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A AMP Agradece!

AMP Says Thank You!

Miguel GUIMARÃES[1,2,3], Tiago VILLANUEVA✉[4,5]
Acta Med Port 2022 Feb;35(2):79-83 ▪ https://doi.org/10.20344/amp.4683

Entre 1 de janeiro e 31 de dezembro de 2021, a Acta Médica Portuguesa recebeu 1515 submissões através da sua plataforma electrónica Open Journal System. Ao longo do ano, os nossos serviços editoriais publicaram 209 artigos distribuídos pelas 12 edições regulares, e 115 artigos em *ahead of print*, o que equivale a mais sete edições. No total, foram publicadas 884 páginas, num esforço sem precedentes por parte de uma equipa dimensionada para a publicação de seis edições e para a gestão de menos de 500 submissões por ano.

Neste contexto, queremos em primeiro lugar agradecer aos Editores-Chefe Adjuntos, aos nossos Editores-Associados e à equipa *in-house* da Acta Médica Portuguesa, pelo extraordinário esforço e dedicação que mais uma vez demonstraram num período particularmente exigente e desafiante. Agradecemos ainda ao Miguel Reis, que ao longo de mais de 40 anos de exclusiva dedicação à AMP assegurou a sua continuidade. É com gratidão que realçamos o contributo inigualável do Miguel, que durante décadas foi a verdadeira "cara" da AMP, com todo o sacrifício pessoal e familiar inerente.

Decidir quais os trabalhos a publicar, procurando constituir uma mais-valia efectiva para os nossos leitores e assim contribuir para a promoção de boas práticas na investigação científica, para a melhoria da prática clínica, e para a divulgação do conceito da moderna autoria científica, é um processo complexo. Neste âmbito, a colaboração dos peritos a quem solicitámos a avaliação dos trabalhos propostos para publicação é fundamental. A Acta Médica Portuguesa é a única revista científica médica portuguesa de âmbito generalista indexada na MEDLINE, com uma audiência de mais de 45 000 médicos portugueses, outros profissionais de saúde, decisores e população em geral. Como tal, é imprescindível o contributo de especialistas das várias áreas, que nos apoiam na identificação dos temas de maior relevância, comentam a pertinência dos estudos propostos, realçam as linhas inovadoras das metodologias apresentadas, etc.

Gostaríamos de salientar a importância de envolvermos mais médicos no processo de revisão por pares da "nossa" Acta Médica Portuguesa, independentemente da fase da carreira em que se encontram ou da sua especialidade. Só assim, todos juntos, alcançaremos o objectivo de consolidar a nossa posição enquanto referência nacional e até internacional. A inscrição na plataforma OJS pode ser feita rapidamente nesta página: https://www.actamedicaportuguesa.com/revista/index.php/amp/user/register, e o *input* de todos quantos queiram arregaçar as mangas e ajudar-nos "a remar" nesta experiência única e enriquecedora será muitíssimo bem vindo.

A todos e a cada um de vós, que de forma contínua doam generosamente o vosso tempo, expressamos o sincero reconhecimento da Ordem dos Médicos e da Acta Médica Portuguesa..

Lisboa, 12 de Janeiro de 2022

Miguel Guimarães
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Editor-Chefe

A lista seguinte enumera os revisores que ao longo de 2021 procederam à avaliação de artigos a pedido da nossa publicação.

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4. Editor-Chefe. Acta Médica Portuguesa. Lisboa. Portugal.
5. Médico de Família. Unidade de Saúde Familiar Reynaldo dos Santos. Póvoa de Santa Iria. Portugal.
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Revisores com cinco avaliações concluídas:

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Marília Antunes

Revisores com quatro avaliações concluídas:

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Retrato da Saúde em Portugal: "Health at a Glance 2021"

A Portrait of the State of Healthcare in Portugal: "Health at a Glance 2021"

Alexandre LOURENÇO✉[1,2,3]
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Palavras-chave: Indicadores Básicos de Saúde; Indicadores de Qualidade em Cuidados de Saúde; Organização de Cooperação e Desenvolvimento Económico; Portugal
Keywords: Health Status Indicators; Organisation for Economic Co-Operation and Development; Portugal; Quality Indicators, Health Care

A publicação anual do relatório para a área da saúde da Organização para a Cooperação e Desenvolvimento Económico (OCDE) constitui uma oportunidade para refletir sobre a avaliação dos sistemas de saúde e, evidentemente, sobre os resultados apresentados pelo sistema de saúde português.

A avaliação de sistemas de saúde é uma tarefa de enorme complexidade e risco. A primeira questão a colocar-se prende-se com o objeto da avaliação. Deverá ser a saúde da população? O desempenho dos sistemas de saúde? Os efeitos das últimas reformas? Magnan *et al*[1] sugerem que a saúde da população depende em 20% da prestação de cuidados de saúde, bem como de outros fatores relevantes: socioeconómicos (40%); comportamentos saudáveis (30%); e ambientais (10%). Logo, ao se centrar a análise únicamente sobre aspetos diretamente relacionados com a prestação de cuidados corre-se o risco de observar apenas uma parcela da realidade. Ao longo dos anos, o relatório da OCDE tem evoluído para além da prestação de cuidados, por exemplo para áreas referentes aos comportamentos saudáveis como tabagismo, riscos alimentares, consumo de álcool e exercício físico.

Ao nível da avaliação do desempenho o Relatório Mundial de Saúde 2000 — sistemas de saúde: melhorar o desempenho representa um marco incontornável. Neste relatório, a Organização Mundial de Saúde (OMS)[3] sugere que a avaliação do desempenho seja medida através da relação entre a despesa *per capita* em saúde e o cumprimento dos objetivos do sistema de saúde: capacidade de resposta (às expectativas não médicas), contribuição financeira justa, e estado de saúde da população. Em relação à capacidade para atingir os objetivos dos sistemas de saúde, Portugal fica classificado na 32.ª posição (nível do estado de saúde da população: 29.ª; capacidade de resposta: 38.ª; justiça contributiva: 58 - 60.ª). Ao nível da despesa *per capita*, Portugal é classificado na 28.ª posição. Na relação entre as duas componentes, o sistema de saúde português é catapultado para a 12.ª posição. Devido à elevada despesa *per capita*, países como a Alemanha, a Suécia, ou a Suíça caem para posições bem menos favoráveis: 25.ª, 23.ª e 20.ª posições, respetivamente.

A relativa boa classificação portuguesa entrou no ideário popular nacional, tendo-se criado o mito de Portugal ter um dos melhores sistemas de saúde do mundo. Para além dos dados se referirem a 1997 – muito aconteceu após esta data – esta ideia tem sido utilizada para obliterar as dificuldades do sistema em garantir acesso a cuidados de saúde de forma satisfatória. Se as entidades portuguesas saíram satisfeitas deste exercício, outras não o apreciaram. De tal modo que, nenhuma entidade multilateral voltou a publicar um relatório a hierarquizar sistemas de saúde.

A publicação deste tipo de classificações pode limitar a melhoria dos sistemas de saúde. Por um lado, as boas classificações podem enfraquecer a necessidade de transformação e melhoria. Este aspeto é particularmente relevante no contexto de sistemas de saúde que apresentam dificuldades em adaptar-se a novos contextos demográficos e tecnológicos. Por outro, as más classificações têm potencial para desmotivar ou mesmo promover a rejeição dos resultados. Demasiadas vezes, face a resultados negativos, verifica-se um comportamento reativo e maniqueísta. Questiona-se a bondade do mensageiro ou o rigor metodológico, esquecendo-se a análise às causas de tais resultados.

A OCDE encontrou um formato elegante para comparar sistemas de saúde. O modelo desenvolvido permite a comparação de indicadores individuais, evitando uma comparação generalizada e a hierarquização de sistemas. Contudo, os dados podem ser alvo de interpretações mais ou menos favoráveis de acordo com a conveniência de cada estado-membro. O relatório sobre o sistema de saúde português da responsabilidade da OCDE e do *European Observatory on Health Systems and Policies*, em cooperação com a Comissão Europeia[2] decorre em grande medida dos dados apresentados no "*Health at a glance 2021*". Contudo, face a aspetos negativos, o relatório sobrevaloriza o impacto de iniciativas governamentais para debelar tais fragilidades.

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2. Unidade de Inovação e Desenvolvimento. Centro Hospitalar e Universitário de Coimbra. Coimbra. Portugal.
3. NOVA School of Business & Economics. Carcavelos. Portugal.
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Basta confrontar a interpretação das medidas enunciadas com o Relatório da Primavera de 2021.[4]

A comparabilidade entre países é fundamental para a identificação de boas práticas e de pontos de melhoria. Avaliar o sistema de saúde é um exercício particularmente relevante para profissionais de saúde, académicos, decisores e governantes. Neste contexto permitam-me destacar três áreas a priorizar quanto ao sistema de saúde português: fatores de risco para a saúde, proteção financeira, e acesso a cuidados de saúde.

As políticas de saúde devem priorizar os comportamentos saudáveis. Portugal mantém uma trajetória positiva na redução consumo de tabaco, álcool e de bebidas açucaradas. Contudo, ao nível das bebidas açucaradas mantém valores superiores à média da OCDE. Mais preocupante é a insuficiente atividade física entre os adultos e adolescentes. Entre os países analisados, Portugal é o país da União Europeia (UE) com o pior resultado neste indicador: 46,4% da população apresenta atividade física insuficiente. Ao analisarmos adolescentes com 11 e 15 anos verificamos que apenas 12,5% e 8,5%, respetivamente, realizam pelo menos 60 minutos por dia de atividade física moderada ou elevada. Estes indicadores redundam numa elevada percentagem de excesso de peso: 67,6% da população adulta e 22,0% dos adolescentes com 15 anos. Nestes últimos apresenta um agravamento entre as medições realizadas em 2009 – 2010 e 2017 – 2018. A elevada prevalência de diabetes em Portugal resulta destes comportamentos: 9,8% da população adulta face a uma média de 6,7% da OCDE. Apenas um plano de ação consistente e abrangente pode contrariar este cenário, incluindo-se várias áreas da governação como educação, economia, juventude e desporto [na área da diabetes, a Associação Portuguesa de Administradores Hospitalares (APAH) juntou vinte especialistas para elaborar um plano que abrange seis áreas educação, prevenção, capacidade resolutiva, governação e cooperação operacional, inovação digital e novos modelos de financiamento. A proposta encontra-se em discussão pública.].

O acesso a cudados de saúde exige uma maior proteção financeira das famílias. Os pagamentos diretos correspondem aos valores pagos pelos doentes devido à falta de cobertura do sistema público ou privado de seguro. Sempre que estes pagamentos diretos competem com as despesas básicas famílias (e.g., comida, rendas ou empréstimos à habitação, água, luz, gás) consideram-se despesas catastróficas. Em Portugal, a percentagem de pagamentos diretos tem crescido ao longo dos últimos anos, atingindo o valor histórico de 30,5% em 2019 — duas vezes mais alto do que a média da UE. Portugal é o país da UE com valor mais elevado de pagamentos diretos em percentagem do consumo das famílias, sendo que mais dos 10% dos agregados familiares portugueses tiveram despesas de saúde catastróficas, em comparação com 6,5%, em média, na UE. Esta situação penaliza primariamente as famílias com menores rendimentos, contribuindo para a perpetuação do ciclo de empobrecimento. Importa destacar que, os pagamentos diretos estão essencialmente relacionados com incapacidade do setor público em prestar cuidados de ambulatório, seguido pela área dos produtos farmacêuticos.

Os portugueses enfrentam graves dificuldades no acesso a cuidados de saúde. Apesar de formalmente toda a população portuguesa ter acesso a cuidados de saúde através do serviço público de saúde, 28% da população opta voluntariamente por aderir a uma cobertura dupla por seguros privados — estes valores não incluem beneficiários da ADSE ou outros subsistemas. Portugal apresenta necessidades não satisfeitas de cuidados de saúde superiores à média da União Europeia, sendo o segundo país com maiores necessidades não satisfeitas na área da saúde oral. Os tempos de espera nacionais para cirurgia são dos mais elevados nas áreas avaliadas: catarata e próteses do joelho e da anca.

A pandemia de COVID-19 veio dilatar estes tempos de espera, destacando-se que 34% dos portugueses relatam necessidades não satisfeitas em saúde durante os primeiros 12 meses da pandemia — o segundo país com pior indicador face a uma média de 21% da UE. Neste campo, a Ordem dos Médicos e a Associação Portuguesa de Administradores Hospitalares cedo alertaram para este problema, tendo apresentado um conjunto de medidas para minimizar o problema no âmbito do Movimento Saúde em Dia. Contudo, o problema de acesso a cuidados de saúde é estrutural, existindo um fosso crescente entre as necessidades em saúde e capacidade de resposta do sistema.

O sistema de saúde português enfrenta sérias dificuldades que se têm vindo a agravar. Evidentemente, existem muitos aspetos positivos que nos devemos orgulhar (e.g., gestão das doenças crónicas, ambulatorização cirúrgica). No entanto, os enormes desafios que enfrentamos obrigam a uma reflexão profunda e baseada em conhecimento. O relatório anual da OCDE oferece um bom ponto de partida. Cabe-nos a nós refletir e agir, sem preconceitos.

CONFLITOS DE INTERESSE

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

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Why is Palliative Care Training During the Portuguese Family Medicine Residency Program Not Mandatory?

Porque é que a Formação em Cuidados Paliativos no Internato de Medicina Geral e Familiar em Portugal Não é Obrigatória?

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Keywords: Family Medicine; Family Physician; Internship and Residency; Medical Education; Palliative Care; Primary Health Care
Palavras-chave: Cuidados Paliativos; Cuidados de Saúde Primários; Educação Médica; Internato Médico; Medicina Geral e Familiar

The Portuguese Family Medicine residency program lasts four years and consists in a number of both mandatory and elective internships, of variable duration. The elective training periods can be decided by residents with the agreement of both the respective trainers and residency bodies, after taking in consideration its relevance and feasibility. Residency training bodies also organize some in-house short courses on specific topics.[1]

One important characteristic of the discipline of Family Medicine is longitudinal care of patients throughout their lives. Because of the ageing population and their increased complexity, it is expected that family physicians will increasingly provide palliative measures to their patients.[2] Therefore, we consider that palliative care training is essential for the resident's growth as a family physician. Even though the current training program is already trying to raise awareness of training in palliative care, there is still no mandatory training during residency.[1]

We believe that a vulnerable human being at the end-of-life can require as much attention as a vulnerable human being after birth. The particularities of those who have disabling and progressive diseases could be just as significant as those who are born and thrive, but doctors must be aware of that. With this in mind, we intend to reflect on the advantages and disadvantages of including mandatory training in palliative care in the Portuguese Family Medicine residency program. Family Medicine is a complex medical specialty that requires considerable training in multiple fields. We realize that it is unrealistic to provide family physicians with advanced training in all the relevant fields. For example, there are many highly prevalent diseases in which family physicians do not have mandatory training, such as cardiovascular diseases; however, due to their high prevalence and widespread availability of training opportunities, family physicians end up being well prepared to treat these patients. Despite the high prevalence of palliative needs in the community, there are not many training opportunities in this area provided by trainers, residency training bodies, or others. Nevertheless, palliative care training exists but is mostly available as a diploma, master's, or PhD programmes, which means a more intense and expensive education altogether but probably not as suitable for the needs of Family Medicine residents or specialists.

Family physicians are in a privileged position to identify patients in need of palliative care since they normally follow their patients and families throughout time, do home visits and are usually the first point of contact for patients.[3] Moreover, they also help patients navigate the healthcare system and may be required to assist their patients in end-of-life decisions.[3] According to Aguiar,[4] approximately 1% of patients in a family physician's patients list will be terminally ill each year. The early identification of these patients and their palliative needs is important as it can lead to the improvement of quality of life by the provision of better and early symptom control and the anticipation of the needs and wishes of both patients and families.[3,5] But for the purposes of early identification, physicians must be aware of which patients may need palliative care.[5] The lack of training in this field is one of the main barriers to the provision of Palliative Care by family physicians and may justify a certain lack of confidence regarding the clinical management of increasingly older and complex patients.[2,3,6] Moreover, excessive bureaucracy, lack of time, resources and communication between primary and secondary health care and high patient complexity, were also mentioned as difficulties.[3,6] Despite these barriers, family physicians improved their abilities, identified more patients with palliative needs and applied more palliative measures after receiving

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training in palliative care.[7] In fact, family physicians believe that they can have an important role in the follow up of patients with palliative needs.[2,3,8] This data shows that it is essential to provide training in palliative care to family physicians in order to improve end-of-life care.

We also believe it would be extremely important that family physicians learn how to define an advanced care plan for their patients proactively, how to anticipate and relieve the suffering of patients and families, how to avoid recurrent trips to hospital and how to provide a death at home if it is the patient's desire.

National initiatives, such as the Portuguese Strategic Plan for Palliative Care Development, mention that family physicians are responsible for the follow-up of patients with low to moderate complexity and should have postgraduate education lasting between 90 and 280 hours.[7] Moreover, international guidelines, such as those from the World Health Organization, mention that palliative care should work in partnership and be incorporated into existing healthcare services.[9]

Considering the lack of training in palliative care during residency and evidence showing that lack of training equals lack of palliative care in the community, how could this aspect be improved? We suggest a change to the Portuguese Family Medicine residency program by the inclusion of a mandatory 30-hour palliative care theoretical course, organized by each Regional Health Administration, during the third or fourth year of residency as well as mandatory practical training for two to four weeks.

We feel that any form of practical training should be organized nationwide depending on the availability of host organizations, such as the Community Palliative Care Support teams (preferably), the hospices and the hospital-based palliative care support teams, to receive family medicine residents. By doing so, we do not expect the need to extend the duration of the Family Medicine residency program.

With this proposal, our main goal is to defend the need for basic training so that family physicians are able to: identify patients with palliative needs, treat the most common symptoms and refer the most complex situations to specialized palliative care teams.

In conclusion, family physicians develop a trust-based relationship with their patients and families that empowers them with the ability to practice palliative care. Family physicians, as care managers, need to have extensive knowledge ('to know'), abilities ('to do'), and skills ('make happen') to be able to follow their patients and families efficiently. Family physicians are the patients' health managers and bear the responsibility to defend their human dignity: in the beginning, during and in the end-of-life. So, wouldn't it be valuable to have mandatory palliative care training during the Family Medicine residency program in Portugal?

AUTHORS CONTRIBUTION

All the authors contributed equally to the conception of the work, the critical review of the manuscript and the final approval of the version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Confirmatory Evaluation of the Modified Medical Research Council Questionnaire for Assessment of Dyspnea in Patients with Chronic Obstructive Pulmonary Disease in Portugal

Análise Confirmatória do Questionário Medical Research Council para Avaliação da Dispneia em Doentes com Doença Pulmonar Obstrutiva Crónica em Portugal

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ABSTRACT

Introduction: The Modified British Medical Research Council Questionnaire is considered an adequate and simple measure of breathlessness in chronic obstructive pulmonary disease. It is widely used in clinical practice in Portugal, but it still lacks confirmatory evaluation for the Portuguese setting. The aim of this study was to perform a cultural adaptation and validation of the Modified British Medical Research Council Questionnaire so that its most suitable version can be made available to researchers and clinicians in Portugal.

Material and Methods: We performed a cross-sectional descriptive study involving patients with chronic obstructive pulmonary disease aged 40 years or older. We applied the Modified British Medical Research Council Questionnaire and the previously validated Portuguese-language version of the clinical questionnaire for chronic obstructive pulmonary disease between January and June 2019. We determined the agreement between the two questionnaires with kappa agreement, with a 95% confidence interval, and we used Spearman correlation to find a correlation between two scores.

Results: The study included 65 patients managed in a hospital pulmonology clinic (aged 68 ± 7 years; with predicted FEV_1 of 49.86% ± 16.5%). The Modified British Medical Research Council scale correlated significantly with all the domains and the overall score of the clinical questionnaire for chronic obstructive pulmonary disease ($0.46 < r < 0.68$; $p < 0.001$). In bilingual patients, interclass correlation coefficient was 0.912 ($p < 0.001$).

Conclusion: The Portuguese version of the Modified British Medical Research Council Questionnaire is a valid instrument for measurement of breathlessness in chronic obstructive pulmonary disease.

Keywords: Portugal; Pulmonary Disease, Chronic Obstructive; Reproducibility of Results; Surveys and Questionnaires

RESUMO

Introdução: O Questionário *British Medical Research Council* (mMRC) Modificado é considerado um instrumento adequado e simples para a medição da dispneia na doença pulmonar obstrutiva crónica (DPOC). Tem sido amplamente usado na prática clínica em Portugal, mas carece de avaliação confirmatória para o cenário português. O objetivo deste estudo é realizar a adaptação cultural e validação do Questionário *British Medical Research Council* Modificado para que a versão mais adequada possa estar disponível a investigadores e clínicos em Portugal.

Material e Métodos: Realizamos um estudo descritivo e transversal com doentes com doença pulmonar obstrutiva crónica e idade ≥ 40 anos. Aplicamos o Questionário *British Medical Research Council* Modificado e o questionário clínico para a doença pulmonar obstrutiva crónica previamente validado para a língua portuguesa, entre janeiro e junho de 2019. Determinámos a concordância entre os dois questionários com *kappa agreement*, com 95% de intervalo de confiança, e usámos o coeficiente de correlação de Spearman para determinar a correlação entre os dois *scores*.

Resultados: O estudo incluiu 65 doentes seguidos em consulta hospitalar de Pneumologia (idades de 68 ± 7 anos; com FEV_1 49,86% ± 16,5% do predito). A Escala Modificada do *British Medical Research Council* correlacionou-se significativamente com todos os domínios e pontuação total do questionário clínico ($0,46 < r < 0,68$; $p < 0,001$). Nos doentes bilingues, o coeficiente de correlação interclasse foi 0,912 ($p < 0,001$).

Conclusão: A versão portuguesa do Questionário Modificado do *British Medical Research Council* é um instrumento válido para a medição da dispneia na doença pulmonar obstrutiva crónica.

Palavras-chave: Estudos Validação; Doença Pulmonar Obstrutiva Crónica; Inquéritos e Questionários; Portugal; Reprodutibilidade dos Testes

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow obstruction, with a consequent decrease of functional capacity. Airflow limitation and dyspnea significantly affect patients' quality of life.[1]

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This disease causes over three million deaths worldwide every year, and the World Health Organization has predicted that COPD will become the third most common cause of death in the world by 2030.[2,3] A study published in 2013 found that the estimated prevalence of COPD in the Lisbon region (Portugal) was 14.2% in adults aged 40 or older, although it is often underdiagnosed.[4]

The major risk factor for the development of COPD is cigarette smoking, but other environmental factors, such as exposure to air pollutants, may contribute as well.[5] Diagnosis requires spirometry testing in subjects with a history of exposure to known risk factors and symptoms such as dyspnea and/or chronic cough with sputum production.[6]

Chronic and progressive dyspnea is the most characteristic symptom of COPD, but cough with sputum production is also frequent.[7] Chronic respiratory symptoms may precede spirometric abnormalities, although the patients' symptoms should be adequately assessed since they can be used to develop earlier and appropriate interventions.[7]

The Modified British Medical Research Council (mMRC) Questionnaire is considered an adequate and simple measure of breathlessness in COPD, and it is easy to apply and understand.[8,9] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 report recommends a combined COPD assessment that includes the use of mMRC in the assessment of dyspnea.[7] The tool already has an European Portuguese version, which is widely used in daily practice, but it lacks confirmatory evaluation.[10] It is important to understand whether a valid and suitable version of the questionnaire is being used in the Portuguese population.

The aim of this study was to perform a cultural adaptation and validation of the Modified British Medical Research Council Questionnaire

MATERIAL AND METHODS

We obtained the Portuguese version of the mMRC Questionnaire using a translation and back-translation carried out by a committee specially created for this purpose. The original version of the mMRC Questionnaire was translated into Portuguese by three independent translators. Another three independent translators performed the back-translation process. The final versions were merged into one by a committee whose members were fluent in English, and the final version was compared with the original version. The committee made all the adjustments, converged, and approved one final Portuguese-language version (see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15208/Appendix_01.pdf). The equivalence between the two versions (English and Portuguese) was also evaluated. Previously, eleven bilingual individuals completed both versions, first the original version and then the Portuguese translation after a week. We calculated correlations between the scores obtained with both versions.

We performed this cross-sectional descriptive study at the COPD clinic in Centro Hospitalar e Universitário de Coimbra from January to June 2019.

The inclusion criteria of the study were a) COPD diagnosis confirmed by spirometry (with a post-bronchodilator FEV_1/FVC *ratio* < 0.7) at least six months before the study period; b) age of 40 years or above; c) attendance at the COPD clinic of the Centro Hospitalar e Universitário de Coimbra – Hospital Geral during the study period.

We applied the following exclusion criteria: a) history of conditions that could influence the dyspnea-related disability, such as asthma, active pulmonary tuberculosis, lung cancer, or pulmonary resection; b) non-pulmonary diseases considered to be disabling, severe, or difficult to control; c) infections or hospitalization within the last three months; d) history of COPD exacerbation (defined as an acute worsening of respiratory symptoms that results in additional therapy) within the last 6 weeks; e) medication change within the last four weeks; f) cognitive deterioration with inability to understand the questionnaire.

For the purposes of the final study, we used a convenience sample, until it reached at least n = 50 of respondents. This protocol was approved by the Human Research Ethics Committee of the Portuguese Regional Health Administration of the Center and every patient provided informed consent before being enrolled in the study.

The mMRC Questionnaire comprises five items. We gave the Portuguese version to each patient and instructed him or her to read the descriptive statements and then select the number which best fit his or her shortness of breath. The Clinical Questionnaire for COPD (CCQ) for the European Portuguese language, validated in 2012, was also applied in order to analyze the correlation between the two questionnaires.[11]

We also obtained patient spirometric and socioeconomic data (age, sex, and educational level).

The mMRC dyspnea scale is a simple grading system for assessing dyspnea levels and is used for grading the impact of dyspnea on daily activities. There are five statements graded from 0 ("Not troubled by breathlessness except during strenuous exercise") to four ("Too breathless to leave the house or breathless when dressing or undressing"). Patients select the statement that most closely corresponds with their level of impairment.[12] In order to assess the severity of dyspnea, GOLD primarily recommends using the mMRC dyspnea Questionnaire.[9] The mMRC Questionnaire is a reliable measure that correlates favorably with lung function measurements, and it is a suitable tool for assessing symptoms in routine clinical practice.[1,8]

The CCQ is a clinical tool for evaluating the health status (symptoms, functional status and mental status) of people with COPD. The questionnaire comprises three domains and 10 items with an overall score consisting of symptoms (four items), functional state (four items), and mental state (two items). Participants must answer the CCQ questions, based on their experience in the last seven days, on a Likert-type scale that assumes the following values: 0) never, 1) hardly ever, 2) a few times, 3) several times, 4) many times, 5) a great many times, and 6) almost all the time.

The total score ranges from 0 to 60. The primary outcome measure of CCQ is the mean total score (divided by 10 items), with higher scores representing a worse health status and quality of life.[11]

We summarized the characteristics of the study population using descriptive statistical methods with percentage, mean, and standard deviation (SD).

The agreement between these two questionnaires was determined with kappa agreement with a 95% confidence interval. Spearman correlation was used to find a correlation between the two scores. We performed all calculations using SPSS Statistics version 26®.

The primary outcome was the concordance of GOLD classification while using mMRC and CCQ. We used the cut-off points at mMRC two and CCQ 1.5 to allocate patients into each GOLD classification.

We did not perform test-retest agreement, since the participants were patients who attended a hospital outpatient clinic and were not hospitalized.

RESULTS

We characterized the group of patients included in the present study (n = 65) with moderate to severe obstruction, as well as with a small rate of exacerbation (Table 1).

Out of all respondents, 4.62% and 12.31%, respectively, scored in the highest category (4) and the lowest category (0) on the mMRC, showing we did not reach a ceiling effect. Comparing the results from both questionnaires, 13.85% (n = 9) of the respondents who had a mMRC score < 2 had a CCQ score ≥ 2. On the other hand, 6.15% (n = 4) of the respondents who had a mMRC score ≥ 2 got a CCQ score < 2 (Table 2).

The mMRC scale correlated significantly with all the domains and the overall score of the CCQ ($0.46 < r < 0.68$; $p < 0.001$) (Table 3).

The mean administration time for mMRC was 58 ± 0.4 seconds. The bilingual patient interclass correlation coefficient was 0.912; $p < 0.001$. Cronbach's alpha was not possible to calculate due to scale characteristics. We also got no blank answers, showing that the mMRC Questionnaire seems to be adequate and feasible.

DISCUSSION

Although it has been used in various studies in different

Table 1 – Sample baseline characteristics

Characteristics	n	(%)	Mean (± SD)
Age (years)			68 (± 7)
Sex (Male)	56	86.15	
Weight (kg)			66.98 (± 9.55)
BMI (kg/m^2)			23.4 (± 3.9)
FEV$_1$% predicted			49.86 (± 16.5)
Gold A	23	35.40	
B	26	40.00	
C	7	10.80	
D	9	13.80	
Smoking history	46	70.77	
Current smoker	4	6.15	
Exacerbations in the last 12 months			
0	28	43.08	
1	21	32.31	
≥ 2	16	24.62	
mMRC dyspnea			1.77 (± 1.12)
0 - 1	30	46.15	
≥ 2	34	52.31	
CCQ total			2.13 (± 0.89)
CCQ Symptoms			2.33 (± 1.15)
CCQ Functional State			2.40 (± 1.20)
CCQ Mental State			1.20 (± 1.20)
CCQ total			2.12 (± 0.92)
Acceptable (CCQ < 1)	6	9.23	
Acceptable for moderate disease (1 ≤ CCQ < 2	19	29.23	
Instable-severe limited (2 ≤ CCQ < 3)	27	41.54	
Very instable-very severe limited (CCQ ≥ 3)	13	30.00	

Table 2 – mMRC questionnaire results and percentage of overlap between mMRC and QQC questionnaires (< 2 versus ≥ 2 scores)

mMRC	n	%
0	8	12.31
1	22	33.85
2	15	23.08
3	17	26.15
4	3	4.62
mMRC 0 - 1	30	46.15
mMRC ≥ 2	35	53.85

mMRC < 2 (n/%)		**mMRC ≥ 2** (n/%)	
CCQ < 2 (n/%)	CCQ ≥ 2 (n/%)	CCQ < 2 (n/%)	CCQ ≥ 2 (n/%)
21/32.3%	9/13.8%	4/6.15%	31/47.7%

Table 3 – Associations between mMRC and QQC scores

CCQ domains *vs* mMRC	*r*	*p*
Symptoms QQC *vs* mMRC	0.52	< 0.001
Functional state CCQ *vs* mMRC	0.46	< 0.001
Mental State CCQ *vs* mMRC	0.68	< 0.001
CCQ Total *vs* mMRC	0.66	< 0.001

languages, we found no description of the validation process or of the cultural and social adaptation of the Portuguese version of the mMRC apart from a translation and validation for the Brazilian setting.[1] This study conducted in Brazil showed that the Portuguese-language version for the Brazilian cultural and social scenario proved reproducible and valid for patients with COPD.[1]

We chose the CCQ as the validation criterion for the European Portuguese language version and cultural adaptation of the mMRC Questionnaire because it is considered as an instrument with proven validity and is widely used in scientific research.[11] There is evidence that both CCQ and mMRC scores have inter-equality and reliability.[13]

The mMRC Questionnaire correlated significantly with all the domains and with the overall score of the CCQ, showing that the translated version is valid (Table 3).

According to GOLD 2019, COPD patients should undergo assessment of either dyspnea using mMRC or symptoms using CAT™. By combining the risk of exacerbation with the score of one of these tools, patients can be grouped in the clusters “A, B, C, D”. The pharmacological approach is different for each cluster profile. Since therapy can have prognostic implications, it is important that we trust the results that are being measured, which further strengthens this validation study and paves the way to a future validation of CAT™ for European Portuguese. In addition, the importance of accurate dyspnea measurement tools, in addition to the prognostic information they provide,(whose paradigmatic example is their inclusion in the BODE index) also have significant implications for clinical practice, for example in monitoring interventions performed in patients with COPD, whether pharmacological, rehabilitation or other.

On the other hand, even though both mMRC and CAT™ are useful tools for clustering patients, they evaluate different dimensions of COPD patients. Future research could compare the performance of both tools in the different patient clusters, different care settings or even for different levels of obstruction. Different performances can lead physicians to choose the most suitable tool for the patient according to these characteristics. This hypothesis becomes even more relevant if this ‘assessment individualization model’ leads to different therapeutic strategies.

Our study only included patients with moderate to severe obstruction and with small rates of exacerbation. This limitation is comprehensive once data was collected in a hospital clinic. Nevertheless, patients with mild obstruction or patients with higher rates of exacerbation, should also be assessed because, as previously mentioned, an individualized approach can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status. In particular, patients with frequent exacerbations, due to the potential for greater symptomatic weight, are a population where the precise characterization of the degree of dyspnea variation can potentially predict important clinical declines and, therefore, it is a population of COPD patients where there is a benefit of greater inclusion in future studies. Primary care and Emergency departments can be settings of great interest for future research both with mMRC and CAT™.

We believe that further validation contributions can have major importance, with larger and more representative samples, of either patients or type of clinical setting, bearing always in mind that establishing a correlation does not imply causality.

An important limitation in this process of cultural validation and adaptation is the lack of test-retest assessment, given the clinical context in which the questionnaires were provided to patients. Test-retest reliability is important when measuring stable variables. The mMRC Questionnaire measures dyspnea, which is a variable that changes over time. Since patients could have different degrees of dyspnea on different assessments, test-retest was not performed. Despite this limitation, we believe that it is not a critical error in our methodology, and it was guaranteed that the Portuguese version of the questionnaire is an effective method for the symptomatic evaluation of the dyspnea of COPD patients. No ceiling effect was observed, like in other studies, allowing us to add validity in the evaluation of outpatients with COPD.[14]

A Portuguese study with outpatients during acute exacerbations of COPD suggests that mMRC is more sensitive to changes with interventions during acute exacerbations than in stable stages of COPD.[15]

Our study showed that the Portuguese-language version of the mMRC Questionnaire is feasible and externally valid when compared with a traditional and previously validated instrument. The confirmatory evaluation and cultural adaptation of mMRC to Portuguese patients can pave the way for future research involving patients with acute

exacerbations of COPD, even in a primary health care setting. Repeating this study with larger samples and in different locations could give more robustness to its conclusions. In future studies, the validation of the mMRC Questionnaire in palliative care may be an advantage in assessing patients with COPD in this context.

