9	3.4
Ever smokers	80	30.2
Never smokers	135	50.9
No answer	50	18.9
Medical conditions		
Already known	**191**	**72**
Most common:		
- Hypertension	70	35
- Diabetes type 2	13	6.5
- Arthritis	10	5
Previous malignancies:	**9**	**4.5**
- Lung adenocarcinoma	1	0.5
- Squamous cell lung cancer	1	0.5
- Prostate carcinoma	2	1.0
- Colorectal cancer	2	1.0
- Squamous cell carcinoma of the skin	1	0.5
- Eyelid basal cell carcinoma	1	0.5
- Chronic lymphocytic leukemia	1	0.5
Diagnosed in the medical evaluation	**9**	**3.4**
- Type 2 diabetes	4	44.5
- Arterial hypertension	2	22.2
- Prostate cancer	1	11.1
- Lung cancer	1	11.1
- Intestinal polyps	1	11.1
No relevant conditions	**65**	**24.6**

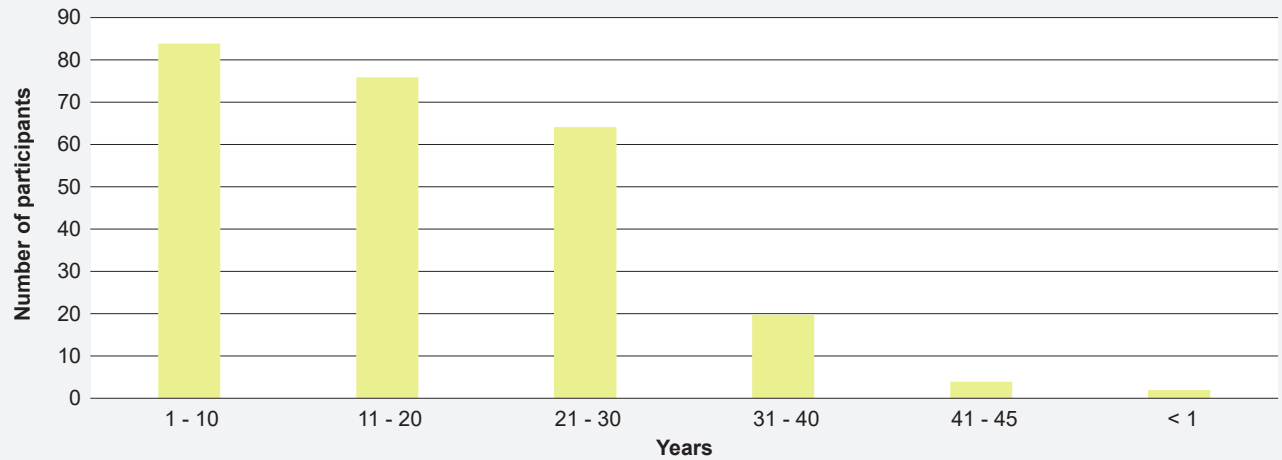

Figure 1 – Distribution for intervals of 10 years of labour of the former employees of the UNC – adapted from 2007 Health Intervention Programme addressed to former miners of Urgeiriça and their families

Table 2 – Data regarding the second phase of the study including a subgroup of former miners of the Uranium National Company

	n = 66
Smoking exposure: smoking load > 20 packs-year	66
Worked directly in mining	66
Documented pulmonary nodules in LDCT	**37**
- Solid	29
- Ground-glass	1
- Calcification	7
Location of the nodules (if multiple, it was considered the largest)	**30**
- Upper lobes	16
- Lower lobes	12
- Middle lobe	2
Nodule spiculation	**1**
Emphysema	
- Centrilobular in the upper lobes	4
Follow-up time	
- No indication for follow-up	41
- 12 months	7
- 18 months	5
- 24 months	12
- 5 years	1

Besides tobacco and uranium exposure, there was no history of thoracic radiotherapy or unequivocal known exposure to asbestos. Radon exposure was a confounding factor in this study.

Seventy-two percent (n = 191) of the participants presented to the first medical evaluation with previously known health conditions. The most frequent were hypertension (n = 70), diabetes/impaired glucose tolerance (n = 13), arthritis (n = 10) and previous malignancies (n = 9), namely two cases of lung cancer (Table 1). Regarding underlying benign pulmonary disease, three cases were identified: bronchitis, chronic obstructive pulmonary disease (COPD) and silicosis.

This initial medical evaluation included chest x-ray, electrocardiogram, abdominal ultrasound, and laboratory tests. Although the analytical parameters supported some previously known diagnoses, such as diabetes, they had limited clinical relevance for this study. New diagnoses were made in nine individuals, including one case of lung cancer.

The second phase of this study included a subgroup of 66 former miners at higher risk of developing lung cancer, who underwent LDCT. The mean age of this subgroup was 66 years (SD = ± 7.4). They were all smokers with a smoking load greater than 20 pack-years and worked directly in mining. The period of exposure was between 11 and 40 years. Thirty-seven participants had pulmonary nodules documented on LDCT, which were calcified in seven cases (Table 2).

Most positive CT scans revealed one nodule (n = 13), with a mean of two nodules detected (1 - 7) (Fig. 2). The mean size of the largest nodule had 5 (1 – 16) mm (Fig. 3) and the most suspicious one had 16 mm and presented spiculation (Fig. 2).

Among the 30 LDCT, 29 showed solid nodules and one pure ground glass nodule with no solid component. Regarding those with single solid nodules, eight scans presented a size below 6 mm and four scans within 6 - 8 mm; one single ground glass nodule had 10 mm. As for the remaining 17 low-dose scans that showed multiple nodules, in six scans the dimensions were below 6 mm, in seven scans within 6 - 8 mm and in four scans were greater than 8 mm. A suspicious nodule with spiculation (Fig. 3) was evaluated with PET/CT. The test revealed, in the apical-posterior segment of the upper left lobe, a spiculated nodule causing lung fissure pulling, with 16 x 12 mm of long axial diameter, hypermetabolic (SUV max: 2.3) and features suggestive of malignancy (Fig. 4). Therefore, a percutaneous lung biopsy was performed. The results showed a chronic inflammatory process with a fibrotic area and with no signs of malignancy. The case was discussed in a multidisciplinary team meeting, and a malignant lung tumor was diagnosed, considering the previously known risk factors and the imaging features of the lesion. Therefore, a surgical extemporaneous biopsy was performed. The anatomopathological results showed a cavitated lesion that may have corresponded to bronchiectasis, with a wall made up of inflammatory repair tissue with fibroblast proliferation and collagen deposition.

Patient follow-up was performed according to the 2017 recommendations of the Fleischner Society for incidental pulmonary nodules. In 36 out of 66 of the initial scans there were no relevant changes, and therefore the need for further imaging follow-up was not indicated. As for the remaining 30 scans, some patients underwent follow-up for 12 months, others 18 months, the majority 24 months, and one patient five years. The periods of radiological follow-up also varied, three-six months or six-twelve months and subsequently, if required, 18 to 24 months, depending on the nodules' dimension and growth, and if they were multiple or not.

Nodular growth was identified in four cases: 1 mm increase in the six-month follow-up of two patients, and 2 mm in the remaining twelve-month follow-up of two patients. Therefore, shorter intervals of surveillance were performed for 24 months. One patient, with nodular growth, also presented two new nodules with 5 and 7 mm, respectively. Attending to the small dimensions, PET-CT was not the primary option for follow-up. Subsequent control scans,

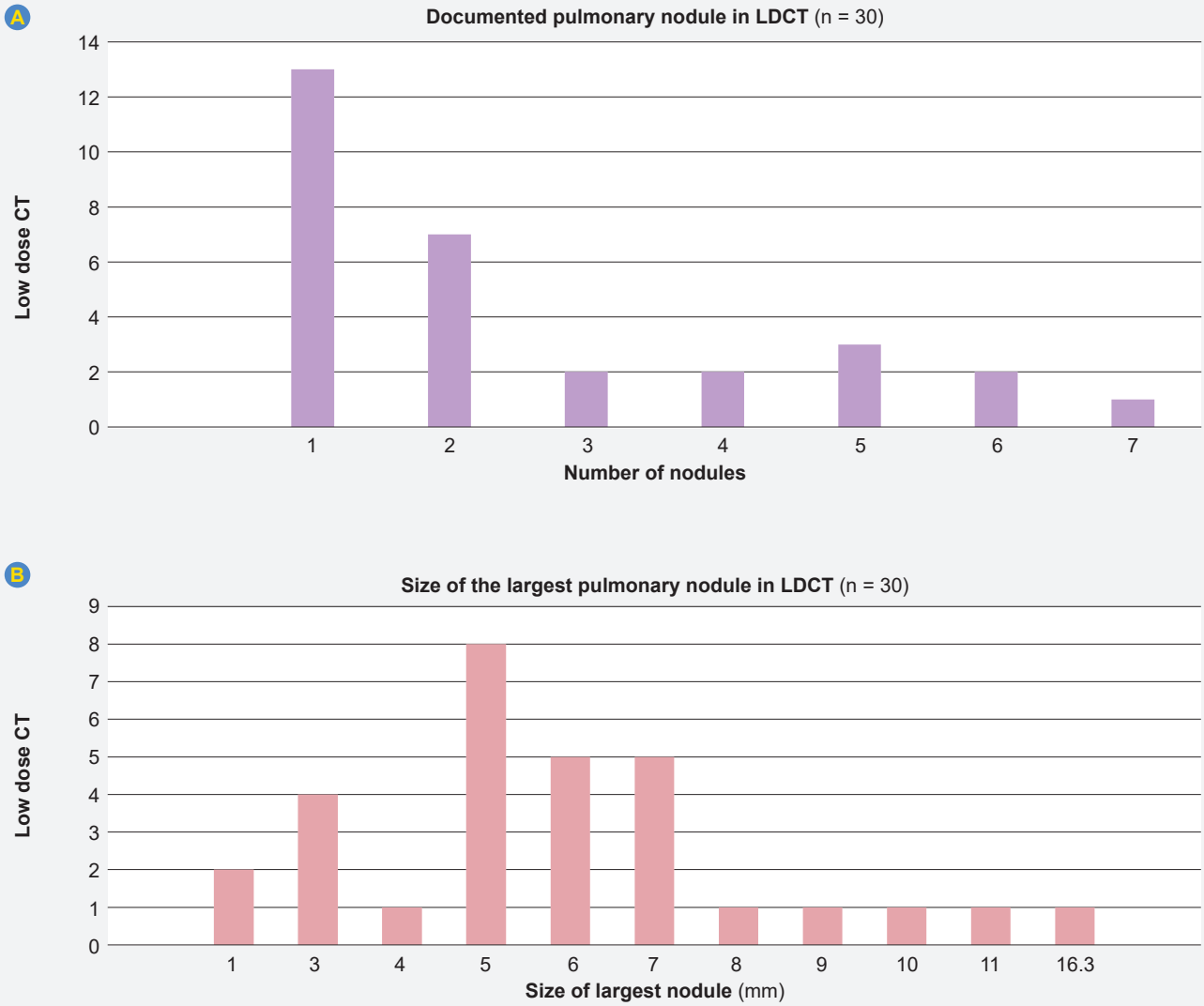

Figure 2 – Number of nodules (A) and size (B) of the largest pulmonary nodule in LDCT performed to a subgroup of 66 former miners of the UNC

in shorter intervals (three-six months), showed stability.

We also calculated the Lung-RADS Score[16] for our population and the prevalence of Scores 1 and 2 was 36/66 and 14/66, respectively, representing altogether 75.8% of the screening tests (50/66). As for the Score of 3 and 4, the prevalence in our study was of 13.6% (9/66) and 10.6% (7/66), respectively.

DISCUSSION

This study found a higher prevalence rate of pulmonary nodules among uranium former miners with a history of smoking compared with the one described in the literature for general population.[16]

Radon exposure was assumed as a confounding factor in this study, since radon results from the gaseous decomposition of uranium and radium, and therefore in uranium mining there is also simultaneous exposure to radon. Protracted exposure to radon decay products is the greatest radiation-related health risk from uranium-related mining, and is causally linked to lung cancer. A large proportion of the epidemiological studies performed, exploring adverse health effects from potential radionuclide releases from uranium mining and processing facilities, have lacked the capacity to evaluate causal inferences because of the ecological study design. Thus, assessing the potential risks of multiple combined exposures from uranium mining and processing activities is considered not feasible in practical terms.[17]

The Fleischner Guidelines were selected for lung nodule classification and to establish follow-up, even though they are formally meant to inform management of incidental pulmonary nodules.[4] The Lung-RADS classification could have been used instead, as it is similar to Fleischner's and is specifically designed for the subset of patients intended for low-dose screening studies.[14,16]

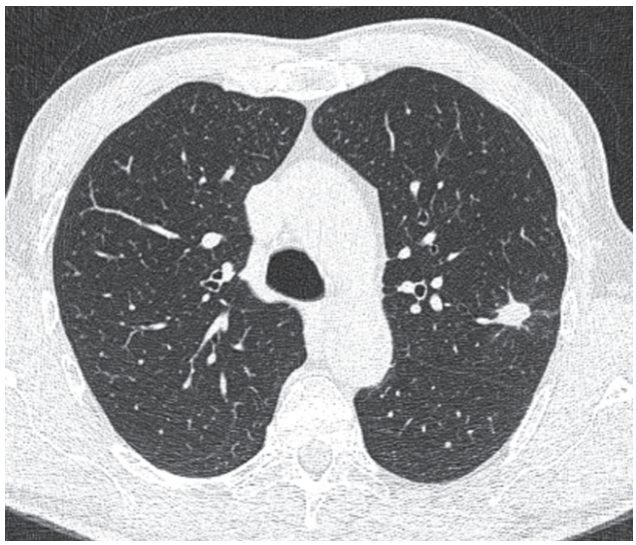

Figure 3 – LDCT reveals in the apical-posterior segment of the upper left lobe a suspect nodule with spiculation

Nonetheless, the minimum threshold size for routine follow-up in the Fleischner classification (nodules ≥ 6 mm), is also the same for a positive screening in Lung-RADS, even though the Fleischner Guidelines recommends follow-up in some nodules below 6 mm (such as with suspicious morphology or upper lobe location).[4]

Apart from that, the classifications are quite distinct, and while Lung-RADS is used in screening programs for lung cancer, the Fleischer classification is used to manage incidental nodules, and therefore separates individuals according to their risk, in low and high-risk, concerning a number of relevant factors.[4] Consequently, the time period for radiological follow-up also has considerable variations. The detection of nodular growth and increase in number are also key-points for scoring in Lung-RADS,[16] while the Fleischner recommendations do not directly include these items.

The estimated prevalence rate in the general population of a Lung-RADS Score of 1 and 2 is 90%.[16] In our group, the Lung-RADS Score of 1 and 2 altogether, presented a lower prevalence rate (75.8%), compared with the estimate for the general population (90%). A Lung-RADS Score of 3 or 4 corresponds to a positive screening. The Score of 3 suggests the presence of benign nodules, with a risk of malignancy of 1% - 2% and short-term follow-up suggested.[15,16] The estimated prevalence rate in the general population is 5%, and in this study, the prevalence rate represented a considerable higher value – 13.6% (9/66). A Lung- RADS Score of 4A or 4B incurs in a higher risk of malignancy, namely 5% - 15% and over >15%, respectively, and an estimated prevalence rate of 2% each in the general population.[14] In this study, a Lung-RADS Score of 4A was obtained in six cases: four revealing nodules with dimensions greater than 8 mm, two revealing nodular growth (increase higher than 1.5 mm), and one presenting simultaneously new nodules and growth. All these results corresponded globally to a prevalence rate of 10.6%, which is a higher figure compared with the general population. A suspicious spiculated nodule (> 15 mm) was scored Lung RADS 4B. PET/CT and a percutaneous and an extemporaneous surgical biopsies were performed and revealed a benign lesion.

These data showed a higher prevalence rate of pulmonary nodules among uranium former miners with a history of smoking compared with the one described in the literature for the general population. This fact justifies a higher need of surveillance imaging, supported by the scientific evidence previously mentioned, of the increased risk of lung malignancy in groups with exposure to known risk factors for lung cancer.

As for the suspicious nodule, and despite the benign anatomopathological result, its imaging features were suspicious: the nodule was in the upper lung lobe and had already a considerable size and spiculation. The PET-CT performed showed a hypermetabolic nodule, probably associated with the previously described inflammatory cavitated lesion with a wall made up of inflammatory repair tissue.

We could not establish comparison with the NELSON classification,[12,13] since the measurement of the nodules was volumetric, and this software was not available in the Radiology Department at the time of the study.

Several studies, particularly in the United States and Europe, indicate that LDCT is absolutely recommended in screening for lung tumours in selected individuals at high-risk,[15] as the NLST[8] and the NELSON[12] studies concluded it reduces mortality from lung cancer.

As for NSLT, the results revealed 247 deaths per 100,000 person-years in the LDCT group and the radiography group showed 309 deaths per 100,000 person-years, which represents a relative reduction in mortality from lung cancer with low-dose screening of 20%.[8,11] In consonance, the NELSON study showed that the use of CT screening for nodule volume management reduces lung cancer mortality in 26% among asymptomatic men at high risk.[11,12]

As described in systematic reviews and meta-analysis,[18] within the highest risk subgroups the number of prevented lung-cancer associated deaths are considerably higher than in the lowest risk populations who reported tobacco consumption, and therefore screening should be performed particularly in those, which was in agreement with our selected criteria.

Even though in the end the suspected nodule had been a false-positive result, this fact concurs with several studies[19] with LDCT having high false-positive rates, which results in unnecessary invasive procedures and patient anxiety. Therefore, LDCT leads to an increase in the frequency of

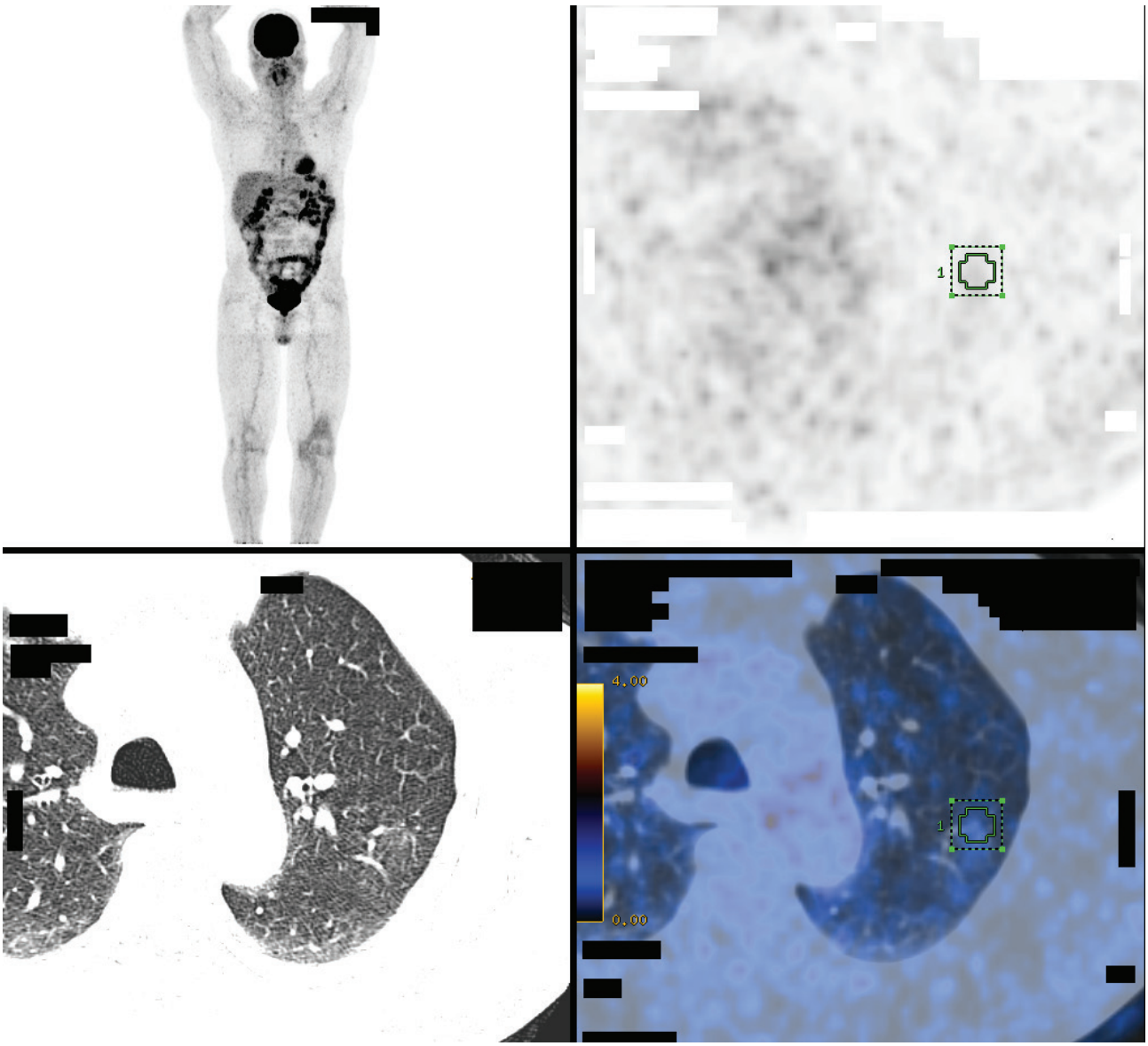

Figure 4 – CT scan and PET-CT: in the apical-posterior segment of the upper left lobe a spiculated nodule causing lung fissure pulling, with 16x12 mm of long axial diameter, hypermetabolic (SUV max: 2.3) and suggestive of malignancy

invasive procedures, such as surgery, biopsy, bronchoscopy or fine needle aspiration cytology but the data from several meta-analyses[19] showed that it does not lead to increased mortality soon after an invasive procedure compared with the control arms. Moreover, LDCT has shown statistically significant mortality benefits, expected to the influenced by the risk of lung cancer in the different target groups.

A risk stratification approach should be used in order to ensure a successful implementation of the LDCT lung cancer screening program in Europe. Therefore, the individuals that enter the screening program should also be provided with the information regarding the benefits and harms of screening and smoking cessation should be offered. Even though COPD and emphysema are the strongest lung cancer risk predictors,[20] they had been less well described in this study: four patients presented with centrilobular emphysema, but we lack data regarding COPD, and therefore we consider that respiratory tests should have been included.

We can also debate the ethical considerations of performing a LDCT in low-risk patients, attending to the harm-to-benefit considerations.[20] Nevertheless, the lower-risk former employees of the UNC were not selected and did not undergo LDCT. Physical harms such as radiation exposure and the potential harms of a biopsy or a resection of a benign lesion, as occurred in our study, should be addressed clearly. This way, these harms can be reduced by ensuring that only patients with a sufficiently high risk of developing lung cancer are screened.[20]

Regarding this study, we can discuss the reasons why no malignant lesion was found until now, considering this was a higher risk population for lung cancer. Primarily, this was a retrospective study and therefore some collected past information could be missing or incomplete. Additionally, another probable reason for the lack of positive results

has to do with the long time period that elapsed between uranium exposure in the mines and the low-dose CT being performed. In the past, this imaging test was not considered since there were no studies published on that matter back then. Furthermore, from the 265 former workers and their families, only 66 participated, and so we lack data about many individuals and their health status.

In future studies, it would be important to collect information about all the former workers of the Urgeiriça mines, in order to gauge both the past and present real impact of uranium exposure in this population.

CONCLUSION

Even though no malignant lesions were detected in LDCT, our data highlights the importance of LCS in high-risk populations. To the best of our knowledge, this was the first study performed in Portugal and can act as a bridge towards a wider implementation in the country.

AUTHOR CONTRIBUTIONS

SMC, DM: Study design, data collection and analysis, drafting, writing and critical review of the manuscript.

IA, AE: Data collection and analysis, critical review of the manuscript.

EC, JP, NM: Study design, drafting and critical review of the manuscript.

AJF, CRC: Study design, drafting and critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Kidney Injury after Cardiac Surgery: Prevention-Associated Cost Reduction

Lesão Renal no Pós-Operatório de Cirurgia Cardíaca: Redução de Custos Associada à Prevenção

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ABSTRACT

Introduction: Cardiac surgery may induce acute kidney injury and the need for renal replacement therapy. It is also associated with higher hospital costs, morbidity and mortality. The aims of this study were to investigate predictors of cardiac surgery associated acute kidney injury in our population and to determine the burden of acute kidney injury in elective cardiac surgery, evaluating the potential cost effectiveness of preventing it through the application of the Kidney Disease: Improving Global Outcomes bundle of care to high-risk patient groups identified by the [TIMP-2]x[IGFBP7] used as a screening test.
Methods: In a University Hospital single-center retrospective cohort study we analyzed a consecutive sample of adults who underwent elective cardiac surgery between January and March 2015. A total of 276 patients were admitted during the study period. Data from all patients was analyzed until hospital discharge or the patient's death. The economic analysis was performed from the hospital costs' perspective.
Results: Cardiac surgery associated acute kidney injury occurred in 86 patients (31%). After adjustment, higher preoperative serum creatinine (mg/L, OR_{adj} = 1.09; 95% CI: 1.01 – 1.17), lower preoperative hemoglobin (g/dL, OR_{adj} = 0.79; 95% CI: 0.67 – 0.94), chronic systemic hypertension (OR_{adj} = 5.00; 95% CI: 1.67 – 15.02), an increase in cardiopulmonary bypass time (min, OR_{adj} = 1.01; 95% CI: 1.00 – 1.01) and perioperative use of sodium nitroprusside (OR_{adj} = 6.33; 95% CI: 1.80 – 22.28) remained significantly associated with cardiac surgery related acute kidney injury. The expected cumulative surplus cost for the hospital linked with cardiac surgery associated acute kidney injury (86 patients) was €120 695.84. Based on a median absolute risk reduction of 16.6%, by dosing kidney damage biomarkers in every patient and using preventive measures in high-risk patients, we would expect a break-even point upon screening 78 patients, which would translate, in our patient cohort, into an overall cost benefit of €7145.
Conclusion: Preoperative hemoglobin, serum creatinine, systemic hypertension, cardiopulmonary bypass time and perioperative use of sodium nitroprusside were independent predictors of cardiac surgery associated acute kidney injury. Our cost-effectiveness modelling suggests that the use of kidney structural damage biomarkers combined with an early prevention strategy could be associated with potential cost savings.
Keywords: Acute Kidney Injury/economics; Acute Kidney Injury/etiology; Biomarkers; Cardiac Surgical Procedures/adverse effects; Hospital Costs; Risk Factors

RESUMO

Introdução: A cirurgia cardíaca pode induzir lesão renal aguda e levar à necessidade de terapêutica de substituição renal. A esta cirurgia associam-se também maiores custos hospitalares, morbilidade e mortalidade. Os objetivos deste estudo foram investigar os preditores de lesão renal aguda associada a cirurgia cardíaca na nossa população e determinar o impacto da lesão renal aguda na cirurgia cardíaca eletiva. Avaliou-se também o potencial custo-efetividade da sua prevenção através da aplicação do *Kidney Disease: Improving Global Outcomes bundle of care* a grupos de doentes de alto risco identificados pelo [TIMP-2]x[IGFBP7] como teste de rastreio.
Métodos: Foi realizado um estudo retrospetivo num centro hospitalar universitário, onde foi analisada uma amostra consecutiva de adultos que foram submetidos a cirurgia cardíaca eletiva entre janeiro e março de 2015. Durante o período do estudo, foram admitidos no total 276 doentes. Os dados de todos os doentes foram analisados até à alta hospitalar ou morte do doente. Foi realizada uma análise económica da perspetiva de custos para o hospital.
Resultados: Oitenta e seis doentes (31%) desenvolveram lesão renal aguda no pós-operatório de cirurgia cardíaca. Após ajuste, os valores elevados de creatinina sérica pré-operatória (mg/L, OR_{adj} = 1,09; IC 95%: 1,01 – 1,17), hemoglobina pré-operatória baixa (g/dL, OR_{adj} = 0,79; IC 95%: 0,67 – 0,94), hipertensão arterial sistémica crónica (OR_{adj} = 5,00; IC 95%: 1,67 – 15,02), tempo prolongado de circulação extra-corporal (min, OR_{adj} = 1,01; IC 95%: 1,00 – 1,01) e o uso perioperatório de nitroprussiato de sódio (OR_{adj} = 6,33; IC 95%: 1,80 – 22,28) mantiveram-se significativamente associados a lesão renal aguda no pós-operatório de cirurgia cardíaca. O custo cumulativo foi de €120 695,84. Baseando-nos numa redução de risco absoluta de 16,6%, ao dosear os biomarcadores de lesão renal estrutural em todos os doentes juntamente com medidas preventivas de lesão renal aguda nos doentes de alto risco, esperaríamos um ponto de equilíbrio ao tratar 78 doentes, que se traduziria, na nossa coorte, num benefício total de custos de €7145.
Conclusão: A hemoglobina pré-operatória, creatinina sérica, hipertensão sistémica, tempo de *bypass* cardiopulmonar e o uso perioperatório de nitroprussiato de sódio foram preditores independentes de lesão renal aguda associada a cirurgia cardíaca. O nosso modelo de custo-efetividade sugere que o uso de biomarcadores renais em combinação com estratégias preventivas precoces poderá estar relacionado com uma potencial poupança de custos.
Palavras-chave: Biomarcadores; Custos Hospitalares; Fatores de Risco; Lesão Renal Aguda/económica; Lesão Renal Aguda/etiologia; Procedimentos Cirúrgicos Cardíacos/efeitos adversos

INTRODUCTION

Acute kidney injury (AKI) complicates 22% to 36% of cardiac surgery (CS) procedures, which ultimately increases hospital costs, morbidity and mortality.[1-3] In the United States, incremental costs go further than one billion

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United States dollars (USD).[4] Cardiac surgery associated acute kidney injury (CS-AKI) requiring dialysis raises risk of progression to end-stage kidney disease and mortality rate up to 60%.[3,5]

Rapidly worsening renal function in CS-AKI is the net result of perioperative insults and its chances of reversibility are poor.[6] Therefore, most efforts have been directed towards the development of prevention strategies in high-risk patient groups.[7,8] The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guideline includes various recommendations to prevent AKI in high-risk patients (KDIGO bundle of care).[7]

There are many known risk factors associated with CS-AKI, reported in Table 1.[9-11] Derived from these, several risk scoring systems have shown high negative predictive value, but lower reliability in high-risk group discrimination.[12] Improved performance of these scoring systems can be achieved by combining clinical risk factors with kidney structural damage and functional biological markers (biomarkers).[13] Biomarkers are indicators of normal biological processes, pathogenic processes, or response to an intervention.[14] The traditional biomarkers of CS-AKI are serum creatinine and urine output, reflecting a decrease in glomerular filtration rate (GFR). These two markers are robust late markers of AKI employed in the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE), Acute Kidney Injury Network (AKIN) and KDIGO scores. However, they fail to translate early nephron stress or injury and can be influenced by non-renal conditions.[15]

Recent advances in biology have yielded finer grained biomarkers (damage biomarkers) that may enable earlier and more specific identification of kidney injury with potential impact in risk prediction.[16] These new molecules, biological substances, and cellular and molecular patterns have been discovered in urine and serum and correlate with different types, phases, and pathways of AKI. Tubular injury can be detected by damage biomarkers, whereas the degree of organ failure is estimated through the use of functional biomarkers such as serum creatinine or urine output, complementing each other.[16]

Point-of-care tests to assess damage biomarkers are available mostly as research tools for neutrophil gelatinase associated lipocalin (NGAL) and combined tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein7 {[TIMP-2]x[IGFBP7]}. TIMP-2 and IGFBP7 are metalloproteinases that induce G1 cell cycle arrest and can be found in urine to predict, diagnose and assess the severity of AKI.[13,16,17] The use of these tests in clinical practice requires considerable investment and its cost-effectiveness is yet to be clarified.[17,18]

The aim of this study was to investigate predictors of CS-AKI in our population and to determine the burden of AKI in elective cardiac surgery. We also modelled the potential cost effectiveness of preventing it through the application of the KDIGO bundle of care to high-risk patient groups identified by the [TIMP-2]x[IGFBP7] used as a screening test.

METHODS

Ethics statement

The study was approved by the local Hospital Ethics Committee. Patient consent was waived due to the retrospective and observational nature of the research.

Study design

A consecutive retrospective cohort of 276 adult patients who underwent elective cardiac surgery of all types between January 2nd and March 31st of 2015 at the Department of Cardiothoracic Surgery of a tertiary university hospital.

Data collection

Data was collected from available electronic health records and physician notes, from the period of 24 hours

Table 1 – Risk Factors for cardiac surgery associated acute kidney injury described in the literature[8-12]

Risk Factors/Predictors				
Anthropometric	**Comorbidities**	**Surgery**	**Nephrotoxic**	**Analytical**
Age	BMI	Urgency	RASI	Preoperative anemia
Female sex	Diabetes	Type of surgery (valvular)	Aminoglycosides	Baseline GFR
	COPD	Reintervention	Non-steroidal anti-inflammatory agents	Preoperative serum creatinine
	Chronic kidney disease	CPB time	Contrast	
	Reduced left ventricular ejection fraction	Clamping time		
	Heart failure (NYHA class)	Nadir HTC		
	HTN	RBC transfusion		
	PAD			

before surgery to hospital discharge or death. Variables were: (i) preoperative data (at admission): age, gender, body mass index (BMI); diagnostic tests: hemoglobin, serum creatinine, serum urea, estimated glomerular filtration rate (eGFR), left ventricular ejection fraction (LVEF); comorbidities: chronic systemic hypertension (HTN) (defined as persistent systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg according to the 2020 International Society of Hypertension and the 2014 Eighth Joint National Committee and/or report of anti-hypertensive therapy), diabetes mellitus [defined as glycated hemoglobin (HbA_1c) ≥ 6.5% and discriminating insulin therapy], active smoking status (self-reported), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) (defined as an eGFR < 60 mL/min/1.73 m^2 calculated according to Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) 2021), peripheral arterial disease (PAD), heart failure [graded according to the New York Heart Association (NYHA) classification]; previous cardiac surgery; European System for Cardiac Operative Risk Evaluation (EuroSCORE) II; ongoing medication and preoperative exposure to renin-angiotensin system inhibitors (RASI, including angiotensin converting enzyme inhibitors and angiotensin receptor blockers), diuretics or aminoglycosides; (ii) intraoperative data: type of surgery, on-pump/off-pump, extracorporeal and aortic cross-clamp times (considering zero minutes for off-pump surgeries), need for blood transfusion during the procedure, lowest (nadir) hematocrit (HTC) during the procedure, perioperative exposure to furosemide, sodium nitroprusside or vancomycin.

The primary outcome was the development of postoperative AKI according to the KDIGO criteria: an abrupt increase in serum creatinine (≥ 0.3 mg/dL within 48 hours or ≥ 50% within seven days) or a reduction in urine output (< 0.5 mL/kg/hr for more than six consecutive hours),[7] calculated from hourly nursing intensive care unit (ICU) records.

Secondary outcomes included: 30-day mortality, hospital and intensive care length of stay (LOS).

Statistical analysis

Continuous and ordinal variables were described as median and interquartile ranges (IQR) and absolute and relative frequencies were reported for categorical variables. Comparison between CS-AKI and non-CS-AKI patients were made using Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables.

A *post-hoc* sub-group analysis of patients with HTN was conducted to evaluate the effect of preoperative RASI on the development of CS-AKI.

Missing data is presented for each variable and bias analysis was performed by CS-AKI status.

A backward stepwise-selection logistic regression was built from predictors with marginal association with AKI development in univariate analysis ($p < 0.2$) upon excluding variables with either evident collinearity (e.g., preoperative serum creatinine and eGFR) or multicollinearity assessment with variance inflation factors (VIF), with a cut-off of 10. A likelihood ratio with a p value > 0.1 was used as cut-off for variable removal. The accuracy of the model was assessed by the area under receiver operating characteristic (AU-ROC) curve and calibration was tested using the Hosmer-Lemeshow goodness-of-fit test. The results of the multivariate model are expressed as β coefficient and adjusted odds ratio (OR_{adj}) with 95% confidence interval (CI) and p-values. The significance level for all tests was defined as two-tailed $\alpha = 0.05$. The multivariate model was reassessed for the effect of RASI-HTN. Data were analyzed using IBM® SPSS Statistics for Windows®, version 28 (IBM® Corp., Armonk, N.Y., USA) and JASP (Version 0.16.1).

Economic analysis

Economic analysis was restricted to hospital costs. Mean daily CS patient costs were retrieved from the institution's financial department, without discrimination between ICU and ward. Cost-center charges included supplies, personnel, laboratory, and other diagnostics, as well as costs related to any treatment (Table 2). Incremental costs of CS-AKI development were obtained with Hedges' g estimate.

Costs associated with the potential introduction of [TIMP-2]x[IGFBP7] (Nephrocheck®) as a screening test were estimated according to Vijayan *et al*[19]: cost of laboratory test machine (€2923.95) and cost of one cartridge per patient (€49.71). Cost adjustment from USD to euros (€) was performed using Campbell and Cochrane Economics Methods Group (CCEMG) – EPPI-Centre Cost Converter as of 2019.[20]

Cost-effectiveness was modeled through break-even analysis (Python 3.9 script with numpy library) assuming absolute risk reduction (ARR) of 16.6% (CI 95% = 5.5% – 27.9%) reported by Meersch *et al* while applying the KDIGO bundle of care[7] to high-risk patients as identified by Nephrocheck® {[TIMP-2]x[IGFBP7] > 0.3}.[21] From our rate of CS-AKI we estimated the number of patients that would have been deemed at high-risk by Nephrocheck® and thus undergo the KDIGO intervention assuming a true positive rate/recall of 0.9 recently summarized in a systematic review and meta-analysis.[22,23]

Table 2 – Estimation of direct hospital costs

Considered costs	Average costs (€)
Average hospitalization daily costs	705.72
[TIMP-2]x[IGFBP7] cartridge costs	49.71

Direct hospital costs estimated considering cost-center charges. Hospitalization daily costs include ward and intensive care unit room, supplies, personnel, laboratory and other diagnostics, as well as costs related to any treatment.

The following formulas were applied:

- Equation 1
  - Costs related to screening = analyzer machine + cartridge x number of patients.
- Equation 2
  - Potential cost benefit of the intervention = difference in postoperative costs (POC) between CS-AKI and non-CS-AKI (median) x expected number of CS-AKI cases prevented (as integer after rounding).
- Equation 3
  - Expected number of CS-AKI cases prevented = number of patients x incidence of AKI in our cohort x high-risk patients/CS-AKI cases (control group in Meersch *et al*)[21] x recall (reported for Nephrocheck®)[22,23] x ARR (and 95%CI).[21]

Break-even points were estimated as patient number needed for the potential cost benefit of the intervention to outweigh the costs related to screening.

RESULTS

Study sample

Two-hundred and seventy-six patients were included in our cohort, of which 86 (31%) developed CS-AKI. All admitted patients were white.

AKI incidence and predictors

In univariate analysis (Table 3), preoperative variables including older age, HTN, CKD, diabetes and insulin-therapy, lower preoperative hemoglobin, higher serum creatinine, higher serum urea, lower eGFR and higher EuroSCORE II were significantly associated with CS-AKI incidence. Need for intraoperative blood transfusion, lower nadir HTC during the procedure and perioperative use of sodium nitroprusside were also significantly associated with CS-AKI. Active smoking, male gender, on-pump surgery, longer cardiopulmonary bypass (CPB), aortic cross-clamp time and perioperative use of furosemide were marginally associated (p > 0.05, but < 0.15) with CS-AKI.

A sub-group analysis of patients with HTN was conducted to evaluate the effect of preoperative RASI on the development of CS-AKI. In the subgroup of patients taking RASI, HTN was not significantly associated with CS-AKI (p = 0.749) but, in those not previously treated with RASI, HTN was significantly associated with CS-AKI (p = 0.005).

The final multivariate model is presented in Table 4. The model's AU-ROC curve was 0.645 (95% CI: 0.567 – 0.732). The Hosmer and Lemeshow test did not show evidence for lack of fit (p = 0.729). After adjustment, higher preoperative serum creatinine, lower preoperative hemoglobin and HTN remained significantly associated with CS-AKI. An increase in CPB time and perioperative use of sodium nitroprusside were also significantly associated with the risk of CS-AKI. Male gender was marginally associated with CS-AKI.

Regarding the subgroup analysis, the final model was re-calculated considering the effect of RASI treatment on patients with HTN (Table 4). Preoperative serum creatinine, preoperative hemoglobin, HTN and perioperative use of sodium nitroprusside remained significantly associated with the risk of CS-AKI. Gender was also significantly associated with CS-AKI.

CS-AKI and other outcomes

Other outcomes were also analyzed in our population and are discriminated in Table 3. Length of stay was significantly higher in patients with CS-AKI.

The postoperative mortality was 2.5%, with one patient dying in the first 24-postoperative hours and six in the first 30-days. The cause of death was cardiogenic shock in all patients but one, who died due to septic shock. Postoperative mortality was not related to CS-AKI: the mortality rate was 3.5% in patients who developed CS-AKI and 2.1% in those who did not (p = 0.623).

Overall, LOS was of 7 (IQR 6 – 10) days, 7 (IQR 6 – 9) days for those without CS-AKI *versus* 9 (IQR 7 – 14) days for those with CS-AKI (p < 0.001). Patients who developed CS-AKI also had longer ICU stays: 4 (IQR 2 – 6) *versus* 3 (IQR 2 – 4) days, with p = 0.0015. Overall ICU stay was three days (IQR 2 – 5).

Missing data - sensitivity analysis

Missing data sensitivity analysis was computed for each variable, by CS-AKI status. Significant bias was found for lowest HTC during the procedure (with data missing for eight patients that developed CS-AKI *versus* six patients without CS-AKI) (Table 5). For the evaluation of the impact of this missing bias, the 75th percentile value for controls (27%) was imputed for all 14 patients with missing data (to decrease the association between lowest HTC during the procedure and CS-AKI). The univariate association between lowest HTC during the procedure and CS-AKI remained significant (p = 0.004 after imputation).

Cost-analysis and modelling

Cost analysis is presented in Table 6. The incremental median cost for CS-AKI was thus €1403.44 (95% CI: 701.72 – 2105.16), p value < 0.001 and Hedges' g = 0.304 (small to medium effect size). Cumulative incremental cost estimation was calculated by multiplying incremental average cost by the number of patients developing CS-AKI. The expected cumulative surplus cost for the hospital, associated with CS-AKI (86 patients), was €120 695.84 (Table 6).

The break-even analysis for cost-effectiveness according to the specified model is depicted in Fig. 1. For a median

Table 3 – Univariate analysis

	Total n = 276		AKI n = 86		Without AKI n = 190		*p*-value
Demographics							
Age (y)	69	(60 – 76)	73	(67 – 77)	67	(58 – 75)	< 0.001*
Male, n (%)	169	(61)	59	(69)	111	(58)	0.110
BMI, kg/m²	26	(24 – 30)	26	(24 – 30)	27	(24 – 30)	0.934
BSA, m²	1.77	(1.64 – 1.89)	1.78	(1.65 – 1.92)	1.77	(1.63 – 1.89)	0.344
Preoperative analytical data							
Hemoglobin, g/dL	8.19	(7.26 – 9.06)	7.7	(6.70 – 8.69)	8.38	(7.51 – 9.06)	0.004*
Serum creatinine, mg/dL	73.39	(61.89 – 91.07)	81.35	(69.85 – 112.29)	71.62	(59.24 – 84.00)	< 0.001*
Serum urea, mg/dL	43	(35 – 53)	47	(38 – 59)	43	(34 – 51)	0.014*
eGFR, ml/min/1.73m²	90	(73 – 99)	79	(57 – 92)	92	(78 – 102)	< 0.001*
LVEF - Good, n (%) **Moderate**, n (%) **Poor**, n (%) **Very poor**, n (%)	201 11 2 -	(76) (4) (1)	60 3 1 -	(75) (4) (1)	138 8 1 -	(77) (4) (1) -	0.892
Comorbidities							
Obesity, n (%)	61	(22)	19	(22)	42	(22)	0.999
HTN, n (%)	217	(79)	77	(90)	140	(74)	0.003*
DM, n (%) **- insulin-therapy**, n (%)	93 28	(34) (10)	38 14	(44) (16)	55 14	(29) (7)	0.019* 0.031*
Active smoker, n (%)	50	(18)	10	(12)	40	(21)	0.065
CKD, n (%)	44	(16)	12	(14)	32	(17)	< 0.001*
PAD, n (%)	31	(11)	11	(13)	20	(10)	0.681
Heart failure (NYHA class)	II	(II – III)	III	(III – IV)	II	(II – III)	0.591
Previous cardiac surgery, n (%)	14	(5)	5	(6)	9	(5)	0.560
EuroSCORE II (%)	3.1	(1.7 – 5.4)	3.7	(2.2 – 6.8)	2.9	(1.6 – 4.8)	0.003*
Preoperative exposure							
ACEi, n (%)	116	(42)	41	(48)	75	(40)	0.236
ARB, n (%)	44	(16)	15	(17)	29	(15)	0.723
Diuretics, n (%)	117	(42)	42	(49)	75	(40)	0.151
Aminoglycosides, n (%)	3	(1)	2	(2)	1	1 (1)	0.380
Surgery details							
Type of surgery **- isolated CABG**, n (%) **- single non-CABG**, n (%) **- 2 procedures**, n (%) **- 3 or more procedures**, n (%)	 95 126 54 1	 (34) (46) (20)	 27 39 19 -	 (31) (45) (22)	 66 90 34 1	 (35) (47) (18) (1)	0.415
On-pump surgery, n (%)	254	(92)	83	(97)	171	(90)	0.091
CPB time, min	103	(79 – 134)	110	(84 – 140)	100	(77 – 132)	0.088
Clamping time, min	67	(50 – 94)	73	(56 – 98)	66	(49 – 94)	0.071
Nadir HTC, %	24	(21 – 27)	22	(21 – 25)	24	(21 – 27)	0.002*
Perioperative exposure							
Intraoperative blood (RBC) transfusion, n (%)	113	(41)	47	(55)	66	(35)	0.002*
Sodium nitroprusside, n (%)	15	(5)	10	(12)	5	(3)	0.007*
Vancomycin, n (%)	8	(3)	3	(4)	5	(3)	0.706
Furosemide, n (%)	229	(83)	66	(79)	164	(88)	0.066
Other outcomes							
Postoperative mortality, n (%)	7	(2.5)	3	(3.5)	4	(2.1)	0.623
LOS (days)	7	(6 – 10)	9	(7 – 14)	7	(6 – 9)	< 0.001*
ICU stay (days)	3	(2 – 5)	4	(2 – 6)	3	(2 – 4)	0.0015*

*: $p < 0.05$

BSA: body surface area; DM: diabetes mellitus; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker

Table 4 – Multivariate analysis including RASI-HTN interaction

	Multivariate analysis (final original model)			Multivariate analysis (with RASI-HTN interaction)		
	β	*p*-value	OR_{adj} (95% CI)	β	*p*-value	OR_{adj} (95% CI)
Male	0.702	0.053	2.02 (0.99 – 4.11)	0.726	0.039*	2.07 (1.04 – 4.12)
Hemoglobin	-0.225	0.012*	0.80 (0.70 – 0.98)	- 0.233	0.006*	0.79 (0.67 – 0.94)
Serum creatinine	0.096	0.022*	1.10 (1.01 – 1.19)	0.085	0.030*	1.09 (1.01 – 1.17)
HTN	1.068	0.014*	2.91 (1.24 – 6.84)	1.610	0.004*	5.00 (1.67 – 15.02)
RASI-HTN interaction	-	-	-	-1.373	0.146	0.25 (0.04 – 1.61)
RASI	-	-	-	1.152	0.188	3.17 (0.57 – 17.62)
CPB time	0.008	< 0.001*	1.01 (1.00 – 1.01)#	0.007	0.001*	1.01 (1.00 – 1.01)#
Sodium nitroprusside	1.670	0.009*	5.31 (1.51 – 18.72)	1.845	0.004*	6.33 (1.80 – 22.28)

*: $p < 0.05$; #: 1.008 (1.003 – 1.013)

ARR of 16.6% as reported by Meersch *et al*[21] we would expect a break-even point upon screening 78 patients, which would translate, in our 276 patients' cohort, in an overall cost benefit of €7145, but the 95% CI are wide and for an ARR of 27.9% these would be 37 patients and €25 410, respectively. On the other hand, for the worst expectation of only 5.5% ARR there would be no expected economic benefit at all, even in the long run.