CONCLUSION

Individualization in the provision of care is increasingly both the present and future. We hypothesized that individualization, may not only be the result of an adequate evaluation, but that the evaluation itself can be improved if it becomes individualized.

Because many Portuguese COPD patients are managed in primary care, we believe it has potential for future research, both in terms of the number of potential patients, but also to assess different health care contexts. Using simple tools also has the advantage of decreasing resistance to use, especially in a scenario where there is already a high workload. Being able to have validated instruments for use in these scenarios, will be an asset in the management of patients with COPD.

The Portuguese version of the mMRC Questionnaire is a valid instrument for measurement of breathlessness in COPD patients. Although it is already widely used in clinical practice, confirmatory evaluation of this tool makes it available for use by Portuguese researchers and empowers its use by clinicians.

AUTHORS CONTRIBUTION

SAR, CSC: Design of the work, draf of the paper, final approval of the manuscript.

MV, JM, JC: Data acquisition and processing, critical review and correction of the paper, final approval of the manuscript.

CR: Critical review and correction of the paper, final approval of the manuscript.

ARM: Statistical work, critical review of the paper, final approval 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 no competing interests to report.

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Process Evaluation of a Mixed Methods Feasibility Study to Identify Hospital Patients with Palliative Care Needs in Portugal

Avaliação de Processo de um Estudo de Viabilidade de Metodologia Mista para Identificar Doentes Hospitalares com Necessidades de Cuidados Paliativos em Portugal

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ABSTRACT

Introduction: Evidence shows most patients are not recognised by their attending healthcare professionals as having palliative needs. This feasibility study aimed to aid healthcare professionals identify hospital patients with palliative needs.

Material and Methods: Mixed-methods, cross-sectional, observational study. The patient inclusion criteria comprised: age over 18 years old, being mentally capable to give consent judged as such by participating healthcare professionals, and if unable, having a legal substitute to consent, having a diagnosis of an incurable, potentially life-threatening illness. Field notes were taken for reflexive purposes. Outcome measures included: Integrated Palliative Care Outcome scale, surprise question, phase of illness, referral request status, The Eastern Cooperative Oncology Group Performance Status and social needs assessment. An interim data collection period meeting assessed implementation outcomes in each context. A web-based survey was sent to all participating healthcare professionals at the end of data collection period to explore overall experiences of participation and implementation outcomes.

Results: Forty-two departments in four hospitals were contacted. The study was presented in nine departments. The field notes were vital to understand the recruitment process and difficulties experienced: time constraints, fear of additional work, department dynamics and organisation, relationships between departments and need of training in palliative care and research. One department agreed to participate. There were six participating healthcare professionals and only 45 patients included. Three participating healthcare professionals responded to the web-based survey.

Conclusion: There is an urgent need to provide generalist palliative care training to clinicians.

Keywords: Decision Making; Health Services Research; Implementation Science; Medical Education; Palliative Care; Patient-centered Care

RESUMO

Introdução: A maioria dos pacientes não são reconhecidos pelos seus profissionais de saúde como tendo necessidades paliativas. Este estudo de viabilidade visou ajudar os profissionais de saúde a identificar doentes hospitalares com necessidades paliativas.

Material e Métodos: Método misto, transversal e observacional. Os critérios de inclusão dos doentes compreenderam: idade igual ou superior a 18 anos; capacidade mental para dar consentimento informado, avaliado pelos profissionais de saúde participantes ou, caso não tenham essa capacidade, presença de um representante legal para consentir; ser portador de doença incurável, ameaçadora do tempo de vida. As notas de campo serviram fins reflexivos. As medidas de resultados utilizadas foram: escala integrada de cuidados paliativos, pergunta surpresa, fase da doença, estatuto de pedido de encaminhamento, Estado de Desempenho do Grupo de Oncologia Cooperativa Oriental (ECOG) e avaliação das necessidades sociais. A reunião intercalar no período de recolha de dados auxiliou-nos a avaliar os resultados da implementação em cada contexto. No final do período de recolha de dados enviámos um inquérito eletrónico aos profissionais de saúde participantes para explorar experiências globais de participação e resultados de implementação.

Resultados: Contactámos 42 serviços em quatro hospitais. Apresentámos o estudo em nove serviços. As notas de campo foram vitais para compreender o processo de recrutamento e as dificuldades vividas: restrições de tempo, medo de trabalho acrescido, dinâmica de serviços e organização, relações entre serviços e necessidade de formação em cuidados paliativos e investigação. Contámos com a participação de um serviço, seis profissionais de saúde e 45 doentes. Três profissionais de saúde participantes responderam ao inquérito eletrónico.

Conclusão: É urgente a formação em cuidados paliativos generalistas a médicos que trabalham em hospitais.

Palavras-chave: Assistência Centrada no Doente; Ciência da Implementação; Cuidados Paliativos; Educação Médica; Investigação sobre Serviços de Saúde; Tomada de Decisão

INTRODUCTION

Most people with an advanced disease would benefit from palliative care (PC) interventions from the moment of diagnosis.[1,2] Evidence shows that most people with an advanced disease are not recognised as such by their healthcare professionals across all levels of care and those who do get referred are in the last weeks of life.[3]

Tools have been and continue to be developed worldwide to aid healthcare professionals identify patients in need and their families earlier in the disease trajectory, thus potentially promoting access to this type of care to all

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patients who need it, and improving opportunities for integrated care.[4-9]

There is no consensus on the best PC needs identification tools to use.[10]

Seven tools were found to identify patients with PC needs in primary care, Europe wide, but none were validated or widely implemented.[5]

Even though there are a few promising measures using predictive scores in the hospital setting, they aren't yet considered optimal as they do not help making decisions on patients whose PC needs are not or are falsely identified. Implementation in clinical practice is challenging and most studies are published as academic work.[4,8,11] A systematic process has defined key primary and secondary criteria to screen patients upon admission, every day during hospital stay and how to improve discussion around continuity of care with other healthcare institutions upon discharge.[9] Indeed, the World Health Organization defines integration as "combining different kinds of (…) services or operational programs to ensure and maximize collective outcomes. It would include referrals from one service to another and is based on the need to offer comprehensive services".[12] Nevertheless, those criteria should be adapted to the local context.[9] Authors also point out that not all clinicians are able to make a basic PC needs assessment and educational initiatives are warranted. Finally, substantial barriers to implementation are described, mainly attitudinal and logistical. This is well aligned with findings from a scoping review of use of complexity theory in health services research: "… the included studies captured how diverse relationships and communication between agents of a system can influence unpredictable changes within the system[13] and with the non-adoption, abandonment, scale-up, spread, and sustainability (NASSS) framework, an evidence-based, theory-informed, and pragmatic framework to help predict and evaluate the success of a technology-supported health or social care program, which takes into account that…" it is not individual factors that make or break a technology implementation effort but the dynamic interaction between them".[14] The framework consists of 13 questions across six domains: 1) the condition (1A: nature of condition or illness, 1B: comorbidities, socio-cultural influences), 2) technology (2A: material features, 2B; type of data generated, 2C: knowledge needed to use, 2D: techology supply model), 3) value proposition (3A: supply-side value to developer, 3B: demand-side value to patient), 4) the adopter system (4A:staff role, identity, 4B: patient simple versus complex input, 4C: carers available, nature of input), 5) health or care organization(s) (5A: capacity to innovate, including leadership, 5B: readiness for this technology/change, 5C: nature of adoption/funding decision, 5D: extent of change, to daily activities which become routine and the extent of those changes that are required in order for new routines to be to implemented, 5E: work needed to implement change), 6) the wider system (6A: political/policy, 6B: regulatory/legal, 6C: professional, 6D: socio-cultural) and 7) embedding and adaptation over time (7A: scope for adaptation over time, 7B: organisational resilience). Authors point out that the framework is intended to be used reflexively to guide conversations and help generate ideas, rather than be used as a checklist.

This paper describes the process evaluation of a feasibility study to aid healthcare professionals identify hospital patients with PC needs. The specific objectives are (a) to explore how participating healthcare professionals (PHP) experience the use of the selected measures, (b) to understand missing data occurrence and (c) to explore the occurrence of implementation outcomes, namely, acceptability (perception among stakeholders that an intervention is agreeable), adoption (intention, or action to try to employ a new intervention), appropriateness (perceived fit or relevance of the intervention in a particular setting or for a particular target audience or issue), feasibility (extent to which an intervention can be carried out in a particular setting), fidelity (degree to which an intervention was implemented as it was designed in an original protocol, plan, or policy), coverage (degree to which the population that is eligible to benefit from an intervention actually receives it) and sustainability (extent to which an intervention is maintained or institutionalized in a given setting).[15,16]

MATERIAL AND METHODS

This was a mixed-methods, cross sectional feasibility study,[17-19] which is a kind of pilot study that is designed to systematically address the different dimensions of feasibility to determine whether a larger definitive trial is likely to be successful in testing the intervention.

Patient inclusion criteria were as follows: eighteen years of age and over, being mentally fit to give consent judged by the PHP, and if unable, have a legal substitute to consent, and having a diagnosis of an incurable, potentially life-threatening illness.

The recruitment procedures included searching online for email contacts of hospital departments and then establishing contact.

The emails that were sent provided information about the existence of the study, requested a meeting to present it locally and invited departments to participate. The 15-minute presentation was divided in two parts: first, briefly define PC and its importance, distinguish palliative from end-of-life care, discuss generalist and specialist PC; second, describe the aim, objectives, procedures and expected results/possible benefits of the study. Each email had two follow-ups as reminders with an interval of two weeks. If we got no reply, we would no longer follow-up with the department by email. Nevertheless, once we started presenting the study in consenting departments, we went in person to those that had not replied and asked for a meeting. The hospital setting was chosen because it is well known to have high numbers of patients with palliative needs and because all contacted hospitals were relatively close to each other, and hence manageable to visit by the researcher. This was important given the low resources available.

A standard operating procedures manual was developed

and distributed to the facilitator PHP leading the study locally (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15294/Appendix_01.pdf). PHPs screened potential participants, explained the study, got written consent, and completed the questionnaire regarding the patient's needs.

One meeting was held during the interim data collection period between PHPs and one member of the research

Table 1 – Description of measures used in the study

Data collected by research team member	
Researcher field notes[21-23]	This method records unique cultural and social situations, including individual aspects of healthcare professionals and their interactions, considering the complexities of health services research. The aim of these field notes was for reflexive purposes. The researcher (BA) has had formal training in this methodology. Field notes were taken consistently immediately after each meeting with potential participating services and include descriptive and critical reflective information and some exact quotes.
Data collection performed by participating healthcare professionals in relation to the patients	
The Portuguese version of the Integrated Palliative care Outcome Scale (IPOS) reported by the health care professional[24-27]	This measure is used in many countries and has been adapted and validated in over 10 languages. It has also been culturally adapted and validated to European Portuguese. IPOS is a brief, 18-item, multidimensional scale that captures core concerns in palliative care. The first item is an open question on the three main problems or worries the patient might have had in the past week (results are not presented in this study); items 2 to 9 are set on a 5 point Likert scale based on descriptors (zero – not at all, 1 – slightly, 2 – moderately, 3 – severely, 4 – overwhelmingly), item two is a list of 10 of the most common physical symptoms in a palliative population, with the possibility of adding up to three more symptoms which are not present in the list (results are not presented in this study); item 3 pertains to anxiety, item 4 asks about family/friends worry, item 5 is on depression; item 6 is about being at peace; item 7 relates to sharing feelings with significant people; item 8 is about information needs and item 9 concerns practical problems related to their illness.
The one-year surprise question[28]	This measure has been culturally adapted and validated to European Portuguese. This is a one item measure directed at the clinician: "Would you be surprised if this patient died in the next year?" In this study a negative response should trigger the consideration of referring the patient to palliative care considering the results of the remaining measures, rather than for predicting mortality.
Phase of illness[29]	This measure is a concept developed in the context of the Australian Case Mix Classification describing the stage of a patient's illness in five clinically meaningful phases—stable, unstable, deteriorating, terminal, bereavement - the latter was not used in the present study. This assessment provides participating healthcare professionals with a clinical picture of a patient trajectory, including a distinction between expected and unexpected fluctuations of the patients' phase of illness, which might trigger changes to the care plan.
Referral request to the hospital based palliative care team status measure	This was developed for the study. Based on the fast-track trial typology "urgent/non-urgent",[30] we developed the question "Has a referral to palliative care been made?" to which the answer has five descriptive levels: yes, urgent; yes, not urgent; no; in doubt, to be discussed in team meeting; already followed by palliative care.
The Eastern Cooperative Oncology Group (ECOG) Performance Status[20]	ECOG describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability. It has 6 descriptive levels: from zero, which is fully active, to 5, which is death. Participating healthcare professionals have used this measure in practice for years to assess the level of functioning and felt so comfortable in its use they requested for the data collection form to present a space for ECOG assessment only, rather than the full measure, as they use it from memory.
Social needs dichotomised measure	Participating healthcare professionals requested for a yes/no item answering the question "Do I feel this patient has social needs?"
Data collection answered by participating healthcare professionals in relation to participating in the feasibility study	
Web-based survey[31]	The web-based survey was developed specifically for this study to explore the overall experience of participation, including usefulness of data collected in real time and how it was used, as well as, to assess all implementation outcomes. It was sent to participating healthcare professionals at the end of data collection period. The Checklist for Reporting Results of Internet E-Surveys (CHERRIES) was followed. We used Google Form and all answers were anonymised. The survey was tested twice before sending to potential respondents. A total of five reminders were used during the subsequent two months. The introductory text explained what the web-based survey pertained to (even though participating healthcare professionals knew they would receive the invitation to respond), ensured anonymisation of data and stated that there were no right or wrong answers. There was a total of 25 items to respond. There was only one screen and participating healthcare professionals were required to scroll down to answer, to complete the survey. The survey never displayed a second time once the user had filled it in. To reduce missing data all fields were mandatory except the last item. There were no incentives offered. Verbal consent was obtained in the interim data collection meeting.

team (BA) with the aim of allowing participating healthcare professionals to express their thoughts on variables that might be important to add and/or remove, based on their context and overall experience. For the purposes of clarity, namely to describe all the measures used in this section, we report that changes to the data collection form were indeed made accordingly after the meeting, namely, the Eastern Cooperative Oncology Group Performance Status (ECOG)[20] and one binary item on social needs were added.

Demographic and clinical data were collected. The date of death was requested eight months after the study collection period closed. Table 1 describes all the measures used.

Ethics committee approval was granted (approval number 107-2018-1 issued on the 19th of July 2018 and authorization received on the 8th of August 2018) by the Hospital Ethics Committee and was in accordance with the 1964 Helsinki declaration and its later amendments in 2013 or comparable ethical standards.[32] All participants gave informed signed consent. Confidentiality and pseudo-anonymity were ensured for the participant's department. All patient data were coded by PHPs before being sent to the research team.

Analysis

Qualitative data from the researcher's field notes were kept as reported and have been translated by BA (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15294/Appendix_02.pdf). Data were analysed deductively, following Thompson et al.'s attributes, namely, connections, communication, learning, adaptation, diversity, equilibrium, agents and unpredictability,[13] and inductive thematic analysis was performed following these steps: familiarising with data (transcribing data, reading and rereading the data, noting down initial ideas), generating initial codes (coding interesting features of the data systematically across the entire data set, collating data relevant to each code), searching for themes (collating codes into potential themes, gathering all data relevant to each potential theme), reviewing themes (checking if the themes work in relation to the coded extracts and the entire data set, generating a thematic map), defining and naming themes (ongoing analysis for refining the specifics of each theme and the overall story that the analysis tells, generating clear definitions and names for each theme) and producing the report (final opportunity for analysis. Selection of vivid, compelling extract examples, final analysis of selected extracts, relating back of the analysis to the research question and literature, producing a report of the analysis).[33]

Descriptive statistics were used for demographic and clinical variables, and SPSS, version 24.0 (SPSS/IBM Corp., Armonk, NY, USA) software was used.

Data from the meeting during the interim data collection period were analysed using thematic analysis.[33]

Data from the web-based survey were translated and presented as reported by participants, (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15294/Appendix_03.pdf).

This study is informed by the Medical Research Council Guidance on developing and evaluating complex interventions.[35-37] We followed the MOREcare guidance for reporting.[38]

RESULTS

Four separate data sources were collected: field notes of hospital departments that were contacted (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15294/Appendix_02.pdf); patient data; meeting during the interim data collection period and web-based survey (see Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15294/Appendix_03.pdf). Results are presented following the chronological order of events.

A total of 42 departments in four hospitals were contacted by service directors' emails. Fourteen replied and nine agreed to a meeting to present the study and were invited to participate. Six services in two hospitals informally agreed to participate right after the presentation but did not participate. There was one participating service which collected patient data. Given the sensitive nature of some data collected, the institution will remain anonymous.

The main themes emerging were time constraints, fear of added work, service dynamics and organisation, relationships within each service, relationships between services, ethical dilemmas regarding referring patients to PC services and training needs in PC and research. It is worth mention that a few services had given up on referring patients as the response from the PC service came late and clinicians felt they were failing patients and families. Hence, for most patients the decision was not to refer and try to manage issues, despite acknowledging their lack of training in PC (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15294/Appendix_02.pdf).

Patient data were collected between the 2nd November 2018 and the 21st February 2019 at one ambulatory oncology department of a major hospital. A total of 1495 patients were seen in this period in 2388 medical consultations with 12 doctors. Six doctors agreed to enter the study. Forty-five patients were included, and 58% were male. The mean age of the sample was 65 years old (SD 11.2), and approximately half, 23 (51%) lived in an urban area and 14 had 4 years of formal education (31.1%). Most participants, 26 (57.8%) had not been admitted to hospital in 2018. Concerning the Integrated Palliative Care Outcome Scale (IPOS), the items scoring highest were patient anxiety, family anxiety and sharing feelings. Social needs were considered to exist in three (33.3%) patients out of eight (data collected after the meeting in the interim data collection period). ECOG data were missing in relation to two patients (25%). Eight months after the end of data collection, 19 (42.2%) patients had died (Table 2).

The meeting during the interim data collection period was held on the 19th December 2018. Notes are categorised according to the following main themes (Table 3):

Table 2 – Results for measures used including missing data rates per item.

IPOS	Not at all (0) n (%)	Slight (1) n (%)	Moderate (2) n (%)	Severe (3) n (%)	Overwhelming/all the time (4) n (%)	Not applicable (5) n (%)	Missing n (%)
2.1. Pain	16 (35.6)	11 (24.4)	10 (22.2)	7 (15.6)	1 (2.2)	0 (0)	0 (0)
2.2. Shortness of breath	32 (71.1)	8 (17.8)	4 (8.9)	1 (2.2)	0 (0)	0 (0)	0 (0)
2.3. Weakness or lack of energy	6 (13.3)	10 (22.2)	16 (35.6)	11 (24.4)	1 (2.2)	1 (2.2)	0 (0)
2.4. Nausea	39 (86.7)	3 (6.7)	2 (4.4)	1 (2.2)	0 (0)	0 (0)	0 (0)
2.5. Vomiting	41 (91.2)	1 (2.2)	2 (4.4)	1 (2.2)	0 (0)	0 (0)	0 (0)
2.6. Poor appetite	15 (33.3)	13 (28.9)	13 (28.9)	4 (8.9)	0 (0)	0 (0)	0 (0)
2.7. Constipation	27 (60.0)	6 (13.3)	6 (13.3)	6 (13.3)	0 (0)	0 (0)	0 (0)
2.8. Sore or dry mouth	24 (53.3)	11 (24.4)	7 (15.6)	2 (4.4)	0 (0)	0 (0)	1 (2.2)
2.9. Drowsiness	20 (44.4)	14 (31.1)	8 (17.8)	3 (6.7)	0 (0)	0 (0)	0 (0)
2.10. Poor mobility	14 (31.1)	13 (28.9)	12 (26.7)	6 (13.3)	0 (0)	0 (0)	0 (0)
3. Patient anxiety	6 (13.3)	5 (11.1)	11 (24.4)	16 (35.6)	7 (15.6)	0 (0)	0 (0)
4. Family anxiety	2 (4.4)	5 (11.1)	8 (17.8)	15 (33.3)	15 (33.3)	0 (0)	0 (0)
5. Depression	15 (33.3)	9 (20.0)	10 (22.2)	8 (17.8)	3 (6.7)	0 (0)	0 (0)
6. Feeling at peace	13 (28.9)	19 (42.2)	8 (17.8)	5 (11.1)	0 (0)	0 (0)	0 (0)
7. Sharing feelings	16 (35.6)	9 (20.0)	8 (17.8)	6 (13.3)	6 (13.3)	0 (0)	0 (0)
8. Information	34 (75.6)	6 (13.3)	3 (6.7)	1 (2.2)	1 (2.2)	0 (0)	0 (0)
9. Practical matters	29 (64.4)	6 (13.3)	4 (8.9)	2 (4.4)	1 (2.2)	3 (6.7)	0 (0)
Phase of Illness	**Stable** n (%)	**Unstable** n (%)	**Deteriorating** n (%)	**Terminal** n (%)	-	-	**Missing** n (%)
	24 (53.3)	14 (31.1)	6 (13.3)	0 (0)			1 (2.2)
Referral Status	**Yes, urgent** n (%)	**Yes, not urgent** n (%)	**No** n (%)	**In doubt** n (%)	**Followed by PC** n (%)	-	**Missing** n (%)
	1 (2.2)	18 (40.0)	11 (24.5)	6 (13.3)	7 (15.6)		2 (4.4)
ECOG*	**0** n (%)	**1** n (%)	**2** n (%)	**3** n (%)	**4** n (%)	-	**Missing** n (%)
	2 (25.0)	2 (25.0)	1 (12.5)	1 (12.5)	0 (0)		2 (25)
Surprise question < 1 year	**No** n (%)						
	33 (73.3)						

* Data collected after the meeting in mid-point data collection period, hence, total N = 8
Percentages may not add up to precisely 100%

usefulness of variables in data collection form, managing patients identified with PC needs, dealing with knowledge provided by the data collection, time constraints during clinical consultation, personal experience in being PHPs and discussing changes to the data collection method.

The web-based survey was sent on the 9th April 2019. Of the six PHPs, three answered (50% response rate), all female, mean age was 36 years old, all oncologists worked in the department between five and nine years. One had a post-graduation course in PC (#1) and two had had more than 30 hours of training in PC. Data are translated and presented as reported by participants (see Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15294/Appendix_03.pdf).

Overall, there seems to be a number of benefits in using IPOS alongside the other measures, namely, to alter PHPs' perception of identifying patients with PC needs and as a communication tool, as one PHP reveals how they used the questionnaire to objectively show a patient who had previously rejected referral to the PC team, and the respective family, that there were a number of physical and non-physical issues occurring and that it would be better if those healthcare professionals would be involved in patient care. The patient agreed to be referred.

Regarding the implementation outcomes, based on the interim data collection period and the web-based survey data results, we consider that appropriateness, acceptability, fidelity and adoption were achieved, and feasibility, coverage and sustainability were not achieved.

Missing data occurrence was minimal, occurring in 4 items (min = 2.2%, max = 25%) caused by 'missed data item in questionnaire',[38] in which the PHP accidently skipped an item. This is known to happen more frequently in paper format.[39]

DISCUSSION

It may not come as a surprise that the only participating department in this study was an oncology department, and that, considering the modern PC movement started with oncology patients, all PHP had, at least, basic PC training. Our findings suggest that, in participating departments, the use of the patient centred outcome measures selected for this feasibility study to aid healthcare professionals identify patients with PC needs is characterized by its appropriateness, acceptability, fidelity and adoption. These can be identified as positive outcomes. Nevertheless, feasibility, coverage and sustainability were not achieved.

One of the main results of this study was the low participation rate. Contacting 42 hospital departments in four hospitals and having only one collecting data, shows how important it was to conduct a feasibility study.

Although field notes are subjective due to being dependent of the observer, in this study these data were vital to understand the recruitment process and the difficulties experienced. It is worth mentioning that field-notes are an important component of PC research, including the

Table 3 – Notes taken during the meeting in interim data period

Usefulness of variables in data collection form: PHPs felt items were lacking for social needs and ECOG and requested that those would be added. The referral status measure was considered useful for the decision-making process.
Managing patients identified with palliative care needs: PHPs try to manage patients with palliative needs as much as possible, as they know the hospital based palliative team is understaffed. Many patients are discussed with the palliative team over the phone so that they don't refer them too early, as the palliative team would not accept them over more priority patients of other services. One PHP stated the measures helped alter their perception, in terms of identifying patients with palliative needs, two disagreed, but stated that phase of illness and IPOS physical items gave a systematic picture of needs, especially in patients with heart and renal comorbidities, which was helpful.
Dealing with knowledge provided by data collection: overall PHPs seemed to be more at ease with physical symptoms and not at all with non-physical symptoms, having verbalised they needed specific training to deal with expressions of patients and relatives regarding emotional needs and psychological and existential suffering. They needed a communication tool kit to best deal with those emotions, as well as their own emotions. One PHP describes feelings of anguish and frustration as they feel more might be done for patients and families, but due to time constraints and poor integration of services, they do not get all the help and care needed. All PHPs reported to have benefits on patient care when using the measures, especially perception of concrete needs that otherwise were being overlooked.
Time constraints during clinical consultation: all six PHPs felt the time of consultation was longer by approximately 10 minutes, due to data collection form being used as an interview guide. This led to not all patients being properly screened, as PHPs perceived that patients they knew better, who already took a bit longer in the consultation, would be in there for too long.
Personal experience in being a PHP: two PHPs stated they would not be able to continue to collect data, for feeling increasingly stressed about time of consultations and apologised for dropping out of the study. The PHP leading the study locally explains that their working contract is 100% clinical. There is no contractual protected time for research or teaching, even though they do all three activities. Research is done mostly in their free time *"… you see, we hardly have time to conduct our own research, so it is extremely difficult to participate in other studies, especially if we are directly participating, like in your study. And yours is so important, but as you can see, we already stay overtime for patient care and filling patient records, that we would only leave here at night!"*
Discussing altering the data collection method: PHPs suggested giving data forms to patients (IPOS filled by patients) to fill at home and bring it to the next appointment. It would be more flexible and appointment time would be reduced. We agree that this is a possibility, but it will not take place. A third PHP will also drop out after this meeting. From this meeting until the end of data collection, 3 PHPs will collect data on 8 patients.

implementation of feasibility studies, as they allow participants and researchers to revisit and critically reflect on their own experience.[40] Indeed, field-notes included comments from PHP and observation of team dynamics, which allowed investigators to realize that departments within the same institution function in different ways. The relationship between each department and the specialised hospital-based PC team is also different.[41]

Having different departments reporting the desire and need of generalist PC training was also an important finding, as was worrying about ethical issues regarding the nature of the study. A few departments had given up on referring patients as the response came late and clinicians felt they were failing patients and families. Hence, the decision was not to refer and try to manage issues, despite acknowledging their lack of training in palliative care. In fact, no matter how accurate a measure is in identifying patients with PC needs, access to and provision of PC must be available, whether generalist or specialist, since otherwise it may not be ethical to perform such identification.[42,43] Ethically difficult situations may occur if healthcare professionals identify these needs but are not able to find the balance concerning the different demands, expectations and values that influence the care that is provided to those patients. Similar concerns were reported by Rasoal *et al*,[44] who considered the impact of these needs, demands and expectations at the system, organisation and personal levels of all the stakeholders involved in the process of care.

Finally, while the international literature suggests the benefits of integrating PC in other healthcare settings (e.g., intensive care),[3,45,46] it is with concern that we notice some existing misperceptions and misconceptions about PC among these professionals, such as "… in our intensive care unit there are no PC cases, only intensive care cases.". This is well aligned with a recent systematic review and narrative synthesis which revealed "… a medical culture of disengagement towards dying patients and varying attitudes of senior doctors."[47]

Interestingly, patient data are well aligned with data from the field notes, as overall, physical symptoms scored lower, thus suggesting being best dealt with by PHPs, and anxiety and sharing feelings items scored the highest. PHPs reported not being at ease and having difficulties with these issues and even asked for training in these matters. Using IPOS systematically seemed to help PHPs to becoming aware of these difficulties.

Our study shows that there are barriers to conducting PC research in hospitals, particularly concerning the involvement of clinicians in the research process. Research is considered a key element of PC development and pivotal in ensuring evidence-based PC practices. In fact, the Portuguese Strategic Plan for the development of PC highlights research as a core element to be fostered.[39] However, the lack of contractual protected time for clinicians to combine both research and clinical practice and develop research competencies challenge the development and implications of studies relevant for clinical practice.

Despite only having three respondents, it appears that, overall, the measures used seemed to help alter clinicians' perceptions regarding patients with PC needs, thus aiding in the decision to refer earlier and contributed directly to improve communication between the clinician and both patient and families. In fact, patient centred outcome measures were never developed to substitute patient-carer communication. But they can be, amongst their many uses, a bridge to address that communicational gap, and therefore aiding the start of very important conversations which will allow patients and families to carry out their psychological, emotional and spiritual tasks in a benign way, culminating in an acceptance that all that there was to be lived, no matter in what shape or form, was hopefully lived. It is possible to train healthcare professionals to achieve this. These are skills that can be acquired with proper training.

Missing data occurrence was minimal, caused by "missed data item in questionnaire".[38] This phenomenon could have been minimised if an electronic format was used, as shown by Oliveira and colleagues.[39]

To the best of our knowledge, this is the first feasibility study that combines the use of various measures, including patient centred outcome measures, in order to identify PC needs in Portuguese outpatients by their attending physicians. This design not only allowed us to achieve all three objectives, but also, by the additional use of field-notes and a web-based survey, also allowed us to identify many challenges occurring in clinical practice. Furthermore, achieving negative outcomes met the purpose of conducting a feasibility study and allowed us to identify barriers to research and develop strategies to address them in the future (Fig. 1).

Even though anecdotally one could argue that the issues encountered in this feasibility study are common to many hospitals, this study allowed us to collect data and add to the evidence on those issues. The main limitation in our study is the low participation rate. Additionally, the paper format data form took around 10 minutes to complete, given that PHPs used IPOS as an interview guide, and clinicians felt its impact on routine clinical care. An electronic format would be preferred. On the other hand, by selecting to use it like that, PHPs were much more aware of non-physical issues that otherwise would not be systematically explored. These were sensed by PHPs as relevant for patients and families. These results provide rich information for future attempts of conducting a full multicentre PC research study.

In 2003, the Council of Europe issued recommendations to all member states regarding PC and its status as an inalienable element of a citizen's right to health care. All member states were advised to make sure that PC is available to all those in need. In 2012, Portugal legislated provision of and access to PC at all care levels. Legislation states that all citizens have the right to timely access and high-quality palliative care interventions in all contexts of healthcare services, and clinicians working in non-specialised PC services are expected to provide generalist PC interventions.[48]

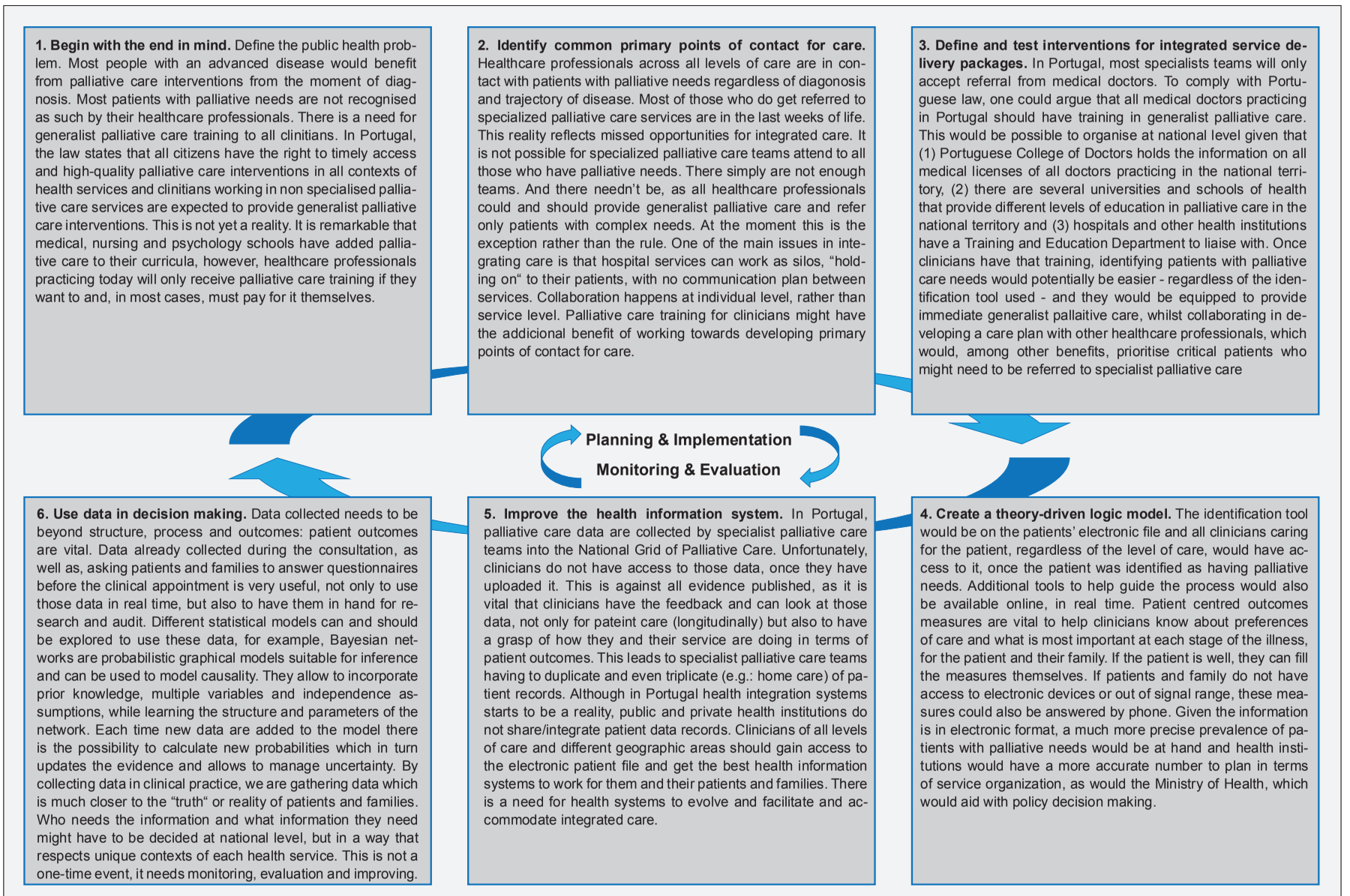

Figure 1 – The 6-step systematic approach to the monitoring and evaluation of integration. Based on Reynolds.[32]

Based in our results, this was not the case. Clinicians lack training, and there are staff and time constraints alongside inexistence of institutional support. This is well aligned with a recent study from the European Association of Palliative Care underpinning the importance of education in knowledge development and skills acquisition in palliative care provision,[49] as is with the Strategic Plan for the Development of Palliative Care in Portugal 2017 - 2018, in which training for clinicians, at different levels is proposed.[50]

The NASSS framework recognises that studies describing lists of facilitators and barriers concerning the implementation of innovative approaches in clinical practice are helpful and useful, but fail to theorise the failure to adopt, scale up, spread or sustain the innovation.[15] Authors recommend the development of studies that are interdisciplinary, nondeterministic, locally situated, and designed to examine the relationship between human action and the wider organizational and system context. We feel we have achieved the latter, with our feasibility study, by relating all data generated from different sources.