DISCUSSION

CS-AKI was associated with higher morbidity, mortality, and increased hospital costs.[1-3] Several studies were developed regarding the development of predictive scores,[24-26] and identification of tools that, adequately and in a timely fashion, allow to recognize and manage CS-AKI[12,21] in order to minimize its impact.

We have conducted an analysis to investigate the predictors of CS-AKI in our population which, according to the tendency demonstrated in literature, showed some conflicting results, although the incidence of CS-AKI in our population (31%) is comparable to previous reports in the literature.[27,28]

The male gender in our population was associated with an increased risk of CS-AKI development, contradicting many previous reports[29,30] but is in agreement with a more recent systematic review and meta-analysis by Neugarten *et al.*[31]

Preoperative creatinine plasma levels, low preoperative hemoglobin and HTN were identified as predictors of CS-AKI in our study. Preoperative creatinine, mirroring the patient's renal reserve, has been consistently identified as an independent risk factor[2,32] and therefore included in several predictive scoring systems for CS-AKI.[24-26,33,34] In our population, an increase of 1 mg/dL was associated with a 9% (95% CI: 1% – 17%) increase in the risk of developing CS-AKI. Low preoperative hemoglobin has been reported as an independent risk factor for the development of CS-AKI, with an attributed 2.6-fold increased risk[35,36]: AKI in anemic patients is associated with inflammation, renal hypoxia and oxidative stress, explaining why these patients have an increased susceptibility to concomitant renal insults, such as hypoperfusion, increasing their vulnerability to CS-AKI when on CPB.[2,37] In our study, a reduction of 1 g/dL in preoperative hemoglobin was associated with a 21% (95% CI: 6% – 33%) increase in the odds of CS-AKI. Red blood cell (RBC) transfusion also exacerbates the risk of CS-AKI in anemic patients, representing, by itself, an independent risk factor.[35,36] Moreover, in an observational study performed in 2014, Kahn *et al* concluded that the risk of AKI was highest in patients receiving more than two units of RBCs.[38] Although several studies[35,37,39] demonstrated that, regardless

Table 5 – Missing data

n (%)	**Missing data**	***p*-value**
Preoperative analytical values		
Hemoglobin	5 (1.8)	0.648
Serum creatinine	5 (1.8)	0.648
Serum urea	5 (1.8)	0.648
eGFR	5 (1.8)	0.648
LVEF	16 (5.8)	0.585
Comorbidities		
NYHA class	63 (22.8)	0.428
EuroSCORE II (%)	5 (1.8)	0.648
Surgery details		
CBP time	6 (2.2)	0.078
Clamping time	6 (2.2)	0.078
Nadir HTC	14 (5.1)	0.04
Perioperative exposure		
Vancomycin	5 (1.8)	0.648
Furosemide	5 (1.8)	0.648

Table 6 – Comparison of patient costs

	AKI (n = 86)	Without AKI (n = 190)	*p*-value
Median POC *per* patient (€)	6 315.48 (4912.04 – 9122.36)	4 912.04 (4210.32 – 6315.48)	< 0.001*
Total POC estimation (n = 276)	= Median POC *per* patient x n = 1476,418.88		
Median POC difference *per* patient (€)	= POC (AKI) – POC (without AKI) = 1403.44 (701.72 – 2,105.16)		
Expected cumulative surplus cost (n = 86) (€)	= Median POC difference per patient x n = 120695.84		

*: $p < 0.05$

of the existence of anemia, transfusion of RBC entails an important risk for AKI, our study was not able to corroborate it, since intraoperative RBC transfusion was significantly associated with CS-AKI only in univariate analysis.

Regarding HTN, in a prospective study of 157 patients, Kenji *et al* found that a drop in mean arterial pressure (MAP) of more than 26 mmHg between preoperative and intraoperative values was associated with the development of CS-AKI, explaining why HTN is considered a risk factor and why this could be the focus of an intervention.[40] In this study, the presence of HTN represented a 5-fold increase in the odds of CS-AKI.

We could not find a significant impact of RASI in the incidence of CS-AKI in our population. Preoperative use of RASI has been associated with an increase in preoperative CS-AKI not mediated by an effect in blood pressure. This association possibly reflects the effects in glomerular capillary pressure caused by renal efferent arteriolar vasodilation and impairment of autoregulation.[41] Nevertheless, some publications showed opposite results, suggesting a treatment benefit in these patients.[2,42-45] On the other hand, in a sub-group analysis of patients with HTN, patients treated with RASI had no increased incidence of CS-AKI, unlike patients not treated with RASI, thus suggesting a protective

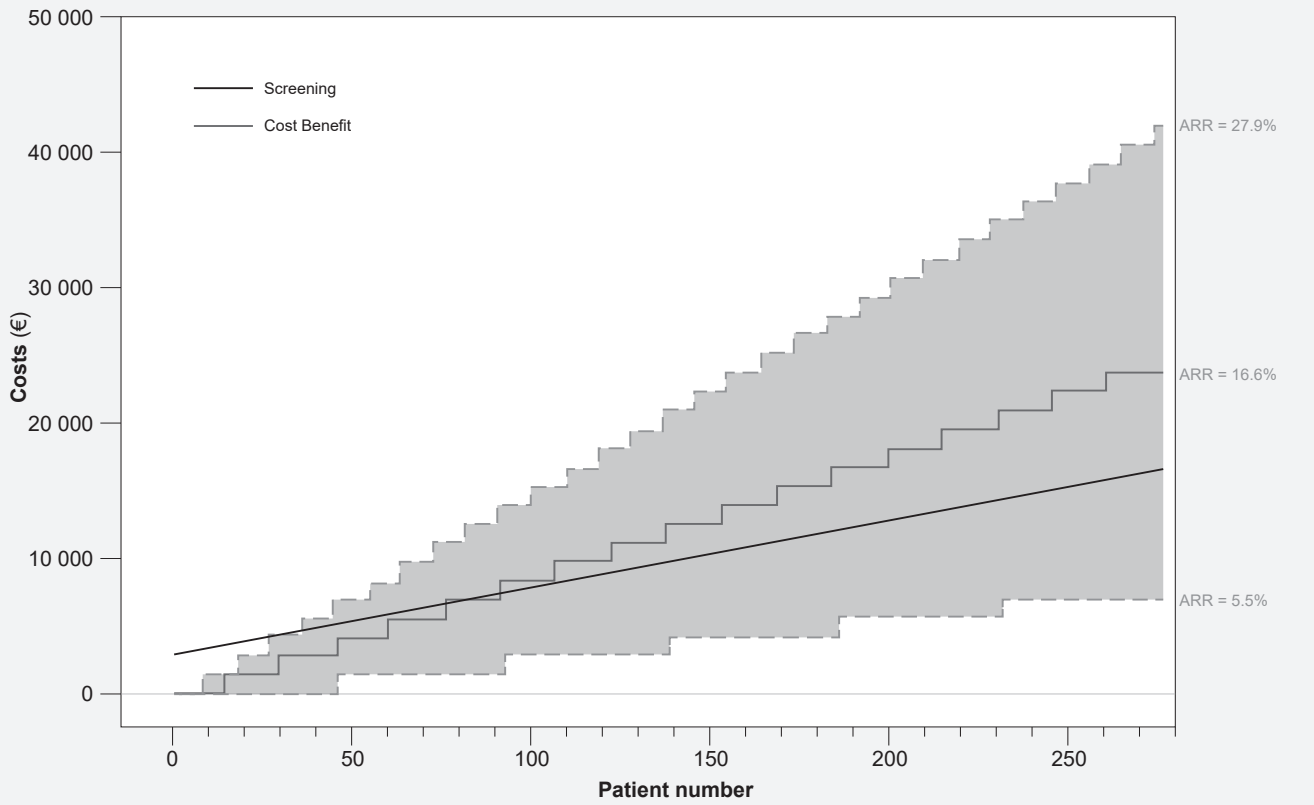

Figure 1 – Modelling of break-even analysis for the introduction of the KDIGO bundle of care in high-risk patients after Nephrocheck® screening. The costs related to Nephrocheck® screening, including the test machine and consumables, are plotted as a black solid line. The potential cost-reduction related to the intervention is plotted as a grey solid line, and the shaded area corresponds to the 95% CI, according to the ARR reported by Meersch *et al*.[21]

role of RASI in hypertensive patients. Our study didn't include both the analysis of preoperative treatment with other anti-hypertensive agents, and of the efficacy of preoperative blood pressure control; however, considering the sub-group analysis, a better control of preoperative HTN might be associated with a lower incidence of CS-AKI.

Amongst intraoperative factors, the duration of CPB was significantly associated with CS-AKI in which a 60-minute increase of extracorporeal circulation represents a 60% increase in CS-AKI (OR_{adj} = 1.61), reflecting the influence in renal outcomes of the contact activated inflammatory response and significant hemodynamic changes associated with CPB.[5] Also, the institution of CPB in coronary artery bypass graft (CABG) surgery is associated with a systemic inflammatory response, coagulopathy, embolism and CS-AKI.[5] It has been proposed that the avoidance of CPB by the implementation of an off-pump CABG (OPCAB) technique would reduce the incidence and severity of CS-AKI. Several systematic reviews and meta-analysis of randomized control trials (RCT)[2,46,47] and one multicenter RCT[48] point to a lower risk of CS-AKI in OPCAB surgery patients, whereas this has not been confirmed by Reents *et al* in his post hoc analysis of 1612 patients.[49] In the present study, on-pump surgery was marginally associated with CS-AKI incidence only in univariate analysis. On the other hand, prolonged aortic cross-clamp time, according to historical reports, increases the risk of low cardiac output state (LCOS) and renal ischemia.[50,51] Our findings did not support the association between longer aortic cross-clamp time and CS-AKI, but the occurrence of LCOS was not determined in our population. Regarding the type of surgery, we did not find an association with CS-AKI, although the literature strongly suggests that patients presenting for CABG develop less CS-AKI in comparison to other types of cardiac surgery,[52-54] probably due to less CPB time.[55] Conversely, a meta-analysis published by Yi Q. *et al* demonstrated otherwise, not establishing an absolute association between these factors.[10]

Still within intraoperative factors, the use of sodium nitroprusside was significantly associated with the development of CS-AKI, determining a 533% increase in the risk of CS-AKI. In most experimental models, renal autoregulation capability was impaired following ischemic injury, suggesting a residual ability to vasodilate and a greater fraction of fixed total resistance, originating a substantial increase (50%) in renal vascular resistance, a 40% decrease in renal blood flow and severe impairment in renal oxygenation in CS-AKI patients, compared with post-cardiac surgery patients with no AKI.[56] The use of vasodilators can further reduce the renal blood flow.[57] Finally, in what concerns nadir HTC, an association with CS-AKI was not demonstrated in our results contrarily to what was to be expected. Ranucci *et al* studied the role of nadir oxygen delivery (DO_2), nadir HTC and pump flow during CPB, and risk of CS-AKI[58,59] and found that a nadir DO_2 of less than 262 mL/min/m^2 during CPB was associated with AKI stage 2 (according to AKIN classification), and nadir DO_2 level was significantly associated with prolonged ICU and postoperative LOS.[58]

As mentioned above, if treatment bundles are to be effective, they need to be applied before the condition of interest develops; in order to achieve this, the right tools are required. Since we were aiming to estimate the potential cost reduction by identifying, in a timely manner, the risk of developing CS-AKI, we decided to use data related to TIMP-2 and IGFBP7 (Nephrocheck®) for our economic analysis, given its very high specificity and very good predictive value.[22,23] In our population, the overall LOS was significantly increased for patients with CS-AKI.

Following the implementation of Nephrocheck® screening alongside with the application of the KDIGO bundle of care to high-risk patients, a cost reduction associated with the estimated decrease of CS-AKI incidence could be achieved.[21]

Limitations

The main limitation of our study is its retrospective nature, regarding data routinely assessed within the hospital stay, and the fact that it was conducted in a single center.

During the period considered, evaluation of HbA_1C was not standardized in the preoperative assessment of diabetic patients, which did not allow us to assess the preoperative metabolic control of our patients. Regarding the remaining variables described as possible risk predictors, we had a low number of missing values in the clinical records consulted and only nadir HTC presented missing bias. Despite this, after missing imputation, this variable remained significantly associated with CS-AKI in univariate analysis.

Our multivariate analysis model had sufficient power to include up to eight variables.[60] Still, due to a sample of just 276 patients, lack of power may not have allowed the analysis of other predictors. A larger sample would also allow a discrimination of CS-AKI stages.

In the estimation of costs, cost-center charges did not discriminate average ICU daily costs per patient, which would enable a more precise calculation of CS-AKI associated cost increase. Our economic analysis was based on average hospitalization costs; not having individualized patient costs could limit our accuracy of value determination. Cost-analysis modelling is based on studies from other groups and data collected was from 2015, which has consequences regarding this study's external validity; consequently, our conclusions may not be completely generalizable to our current population. Data regarding sensibility/recall are predominantly based on studies performed in

critical patients; however, there is a low sample study on the post-operative period after cardiac surgery with similar values/outcomes to our study (0.92).[22] Additionally, further studies are needed to precisely calculate the direct savings of applying [TIMP-2]x[IGFBP7] only to high-risk patients estimated by risk prediction scores[9-12] *versus* all patients, and to evaluate the economic benefit of applying the KDIGO bundle of care for all patients.

CONCLUSION

Our work reinforces the existing evidence that increased preoperative creatinine, HTN, low preoperative hemoglobin, long CPB time and intraoperative sodium nitroprusside were independent risk factors for CS-AKI. Moreover, our cost-effectiveness modelling suggests that the use of kidney structural damage biomarkers combined with an early prevention strategy could be cost saving.

AUTHOR CONTRIBUTIONS

JM, AFR, CA: Study design, data collection and analysis, writing of the manuscript.

ALD: Study design, statistical analysis, data interpretation, writing of the manuscript.

BA, AL: Study design, data collection.

ALM: Study design, data interpretation.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Picturing Prevalence and Inequalities in Cancer Screening Attendance to Population-Based Programs in Portugal

Retrato da Prevalência e Desigualdades na Participação em Rastreios Oncológicos de Base Populacional em Portugal

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ABSTRACT

Introduction: Screening is effective in reducing cancer-related morbidity and mortality. The aim of this study was to analyze the level of, and income-related inequalities in, screening attendance, in Portugal for population-based screening programs.

Methods: Data from the Portuguese Health Interview Survey 2019 was used. Variables included in the analysis were self-reported: mammography, pap smear test, fecal occult blood test. Prevalence and concentration indices were computed at national/regional level. We analyzed: up-to-date screening (within recommended age/interval), under-screening (never or overdue screening), and over-screening (due to frequency higher than recommended or screening outside target group).

Results: Up-to-date screening rates were 81.1%, 72%, and 40%, for breast, cervical and colorectal cancer, respectively. Never-screening was 3.4%, 15.7%, and 39.9%, for breast, cervical, and colorectal cancer, respectively. Over-screening related with frequency was highest for cervical cancer; in breast cancer, over-screening was observed outside recommended age, affecting one third of younger women and one fourth of older women. In these cancers, over-screening was concentrated among women with higher income. Never-screening was concentrated among individuals with lower income for cervical cancer and higher income for colorectal cancer. Beyond the recommended age, 50% of individuals never underwent screening for colorectal cancer and 41% of women never underwent screening for cervical cancer.

Conclusion: Overall, screening attendance was high, and inequalities were low in the case of breast cancer screening. The priority for colorectal cancer should be to increase screening attendance.

Keywords: Early Detection of Cancer; Mass Screening; Neoplasms/diagnosis; Neoplasms/prevention and control; Portugal; Socioeconomic Factors

RESUMO

Introdução: Os rastreios reduzem a morbilidade e mortalidade associadas ao cancro. O objetivo deste estudo foi analisar os níveis de participação em rastreios oncológicos de base populacional em Portugal, e respetivas desigualdades.

Métodos: Os dados provêm do Inquérito Nacional de Saúde 2019. As variáveis utilizadas são: mamografia, citologia e a pesquisa de sangue oculto nas fezes. Calculámos prevalências e índices de concentração ao nível nacional e regional. Analisámos a participação 'devida' (idade/intervalo recomendados), 'insuficiente' (nunca ou em atraso), e 'excessiva' (frequência superior à recomendada ou em idade não recomendada).

Resultados: A participação 'devida' atingiu 81,1%, 72% e 40%, enquanto a participação 'insuficiente-nunca' atingiu 3,4%, 15,7% e 39,9% para cancro da mama, cancro do colo do útero e cancro colorretal, respetivamente. A prevalência de participação 'excessiva' foi mais alta no cancro do colo do útero; relativamente ao cancro da mama, um terço das mulheres mais novas e um quarto das mulheres mais velhas fez mamografia. Este 'excesso' está concentrado nas mulheres com rendimento mais elevado. A participação 'insuficiente-nunca' está concentrada nos indivíduos com rendimentos mais baixos no cancro do colo do útero e nos rendimentos mais altos no colorretal. Acima da idade recomendada, 50% dos indivíduos nunca rastrearam para cancro colorretal e 41% das mulheres nunca o fizeram para cancro do colo do útero.

Conclusão: No rastreio do cancro da mama, no geral, a participação foi elevada e as desigualdades foram reduzidas. No cancro colorretal, a prioridade deve ser aumentar a participação no rastreio.

Palavras-chave: Detecção Precoce de Cancro; Factores Socioeconómicos; Neoplasias/diagnóstico; Neoplasias/prevenção e contolo; Portugal; Rastreio

INTRODUCTION

In Portugal, colorectal cancer (CRC) is the most frequent cancer (10 501 new cases in 2020) when considering both men and women combined. It is surpassed by prostate cancer in men, and breast cancer in women. In 2020, there were 7041 new cases of breast cancer and 1238 new cases of cervical cancer (fifth most frequent among women[1]). For CRC, the estimated age-standardized mortality rates (per 100 000) in Portugal in 2020 are 18.6 and 8.8 for men and women, respectively, which compare with 16.1 and 9.5 in Europe. Regarding breast and cervical cancers, in Portugal, the estimated age-standardized mortality rates (2020) are 12.7 and 3.2, respectively. These figures compare with 14.8 and 3.8 in Europe.[1]

Several studies have shown that screening people of average risk is effective in reducing cancer-related morbidity and mortality for CRC[2] as well as for breast and cervical cancers.[3,4] Since 2003, the Council of the European Union has recommended the implementation of population-based screening programs (individuals within target groups are systematically tested) for breast, cervical, and colorectal

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cancers.[5] In Portugal, there are population-based screening programs for only these three cancers, although the implementation of the programs has varied depending on cancer type and region. In mainland Portugal, the earliest programs that were implemented were breast and cervical cancer screening in the Center region (1990) and the latest programs, implemented in 2017, were CRC screening in Lisbon and the Algarve, as well as cervical cancer screening in Lisbon.[6,7] In Madeira, only in 2022 did CRC screening change from opportunistic (where participation in screening follows from recommendation made by healthcare professionals or the individuals' own choice) to a population-based program.[8] In the Azores, CRC screening was also the latest program implemented (2019), in two islands (S. Jorge and Graciosa).[9]

Screening guidelines were updated in 2017 by the Ministry of Health, with the main aim of homogenizing the criteria followed by health regions.[10] For CRC, the primary screening test is the fecal immunochemical test (FIT), every two years, for individuals aged 50 to 74 years old; colonoscopy should be performed in cases with a positive FIT. For breast cancer, the recommendation is for women aged 50 to 69 years old to undertake a mammography biannually. For cervical cancer, the target group is women aged 25 to 60 years old; the interval of screening is five years with the human papillomavirus (HPV) test.

Previous evidence suggests that population-based programs, as opposed to opportunistic ones lead to higher attendance rates[11] and lower levels of inequality.[12] According to the World Health Organization (WHO), both the average level of health and inequalities are important to assess the performance of healthcare systems.[13,14] Most studies on cancer screening have analyzed these dimensions for target groups (overlooking over-screening which occurs outside the target population), and have followed a conservative view assuming that what matters is to monitor up-to-date screening even if this means screening more frequently than recommended.[15-17] However, over-screening is not only a waste of resources but can also cause harm.[18] In addition, individuals for whom screening is overdue include both those whose last test was performed more than two or three years ago and those who were never screened. Most studies do not distinguish between them, but these are different situations.[19] Based on previous evidence, over-screening is more likely in opportunistic programs and among individuals of higher socioeconomic status.[20,21] Now that population-based screening programs are implemented in all Portuguese regions for CRC, breast, and cervical cancers, our aims were to analyze the level of, as well as income-related inequalities in screening attendance across Portuguese regions for these cancers, based on data from the Portuguese Health Interview Survey 2019 (PHIS 2019). We aimed to analyze not only up-to-date screening, but also non-target groups and different time frames, as these are important indicators of under-, and over-screening.

METHODS

Data

The data used in this study came from the PHIS 2019, collected between September 2019 and January 2020 (access to data was granted under the project registered in the Portuguese Office for National Statistics with the number 977). The database contains 14 617 individualized observations.[22] The samples used in this study included 8194, 8032, and 9940 observations for the analysis of breast, cervical, and colorectal cancer screening, respectively. Data by NUT 2 regions support the regional analysis. The NUT classification (Nomenclature of Territorial Units for Statistics) is a hierarchical system that divides the European Union (EU) territory. NUTS 2 corresponds to the second level of the hierarchy and refers to basic regions. Portugal is divided into seven NUT 2 regions: five in mainland Portugal (North, Center, Lisbon Metropolitan Area, Alentejo, Algarve) and two archipelagos (Madeira and Azores).

Variables

We used the variables from the PHIS 2019, corresponding to self-reported screening attendance for colorectal, breast, and cervical cancers, respectively. Individuals were asked about the last time they were screened. The options for CRC (presence of occult blood in feces) were: 'in the last 12 months', 'between one year and less than two years', 'between two years and less than three years', 'three years or more', and 'never'. We only considered individuals who never performed a colonoscopy. The reason for this procedure is that, according to the national guidelines,[10] colonoscopy is not the primary test, and our analysis is about screening of individuals with average risk for cancer. For breast and cervical cancer, the options for the last time women performed a mammography and cervical cytology (pap smear) were: 'in the last 12 months', 'between one year and less than two years', 'between two years and less than three years', 'between three years and less than five years', 'five years or more', and 'never'. Sex and age bands were used to define target and non-target groups. Net monthly equivalized income of the household (quintile), in PHIS, was used to rank individuals in the inequality analysis. Equivalized income is a measure of household income that considers the household's size and composition.[23] Observations with missing values in these variables were dropped.

Statistical analysis

To analyze screening in target as well as in non-target

groups and different time frames (to evaluate under-, and over-screening), we used the matrix proposed by Quintal and Antunes[24]: Fig. 1 identifies different situations, depending on the age interval of individuals and the last time they were screened for a given cancer.

As explained by the authors,[24] cells A+B reflect compliance with guidelines (up-to-date screening). Within this group, annual screening might happen in cell A, which consists of over-screening due to screening more frequently than recommended. Cell C represents cases where screening has been done before but is overdue. Cell D corresponds to never-screeners within the target group. Over-screening might occur not only due to excessive frequency but also due to screening of individuals younger, or older, than the recommended age (cells E and G, respectively). Cell F accounts for cases where screening rightfully never took place. Similarly, cases of individuals older than the recommended age, who did their last screening test outside the recommended interval (cell H) also conform to guidelines. Individuals who were never screened and are already beyond the recommended age (cell I) have lost their opportunity to benefit from screening.

For breast cancer and CRC screening, the target groups and recommended intervals were defined according to the criteria set up in 2017[10]: women aged 50 - 69 years/mammography biannually; individuals aged 50 - 74 years/FIT biannually. For cervical cancer screening, considering that the new guidelines were published in 2017 and the PHIS took place in 2019, the time in between was not enough to roll out every woman in the new program. Therefore, we assumed that the target group included women aged 25 - 64 years and the recommended interval is three years (except for the North, where since 2009 the criterion is HPV test/five years). In the analysis of women younger than the target group, in the case of breast cancer screening, the age band 45 - 49 years was dropped because, prior to 2017, these women were included in the eligible population for screening in several regions. This procedure ensures that our estimations of over-screening hold even in the light of previous criteria. In the analysis of individuals older than the target group, for all cancers, the age band adjacent to target was also dropped from the analysis – for example, a woman who just turned 71 years might have been screened in the last 12 months or in the last two years for breast cancer, but this is in accordance with the guidelines. Here, too, our estimates of over-screening were conservative.