Based on our findings, the measures selected altered clinicians' perception regarding patients with PC needs, and thus aiding in the decision to refer earlier and contributed directly to improved communication between the clinician and both patient and families. However, because there was only one participating department, results are not generalisable. The study design used was not feasible, but informative and comprehensive, as most departments did not participate due to attributes of complexity in health services research. Indeed, as Smets and Deliens propose *"…* health services research in palliative care and end-of-life care involves the study of palliative care needs, access and quality of palliative care, and the feasibility, effectiveness, and cost of palliative and end-of-life care services and interventions. The evaluation of services and interventions involving patients with advanced illness presents unique challenges, both ethical and methodological.".[51] Indeed, there were undoubtedly a number of challenges occurring throughout the development of this work relating to organisational and interpersonal issues, funding and education. Our field notes, interim data collection period meeting and web-based survey data show that there is an urgent need to provide generalist PC training to clinicians.

CONCLUSION

There needs to be an integrated PC plan at institution level, alongside the development of a specialist hospital-based PC team for clinical and research work. In order to conduct quality PC health services research, there needs to be contractual protected time for clinicians to conduct research, alongside clinical work. One could argue that legislating the provision of and access to PC by governments is not enough. There is a need for generalist PC training to clinicians working in hospitals. This could be part of an integrated PC plan at both country and institution level, alongside the existing development of specialist hospital-based PC teams, to ensure timely provision of generalist PC to all in need and development of quality research work.

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AUTHORS CONTRIBUTION

BA: Design of the work, data acquisition, analysis and interpretation. Draft of the paper.

PPR, IJH, PLF: Conception and design of the study. Critical review of the paper.

PROTECTION OF HUMANS AND ANIMALS

This study was approved by the institutional ethics review board on the 8th of august 2018, reference number 107-2018-1. The authors declare that the procedures were followed according 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 data were obtained directly from patients using paper format questionnaires by the participating healthcare professionals, which were entered into a deidentified electronic database by a research team member. Deidentified data are available for external researchers upon reasonable request.

PATIENT CONSENT

All participants signed an informed consent.

COMPETING INTERESTS

The authors declare that there are no conflicts of interest.

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Hyponatremia in Cancer Patients Hospitalized in a Palliative Care Department: A Cross-Sectional Analysis

Hiponatremia em Doentes com Cancro Internados num Serviço de Cuidados Paliativos: Uma Análise Transversal

ARTIGO ORIGINAL

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ABSTRACT

Introduction: Hyponatremia is frequent in cancer patients, as many studies carried out in these patients have shown. However, there are only a few studies carried out at the end of life and in palliative care. The aim of this study was to determine the prevalence of hyponatremia in cancer patients in the palliative care department of an oncology center and its association with survival.

Material and Methods: The study included the first 300 patients hospitalized in the palliative care department in 2017. Survival was measured from the day of hospitalization until death.

Results: Serum sodium was measured in 170 (59%) patients. The median serum concentration was 135 mmol/L (109 to 145). Among 91 (54%) patients, serum sodium was within the normal range, 59 (35%) had mild hyponatremia, 13 (8%) had moderate and seven (4%) had profound hyponatremia. The median survival was 13 days (1 to 1020). Serum sodium was not significantly associated with survival (p = 0.463). Regarding other variables, the Eastern Cooperative Oncology Group performance status was significantly associated with survival, while gender, age, primary cancer and number of metastatic sites were not.

Conclusion: Hyponatremia is common in cancer patients receiving palliative care but did not seem to influence survival.

Keywords: Hyponatremia; Neoplasms/complications; Palliative Care

RESUMO

Introdução: A hiponatremia é frequente em doentes com cancro, como muito estudos realizados nesses doentes mostraram. Contudo, há poucos estudos no fim da vida e em cuidados paliativos. O objectivo deste trabalho foi estudar a prevalência da hiponatremia em doentes oncológicos num serviço de cuidados paliativos de um centro oncológico e a sua associação com a sobrevivência.

Material e Métodos: O estudo incluiu os primeiros 300 doentes internados no serviço de cuidados paliativos em 2017. A sobrevivência foi medida do dia da hospitalização até à morte.

Resultados: O sódio plasmático foi medido em 170 (59%) doentes. A mediana da concentração de sódio plasmático foi 135 mmol/L (109 a 145). Em 91 (54%) doentes, o sódio plasmático estava dentro dos valores de referência, 59 (35%) tinham hiponatremia ligeira, em 13 (8%) era moderada e sete (4%) tinham hiponatremia profunda. A mediana da sobrevivência foi de 13 dias (1 a 1020). O sódio plasmático não apresentou uma associação estatisticamente significativamente associado com a sobrevivência (p = 0,463). Quanto a outras variáveis, o estado de performance do *Eastern Cooperative Oncology Group* associou-se significativamente à sobrevivência, o que não se verificou com o género, a idade, o tumor primário e o número de locais de metástases.

Conclusão: A hiponatremia é comum nos doentes oncológicos em cuidados paliativos, mas não parece influenciar a sobrevivência.

Palavras-chave: Cuidados Paliativos; Hiponatremia; Neoplasias/complicações

INTRODUCTION

Hyponatremia is a water balance disorder which develops when the amount of water is excessive in relation to the existing sodium stores in the body. It is the most frequent hydroelectrolytic imbalance found in clinical practice.[1] Hyponatremia is usually defined as a serum sodium concentration below 135 mEq/L. The clinical symptoms may be very varied, from none to life-threatening, depending on the level of serum sodium concentration, the speed of development and the previous general clinical condition of the patient.

The most common causes of hyponatremia are the syndrome of inappropriate antidiuretic hormone secretion (SIADH), diuretic use, polydipsia, adrenal insufficiency, hypovolemia, heart failure and liver cirrhosis.[2] There are other possible causes, such as iatrogenesis from drugs[3-5] and hypotonic intravenous fluids,[6] and pseudo-hyponatremia due, for example, to hyperlipidemia.[7]

In cancer patients, hyponatremia is often caused by SIADH triggered by the ectopic antidiuretic hormone (ADH) secretion by tumor cells.[8] Drugs used in cancer treatment, such as vinca alkaloids, vincristine and vinblastine, alkylating agents, such as cyclophosphamide, and targeted

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therapies (monoclonal antibodies, tyrosine kinase inhibitors, immunomodulators and mammalian target of rapamycin inhibitors) may also induce SIADH. Moreover, platinum compounds stimulate ADH secretion, but can also cause hyponatremia by interfering with sodium reabsorption by directly damaging renal tubules and causing renal salt wasting syndrome or acquired nephrogenic diabetes insipidus.[3] Opioids, antidepressants, tricyclics and selective serotonin reuptake inhibitors stimulate ADH secretion and nonsteroidal anti-inflammatory drugs potentiate its effects on the renal tubules.[4,8] Another cause of hyponatremia is cerebral salt wasting, which may result from brain metastases, head trauma, meningitis or central nervous system (CNS) surgery.[8] In cancer patients, hyponatremia occurs most frequently in small cell lung cancer, but it may occur in many other cancer types, both solid and hematologic. Hyponatremia was identified as an independent negative prognostic factor for survival in cancer patients.[9-11] The non-normalization of hyponatremia with antineoplastic treatment has also been associated with a worse prognosis.[8]

As far as we know from the few studies carried out concerning hyponatremia in palliative care, only two of them looked at the association of hyponatremia with survival.[9,12] As data on hyponatremia in palliative care are so scarce, we carried out a study in our palliative care department with the aim of evaluating its prevalence and prognostic value.

MATERIAL AND METHODS

This study was carried out in the palliative care department (PCD) of an oncology center. The first 300 patients that were hospitalized in the PCD in 2017 were included in the study. The sample size was calculated based on 1000 admissions per year (historical data), a 95% confidence interval and assuming a 50% prevalence of hyponatremia (heterogeneous in previous studies). Only patients with a blood sample collected for other reasons within three days of, or during admission, were studied. For ethical reasons, no blood samples were specifically collected from any patient for this study.

Hyponatremia was classified according to the Guideline on Diagnosis and Treatment of Hyponatraemia[1]: 'mild' - serum sodium between 130 and 135 mEq/L; 'moderate'- serum sodium between 125 and 129 mEq/L; 'profound' – serum sodium < 125 mEq/L.

This study was approved by the ethics committee of the hospital.

Descriptive methods were used for the statistical analysis and the chi-squared test was used to assess the

Table 1 – Demographic data and comparison of patients tested and not tested

	Total		Patients tested		Patients not tested		
Gender	**n**	**%**	**n**	**%**	**n**	**%**	***p***
Male	167	58	102	60	65	56	0.280
Female	120	42	68	40	52	44	
Age							
≤ 69 years	145	51	81	47	64	55	0.467
> 69 years	142	49	89	53	53	45	
Primary cancer							
Esophageal/ gastric	56	20	33	19	23	20	0.673
Colorectal	43	15	28	17	15	13	
Lung	32	11	18	11	14	12	
Head and neck	30	11	17	10	13	11	
Breast	29	10	17	10	12	10	
Prostate	19	7	15	9	4	3	
Gynecological	14	5	8	5	6	5	
Other	64	21	34	20	30	26	
Total	287	100	170	100	117	100	
Disease extension/ Number of metastatic sites							
1	77	27	40	24	37	32	0.451
2	102	36	62	37	40	35	
3	68	24	44	26	24	21	
≥ 4	36	13	21	13	15	13	
ECOG							
1 and 2	21	7	10	6	11	9	0.222
3	103	36	67	40	36	31	
4	162	56	92	54	70	60	

existence of associations between variables. Survival was defined as the time from admission until death. Survival curves were calculated using the Kaplan–Meier estimator and compared using the log-rank test. The level of significance was deemed to be 0.05 and the software used was IBM SPSS version 25. Missing data were dealt with by listwise deletion.

RESULTS

From the 300 patients, three had hypernatremia (serum sodium > 145 mEq/L) and 20 had duplicate records from which the 10 oldest records were deleted. Therefore, the records of 287 patients were analyzed.

Of the 287 patients, 167 (58%) were men and the median age was 69 years (range: 19 to 99; 1st quartile 60, 3rd quartile 77). The most frequent primary cancers were in the digestive tract, namely esophageal/gastric and colorectal cancers (Table 1). The most common metastatic sites were lymph nodes and pleura/lungs; many cancers were locally advanced. Most patients had an Eastern Cooperative Oncology Group (ECOG) performance status of four, 162 (56%).

There were no significant differences between the group of patients tested for sodium and the group of patients not tested in terms of gender, age, primary cancer, number of metastatic sites or ECOG performance status (Table 1).

Sodium was measured in 170 (59%) patients. The median serum sodium concentration was 135 mEq/L (109 to 145). In 91 (54%) patients, it was in the normal range, while 59 (35%) had mild hyponatremia, 13 (8%) had moderate hyponatremia and seven (4%) had profound hyponatremia (Fig. 1). There were no significant differences between the group of patients with and without hyponatremia (Table 2).

Overall, median survival was 13 days (1 to 1020). The median survival of patients who were not tested for serum sodium levels was 10 days (95% CI: 6.21 - 13.79) and the median survival of patients who were tested was 14 days (95% CI: 9.12 - 18.89), with the difference not being statistically significant (p = 0.131) (Fig. 2). The level of serum sodium did not significantly influence survival (p = 0.463). Gender (p = 0.372), age (p = 0.928), primary cancer (p = 0.059) and number of metastatic sites (p = 0.185) were not associated with survival and, of the variables analyzed, only the ECOG performance status had a significant association with survival: patients with ECOG 1 and 2 had a median survival of 54 days, patients with ECOG 3 had a median survival of 23 days and patients with ECOG 4 had a median survival of nine days (p < 0.001) (Fig. 3).

DISCUSSION

Hyponatremia is the most frequent body fluid and electrolyte imbalance encountered in clinical practice.[1] In the few studies carried out in palliative care, the prevalence of hyponatremia has been reported differently: 28.8%,[13] 38.7%[14] and 63.7%.[9] The latter[9] was also carried out solely on cancer patients, as was the present study. In the study by Kremeike *et al*, 92.7% of the patients had cancer[14] and in the study by Nair *et al*, 61.1 % had oncological diseases.[13] In the present study, the prevalence of hyponatremia was 49%. However, the real prevalence of hyponatremia in palliative care remains unknown because, for ethical reasons, a blood test was not obtained from all patients, but only from those who needed a blood test for reasons other than the prevalence study.

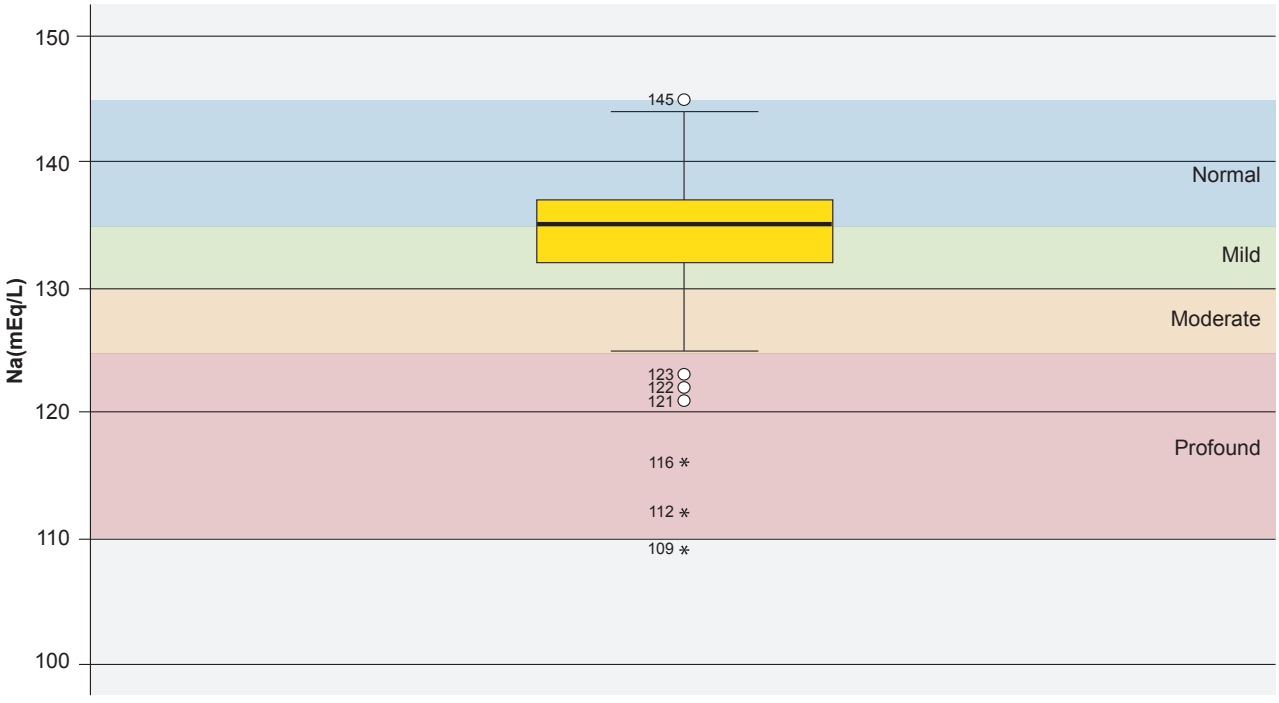

Figure 1 – Distribution of serum sodium levels

Table 2 – Comparison of patients with normal and low sodium

	Total		Normal Na		Low Na		
Gender	**n**	**%**	**n**	**%**	**n**	**%**	***p***
Male	102	60	55	60	47	60	0.900
Female	68	40	36	40	32	40	
Age							
≤ 69 years	81	48	39	43	42	53	0.218
> 69 years	89	52	52	57	37	47	
Primary cancer							
Esophageal/ gastric	33	19	19	21	14	18	0.555
Colorectal	28	17	10	11	18	23	
Lung	18	11	11	12	7	9	
Head and neck	17	10	8	9	9	11	
Breast	17	10	9	10	8	10	
Prostate	15	8	10	11	5	6	
Gynecological	8	5	5	6	3	4	
Other	34	20	19	21	15	19	
Total	170	100	91	100	79	100	
Disease extension/ Number of metastatic sites							
1	40	24	24	26	16	21	0.430
2	62	37	30	33	32	42	
3	44	26	23	25	21	28	
≥ 4	21	13	14	15	7	9	
ECOG							
1 and 2	10	6	6	7	4	5	0.333
3	67	40	31	34	36	46	
4	92	54	53	59	39	49	

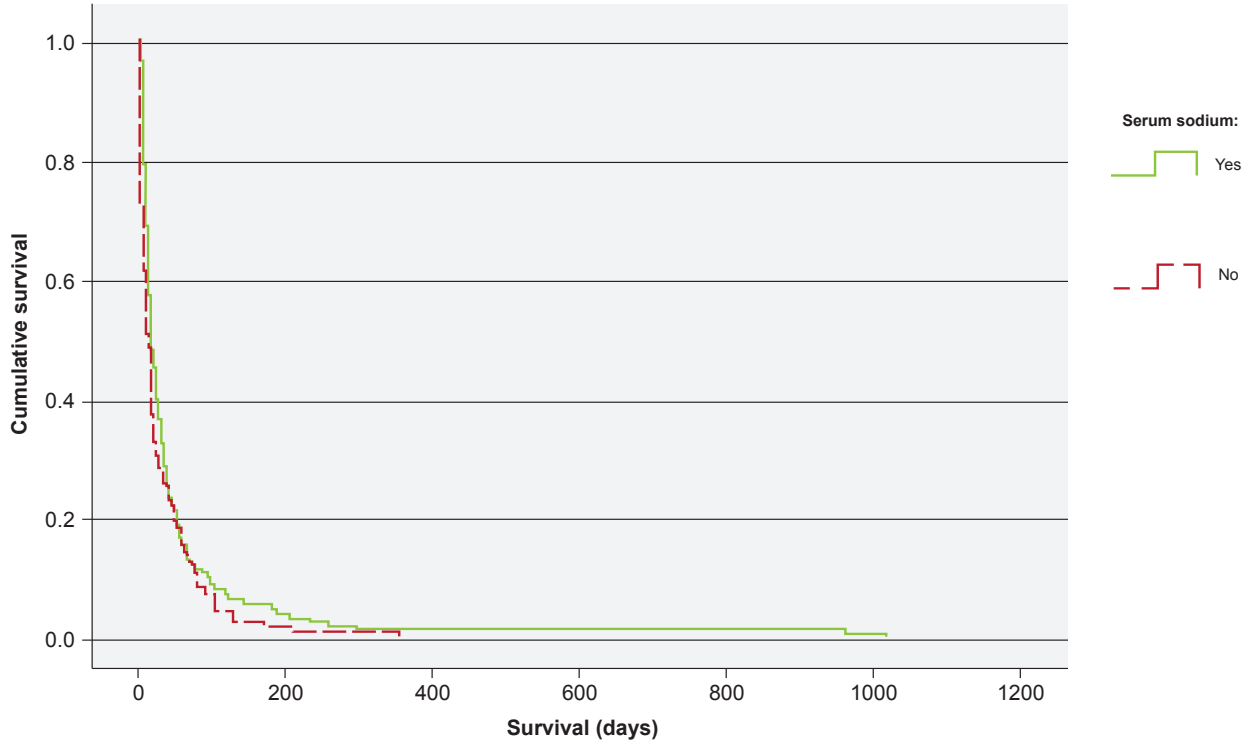

Figure 2 – Survival comparison between patients tested and not tested

In these studies, like in ours, hyponatremia was defined as a serum sodium below 135 mEq/L, except for one which defined hyponatremia as a serum sodium below 136 mEq/L. However, different studies in cancer patients have defined hyponatremia diversely from below 130 mEq/L to below 138 mEq/L2.[8]

A recent study reported an association between hyponatremia and symptom burden.[14] Nonetheless, symptoms in advanced cancer may result directly from advanced disease and it may be difficult to distinguish what is due to hyponatremia alone and what is the result of other causes. Given these reasons, we did not try to investigate the symptoms that could perhaps result from hyponatremia itself.

There are several studies reporting hyponatremia as an independent factor of a poorer prognosis in patients with cancer.[15-20] But there are divergences in some of them according to the cancer extension, with one identifying hyponatremia as a prognostic factor in extensive disease[19] whereas another only in limited disease.[18] There are also some studies in advanced cancer showing that hyponatremia was independently associated with lower survival,[9] an increased risk of death among inpatients in palliative care units,[12] longer hospital stays and higher risk of death[10] and costs.[11] However, the association of hyponatremia with a poorer prognosis does not imply causality as it may be a marker of general debility in advanced cancer[21] or in other diseases.[22] If this is the case, the correction of hyponatremia would have little impact, if any, on the outcome, but a meta-analysis indicated that the improvement of hyponatremia was associated with a reduction in overall mortality for several diseases.[23] Nevertheless, this remains debatable and there is a need for randomized controlled trials to evaluate if the correction of hyponatremia improves outcomes.[24]

In this study, we did not find that hyponatremia was associated with a poorer prognosis. The prognosis for inpatients in this group was, in general, poor, as the median survival for patients who had serum sodium levels available was only 14 days. However, another study with similar median survival found an influence of hyponatremia on survival. [9] We looked at the survival of patients who had not had a blood test (as patients might not have been tested because they could have appeared worse than the others) and we found that, even though median survival was lower, the difference was not statistically significant.

This study has some weaknesses. It was carried out in a single institution, which may limit its generalizability to other settings. Additionally, patients were in a very advanced stage of disease with a consequently short overall life expectancy that may have masked the influence of hyponatremia on the prognosis. Nevertheless, these data suggest that the correction of hyponatremia may not be a priority, as it does not seem to influence survival in this setting.

CONCLUSION

Around half of the cancer patients hospitalized in the palliative care department had hyponatremia. However, in this end-of-life setting, hyponatremia was not associated with a poorer prognosis.

AUTHORS CONTRIBUTION

JFG: Conceipt and design of the work and of the protocol, draft of the paper.

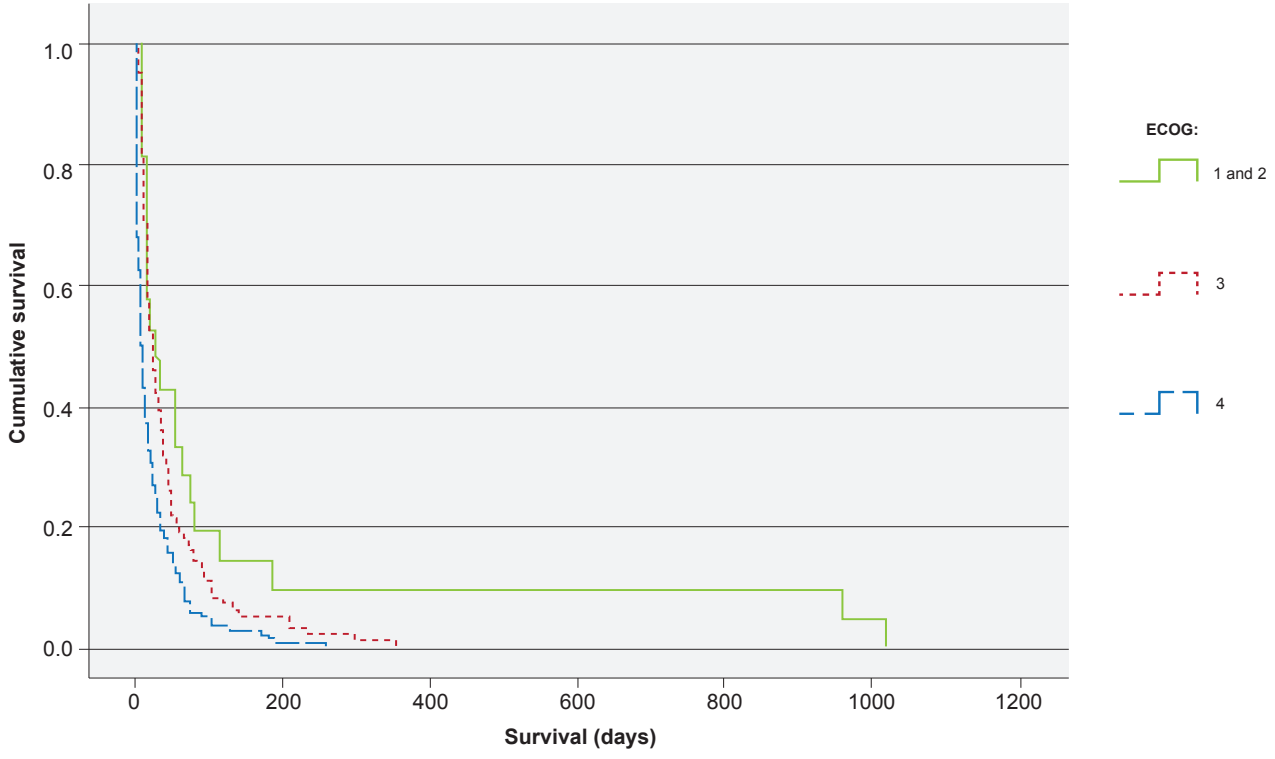

Figure 3 – Survival related with ECOG performance status

MB: Design of the work and of the protocol, critical review of the paper, final approval of the manuscript.

AA, BP, IG, SF, IC, OM, VA: Criticial review of the protocol and of the different versions of the paper, data acquisition, final approval of the manuscript.

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PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Palliative Care in Patients with Advanced Heart Failure: A Systematic Review

Cuidados Paliativos em Doentes com Insuficiência Cardíaca Grave: Uma Revisão Sistemática

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ABSTRACT

Introduction: Heart failure is a disease with survival estimates of around 10% after 10 years of the disease. Being a chronic and debilitating illness, it is important to investigate the potential efficacy of a palliative care approach for these patients. The aim of this study is to systematically review the efficacy of integrating palliative care in patients with advanced heart failure, including the outcomes overall quality of life and well-being, overall symptom burden and possible specific symptoms, hospital admission rates and mortality.

Material and Methods: The MEDLINE, Cochrane, EMBASE and CINAHL databases were searched for articles published between January 2010 and December 2020 about palliative care interventions in patients with heart failure. Clinical studies with humans with symptomatic heart failure were included, comparing the integration of palliative care with usual cardiac care.

Results: The search protocol resulted in seven eligible studies for review and qualitative synthesis. The overall risk of bias within studies was moderate to high. Most studies demonstrated improvements with the integration of palliative care in terms of quality of life and reduction of admission rates. The evidence to support a significant improvement in overall symptom burden was not so robust among studies.

Conclusion: Palliative care interventions seem, overall, to be significantly effective in patients with heart failure. Future studies with more rigorous study designs are needed, in order, to further develop the role of palliative care in heart failure patients.

Keywords: Heart Failure; Palliative Care; Quality of Life

RESUMO

Introdução: A insuficiência cardíaca apresenta estimativas de sobrevivência de cerca de 10% após 10 anos de doença. Tendo em conta que se trata de uma doença crónica debilitante, é importante investigar os potenciais benefícios e eficácia de uma abordagem de cuidados paliativos. Foi objectivo deste estudo rever de forma sistemática a eficácia dos cuidados paliativos destinados a doentes com insuficiência cardíaca avançada, em termos de qualidade de vida, controlo sintomático, admissões hospitalares e mortalidade.

Material e Métodos: Pesquisa na base de dados MEDLINE, Cochrane, EMBASE e CINAHL por artigos publicados entre janeiro de 2010 a dezembro de 2020, tendo sido incluídos estudos clínicos em humanos com insuficiência cardíaca sintomática que compararam a integração de cuidados paliativos com a terapêutica padrão. Os *outcomes* selecionados para extração de dados foram a qualidade de vida, controlo sintomático, internamentos hospitalares e mortalidade.

Resultados: O protocolo de pesquisa resultou em sete estudos elegíveis para revisão e análise qualitativa. O risco geral de viés foi considerado moderado a alto. A maioria dos estudos demonstrou uma melhoria com a integração de cuidados paliativos em termos de qualidade de vida e redução de hospitalizações. A evidência de suporte de uma melhoria significativa no controlo sintomático geral não foi tão robusta.

Conclusão: Os cuidados paliativos aparentam ser, em geral, significativamente eficazes para doentes com insuficiência cardíaca avançada. É necessária investigação futura, com estudos mais rigorosos, para realçar o papel dos cuidados paliativos nos doentes com insuficiência cardíaca.

Palavras-chave: Cuidados Paliativos; Insuficiência Cardíaca; Qualidade de Vida

INTRODUCTION

Rationale

Heart failure (HF) affects more than 26 million people globally, being responsible for a large number of deaths worldwide, with survival estimates of around 10% after 10 years of the disease.[1,2] However, the impact of the mortality associated with HF might be less important than the morbidity associated with this disease. In fact, the quality of life (QOL) in patients with HF is significantly reduced, given the symptoms of fatigue, dyspnea, pain, cognitive decline and depression.[1,3,4] Indeed, being a chronic illness with increasing survival rates, HF is responsible for a significant disease burden, with a QOL as poor as in patients with cancer and has a significant economic impact.[2,3,5–7]

Therefore, interventions directed to the improvement of physical or psychological QOL and disease acceptance might be of interest. It has been shown that the extent of the patient's coping strategies and acceptance of the diagnosis correlates with more positive outcomes, such as hospitalization rates and disease burden.[4,5,8] Moreover, it is relevant to have in mind that QOL is considered equally or even more important than longevity by patients. Approximately 50% of the patients are willing to prefer therapies that improve QOL

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even though at the cost of shortening life expectancy.[9,10]

Considering recent evidence that comprehensive and integrative HF care, including palliative interventions, can have such an important effect for both patients and health care systems, several current HF guidelines have stated the importance of this approach.[1] According to the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF, it is recognized that palliative and end of life care should ideally be introduced early in the disease trajectory.[11] Palliative care (PC) interventions for HF include symptom relief, such as increasing inspired oxygen concentration, diuretic management and decreasing the use of drugs that reduce blood pressure. However, these interventions occur in parallel with advanced care planning, as well as psychological and spiritual support.[3,11–13]

Although PC approaches for HF are increasingly considered of interest in addition to evidence-based-disease-modifying interventions, there are still some barriers regarding the referral of patients to this type of integrative care.[3] Therefore, further evidence and review of evidence is still needed to assess the effects of timely PC intervention for HF patients.

Objectives

The aim of this study is to systematically review the literature for qualitative evidence to evaluate outcomes of PC for HF patients. To this end, the proposed systematic review will focus on three main questions, which are whether PC is more effective than the usual HF care in the improvement of different health related QOL aspects and symptomatic control. Specifically, the chosen outcomes were the overall QOL and well-being, overall symptom burden and possible specific symptoms, hospital admission rates and mortality. Quantitative synthesis and meta-analysis were not performed due to the heterogeneity and various types of outcome assessment between studies.

MATERIAL AND METHODS

Protocol and registration

This systematic review is not registered.

Eligibility criteria

The articles were selected based on several characteristics, as explained below.

Study design

We anticipated a reduced number of randomized controlled trials (RCT) concerning PC interventions. Therefore, we included as possible study designs RCT as well as other clinical study types, such as controlled clinical trials (CCT), interrupted time series (ITS) studies, prospective and retrospective cohort studies and case-control studies.

Participants

The participants in the included studies were adults of any age or gender diagnosed with symptomatic HF (New York Heart Association Class II or higher). We anticipated a reduced number of studies about PC interventions in HF. Therefore, studies with participants being functionally classified as class II HF, or higher, were included, as opposed to only including patients with advanced or end-stage HF. This also allowed to further qualify the impact and outcomes of earlier referral of patients with HF to palliative medicine.

Interventions

Studies related to PC interventions with assessment of symptom burden, QOL, hospital admission rates or mortality were included. For inclusion, an objective description about the intervention provided was required. PC interventions included were integrative care in addition to evidence-based HF care, home-based PC programs, transitional PC models and hospice enrollment.

Comparators

In the included controlled studies, the control group received usual care for HF patients.

Outcomes

The most common outcomes regarding PC interventions for HF and the most important for decision-making are based on overall QOL assessment and well-being, overall symptom burden and possible specific symptom control, hospital admission rates and mortality. Studies that involved this type of outcomes were included. Eligible studies should have clear recognized and validated QOL and symptom assessment scales, such as the Edmonton Symptom Assessment scale (ESAS), the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Hospital Anxiety and Depression Scale (HADS).