The prevalence of attendance to screening was assessed both at the regional and national levels.

Sample weights (the inverse of the probability of selection of each unit) provided in the database have been used. National averages were calculated from the individualized observations in the dataset.

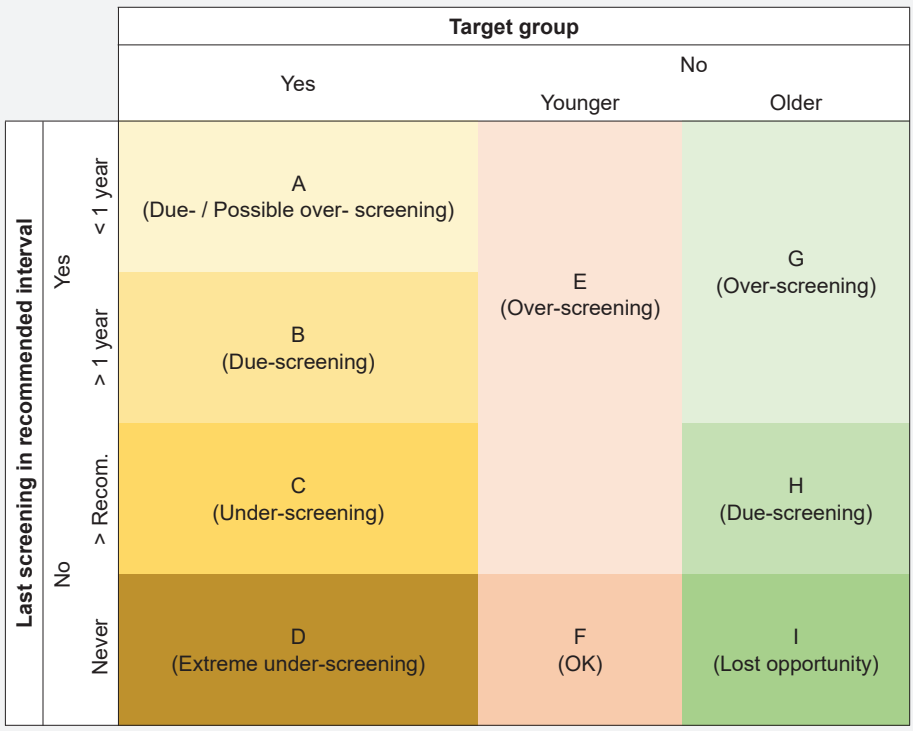

Figure 1 – Matrix proposed by Quintal and Antunes to analyse due-, under-, and over-screening.
Reprinted with permission.[24]

In the assessment of over-screening, within each target group, due to a frequency higher than recommended, we considered that if the proportion of women/individuals performing a mammography/FIT in the last 12 months comprised more than 50% of women/individuals screening in the last two years, then there was over-screening. This procedure assumes that screening was evenly distributed over the two years of the recommended interval. The same procedure was followed in other studies[18,24] and it is also in accordance with the methodology followed by the Directorate-General of Health, in Portugal, to determine the annual eligible population for screening.[6] In the case of cervical cancer screening, because the recommended interval is three years, if the percentage of women screened in last 12 months is more than 33% of women screening in the recommended period, then there is over-screening. In the case of the North, the proportion which defines over-screening is 20% (five-year interval).

To quantify inequalities in screening attendance, we resorted to the computation of concentration indices (CI). This methodology has been used to assess inequalities and inequities in the use of healthcare services, including doctor visits and hospitalizations[25-28] as well as cancer screening attendance.[24,29] In our case, concentration indices measure relative inequality in screening attendance over the distribution of income, thus being a tool to measure income-related inequality in the use of healthcare. The index is bounded between -1 and 1, meaning (extreme) disproportionate concentration of screening attendance among the poorer and the richer, respectively.[30] When there is no income-related inequality in screening attendance, the CI is zero. Hence, when testing the statistical significance of the CI, if the null hypothesis (CI = 0) cannot be rejected, then one cannot rule out an equal distribution of screening attendance. In contrast, if the null hypothesis is rejected, then we can conclude that there is inequality in screening attendance. In this work, the CI was computed using the *conindex* command from Stata 15.1[31] and the statistical significance of the CI is assessed at the 5% level. Further details about the computation and statistical significance of the CI are provided in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19443/15154).

Since we used anonymized secondary data, it was not necessary to request ethics committee approval.

RESULTS

Table 1 displays, for the cases of breast, cervical, and colorectal cancers, the levels of screening attendance (or absence of screening, where it applies) for all the situations identified in Fig.1, for all regions and nationwide as well.

Screening attendance in target group

Starting with breast cancer, for the target group, 81.1% of women were screened within the recommended interval (this value is not directly observable in Table 1; it results from the sum of the percentage of women being screened in last 12 months with the percentage of women being screened between one and two years). There was some variation across regions, with the North reaching 85.5%, while in Algarve this figure is the lowest (70.9%). The scenario was not so favorable for cervical cancer, with 72% of women in the target group being screened within the recommended interval. The North emerged with the highest percentage (86.7%) and Azores with the lowest (53.9%). As for CRC, only 40% of men and women underwent screening within the recommended period. Again, the North showed the highest figure (51.9%), and the lowest value occurred in the Center (26.2%). At the country level, under-screening was not so different across cancers, even though, there were some discrepancies within regions. However, extreme under-screening varied across cancers: in breast cancer, at the country level, only 3.4% of women in target group never performed a mammography, while this figure rose to 15.7% of women who never did an HPV/Pap Smear test, reaching 48.6% in the case of individuals who never did a FIT. Unlike in the case of breast cancer, for cervical and especially for colorectal cancer screening, for those individuals who were not screened within the recommended interval, the problem is above all not having been screened at all. In the Azores, basically one third of women in the target group had never been screened for cervical cancer (Madeira and Alentejo were close). In three regions (Center, Alentejo and Azores), 60% or more individuals of the target group (excluding those who already had a colonoscopy) never underwent screening for CRC.

In the case of cervical cancer screening, because the target group included women within a wide age band (25 - 64 years), we checked whether never screeners, in Portugal, were the youngest women. That is, we computed the prevalence rate of never screeners by age bands and found that the prevalence rates do not noticeably differ across groups [as can be seen in Appendix 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19443/15155)].

Based on Fig. 2, in the case of breast cancer, more than half of the women being screened within the recommended interval had screened in the last 12 months, in the whole country. In terms of regions, the North, Lisbon and the Algarve were slightly above the national average. Concerning cervical cancer screening, 49% of women being screened within the recommended interval had done so in the last 12 months. In the North, if screening was evenly distributed over the five years of the recommended interval, the ex-

Table 1 – Prevalence of due-, under-, and over screening in target and non-target groups for breast, cervical and colorectal cancers

			Target group										
			Yes			No							
						Younger				Older			
			BC	CC	CRC		BC	CC	CRC		BC	CC	CRC
Last screening in recommended interval	Yes	< 1 year	N:	54.5	37.5	30.6	N:	34.8	20.3	13.5	N:	20.4	13.5	21.5
			C:	44.1	32.7	18.8								
			L:	50.4	37.3	26.7					C:	18.9	8.2	12.6
			Al:	42.6	25.5	14.7	C:	29.3	15.7	9.9				
			Alg:	45.6	33.5	22.8					L:	32.9	19.8	27.7
			Az:	27.3	18.7	14.1								
			M:	47.4	34.4	29.3	L:	35.5	17.8	12.6	Al:	18.8	8.5	9.2
			PT:	49.7	35.4	25.3								
		> 1 year	N:	31.0	49.2	21.3								
			C:	38.3	35.3	7.4					Alg:	9.4	10.7	20.1
			L:	27.3	32.1	14.0	Al:	25.8	23.2	12.4				
			Al:	37.8	33.5	10.3					Az:	17.7	12.4	10.1
			Alg:	25.3	34.1	11.8								
			Az:	49.8	34.7	13.3	Alg:	31.5	15.6	11.6	M:	11.4	14.5	31.3
			M:	29.1	29.5	10.8					PT:	23.6	15.4	20.7
			PT:	31.4	36.6	14.7								
	No	> Recommended	N:	13.0	4.3	14.3					N:	65.5	31.2	24.4
			C:	14.2	11.8	8.9	Az:	13.8	13.0	10.7	C:	65.2	37.8	7.2
			L:	17.7	13.1	10.9					L:	59.9	44.0	30.4
			Al:	16.9	14.0	11.4					Al:	66.4	25.0	7.4
			Alg:	20.5	19.3	8.3	M:	28.2	22.8	16.1	Alg:	57.8	32.7	11.1
			Az:	17.2	13.9	9.1					Az:	62.0	25.2	11.9
			M:	18.8	9.1	9.5	PT:	33.0	18.5	12.5	M:	62.0	35.4	11.3
			PT:	15.5	12.3	11.4					PT:	63.0	44.1	20.4
		Never	N:	1.6	9.0	33.8	N:	65.2	79.7	86.5	N:	14.1	29.6	54.1
			C:	3.3	20.3	64.9	C:	70.7	84.3	90.1	C:	15.9	54.0	80.2
			L:	4.6	17.6	48.5	L:	64.3	82.2	87.4	L:	7.2	36.1	41.9
			Al:	2.7	27.0	63.6	Al:	74.2	76.8	87.6	Al:	20.8	66.4	83.3
			Alg:	8.5	13.1	57.2	Alg:	68.5	84.4	88.4	Alg:	32.7	56.6	68.8
			Az:	5.7	32.7	63.4	Az:	86.1	87.0	89.3	Az:	20.3	62.4	78.0
			M:	4.7	27.0	50.4	M:	71.8	77.2	83.9	M:	26.7	50.1	57.5
			PT:	3.4	15.7	48.6	PT:	66.9	81.5	87.5	PT:	13.4	40.6	58.9

BC: breast cancer; CC: cervical cancer; CCR: colorectal cancer.
N: North; C: Center; L: Lisbon Metropolitan Area; Al: Alentejo; Alg: Algarve; Az: Azores; M: Madeira; PT: Portugal.
All values are in percentage; For each column/region, the total sum is 100%.
Cell colour key on Fig. 1.

pected proportion of women being screened in the last 12 months would be 20%. Fig. 2 shows that the actual percentage more than doubles this level. Lisbon, Madeira, and the Algarve also stand out with a proportion of women screening in the last 12 months more than 1.5 times the value corresponding to an even distribution of screening. Regarding CRC, results should be read with caution as, by 2019, geographic coverage of the program had reached 100% only in the Azores and in Lisbon.[7]

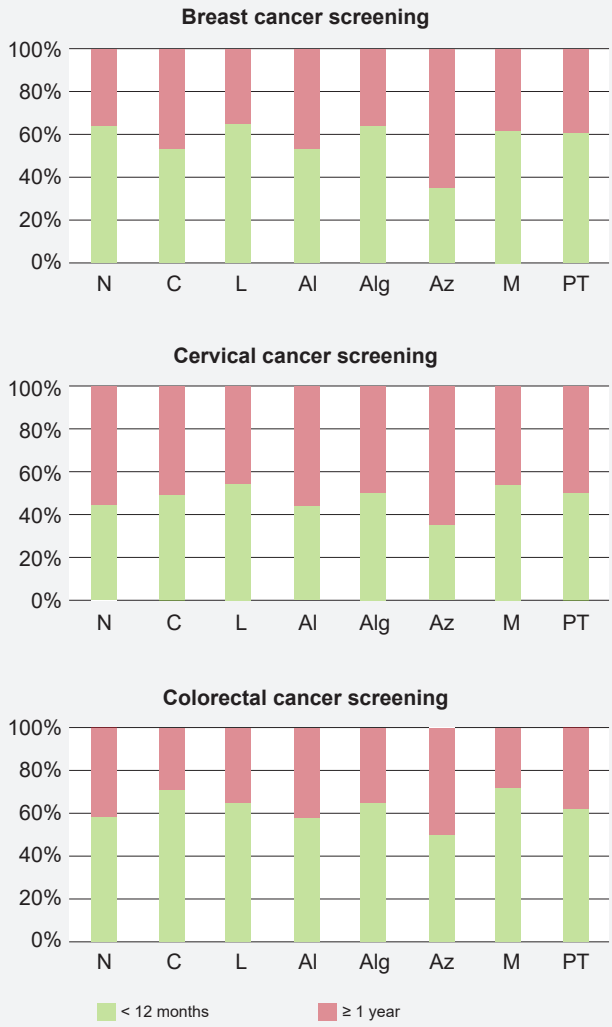

Figure 2 – Breakdown of target group screening within recommended interval: screening in last 12 months *versus* remaining intervals
N: North; C: Center; L: Lisbon Metropolitan Area; Al: Alentejo; Alg: Algarve; Az: Azores; M: Madeira; PT: Portugal.

Screening attendance outside the target group

Looking at Table 1 we see that for breast cancer, on average, one third of younger women had already performed a mammography (only in the Azores this proportion was relatively low – 13.8%). For cervical cancer the proportion of younger women who received screening is not particularly high, but it surpasses 20% in Alentejo and Madeira. CRC shows the lowest figures for screening among younger groups, in all regions. Among older women, on average, almost one fourth underwent breast cancer screening. In Lisbon, this proportion was the highest, corresponding to one third of women. For cervical cancer, the figures are the lowest in the older group, while, for CRC, the results are a bit surprising. Among individuals younger than 50 years, the vast majority never performed a fecal occult blood test, which conforms to the guidelines (in no region this value falls below 80%). But, on average, 21% of individuals above the target group was screened in the last two years, when the equivalent proportion in the target group is 40%. Over-screening in the older group was particularly high in Madeira, followed by Lisbon.

The last case to be analyzed in Table 1 concerns individuals beyond the recommended age for screening, who never underwent screening in their lives. At the country level, this figure was the lowest for breast cancer (13.4%); however, there were marked differences between regions. For instance, in the Algarve, about one third of older women never performed a mammography. There was a clear difference in the results, with Lisbon (by far the region with the best result with only 7.2% of 'never' users), North and Center in more favorable positions compared to the remaining regions. Two fifths of women and almost 60% of individuals above the target age never underwent screening for cervical cancer and CRC, respectively. The highest values, for both cancers, were observed in Alentejo. The North was the region with fewer 'never' users in both cases.

Income-related inequalities in screening attendance

Fig. 3 combines information on prevalence (vertical axis) with information on income-related inequality (horizontal axis) in screening attendance in the target group, within the recommended interval, for all three cancers analyzed in this study. Note that Fig. 3 shows the situation of up-to-date screening (corresponding to the joint analysis of screening in last 12 months -'Due/Possible over-screening' - and screening between one year and the upper-limit of recommended interval – 'Due-screening').

Breast cancer screening was, in general, characterized by high levels of attendance and no inequalities across income groups. The concentration index (CI) for Portugal was not significant and was virtually null (0.006). Zooming into the regions, except for the Center and Algarve, the remaining CIs are positive, suggesting a disproportionate concentration of screening among women with higher income. Nonetheless, we only observed a statistically significant CI in the Azores (0.047), meaning that in most regions we cannot rule out an equal distribution of screening. The picture was different for cervical cancer screening. Not only the level of attendance was lower compared to breast cancer, but virtually all CIs were positive and significant for four regions as well as for the whole country. At the country level the CI was 0.028 (statistically significant at the level of 1%), indicating the concentration of screening among women with a higher socioeconomic status. Inequalities were more pronounced in the Azores (CI = 0.076), Madeira (CI = 0.059) and Lisbon (CI = 0.052), and to a lesser extent in the North

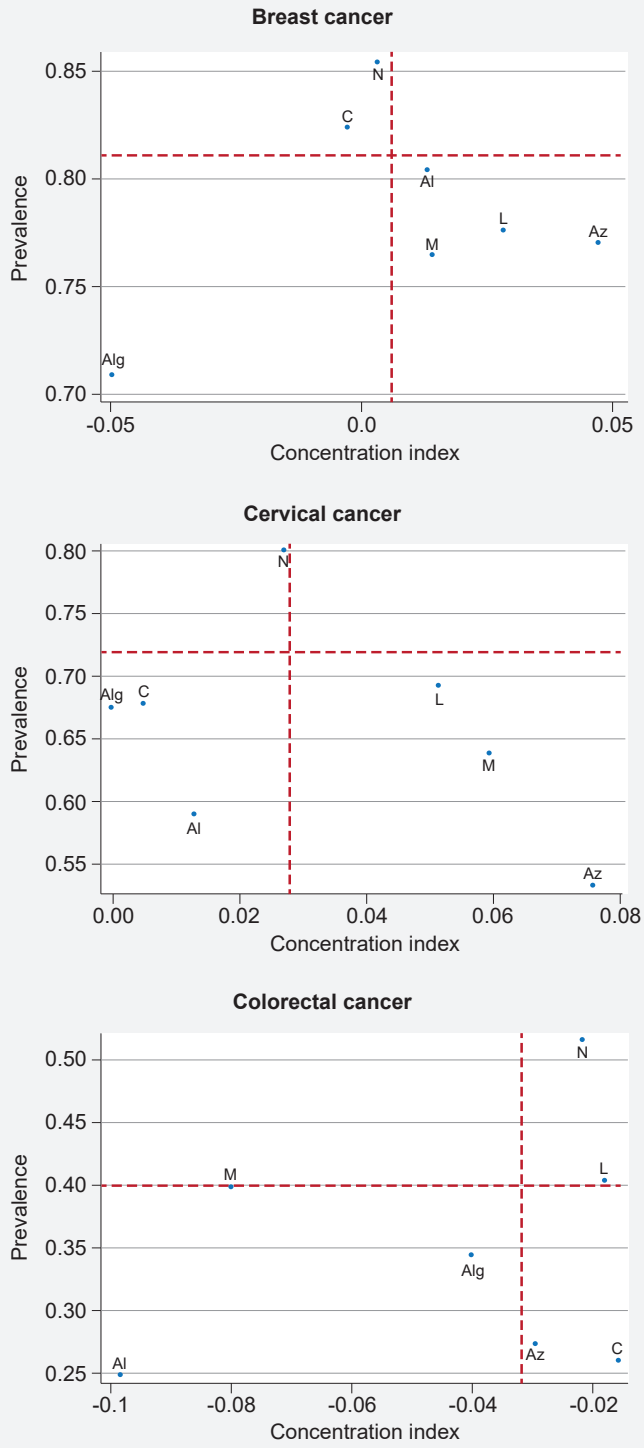

Figure 3 – Prevalence and income-related inequality in screening in target group, within recommended interval
N: North; C: Center; L: Lisbon Metropolitan Area; Al: Alentejo; Alg: Algarve; Az: Azores; M: Madeira.

(0.027). In the other regions, the null hypothesis of equality of screening across income groups cannot be rejected. The scenario changes again when we look at CRC screening. The level of attendance was lower when compared to the previous cancers, and CIs were all negative, pointing to the concentration of screening among individuals with a lower socioeconomic status. The coefficients were statistically significant in Alentejo and Madeira, and therefore, in these cases, we are confident that screening was concentrated in men and women with lower income. Table 2 provides information for CIs for all cases identified in Fig. 1.

Overall, there were no income-related inequalities in screening attendance as most coefficients were not statistically significant. Some exceptions apply; namely, the concentration of screening for cervical cancer in the last 12 months among women with a higher socioeconomic status in Portugal as well as in the Azores, Lisbon and North. Extreme under-screening, for cervical cancer, was concentrated among women with a lower socioeconomic status in the North, Azores, Madeira, and nationwide. CRC shows the opposite signals: concentration of screening in last 12 months among individuals with a lower socioeconomic status, while extreme under-screening was concentrated among individuals with a higher socioeconomic status. However, considering the regions, the coefficient was significant only for Madeira. Restricting the analysis of CRC screening to those individuals from the target group who never performed a FIT (3001 observations), we found that two-thirds of these individuals had not performed a colonoscopy either. We also checked differences between men and women, but very few were statistically significant [as shown in Appendix 3 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/19443/15156)].

Some inequalities emerged in screening among younger groups – always concentrated in individuals with a higher socioeconomic status for all cancers. Lastly, for the case of cervical cancer, 'never' screeners in the older group (women who are not eligible for screening anymore) were concentrated among women with a lower socioeconomic status.

DISCUSSION

This study aimed to analyze the level of, and income-related inequalities in, cancer screening attendance in all population-based programs implemented in Portugal. Overall, the findings suggest that screening attendance is the highest for breast cancer, followed by cervical cancer, and CRC. The prevalence of CRC screening attendance is quite below the prevalence of screening attendance for the other two cancers (in the whole country, screening attendance in target group within recommended interval for CRC was about half the equivalent value for breast cancer).

Table 2 – Concentration indices for due-, under-, and over screening in target and non-target groups for breast, cervical and colorectal cancers

			Target group										
			Yes			No							
						Younger				Older			
			BC	CC	CRC		BC	CC	CRC		BC	CC	CRC
Last screening in recommended interval	Yes	< 1 year	N:	0.057	**0.069**	-0.018	N:	0.005	0.107	0.081	N:	0.168	0.137	-0.072
			C:	0.015	0.003	-0.044								
			L:	0.020	**0.071**	-0.039					C:	0.067	0.067	-0.042
			Al:	-0.004	0.030	-0.012	C:	0.070	**0.332**	0.064				
			Alg:	**-0.088**	0.039	-0.031					L:	0.108	**0.141**	0.112
			Az:	0.030	**0.155**	0.038								
			M:	0.036	0.053	**-0.112**	L:	**0.158**	-0.015	0.094	Al:	0.070	0.086	0.011
			PT:	0.030	**0.058**	-0.034								
		> 1 year	N:	**-0.091**	-0.006	-0.028								
			C:	-0.024	0.006	0.056					Alg:	0.079	0.126	0.231
			L:	0.043	0.029	0.022	Al:	0.097	0.216	0.089				
			Al:	0.032	0.000	**-0.221**					Az:	0.152	0.006	-0.077
			Alg:	0.019	-0.039	-0.059								
			Az:	0.056	0.033	-0.101	Alg:	-0.009	-0.131	0.107	M:	0.209	**0.137**	-0.220
			M:	-0.022	0.067	0.007								
			PT:	-0.032	-0.001	-0.028					PT:	**0.132**	**0.218**	0.057
	No	> Recommended	N:	-0.049	-0.038	0.042					N:	-0.033	-0.041	0.030
			C:	0.030	**0.141**	-0.025	Az:	**0.198**	0.129	0.084	C:	-0.039	**0.091**	0.157
			L:	-0.077	**-0.147**	-0.060					L:	-0.054	-0.048	-0.066
			Al:	-0.045	-0.036	0.062					Al:	-0.010	0.014	0.189
			Alg:	**0.211**	-0.020	0.019	M:	0.046	0.158	**0.261**	Alg:	-0.009	**0.205**	0.058
			Az:	**-0.210**	-0.040	0.047					Az:	-0.031	0.021	0.128
			M:	-0.076	0.003	-0.036	PT:	**0.088**	0.106	**0.092**	M:	-0.058	0.068	0.257
			PT:	-0.026	-0.033	-0.007					PT:	**-0.041**	-0.006	-0.005
		Never	N:	0.235	**-0.236**	0.015	N:	-0.003	-0.027	-0.013	N:	-0.087	**-0.159**	0.042
			C:	-0.057	-0.098	0.010	C:	-0.029	**-0.062**	-0.007	C:	0.080	**-0.074**	-0.008
			L:	-0.176	-0.094	0.029	L:	**-0.088**	0.003	-0.014	L:	-0.047	-0.019	-0.026
			Al:	-0.106	-0.009	0.028	Al:	-0.034	-0.065	-0.013	Al:	-0.011	-0.016	-0.018
			Alg:	-0.095	0.030	0.022	Alg:	0.004	0.024	-0.014	Alg:	0.039	**-0.142**	-0.077
			Az:	0.000	**-0.107**	0.006	Az:	**-0.032**	-0.019	-0.010	Az:	-0.039	-0.036	-0.009
			M:	0.074	**-0.142**	**0.070**	M:	-0.018	-0.047	**-0.050**	M:	0.045	-0.050	0.070
			PT:	-0.026	-0.101	**0.028**	PT:	**-0.043**	-0.024	**-0.013**	PT:	-0.036	**-0.076**	-0.018

BC: breast cancer; CC: cervical cancer; CRC: colorectal cancer.
N: North; C: Center; L: Lisbon Metropolitan Area; Al: Alentejo; Alg: Algarve; Az: Azores; M: Madeira; PT: Portugal.
Coefficients in bold are statistically significant at the level of 1% or 5%.
Negative (positive) coefficients indicate disproportionate concentration among poorer (richer) individuals. In the absence of statistical significance, the null hypothesis of equal distribution cannot be rejected.
Cell colour key on Fig. 1.

This might be explained by the fact that CRC was the last program to be implemented in all regions. Still, the North was one of the last regions to implement it (in 2016) and still is the best performing region. In fact, this situation of more favorable results in the North (with the worst being in Alentejo and in the Azores) is a general pattern across

programs, already identified in studies based on data from previous rounds of the PHIS.[32-36] On the other hand, screening attendance seems to have improved over time. For CRC, both extreme-, and under-, screening decreased 10 percentage points between 2014 and 2019.[32] Extreme under-screening for breast cancer was about the same in 2019 as in 2014, but it was already low in 2014 (3.8%).[34] The proportion of older women who never underwent screening for breast cancer also decreased from 20% in 2014, to 13.4% in 2019. Extreme under-screening for cervical cancer was slightly above the value found in the past (15.7% in 2019 *vs* 13.2% in 2014).[36] Over-screening for breast cancer in younger women was still an issue. In 2014, 50% of women between 30 and 44 years had undergone screening.[34] In this study, the percentage was lower (33%), even though we considered all women aged 15 to 44 years old (over-screening would likely be higher if we restricted the analysis to women closer to the target group). In the case of cervical cancer, the problem with over-screening seems to be, above all, a matter of screening more frequently than recommended. Although there is an organized screening program for this cancer, opportunistic screening, under which over-screening is more likely,[20] might still exist. Based on the data used in this study, it is not possible to know if women screened within or outside organized programs or if they screened in the public or the private sector. De Prez *et al*[18] found that reimbursement initiatives can alter over-screening. In Portugal, reimbursement schemes do not penalize repeated tests. Soon, over-screening for cervical cancer might increase as doctors and patients might take some time to adjust to the new guidelines which recommend longer intervals between tests.[10] This phenomenon has been reported in the US.[37]

Regarding the inequality analysis, previous evidence for Portugal is scarce. Compared with 2014, inequality in target group/recommended interval (whole country) was the same for breast cancer, that is, the CI was basically null (and not significant) in both years, while it seems to have worsened for cervical cancer, given that the concentration of screening among women with a higher socioeconomic status has increased (CI = 0.038 in 2019 *vs* CI = 0.028 in 2014).[24] For cervical cancer, 'never' screening within the target group was concentrated among women with a lower socioeconomic status, even though it seems to have slightly improved (CI = -0.101 in 2019 *vs* CI = -0.148 in 2014).[24] The situation seems quite worrisome in Madeira and Azores where large and negative CIs were combined with high prevalence of 'never' screeners. As previously noted, the absence of screening is not concentrated in any particular age band, similarly affecting women within the target group, from younger to older ages. Women who lost the opportunity to undergo screening for cervical cancer were also concentrated among groups with a lower socioeconomic status. In the Algarve and Center, a negative (and significant) CI combined with high prevalence, which is a worrying finding. Although there are organized programs, it seems that the access is still affected by income, at least to some extent. In the Algarve, for example, a low adherence to cervical cancer screening by doctors and patients in primary care services has been reported. Doctors themselves do not feel comfortable or capable of performing the tests.[38] This means that in practice, there are still many constraints. Results for CRC were somewhat puzzling because, while screening in target group/recommended interval seemed to be equal across income groups, extreme under-screening was concentrated among individuals with a higher socioeconomic status. Are individuals with a higher socioeconomic status not undergoing screening as they should or are they bypassing FIT and using colonoscopy as their primary test? Based on our results (when we restricted the analysis to those individuals who never did a FIT), it does not seem to be a matter of substitution between FIT and colonoscopy. Based on the findings from the comparison between men and women, it does not seem to be a sex-specific issue either.

In the future, more attention should be paid to over-screening to ensure that individuals are making informed choices. Regarding cervical cancer screening, two extreme situations seem to coexist. For the target group, the findings suggests that some women are undergoing screening annually while other women, of lower income, are not receiving screening at all. In the case of CRC, screening attendance was clearly lower than for breast and cervical cancers, probably reflecting the fact the CRC screening program was the last to be implemented. Somewhat unexpectedly, the evidence suggests that extreme under-screening is concentrated among individuals with a higher income. Once the program becomes completely implemented, these issues should be further investigated.

Limitations

Our results are based on self-reported data, meaning that there might be an overestimation of attendance[39] or inequalities,[40] but this is the usual procedure due to difficulties in accessing administrative data.[41] While we focused on levels of attendance, it is essential to ensure that services are of high quality and that there is an adequate follow-up.[42] Still, a study that looked at the North reported high standards in terms of the tests performed and detection rate.[43] As acknowledged in previous studies,[32,34,36] the analysis for regions relied on data for NUTS 2, which do not entirely correspond to the health regions responsible for implementing screening programs.

CONCLUSION

This study aimed to diagnose the levels of attendance and the respective inequalities in cancer screening for breast, cervical, and colorectal cancers in Portugal. Situations vary depending on the program and region, but overall, the attendance was high, and the inequalities were low in the case of breast cancer screening. For cervical and colorectal cancers, challenges still lie ahead and there is the need to involve both healthcare professionals and patients if screening guidelines are to be effectively implemented.

AUTHOR CONTRIBUTIONS

CQ: Study design, literature review, analysis of results, writing of the manuscript.

MA: Study design, database preparation, empirical analysis, analysis of results, writing of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Diagnóstico e Tratamento do Neuro-Behçet: Uma Actualização Clínica

Diagnosis and Treatment of Neuro-Behçet: A Clinical Update

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RESUMO

A doença de Behçet é uma síndrome inflamatória multissistémica recidivante, caraterizada por úlceras orais e/ou genitais recorrentes, uveítes, artrite, lesões cutâneas e envolvimento gastrointestinal e neurológico. O neuro-Behçet corresponde ao envolvimento do sistema nervoso e é uma das complicações mais graves da doença de Behçet. Ocorre em 3% a 30% dos casos e categoriza-se em doença parenquimatosa (mais frequente) ou não-parenquimatosa. A manifestação mais comum do neuro-Behçet parenquimatoso é a meningoencefalite com acometimento do tronco cerebral, sendo que os doentes se apresentam com neuropatias cranianas, encefalopatia, síndromes sensitivo-motoras, epilepsia ou mielite. A principal manifestação não-parenquimatosa é a trombose venosa cerebral. O neuro-Behçet apresenta uma evolução maioritariamente subaguda, com remissão em semanas, ou com progressão clínica, em um terço dos casos. O diagnóstico é essencialmente clínico e os exames complementares auxiliam a corroborar a suspeita, a diferenciar de diagnósticos diferenciais e a excluir complicações. A ressonância magnética cerebral permite observar lesões agudas (hipo ou isointensas em T2 e hipointensas em T1) que captam contraste, e lesões crónicas caraterizadas por pequenas lesões que não captam contraste e atrofia do tronco cerebral. Na suspeita de envolvimento não-parenquimatoso deve ser realizada venoressonância magnética/tomografia computorizada cerebral. O líquido cefalorraquidiano apresenta elevação da proteinorraquia e da pleocitose no neuro-Behçet parenquimatoso e não tem alterações no não-parenquimatoso (exceto aumento da pressão de abertura). Os surtos de doença parenquimatosa devem ser tratados com corticoterapia endovenosa em alta dose, com posterior desmame para corticoterapia oral, seguida de terapêutica biológica, habitualmente anti-TNF. O tratamento da trombose venosa cerebral é controverso, podendo consistir na associação de corticoterapia e anticoagulação. Tendo em conta a gravidade desta entidade e o facto de ser potencialmente tratável, é fundamental que seja reconhecida precocemente. Assim, foi realizada uma revisão teórica no sentido de compilar as informações mais relevantes sobre o neuro-Behçet, para auxiliar os clínicos na abordagem a este tipo de doentes.
Palavras-chave: Doenças do Sistema Nervoso Central/diagnóstico; Doenças do Sistema Nervoso Central/tratamento farmacológico; Síndrome de Behçet/complicações; Síndrome de Behçet/diagnóstico; Síndrome de Behçet/tratamento farmacológico

ABSTRACT

Behçet's disease is a relapsing multisystemic inflammatory syndrome characterized by recurrent oral and/or genital ulcers, uveitis, arthritis, skin lesions, and gastrointestinal and neurological involvement. Neuro-Behçet corresponds to nervous system involvement and is one of the most severe complications of Behçet disease. It occurs in 3% to 30% of cases and is categorized into parenchymal (most common) or non-parenchymal disease. The most common manifestation of parenchymal neuro-Behçet is meningoencephalitis with involvement of the brainstem, where patients present with cranial neuropathies, encephalopathy, sensory-motor syndromes, epilepsy, or myelitis. The main non-parenchymal manifestation is cerebral venous thrombosis. Neuro-Behçet has a predominantly subacute course, with remission within weeks, or clinical progression in one third of the cases. The diagnosis is essentially clinical and diagnostic tests help to corroborate the suspicion, distinguish from differential diagnoses, and exclude complications. Brain magnetic resonance imaging allows the identification of acute lesions (hypointense or isointense on T2-weighted and hypointense on T1-weighted sequences) contrast-enhanced, and chronic lesions characterized by non-contrast enhanced small lesions and brainstem atrophy. If non-parenchymal involvement is suspected, cerebral veno-magnetic resonance imaging /computed tomography should be performed. Cerebrospinal fluid shows elevated proteinorachia and pleocytosis in parenchymal and no changes in non-parenchymal neuro-Behçet (except increased opening pressure). Outbursts of parenchymal disease should be treated with high dose intravenous corticosteroid therapy, with subsequent switch to oral corticoids, followed by biologic therapy, usually an anti-TNF. The treatment of cerebral venous thrombosis is controversial and may consist of a combination of corticosteroids and anticoagulation. Given the severity of this entity and the fact that it is potentially treatable, it is essential to recognize it early. Therefore, a narrative review was carried out in order to collate the most relevant information on neuro-Behçet, to help clinicians manage this type of patient.
Keywords: Behcet Syndrome/complications; Behcet Syndrome/diagnosis; Behcet Syndrome/drug therapy; Central Nervous System Diseases/diagnosis; Central Nervous System Diseases/drug therapy

INTRODUÇÃO

A doença de Behçet (DB) é uma condição multissistémica inflamatória crónica rara, com progressão do tipo remissão-recorrência. Não se conhece ainda a etiologia nem os mecanismos associados à sua fisiopatologia. A prevalência é relativamente maior no Médio Oriente e Mediterrâneo (na conhecida região da Rota de Seda), embora seja globalmente reportada.[1] Afeta maioritariamente jovens entre os 20 e 40 anos. O diagnóstico é essencialmente clínico, pois não existem testes laboratoriais patognomónicos, obrigando a um elevado índice de suspeição. Os critérios de classificação diagnóstica da DB foram propostos pelo International Study Group for Behçet's Disease (ISGBD) em 2014, com base numa coorte de 27 países, incluindo Portugal (Tabela 1).[2]

As lesões mucocutâneas são os sinais mais caraterísticos e a aftose oral é o mais sensível, reportada em 90% a

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100% dos doentes, nos estudos de populações nacionais. As aftas orais são muitas vezes o primeiro sintoma da doença, podendo preceder em 10 a 15 anos o aparecimento dos outros sintomas.[3-5] As úlceras/aftas genitais têm, pelo contrário, mais especificidade e, portanto, são melhores preditoras da doença. O envolvimento ocular é muito típico e específico, sendo a uveíte a manifestação ocular mais comum.[6] Associadamente pode existir envolvimento cutâneo (eritema nodoso, pseudofoliculite, lesões papulopustulares), vascular (envolvimento arterial e venoso, em vasos com vários calibres), articular (artralgias), gastrointestinal (úlceras esofágicas, diarreia crónica) e, ocasionalmente, neurológico. O envolvimento multiorgânico nem sempre se manifesta simultaneamente, dificultando o diagnóstico.

O teste da patergia consiste numa reação cutânea inespecífica de hipersensibilidade à picada com agulha. O resultado é positivo quando surge uma pústula, 24 a 48 horas após a picada. A adição deste teste aumenta a sensibilidade diagnóstica, embora não seja patognomónico, nem obrigatória a sua realização.[2] Os portadores do HLA-B51/B5 têm maior suscetibilidade para a DB e, embora não seja critério de diagnóstico, é útil para o seguimento dos doentes que ainda não completaram manifestações clínicas suficientes para se poder confirmar o diagnóstico.[7-9]

Neuro-Behçet (NB) corresponde ao envolvimento neurológico da DB e atinge predominantemente o sistema nervoso central (SNC).[10-12] Este artigo pretende rever os dados mais recentes acerca desta entidade, de modo a facilitar o diagnóstico e tratamento precoce dos doentes afetados.

CARATERIZAÇÃO

O acometimento neurológico da DB manifesta-se, em média, cinco anos após o início de sintomas sistémicos, mais frequentemente no sexo masculino, entre a terceira e quinta décadas de vida.[13] Apesar de pouco frequente, é das complicações com maior morbimortalidade e o tratamento não pode ser atrasado, sob pena da instalação de sequelas irreversíveis.[14]

A maioria dos estudos reporta uma prevalência inferior a 10%, apesar de ser variável (3% - 30%) de acordo com as séries hospitalares.[9,10] Numa série de um centro hospitalar do Norte de Portugal (1993 - 2013), identificaram-se 138 doentes com DB, dos quais 25 (18,1%) desenvolveram NB.[11,12]

Tabela 1 – *Score* de pontuação para diagnóstico de doença de Behçet

Lesões oculares	2
Aftose genital	2
Aftose oral	2
Lesões cutâneas	1
Manifestações neurológicas	1
Manifestações vasculares	1
Teste de patergia positivo	1[a]

Pontuação ≥ 4 indica diagnóstico
[a]: O teste de patergia é opcional e o sistema de pontuação primário não inclui este teste. Contudo, quando é realizado, deve ser adicionado um ponto extra, se for positivo (adaptação do ISGBD).

O envolvimento do SNC é geralmente classificado em parenquimatoso e não-parenquimatoso. O parenquimatoso é a complicação neurológica mais comum, correspondendo a um processo inflamatório meningoencefalítico, geralmente associado a exacerbação dos sintomas sistémicos.[15] A clínica neurológica varia, e as manifestações mais comuns são cefaleia, sintomas ou sinais sensitivo-motores, crises epiléticas, doenças do movimento, encefalopatia, ataxia cerebelosa ou neuropatias cranianas.[16]

A cefaleia é o sintoma neurológico mais comum na DB, mas a maioria está relacionada com cefaleias primárias (como enxaqueca ou cefaleia de tensão), pelo que estas hipóteses devem ser sempre consideradas.[17] A cefaleia diretamente relacionada com o envolvimento neurológico da DB apresenta-se em cerca de 10% dos casos.[9] A investigação deste sintoma deverá ser aprofundada na presença de sinais de alarme, nomeadamente, cefaleia progressiva ou persistente; severa ou incapacitante; alteração do caráter habitual da dor; primeira e mais intensa cefaleia sentida pelo doente ou sinais/sintomas neurológicos associados.

As manifestações clínicas dependerão da localização das lesões inflamatórias, sendo as mais comuns no tronco cerebral, gânglios da base, via corticoespinhal e substância branca periventricular. A síndrome do tronco cerebral pode estender-se desde o mesencéfalo, gânglios da base, até ao diencéfalo. Associado às lesões cerebrais ou do tronco, ou isoladamente (menos frequente), pode existir envolvimento medular, conferindo pior prognóstico.[18] Neste caso, os doentes podem apresentar sinais piramidais, nível sensitivo e/ou disfunção esfincteriana. Défices neurocognitivos também têm sido associados a esta patologia, em comparação com controlos, sendo que uma revisão sistemática concluiu que os domínios mais afetados são a capacidade visuoespacial, a memória de trabalho e a aquisição de novos conhecimentos.[19]

As manifestações neurológicas apresentam-se comummente de forma aguda ou subaguda e podem ser seguidas de remissão, com ou sem sequelas. Num terço dos casos pode haver progressão posterior ao surto inicial (curso crónico secundariamente progressivo) e mais raramente, a clínica persiste sem melhoria desde o surto inicial (curso crónico primariamente progressivo).[18] Segundo uma meta-análise que comparou os tipos de evolução, verificou-se que na aguda ocorre mais frequentemente febre e pleocitose no líquido cefalorraquidiano (LCR), enquanto na crónica prevalecem alterações esfincterianas, ataxia e confusão, e a ressonância magnética (RM) cerebral revela atrofia do

tronco cerebral.[20]

O NB não parenquimatoso ocorre em cerca de um quinto dos casos e corresponde a doença secundária ao envolvimento vascular.[21] A apresentação é mais frequentemente subaguda ou crónica, embora possa ter um início agudo (< 48 h), em um terço dos casos.[22] O envolvimento venoso pode apresentar-se sob a forma de trombose venosa cerebral (TVC), manifestação mais comum, ou de hipertensão intracraniana sem alterações na imagem (TC/RM) cerebral, denominada hipertensão intracraniana idiopática. Os doentes apresentam-se com cefaleias, alterações visuais, papiledema, sinais neurológicos focais, oftalmoplegia ou encefalopatia.[23] Nestes casos é frequente o envolvimento vascular extracraniano.[24] A doença arterial é menos frequente e inclui tromboses agudas, disseções ou aneurismas. Estas entidades geralmente apresentam um padrão monofásico (raramente recorrem) e, portanto, conferem melhor prognóstico.

O sistema nervoso periférico também pode ser acometido, embora raramente e de forma assintomática ou com sintomas ligeiros. Existem casos reportados de neuropatia ou miopatia, com estudos de condução nervosa e biópsias a revelar neuropatia axonal não-vasculítica.[25]

DIAGNÓSTICO

O diagnóstico do NB é maioritariamente adquirido com base em achados clínicos. Os exames complementares auxiliam na distinção entre diagnósticos diferenciais e na exclusão de complicações, mas não existem testes específicos para confirmar o diagnóstico. Como os sinais e sintomas sistémicos estão geralmente presentes aquando do envolvimento neurológico, é fundamental reconhecê-los, para se ponderar este diagnóstico (Tabela 1).

Em 2014 foram publicadas recomendações de um consenso internacional, com critérios de diagnóstico de NB, no sentido de uniformizar a clínica.[26] O grupo de peritos propôs critérios 'definitivos' e 'prováveis', de acordo com os diferentes graus de certeza do diagnóstico de DB e os detalhes das manifestações neurológicas (Tabela 2).

Apesar do maior reconhecimento desta entidade, é importante relembrar que as manifestações neurológicas podem não corresponder a NB, já que doenças primárias, como a enxaqueca ou o acidente vascular cerebral, são mais frequentes. Adicionalmente, esses sinais ou sintomas podem corresponder a efeitos adversos do tratamento, como infeções ou neoplasias secundárias.

INVESTIGAÇÃO

A RM cerebral é o exame *gold standard* para avaliar o envolvimento do SNC. Recomenda-se a utilização de contraste e realização de veno-RM para auxiliar o diagnóstico diferencial com doenças inflamatórias do SNC e para excluir TVC. As lesões cerebrais agudas e subagudas são hipo ou isointensas nas sequências em T1 e hiperintensas em T2, FLAIR (*fluid attenuated inversion recovery*) e difusão, geralmente com captação de contraste (Fig. 1). Na fase crónica, as lesões são tendencialmente menores e pode existir atrofia do tronco cerebral e lesões inespecíficas da substância branca, que não captam contraste.[26]

A realização de punção lombar é fundamental, tanto para suportar o diagnóstico, como para excluir infeção do SNC ou outros mimetizadores. No envolvimento parenquimatoso é frequente a elevação da proteinorraquia e da pleocitose, com glucorraquia normal, embora a ausência de alterações não exclua o diagnóstico. A presença de bandas oligoclonais com origem intratecal é pouco frequente, embora possa existir em até 17% dos casos. A interleucina-6 no LCR correlaciona-se com a atividade da doença pelo que poderá ser útil na monitorização do NB parenquimatoso, especialmente na ausência de outros sinais inflamatórios.[27] No NB não-parenquimatoso, o LCR tende a ser normal, com exceção de aumento da pressão de abertura. Pela baixa especificidade e sensibilidade, não existem marcadores sistémicos que auxiliem o diagnóstico. Tanto a proteína C reativa como a velocidade de sedimentação podem estar elevadas, mas têm valor limitado no diagnóstico.

A clínica, neuroimagem e alterações no LCR são geralmente suficientes para assumir o diagnóstico, sendo rara

Tabela 2 – Critérios para o diagnóstico de neuro-Behçet, segundo as recomendações do *consensus* internacional

NB definitivo (cumpre os três seguintes critérios)
1. Cumpre os critérios para diagnóstico de DB (pelo ISGBD)
2. Apresenta síndrome neurológica (com sinais neurológicos objetivos) reconhecida como causada pela DB e suportada por alterações típicas em um dos: **a**. Neuroimagem **b**. LCR
3. Não existe outra melhor explicação para a clínica neurológica
NB provável (cumpre um dos dois seguintes critérios, na ausência de outra melhor explicação para a clínica neurológica)
1. Apresenta síndrome neurológica sugestiva, com manifestações típicas de DB mas que não cumprem os critérios do ISGBD
2. Apresenta síndrome neurológica não-caraterística num doente que cumpre os critérios para DB (pelo ISGBD)

Adaptação de Kalra S, et al[26]

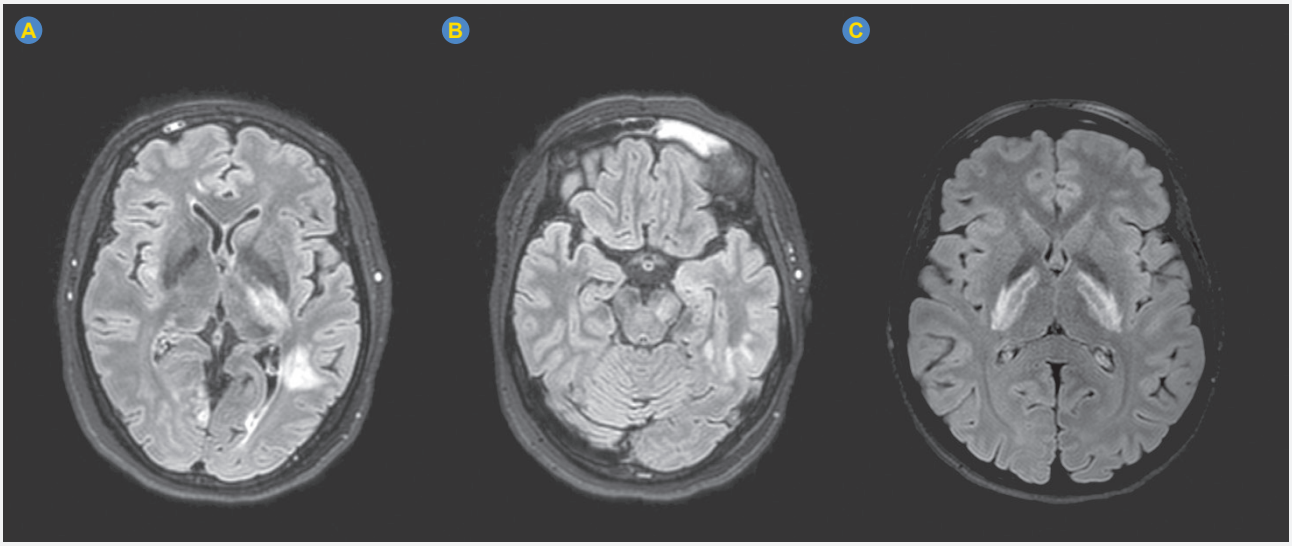

Figura 1 – Exemplos de ressonância magnética cerebral em doentes com neuro-Behçet. Áreas de hipersinal em T2 e T2/FLAIR em topografia justacortical e nas coroas radiadas (A), na amígdala temporal e cabeça do hipocampo à esquerda, com atingimento profundo da cápsula interna e transição tálamo-mesencefálica à esquerda (B), núcleos lentiformes e tálamos bilateralmente (C).

a necessidade de realizar biópsia cerebral. Os achados anatomopatológicos também não são patognomónicos, mas existem achados comuns descritos na literatura. Na fase aguda/subaguda encontram-se sinais de perivasculite, com infiltração perivascular de linfócitos, neutrófilos e, raramente, eosinófilos, com ou sem sinais de necrose. Em fases mais tardias, a infiltração inflamatória é menos evidente e predomina a perda axonal e gliose.[28]

Estudos neurofisiológicos também podem auxiliar o diagnóstico em determinadas situações. A eletromiografia pode ser útil para caraterização dos raros casos de suspeita de neuropatia ou miopatia associadas à DB. Apesar do eletroencefalograma não apresentar alterações específicas, pode ser vantajoso no diagnóstico diferencial com outras entidades, nomeadamente encefalites víricas.[9] Os potenciais evocados visuais podem ser úteis para determinar eventual envolvimento subclínico do nervo ótico e, adicionalmente, comprovar o benefício do tratamento.[29]

DIAGNÓSTICO DIFERENCIAL

O diagnóstico diferencial inclui doenças inflamatórias do SNC, nomeadamente esclerose múltipla (EM), infeções do SNC, síndromes uveomeningíticas (lúpus eritematoso sistémico, sarcoidose, síndrome de Sjögren), síndrome antifosfolipídica, acidente vascular cerebral em idade jovem ou linfoma primário do SNC.[21]

A EM é a principal hipótese diagnóstica tendo em conta a similaridade da idade de início, o tipo de evolução e as lesões inflamatórias na RM cerebral. Assim, na presença de atipias para EM, especialmente se sintomas sistémicos, deve considerar-se a hipótese de NB. Enquanto este se manifesta frequentemente com cefaleias, sintomas motores, disartria pseudobulbar e alterações cognitivo-comportamentais, na EM predominam sintomas sensitivos, nevrite ótica, oftalmoplegia internuclear, ataxia e/ou disartria cerebelosa.[30] Relativamente à neuroimagem, no NB identifica-se, por vezes, atrofia do tronco cerebral e lesões cerebrais maioritariamente subcorticais, enquanto na EM predominam lesões medulares e as cerebrais têm um padrão periventricular mais característico. O LCR pode auxiliar a diferenciação pela presença de bandas oligoclonais, que são raras no NB.[31] Apesar do neurolúpus também poder apresentar lesões da substância branca, é raro envolver os gânglios da base ou o tronco cerebral. Manifesta-se com sintomas neuropsiquiátricos, alterações mnésicas e crises epiléticas, mais frequentemente do que no NB.[32] Nestes casos, deve-se descartar síndrome antifosfolipídica primária ou secundária associada.