Information sources, search strategy and study selection

MEDLINE, Cochrane, EMBASE and CINAHL databases were researched for articles published between January 2010 and December 2020. No manual search was performed, and article authors were not contacted. The search included free-text terms and database specific headings, according to the structure of: Heart failure AND (palliative care OR terminal care OR hospice care OR end of life). Filters for clinical studies and randomized controlled trials were applied. All the identified titles and abstracts during the search process were screened by the first author. The articles considered potentially eligible were selected for full-text analysis by two independent reviewers. The process of study selection was described in a flow diagram, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[14]

Data management

Full-text articles of the included studies were assessed for eligibility criteria and methodological quality by two independent reviewers. Any disagreement between reviewers was resolved by discussion until a consensus was reached.

Table 1 – Individual study's characteristics (n = 7)

Study	Type of study	Population	Intervention	Control	Main outcomes	Observations
Brännström and Boman, 2014[17]	Single-center, open non-blinded, prospective randomized controlled trial	Patients with chronic HF (NYHA III-IV)	Person-centered integrated PC and active HF care combined with PC at home	Usual HF care	Symptom burden (according to the ESAS) and health-related QOL (according to the EQ-5D and the KCCQ)	
Ng and Wong, 2018[18]	Multi-center, non-blinded, randomized controlled trial	Patients with HF with two of the following: NYHA class III-IV; one year life expectancy; repeated hospitalizations due to HF-related symptoms and physical or psychological symptoms	Home-based palliative HF program	Usual HF care	QOL; symptom burden; functional status; patient satisfaction and caregiver burden	Data collected four and 12 weeks after hospital discharge
Wong *et al*, 2016[19]	Multi-center, randomized controlled trial	End stage HF patients (NYHA III-IV) after hospital discharge	Home-based transitional PC	Placebo calls (light conversation topics unrelated to clinical issues)	Readmission rates and symptom burden (according to the ESAS)	Data collected at baseline, four and 12 weeks after hospital discharge
Hua *et al*, 2017[20]	Randomized, controlled cohort study	Chronic HF patients	Collaborative care model	Usual care	Self-care ability; QOL; Left ventricle ejection fraction; NT-proBNP levels and the six-minute walk test performance	Intervention lasted for three months
Rogers *et al*, 2017[21]	Single-center, randomized, controlled, unblinded clinical trial	Advanced HF patients	Interdisciplinary PC intervention in addition to evidence-based care	Usual care	QOL measurements (according to the KCCQ and the FACIT-Pal); depression and anxiety (according to the HADS); spiritual well-being; hospitalizations and mortality	
Lewin *et al*, 2017[2]	Nonrandomized, controlled prospective study	End-stage HF patients	PC, in addition to standard cardiac care	Standard cardiac care alone	Advanced care planning documentation; Emergency department visits; hospital readmissions	Outcomes were compared over a six-months period. All patients in the Intervention group had a PC consult before starting
Yim *et al*, 2017[23]	Longitudinal, observational, uncontrolled cohort study	Advanced HF patients	Hospice care enrollment		Number of hospital admissions; intensive care unit stay and Emergency room visits	Comparison was made between before and after six months of hospice enrollment

EQ-5D: EuroQol's Quality of Life (five dimensions); ESAS: Edmonton Symptom assessment scale; FACIT-Pal: functional assessment of chronic illness therapy-palliative care; HADS: Hospital anxiety and depression scale; HF: heart failure; KCCQ: Kansas City cardiomyopathy questionnaire; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association; PC: palliative care; QOL: quality of life
CHFQ: Chronic Heart Failure questionnaire; ESAS: Edmonton Symptom assessment scale; FACIT-Pal: functional assessment of chronic illness therapy-palliative care; KCCQ: Kansas City cardiomyopathy questionnaire; MQOL: McGill quality of life questionnaire; QOL: quality of life

The second evaluator allowed for resolution of potential disagreements regarding the quality of the included studies.

Risk of bias in individual studies and across studies

For randomized studies, the risk of bias was assessed via Cochrane tools for RCT.[15] For nonrandomized studies, ROBINS-I was used to evaluate risk of bias.[16] Two independent reviewers were responsible for quality evaluation of studies and any disagreements were discussed between reviewers until consensus was achieved. The risk of bias across studies was not performed due to the lack of information.

Summary measures, synthesis of results and analysis

Since a small number of studies and a high level of heterogeneity was expected between studies, it was chosen not to perform a meta-regression analysis. Therefore, a qualitative analysis of studies was preferred, considering the methodological differences between included studies. For a better understanding of the different results among studies, summary tables referring to study variables, characteristics and key findings were made for a better visual comparison of results (Table 1).

RESULTS

Study selection

A total of 549 references from the MEDLINE, Cochrane, EMBASE and CINAHL databases were identified (Fig. 1). No other references were added through manual search or other sources. After removal of duplicates, 405 references remained. Of the 405 screened papers, fourteen full-text articles were examined and seven records[17–23] were eligible for review and qualitative synthesis. In these seven studies the total number of patients included who received PC interventions was 5388.

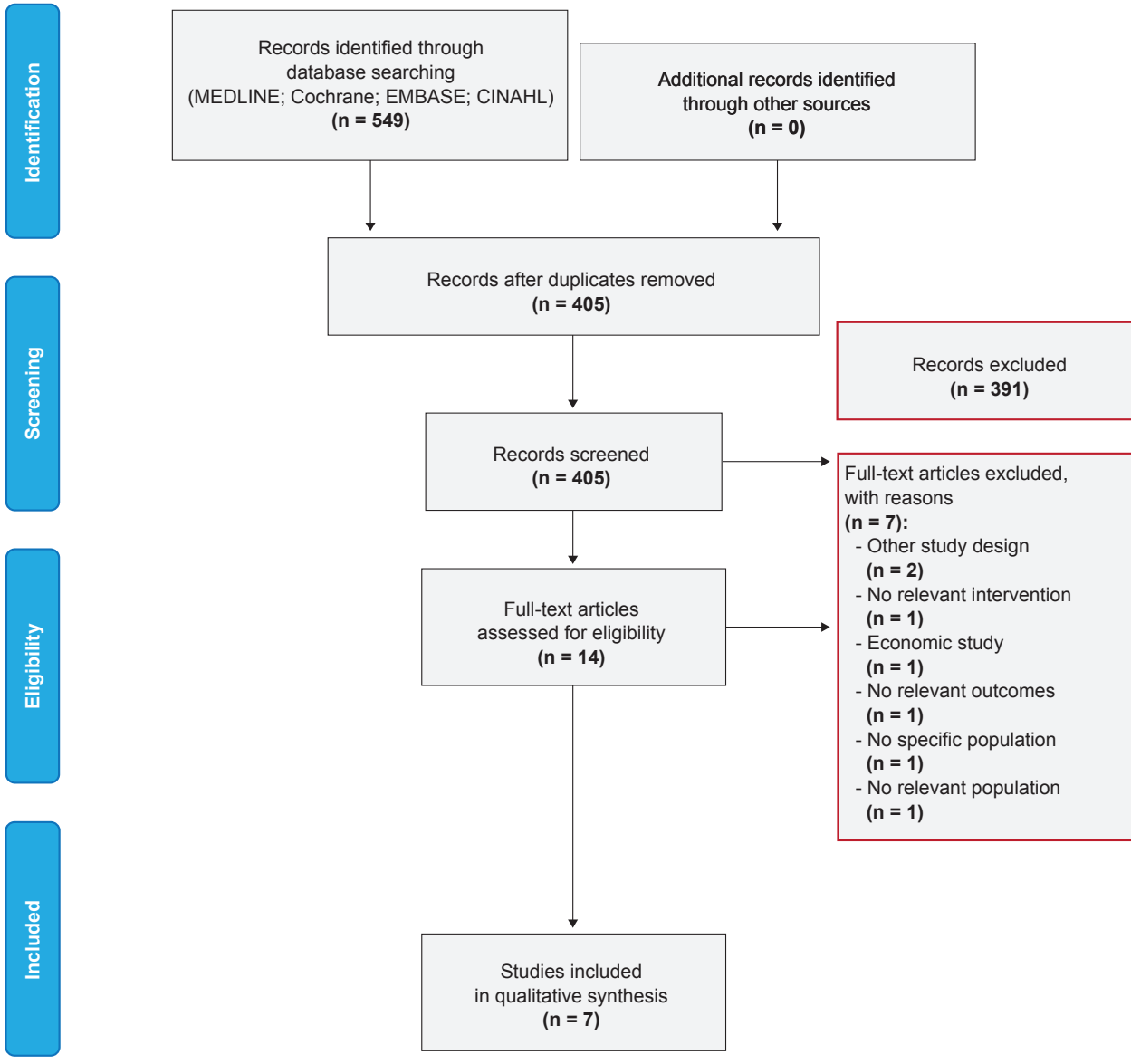

Figure 1 – Flow diagram

Study characteristics

Table 1 summarizes the characteristics of the included studies. Different study designs and PC approaches for advanced HF were included. All of them compared usual HF care with a PC approach. Overall, four RCT,[17–19,21] one cohort study,[20] as well as two other non-randomized prospective clinical studies were included.[22,23]

Risk of bias

The overall risk of bias within studies was moderate to high. Considering the included randomized studies,[17–21] blinding of outcome assessment (detection bias) was the only item that was considered of high risk in all included studies (Fig. 2). This was mostly attributable to the fact that the studies were not blinded. However, even in an unblinded scenario, the performance bias was considered of low risk in three of the included studies,[17,18,21] taking into account that this methodology was not likely to influence the results. In fact, blinded PC interventions for HF are not feasible, given the fact that they require a comprehensive and integrated approach with both symptomatic control and psychosocial support, based on resources such as communication.[3] This was also referred in the Methods section.

Random sequence generation was considered of low risk in every included randomized study, except for Hua *et al*,[20] because there was no available information regarding this topic. In both Brännström and Boman[17] and Hua *et al*[20] there was some risk of selection bias. However, in the other three studies[18,19,21] there was a low risk of selection bias, because sealed opaque envelopes[18] and a computer software randomizer were used for randomization.[19]

In all of the five included studies[17–21] there was, in general, a low risk of incomplete outcome data and selective reporting.

Additionally, there were two studies[18,20] with other potential sources of bias. In Hua *et al*[20] there was the risk of using an unusual population given the fact that not all patients had advanced III-IV NYHA class HF. In the study by Ng and Wong there was the additional risk of using blocked randomization in an unblinded trial.[18]

Considering the included nonrandomized studies (Table 2),[22,23] the risk of bias was considered serious in both studies which are not comparable to randomized trials in terms of methodology. In general, the description of the

Figure 2 – Risk of bias summary for randomized studies included for review (n = 5)

interventions was less clear in these two studies and there was a higher discrepancy in the number of patients included.

Results of individual studies

The main results of individual studies for the outcomes included in this review are presented in Table 3.

All of the analyzed studies with outcomes regarding overall QOL, measured through different scores and questionnaires, showed significant improvement when PC was used versus the control interventions.[17–21] It is important to state that different scales of QOL assessment were used between studies, which decreases the homogeneity of evidence and makes a global quantitative assessment more difficult. Therefore, we chose to pursue only a qualitative analysis and synthesis of studies. A specific quantitative analysis by Brännström and Boman showed a 26% percent improvement in QOL with PC, compared with only 3% with standard care.[17] Quantitative evidence in Rogers *et al* showed that patients who received PC had higher scores in the KCCQ, with a difference of 9.49 in QOL when compared to standard care.[21]

Regarding hospital readmission rates, whereas Brännström and Boman,[17] Wong *et al*,[19] and Yim *et al*[23] found significant reduction of the number of hospital admissions when PC approaches where used, all the other studies which analyzed this outcome failed to demonstrate significant reductions. Specific independent quantitative analysis of outcomes in the study by Brännström and Boman indicates that standard care was responsible for 3.5 times more hospital readmissions than the PC approach.[17] In the study by Wong *et al*,[19] PC allowed for a reduction in hospital admissions of 55%. These examples reflect the quantitative magnitude of these results, even though only a qualitative analysis was carried out.

Long-term overall symptom burden and specific symptom control showed significant improvement versus control interventions when PC was used in three of the included studies, as specified in Table 3, with the appropriate indication of statistical significance.[17,19,21] However, one of the included studies did not show any significant improvement.[18]

DISCUSSION

Summary of evidence and limitations

This systematic review focused on PC interventions for advanced HF patients, and looked specifically at outcomes such as QOL, symptom burden, hospital admission and mortality. First, it is important to recognize that there was a lot of heterogeneity between studies, both clinically and methodologically, which limits the efficacy analysis of these outcomes. However, there were convergences among studies, namely towards the significant efficacy of PC interventions when it comes to the improvement of the overall QOL. In fact, every included article that evaluated this outcome[17–21] suggested a significant difference between PC

Table 2 – Risk of bias in nonrandomized studies (n = 2)

Study	Domain 1: Confounding bias	Domain 2: Selection	Domain 3: Classification of intervention	Domain 4: Deviation from interventions	Domain 5: Missing data	Domain 6: Measurement of outcomes	Domain 7: Selection of reporter result	ROBINS-I Overall
Lewin *et al*, 2017[22]	1	1 - 2	1 - 2	3 - 4	1	3 - 4	1 - 2	3 Serious
Yim *et al*, 2017[23]	1	3 - 4	1 - 2	3 - 4	1	2 - 3	1 - 2	3 Serious

Table 3 – Key findings of individual studies (n = 7)

Study	Significant difference	No significant difference
Brännström and Boman, 2014[17]	Health related QOL (p = 0.02); nausea (p = 0.02); number of Hospitalizations (p = 0.009) and days spent in the hospital (p = 0.011).	Symptom burden (the ESAS; the KCCQ).
Ng and Wong, 2018[18]	QOL (the MQOL, p = 0,016); overall symptom burden at 4 weeks (the CHFQ, p = 0.01).	Overall symptom burden at 12 weeks (the CHFQ and the ESAS).
Wong *et al*, 2016[19]	Hospital readmission rate at 12 weeks (p = 0.009); depression (p < 0.05), cyspnea (p < 0.05) and symptom burden (Total ESAS, p < 0.05); QOL (the CHFQ, p < 0.01; the MQOL, p < 0.05).	Hospital readmission rate at 4 weeks.
Hua *et al*, 2017[20]	Self-care maintenance ability (p < 0.05); mental QOL (p < 0.05) and physical QOL (p < 0.01).	-
Rogers *et al*, 2017[21]	Improvement in the KCCQ and the FACIT-Pal functional and QOL scores; depression (p = 0.020); anxiety (0.048); spiritual well-being (p = 0.027).	Hospital readmission rates and mortality.
Lewin *et al*, 2017[22]	-	Hospital readmissions.
Yim *et al*, 2017[23]	Hospital Admissions and Emergency Room visits (p < 0.001).	-

KCCQ: Kansas City Cardiomyopathy questionnaire; MQOL: McGill Quality of Life questionnaire; QOL: quality of life

and standard HF care, with better QOL with a palliative approach. This could be explained because the quality of care in palliative medicine is mainly evaluated and measured by the improvement in the overall QOL of both patients and their families, even though it is difficult to measure objectively.[24] Therefore, this allows for more focus on the individual patient, including the social sphere, family problems and the fear of death,[24] all of which are present in advanced HF patients and are a cause of serious suffering that mandates intervention.

Unlike the health related QOL, the evidence related to the outcome of symptom burden is not so robust. Although two studies revealed significant improvement in long-term overall symptom burden with PC,[19,20] other studies showed similar results with standard care. However, it is important to recognize some aspects, namely that PC may provide earlier symptomatic control, as suggested by Ng and Wong,[18] and possibly explained by the importance attributed to the prevention of expected symptoms in palliative medicine, with a faster approach. Moreover, although the overall symptomatic control may be similar, there is a tendency for PC to significantly better improve specific psychological symptoms, such as depression and anxiety, contributing to a better spiritual well-being.[19–21] This further reinforces the fact that PC professionals tend to be more experienced in dealing with this type of psychological symptoms, having already been demonstrated that psychotherapy plays an important role in these patients.[25]

The number of hospital admissions, duration of hospital stay and emergency room visits are also very important outcomes nowadays, especially considering that the economics of care are a worldwide priority due to the lack of financial resources.[26] Several of these studies[17,19,23] showed that referral of patients to palliative medicine had a significantly positive effect in reducing the pressure on healthcare systems, whether in terms of readmission rates, emergency room visits or duration of hospital stay, which can contribute to reducing costs and better healthcare allocation. Moreover, in a recent study, it has been shown that for non-cancer patients who received PC while hospitalized with a serious illness there was a statistically significant reduction of cost of US$2105 per patient.[27] Therefore, palliative medicine must and has become a concern and an increasing public health priority .[28,29]

The fact that reducing mortality is not a necessary goal of PC approaches makes it a less studied outcome, which was only evaluated in one included study. However, it is an interesting topic and further studies could help establishing if it is beneficial.

Our systematic review has both strengths and limitations. On one hand, it shows evidence of benefit of PC in HF patients across various outcomes. On the other hand, it has several limitations, as already stated, such as a moderate to high of risk of bias among studies, and the presence of different methodologies and approaches between studies, which limits the comparison between them.

The findings of this review have implications for future research and planning. We identified several PC interventions that should be further integrated in future HF treatment guidelines. It is also important to investigate whether early referral of patients to PC will allow for a reduction in the number of hospital deaths from HF, considering that the last six months of life for these patients are still often marked by frequent hospital admissions, culminating in hospital deaths.[30] Also, this review identified that more rigorous studies and study designs are needed in order to further continue to develop PC approaches for advanced HF.

Another important issue in this review was to evaluate how soon HF patients received PC interventions. Only three of the selected studies[20,21,23] included patients with early-stage HF, namely NYHA class I to II or weakly symptomatic patients. Therefore, robust conclusions regarding the effectiveness of early PC interventions in HF cannot yet be made, because that was not the major factor studied in most articles. However, having in mind that these studies indicated effectiveness with PC interventions, a tendency towards an advantage in early referral of HF patients can be assumed, with the concomitant disease-modifying treatments.

In parallel with the development of PC approaches for advanced HF patients, there have been developments in terms of new treatments and devices for these patients. This is the case of the left ventricle assist device, which can be used for patients not expected to survive without further hemodynamic support, either as a bridge to transplant or a destination therapy, although with strict eligibility criteria and a high cost.[31,32] Furthermore, vericiguat, a novel guanylate cyclase stimulator, has been shown to reduce incidence of death due to cardiovascular causes and the hospitalization of patients with high-risk HF.[33] In fact, palliative medicine should take into account all the novel advances that can benefit advanced HF patients. It is mandatory to integrate all the best possible care, PC included, in the relief of suffering of HF patients.

In line with our outcomes for this review, PC seems effective in advanced HF patients, especially when we consider the overall QOL of the patients and the pressure imposed upon healthcare systems. A PC approach in HF patients should include advance care planning, routine evaluation of QOL indexes, symptom burden, and shared decision-making.

CONCLUSION

The readiness for healthcare services to provide PC for patients with chronic diseases, such as HF, has never been more imperative, considering the disease burden. Nevertheless, this review showed that there are still few studies on PC Interventions in HF with more rigorous designs such as RCT. However, several other studies with other designs were included,. PC for HF patients improves the QOL and reduces the number of hospital admissions and number of emergency room visits, when compared to standard care alone. The evidence related with the efficacy of symptom burden control and reduction in mortality is not so robust.

Studies focusing on early referral of HF patients to palliative medicine are still lacking, even though this is recommended in most guidelines. Therefore, this review highlights that this topic is still understudied and that studies are heterogeneous.

AUTHORS CONTRIBUTION

JFP: Draft of the manuscript, approval of the final version of the paper

PRP: Design of the review protocol, data analysis, critical review and final approval of the paper

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Impact of Air Pollution on Daily Asthma Symptoms

Impacto da Poluição Atmosférica nos Sintomas Diários de Asma

ARTIGO ORIGINAL

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ABSTRACT

Introduction: The impact of air pollution on respiratory diseases, particularly in asthma, has been the subject of several studies. The impact of pollution on the daily symptoms of patients with asthma has been less studied. The aim of this study is to assess the association between the intensity of asthma symptoms and the variation of pollution levels.

Material and Methods: Patients with a diagnosis of asthma were instructed to record the intensity of their respiratory symptoms daily, expressed on a scale from 0 to 5, in the months of March and April 2018. The website of the Portuguese Environment Agency was consulted in order to obtain the daily levels of pollutants measured by the two local monitoring stations during the same period of time. Data was analyzed using a temporal causal model to study the association between pollutant levels – particulate matter, ozone, nitrogen dioxide and carbon monoxide – and the intensity of respiratory symptoms.

Results: From the 135 schedules delivered, 35 were correctly filled out and returned. The patient median age was 47.0 years, 18 being females. The best statistical model obtained identified ozone as the most relevant 'Granger cause' of asthma symptoms. Particulate matter, carbon monoxide and nitrogen also appeared as lower impact factors. The quality of the model was expressed by an R^2 of 0.92. The correlation between ozone values and asthma symptoms was more significant after five days. For the other identified factors there was a lag of four to five days.

Conclusion: In the place and period studied the air pollutants behaved as factors of variation in the intensity of asthma symptoms. The ozone level was the best predictive factor of symptom variation. Levels of particulate matter, carbon monoxide and nitrogen were identified as secondary markers. The time lag between the variables with the best correlation suggests there could be a delayed effect of pollutants on respiratory symptoms.

Keywords: Air Pollutants; Air Pollution; Asthma; Hypersensitivity

RESUMO

Introdução: O impacto da poluição atmosférica nas doenças respiratórias, nomeadamente na asma, tem sido objeto de numerosos estudos. A repercussão da poluição na sintomatologia diária dos doentes asmáticos tem sido menos estudada. Pretendemos estudar a relação entre a intensidade dos sintomas diários de asma e a variação dos níveis de poluição.

Material e Métodos: Foram selecionados doentes com diagnóstico de asma, sendo instruídos para anotar diariamente a intensidade dos seus sintomas respiratórios, expressa numa escala de 0 a 5, nos meses de março e abril de 2018. O *website* da Agência Portuguesa do Ambiente foi consultado e registaram-se os níveis diários de poluentes medidos pelas duas estações locais de monitorização durante o mesmo período. Os dados foram analisados utilizando um modelo causal temporal com a finalidade de relacionar os níveis de poluentes – partículas inaláveis com diâmetro menor que 10 µm, ozono, dióxido de nitrogénio e monóxido de carbono - com a intensidade dos sintomas de asma dos doentes.

Resultados: Dos 135 calendários entregues, 35 foram corretamente preenchidos e devolvidos. A mediana de idades dos doentes foi de 47,0 anos, sendo 18 do sexo feminino. O melhor modelo estatístico obtido identificou o ozono como a 'causa Granger' mais relevante para os sintomas de asma. A qualidade do modelo traduziu-se por um R^2 de 0,92. A correlação entre os valores de ozono e os valores dos sintomas de asma foi mais significativa após cinco dias. Para os outros fatores identificados verificou-se um desfasamento de quatro a cinco dias.

Conclusão: No período e local estudados, os poluentes atmosféricos comportaram-se como fatores de variação da intensidade dos sintomas de asma. O nível de ozono foi o melhor fator preditivo das variações da sintomatologia. Os níveis de partículas inaláveis, com diâmetro menor que 10 µm, de monóxido de carbono e de dióxido de nitrogénio foram identificados como marcadores secundários. O desfasamento temporal entre as variáveis com melhor correlação sugere um possível efeito retardado dos poluentes sobre os sintomas respiratórios.

Palavras-chave: Asma; Hipersensibilidade; Poluentes Atmosféricos; Poluição do Ar

INTRODUCTION

Outdoor air pollution is defined as the change in purity and air quality caused by the emission of chemical or biological substances released naturally or produced by anthropogenic sources.[1]

The contribution of human activities far exceeds natural sources, and several studies have shown that exposure to air pollution, in the short or long term, can have harmful consequences for health.[2-8]

Among the various pollutants present in the atmosphere, carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3) and particles smaller than 10 µm (PM10) are those with greatest evidence for health effects.[9-12] The evidence for a causal relationship of asthma with ambient pollution is still emerging, based on studies that have

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repeatedly shown associations of pollution with various asthma phenotypes and proxy markers, such as emergency room visits, school absenteeism, and steroid dependency.[13-15] In a Lancet Planetary Health publication, Pattanun Achakulwisut *et al*[16] estimated that 4.0 million (95% UI 1.8 – 5.2) new childhood asthma cases could be attributable to NO_2 pollution annually, accounting for 13% of the worldwide incidence. NO_2, mainly emitted by power generation, industrial and traffic sources, is an important constituent of particulate matter and ozone. There is increasing evidence that, independently, NO_2 can increase the symptoms of bronchitis and asthma, as well as facilitate respiratory infections and reduce lung function and growth.[17] Moreover, it may be responsible for premature death and increased morbidity associated with a broad spectrum of cardiovascular and respiratory conditions.[18,19]

Ozone in the lower atmosphere, to which humans are potentially exposed, is one of the major health risks associated with respiratory problems, such as asthma, reduced lung function and respiratory diseases. It is produced when carbon monoxide, methane or other volatile organic compounds (VOCs) are oxidized in the presence of nitrogen oxides (NOx) and sunlight.[20] One study in children reported higher propensity to develop asthma in areas with higher concentrations of ozone,[21] Li X *et al* report that maximal values of exposure measured daily in one or eight hour periods were more consistently associated with asthma exacerbations than 24 hour average exposure during the warm season[22] and Mengmeng Xua *et al* indicated that acute ozone exposure induces mitochondrial dysfunction and NLRP3 inflammasome activation, inducing airway inflammation and bronchial hyperresponsiveness.[23]

PM10 represents a particular health risk because it is able to enter the lungs and the bloodstream. Co-exposure to diesel and aeroallergens has been shown to increase levels of allergen-specific IgE, asthma severity, and bronchial hyperreactivity.[24,25] According to the World Health Organization (WHO), the acceptable daily exposure limit for PM10 is 50 µm/m^3. Annual mean values for PM10 should not exceed 20 µm/m,[3,26] or otherwise else ways the health impact associated with this pollutant could increase.

According to the WHO, some cities in Portugal, such as Albufeira, Almada, Aveiro, Barreiro, Coimbra, Estarreja, Faro, Loures, Marateca, Odivelas, Perafita, Portimão, Santiago do Cacém, Senhora da Hora, Setúbal and Sines are the cities with the highest levels of PM10 (exceeding 20 µm/m^3 annual average).[27]

Some studies demonstrate the ability of air pollutants to affect the course of asthmatic disease in different ways: acting as triggering stimuli; increasing pre-existing inflammation of the airways and/or modifying the response to aeroallergens or substances that act as irritants to the airways.[10,26]

The aim of this study is to study the impact of O_3, NO_2, CO and PM10 variations on intensity of asthma symptoms.

MATERIAL AND METHODS

Geographical area and monitoring stations

The Setúbal municipality occupies an area of 230.33 km^2.[28] The city of Setúbal lies in the eastern zone and accounts roughly for half of this area. The monitoring stations are implanted in the urban area and are separated from each other by a short distance, with Arcos being classified as a 'background' (i.e., not under the direct influence of traffic lanes or any nearby source of pollution) and Quebedo as a 'traffic' station (i.e., located close to high traffic routes allowing the evaluation of the maximum risk of population exposure to car traffic emissions) (Fig. 1).

Population

Among patients observed in the Immunoallergology Department of Setúbal Hospital in January and February 2018, those with asthma diagnosis and living in the city of Setúbal were invited to participate in the study, with their consent.

Patients with other pulmonary or cardiac diseases were excluded, as well as patients with history or clinical signs of respiratory infection during the study period or until 6 weeks before.

Only fully completed inquiries were considered.

Schedule

A calendar of March and April 2018 was given to each patient, and they were instructed to record the intensity of bronchial symptoms (shortness of breath, chest tightness, cough, wheezing) in each day, expressed on a visual analogue scale, graded 0 to 5: 0 - "no symptoms", 1 - "very few symptoms", 2 - "slight symptoms", 3 - "moderate symptoms", 4 - "severe symptoms", 5 - "unbearable symptoms".

In the case of children, the calendar was filled by their legal representative(s).

Pollution indices

The website of the Portuguese Environment Agency (APA) was consulted in order to extract data on the daily levels of pollutants measured by two monitoring stations, one 'background' and one 'traffic', from the same region and in the same period of time (March and April of 2018). The available data was the daily maximum values of O_3 at the 'background' station, the daily maximum values of NO_2 and CO at both stations, and the average daily PM10 in both stations.

Statistical treatment of data

Possible causal relationships between levels of pollutants and asthma symptomatology were analyzed, using an autoregressive time series model based on the concept of 'Granger causality', that provides a probabilistic approach for determining whether one time series is useful in forecasting another.

The scores recorded by the patients in each day were added together in order to obtain a day score. The resultant variable, the Sum of the Scores of Asthma Symptoms (SSAS), served as the dependent variable of our model. As

independent variables the PM10, O_3, NO_2, SO2, CO levels of both stations were used.

For correlation between variables Pearson's coefficient (r) was calculated.

Statistical analysis was performed using SPSS for Windows, version 23.0 [29].

The study was authorized by the Ethics Committee for Health of the Setúbal Hospital.

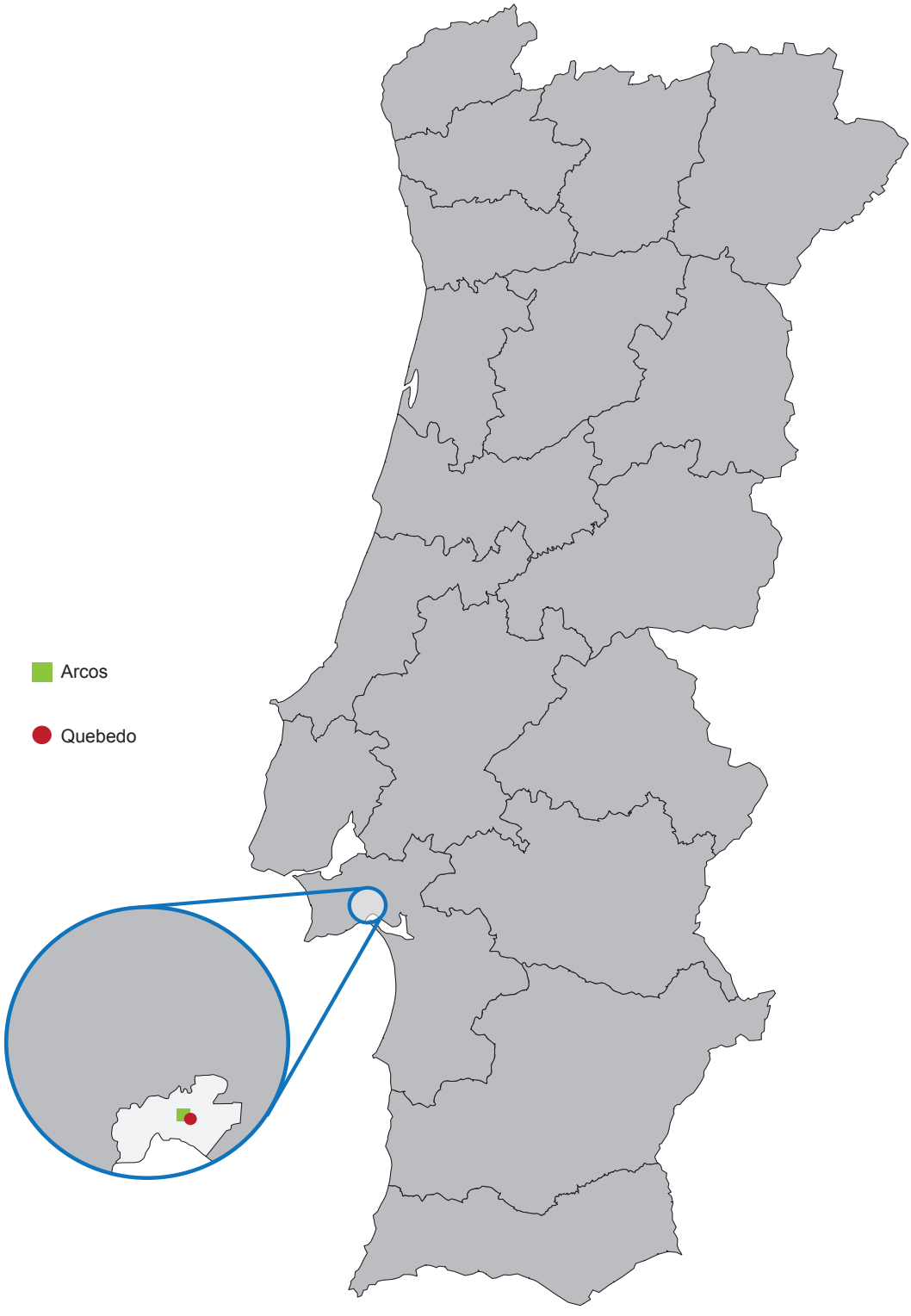

Figure 1 – Map of Portugal with the city of Setubal signposted on the right. On the left, the city of Setúbal, in white, with monitoring stations: green mark for Arcos and red mark for Quebedo.

Map of Portugal obtained in the site of Judicial Court of the Council of Setúbal. [accessed 2019 Aug 2]. Available from: https://comarcas.tribunais.org.pt/comarcas/apresentacao_mp.php?com=setubal.

Map of monitoring stations in the city of Setúbal obtained in the site of Lisbon and Tagus Valley Regional Coordination and Development Commission. [accessed 2019 Aug 2]. Available from: http://www.ccdr-lvt.pt/pt/avaliacao-da-qualidade-do-ar-na-rlvt/8085.htm.

Both maps were remade in vectorial format, using the above mentioned sources, by Acta Médica Portuguesa.

RESULTS

Of the 135 calendars delivered, 35 were correctly filled out and returned. The median age of patients was 47.0 years, ranging from 7 to 81 years, 18 being females (51.4%). Nine patients were younger than 18 years.

In the model, the O_3 measured in the 'background' station appears as the main impact factor in asthma symptoms, with a level of significance lower than 0.05 and a more significant correlation in Lag 5.

The model identified as factors of lower impact the CO (traffic station), NO_2 (background station) and PM10 (traffic station) with more significant correlations in Lag 5, 4 and 4 respectively. Fig. 2 shows the respective impact diagram.

Fig. 3 demonstrates the time evolution of the series studied expressed in Z scores, that is, each value corresponding to its distance from the mean in terms of standard deviation.

The R^2 of the model was 0.92 and the root mean square error was 0.05. Fig. 4 represents the expected and observed values of SSAS.