A evidência de sintomas constitucionais, uveíte e lesões mucocutâneas também relembram a sarcoidose. A neuro-sarcoidose apresenta-se comumente com neuropatias cranianas e síndrome meníngea, embora possa envolver qualquer parte do SNC.[33] Algumas infeções, como a tuberculose e a brucelose, também são incluídas no diagnóstico diferencial pois podem apresentar-se com quadros subagudos a crónicos, caraterizados por meningite e manifestações orais, mucocutâneas e/ou gastrointestinais.[34]

Outras síndromes mais raras também devem ser consideradas em determinados casos atípicos, nomeadamente a síndrome de Cogan, que corresponde a uma vasculite

de grandes vasos com envolvimento predominantemente ocular e vestíbulo-auditivo, mas também vascular e com sintomas constitucionais.[35] A síndrome de Susac é uma doença imune rara que afeta a microcirculação sistémica, caraterizando-se pela tríade clínica: encefalopatia, hipoacusia neurossensorial e alterações visuais.[36]

TRATAMENTO

Os modos de abordagem terapêutica são diferentes dependendo do tipo de envolvimento do SNC, da experiência de cada centro e/ou da gravidade de cada caso. A maioria das recomendações fundamentam-se em estudos observacionais controlados, já que não existem ensaios clínicos randomizados nesta área.

Segundo as recomendações da EULAR 2018, os surtos com envolvimento parenquimatoso tratam-se com corticoide em alta dose (metilprednisolona endovenosa 1 g/dia durante sete dias), seguido de prednisolona oral (1 mg/kg/dia durante um mês e posterior desmame de 5 – 10 mg a cada 10 - 15 dias, durante dois a três meses).[37] Visto que os efeitos imunossupressores das terapêuticas modificadoras de doença (TMD) podem durar três a seis meses para atingir o pico de eficácia, recomenda-se um desmame progressivo e lento da corticoterapia. A altura para o início das TMD não está claramente definida. No entanto, estas terapêuticas são essenciais para controlar o processo inflamatório, prevenir ou reduzir o risco de recidivas, minimizar a exposição à corticoterapia e ajudar a controlar os outros sintomas sistémicos. Recomendam-se vários tipos de imunossupressores, nomeadamente a azatioprina, preferível pelo menor risco de efeitos adversos e maior acessibilidade. A dose inicial corresponde a 1 - 1,5 mg/kg/dia, que pode ser gradualmente aumentada a cada cinco a sete dias, até à dose terapêutica máxima (2,5 mg/kg/dia). Os imunossupressores alternativos são o metotrexato (12,5 – 25 mg/semana) ou micofenolato de mofetil (dose inicial de 1000 mg/dia e manutenção de 2000 – 3000 mg/dia). A Comissão Nacional Japonesa para Doença de Behçet de 2020 recomenda preferencialmente a colchicina (1 - 2 mg/dia) no primeiro surto, após avaliação do risco-benefício individual, devendo ser introduzida na fase de desmame da corticoterapia, e mantida durante cinco anos. Este fármaco é considerado mais benéfico na prevenção de novos surtos que os outros imunossupressores, como a azatioprina.[38]

Os anticorpos monoclonais anti-TNF devem ser considerados como primeira opção na doença grave (com fatores de pior prognóstico) ou refratária.[39,40] O infliximab provou ser o mais eficaz na DB com envolvimento ocular refratário e neurológico e é aquele com mais dados na literatura.[39] As recomendações japonesas também consideram o uso concomitante de infliximab em doentes com reduzida resposta a altas doses de corticoide.[38] Apresenta uma resposta clínica favorável em mais de 80% dos casos e uma redução do risco de recidiva e da progressão para incapacidade.[41,42] O tratamento é administrado via endovenosa (5 mg/kg) nas semanas 0, 2 e 6 e depois a cada 8 semanas. O adalimumab e o etanercept são alternativas ao infliximab, administrados via subcutânea, 40 mg bimensal e 50 mg semanal, respetivamente.[10] A ciclofosfamida é outra alternativa, com formulação oral (1 – 3 mg/kg/dia) ou endovenosa (500 – 1000 mg/m^2 mensal) durante seis a nove meses.[43]

Estudos recentes têm demonstrado benefício com inibidores da interleucina-1 (em particular a anakinra), no tratamento das manifestações mais severas (oculares e neurológicas), nomeadamente nos casos refratários aos fármacos de primeira linha.[44] A ciclosporina é recomendada no tratamento da DB com envolvimento ocular, mas deve ser evitada no NB, pois associa-se a neurotoxicidade, podendo acelerar o desenvolvimento de sintomas neurológicos nestes doentes.[21,45]

O tratamento da TVC acarreta algumas controvérsias.[46] Por um lado, é recomendada a utilização de corticoterapia, dada a hipótese de que é o processo inflamatório que leva à aderência do trombo no vaso. No entanto, não existem dados definitivos sobre o benefício em adicionar imunossupressores nestes casos, tendo em conta a baixa probabilidade de recidiva. A hipocoagulação, sendo o tratamento *standard* da TVC com outras etiologias, é recomendada por um período curto (três a seis meses). Alguns centros iniciam tratamento com heparina de baixo peso molecular ou heparina não-fracionada (cinco dias) e no terceiro dia sobrepõem a varfarina, até obtenção do INR alvo (2,5 - 3) e posterior suspensão da heparina.[47] Algumas recomendações sugerem a exclusão de doença vascular extracraniana, nomeadamente aneurismas sistémicos, para evitar complicações da hipocoagulação.[23] Certos peritos sugerem exclusão de trombofilias, após suspensão da hipocoagulação, para aferir a necessidade de manutenção da terapêutica a longo prazo.[10]

PROGNÓSTICO

Os fatores de pior prognóstico incluem o envolvimento parenquimatoso do SNC, a extensão das lesões, as alterações inflamatórias do LCR (elevação da pleocitose), as recidivas (essencialmente quando associadas ao desmame da corticoterapia) e a progressão precoce da doença.[48,49] A presença de disfunção cognitiva, alteração esfincteriana, sinais piramidais e do tronco cerebral estão associados a maior incapacidade.[22] Embora o prognóstico seja predominantemente melhor em pacientes com TVC, estes podem ter morbimortalidade significativa devido ao envolvimento sistémico mais grave.[50] Fatores como o sexo, a presença de outras manifestações sistémicas da DB e a idade de

início dos sintomas não parecem influenciar o prognóstico.[51] A taxa de mortalidade destes doentes pode atingir 8% a 10%, de acordo com os estudos.[13,51] Não existem escalas validadas para avaliar a incapacidade dos doentes com NB e as que existem ainda necessitam de melhorias.[52]

CONCLUSÃO

O NB consiste numa das manifestações mais graves e incapacitantes da DB, e deve, portanto, ser sempre considerado na presença de clínica neurológica associada a história de úlceras genitais ou orais, uveíte ou outros sintomas sistémicos. Apesar de relativamente rara, é uma entidade potencialmente tratável, pelo que a sua suspeição é fundamental para evitar sequelas irreversíveis, em caso de atraso no tratamento. Esta entidade pode apresentar vários tipos de manifestação, desde formas praticamente assintomáticas até evolução progressiva com disfunção neurológica incapacitante. Assim, deve ser incluída no diagnóstico diferencial de doenças inflamatórias, infeciosas ou desmielinizantes do SNC.

O reconhecimento de fatores de mau prognóstico é fundamental na decisão terapêutica. O envolvimento parenquimatoso, especialmente se existir acometimento do tronco cerebral, e alterações do LCR podem justificar terapêuticas mais agressivas. A imunomodulação com terapêutica biológica é indicada nos casos de refratariedade ou pior prognóstico.

A necessidade de ensaios clínicos randomizados é muito evidente, no sentido de comparar os diferentes fármacos quanto à sua eficácia, segurança e efeitos adversos, para que se possa assegurar o melhor tratamento a estes doentes.

CONTRIBUTO DOS AUTORES

LS: Aquisição, recolha e tratamento dos dados, redação do trabalho e aprovação da versão final.

JC, ES: Conceção do trabalho, revisão critica, interpretação dos dados e aprovação da versão final.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFLITOS DE INTERESSE

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

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ACTA MÉDICA PORTUGUESA
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A Exposição ao Chumbo na Base de um Quadro de Arritmias Cardíacas

Lead Exposure as Cause of a Clinical Scenario of Cardiac Arrhythmias

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RESUMO

A reciclagem de baterias usadas tem suscitado preocupações de saúde pública uma vez que esta atividade está associada à exposição ocupacional e ambiental ao chumbo. Descreve-se o caso de uma mulher de 26 anos que iniciou quadro de palpitações associado a cefaleias, fadiga e insónias, cerca de quatro meses após iniciar funções numa empresa de reciclagem de baterias. Analiticamente, observou-se anemia (Hb 11,9 g/dL) e plumbémia de 59 µg/dL. Cessou funções na empresa e, após um mês, referiu uma diminuição progressiva da sintomatologia. O estudo analítico revelou uma normalização dos valores da hemoglobina (12,2 g/dL) e uma diminuição do valor de chumbo no sangue para 23,4 µg/dL. Os efeitos na saúde da exposição ao chumbo são inespecíficos e o seu diagnóstico requer um alto grau de suspeição. Neste âmbito revela-se importante a articulação entre o médico assistente e os serviços de Saúde, Higiene e Segurança no Trabalho das empresas.
Palavras-chave: Arritmias Cardíacas/induzidas quimicamente; Exposição Ocupacional; Intoxicação por Chumbo

ABSTRACT

The recycling of used batteries has raised public health concerns as this activity is associated with occupational and environmental exposure to lead. We describe the case of a 26-year-old woman who experienced palpitations associated with headaches, fatigue and insomnia. Blood tests showed anemia (Hb 11.9 g/dL) and a lead concentration of 59 µg/dL. This was reported about four months after starting work in a battery recycling company. She left the company and, reported a gradual decrease in symptoms about one month later. The analytical study revealed a normalization of hemoglobin levels (12.2 g/dL) and a decrease in blood lead levels to 23.4 µg/dL. The health effects of lead exposure are nonspecific, and its diagnosis requires a high degree of suspicion. In this context, the collaboration between the Attending Physician and the Health and Safety Departments of companies is important.
Keywords: Arrhythmias, Cardiac/chemically induced; Lead Poisoning; Occupational Exposure

INTRODUÇÃO

O chumbo é um elemento tóxico com capacidade de se acumular no organismo. Apesar de não ter um papel fisiológico conhecido, interfere com uma série de funções biológicas afetando virtualmente todos os sistemas do organismo.

Tem sido feito um esforço no sentido da eliminação do chumbo em diversos produtos (por exemplo, ao nível das canalizações, tintas e gasolina). No entanto, a exposição ao chumbo é ainda um problema atual, nomeadamente em contexto ocupacional como acontece com os trabalhadores de fundições, fábricas de reciclagem de baterias ou renovação de casas.[1]

As vias de exposição podem ser a inalatória, digestiva e, em menor extensão, a cutânea.[2]

Os sintomas de intoxicação aguda ao chumbo variam de indivíduo para indivíduo e podem ocorrer após dias ou semanas de elevada exposição.[3]

A semiologia de intoxicação é frequentemente não específica e pode incluir sintomas constitucionais (como fadiga, anorexia e cefaleias), gastrointestinais (dor abdominal e obstipação), musculoesqueléticos (artralgias, mialgias) e neuropsiquiátricos (distúrbios do sono, dificuldade na concentração e de memória, depressão e/ou ansiedade). A toxicidade causada pelo chumbo pode também levar ao aparecimento de anemia, geralmente ligeira, pelo efeito da inibição de algumas enzimas da síntese da hemoglobina.[3]

A exposição crónica ao chumbo, ainda que a níveis baixos (a partir de 5 a 10 µg/dL), pode não provocar sintomas imediatos, mas ter efeitos a longo prazo a nível renal (nefropatia por chumbo), cardiovascular (hipertensão), neuropsiquiátrico (declínio das funções cognitivas, neuropatia motora distal, sintomas psiquiátricos) ou reprodutivo (alterações a nível do esperma). Tem sido associada também ao aumento do risco de doenças relacionadas com a idade, como é o caso de cataratas, doença periodontal e gota.[3]

Alguns dos efeitos tóxicos do chumbo (como a dor abdominal e a anemia) são reversíveis se a fonte da exposição for atempadamente identificada e controlada. No entanto, altos níveis de chumbo ou níveis moderados por longos períodos podem resultar em danos irreversíveis ao sistema nervoso central e periférico, rins e outros órgãos.[3]

Dada a inespecificidade das manifestações clínicas da exposição ao chumbo, a sua consideração como diagnóstico diferencial requer uma anamnese cuidada, nomeadamente a nível ocupacional.

Em Portugal, o Decreto-Lei 24/2012 de 6 de fevereiro[4] clarifica algumas normas laborais associadas a este agente químico. Entre outros, fixa os valores limite da sua concentração no ar nos locais de trabalho, o valor limite da plumbémia e a periodicidade dos exames médicos a realizar em contexto de vigilância de saúde dos trabalhadores.

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CASO CLÍNICO

Relatamos o caso de uma mulher de 26 anos, que iniciou funções numa empresa de reciclagem de baterias, em outubro de 2018.

A trabalhadora refere o aparecimento de palpitações em fevereiro de 2019, sintoma pelo qual recorreu ao médico assistente. Não apresentava antecedentes patológicos relevantes, nem tomava medicação habitual. Realizou um Holter de 24 horas que evidenciou ritmo sinusal alternando com períodos de ritmo juncional, extrassistolia supraventricular ocasional (1/23h), extrassistoles ventriculares muito frequentes (9256/23h) e alterações inespecíficas do segmento ST-T. O ecocardiograma não revelou alterações de relevo. O estudo analítico revelou anemia (Hb 11,9 g/dL) sem outras alterações, nomeadamente a nível da função tiroideia ou do ionograma. O valor do chumbo quantificado no sangue foi de 59 µg/dL (> 5 µg/dL). Foi medicada com bisoprolol 5 mg/id. Nos três meses seguintes, apresentou agravamento progressivo do quadro sintomático, com surgimento de dispneia, toracalgia agravada em decúbito dorsal, tonturas, cefaleias, fadiga, insónia, diarreia, perda ponderal importante (14 kg em quatro meses), alterações na coordenação motora e vertigem.

Em maio de 2019 cessou funções na empresa, com subsequente diminuição progressiva da sintomatologia. Um mês após a saída da empresa refere recuperação da qualidade do sono, diminuição das palpitações e da fadiga. O estudo analítico de junho revelou uma normalização dos valores da hemoglobina (12,2 g/dL) e uma diminuição do valor da plumbémia para 23,4 µg/dL.

DISCUSSÃO

A sintomatologia presumivelmente atribuída à contaminação por chumbo teve origem cerca de quatro meses após início de funções na empresa, e reverteu dois meses após a suspensão da exposição.

O conhecimento da história profissional da paciente e, especificamente, da sua exposição ocupacional ao chumbo, possibilitou a suspeita de uma intoxicação por chumbo na base do quadro clínico, permitindo o rápido afastamento da trabalhadora do seu posto de trabalho e a reversão dos sintomas.

A reciclagem de baterias constitui uma das indústrias com maior risco potencial de exposição ao chumbo. A contaminação por chumbo nestas empresas não se limita ao espaço laboral onde o material contendo chumbo é processado, podendo atingir também o ar, o solo e a água das regiões circundantes, sendo que os resíduos permanecem no local, mesmo após o término da atividade.[5]

Intoxicações por chumbo têm sido descritas em trabalhadores de fábricas de reciclagem de baterias,[6-9] onde nem sempre se observa o cumprimento das normas de higiene e segurança apropriadas.

As principais manifestações clínicas descritas em trabalhadores de empresas de reciclagem de baterias após intoxicação aguda por chumbo são mal-estar, dores abdominais e anemia.[7-9] No presente caso, um dos achados mais significativos foi a presença de arritmias cardíacas, nomeadamente de extrassístoles ventriculares muito frequentes. A ocorrência de arritmias cardíacas não é habitualmente descrita na literatura em associação com a intoxicação por chumbo, e pode ser um dado importante em futuras investigações clínicas.

Este caso mostra que o chumbo continua a constituir um risco ocupacional significativo em determinadas atividades, e a monitorizar com regularidade em qualquer trabalhador que desenvolva uma atividade suscetível de exposição ao chumbo.

A participação de uma suspeita de intoxicação ocupacional por chumbo como doença profissional reveste-se de grande importância pois permite não só que o trabalhador tenha direito a eventual reparação,[10,11] mas também o desencadeamento ou reforço de medidas preventivas e corretivas no posto de trabalho, evitando ou minimizando a exposição de outros trabalhadores a fatores semelhantes de risco profissional.[12]

Finalmente, salienta-se a importância que a articulação entre o médico assistente e os serviços de Saúde, Higiene e Segurança no Trabalho das empresas pode ter no âmbito da investigação de quadros clínicos com possível etiologia em exposições ocupacionais, sobretudo em indivíduos sem exposição profissional claramente reconhecida a um agente específico.

APRESENTAÇÕES PRÉVIAS

Este trabalho foi apresentado sob a forma de poster no 15.º Fórum Nacional de Medicina do Trabalho "Benefícios da Saúde Ocupacional para a Saúde Pública", organizado pela Sociedade Portuguesa de Medicina do Trabalho, que decorreu em Lisboa entre 21 e 23 de novembro de 2019.

CONTRIBUTO DOS AUTORES

MC: Conceção do trabalho, entrevistas, recolha de informação, análise e interpretação dos dados, revisão.

DA, LS, MP: Análise e interpretação dos dados, revisão.

FM: Conceção do trabalho, análise e interpretação dos dados, revisão.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFIDENCIALIDADE DOS DADOS

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

CONSENTIMENTO DO DOENTE

Obtido.

CONFLITOS DE INTERESSE

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

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

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Arrhythmogenic Left Ventricular Cardiomyopathy: A Successful Case of Extracorporeal Cardiopulmonary Resuscitation

Miocardiopatia Arritmogénica do Ventrículo Esquerdo: Um Caso de Sucesso de Ressuscitação Cardiopulmonar Extracorporal

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ABSTRACT

A 24-year-old man suffered a witnessed cardiac arrest after a padel game. Basic life support was immediately provided. The pre-hospital emergency services team continued the resuscitation efforts, and the patient was accepted for extracorporeal cardiopulmonary resuscitation. The return of spontaneous circulation was achieved in 45 minutes. The initial assessment revealed a ST-segment elevation in leads V_4-V_6 and a dilated left ventricle with severe systolic dysfunction. Coronary angiography was normal. An improvement in left ventricular systolic function was observed and extracorporeal cardiac support was discontinued after 48 hours. Cardiovascular magnetic resonance imaging demonstrated hypokinesia and subepicardial fatty infiltration of the left ventricle lateral wall. Genetic testing detected a variant of uncertain significance in the *ANK2* gene. The diagnosis of arrhythmogenic left ventricular myocardiopathy did not fulfill all the current diagnostic criteria, but it is a very likely diagnosis. An implantable cardioverter-defibrillator was placed. The patient was discharged without physical or cognitive impairment.
Keywords: Arrhythmogenic Left Ventricular Cardiomyopathy; Cardiopulmonary Resuscitation; Extracorporeal Membrane Oxygenation; Heart Arrest/therapy

RESUMO

Homem de 24 anos sofreu uma paragem cardiorrespiratória presenciada após um jogo de padel. O suporte básico de vida foi imediatamente iniciado. A equipa de emergência pré-hospitalar manteve os esforços de ressuscitação e o doente foi aceite para ressuscitação cardiopulmonar extracorporal. O retorno da circulação espontânea foi atingido de imediato após 45 minutos. A avaliação inicial evidenciou elevação do segmento ST nas derivações V_4-V_6 e dilatação do ventrículo esquerdo com disfunção sistólica grave. Angiografia coronária sem alterações. Foi observada uma melhoria da função sistólica do ventrículo esquerdo e a oxigenação por membrana extracorporal veno-arterial foi suspensa após 48 horas. A ressonância magnética cardiovascular demonstrou hipocinésia da parede lateral e infiltração gordurosa subepicárdica na parede lateral do ventrículo esquerdo. O teste genético revelou uma variante de significado incerto no gene *ANK2*. Apesar do diagnóstico de miocardiopatia arritmogénica do ventrículo esquerdo não preencher todos os critérios diagnósticos atuais, é, no entanto, um diagnóstico muito provável. Foi colocado um cardioversor desfibrilador implantável. O doente teve alta sem compromisso físico ou cognitivo.
Palavras-chave: Miocardiopatia Arritmogénica do Ventrículo Esquerdo; Oxigenação por Membrana Extracorporal; Paragem Cardíaca/tratamento Ressuscitação Cardiopulmonar

INTRODUCTION

Sudden cardiac death is a devastating event that occurs unexpectedly. A significant number of cases are attributed to non-coronary causes with a genetic basis, such as cardiomyopathies, channelopathies and malignant arrhythmias.

The arrhythmogenic cardiomyopathy (ACM) is a heart muscle disease that affects the right ventricle (RV), the left ventricle (LV) or both, according to the 2020 International criteria for ACM. It is characterized structurally by a myocardial scar (fibro or fibrofatty myocardial replacement) and functionally by ventricular dysfunction. This myocardial scar is a predisposing factor for ventricular arrhythmias, which could present as sudden cardiac arrest, regardless of the severity of pump failure.[1,2]

The diagnosis of ACM is made by meeting the Padua criteria. A definitive diagnosis of arrhythmogenic left ventricle cardiomyopathy (ALVC) must meet one major structural LV criterion along with the presence of a gene mutation for ACM.[1,3]

A complete understanding of the genetic basis of certain cardiac conditions is an area of medical knowledge that has significant potential for development. Advances in genomic technology and research have allowed for the identification of specific genes and mutations that play a role in the development of these conditions.

The authors consider that this case report serves as an important warning about the association between mutations in the *ANK2* gene with structural changes in the myocardium, which can increase the likelihood of malignant arrhythmias and sudden death.

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CASE REPORT

We describe a case of a 24-year-old man, without relevant personal or family history. The individual suffered a witnessed cardiac arrest after a padel game. Basic life support (BLS) was immediately provided by laypeople. Eight minutes later the pre-hospital emergency services team arrived and continued the resuscitation efforts in accordance with advanced life support (ALS) best practice. The initial arrest rhythm was ventricular fibrillation (VF). The field team established early liaison with the Intensive Care Unit (ICU), and the patient was accepted for extracorporeal cardiopulmonary resuscitation (eCPR). During transport, quality mechanical chest compressions were assured. The patient arrived at the ICU 40 minutes after the onset of cardiac arrest in refractory VF. The right common femoral artery and vein were cannulated percutaneously with ultrasound guidance, and veno-arterial extracorporeal membrane oxygenation (VA-ECMO) was started within five minutes. The return of spontaneous circulation was achieved 45 minutes after the onset of cardiac arrest in sinus rhythm (with eight minutes of BLS, 32 minutes of ALS, and five minutes for canulation to establish VA-ECMO). For distal limb perfusion, the ipsilateral superficial femoral artery was cannulated.

The initial 12-lead electrocardiogram presented with a ST-segment elevation in leads V_4-V_6 (Fig. 1). Transthoracic echocardiography (TTE) revealed a dilated LV with severe systolic dysfunction due to global diffuse hypokinesia. The cardiac output was severely depressed [left ventricular outflow tract velocity time integral (LVOT VTI) of 4.8 cm], a non-dilated RV with a mild systolic dysfunction on visual assessment. Coronary angiography revealed normal coronary vessels.

For neuroprotection, the patient underwent deep sedation monitored by continuous electroencephalogram and therapeutic temperature management (33ºC) with an external cooling device in the first 24 hours.

Initially, the patient was kept on VA-ECMO support (blood flow of 2.5 – 3.0 L/minute and sweep gas flow of 1 L/minute). Limb perfusion was monitored with bilateral near-infrared spectroscopy.

After 24 hours of neuroprotection bundle, the patient was slowly reheated to normothermia. With sedative reduction, the patient had spontaneous eye opening and was able to follow the observer and obey commands.

As cardiac function improved, VA-ECMO support was slowly reduced with no cardiovascular dysfunction or perfusion imbalance. TTE revealed an improvement of LVOT VTI to 17.6 cm and RV function (tricuspid annular plane systolic excursion of 18 mm and S´ RV of 11 mm). A mild acute renal injury was observed in the acute phase and was rapidly resolved.

After 48 hours of VA-ECMO, the patient was successfully weaned and decannulated. Respiratory function was normal, and he was successfully extubated. No other organ support was required. Repeated clinical neurological examination revealed a progressive improvement in brain function to a cerebral performance category (CPC) score of 1 (CPC 1 – good cerebral performance).

Four days after the cardiac arrest, the patient was transferred to the Cardiology ward for further studies to clarify the cause of cardiac arrest.

Cardiovascular magnetic resonance imaging (CMR)

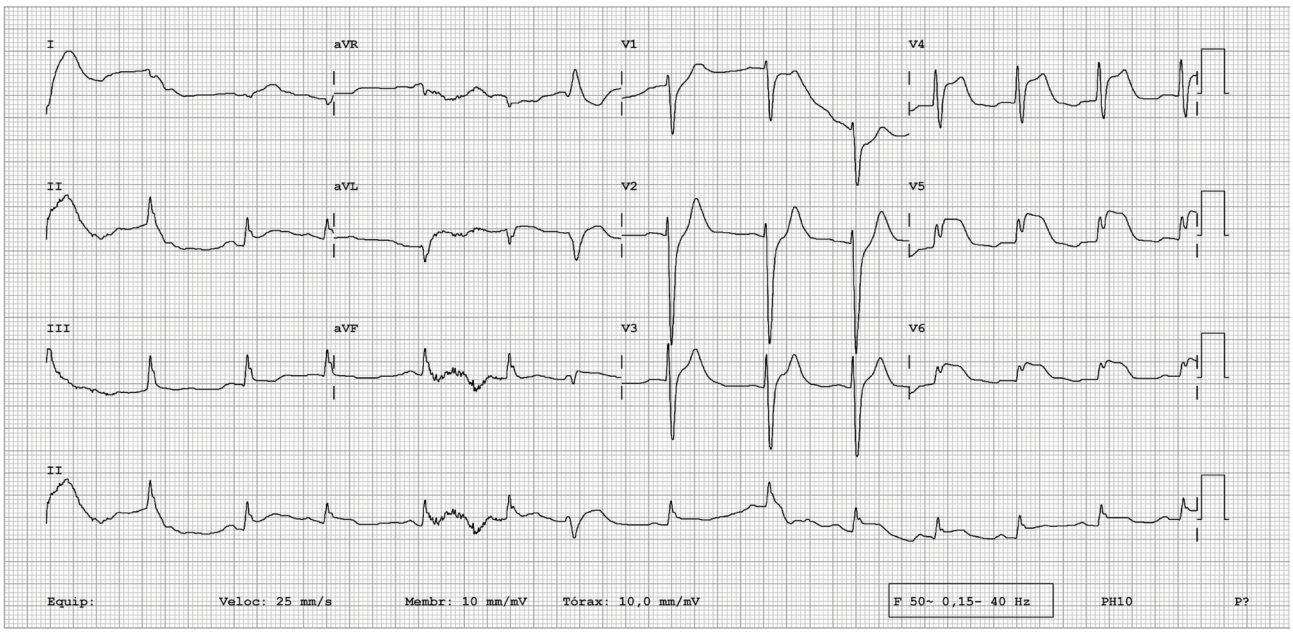

Figure 1 – Initial 12-lead electrocardiogram presented with a ST-segment elevation from V_4 to V_6

demonstrated non-dilated moderately impaired LV [LV ejection fraction (EF) of 48%], hypokinesia of the lateral wall and subepicardial fatty infiltration of the LV lateral wall. T2 mapping was increased in the lateral walls suggesting myocardial oedema. Extensive subepicardial late gadolinium enhancement (LGE) was noted in the anterior, lateral and inferior walls. Preserved systolic function of RV (RV EF 51%) with no regional wall motion abnormalities and no LGE in the RV wall was also noted (Fig. 2).

Based on the clinical history and the imaging findings, ALVC was the most likely diagnosis. Genetic tests were performed. An implantable cardioverter-defibrillator (ICD) was placed for secondary prevention of sudden cardiac death.

The patient was discharged from the hospital on the 18th day after cardiac arrest. The patient demonstrated no physical or cognitive impairment and was found to be completely independent (with Medical Research Council sum-score of 60 – normal strength) and CPC 1.[4] The 12-lead electrocardiogram at the time of discharge showed no abnormalities (Fig. 3). The patient received follow-up in the cardiomyopathy clinic and in the following seven months there were no arrhythmic events.

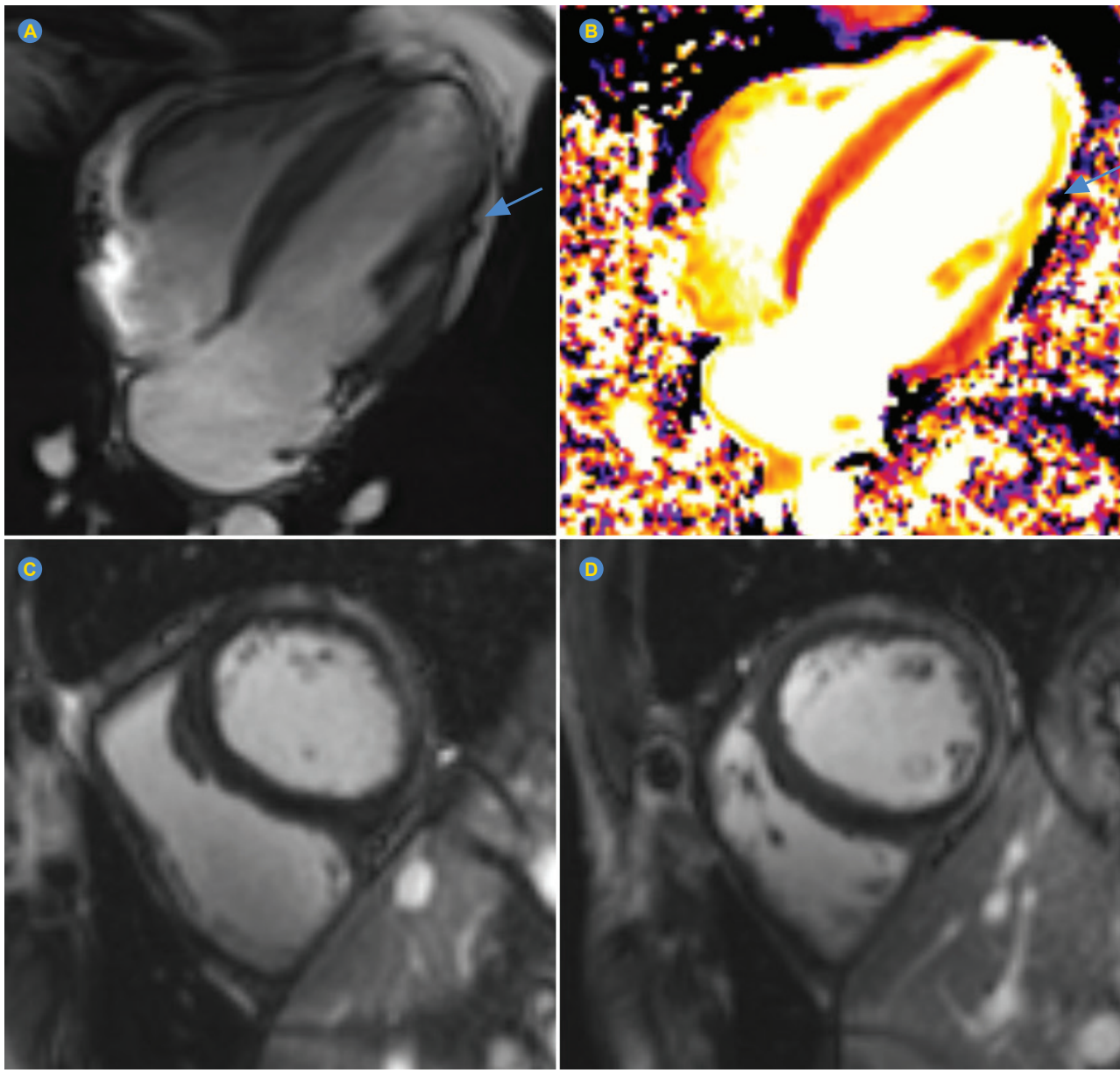

Figure 2 – Cardiovascular magnetic resonance imaging showing subepicardial fatty infiltration of the left ventricular lateral wall (arrows) in cine images (A) and native T1 mapping (B); extensive subepicardial late gadolinium enhancement in the anterior, lateral and inferior walls (C and D)

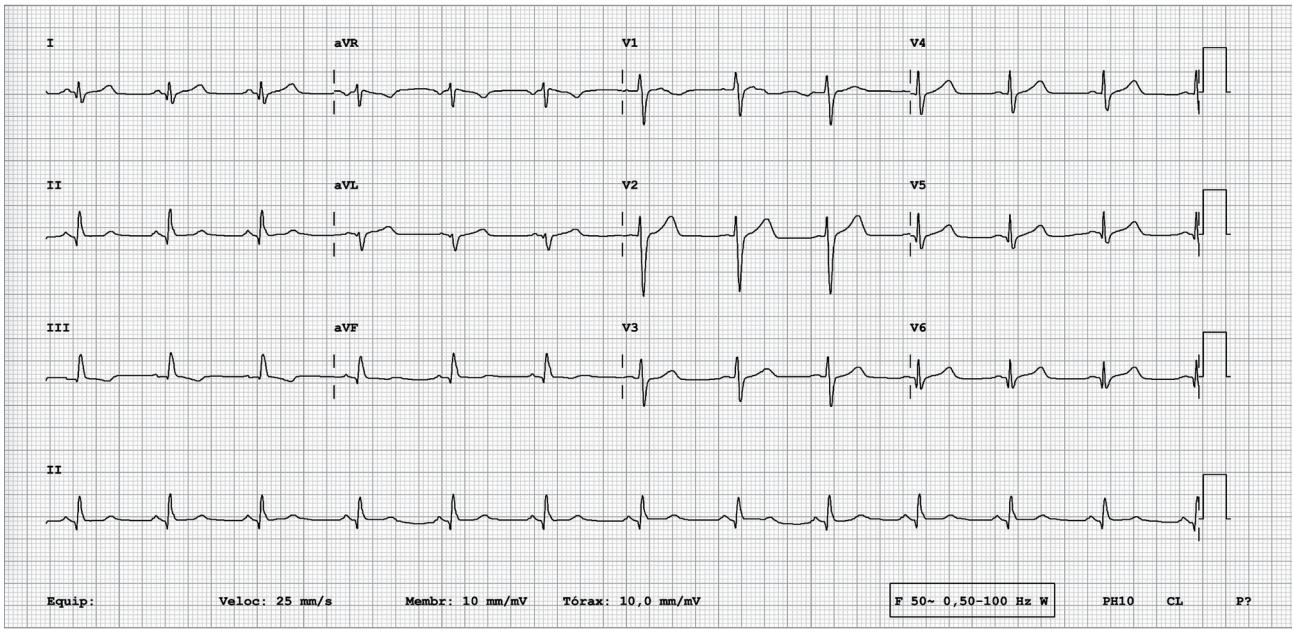

Figure 3 – The 12-lead electrocardiogram at discharge without alterations

Genetic testing detected a variant c.11081A>G, p.(Lys3694Arg), in the *ANK2* gene which is classified as a variant of uncertain significance. The diagnosis of ALVC does not fulfill all the current diagnostic criteria.

DISCUSSION

This case represents a successful case of eCPR in refractory cardiac arrest. The following factors predicted a high probability of survival with favorable neurological outcome: younger age, no comorbidities, witnessed arrest, no-flow interval of less than five minutes, initial cardiac rhythm of VF, transportation with high quality chest compressions, refractory VF and low-flow interval of less than 60 minutes. For the same reason, those are typically considered the inclusion criteria for admission to eCPR.[5]

This case is compatible with the diagnosis of ALVC due to the clinical picture of recovered cardiac arrest after a refractory VF, imaging findings with mild LV systolic dysfunction and myocardial scar on CMR, and exclusion of ischemic, valvular, or infectious disease. Genetic testing did not fully confirm the hypothesis since it is a poorly described mutation without definitive clinical relevance.

The *ANK2* gene mutation was initially identified as a causative mutation for long QT syndrome and later for Brugada syndrome.[6,7] Interestingly, the *ANK2* gene mutations have also been found in individuals with structural myocardial changes, even without a prolonged QT interval, which increases their susceptibility to malignant arrhythmias and sudden death.[8,9] Therefore, additional genotyping and phenotyping studies are necessary and encouraged.

According to the International criteria for ACM, it is mandatory to have ACM-related genetic mutations associated with LV structural abnormalities to confirm the diagnosis.[1] In fact, morpho-functional and structural LV abnormalities of ACM do not provide sufficient disease specificity because of the overlap with the phenotypic features of other heart muscle diseases, and hence the stricter criteria.[3]

This patient fulfilled one major criteria (LV LGE) and two minor criteria (global LV systolic dysfunction and regional LV hypokinesia of LV free wall). Therefore, the diagnosis of ALVC was not confirmed, although it is very likely.[2]

As the diagnostic criteria for arrhythmogenic cardiomyopathies have changed with the development of knowledge about the diseases, the diagnostic criteria that define ALVC may change, or other genetic mutations related to ACM may be found in the future.

These types of conditions do not have a specific treatment and ICD implantation is the only strategy that may prevent sudden cardiac death.

The authors consider this case report helpful to other clinicians or researchers in various aspects. First, we demonstrated a successful case of an eCPR in the presence of adequate patient selection, teamwork and appropriate interventions in the different stages of patient care. Second, it adds to the literature by highlighting a possible additional genetic pathway to be explored and researched in future cases of cardiac arrest, arrythmia, heart muscle diseases and ALVC.

AUTHOR CONTRIBUTIONS

MG: Conceptualization, writing, review and editing of the final version of the manuscript.

IC, MPA, SAR, PGC, PF: Writing, review and editing 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.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

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ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Úlceras Cutâneas Disseminadas Associadas ao Metotrexato

Disseminated Skin Ulcers Associated with Methotrexate

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Acta Med Port 2023 Sep;36(9):603-604 ▪ https://doi.org/10.20344/amp.18462

Palavras-chave: Metotrexato/efeitos adversos; Úlcera Cutânea/induzida quimicamente
Keywords: Methotrexate/adverse effects; Skin Ulcer/chemically induced

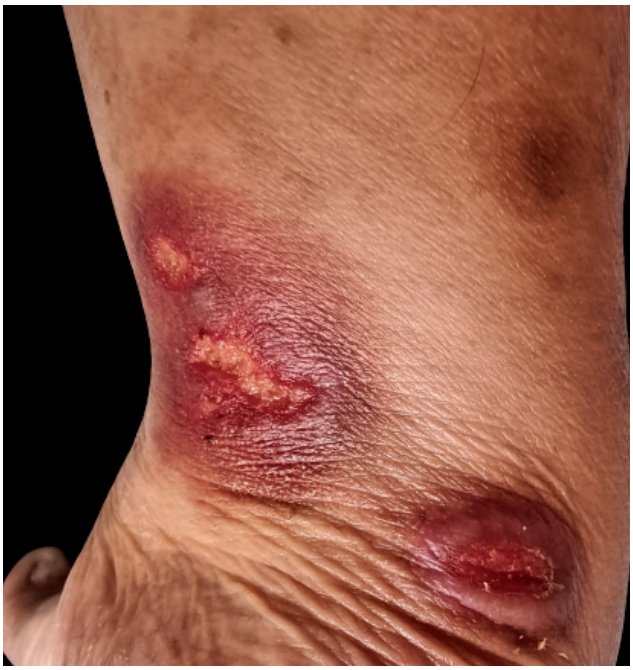

Figura 1 – Úlceras cutâneas bem delimitadas, com bordo eritematoso e cerca de 1 a 3 cm, localizadas no tornozelo

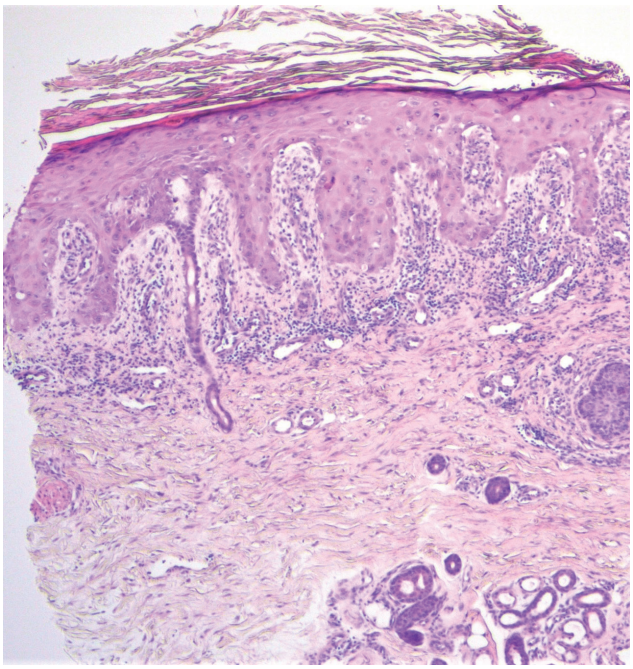

Figura 2 – No exame histopatológico observa-se acantose e hiperplasia da epiderme com focos de ulceração, com alterações dismaturativas dos queratinócitos e necrose isolada destes, coberta por hiperqueratose ortoqueratósica com focos de paraqueratose e um infiltrado linfocitário em banda na derme superficial (Hematoxilina-eosina, x40)

Doente do sexo feminino de 62 anos com doença renal crónica, foi referenciada por úlceras cutâneas dolorosas no lábio inferior, coxa, região interglútea e tornozelo com dois meses de evolução (Fig. 1). A doente realizava frequentemente anti-inflamatórios não esteroides (AINEs) e tinha iniciado terapêutica com metotrexato injetável 25 mg por semana há oito meses por suspeita, não confirmada, de artrite reumatóide. Laboratorialmente, apresentava anemia normocítica normocrómica e níveis de ácido fólico reduzidos. A biópsia cutânea foi compatível com ulcerações cutâneas induzidas pelo metotrexato (Fig. 2). Suspendeu-se o metotrexato e iniciou-se ácido fólico 5 mg uma vez por dia, verificando-se resolução completa das úlceras após três semanas.

As úlceras cutâneas são um efeito adverso incomum do metotrexato, sendo particularmente raras nos doentes sem psoríase. A doente apresentava vários fatores de risco que potenciaram esta toxicidade, nomeadamente idade superior a 55 anos, doença renal crónica, administração de elevada dose de metotrexato, reduzidos níveis de ácido fólico e utilização de AINEs.[1-3]

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CC: Recolha dos dados clínicos; revisão bibliográfica; elaboração do manuscrito.

LSA, PF: Revisão 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 e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial atualizada em 2013.

CONFIDENCIALIDADE DOS DADOS

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

CONSENTIMENTO INFORMADO

Obtido.

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FONTES DE FINANCIAMENTO

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Pigmentação Cutânea Secundária a Minociclina

Minocycline-Induced Hyperpigmentation

Palavras-chave: Hiperpigmentação/induzida quimicamente; Minociclina/efeitos adversos
Keywords: Hyperpigmentation/chemically induced; Minocycline/adverse effects

Um homem de 36 anos foi observado em consulta por extensas manchas cinzento-azuladas em ambas as pernas, assintomáticas e com agravamento progressivo ao longo de dois anos (Fig. 1A). Não existia pigmentação no restante tegumento incluindo face ou mucosas. Apresentava antecedentes de síndrome nefrótico desde a infância, secundário a doença de lesões mínimas, estando medicado cronicamente com ciclosporina e prednisolona. Apresentava acne facial e da região pré-esternal secundário à corticoterapia crónica, tendo sido observado 15 anos antes, em consulta de Dermatologia, onde iniciou minociclina 100 mg/dia planeada para dois meses. O doente perdeu seguimento em consulta, tendo mantido a antibioterapia durante vários anos por recorrência das lesões quando suspendia a medicação. Foi efetuada biópsia cutânea e o exame histopatológico revelou deposição de pigmento hemossiderínico, confirmado na coloração de Perls, na derme superficial, profunda e hipoderme (Figs. 1B e 1C). Os achados clínicos, histológicos e evolução temporal foram compatíveis com pigmentação secundária à minociclina do tipo II. Foi suspensa a terapêutica com minociclina, não se verificando, contudo, redução da pigmentação após 12 meses.