Considering the values from the two stations the Pearson's r for each pollutant were: NO_2 0.88, CO 0.65 and PM10 0.87.

The mean value of NO_2 was higher in the 'traffic' station; the values of CO and PM10 were similar in the two stations (Fig. 5). The averages of the variables included in the model were: SSAS 37.9 ± 7.7; O_3 97.3 µg/m^3 ± 8.9; NO_2 26.9 µg/m^3 ± 15.1; CO 0.23 mg/m^3 ± 0.07; PM10 19.7 µg/m^3 ± 7.9.

During the period studied every day had an air quality index classified as 'good', according to the Portuguese Environment Agency.

DISCUSSION

Ozone appeared as the main predictor of asthma symptoms in our model, with the most significant correlation between O_3 values and asthma symptoms after five days (Lag 5). For the other identified factors (PM10, CO, NO_2) there is a lag of four to five days (Lag 4 and 5). The late effect of pollutants on respiratory symptoms has already been described in the literature, and Bakonyi *et al*[19] reported a relationship of O_3 with respiratory diseases, which was only significant when the 3-day moving average of O_3 was used.

The model we present demonstrated good quality, with 92% of the variation of asthma symptoms explained by the variations of the identified factors (R^2 = 0.92) and a root mean square error, that is, a percentage difference between expected and observed values for the asthma symptoms of only 5%.

By using a statistical model based on the 'Granger causes' we are really looking for a relationship in which the values of a variable correlate with values of the target variable at a later time. In fact, this relationship is necessary but not enough to affirm a variable as the cause of another.

In fact, the proinflammatory effect of diesel exhaust particles on the respiratory epithelium level, which includes the release of cytokines involving Th17 cell differentiation observed in severe asthma, is documented in the literature.[32] Epidemiological studies in humans and animals suggest that atmospheric pollutants are involved in the pathogenesis of respiratory allergic diseases, both in terms of their development and exacerbations.[25]

Bakonyi *et al*[19] demonstrated a positive association between particulate pollutants, NO_2 and O_3, and respiratory diseases in children, by measuring daily levels of PM10, NO_2 and O_3 and assessing their association with daily am-

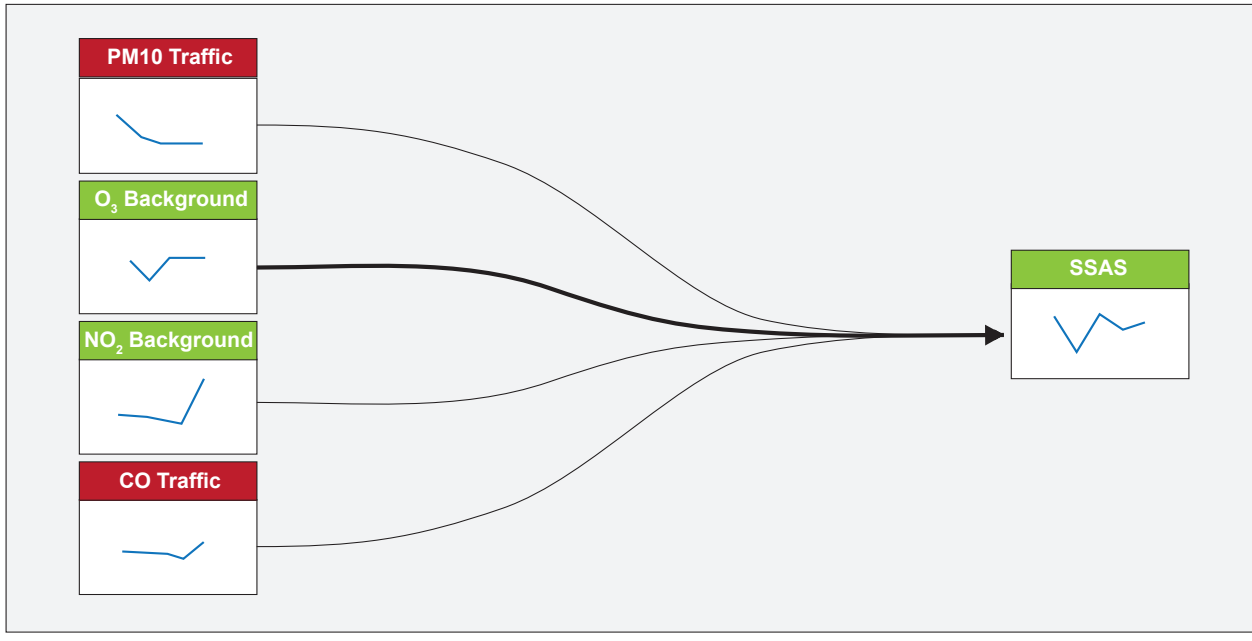

Figure 2 – Impact diagram of pollutants on the sum of the scores of asthma symptoms (SSAS). The thickness of the connection lines is proportional to the size of the impact. O_3 shows the highest impact.

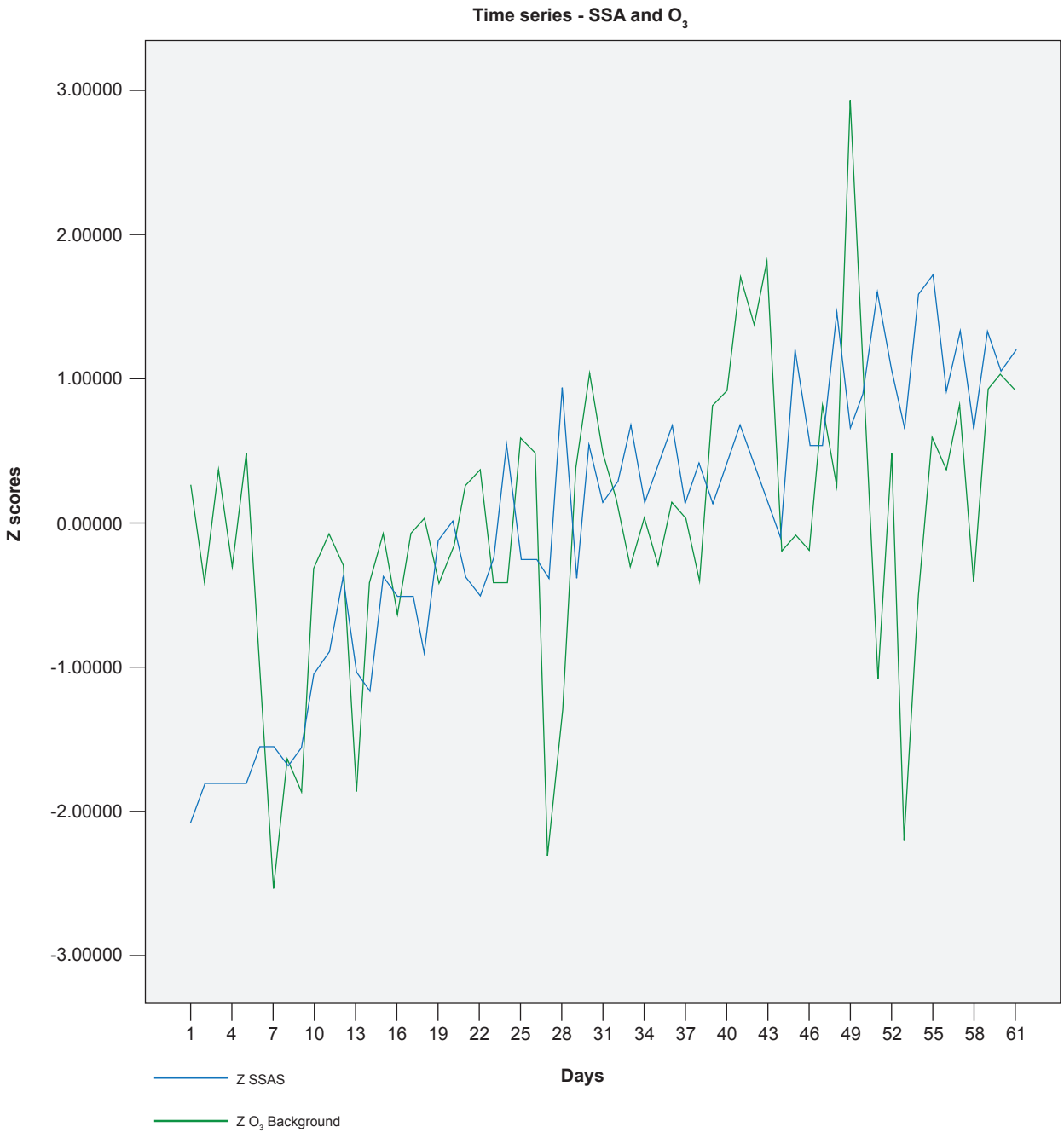

Figure 3 – Evolution lines of the sum of the scores of Asthma symptoms (in blue) and ozone (in green), values expressed as z scores. It is possible to observe an almost parallel variation of z scores of SSAS and O_3.

bulatory visits for respiratory disease (ICD-9 between 460 and 519). Although Bakonyi *et al* did not specifically correlate asthmatic disease with the levels of air pollutants, they were able to verify that the levels of pollution interfered in the respiratory morbidity of the child population of the city of Curitiba.

As for Portugal, only a few articles have focused on the impact of pollution on asthma and none of them concerns our region, Setúbal. Besides, these studies disclosed associations between pollutant levels and emergency room visits for acute effects,[30] or with causes of death by region for long term outcomes.[31] Our study presents an original approach, allowing an insight into the effects of low-level pollutant exposure on chronic mild symptoms evaluating the daily symptom variation rather than severe asthma events.

The months of March and April were selected to avoid the seasonality of respiratory infections, as well as high levels of atmospheric pollens, thus reducing the effect of confounding factors.

By aiming to obtain a daily symptom index for a two-month period we chose a very simple way of recording consisting of filling a calendar with a global assessment of symptoms according to a visual analogue scale, with the aim of minimizing dropouts. Even so, the study demanded

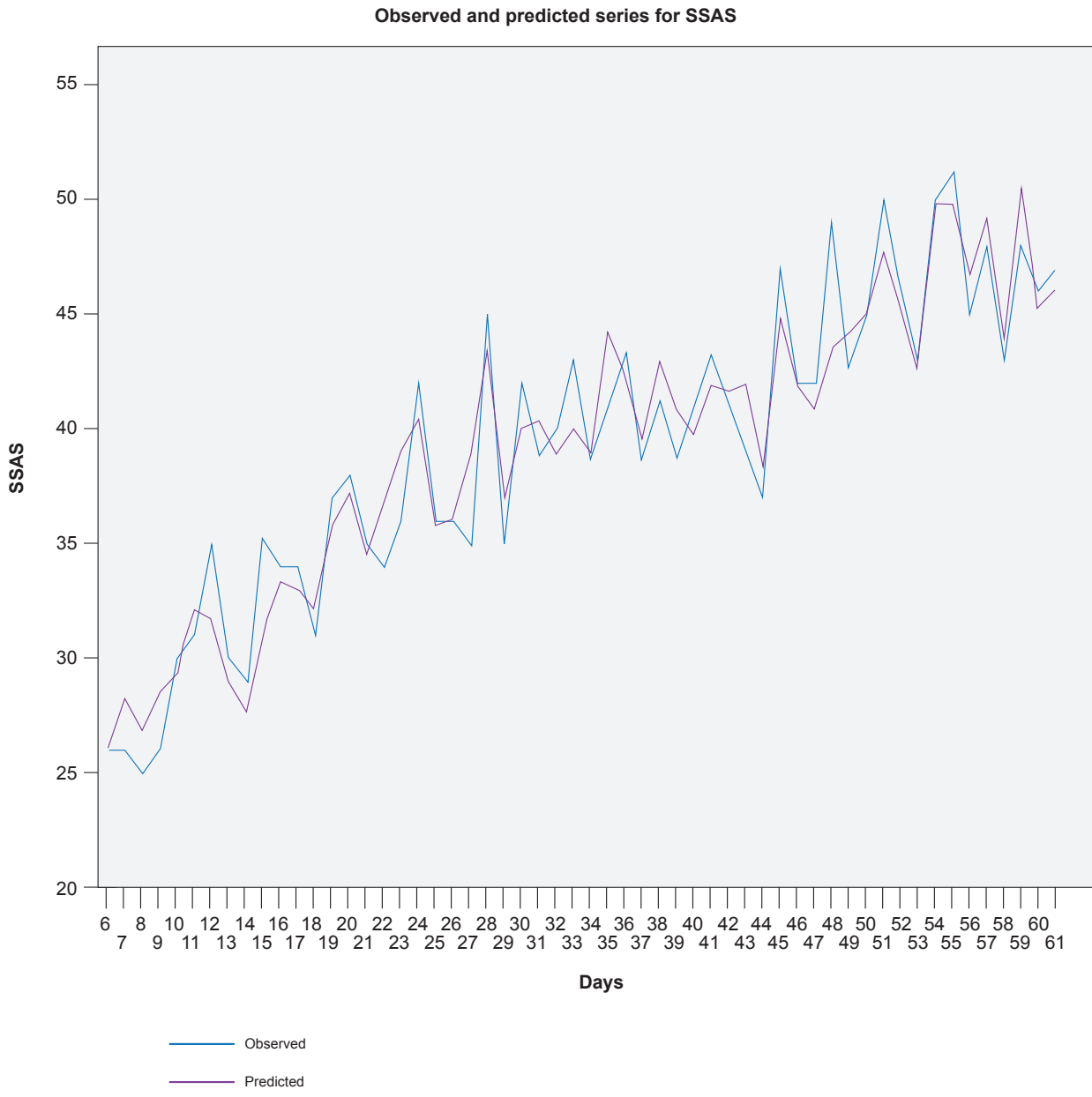

Figure 4 – Evolution of the observed and expected series concerning the sum of the scores of asthma symptoms (SSAS). It is possible to observe the overlap between the two lines, reflecting the good model quality.

a high level of patient collaboration which reflected on the small sample size. This implied some limitations with the analysis, with other potential, demographic, socioeconomic or clinical factors not being considered. However, it was compensated to some extent by the fact that all the accepted inquiries were fully completed.

The pollutants that were analyzed were necessarily restricted to those provided by the APA website, and it was not possible to include others mentioned in the literature that are implicated in respiratory symptoms. This also was a limitation of our study.

It should be noted that our results suggest an association between pollution and the daily fluctuations of asthma symptoms, which do not necessarily correspond to significant exacerbations of the disease. We also underline that this relationship was identified at a time in which the air quality index was always classified as 'good', suggesting that even acceptable levels of pollutants may have some effect on asthma symptoms.

CONCLUSION

All the air pollutants studied behaved as factors of variation of the intensity of asthma symptoms in the place and period that were examined. During this period the O_3 level was the best predictive factor of symptom variability. Levels of PM10, CO and NO_2 were identified as secondary markers. We also verified that the time lag between the variables with the best correlation suggests there could be a delayed effect of the pollutants on the respiratory symptoms, and even levels of pollution which are considered acceptable

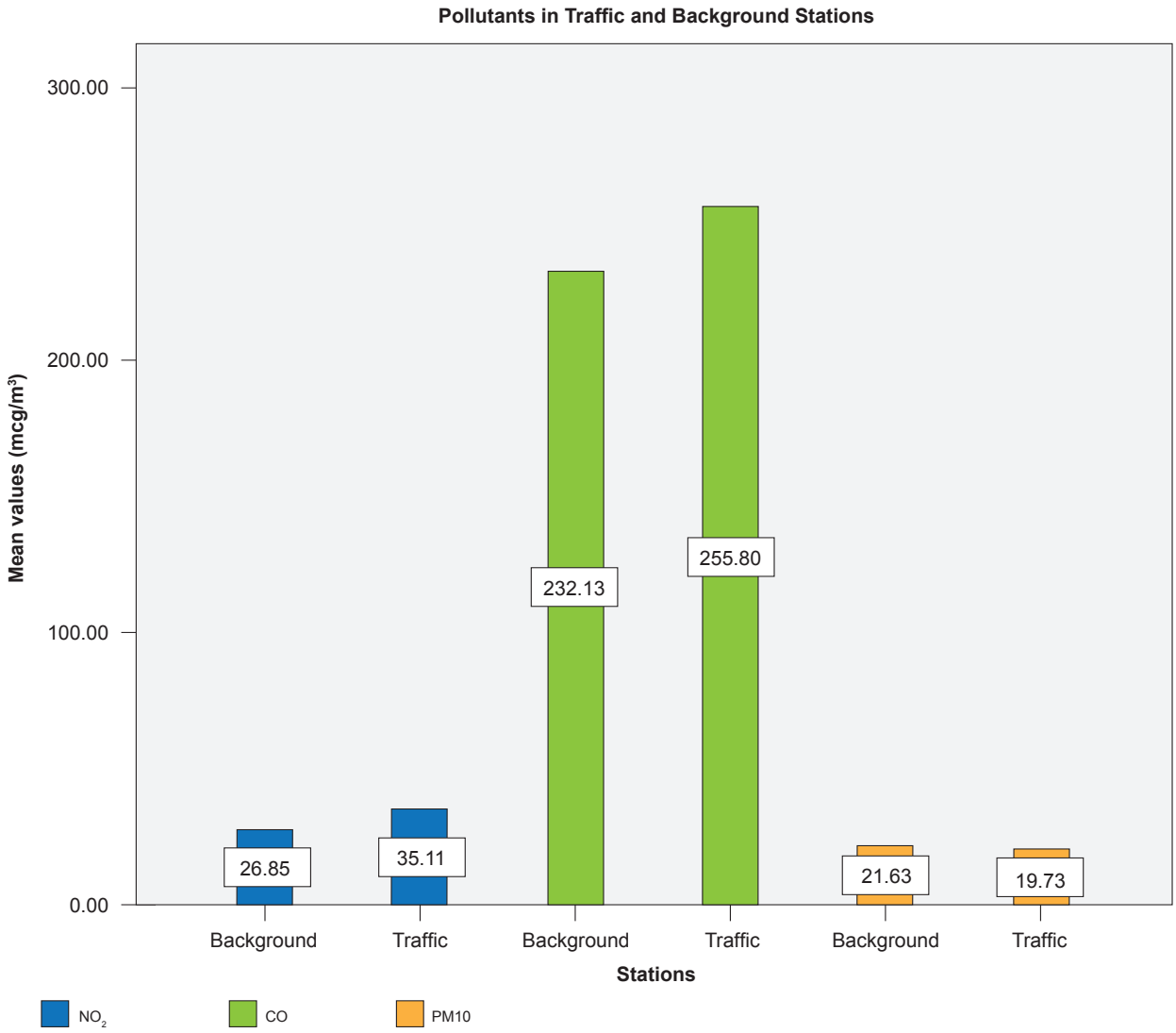

Figure 5 – Average of pollutant levels recorded at the two monitoring stations

may have repercussions on asthma symptoms.

A better understanding of the pollutant-related effects on asthma at a global level is crucial in order to implement policy initiatives aimed at addressing the improvement of asthma outcomes.

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AUTHORS CONTRIBUTION

SF, BKC: Data aquisition, conception of the paper, draft and critical review.

MM: Critical review, approval of the vinal version of the manuscritp.

LC: Data aquisition, analysis of the leaflets.

ET: Statistic analysis, draft and critical review of the paper.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

None of the authors has conflict of interests to declare.

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Nationwide Access to Endovascular Treatment for Acute Ischemic Stroke in Portugal

Acesso a Tratamento Endovascular para Acidente Vascular Cerebral Isquémico em Portugal

ARTIGO ORIGINAL

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ABSTRACT

Introduction: Since the publication of endovascular treatment trials and European Stroke Guidelines, Portugal has re-organized stroke healthcare. The nine centers performing endovascular treatment are not equally distributed within the country, which may lead to differential access to endovascular treatment. Our main aim was to perform a descriptive analysis of the main treatment metrics regarding endovascular treatment in mainland Portugal and its administrative districts.

Material and Methods: A retrospective national multicentric cohort study was conducted, including all ischemic stroke patients treated with endovascular treatment in mainland Portugal over two years (July 2015 to June 2017). All endovascular treatment centers contributed to an anonymized database. Demographic, stroke-related and procedure-related variables were collected. Crude endovascular treatment rates were calculated per 100 000 inhabitants for mainland Portugal, and each district and endovascular treatment standardized ratios (indirect age-sex standardization) were also calculated. Patient time metrics were computed as the median time between stroke onset, first-door, and puncture.

Results: A total of 1625 endovascular treatment procedures were registered. The endovascular treatment rate was 8.27/100 000 inhabitants/year. We found regional heterogeneity in endovascular treatment rates (1.58 to 16.53/100 000/year), with higher rates in districts closer to endovascular treatment centers. When analyzed by district, the median time from stroke onset to puncture ranged from 212 to 432 minutes, reflecting regional heterogeneity.

Conclusion: The overall national rate of EVT in the first two years after the organization of EVT-capable centers is one of the highest

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among European countries, however, significant regional disparities were documented. Moreover, stroke-onset-to-first-door times and in-hospital procedural times in the EVT centers were comparable to those reported in the randomized controlled trials performed in high-volume tertiary hospitals.

Keywords: Endovascular Procedures; Ischemic Stroke; Mechanical Thrombolysis; Portugal; Thrombectomy

RESUMO

Introdução: A aprovação do tratamento endovascular para o acidente vascular cerebral isquémico obrigou à reorganização dos cuidados de saúde em Portugal. Os nove centros que realizam tratamento endovascular não estão distribuídos equitativamente pelo território, o que poderá causar acesso diferencial a tratamento. O principal objetivo deste estudo é realizar uma análise descritiva da frequência e métricas temporais do tratamento endovascular em Portugal continental e seus distritos.

Material e Métodos: Estudo de coorte nacional multicêntrico, incluindo todos os doentes com acidente vascular cerebral isquémico submetidos a tratamento endovascular em Portugal continental durante um período de dois anos (julho 2015 a junho 2017). Foram colhidos dados demográficos, relacionados com o acidente vascular cerebral e variáveis do procedimento. Taxas de tratamento endovascular brutas e ajustadas (ajuste indireto a idade e sexo) foram calculadas por 100 000 habitantes/ano para Portugal continental e cada distrito. Métricas de procedimento como tempo entre instalação, primeira porta e punção foram também analisadas.

Resultados: Foram registados 1625 tratamentos endovasculares, indicando uma taxa bruta nacional de tratamento endovascular de 8,27/100 000 habitantes/ano. As taxas de tratamento endovascular entre distritos variaram entre 1,58 e 16,53/100 000/ano, com taxas mais elevadas nos distritos próximos a hospitais com tratamento endovascular. O tempo entre sintomas e punção femural entre distritos variou entre 212 e 432 minutos.

Conclusão: Portugal continental apresenta uma taxa nacional de tratamento endovascular elevada, apresentando, contudo, assimetrias regionais no acesso. As métricas temporais foram comparáveis com as observadas nos ensaios clínicos piloto.

Palavras-chave: Acidente Vascular Cerebral Isquémico; Portugal; Procedimentos Endovasculares; Trombólise Mecânica; Trombectomia

INTRODUCTION

Endovascular treatment (EVT) is the state-of-the-art treatment for acute ischemic stroke due to large vessel occlusion. It has been estimated that 7% - 13% of acute ischemic stroke patients admitted are eligible for EVT.[1,2] This number could be as high as 26% when using advanced imaging techniques to select patients.[2,3]

Since the publication of the EVT trials,[4-8] the EVT rate has increased worldwide. However, this growth varies between and within countries. In 2016, Portugal had one of the highest rates of patients with ischemic stroke treated with EVT (4.6%) among European countries, according to the ESO/ESMINT/EAN/SAFE expert survey.[9] Nevertheless, the distribution of EVT centers in Portugal reflects the population density and existing healthcare resources, namely the network of stroke centers. This distribution may lead to unequal EVT access in more remote areas. However, published data regarding regional disparities within countries is scarce.[10-13]

The network of primary stroke centers and EVT stroke centers in Portugal is organized so that patients initially admitted to a primary stroke center may end up being transferred to an EVT center. Patients who need to be transferred between hospitals for EVT experience longer time from symptom onset to treatment, resulting in worse outcomes in routine clinical practice, even in a country where between-center distances are short.[14] Nevertheless, patients transferred to high-volume centers were found to have reduced mortality compared to patients directly admitted to low-volume centers. Thus, the benefit of treatment in high-volume institutions may outweigh the detrimental effect of hospital transfer.[15]

Our main aim was to perform a descriptive analysis of the frequency of EVT in mainland Portugal. We quantified the crude and adjusted rates for all EVTs performed nationally and by administrative districts. As a secondary objective, we described and analyzed differences in time-to-treatment metrics.

MATERIAL AND METHODS

Setting

Mainland Portugal has a surface area of 89 015 km^2, a resident population of 9 792 797 (2017),[16] and a national road network of over 17 000 km. Most of the population lives in areas where road transportation to EVT centers takes under two hours. The stroke code has been gradually implemented in most public hospitals since 2004, while EVT was introduced nationwide during the first semester of 2015. Thus, the study period starts from 2015 to reflect the initial organization of centers capable of performing EVT after the publication of the European guidelines.[17] During the study period, nine stroke centers performed all mainland EVT: four in the North, one in the Center, and four in the Lisbon metropolitan area (Fig. 1). Patients admitted to a primary stroke center would undergo thrombolysis if indicated and then, after contact with the on-call EVT center, would be transferred for further treatment.

Data sources

The analyzed data were obtained from the Portuguese EVT registry (EVT-PT) – a centralized anonymized database specially designed for the present study. The database was built from prospective local registries of consecutive EVT procedures. Data was collected from the registries, collated, and curated from April 2018 to April 2019 (database lock date).

Study design and population

We conducted a retrospective national multicenter cohort study, including all patients treated with EVT for acute ischemic stroke in mainland Portugal between July 1st, 2015, and June 30th, 2017. During the study period, each treating physician determined the indication for EVT procedure and

largely followed the European guidelines published until July 2017.[17] The study was coordinated by the Portuguese Stroke Society (SPAVC), which invited all EVT centers to participate. The study was approved by local Ethics Committees of the different institutions and the Portuguese Data Protection Authority.

Patient characteristics

We analyzed demographic (age, sex, residential postal code), stroke-related (time of stroke onset, time of admission at the first center, time of thrombolytic administration), and procedure-related (time of admission at the second center, if applicable, time of groin puncture) variables. The time of stroke onset was defined as the last time the patient was seen well. Admission times and demographic variables were gathered from administrative records. Treatment times were obtained from medical records and timestamps in digital angiography images. In-hospital stroke patients were defined as patients who were already hospitalized at symptom onset, regardless of the reason for their hospital admission. The patients' residential postal code was based on their address at the time of stroke. This data was used to map all patients into their corresponding district. The division into districts was based on their limits as defined by article 291 of the Portuguese Constitution, which subdivides mainland Portugal into 18 administrative areas called districts (Fig. 1A).

Statistical analysis

We assessed data integrity and missing information to ensure the quality of the data. Patients residing outside mainland Portugal or patients without a retrievable postal code were excluded from the study, as this data was imperative for rate calculations. In-hospital stroke code activations (which allowed for a chain of care that would not be comparable to activations outside the hospitals), and those patients whose stroke onset, admission, or puncture times were unknown were excluded from time calculations.

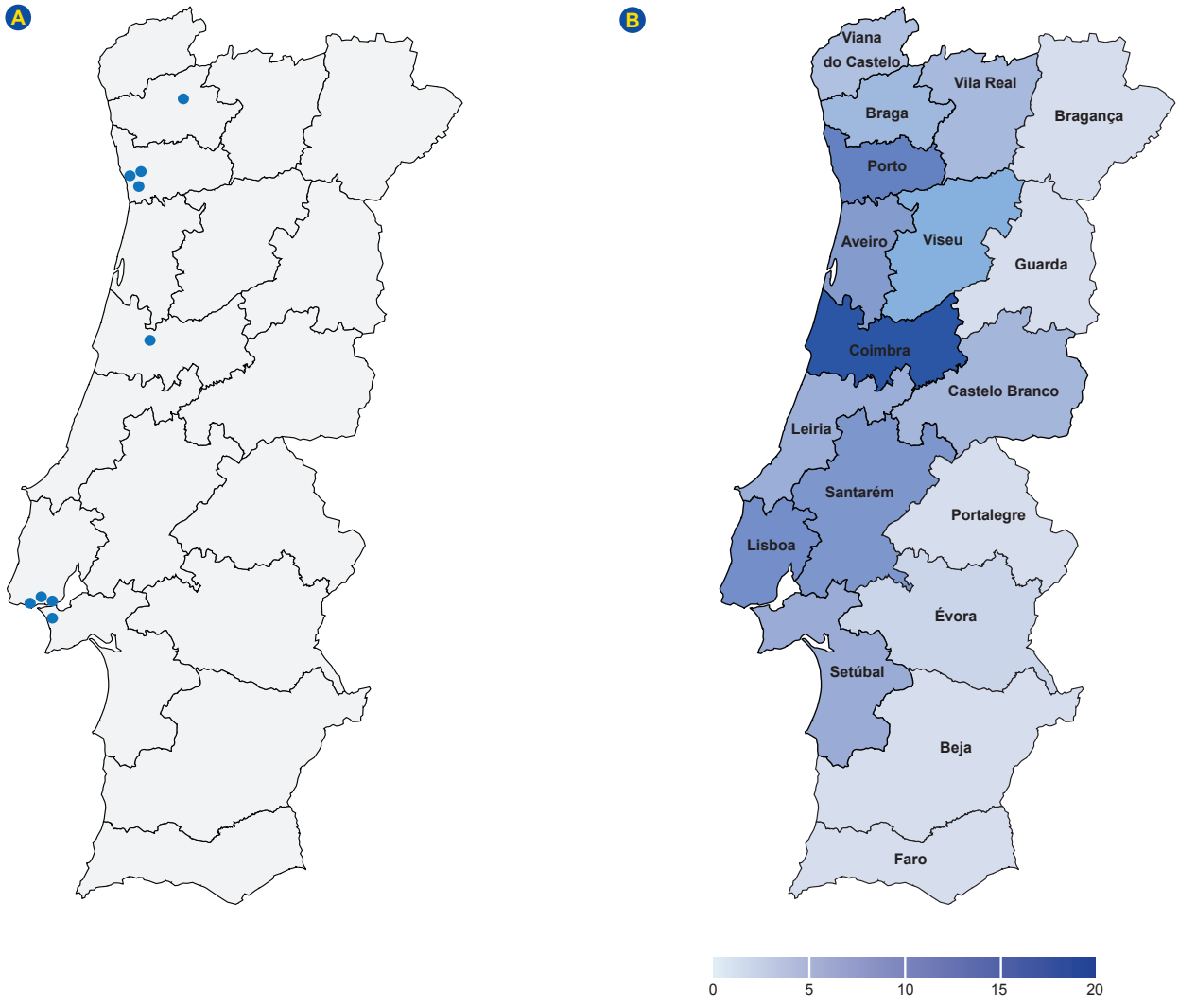

Figure 1 – (A) Portugal map depicting the location of all comprehensive stroke centers (blue dots); (B) EVT rates for the study period per district (scale represents EVT rates per 100 000 inhabitants/year).

Patient characteristics were summarized according to a variable distribution. Crude EVT rates were calculated per 100 000 inhabitants for mainland Portugal and for each district. Rates were calculated for the whole study period, year one (July 2015 – June 2016) and year two (July 2016 – June 2017). Indirect standardization was carried out using the Portuguese 2016 population as reference.[18] The standardized event (EVT) ratio (SER) was computed as the *ratio* between the numbers of events observed and events expected in each district. The number of events expected for each district was calculated based on the national EVT rates standardized using the Portuguese 2016 population as reference.[18] The SER was used to signal districts with rates larger (SER > 1) or lower (SER < 1) than the overall national EVT rates.

Time metrics were defined in minutes and included the time from onset to first-door, from first-door to puncture, and from onset to puncture. The first-door-to-puncture time was defined as the time between the first admission and the groin puncture, both for patients presented directly to an EVT center and patients that presented first to a primary stroke center. The specific time from arrival at the EVT center to puncture was also calculated both for patients transferred and primary admissions to EVT centers. The data on time to treatment were summarized using their median [interquartile range (IQR)] and computed for the whole period, across years one and two, per district and per transfer status. Statistical comparisons between transferred vs. non-transferred patients, year one *versus* year two, and in-hospital strokes vs. outpatient strokes were calculated using the Wilcoxon rank-sum test. Geographical differences were represented using color-graded maps generated using Highmaps®. All calculations used IBM SPSS Statistics® 25.0.

RESULTS

Geographical distribution of EVT rates

During the study period, 1640 EVTs were performed. Fifteen patients were excluded due to living outside

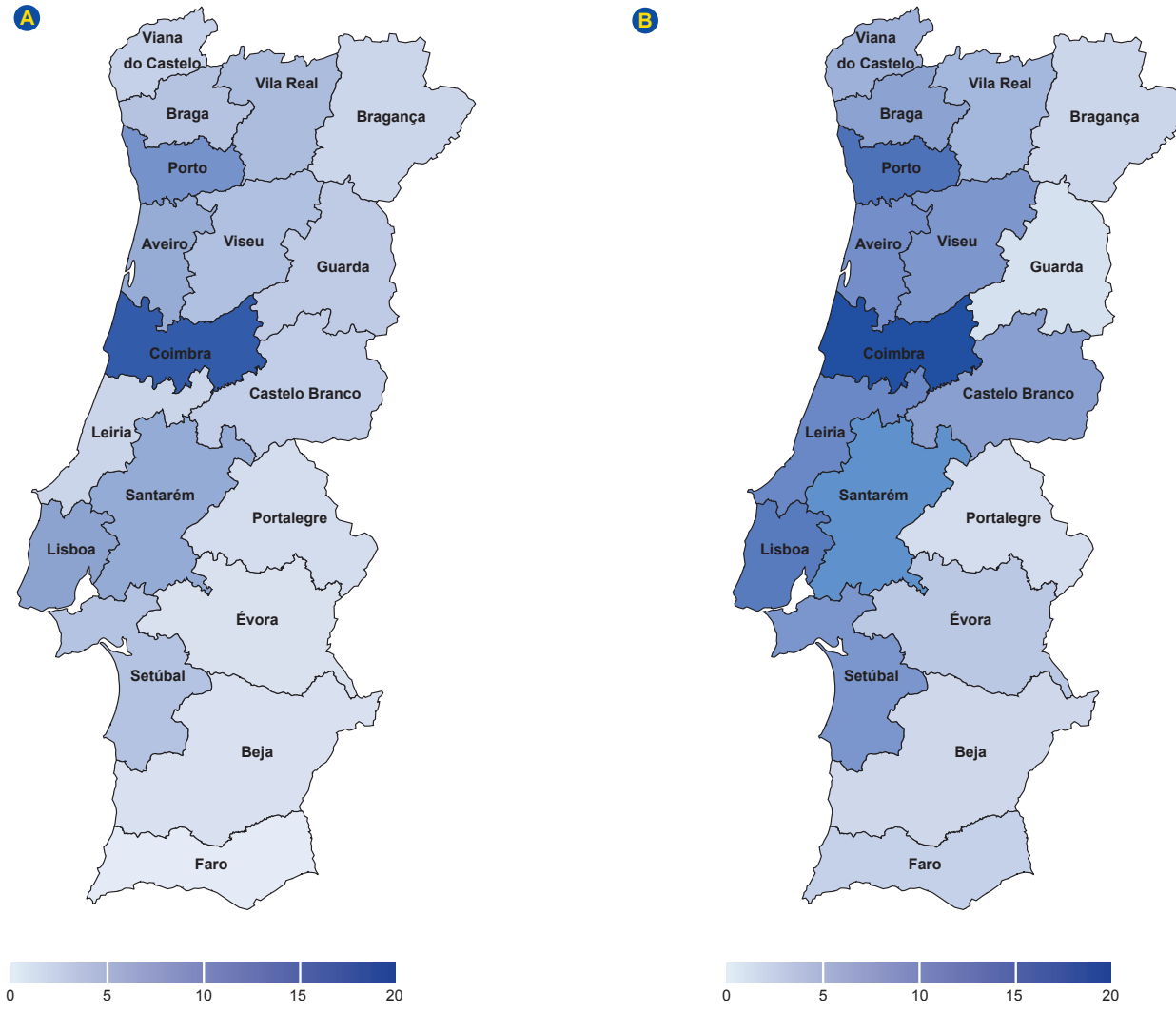

Figure 2 – (A) EVT rates in the first year, per district; (B) EVT rates in the second year, per district (scales represent EVT rates per 100 000 inhabitants for each year).

mainland Portugal (13 from other countries and two from Azores/Madeira), leading to a final inclusion of 1625 EVT patients. The median age of patients was 75 years (IQR 64 - 81) and 54.9% (n = 892) were female. Patients who were 80 years old or older accounted for 32.1% of EVTs (n = 521; 28.2% in year one; 34.5% in year two).

The study period's EVT rate was 8.27/100 000 inhabitants/year, increasing from year one (6.41/100 000 inhabitants) to year two (10.13/100 000 inhabitants per year) in almost all districts (Fig. 2). However, EVT rates were markedly heterogeneous between regions (from 1.58/100 000/year to 16.53/100 000/year), being higher in districts closer to the EVT centers, where EVT is performed (Fig. 1B). This heterogeneity remained after applying the indirect age-standardized method, using the Portuguese 2016 population as the standard, with an SER ranging between 0.14 and 1.44 during the study period [Appendix 1, Fig. 1A (Appendix_01: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15031/Appendix_01.pdf)]. The SER also increased from year one to year two in almost all districts [Appendix 1, Figs. 1B, 1C (Appendix_01: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15031/Appendix_01.pdf)].

Time metrics

For this analysis, in-hospital stroke code activations (n = 83; 5.1%) were excluded, and a total of 1542 EVT procedures performed during the study period (including patients admitted directly to an EVT center and patients transferred from a primary stroke center) was considered. The median stroke-onset-to-first-door time was 87 minutes (IQR 60-142), the median first-door-to-puncture time was 156 minutes (IQR 107 - 232), and the median stroke-onset-to--puncture time was 272 minutes (IQR 205 - 355) (Table 1). During the study period, the number of patients transferred between centers increased from year one (49.8%, n = 299) to year two (60.4%, n = 569) (Table 1).

When analyzing the data by district, the median time from stroke onset to first door ranged between 44 and 230 minutes, the median time from first-door to puncture between 114 and 312 minutes, and the median time from stroke onset to puncture between 212 and 432 minutes. Fig. 3 shows the differences between year one and two for door--to-puncture times by district. Regarding the evolution of national time-to-treatment metrics from year one to year two, there was a statistically significant increase in first-door-to--puncture time (147 *vs* 159 minutes, $p = 0.044$), while the time from the EVT center door to puncture decreased (78 *vs* 70 minutes, $p = 0.004$); the onset-to-first-door (86 *vs* 87, $p = 0.77$) and onset-to-puncture times (271 *vs* 273, $p = 0.47$) did not vary with time. Appendix 2 (Appendix_02: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15031/Appendix_02.pdf) shows data comparing patients with in-hospital vs. out-hospital stroke onset. In-hospital stroke patients were younger and had shorter onset-to-puncture times.

DISCUSSION

The study shows that (1) the EVT rate for the two years of the study period was 8.27/100 000 inhabitants/year, (2) the EVT rate increased from the first to the second year,

Table 1 – Median (IQR) times from onset to first door, first door to puncture and onset to puncture. Additional time metrics are presented distinguishing between patients transferred from a primary stroke center and primary admissions to EVT centers (non-transferred). The *p*-value presented represents the statistical significance of the Wilcoxon rank-sum tests comparing transferred with non-transferred patients. A statistically significant difference was assumed for *p*-values < 0.05.

	Total (n = 1542)		**Transferred** (n = 868)		**Non-transferred** (n = 674)		
Study Period	Median [IQR]	missing	Median [IQR]	missing	Median [IQR]	missing	*p*
Onset – 1st door time	87 [60 - 142]	187	83 [56 - 129]	97	95 [64 - 156]	90	< 0.001
1st door – puncture	155 [105 - 230]	54	211 [158 - 271]	40	107 [78 - 140]	14	< 0.001
Onset – puncture	260 [192 - 345]	177	308 [249 - 382]	80	208 [165 - 287]	97	< 0.001
EVT center door - puncture	73 [37 - 115]	50	43 [27 - 77]	36	107 [78 - 140]	14	< 0.001
Year 1	**Total** (n = 600)		**Transferred** (n = 299)		**Non-transferred** (n = 301)		
Onset – 1st door time	87 [60 - 148]	73	83 [55 - 145]	35	90 [63 - 150]	38	0.048
1st door – puncture	147 [94 - 228.5]	36	215 [164 - 279]	23	104 [73 - 140]	13	< 0.001
Onset – puncture	259.5 [180 - 347.5]	68	318 [260 - 390]	24	205 [160 - 289]	44	< 0.001
EVT center door - puncture	78 [43 - 118]	29	52 [29 - 86]	16	104 [73 - 140]	13	< 0.001
Year 2	**Total** (n = 942)		**Transferred** (n = 569)		**Non-transferred** (n = 373)		
Onset – 1st door time	86 [60 - 137.5]	114	83 [58 - 124]	62	95 [65 - 161]	52	< 0.001
1st door – puncture	159 [113 - 232]	18	209 [155 - 267]	17	107 [81 - 140]	1	< 0.001
Onset – puncture	260 [198 - 345]	109	301 [245 - 380]	56	213 [170 - 286]	53	< 0.001
EVT center door - puncture	70 [35 - 112]	21	40 [26 - 73]	20	107 [81.5 - 139.5]	1	< 0.001

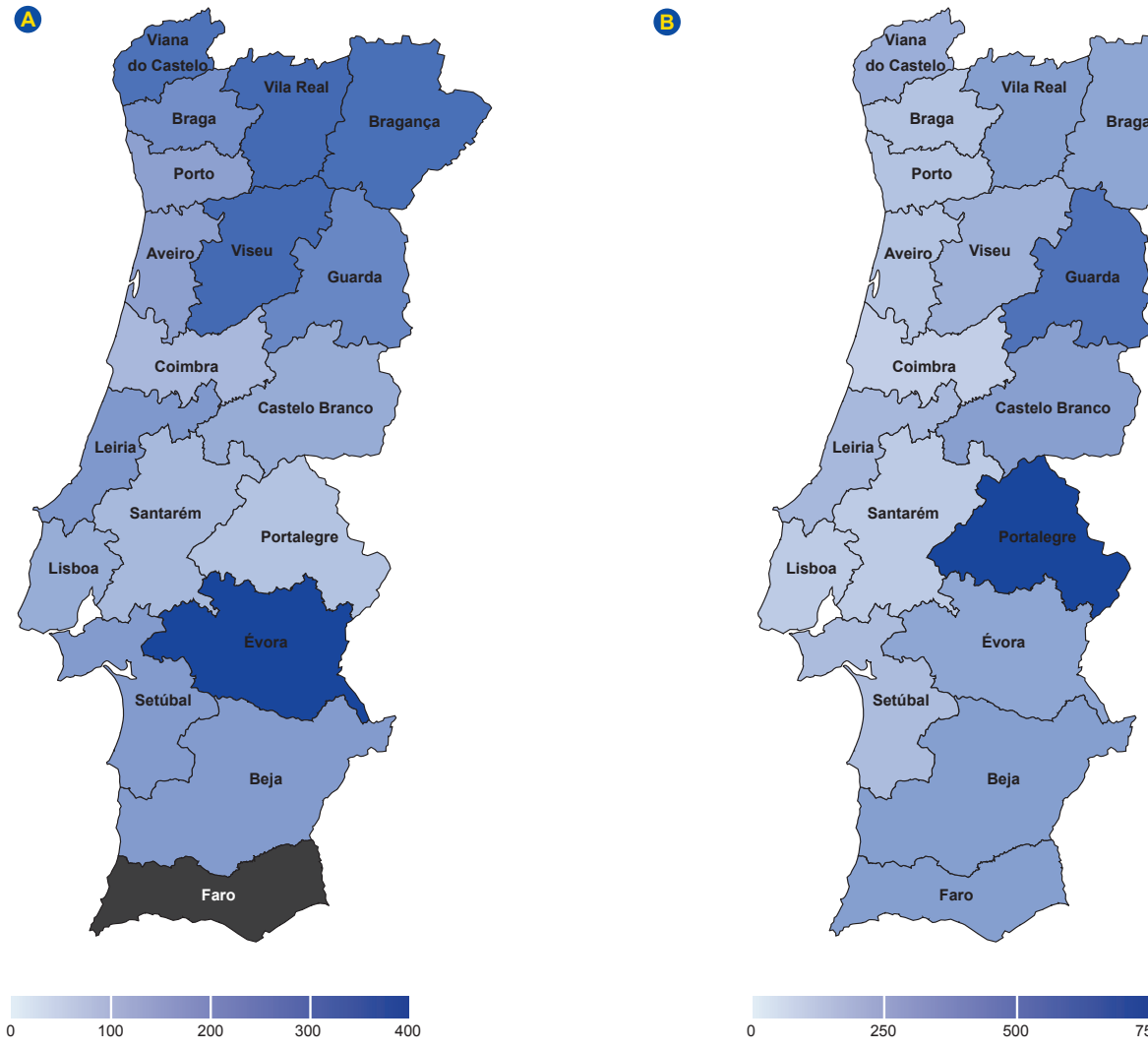

Figure 3 – (A) Median door-to-puncture times per district during the study's first year; (B) Median door-to-puncture times per district during the study's second year. Times are presented in minutes. Black shaded regions did not register any thrombectomy procedures

(3) EVT rates were markedly heterogeneous between regions (from 1.58/100 000/year to 16.53/100 000/year), and (4) there were regional differences in the time from stroke onset to puncture, with similar onset-to-first-door times.

Comparing our results to the available information regarding the number of acute ischemic strokes that could be potential EVT candidates, our national EVT rate matched the expected rate and is among the highest in Europe.[9] Although the rate increase from the first to the second year likely reflects the effects of several factors, the authors highlight the fast learning and optimization processes that occurred after the efforts to implement a new treatment strategy. These efforts were sustained in subsequent years by creating National Reference Centers for Interventional Neuroradiology in Portugal, which led to further optimization of processes involving EVT.

Comparing our time metrics to those reported in EVT trials,[5-8] we found slightly higher median stroke-onset-to-puncture times (272 min *vs* 200 - 269 min in EVT trials) but similar door-to-puncture times for patients directly admitted to EVT centers (107 min *vs* 90 - 113 min in EVT trials). These differences likely reflect distinct time-based indications in a real-world setting and inter-hospital transfer delays. Moreover, the number of patients transferred to EVT centers increased from the first to the second year, which improved in-hospital time metrics, reflecting a continuous increase in EVT access.

We found a marked geographic heterogeneity in EVT rates and time metrics that follows the distribution of healthcare resources, with areas from the south and the inner country having poorer access to EVT than areas closer to EVT centers with more public resources. An improvement of the EVT's organization in Portugal must consider not only the travel time from remote areas to EVT centers but also strategies to optimize diagnosis and treatment decisions in primary stroke centers and improve inter-hospital transport. However, it must still ensure that EVT centers have enough case volume and expertise to provide safe and high-quality

EVT.

Our survey's major strengths are that all Portuguese EVT centers participated in the study and the data were collected from the prospective stroke registries at each center by experienced stroke physicians. Another strength is that our results are adjusted to age and each district's population.

The study limitations include the assumption of the patient's address as the location of stroke occurrence, as some patients may have been at other locations when the stroke occurred. Moreover, regional stroke incidence was not studied because this data was not available for analysis. Despite the relevance of this limitation, considering the geographically small country analyzed (Portugal), and the fact that different regions share a common genetic background, it seems reasonable to expect that the statistical adjustment for the population's size and age would likely limit this potential bias.

It should also be pointed out that medical, social, and economic factors may also contribute to regional heterogeneity in treatment access, and these variables were not available for analysis. Furthermore, regarding time differences, EVT logistic and chain of care protocols are heterogeneous across different centers. Therefore, our results should be interpreted with these limitations in mind. Additional limitations include insufficient time metrics to precisely identify bottlenecks in terms of access to EVT and the absence of outcome measures, such as post-EVT functional status, which were outside of this survey's scope. Moreover, patients might have been treated more than once (different events), but each admission was considered independently.

CONCLUSION

The overall national rate of EVT in the first two years after the organization of EVT-capable centers is one of the highest among European countries. Moreover, stroke-onset-to-first-door times and in-hospital procedural times in the EVT centers were comparable to those reported in the randomized controlled trials performed in high-volume tertiary hospitals. However, there are still significant regional disparities in terms of access and inter-hospital transit times that require improvements.

AUTHORS CONTRIBUTION

MCD, RSR: were responsible for the writing of the first draft of the manuscript.

MCD, RSR, APN, PF, BM, IF, JR, JRL, LC, GS, EM, DG, RF, HM, AC, MC, LMV, PB, TG, AC, MR, PT, LN, TPM, PC, JPF, GM, EA, MLS, ECC, GO, LP, LN, MR, JPM, SC, FG, GB, TB, JR, CF, JP, JMA, JMA, JSF: collected the data.

JVS, RMN, JV, ML, AF: conducted the statistical analyses.

VTC, JSF, JCL: were responsible for the idea and design of the study and critically reviewed the final version of the manuscript.

All authors contributed to the writing of the manuscript and reviewed the final manuscript.

DATA AVAILABILITY STATEMENT

The dataset generated for this study can be made available by the corresponding author after reasonable request and for research purposes.

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

Patients were not directly studied, and their informed consent was not deemed necessary because the data collected was retrospective and immediately anonymized.

COMPETING INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Inibidores da PARP: Do Mecanismo de Ação à Prática Clínica

PARP Inhibitors: From the Mechanism of Action to Clinical Practice

ARTIGO DE REVISÃO

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RESUMO

A reparação dos danos que ocorrem na molécula de ADN é fundamental para manter a integridade do genoma e a viabilidade celular. Défices nos mecanismos de reparação desta molécula cursam com um aumento do risco para instabilidade genética e contribuem para a transformação neoplásica. As *poly* (*ADP-ribose*) *polymerases* (PARP) são um grupo de enzimas que apresentam um papel chave na sinalização e reparação dos erros no ADN. A inibição da sua atividade é uma estratégia terapêutica que tira partido do mecanismo de letalidade sintética e que pode ser usada no tratamento de tumores com defeitos específicos nas vias de reparação de ADN, nomeadamente em tumores com mutações nos genes supressores tumorais *BRCA1* e *BRCA2*. Existem vários inibidores das PARP (iPARP) já aprovados pela Food and Drug Administration dos Estados Unidos da América e pela Agência Europeia do Medicamento e utilizados no tratamento do cancro da mama, ovário, pâncreas e próstata. No entanto, tal como acontece com outras terapias alvo, a resistência aos iPARP é comum apesar de bem tolerados e amplamente utilizados na prática clínica, e pode desenvolver-se através de vários mecanismos moleculares. Neste artigo, pretendemos realizar uma revisão atualizada sobre os iPARP e o seu principal modo de ação em células tumorais, dando a conhecer os vários mecanismos de resistência que têm sido recentemente revelados, assim como as atuais aplicações clínicas e a toxicidade associada a esta terapia alvo.

Palavras-chave: Genes BRCA1; Genes BRCA2; Inibidores de Poli(ADP-Ribose) Polimerases; Neoplasias

ABSTRACT

Repairing damage and errors that occur in the DNA molecule is essential to maintain the integrity of the genome and cell viability. Deficits in DNA repair mechanisms lead to an increased risk of genetic instability and contribute to neoplastic transformation. Poly (ADP-ribose) polymerases (PARP) are a group of enzymes that play a key role in signalling and repairing DNA errors. The inhibition of its activity is a therapeutic strategy that takes advantage of the mechanism of synthetic lethality and that can be used in the treatment of tumours with specific defects in DNA repair pathways, namely in tumours with mutations in the tumour suppressor genes *BRCA1* and *BRCA2*. There are several PARP inhibitors (iPARP), already approved by the USA Food and Drug Administration and the European Medicines Agency used in the treatment of breast, ovarian, pancreatic and prostate cancer. However, as with other target therapies, despite being well tolerated and widely used in the clinical practice, iPARP resistance is common and can be developed through various molecular mechanisms. In this article, we intend to make an updated review on iPARP and its main role in tumour cells, highlighting the several resistance mechanisms that have been recently revealed, as well as the current clinical applications and toxicity associated with this target therapy.

Keywords: Genes, BRCA1; Genes, BRCA2; Neoplasms; Poly(ADP-ribose) Polymerase Inhibitors

INTRODUÇÃO

O cancro é um problema de saúde pública, tendo-se tornado numa das principais causas de mortalidade prematura nas últimas décadas.[1]

De acordo com os dados disponíveis, e reconhecendo que as armas terapêuticas existentes são limitadas, o desenvolvimento de novas terapias tem sido uma área com um interesse crescente nos últimos anos. O foco tem sido no âmbito das terapias dirigidas que visam matar, seletivamente, as células tumorais.[2]

A letalidade sintética, um conceito que visa proporcionar uma via alternativa aos tratamentos mais convencionais do cancro está, atualmente, a ser amplamente investigado e aplicado na prática clínica. Assume-se que dois genes estão numa relação de letalidade sintética se a presença de mutações em apenas um dos genes for compatível com a viabilidade celular, mas a inativação de ambos provoque a morte da célula.[2-4]

A primeira aplicação clínica deste conceito foi com a utilização dos inibidores da *poly (ADP-ribose) polymerase* (iPARP) no tratamento de tumores com mutações nos genes supressores tumorais *BRCA1* e *BRCA2*, que estão envolvidos no processo de reparação homóloga (HR) dos danos que ocorrem na molécula de ADN.[5,6]

VIAS DE REPARAÇÃO DA SEQUÊNCIA DE ADN

A integridade do ADN está continuamente a ser desafiada por uma variedade de agentes e processos que podem alterar, direta ou indiretamente, a sequência desta molécula. Os danos que surgem no ADN, a sua reparação, ou a ausência dela, são aspetos centrais no aparecimento de mutações que iniciam e promovem a tumorigénese.[4] A instabilidade genética, secundária às alterações na molécula de ADN e do número e/ou estrutura dos cromossomas, está presente na maioria dos tumores sólidos.[7] Dado o seu

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efeito potencialmente devastador, as células evoluíram no sentido de se defenderem dos efeitos deletérios que os danos no ADN provocam, através de várias vias moleculares que, no seu conjunto, se denominam por vias de *DNA Damage Response* (DDR). Estas têm a capacidade de identificar os danos presentes no ADN, promover a paragem do ciclo celular e, por fim, proceder à sua reparação, contribuindo para a manutenção da integridade do genoma.[4,7,8]

Em termos gerais, o *DDR* pode ser dividido em vias distintas mas funcionalmente interligadas, que processam a reparação dos danos existentes, nomeadamente a reparação dos danos de cadeia dupla [*double strand DNA breaks* (DSB)], nas quais se incluem a reparação por HR e a recombinação não-homóloga. Existem ainda vias de reparação dos danos de cadeia simples [*single strand breaks* (SSB)], da qual faz parte o *base excision repair* (BER). Para o funcionamento de cada um destes processos contribuem várias proteínas-chave. As proteínas BRCA1, BRCA2, PALB2, ATM, CHEK1, CHEK2, e RAD51 são intervenientes do processo de HR. Pelo contrário, as enzimas *Poly (ADP-Ribose) Polymerase 1 e 2* (PARP1 e PARP2) são os pilares do processo BER.[7]

MECANISMO DE AÇÃO DAS ENZIMAS PARP

As PARP constituem uma superfamília de proteínas que desempenham um papel crucial como reguladores do processo de identificação e reparação dos SSB da molécula de ADN através da via *BER*. Apresentam ainda um papel chave na reparação dos DSB, ao facilitarem a ativação da reparação por HR e ao contribuírem para a inibição de vias de reparação menos conservadoras, como a via *non-homologous end joining (NHEJ)*. Assim, a ausência das PARP contribui para que o processo de HR seja disfuncional, tornando os processos de reparação do ADN não conservadores como vias dominantes.[9]

A *poly(ADP-ribosyl)ation* (ou *PARylation*) é responsável pela modificação de proteínas após o processo de tradução.[10] Sendo fulcral para a regulação do *DDR*, caracteriza-se como uma reação dependente do ADN que consome *nicotinamide adenine dinucleotide* (NAD^+), com o objetivo de sintetizar cadeias *poly(ADP-ribose)* (PAR) que são posteriormente adicionadas a proteínas aceitadoras, induzindo a remodelação da cromatina para uma conformação passível de ser reparada. Este processo é catalisado pela PARP1 e PARP2, que ligam covalentemente uma unidade de ADP-ribose a aminoácidos da estrutura das proteínas, preferencialmente a glutamato e lisina, usando o NAD^+ como dador de ADP-ribose. Ocorre ainda em proteínas especificas, incluindo na própria PARP, um mecanismo denominado de auto-PARylation, que permite que esta se liberte do ADN e que as proteínas reparadoras sejam recrutadas e restaurem a sequência original do ADN.[4,5,11,12] O processo de formação de cadeias PAR é extremamente rápido, tal como a sua degradação. O seu *turnover* é fundamental para que a reparação do ADN seja eficaz, sendo levado a cabo pelas enzimas *poly(ADP-ribose)-glycohydrolase* (PARG), *ADP-ribose hydrolase* (ARH3) e *O-acyl-ADP-ribose deacylase 1* (OARDH1).[13] Defeitos na hidrólise das cadeias PAR levam a um aumento dos danos no ADN, podendo mesmo ser deletérios para a célula, uma vez que impedem que a PARP1 reconheça os erros e inicie um novo ciclo catalítico.[4,13,14] A PARylation, além de intervir no *DDR*, também regula outros processos, incluindo a transcrição, a apoptose e a mitose.

A PARP1 é a mais abundante e sobre a qual existe um maior conhecimento em relação aos seus componentes estruturais e atividade funcional (Fig.s 1A, 1B). Esta enzima está envolvida em vários processos nucleares, sobretudo nas diferentes vias de reparação do ADN, apresentando um papel-chave na manutenção da integridade do genoma. A função catalítica da enzima é ativada após ligação aos SSB, mediando a formação de cadeias PAR que recrutam proteínas reparadoras desses danos. A PARP1 pode também regular a transcrição através da modulação da estrutura da cromatina, atuar como um coregulador dos fatores de transcrição, alterar os padrões de metilação do ADN, estabilizar a forquilha de replicação do ADN, bem como facilitar o processo de HR, uma vez que o recrutamento da maquinaria desta via é dependente da formação de cadeias PAR.[4,13,14] Assim, esta enzima está envolvida em múltiplos aspetos da resposta molecular aos danos no ADN e é dividida em quatro domínios funcionais (Fig. 1A): um domínio de ligação ao ADN *(DBD),* que é constituído por três resíduos de zinco, fundamentais para a ligação da PARP1 aos danos na molécula de ADN, e um sinal de localização nuclear (*NLS*); um domínio central automodificador, no qual os resíduos de glutamato e lisina servem como aceitadores de unidades de ADP-ribose, permitindo que a PARP1 sofra o processo de PARylation.[14] Este domínio é também constituído por um terminal carboxílico BRCA1 (*BRCT*), que medeia a interação entre proteínas, nomeadamente as que permitem a reparação do ADN[15,16]; um domínio *WGR*, assim designado pela presença de uma região altamente conservada de aminoácidos (*Trp-Gly-Arg*), que permite o contacto com os outros domínios da enzima e com o ADN[17]; e por fim, um domínio catalítico que é composto por dois subdomínios: domínio helical (*HD*) que funciona como um domínio autoinibidor, evitando a ligação do NAD^+ ao local de ligação na PARP1, quando a enzima não está ligada ao ADN e um domínio *ADP-ribosyltransferase (ART),* ao qual se liga o NAD^+.[4,13,14]

Após a indução de erros na molécula de ADN, a PARP1 é rapidamente recrutada, ligando-se ao ADN através do DBD (Fig. 1B). Esta ligação leva a uma alteração da conformação do domínio HD, que perde a capacidade de autoinibição, resultando na ativação da função catalítica da enzima. Posteriormente, através do subdomínio ART, a PARP1 inicia a transferência de unidade de ADP-ribose para proteínas aceitadoras, formando cadeias PAR – *PARylation*. A própria PARP1 adiciona cadeias PAR à sua estrutura – *autoPARylation.* Uma vez que as cadeias PAR apresentam uma carga negativa muito superior à do ADN, as cargas repelem-se e a PARP1 perde a afinidade para a molécula de ADN, permitindo o recrutamento de proteínas reparadores para os locais de dano, reconstituindo assim a

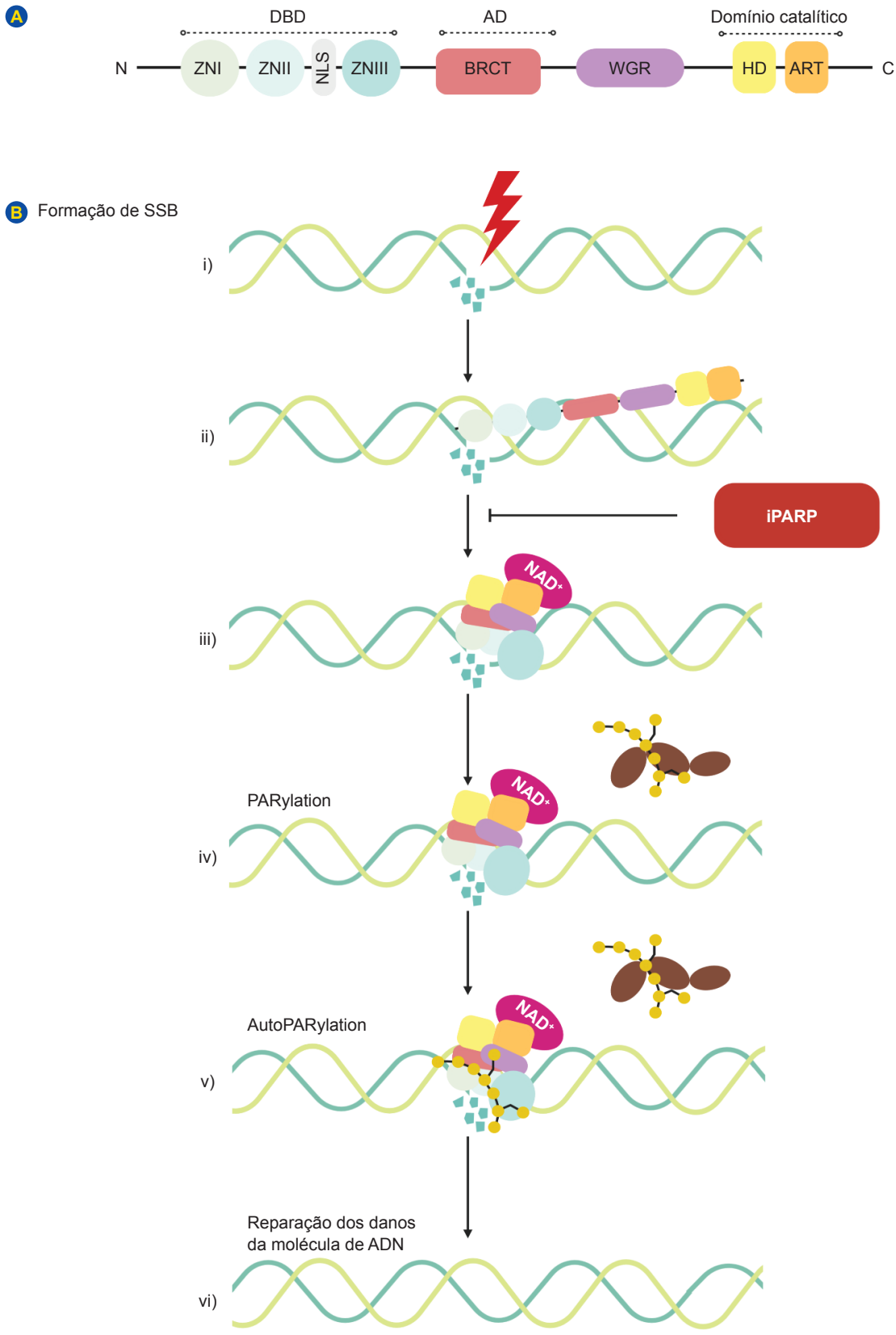

Figura 1 – A: Estrutura da enzima PARP1; B: Ativação da PARP1 secundária à ocorrência de erros na molécula de ADN. (i) Formação de SSB. (ii) Ligação da PARP1 aos SSB. (iii) Ativação da função catalítica da enzima. (iv) Formação de cadeias PAR em proteínas aceitadoras (PARylation) e na PARP1 (autoPARylation) (v). (vi) Recrutamento de proteínas reparadoras dos erros no ADN. Os iPARP competem com o local de ligação do NAD^+ ao domínio catalítico da enzima, evitando a formação de cadeias PAR e aprisionam a PARP1 na molécula de ADN.

sequência original da molécula.[4,13,14]

INIBIDORES DA PARP E LETALIDADE SINTÉTICA

A investigação na área do tratamento do cancro evoluiu no sentido de identificar estratégias de intervenção capazes de aumentar a eficácia dos tratamentos, reduzir a sua toxicidade e aumentar a qualidade de vida dos doentes. Uma destas estratégias passa pela identificação de agentes capazes de se ligar a alvos específicos, nomeadamente a defeitos moleculares presentes em determinadas células tumorais.[18]

A descoberta da família das enzimas PARP, e o conhecimento do seu papel nas vias de reparação do ADN, tornou possível o desenvolvimento de uma nova classe de fármacos anti-neoplásicos – os inibidores da PARP (iPARP).[18] Os iPARP têm como alvo a enzima PARP e foram os primeiros fármacos, clinicamente aprovados, a explorar o mecanismo de letalidade sintética.[4,5]

A letalidade sintética é um conceito genético no qual, a perda funcional de dois genes resulta na morte celular, enquanto que a perda funcional de um deles, isoladamente, é compatível com a viabilidade celular (Fig. 2).[2,7] Assim, os iPARP são uma estratégia terapêutica inovadora no tratamento de tumores com mutações nos genes *BRCA1/2*, ou em tumores *BRCAness*, uma vez que estes apresentam défices na HR (HRD).[19]

O *BRCA1* e *BRCA2* são genes supressores tumorais envolvidos na regulação da transcrição e na reparação dos DSB na molécula de ADN, desempenhando um papel chave na via HR.[6] As células com perda de função nestes genes são incapazes de reparar os erros no ADN, dependendo assim da capacidade que as PARP têm em detetar esses danos e em ativar vias de reparação alternativas. Estas células, ao dependerem das PARP para manter a integridade do genoma, são extremamente vulneráveis aos iPARP.[20,21] Embora a perda funcional de apenas um dos genes seja tolerada (*BRCA* ou *PARP*), a inibição da função das PARP, em células com mutações nos genes *BRCA*, torna-as incapazes de reparar os danos no ADN, causando a acumulação de erros e, em última instância, levando à morte celular (letalidade sintética).[4,22-24]

Os iPARP mimetizam estruturalmente o NAD^+ e interferem com o seu local de ligação ao domínio catalítico das enzimas PARP1 e PARP2. No entanto, apesar desta semelhança no modo de atuação, os efeitos citotóxicos, a sua potência e a capacidade de reter a PARP1 na molécula de ADN difere entre iPARPs.[4,25] Há várias hipóteses que tentam explicar o mecanismo através do qual os iPARP exercem a sua toxicidade nas células tumorais, provocando a sua morte. Apesar de se reconhecer que os mecanismos preferenciais de atuação destes fármacos passam, essencialmente, pela inibição do ciclo catalítico das PARP e aprisionamento da enzima na molécula de ADN (*trapping*), há ainda outros mecanismos que permitem explicar a ação destes fármacos e que continuam a ser investigados.[23,26,27]

O modelo clássico que demonstra a sensibilidade das células tumorais aos iPARP baseia-se no mecanismo de letalidade sintética, que se deve aos seguintes eventos:

1. **Inibição da via BER:** Sob a inibição farmacológica da PARP, não ocorre a reparação dos SSB pelo BER. Isto pode levar à sua conversão em DSB que, em circunstâncias normais, seriam rapidamente reparados pela HR, preservando-se assim a viabilidade celular. No entanto, quando a HR está comprometida, como acontece em células com mutações nos genes *BRCA* ou em tumores *BRCAness*, estes danos não são reparados, havendo uma acumulação de erros que levam à morte celular;[9,28]

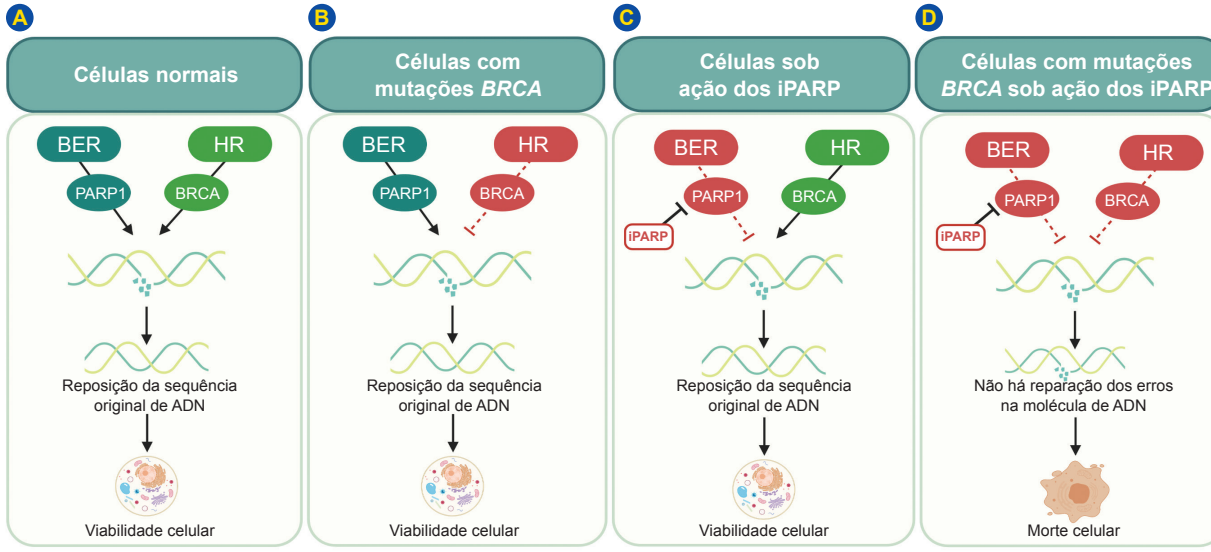

Figura 2 – Morte celular através do mecanismo de letalidade sintética. A: A célula apresenta a via do *base-excision repair* (BER) e da recombinação homóloga (HR) funcionais, mantendo a viabilidade celular. B e C: Através dos iPARP ou de mutações *BRCA,* uma das vias de reparação é inibida. Uma vez que a outra via é funcional, a célula mantem a sua viabilidade. D: Ambas as vias de reparação do ADN estão inibidas e, por isso, os erros no ADN não são reparados, ocorrendo, consequentemente, morte celular.