Pigmentação cutânea adquirida é um efeito secundário comum de fármacos incluindo agentes quimioterápicos, antibióticos, hidroxicloroquina, amiodarona e clofazimina.[1] A minociclina é um antibiótico oral do grupo das tetraciclinas usado frequentemente em Dermatologia pelas propriedades anti-inflamatórias, nomeadamente no tratamento de acne e rosácea. A pigmentação cutânea induzida pela minociclina é um efeito secundário conhecido que ocorre em quatro padrões distintos: tipo I, caracterizado por máculas azuladas em áreas de cicatriz ou inflamação, geralmente cicatrizes de acne facial; tipo II, com pigmentação cinzenta azulada em pele saudável, mais frequentemente nas pernas; tipo III, coloração acastanhada em zonas fotoexpostas; e tipo IV, semelhante a tipo III mas não limitada a zonas fotoexpostas, ocorrendo em áreas de cicatriz.[1] A hiperpigmentação pode envolver também a mucosa oral, esclera, unhas e dentes. É um efeito dose-dependente com incidência entre 3% - 20% dos doentes que atingem uma dose cumulativa de 100 g.[2] Apesar de inofensiva, tem implicações estéticas. O diagnóstico precoce permite a suspensão atempada do fármaco. Esta condição pode persistir meses a anos após a cessação da terapêutica.[2] O tratamento com laser poderá reduzir a hiperpigmentação.[3]

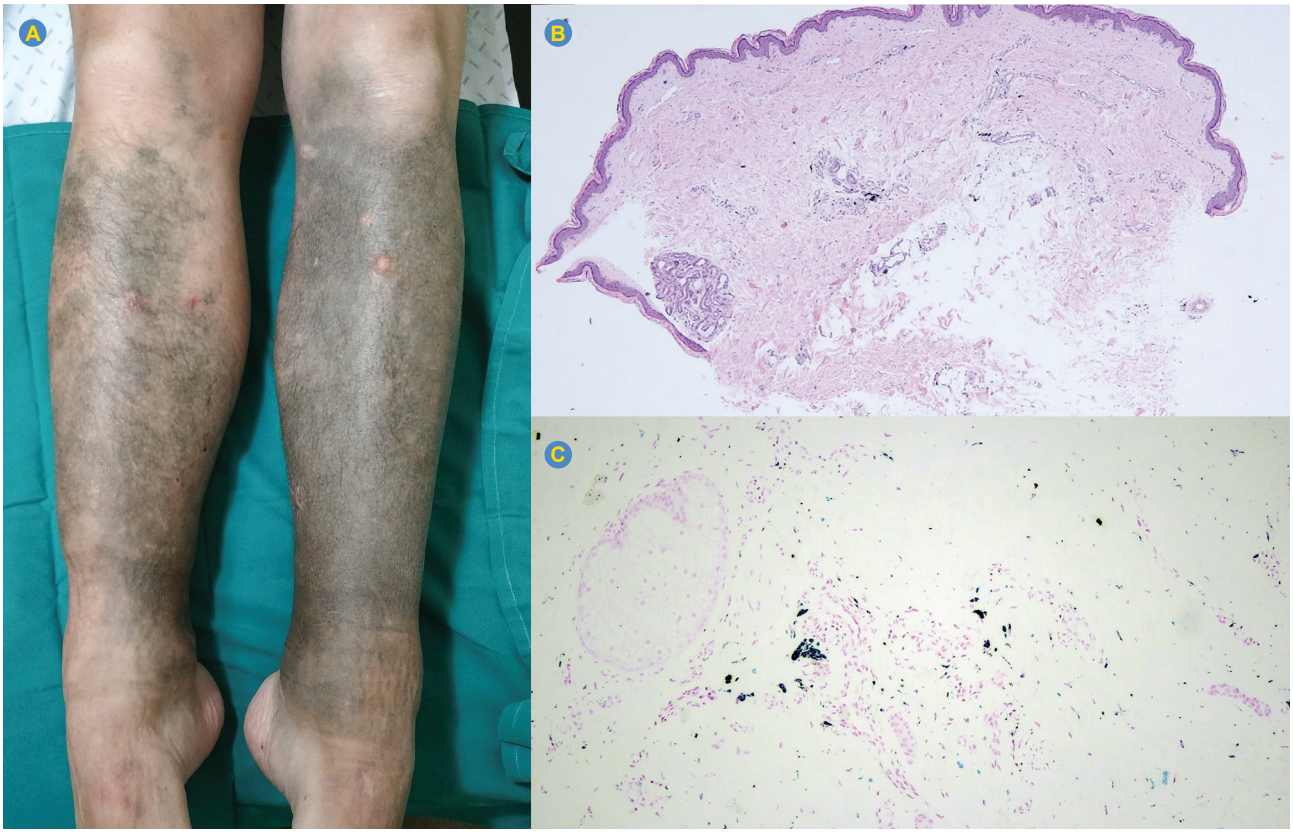

Figura 1 – Pigmentação cinzento-azulada na face anterior das pernas (A). Imagem histopatológica com deposição de pigmento na derme e hipoderme (H&E) (B). Pigmento hemossiderínico confirmado pela reatividade na técnica de Perls (C).

CONTRIBUTO DOS AUTORES

CF: Recolha dos dados clínicos, revisão bibliográfica e elaboração do manuscrito.

MMX: Revisão do manuscrito

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CONFIDENCIALIDADE DOS DADOS

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Mecillinam: A Possible Alternative Option for Non-Complicated Urinary Tract Infections Treatment Caused by Enterobacterales

Mecillinam: Uma Possível Alternativa Terapêutica para o Tratamento de Infeções Não Complicadas do Trato Urinário Causadas por Enterobacterales

Keywords: Amdinocillin/therapeutic use; Enterobacteriaceae Infections/drug therapy; Urinary Tract Infections/drug therapy
Palavras-chave: Amdinocilina/uso terapêutico; Infecções por Enterobacteriaceae/tratamento farmacológico; Infeções do Trato Urinário/tratamento farmacológico

Urinary tract infections (UTIs) are the second most common type of infections requiring antibiotics, with *Enterobacterales* being the most common agents of infection.[1] Due to the extensive use of broad-spectrum antibiotics, the prevalence of multidrug-resistant *Enterobacterales* has increased in the community, which makes therapeutic choices a great challenge.

Pivmecillinam (orally active prodrug of mecillinam) is one of the first-line drugs recommended for the treatment of uncomplicated UTIs in the European clinical practice guidelines due to its selective activity against gram-negative bacteria, its pharmacokinetic properties with high drug concentration in urine, and its low community resistance rate.[2-4]

A prospective study was performed from March to September 2021 in a Portuguese community hospital, to determine the sensitivity profiles of *Enterobacterales* isolated from urine samples of UTI patients to the following antibiotics: mecillinam, fosfomycin, nitrofurantoin, amoxicillin-clavulanate, cefuroxime, and trimethoprim-sulfamethoxazole. *Enterobacterales* isolates were recovered from urine samples of patients with clinical UTI diagnoses made by their family physician and identified using automated identification systems (VITEK®MS, bioMérieux). Susceptibility testing was performed on Vitek®2 (bioMérieux) with the AST-N355 card. Mecillinam susceptibility (10 mg) was confirmed by disc diffusion methodology. Results were interpreted according to the EUCAST breakpoints (version 13.0). For extended-spectrum beta-lactamase (ESBL) confirmation, a combination disk test was performed (Mast Group®, U.K.).

A total of 1943 organisms were isolated from the urine samples of 1865 patients. Most isolates were from female patients (n = 1494; 76.9%, median age 71 years old). *Escherichia coli* was the most frequent agent (70.2%, n = 1364), followed by *Klebsiella* (19.0%, n = 370), *Proteus* (7.2%, n = 139), *Enterobacter* (1.4%, n = 26) and *Citrobacter* (2.2%, n = 44) species.

Of all *E. coli* isolates, approximately 99%, 98%, and 90% were sensitive to nitrofurantoin, fosfomycin, and mecillinam, respectively (Table 1). When compared with the

Table 1 – Susceptibility pattern of *E. coli*, *Klebsiella* spp. and *Proteus* spp. to six different oral antibiotics and susceptibility comparison between mecillinam and the other oral antibiotics

Organisms	Missing pairs	Mecillinam sensitivity p_1 (ns)	Sensitivity of other antibiotics p_2 (ns)		*p*-value	95% CI for $p_1 - p_2$
E. coli (*n = 1364*)	36	**0.90** (1198)	NFE	**0.99** (1308)	< 0.001	(-0.10, -0.07)
	36	**0.90** (1198)	FOS	**0.98** (1301)	< 0.001	(-0.10, -0.06)
	63	**0.90** (1173)	AMC	0.71 (924)	< 0.001	(0.16, 0.22)
	36	**0.90** (1198)	CXM	0.88 (1167)	0.043	(< 0.001, 0.05)
	38	**0.90** (1197)	SXT	0.80 (1057)	< 0.001	(0.08, 0.13)
E. coli ESBL (*n = 64*)	7	**0.89** (51)	NFE	**0.96** (55)	0.157	(-0.18, 0.03)
	7	**0.89** (51)	FOS	**0.98** (56)	0.059	(-0.20, 0.001)
	9	**0.89** (49)	AMC	0.22 (18)	< 0.001	(0.51, 0.79)
	7	**0.89** (51)	CXM	0 (0)	< 0.001	(0.82, 0.97)
	7	**0.89** (51)	SXT	0.40 (23)	< 0.001	(0.33, 0.63)
Klebsiella spp. (*n = 370*)		————	NFE	————	——	————
		————	FOS	————	——	————
	68	**0.85** (256)	AMC	**0.67** (201)	< 0.001	(0.12, 0.25)
	56	**0.85** (267)	CXM	**0.81** (253)	0.045	(-0.01, 0.10)
	56	**0.85** (267)	SXT	**0.84** (265)	0.768	(-0.05, 0.06)
Proteus spp. (*n = 139*)		————	NFE	————	——	————
		————	FOS	————	——	————
	20	**0.75** (89)	AMC	**0.92** (109)	< 0.001	(-0.26, -0.08)
	12	**0.73** (93)	CXM	**0.94** (120)	< 0.001	(-0.30, -0.13)
	12	**0.73** (93)	SXT	0.67 (86)	0.223	(-0.06, 0.17)

McNemar's test was used for the difference between two paired proportions. Statistical significance level was set at 5%.
MEC: pivmecillinam; NFE: nitrofurantoin; FOS: fosfomycin; AMC: amoxixillin-clavulanate; CXM: cefuroxime; SXT: trimethoprim-sulfamethoxazole.
ns is the number of susceptibles and missings are the number of missing values in the pairwise comparison.

other oral treatment options, mecillinam has an overall higher rate of sensitivity in both *E. coli* and *Klebsiella* spp., but not in *Proteus* spp. Regarding multidrug-resistant *Enterobacterales* (n = 114), ESBL-positive *E. coli* was the most frequent organism (n = 64), reaching similar mecillinam sensitivity as non-ESBL *E. coli* (89% *versus* 90%). In ESBL-positive *E. coli*, mecillinam sensitivity was shown to be significantly higher ($p < 0.001$) compared to amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, and cefuroxime, and non-significantly lower compared to fosfomycin and nitrofurantoin ($p = 0.059$ and $p = 0.157$, respectively) (Table 1). Unfortunately, our sample was not large enough to establish the susceptibility of multidrug-resistant *Enterobacterales* to mecillinam other than ESBL-*E. coli*.

The results showed an *in vitro* mecillinam resistance rate under 20% for the most prevalent ITU species, suggesting that mecillinam could be considered an appropriate empirical antibiotic for uncomplicated UTIs in Portugal. Although nitrofurantoin and fosfomycin are equally recommended for UTI treatment, none of them is an option to treat uncomplicated UTIs other than those caused by *E. coli*.[5] In this context, mecillinam appears to be a good alternative first-line beta-lactam option since its overall *in vitro* activity is higher than that of amoxicillin-clavulanate (even in ESBL isolates). However, more studies are needed to prove its efficacy *in vivo*.

AUTHOR CONTRIBUTIONS

MF: Practical work, data analysis, writing of the manuscript.

VA: Supervision of the practical work, 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 declared that there are no competing interests and that they have no connection with any company or laboratory that produces or markets the antibiotic that is the subject of this study.

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First Report of *Salmonella* Serovar Typhimurium and Monophasic Typhimurium Clinical Isolates Harboring *mcr*-9 in Portugal

Primeiros Casos Reportados de Isolados Clínicos de *Salmonella* Serovar Typhimurium e Typhimurium Monofásica com *mcr*-9 em Portugal

Keywords: Colistin/pharmacology; Drug Resistance, Bacterial; Microbial Sensitivity Tests; Salmonella typhimurium/genetics
Palavras-chave: Colistina/farmacologia; Farmacorresistência Bacteriana; Salmonella typhimurium/genética; Testes de Sensibilidade Microbiana

Dear Editor,

During the 1990s, the emergence of multidrug resistance (MDR) microorganisms led to the rediscovery of colistin as a last-resort therapeutic solution for MDR Gram-negative infections.[1] Naturally, the rate of colistin resistance began to increase, and the first reports of resistance described chromosomally mediated mechanisms. Since 2016, when plasmid-mediated colistin resistance was firstly described, ten alleles (*mcr*-1 to *mcr*-10) and several variants have been identified.[1]

Even though reports of plasmid-mediated colistin resistance in *Salmonella* are not frequent, *mcr* genes have been identified in several isolates from different sources in recent years.[2–4] We report the first two clinical isolates of *Salmonella* spp. harboring *mcr*-9, identified in Portugal.

Both isolates, recovered from feces of a 4-month-old baby and a 2-year-old child with gastrointestinal disease, were sent to the National Reference Laboratory for Gastrointestinal Infections of the National Institute of Health Doutor Ricardo Jorge (INSA) for serotyping, and were sequenced in 2021. Resistance to antibiotics was determined by disk diffusion and broth microdilution for colistin, according to EUCAST guidelines. DNA was extracted and short reads were obtained by paired-end sequencing on a NextSeq 550 instrument (Illumina, USA). Read quality analysis, improvement, and trimming were performed using FastQC v0.11.5 and Trimmomatic v0.36. Raw reads were submitted on the web server of the Center for Genomic Epidemiology (https://cge.cbs.dtu.dk/), for identification of antimicrobial resistance genes, *in silico* sequence type (ST) and presence of plasmids. BLAST search (https://blast.ncbi.nlm.nih.gov/Blast.cgi) was used to confirm the presence of *mcr*-9 gene in the IncHI2/ST1 plasmid. Sequencing reads were deposited on the European Nucleotide Archive (ENA) under the bioproject PRJEB32515 (Table 1).

The two isolates revealed a MDR phenotype (Table 1), both presenting resistance to beta-lactams, sulfonamides, and tetracycline. Additionally, isolate Se_248167 presented resistance to fluoroquinolones and aminoglycosides. Although whole genome sequencing (WGS) revealed the presence of a *mcr*-9 gene in the IncHI2/ST1 plasmid, both isolates were susceptible to colistin (2 µg/mL). The wide spread of $bla_{CTX\text{-}M\text{-}9}$/*mcr*-9 in the IncHI2/ST1 plasmid has been previously described in *Escherichia coli* and *Enterobacter cloacae* isolated from wild animals.[5] Here we confirm the presence of IncHI2/ST1 harboring *mcr*-9 and $bla_{CTX\text{-}M\text{-}9}$ genes, in *Salmonella* clinical isolates. The presence of *mcr*-9 has been previously described in *Salmonella,* and seems to confer resistance in some isolates.[2,3] Indeed, the presence of this gene in a highly successful mobile element such as the IncHI2/ST1 plasmid is worrying, since the spread of this resistance marker can occur intra- and inter-species of Enterobacterales.[5] Additionally, as previously described, exposure to sub-inhibitory concentrations of antimicrobials can induce the expression of silent genes, leading to resistant phenotypes.[4] To our knowledge, this is the first report in Portugal of *Salmonella* isolates carrying *mcr*-9 gene recovered from human samples.

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Table 1 – Isolate characterization

Isolate	Year of isolation	Patient age	Serovar	Resistance phenotype	Antibiotic resistance genes	ST	Plasmid incompatibility type	Ena acession #
Se_10169	2019	4 months	Monophasic Typhimurium	AMP, TET, FOX, FEP, SMX	*aac(6')-Iaa*, *ant(2")-Ia*, *aph(6)-Id*, *aph(3")-Ib*, *blaCTX-M-9*, *blaTEM-1B*, *mcr-9*, *sul1*, *sul2*, *tet(B)*	34	IncHI2/ST1, IncHI2A IncQ1	ERS13570778
Se_248167	2021	2 years	Typhimurium	AMP, TET, CAZ, FOX, FEP, CRO, GMN, PEF, SMX	*aac(6')-Iaa*, *ant(2")-Ia*, *blaCTX-M-9*, *mcr-9*, *qnrA1*, *sul1*, *tet(A)*	19	IncHI2/ST1, IncHI2A, IncFIB(S), IncFII(S)	ERR10372088

ST: sequence type; AMP: ampicillin; TET: tetracycline; CAZ: ceftazidime; FOX: cefotaxime; FEP: cefepime; CRO: ceftriaxone; GMN: gentamycin; PEF: pefloxacin; SMX: sulfamethoxazole

Laboratory, under the scope of the national surveillance program.

AUTHOR CONTRIBUTIONS

LS: Study design, data analysis, research, and writing of the manuscript.

AP: Study design, data analysis, research, 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 have declared that no competing interests exist.

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Carta ao Editor: Recomendações na Abordagem do Doente com Hidradenite Supurativa

Letter to the Editor: Guidelines for Management of Patients with Hidradenitis Suppurativa

Palavras-chave: Cuidados de Saúde Primários; Hidradenite Supurativa; Qualidade de Vida
Keywords: Hidradenitis Suppurativa; Primary Health Care; Quality of Life

Caro Editor,

O artigo 'Recomendações na Abordagem do Doente com Hidradenite Supurativa'[1] suscitou-nos particular interesse, uma vez que já nos foi possível abordar e diagnosticar um caso clínico desta patologia nos Cuidados de Saúde Primários (CSP).

A hidradenite supurativa (HS) apresenta uma baixa prevalência, entre 1% e 4%, devido não só ao seu subdiagnóstico, mas também ao atraso na procura por ajuda médica. Na verdade, o tempo médio desde o início dos sintomas até ao diagnóstico correto é de, aproximadamente, 10 anos.[2] Num estudo multicêntrico internacional realizado em 2020, concluiu-se que os médicos dos CSP diagnosticaram HS apenas a 20,4% de todos os doentes com esta patologia.[3]

A HS está associada a um aumento do risco de mortalidade por todas as causas em 14%, sendo que algumas das suas comorbilidades incluem patologias endócrinas, cardiovasculares, gastrointestinais, musculosqueléticas e, por fim, mas não menos importantes, doenças psiquiátricas. Estas são das comorbilidades mais frequentes, sendo que a probabilidade de os doentes com HS sofrerem depressão ou mesmo suicídio é de 1,3 a 4,8 vezes superior comparativamente a quem não tenha HS.[2]

No caso clínico referido anteriormente (indivíduo do sexo masculino na quinta década de vida, fumador e com excesso de peso) o primeiro contacto devido a lesões cutâneas foi realizado cerca de dois anos antes do diagnóstico. Inicialmente a resposta a antibioterapia foi positiva, sendo que após este período decorreu um agravamento importante com incontáveis lesões inguinais e perianais, sem resposta a múltiplas drenagens e abordagens terapêuticas. Neste momento, o doente encontra-se a ser acompanhado pelas especialidades de Medicina Geral e Familiar, Dermatologia e Cirurgia, aguardando início de tratamento biológico. Desde o agravamento do quadro este doente encontra-se incapacitado para a sua atividade laboral, tendo também elevados prejuízos ao nível pessoal e social.

Dado o impacto multissistémico e a progressiva degradação da qualidade de vida destes doentes, torna-se urgente a sensibilização e educação dos médicos de família, que habitualmente são a primeira linha na sua abordagem.[3] É necessário que estes profissionais sejam treinados a reconhecer precocemente os sintomas, evitando assim o atraso no diagnóstico e o avanço da gravidade sintomática. Para além disso, é também fundamental gerirem as suas comorbilidades, tendo um papel ativo tanto na comunicação com outras especialidades (por exemplo dermatologia, reumatologia, cirurgia geral ou plástica) como também no controlo do seu risco cardiovascular, da patologia psiquiátrica e no reforço da cessação tabágica destes doentes.[1]

CONTRIBUTO DOS AUTORES

SFS, RRR: Conceção e organização do trabalho, aquisição, análise e interpretação, redação do manuscrito.

MC: Revisão crítica do trabalho, aprovação da versão final a publicar.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFIDENCIALIDADE DOS DADOS

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

CONSENTIMENTO DO DOENTE

Obtido.

CONFLITOS DE INTERESSE

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

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

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Can the 'Five Challenges' Overcome the Problem of 'Reform Without Change' in Medical Education? Reexamining the 'Hidden Curriculum'

Os 'Cinco Desafios' Podem Superar o Problema da 'Reforma Sem Mudança' na Educação Médica? Reexaminando o 'Currículo Oculto'

Keywords: Curriculum; Education, Medical
Palavras-chave: Currículo; Educação Médica

Dear Editor,

We found the article published in 2020 by Guimarães *et al* in Acta Médica Portuguesa[1] very interesting, because we believe that their 'five challenges for the near future' are equally applicable to medical education in Japan today. However, we propose discussing whether these 'challenges' can settle the unsolved problem of 'reform without change' promoted by the negative impact of some aspects of the 'hidden curriculum', an issue which has not changed in the last 10 years in medical education.[2]

The term 'hidden curriculum' was first used in the 1960s by Philip W. Jackson,[3] and was later defined as "a set of influences that function at the level of organizational structure and culture".[4] It refers to the unintentional transmission of standards, values, perspectives, and beliefs by instructors and peers within an organization or learning environment. The 'hidden curriculum' is more latent, less visible, and harder to improve than the formal curriculum that is officially stated, intended, and explicitly defined.

We had interviewed Japanese medical students more than 10 years ago,[5] and recently we conducted similar interviews with 32 students about what they perceived the hidden curriculum to be about, and found the following seven categories: 1) low priority for education; 2) impact of relationships with colleagues; 3) impact of role models; 4) an excessive amount of knowledge and information; 5) hierarchy in the institution; 6) gender issues and sexual harassment; and 7) the influence of the recent historical context. Categories 1 - 6 were similar in both interviews, demonstrating that the effects of the hidden curriculum may persist over time. However, the last category was new. For examples of statements see Table 1.

New challenges that Guimarães *et al* propose include the 'integration of medical education and technology. If new technologies change the way clinical education is delivered, the hidden curriculum may be positively affected. Hierarchies born from old traditional styles and male-dominated environments may improve, and opportunities to interact with classmates or close seniors using social networking services may increase. The development of telemedicine may also improve the shortage of doctors in rural areas. Addressing the cost-effectiveness problem may lead to prioritizing medical education and solving the problem of low priority.

We expect that technological innovation, which has increased globally because of COVID-19, will positively impact the problem of the 'hidden curriculum', the invisible learning environment.

AUTHOR CONTRIBUTIONS

MM: Research concept, design of the study, literature review, data collection, analysis and interpretation, drafting and approval of the manuscript.

Table 1 – Examples of statements

Categories	Examples of statements
1. Low priority for education	"I have not been able to learn '…ology' because the teachers in charge of the lectures have not cooperated. In the very first class, I suddenly learned individual specific illnesses without lectures of general remarks. I cannot learn systematically." (negative impact)
2. Impact of relationships with colleagues	"Every time I attend the lectures with my friends, my relationships grow. Even when I have to study for an exam, we study in a group together and build unity. Even if we cannot meet, we share information using LINE." (positive impact)
3. Impact of role models	"When I wrote in the report that I had a dream of becoming a general physician, it was taken up as a topic by a teacher, and he made kind comments like 'I'll wait for you!'. I was glad to communicate, and my motivation for future learning increased." (positive impact)
4. Excessive amount of knowledge and information	"(Due to COVID-19,) I have so much homework even on weekends that I just managed to finish it, and I do not feel like I have a good understanding of the basics. I feel that it is difficult to achieve my goals of acquiring systematic knowledge." (negative impact)
5. Hierarchy in the institution	"It was education by a teacher that put pressure on a student, and it felt like it had been explained many times before. Actually, it was explained only once, and the student just forgot. I felt like I made a bad impression on the teacher..." (negative impact)
6. Gender issues and sexual harassment	"In the early morning class, one male teacher asked all the female students questions, made them turn on the web camera, and looked at their faces without makeup as well as inside the students' rooms. He would not do that for male students. I was very uncomfortable, and [I] disliked [this]." (negative impact)
7. Influence of the the recent historical context	"(Even if we could not do face to face lessons,) I met a friend for the first time in the ZOOM breakout room, and our friendship grew; I started to make a group using LINE. I could make friends in the breakout room by pairing and communicating repeatedly." (positive impact)

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