2. Aprisionamento da PARP1 no ADN: Os iPARP promovem também a morte celular através do aprisionamento ("*trapping*") da PARP1 nos erros no ADN e esta via de atuação pode ser muito mais citotóxica do que a perda da atividade catalítica da enzima.[29,30] Embora o mecanismo exato que explica o aprisionamento da PARP1 no ADN permaneça ainda por esclarecer, existem dois mecanismos que têm sido propostos[29]: a) os iPARP evitam a libertação da PARP1 do ADN através da inibição da auto-PARylation; b) os iPARP ligam-se ao local catalítico da PARP e provocam uma série de alterações na estrutura terciária ou quaternária da enzima que aumentam a sua avidez para o ADN. De ambas as maneiras, os iPARP evitam que a enzima se dissocie do ADN, comprometendo o ciclo catalítico da PARP1 e a reparação dos erros. Igualmente, o aprisionamento da PARP1 na forquilha de replicação pode provocar a sua obstrução e colapso, convertendo os SSB em DSB que, se não forem reparados como acontece em células tumorais com mutações em genes que codificam proteínas chave do processo HR (*BRCA1*, *BRCA2*, *PALB2* ou *RAD51*), serão altamente deletérios para a célula e levarão à sua morte.[9,25,28,31]

3. Alteração do recrutamento do *BRCA1*: A PARP1 é essencial para o recrutamento do *BRCA1* para os danos no ADN. Todavia, existem interações entre o *BRCA1* e outras proteínas que se tornam a via preferencial do seu recrutamento quando a PARP1 é inibida. Se o *BRCA1* apresentar uma mutação, essas interações ficarão também comprometidas e, na presença dos iPARP, nenhuma proteína será recrutada para a reparação do ADN e a célula acabará por morrer. Contudo, este modelo não permite explicar os efeitos dos iPARP em células cujo *BRCA1*, e consequentemente a HR, está ativo e funcional.

4. Ativação do NHEJ: Outro mecanismo proposto para a atividade dos iPARP é baseado no papel que a PARP1 tem em inibir a via do NHEJ. Com a utilização dos iPARP, a via do NHEJ passa a ser uma via alternativa de reparação do ADN e, sendo propensa a erros, cursa com um maior número de mutações, rearranjo de cromossomas e, consequentemente, com a morte celular.[9,28]

5. Dado que as células tumorais com mutações nos genes *BRCA* apresentam uma via HR disfuncional, estas vão depender de vias alternativas para reparar esses erros, nomeadamente do *microhomology-mediated end joining* (MMEJ), que depende das enzimas PARP1 e POLQ (*tranlesion polymerase*). A PARP1 é crucial para recrutar a POLQ para os DSB; assim, um inibidor da POLQ ou da PARP1 irá bloquear a via do MMEJ e matar as células com défices na HR.[26,32]

UTILIZAÇÃO CLÍNICA DOS INIBIDORES DA PARP EM ONCOLOGIA

Inicialmente postulou-se que os iPARP seriam apenas eficazes em tumores com mutações nos genes *BRCA1/2*. Nos estudos clínicos mais recentes verificou-se que também os tumores sem mutações *BRCA1/2* e com HRD bem como tumores sem HRD podem responder a este tratamento, embora a magnitude do seu benefício seja inferior.[33,34] Assim, com base nestas observações, o número de doentes que pode, teoricamente, beneficiar dos iPARP foi amplamente alargado.

Os iPARP podem ser utilizados em monoterapia ou em associação com outros fármacos, nomeadamente em combinação com quimioterapia, imunoterapia e outras terapias alvo que limitam a reparação dos danos no ADN.[28,35] A associação de fármacos apresenta um efeito sinérgico e vantajoso, na medida em que permite superar a resistência aos iPARP e aumentar a eficácia destes fármacos.[35,36] Neste momento existem pelo menos quatro iPARPs já aprovados pela Food and Drug Administration (FDA) para serem utilizados no tratamento de certas neoplasias:

Olaparib

O olaparib, inicialmente aprovado pela FDA apenas no tratamento de doentes com cancro do ovário avançado, com mutações na linha germinativa *BRCA1/2* (gBRCAm), submetidos a três ou mais esquemas de quimioterapia, foi o primeiro iPARP a entrar na prática clínica. Alguns anos mais tarde, o fármaco foi aprovado pela FDA e pela Agência Europeia do Medicamento (EMA) para o tratamento de manutenção de tumores do ovário avançados, das trompas ou peritoneais primários, com resposta completa ou parcial aos platinos[37,38] e também para o tratamento de manutenção em doentes com cancro do ovário, das trompas ou do peritoneu avançado, com mutações germinativas ou somáticas do *BRCA* com resposta parcial ou completa à quimioterapia de primeira linha, à base de platinos[39]. Adicionalmente, as duas agências, aprovaram o uso do Olaparib no tratamento dos tumores da mama com gBRCAm, HER2 negativos, com metastização à distância e previamente tratados com quimioterapia.[35,40] Para além da sua utilização nos tumores acima referidos, fruto dos resultados do estudo POLO, este fármaco foi aprovado para tratamento de manutenção do adenocarcinoma do pâncreas metastizado, em doentes com gBRCAm nos quais não existiu progressão de doença pelo menos após 16 semanas do tratamento com platinos.[35,41] No inicio de 2020, a FDA aprovou ainda o olaparib no tratamento de doentes com cancro da próstata metastizado resistente à castração (mCRPC) e com mutações somáticas ou germinativas nos genes que intervém na HR, e que tenham progredido após o tratamento prévio com enzalutamide ou abiraterone.[42] A mesma entidade aprovou ainda a associação do olaparib com o bevacizumab como tratamento de manutenção em doentes com cancro do ovário, das trompas ou peritoneu avançado com resposta parcial ou completa à quimioterapia de primeira linha à base de platino e cujos tumores

apresentem HRD[43].

Rucaparib

A eficácia do rucaparib foi avaliada no estudo ARIEL3, no qual se estimou a sobrevivência livre de progressão em doentes com tumores epiteliais do ovário recorrentes, das trompas de Falópio ou peritoneais primários a serem tratados com este fármaco. Observou-se que este poderia melhorar o prognóstico destes doentes, independentemente da presença de mutações no *BRCA1/2*.[44] Com base nestes resultados, a FDA e a EMA aprovaram, o uso do rucaparib no tratamento de manutenção dos tumores epiteliais do ovário recorrentes, das trompas de Falópio ou peritoneais primários com resposta completa ou parcial aos platinos. Além disso, o rucaparib foi também aprovado para o tratamento de doentes com cancro do ovário avançado associado a mutações nos genes *BRCA* (germinativas e/ou somáticas), previamente tratados com dois ou mais esquemas de quimioterapia.

Niraparib

O estudo NOVA permitiu a aprovação do niraparib no tratamento de manutenção dos tumores epiteliais do ovário, das trompas de Falópio ou peritoneais primários, recidivantes e sensíveis aos platinos.[33,35] Neste estudo, verificou-se que o benefício do niraparib é transversal aos tumores do ovário, independentemente do estado da HR e das mutações *BRCA*.[33] Assim, mesmo mulheres que não apresentem mutações nos genes *BRCA*, e cuja HR seja funcional, parecem beneficiar do tratamento com niraparib; apesar do maior benefício ser observado em mulheres com mutações *BRCA1/2* e na presença de défices na HR.[25,45] O niraparib está também aprovado no tratamento de doentes com cancro do ovário avançado, das trompas de Falópio ou peritoneal primário, tratados previamente com três ou mais esquemas de quimioterapia e cujos tumores estão associados a défices na HR. Mais recentemente, o estudo PRIMA,[34] no qual se observou uma melhoria significativa da sobrevivência livre de progressão em doentes com cancro do ovário avançado a receberem niraparib após terem respondido aos platinos, permitiu a aprovação do fármaco no tratamento de manutenção dos tumores do ovário, das trompas ou do peritoneu avançados, com resposta (parcial ou completa) à quimioterapia de primeira linha, à base de platinos.

Talazoparib

O talazoparib é um potente inibidor das PARP. Além de apresentar uma elevada capacidade de inibir a atividade catalítica das enzimas, apresenta maior potencia para aprisionar a PARP1 aos erros no ADN.[46] De acordo com os resultados do estudo EMBRACA,[46] o talazoparib foi aprovado para o tratamento dos tumores da mama associados a gBRCAm, HER2 negativos, localmente avançados ou metastizados.[35,47]

TOXICIDADE DOS INIBIDORES DA PARP

Apesar de apresentaram um perfil de segurança bastante favorável, os iPARP demonstraram, nos ensaios clínicos fase III,[33,37,44,46] alguns efeitos adversos, dos quais a fadiga, os sintomas gastrointestinais (GI) e a mielossupressão são os mais comuns. As principais reações adversas destes fármacos (Tabela 1) apresentam uma gravidade ligeira a moderada [grau 1 ou 2 da *common terminology criteria for adverse events* (CTCAE)] e, de um modo geral, não necessitam de descontinuação do tratamento.[48] A fadiga é o efeito adverso mais frequentemente observado e parece ser transversal a todos os iPARP. Uma vez que pode apresentar um impacto muito negativo na qualidade de vida dos doentes, torna-se fundamental implementar estratégias para a minimizar. Os tratamentos não farmacológicos como o exercício, a terapia cognitivo-comportamental e as massagens terapêuticas podem ser eficazes a reduzir os sintomas. Para os doentes mais sintomáticos, podem ser prescritos psicostimulantes, como o metilfenidato.[48,49] Os efeitos adversos GI são extremamente comuns e tendem a ocorrer em todos os doentes tratados com iPARP. As náuseas são o efeito adverso mais prevalente, ocorrendo em 148 (76%) dos 195 doentes tratados com olaparib, 280 (75%) dos 372 doentes tratados com rucaparib, 270 (74%) dos 367 doentes tratados com niraparib e 139 (49%) dos 286 doentes tratados com talazoparib, seguindo-se os

Tabela 1 – Toxicidade dos iPARP descrita nos ensaios de fase 3[33,37,44,46]

	Olaparib	Niraparib	Rucaparib	Talazoparib
Efeitos adversos mais frequentes	Náuseas 76%	Náuseas 74%	Náuseas 75%	Fadiga 50%
	Fadiga 66%	Fadiga 59%	Fadiga 69%	Náuseas 49%
	Vómitos 38%	Obstipação 40%	Vómitos 37%	Cefaleias 33%
	Diarreia 33%	Vómitos 34%	Obstipação 37%	Alopecia 25%
	Dor abdominal 25%	Cefaleias 26%	Aumento da AST ou ALT 34%	Vómitos 25%
		Dor abdominal 23%	Diarreia 32%	Diarreia 22%
		Diarreia 20%	Dor abdominal 30%	
	Anemia 43%	Anemia 50%	Anemia 37%	Anemia 53%
	Neutropenia 19%	Neutropenia 30%	Neutropenia18%	Neutropenia 35%
	Trombocitopenia 14%	Trombocitopenia 61%	Trombocitopenia 28%	Trombocitopenia 27%

vómitos, a diarreia, a obstipação e a dor abdominal. Algumas opções para ultrapassar a toxicidade GI associada a estes fármacos, passam pela interrupção ou redução da dose e/ou terapêutica antiemética.[48,49] A toxicidade hematológica tende a ocorrer precocemente após o inicio do tratamento com iPARP e a resolver alguns meses após a toma dos fármacos. A anemia é o principal efeito adverso hematológico, ocorrendo em 85 (44%) dos 195 doentes tratados com olaparib,[37] em 184 (50%) dos 367doentes tratados com niraparib,[33] 139 (37%) dos 372 dos doentes tratados com rucaparib[44] e em 151 (53%) dos 286 doentes tratados com talazoparib[46]. Para além desta, também a neutropenia e a trombocitopenia são comumente observadas. Em algumas situações, quando a gravidade dos efeitos adversos é ³ 3 CTCAE, pode ser necessário interromper ou reduzir a dose do fármaco e, quando apropriado, realizar transfusão de sangue para resolução da anemia.[48,49] De todos os iPARP, o niraparib é o que apresenta a maior toxicidade hematológica. Assim, recomenda-se que o tratamento com este fármaco não se inicie até que a mielossupressão causada pela quimioterapia seja resolvida.[45]

RESISTÊNCIA TERAPÊUTICA AOS INIBIDORES DA PARP

Tal como acontece com outras terapias alvo, a resistência aos iPARP tem-se observado na maioria dos doentes com tumores avançados. São vários os mecanismos de resistência propostos até ao momento que demonstram de que forma as células tumorais deixam de responder aos efeitos citotóxicos dos iPARP. Contudo, esta é uma área extremamente complexa, que necessita de uma investigação continuada, para que se obtenha uma uniformização relativamente aos mecanismos clinicamente evidentes e para que sejam desenvolvidas estratégias para ultrapassar essa resistência. Geralmente, os principais mecanismos de resistência podem ser agrupados da seguinte forma:

1. **Mecanismos de resistência que restauram a via HR:**

   a. Mutações secundárias que restauram a *open reading frame* (ORF) dos genes que intervêm na HR (*BRCA1/2, PALB2, RAD51C/D*), permitindo a síntese de proteínas funcionais que, consequentemente, restauram a capacidade de reparar os erros no ADN causados pelos iPARP.[5,25,32] Este mecanismo é também responsável pela resistência aos platinos.[26,50]

   b. Expressão de variantes hipomórficas *BRCA1/2*.

   c. Alterações epigenéticas nos genes que intervêm na HR, como a desmetilação do promotor dos genes *BRCA1* e *RAD51C*, que está associada com uma reexpressão proteica e desenvolvimento de resistência aos iPARP.[26,32]

   d. Mutações que comprometam a regulação do ADN *end-resection* através da perda da 53BP1, REV7/MAD2L2, ou complexo de Shieldin, permitindo manter a HR na ausência de *BRCA1*. A 53BP1 apresenta um papel crucial ao facilitar a via do NHEJ e a inibir a via HR. A perda deste fator restaura a HR em células com mutações *BRCA1* e confere resistência aos iPARP.[25,50,51] O complexo de Shieldin, formado pelas proteínas FAM35A e C20ORF19, interage com MAD2L2, que faz parte da via do 53BP1. A interação entre o complexo de Shieldin e MAD2L2 facilita a ocorrência da NHEJ e evita a HR, sensibilizando as células tumorais com défices nos genes *BRCA1* à inibição das PARP. Por outro lado, a inativação do complexo de Shieldin evita a ocorrência do NHEJ e promove a HR, conferindo resistência aos iPARP.[26,32,50,51]

2. **Mecanismos de resistência independentes da via HR:**

   a. Estabilização da forquilha de replicação, processo onde as proteínas BRCA1/2 e PARP1 têm um papel crucial. Na sua ausência, a forquilha de replicação não é estabilizada, não ocorrendo reparação dos erros no ADN e, consequentemente, levando à morte celular. Células tumorais com mutações no gene *BRCA2* reduzem a expressão da proteína PTIP, inibindo o recrutamento da nuclease MRE11, o que favorece a estabilização e proteção da forquilha de replicação,[52] contribuindo para a reparação dos erros no ADN e prevenção da letalidade induzida pelos iPARP.[25,32,53,54]

   b. Redução da expressão das enzimas PARP, que contribui para a redução da atividade do fármaco e redução do aprisionamento da PARP1.[5,26,50]

   c. Efluxo do fármaco devido à expressão dos transportadores *ATP-binding cassette (ABC)* nas células tumorais, como a P-glicoproteína, aumentando o efluxo dos iPARP, reduzindo a disponibilidade do fármaco e, consequentemente, contribuindo para que os seus efeitos sejam diminuídos.[5,26,50,51]

   d. POLQ: Doentes com mutações reversas no gene *BRCA1* exibem sinais de MMEJ, sugerindo a POLQ como um veículo de resistência aos iPARP. Assim, inibidores da POLQ podem suprimir a resistência adquirida aos iPARP, conferindo letalidade sintética nos tumores com défices na HR e NHEJ.[32]

   e. Mutações nas enzimas *poly(ADP-ribose)-glycohydrolases* (PARG) podem levar a resistência através de um mecanismo que não restaura a HR. A perda das PARG resulta na acumulação de cadeias PAR que, ao não serem degradadas, mantém a atividade das enzimas.

BIOMARCADORES DE RESPOSTA AOS INIBIDORES DA PARP

Os biomarcadores preditivos aos iPARP são fundamentais para a seleção do tratamento mais adequado para os doentes com cancro. De facto, a presença de mutações nos genes *BRCA1/2* permanece como o único biomarcador de resposta.[4,9,53] No entanto, recentemente, têm sido propostos novos biomarcadores, tais como a resposta

aos platinos (nem sempre consensual com a resposta aos iPARP), a análise da perda de heterozigotia, os elevados níveis de PARP1 e PARP2, as alterações genéticas e mutações em genes envolvidos na reparação por HR (*PALB2, ATM, RAD51C/D*).[21,55-58] A determinação da sensibilidade e especificidade destes biomarcadores irá aumentar o alcance terapêutico dos iPARP para uma população mais ampla de tumores.

CONCLUSÃO

Os iPARP mudaram o paradigma do tratamento dos tumores do ovário e da mama com mutações nos genes *BRCA1/2*. Os ensaios clínicos procuram expandir a aplicação clínica destes fármacos para um grupo de tumores mais abrangente, nos quais se incluam não só tumores da mama e do ovário com mutações *BRCA1/2*, mas também outros tumores portadores de défices genéticos, como é o caso de alterações na HR. Atualmente, a EMA e a FDA aprovaram a utilização de quatro iPARP (olaparib, rucaparib, niraparib e ralazoparib) para o tratamento de determinados tumores tais como os do ovário recorrentes, mama, pâncreas e próstata.

Apesar da evolução científica em oncologia e dos iPARP representarem uma estratégia inovadora, existem ainda questões por responder. O desenvolvimento de biomarcadores preditivos que permitam definir o grupo de doentes elegíveis ao tratamento é uma área pouco explorada e que necessita de mais estudos para apurar a sua relevância clínica, de forma a aumentar o potencial de resposta aos iPARP e estratificar os doentes que poderão obter um maior benefício. A uniformização dos mecanismos de resistência envolvidos na redução dos efeitos citotóxicos dos iPARP e o desenvolvimento de estratégias para a ultrapassar, como através da utilização dos inibidores da POLQ, são uma abordagem crucial para potenciar a aplicação destes fármacos a um maior número de tumores. Além disso, é ainda prematuro concluir sobre qual dos iPARP é mais eficaz num grupo de doentes e/ou tumores, uma vez que não existem estudos comparativos entre iPARPs; assim, não podemos saber se a maior potência de um iPARP se traduz em maior eficácia clínica quando as indicações para o uso de iPARPs se sobrepõem.

Finalmente, acreditamos que é necessária uma investigação clínica continuada para que seja possível obter mais conhecimento em relação a esta classe de fármacos e ao seu papel nas estratégias futuras de tratamento.

CONTRIBUTOS DOS AUTORES

CB: Conceção do trabalho; pesquisa bibliográfica; redação do manuscrito.

JP: Revisão crítica do manuscrito.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

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

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A Multidisciplinary Approach to the First Autochthonous Case of Tularemia Reported in Portugal

Abordagem Multidisciplinar do Primeiro Caso Autóctone de Tularémia Notificado em Portugal

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ABSTRACT

Francisella tularensis, a Gram-negative coccobacillus, is a highly virulent pathogen responsible for several zoonotic outbreaks in Europe in the last few decades. The authors report the case of a 46-year-old male who developed fever, myalgias and headache a week after having contact with animal feed contaminated by rodents. Serological tests were positive for *Francisella tularensis*. This first case of autochthonous tularemia in Portugal led to an intensive investigation involving several healthcare services and national governmental authorities. The authors address the possible underdiagnosis of this infection in the country.

Keywords: Francisella tularensis; Portugal; Public Health; Tularemia

RESUMO

Francisella tularensis, um cocobacilo Gram-negativo, é um microrganismo infecioso altamente virulento, responsável por vários surtos de doença na Europa nas últimas décadas. Os autores apresentam o caso de um homem de 46 anos com febre, mialgias e cefaleias cerca de uma semana após contacto com ração de animais contaminada por roedores. O estudo serológico foi positivo para *Francisella tularensis*. Este caso, o primeiro caso de tularémia autóctone notificado em Portugal, originou uma intensa investigação envolvendo diversas autoridades de saúde e governamentais portuguesas. Os autores alertam para a possibilidade de subdiagnóstico desta doença no país.

Palavras-chave: Francisella tularensis; Portugal; Saúde Pública; Tularémia

INTRODUCTION

Francisella tularensis is the etiologic agent of tularaemia. There are four subspecies that have been described: *F. tularensis tularensis* (type A strain), *F. tularensis holarctica* (type B strain), *F. tularensis novicida* and *F. tularensis mediasiatica*.[1–3] The subspecies *tularensis* and *holarctica* are responsible for the majority of tularaemia infections worldwide.[1] Small rodents and lagomorphs are the main hosts of *F. tularensis*, but a wide range of both wild and domestic animals may be infected. A number of different arthropods can also act as vectors.[1–3] Transmission to humans occurs directly from the animal reservoir (handling tissues or fluids, ingestion of undercooked meat or animal bite), through arthropod bites, following exposure to contaminated environmental sources (water, soil, dust) or during sample manipulation in the laboratory.[1,2,4] Hunters, trappers, veterinarians, animal trimmers, landscapers, farmers and laboratory workers are deemed as high-risk groups.[1,2]

Tularaemia has a short incubation period, ranging from 3-5 days up to two weeks.[1,5] Six major clinical syndromes have been described: ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic and typhoidal, usually associated with the route of inoculation.[1]

Due to its high virulence, possibility of aerosolization and ability to cause severe disease, *F. tularensis* is classified as Category A potential bioterrorism agent, according to the Centers for Disease Control and Prevention (CDC). Tularaemia is under epidemiological surveillance in Europe since 2003. Despite being a disease of compulsory notification in Portugal since 2014, there were no human cases reported until 2018.[6]

The authors report the first notified autochthonous case of tularaemia in Portugal and intend to raise clinical awareness to this diagnosis.

CASE REPORT

A previously healthy 46-year-old male was admitted with a 4-day history of fever (40ºC maximum), malaise and myalgia. He was a small game hunter and had regular contact with rabbits in a domestic warehouse, apart from a history of contact with livestock feed contaminated by rodents the week before, in the store he owned. He denied recent travel, consumption of suspicious food or water or tick bites.

On admission, he was febrile and hypotensive with no further findings in the physical examination. Laboratory results (Table 1) revealed leucocytosis, thrombocytopenia, elevated C-reactive protein and mild cytocholestasis. Renal function was preserved. Abdominal ultrasound revealed no abnormalities.

Considering the epidemiology, leptospirosis was suspected. Fluids and empiric antibiotic treatment with doxycycline 100 mg twice a day (bid) were administered. Serological tests for *Brucella* spp., *Rickettsia* spp., *Coxiella burnetti*

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Table 1 – Laboratory tests performed during hospital admission

Laboratory analysis (units)	**Results** (reference values)
Hemoglobin (g/dL)	15.6 (11.8 - 15.8)
Leucocytes (x10^9/L)	21.8 (3.6 - 10.5)
Neutrophils (x10^9/L)	18.3 (1.5 - 7.7)
Platelets (x10^9/L)	148 (150 - 400)
CRP (mg/dL)	22.4 (< 0.5)
ALT (U/L)	69 (< 34)
AST (U/L)	58 (< 31)
Total bilirubin (mg/dL)	1.8 (0.2 - 1.2)
Direct bilirubin (mg/dL)	0.5 (< 0.5)
LDH (U/L)	338 (< 247)
HIV antibodies	Negative
HAV IgM/IgG	Negative
HBsAg	Negative
HBsAb	Negative
HBcAb IgM	Negative
HCV IgM/IgG	Negative
EBV IgM	Negative
CMV IgM	Negative
RPR	Negative
Coxiella burnetti IgG	Negative
Rickettsia sp. IgG	Negative
Brucella sp. IgM/IgG	Negative
Leptospira sp. IgM/IgG	Negative
Leptospira 16S (RNA) - urine	Negative
***Francisella tularensis* (TAT)**	**Positive**
Blood cultures	Negative
Urine culture	Negative

ALT: alanine transaminase; AST: aspartate transaminase; CMV: cytomegalovirus; CRP: C-reactive protein; EBV: Epstein-Barr virus; HAV: hepatitis A virus; HbsAg: hepatitis B surface antigen; HbsAb: hepatitis B surface antibody; HbcAb: hepatitis B core antibody; HCV: hepatitis C virus; HIV: human immunodeficiency virus; Ig: immunoglobulin; LDH: lactate dehydrogenase; RNA: ribonucleic acid; RPR: rapid plasma regain; TAT: tube agglutination test

and *Leptospira* spp. turned up negative, as well as for HIV, hepatitis, EBV, CMV and syphilis. *Leptospira* spp. was not detected in urine. Blood cultures were negative.

The patient's condition improved, and he was discharged without a final diagnosis. The case was later reviewed, and less frequent causes of zoonosis were considered, namely tularaemia. Due to this suspicion, he completed 21 days of treatment with doxycycline 100 mg bid in outpatient setting, without further complications. Convalescent serum samples were tested either for the previous zoonotic agents (without seroconversion) and *F. tularensis*. *F. tularensis* antibodies were detected by an agglutination test (TAT) with a titre of 1:40 (cut-off for antibody detection is a titre > 1:20).[7] Typhoidal tularaemia was diagnosed, considering the presence of fever with no specific signs or symptoms and the immunological response for *F. tularensis*.

Public Health investigation and control

After being notified, local and regional Public Health professionals conducted an epidemiological investigation. The patient mentioned a history of direct manipulation of dead rats in the animal feed warehouse where he worked (which led him to relocate) and domestic rabbits. Sherman traps (rectangular-shaped box traps designed for the live capture of small mammals) were placed next to the store, the previous warehouse and its surroundings. The traps were checked three times a day during the investigation, that lasted for several days, and complied with animal comfort and safety; no rats or other vectors were captured. Water samples collected from a stream nearby were within normal microbiological parameters. However, signs of recent environmental cleaning and disinfestation in the nearby area where detected. The environmental assessment also involved the National Institute of Health, Portuguese National Authority for Animal Health, Food and Economic Safety Authority, Institute for Conservation of Forests and Nature and the Environment Protection Police Department services.

DISCUSSION

Typhoidal tularaemia is a potentially severe systemic disease and may be the result of any transmission pathway. It is a less prevalent presentation, accounting for 7.7% - 14.4% of cases in several case series.[8,9] Its diagnosis may represent a challenge for physicians, particularly in non-endemic areas, due to the absence of pathognomonic signs and symptoms. Two large outbreaks were reported in northwestern Spain, with over 1000 human cases during 1997 - 1998 and 2007 - 2008.[3,10] Due to geographic proximity, a seroepidemiological study was conducted in the northern region of Portugal after the first outbreak in Spain and found a seroprevalence rate of 8.9%.[11] The *F. tularensis* subspecies *holarctica* was detected in one human sample.[12] *F. tularensis* subsp. *holarctica* was also found in different tick species and lagomorphs.[13] Given these results, awareness of autochthonous tularaemia should be raised. In this case, the presence of a febrile illness, nonspecific laboratory findings and exposure to rats led to the hypothesis of leptospirosis. Considering the higher prevalence of leptospirosis and other zoonosis in Portugal, tularaemia is not often suspected and may be underdiagnosed. Cross-reactivity between zoonotic agents should be considered despite its weak impact in the diagnosis of *F. tularensis*,[14] and was excluded in this case.

Aminoglycosides remain the first line treatment of all forms of tularaemia, except for meningitis and endocarditis, where combination therapy is recommended. Oral fluoroquinolones and doxycycline can be used for mild disease. Empirical therapy failure and symptom relapse have been described, either due to delay in the correct treatment or treatment regimens shorter than 14 days.[4,7] Considering the uncertainty of the diagnosis at discharge and subsequent suspicion of tularaemia, physicians chose a doxycicline 21-day regimen.

After six months, the laboratory test was repeated and

it was negative for *F. tularensis*, In tularaemia, antibodies appear approximately two to three weeks after infection and may be detected several years after recovery, depending on the patient's immune system.[15] In this case, the serological test used detects primarily IgM-type antibodies,[14] suggesting resolution of the acute infection.

CONCLUSION

In this case, despite the epidemiological investigation that was conducted, the source was not confirmed, possibly due to the time lapse between clinical presentation and its notification. Disease notification in real time, whenever possible, is crucial for an effective intervention by Public Health departments.

We highlight raising awareness to the possible misdiagnosis of tularaemia and the importance of coordination between physicians, laboratory and Public Health departments. A prompt response is crucial in order to determine the source of the infection and contain a potential outbreak.

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AUTHORS CONTRIBUTION

FC, ILC, CT: Case description and discussion.

RG: Critical review of the work.

PROTECTION OF HUMANS AND ANIMALS

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DATA CONFIDENTIALITY

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

INFORMED CONSENT

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Pharmacological Prophylaxis of Venous Thromboembolism in Terminally Ill Patients: A Need or Futility?

Profilaxia Farmacológica do Tromboembolismo Venoso em Doentes Terminais: Uma Necessidade ou um Desperdício?

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ABSTRACT

The aim of this case is to clarify the need to maintain the terminally ill oncological patients who have had a thrombotic event in the course of their underlying disease under antithrombotic therapy. This case addresses a 63-year-old man with stage IV gastric antrum adenocarcinoma, completely bed-ridden and anticoagulated with subcutaneous enoxaparin for more than a year, following deep venous thrombosis of the left lower limb. After reviewing the literature, it was found that, for end-of-life patients, anticoagulation seems to have little benefit as the main objective is not the extension of life itself, but rather the preservation of the best quality of life through practices that are well established in the relief of suffering.

Keywords: Anticoagulants/therapeutic use; Enoxaparin; Fibrinolytic Agents; Palliative Care; Venous Thromboembolism/prevention & control

RESUMO

O presente caso pretende clarificar qual a verdadeira necessidade de manter sob terapêutica anti-trombótica os doentes oncológicos terminais que tiveram um evento trombótico no decorrer da evolução da sua doença de base. O caso em questão aborda um doente de 63 anos com uma neoplasia do antro gástrico em estadio IV, totalmente acamado, hipocoagulado com enoxaparina subcutânea há mais de um ano, no seguimento de uma trombose venosa profunda no membro inferior esquerdo. Após revisão da literatura, constatou-se que em doentes em fim de vida, a anticoagulação parece ter pouco benefício, visto que o principal objetivo não é o prolongamento da vida, mas sim a preservação da melhor qualidade de vida possível através de práticas cuja evidência no alívio do sofrimento está bem documentada.

Palavras-chave: Agentes fibrinolíticos; Anticoagulantes/uso terapêutico; Cuidados Paliativos; Enoxaparina; Trombose Venosa/prevenção e controlo

INTRODUCTION

Advanced cancer patients are at increased risk of venous thromboembolism (VTE) due to age, local and distal spread of the malignancy and bed confinement, among other factors.[1] The prevalence of asymptomatic VTE among palliative care (PC) patients has been found to reach 50%,[1] so VTE is considered clinically relevant only if it confers a patient-reported symptom burden.[2] Many of the available guidelines advocate the implementation of thromboprophylaxis in cancer patients. However, in hospice care, where the priority goal is not life extension but assurance of the best quality of life trough symptom relief, the problem for cancer patients becomes ethically controversial.[1]

With this case we intend to discuss futility of starting antithrombotic therapy in terminal patients.

CASE REPORT

Male, 63 years-old, unemployed, with a prior clinical history of hypertension, dyslipidaemia, benign prostatic hyperplasia, obstructive sleep apnoea under continuous positive airway pressure and hepatitis C (cured). He was a former smoker (43 pack-years), in abstinence for over 30 years after a long history of intravenous drug use.

He was apparently well until December 2017, when he reported to his attending physician a weight loss of 20 kg in one month, heartburn and postprandial bloating (the latter with a more prolonged evolution and overlooked by the patient). In January 2018 he was diagnosed with stage IV gastric adenocarcinoma. Both chemotherapy (platinum agents) and radiotherapy were proposed as part of the palliative strategy. Due to repeated episodes of dysphagia between March 2018 and June 2019, caused by tumour ingrowth, he had four unpainted transpyloric metal prostheses placed. In April 2018 he had deep venous thrombosis (DVT) in the left lower limb and since then he had been treated with subcutaneous (SC) enoxaparin 60 mg. In October 2018, given the advanced stage of the gastric cancer and his reduced performance status (capable of only limited self-care, confined to bed or chair 50% or more of his waking hours), all diagnostic and disease-specific therapeutic attitudes with curative intent were discontinued. In February 2019, he began PC consultation at the referral hospital.

Six days before PC unit admission, the patient presented dysphagia for solids, increasing dyspnoea and hyperactive *delirium*. At that time, he weighed 51 kg. His regular

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medicines were omeprazole 20 mg *qd*, gabapentin 300 mg *bid*, metoclopramide 10 mg *tid*, furosemide 60 mg *qd*, spironolactone 100 mg *qd*, levomepromazine 2.5 mg *qd*; all of these were administered *per os.*

In July 2019, he was admitted to a PC unit for symptomatic control. Upon admission to the unit, the patient was conscious, oriented, apyretic, and pale. He had bilateral stasis; painless distended abdomen with central tympanism and peripheral dullness; lower limb oedema up to the thigh root. Subjectively and according to the Edmonton Symptom Assessment System (self-assessment, increasing intensity from zero to ten), the patient had: pain = 8, tiredness = 9, nausea = 3, depression = 8, anxiety = 2, appetite = 5, drowsiness = 4, wellbeing = 8, shortness of breath = 7, constipation = 4. According to the Palliative Performance Scale (PPS), he had an estimated physical performance of 30%.

A medication review was performed: SC (dexamethasone 4 mg *bid*, butylscopolamine 20 mg *tid*, haloperidol 5 mg *qd*, furosemide 20 mg *qd*), *per os* (lactulose 15 mLl *tid*, orodispersible omeprazole 20 mg *qd*) and transdermal fentanyl 50 µg/h *qd*.

The patient died two days after PC unit admission.

DISCUSSION

The case concerns a man with stage IV gastric antrum adenocarcinoma, who had DVT in the left lower limb in April 2018, and was bed-ridden.

This patient was still on treatment when DVT was diagnosed. Patients with inoperable locally advanced and/or metastatic stage IV cancer should be considered for systemic treatment, like chemotherapy, which has shown to improve survival and quality of life compared with the best supportive care alone.[3] It is known that adenocarcinomas and advanced disease,[4] as well as chemotherapy with platinum or antiangiogenic agents,[3,5] are associated with higher risk of cancer related VTE.

By the time of DVT diagnosis, three things were a given: the patient was receiving chemotherapy, his performance status was low, and cancer disease was in progression. All of these influence the anticoagulation decision.[6] It is not possible to know whether direct oral anticoagulants were added as options for VTE treatment.[7]

The standard initial treatment of an acute episode of VTE in cancer patients consists of SC low molecular weight heparin (LMWH) at a dose that is adjusted to body weight and long-term treatment is recommended.[8] For cancer patients receiving chemotherapy, indefinite LMWH treatment should be discussed with them.[9-12] The usual dose of SC enoxaparin must be 1.5 mg/kg od or 1.0 mg/kg bid, either for prophylaxis or treatment purposes.[9] Before admission into the PC unit his weight was 51 kg, which means that he was on a sub-therapeutic prophylactic scheme. Reasons for that were not elicited. Portuguese guidelines recommend that in men with low weight (below 57 kg), SC injections of LMWH should be used with caution, given the uncertainty of the dose.[9]

Some elements for consideration in the decision of not treating or not using prophylaxis for VTE are: patient refusal; non-therapeutic advantages (limited survival, high risk, unplanned oncologic interventions, etc.); non-palliative benefits (for instance, dyspnoea is already controlled and/or pain, associated to leg swelling, is reduced); and unreasonable burden of anticoagulation treatment (painful injections, frequent monitoring with phlebotomies, etc.).[10]

For people who are having PC pharmacological VTE prophylaxis is recommended and should be reviewed daily, considering the views of the person, family members or carers and the multidisciplinary team.[11] In PC, the likely life expectancy should always be considered before VTE prophylaxis.[11]

In patients in PC, temporary increases in thrombotic risk factors and risk of bleeding should impact decisions regarding the use of thromboprophylaxis.[11,13] This risk is greatly increased in cancer patients due to the tumour itself, renal and liver failure, malnutrition or the metastatic process involving organs participating in homeostasis (liver, bone marrow).[1] Most patients with metastatic cancer disease remain anticoagulated until their death. Despite the limitations of retrospective data across healthcare settings, it appears that anticoagulation, as death approaches, confers a significant bleeding risk without the additional benefit of preventing VTE symptoms.[14]

Few doctors believe that patients at the end of life should always be treated for VTE.[15] Some argue it is reasonable to maintain anticoagulation, if the patient agrees to it, is somewhat independent in carrying out activities of daily living and tolerates SC injections.[16] However, if the patient declines therapy, has a low performance status or is entering the dying phase, discontinuing anticoagulation is reasonable.[16] Many doctors wondered if it was 'fair' to give a daily SC injection of LMWH to a patient in the last few weeks of life.[15] The treatment for VTE in PC patients is intrinsically bound to the doctor's own moral and ethical framework.[15] It could be argued that clinicians who withhold LMWH injections – because they do not want to subject the patient to the perceived discomfort of the injection – are taking a moral decision which may run contrarily to the patient's own choice.[15] The pivotal variable that influences a doctor's decision to prescribe SC injections of LMWH appears to be the prognosis of the patient, with treatment said to be largely unbeneficial at end of life. This is because, in the short time left, the patient's symptoms may not be ameliorated by LMWH injections.[15]

When this patient was admitted to the PC unit, he had been anticoagulated for over a year and had had a progressive deterioration of his clinical condition, with no perspective of cure. Upon admission, survival was estimated in less than three weeks according to the Palliative Prognostic Index (dysphagia, dyspnoea, delirium, oedema, PPS 30%).[17] The PC unit team decided not to prescribe VTE prophylaxis because the patient was in his dying process. Indeed, he died two days after PC unit admission. VTE prophylaxis should not be offered to people in the last days of life.[11]

CONCLUSION

In PC the ethical principle of "nonmaleficence" should be of paramount consideration in ethical-clinical decision making.

There is no robust data supporting the use of thromboprophylaxis in hospice. It seems that thromboprophylaxis in this group of patients should not be routine practice.[1] The indications for anticoagulation should be assessed individually, with previous assessment of VTE risk, comorbidities and possible hemorrhagic complications.[1] With that in mind, the final decision to initiate and maintain anticoagulation should be based largely on patient's own opinion, if mentally able to decide in their best interest.[15]

AUTHORS CONTRIBUTION

LS, PRP: Both authors contributed equally to the conceipt of the work, draft of the paper, criticial review and approval of the final version.

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Lung Cancer-Related Pneumopericardium

Pneumopericárdio Secundário a Cancro do Pulmão

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Keywords: Lung Neoplasms; Pneumopericardium; Tomography, Spiral Computed; X-Ray Film
Palavras-chave: Filme para Raios X; Neoplasias do Pulmão; Pneumopericárdio; Tomografia Computadorizada Espiral

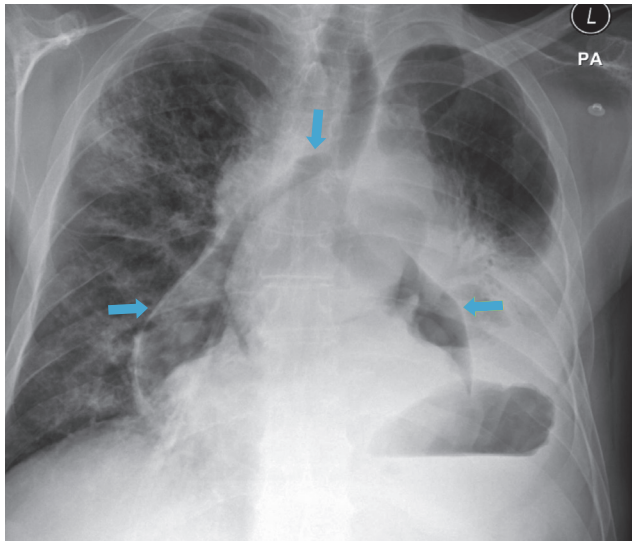

Figure 1 – Chest PA view radiograph showing air (blue arrows) around the heart, the aorta and the main pulmonary artery

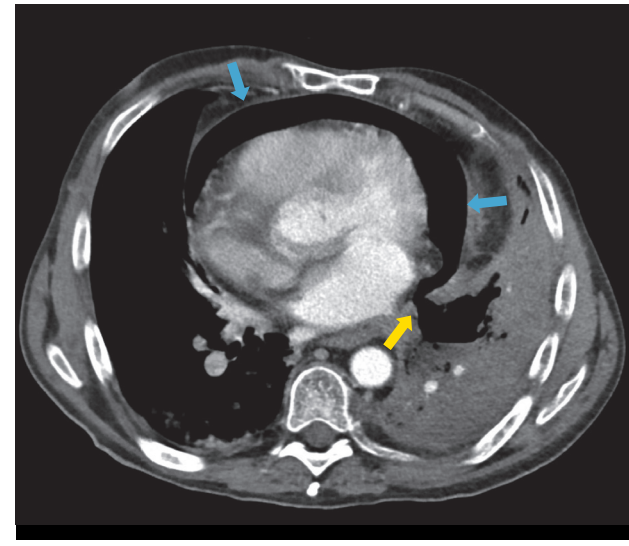

Figure 2 – Axial computed tomography image depicting the pneumopericardium (blue arrows), the broncho-pericardial fistula (yellow arrow) and the necrotic lung tumor

A 52-year-old man presented to our hospital with chest pain and shortness of breath. He was being treated with chemotherapy for a peri-hilar, infiltrative squamous cell carcinoma of the left lung with nodal involvement.

The chest radiograph (Fig. 1) revealed air outlining the inner surface of the mediastinal pleura, particularly around the aorta and the main pulmonary artery, consistent with pneumomediastinum. A computed tomography (Fig. 2) confirmed the pneumopericardium diagnosis, associated with a sizeable broncho-pericardial fistula created by the necrotic tumour.

Pneumopericardium consists of air around the mediastinal structures, often extending to the neck, chest wall or even causing pneumothorax.[1,2] It is a rare and often fatal entity.[3,4] Although pneumopericardium is commonly associated with blunt trauma or iatrogenic causes (such as invasive procedures or mechanical ventilation), other causes should be considered, such as cancer (particularly esophageal and lung cancer).[1,3,4]

AUTHORS CONTRIBUTION

POS: Analysis of the clinical file of the patient. Draft of the paper and selection of images.

JPC: Interpretation of medical images. Critical review of the paper and final approval of the manuscript.

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COMPETING INTERESTS

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Time to Rethink Dementia Care in the Acute Care Hospital: What are the Palliative Care Needs of this Population?

Repensar o Cuidado dos Doentes com Demência no Hospital de Agudos: Quais as Necessidades Paliativas desta População?

Keywords: Dementia; Hospitalization; Hospitals, Psychiatric; Palliative Care
Palavras-chave: Cuidados Paliativos; Demência; Hospitais Psiquiátricos; Hospitalização

Dear Editor,

Dementia is considered a global public health priority by the World Health Organization, especially in countries with an ageing population.[1] Between 2000 and 2014, the proportion of hospitalized patients with dementia increased 470% in Portugal, with an estimated one in every 5 - 6 inpatients having dementia.[2] Consequently, hospital wards face the enormous challenge of caring for people with cognitive impairment, making it urgent to know and adequately respond to the needs of these patients and their families.

In a quantitative, descriptive, retrospective, cross-sectional and observational study, which included 39 patients with dementia admitted to an Internal Medicine Department, we identified their palliative needs using the Catalan Institute of Oncology tool (NECPAL-CCOMS-ICO© version 3.0) developed for chronic patients.[3] Ethics committee and data protection society approvals were granted. It is noteworthy, from the results, that 64.1% of the patients had severe or very severe dementia according to the Global Deterioration Scale/Functional Assessment Staging (GDS/FAST).[3] In 82% of patients, the medical team would not be surprised if the patient died within 12 months. There was an average of 7.5 (out of 13) positive NECPAL questionnaire questions per patient (median 7, interquartile range 3.5), denoting the presence of palliative needs, including a high symptomatic burden before admission (Table 1).

Dementia is a progressive, irreversible and life-limiting disease, and leads to considerable suffering. Elderly patients with dementia hospitalized in Internal Medicine wards usually have clear palliative needs. However, the classic hospital-centric approach of contemporary medicine, centered on resolving a curable acute illness, may not guide

Table 1 – Palliative care needs identified by the NECPAL-CCOMS-ICO© tool (n = 39)

Questions	Positive n (%)
Would you be surprised if this patient died within the next year? (Positive if not)	32 (82%)
Are there more than two chronic diseases?	38 (97%)
Cognitive decline, that is, deterioration in the Mini Mental State Examination test or the Pfeiffer's Short Portable Mental Status Questionnaire? Or, if it is not possible to obtain prior scale, has there been a significant decline in the ability to think, remember and reason?	32 (82%)
Does the patient have any of the following geriatric problems more than twice in the past six months (geriatric syndromes - delirium, falls, pressure ulcers, recurrent infections) or is any of these problems persistent?	30 (77%)
Functional decline, that is Karnofsky or Barthel scales showing a performance deterioration greater than 30%? Or, if it is not possible to obtain a previous scale, was there a significant decline in the ability to perform daily life activities?	29 (74%)
Did the patient present any persistent symptoms (with a maximum intensity equal to or greater than 5 out of 10) in his/her daily life, in the month before this admission? **Namely:** Sonolemnce ..... 17 (61%) Tiredness ..... 14 (50%) Absence of wellbeing ..... 13 (46%) Pain..... 12 (43%) Appetite ..... 12 (43%) Dyspnoea ..... 11 (39%) Anxiety..... 9 (32%) Depression ..... 8 (29%) Nausea/Sickness ..... 2 (7%) Other 2 (7%)	28 (72%)
Were there more than two urgent/unplanned admissions in the last 6 months? Is there an increase in the demand or intensity of interventions?	28 (72%)
Nutritional decline, that is, weight loss greater than 10%?	25 (64%)
Has there been any implicit or explicit expression of limitation of the therapeutic effort or request for palliative care from the patient, family or team members?	21 (54%)
Presence of specific indicators of advanced organ disease (detailed on the original formulary)?	21 (54%)
Severe dependency, that is, Karnofsky less than 50 or Barthel less than 20?	19 (49%)
Have palliative needs already been identified by professional team members?	17 (44%)
Is there severe anxiety or adjustment disorder, that is, with psychological symptoms (sustained, intense, and progressive) not associated with the acute condition?	4 (10%)
Is there severe social vulnerability? (economic or social difficulties that weaken the patient's situation)	1 (3%)

medical teams towards the most suitable environment and type of care for this population. Palliative Care has been presented as a more appropriate model of care for these patients, especially in the more advanced stages of dementia. Its goals are to promote the alleviation of the suffering of people with serious and/or advanced and progressive diseases, regardless of their age, diagnosis or stage of the disease.[5]

It is urgent to rethink the care provided to patients with dementia admitted to medical wards and consider the contribution of palliative medicine in order to better respond to the needs of this growing population.

AUTHORS CONTRIBUTION

FBA, ACP, MB, PRP: All the authors contributed equally to the draft, critical review and final approval of the final version of the paper.

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A Importância de uma Consulta Especializada de Psiquiatria de Ligação no Seguimento de Insuficiência Cardíaca

The importance of a Specialized Outpatient Clinic of Liaison Psychiatry in the Follow-Up of Patients with Heart Failure

Palavras-chave: Insuficiência Cardíaca; Perturbações Mentais; Saúde Mental
Keywords: Heart Failure; Mental Disorders; Mental Health

De acordo com a Sociedade Portuguesa de Cardiologia, a insuficiência cardíaca (IC) atinge uma prevalência de cerca de 5,2% na população portuguesa, apresentando-se como um problema crescente de saúde pública.[1]

A IC associa-se a diminuição da funcionalidade e da qualidade de vida, com os doentes a necessitarem de hospitalizações frequentes.[2] Dessa forma, não só tem um grande impacto para de quem dela padece, mas também para o próprio sistema de saúde, dado os elevados custos subjacentes ao seu tratamento. Almeida Gouveia *et al* calcularam que os custos diretos ligados à IC em 2014 atingiram os €299 milhões, e os indiretos cerca de €106 milhões, sendo que previram que o impacto económico da IC poderia atingir os €503 milhões em 2036.[3]

As doenças psiquiátricas são comorbilidades bastante frequentes nos pacientes que sofrem de IC. A doença cardíaca pode ser percebida pelo indivíduo como uma ameaça à vida, à sua identidade e ao seu papel na sociedade,[4] fazendo com que a depressão e a ansiedade sejam comuns e que a patologia depressiva possa atingir taxas duas a três vezes superiores relativamente à população em geral.[5]

A depressão e a ansiedade estão relacionadas com um prognóstico adverso dos pacientes com IC devido a mecanismos fisiológicos e comportamentais. Os primeiros estão relacionados com um aumento do estado pró-inflamatório, disfunção autonómica, alterações da agregação plaquetária e disfunção do endotélio. Em termos comportamentais, os pacientes com estes sintomas podem apresentar maior dificuldade em adotar um estilo de vida saudável, visto que estão associados a uma dieta mais precária, pior adesão terapêutica, aumento da carga tabágica e diminuição da atividade física. Assim, por vários mecanismos, a patologia psiquiátrica associa-se à progressão da IC levando a aumento de hospitalizações e da mortalidade.[5]

Apesar da elevada prevalência de comorbilidades psiquiátricas em doentes com IC, estas continuam a ser subdiagnosticadas.[5] A consulta especializada de Psiquiatria de Ligação poderá colmatar este défice, com vista a prontamente diagnosticar e implementar o adequado tratamento, o qual poderá assim reduzir o impacto das comorbilidades psiquiátricas, promover a adesão terapêutica e aumentar a sobrevida e a qualidade de vida dos doentes com IC.

Em suma, a criação desta consulta é de manifesta importância no seguimento da IC em Portugal, de modo a minimizar o impacto que esta patologia tem na morbilidade e mortalidade dos pacientes.

CONTRIBUTO DOS AUTORES

SM: Redação do artigo, revisão bibliográfica.
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Reply to Letter to the Editor Concerning "HIPTCN: Prospective Observational Study of Hypocoagulated Head Trauma Patients with Normal Admission Computed Tomography Scan"

Resposta à Carta ao Editor Relativa a "HIPTCN: Estudo Prospetivo Observacional de Doentes Traumatizados Cranioencefálicos Hipocoagulados com Tomografia Computorizada Inicial Normal"

Keywords: Anticoagulants; Brain Injuries, Traumatic; Intracranial Hemorrhage, Traumatic; Neurosurgical Procedures; Tomography, Spiral Computed
Palavras-chave: Anticoagulantes; Hemorragia Intracraniana Traumática; Lesões Encefálicas Traumáticas; Procedimentos Neurocirúrgicos; Tomografia Computorizada de Feixe Cónico Espiral

In reply:

We appreciate the insightful comments made by our colleague Dr. Mascarenhas[1] regarding our article "HIPTCN: Prospective Observational Study of Hypocoagulated Head Trauma Patients with Normal Admission Computed Tomography Scan"[2] and the opportunity to address his concerns. We would also like to thank Dr. Mascarenhas for his interest in our work and for taking the time to share his concerns.

In his letter, Dr. Mascarenhas starts by showing his apprehension regarding the surveillance complications reported. In HIPTCN we report complications in seven patients (3.9%) including agitation/confusion that started during surveillance (5), atrial fibrillation (1) and stridor with dyspnea (1). Dr. Mascarenhas states that agitation/confusion should not be considered maladaptation to the hospital environment and, hence, a complication, because these symptoms can be attributed to a post-concussion syndrome, which was not excluded. A 2014 systematic review and concussion guidelines[3] define as indicators of concussion the following: (1) observed and documented disorientation or confusion immediately after the event; (2) impaired balance within 1 day after injury; (3) lower reaction time within two days after injury; and/or (4) impaired verbal learning and memory within two days after injury. In our study, all five patients with agitation/confusion developed these symptoms hours after they were admitted to the hospital, which led to the exclusion of concussion as a diagnosis. Confusion due to maladaptation to the hospital environment is a well described complication of hospital admissions and is associated with longer hospital stays. Both the case of stridor due to nasogastric intubation and the case of atrial fibrillation due to withdrawal of beta-blockers were indeed cases of iatrogenic disease. In a multicenter observational study such as HIPTCN it is not up to the authors to judge the appropriateness of every medical decision. Iatrogenic disease is an ubiquitous problem in the hospital setting, reaching a prevalence of up to 12%.[4] The two occurrences seemed associated with the admission and had important clinical consequences. Therefore, they were accounted as complications.

Considering the results of HIPTCN we discuss some ideas to replace the current national protocols. One of them is home-surveillance in selected patients after proper education of patients and/or caregivers. Dr. Mascarenhas expresses his reluctance in discharging elderly patients from the emergency room relying solely on the information provided by the patient or caregivers. Indeed, there is no perfect way to reliably assess the quality of the information obtained in an emergency setting. The same applies to the quality of information transfer from practitioners to patients or caregivers. We share these concerns but, to our knowledge, in everyday practice, most patients or caregivers are considered reliable and are discharged home if possible. Patients, caregivers and practitioners are equally responsible for the health and well-being of the former.

This takes us to the matter on the consequences of delayed intracranial hemorrhage (DIH) in a non-hospital environment. It is true that in cases of a clinically significant DIH after discharge, these patients would have to be transported back to the hospital with the associated risks and costs. The authors agree that symptomatic DIH can be a very serious, possibly fatal complication, but, as stated by the UK National Screening Committee, when deciding to screen any disease, one needs to consider not only the severity of the disease, but also its prevalence in the studied population.[5] In HIPTCN, four out of 178 patients had a DIH (2.3%), but all were asymptomatic. In our combined cohort of 363 patients, only 1.9% had DIH, again, all asymptomatic. All these patients had a favorable outcome. Indeed, there were four patients whose Glasgow Coma Score (GCS) deteriorated during surveillance, but as stated in the article, all worsened due to a complication of surveillance. None had DIH on post-surveillance computed tomography. Hence, it seems that clinically significant DIH is a very rare outcome. As for costs, if we extrapolate the percentage of DIH in HIPTCN to a population where every patient is discharged home without surveillance, it seems unreasonable to worry about transportation costs of a residual number of patients, compared with the hospitalization costs of most of the population. This rationale is in line with a population-based approach for healthcare decision making, used for the development of healthcare protocols and guidelines. Healthcare resources are limited and, therefore, must be judiciously managed to serve the largest part of the population. Obviously, individual decision making still has its place in modern medicine, but these cases should be exceptional and never used as a single factor to guide general guidelines.

We thank Dr. Mascarenhas for bringing the case report of Itshayek *et al*[6] to our attention. In this paper from 2006, the authors describe four cases of DIH. However, it is impossible to calculate the incidence of this entity, since the total population number and the total number of years between cases were not stated. Consequently, we can only conclude that this complication exists, and we would thus not dare to disagree. Nevertheless, we need to have in mind that

this case report was published 15 years ago, and the reality back then was not the same as today. Firstly, the anticoagulants used were different. In 2006, there were no new oral anticoagulants (NOAC), a type of anticoagulant that represented almost 70% of the cases in HIPTCN. These NOACs are easier to use since they have less food and drug interactions compared to Warfarin. This leads to less warfarin overdoses and, possibly to lower hemorrhagic risk for these patients. Secondly, we should consider CT technology. Due to advances in this field the negative predictive value of a negative CT is much higher today than it was in 2006. Some other interesting aspects are worth mentioning regarding these cases. Firstly, two patients developed DIH as inpatients, and one of them was found in deep coma (GCS 3 with fixed pupils), regardless of being under surveillance, and died six days after surgery. Secondly, one of the outpatients was found unconscious at home, so we cannot exclude a second head trauma. Lastly, the mortality rate of inpatients and outpatients was equivalent (50% for both groups). By analyzing this paper, one cannot conclude that surveillance and repeat CT scan within a 6-to-24-hour time frame allows for the timely diagnosis of DIH in hypocoagulated patients, as stated by Dr. Mascarenhas.

We would like to finish by once again thanking Dr. Mascarenhas for allowing us to further elaborate on this topic. The management of these patients is still not settled, but through an open and evidence-based approach we can get closer to developing an improved protocol for these patients.

AUTHORS CONTRIBUTION

PDB: Draft of the paper.

JHR, JS: Draft and critical review of the paper.

SSL, NCF, RM, JPP, RT, CA, MJM, JB, DR, DS, NS, WT, CF, MF, LR, GF, CN, VP, FS, AF, OS: Critical review of the paper.

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Carta ao Editor Referente a "Problemas de Saúde Durante e Após a Viagem: Um Estudo Observacional Prospetivo Numa Consulta de Viajante em Portugal"

Letter to the Editor Concerning "Health Problems During and After Travel: A Prospective Observational Study in a Travel Clinic in Portugal"

Palavras-chave: Africa; COVID-19; Doença Relacionada a Viagens; Medicina de Viagem
Keywords: Africa; COVID-19; Travel Medicine; Travel-Related Illness

Caro Editor,

Conceição *et al* descrevem, no artigo "Problemas de Saúde Durante e Após a Viagem: Um Estudo Observacional Prospetivo Numa Consulta de Viajante em Portugal",[1] publicado no número de dezembro de 2021 da Acta Médica Portuguesa, as características mais frequentes do viajante internacional com partida em Portugal. Este é do sexo masculino, viaja em trabalho, com destino ao continente Africano (Angola e Moçambique, maioritariamente).

Apesar dos resultados do estudo não poderem ser generalizados a todas as viagens de Portugal, pelas particularidades do IHMT/ADMT assinaladas pelos autores do estudo, as características dos viajantes e das viagens internacionais encontradas são alarmantes, caso se mantenham no atual contexto de pandemia de COVID-19, por diversas razões que tentarei enumerar de seguida.

Primeira, ao contrário da revisão de Angelo *et al*[2] na qual a principal razão para viajar foi a turística/férias, que em contexto de pandemia de COVID-19 é expectável que reduza, no atual estudo de Conceição *et al*[1] a principal razão foi a laboral, que poderá reduzir mais dificilmente ou que possivelmente aumentará após uma redução inicial.

Segunda, o sexo masculino está identificado como um fator de risco para morte e admissão na unidade de cuidados intensivos por COVID-19.[3]

Terceira, de acordo com as recomendações do Centers for Disease Control and Prevention os viajantes para Angola e Moçambique correm o risco de contrair e disseminar novas variantes de COVID-19 e os indivíduos – principalmente não vacinados – devem evitar viagens não essenciais para estes países.[4]

Quarta, África continua a ser uma região com uma baixa percentagem da população totalmente vacinada contra a COVID-19 com duas doses, na qual as mortes por COVID-19 se mantêm elevadas e onde surgem mais infeções com novas variantes de COVID-19.[5]

Por último, alguns dos sintomas de doenças do viajante descritas no estudo de Conceição *et al*[1] também podem estar presentes em pessoas com COVID-19 (e.g. febre, diarreia, náuseas, vómitos, entre outros) dificultando o diagnóstico diferencial e a procura atempada de cuidados de saúde de forma a evitar a transmissão do SARS-CoV-2 a outras pessoas durante e após a viagem.

As razões previamente enumeradas podem ser abordadas nas consultas do viajante para que o potencial viajante possa decidir de forma informada da efetiva necessidade de viajar em contexto de pandemia de COVID-19 e ainda ser alertado a seguir as recomendações ou requisitos do país para onde vai viajar, incluindo o uso de máscara, o distanciamento social e a vacinação.

CONFLITOS DE INTERESSE

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

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Adults with Autism Spectrum Disorders, from Child Psychiatry Departments to Forensic Psychiatry Units: An Embarrassing Trajectory?

Adultos com Perturbação do Espectro do Autismo, da Psiquiatria da Infância e da Adolescência para as Unidades Forenses: Uma Trajetória Embaraçosa?

Keywords: Autism Spectrum Disorder; Criminal Law
Palavras-chave: Direito Penal; Perturbação do Espetro do Autismo

Dear Editor,

Halpern *et al*[1] presented the experience of their clinical center on early diagnosis of autism spectrum disorder (ASD) and commented on the diagnostic challenges. We applaud the efforts concerning the use of early effective diagnostic protocols, as early interventions have been shown to improve outcomes. People with ASD face several challenges during their lifetime that may complicate interpersonal relationships and life in society. Our aim is to raise awareness of both the diagnosis of ASD and the legal implications of the lack of specialized care.

Individuals with ASD rarely commit crimes, as rules and laws typically help people with ASD to navigate the complexities of life in society. Surprisingly, there appears to be an overrepresentation of people with ASD in forensic psychiatry units; despite the lack of Portuguese empirical data, international studies support this increased prevalence.[2] It is possible that ASD-specific vulnerability factors may increase an individual's risk within challenging circumstances.

First, there could be difficulties with theory of mind (the cognitive capacity to assess the mental state of others and which is essential in the development of social communication and is often absent in ASD patients) and certain dimensions of executive functioning and central cohesion, which affect a significant proportion of people with ASD, may increase the risk of committing offenses, as the capacity to judge the full range of consequences of their actions may be compromised.[3] Additionally, it is not unusual for disturbances of fixed routines or episodes of sensory overload to cause extreme distress leading to challenging actions and behaviors.[4] A lack of understanding of social rules and social naivete may also put people with ASD at risk of committing law-breaking actions (such as stalking).[4] The pursuit of obsessive interests may also lead the individual to commit crimes (hacking being a prime example).[4]

Finally, people with ASD who commit offenses appear to have a high prevalence of mental disorders, particularly substance use disorder, schizophrenia spectrum disorders and other neurodevelopmental disorders.[5]

Early diagnosis and therapeutic intervention, along with specialized care throughout the lifespan, may help provide support that is tailored to the individual's needs and difficulties. Notwithstanding the need of an adequate diagnosis of ASD, inappropriate understanding of the impairments caused by ASD and their implications in everyday functioning significantly compromises the provision of appropriate care and prolongs the existence of unmet needs in this population.[3]

Specialized care and proper treatment not only improve the quality of life, but have also been shown to reduce criminal behavior in people with ASD. Therefore, the transition from child psychiatry to adult psychiatry services should be seen as a window of opportunity. Closing this window might be forensically costly.

AUTHORS CONTRIBUTION

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O Podcast como Inovação na Pedagogia em Medicina

Podcast as an Innovative Learning Tool in Medicine

Palavras-chave: COVID-19; Educação Médica; Ginecologia; Webcasts como Assunto
Keywords: COVID-19; Education, Medical; Gynecology; Webcasts as Topic

Caros Editores,

Perante a grave ameaça à saúde pública causada pela infeção por SARS-CoV-2, esta foi declarada como pandemia pela Organização Mundial da Saúde no dia 11 de março de 2020.

A educação por via remota tornou-se uma realidade imposta face às medidas de isolamento e distanciamento social implementadas. É claramente inevitável que esta nova mundividência pedagógica impacte o ensino pré-graduado em Medicina, sobretudo ao longo dos anos clínicos, uma vez que se prevê que grande parte da formação médica resulte do contacto aluno-doente. De facto, pretende-se que seja cultivado o saber estar em ambiente hospitalar, sejam desenvolvidas *soft skills* médicas, nomeadamente a empatia com o doente, para além de toda a semiologia que deverá ser compreendida através da realização de uma história clínica à cabeceira e de um exame objetivo completo.

No Outono de 2020, *The Master Surgeon Trust Collaborative* realizou um inquérito internacional a 1604 estudantes do ensino pré-graduado em medicina, para avaliar o impacto da pandemia de COVID-19 na sua formação. Os resultados deste estudo evidenciaram que a maioria dos estudantes referiu um impacto negativo significativo no seu percurso formativo em medicina (81,4% *vs* 16,4%), associando a esta má experiência educativa a fraca qualidade na pedagogia perante o cenário pandémico.[1] Neste contexto, o apelo à criação de métodos de ensino eficazes inseridos neste relacionamento interpessoal virtual assumiu particular importância.

O recurso ao *podcast* como ferramenta pedagógica reflete o galopante crescimento e desenvolvimento do sector tecnológico e a simbiose que se tem verificado entre o ensino e a tecnologia.[2] De acesso fácil e gratuito, os *podcasts* encontram-se disponíveis de forma instantânea e vitalícia após a sua publicação, o que permite a sua utilização em tempo diferido.

O corpo docente da unidade curricular de Ginecologia da Faculdade de Medicina da Universidade de Coimbra (FMUC) desenvolveu, no presente ano letivo 2021/2022, o *podcast "The Gin´ Voice",* nome que surge da ideia de 'dar voz à Ginecologia'. Através da discussão de casos clínicos, em cada episódio são explorados os diferentes temas teóricos incluídos no programa curricular de ginecologia. Esta inovação no ensino pré-graduado está a ter uma excelente adesão por parte dos alunos do mestrado integrado em Medicina da FMUC, que têm confirmado, de forma inequívoca, a utilidade do *"The Gin´Voice"* como método eficaz de aprendizagem.

A pedagogia com recurso a *podcasts*, mergulhada neste sistema de inovação disruptiva, parece reunir as condições ideais para se tornar extensível ao ensino pós-graduado.

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