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Conselho Científico

Sustentabilidade Ambiental nos Sistemas de Saúde: O Papel da Anestesiologia

Environmental Sustainability in Healthcare Systems: The Role of Anaesthesiology

Carlos BARBOSA✉[1,2], Tiago FERNANDES[1,2]
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Palavras-chave: Alterações Climáticas; Anestesia; Anestésicos; Poluentes Ambientais; Poluição Ambiental
Keywords: Anesthesia; Anesthetics; Climate Change; Environmental Pollutants; Environmental Pollution

INTRODUÇÃO

Desde a Revolução Industrial que a atividade humana altera o ambiente terrestre de forma cada vez mais significativa. Em particular, as emissões de gases com efeito estufa (GEE) aumentam a um ritmo exponencial, resultando em concentrações atmosféricas de dióxido de carbono (CO_2), metano (CH_4) e protóxido de azoto (N_2O) sem precedentes. Uma característica destes gases é a capacidade de absorverem radiação IV (radiação emitida pela superfície terrestre) e de a reemitir para a superfície terrestre, limitando o mecanismo de perda de radiação terrestre. Este facto leva a um saldo energético positivo e, como consequência, a temperatura média da Terra subiu 1 a 1,2º C desde o ano de 1850.[1]

A Organização Mundial de Saúde declarou as alterações climáticas como o principal desafio para os cuidados de saúde no século XXI. O impacto na morbilidade e mortalidade é já hoje significativo. A poluição é responsável por nove a 12 milhões de mortes anualmente e a poluição atmosférica, em particular, por quatro milhões de mortes prematuras anuais.[2] A maioria do impacto deve-se ao seu contributo em 25% das mortes por doença cardiovascular e 50% das mortes por doença pulmonar obstrutiva crónica e cancro do pulmão.[2] Por sua vez, as alterações climáticas propriamente ditas provocam 150 000 mortes anualmente, devido a eventos climáticos extremos, escassez de água e alimentos, e aumento da incidência de certas doenças infeciosas, estimando-se que este valor suba para 250 000 já a partir da próxima década.[3] O sector da saúde é chamado a lidar com as crescentes consequências na saúde populacional, também por se encontrar do lado do problema como importante emissor de GEE.

IMPACTO CLIMÁTICO DOS CUIDADOS DE SAÚDE

Nos países ocidentais, estima-se que os cuidados de saúde sejam responsáveis por 4% a 10% das emissões de GEE.[4] Pela dimensão destes valores, percebe-se a importância de se procurarem medidas que visem a sua redução. As instituições podem avaliar a sua pegada de carbono através dos três Âmbitos do *Greenhouse Gas Protocol*. (Tabela 1). Enquanto o Âmbito 1 refere-se à emissão direta de GEE por parte da instituição, já os Âmbitos 2 e 3 correspondem a emissões indiretas, isto é, emissões que, apesar de serem consequência da atividade da instituição, ocorrem noutra entidade. A maioria das emissões associadas aos cuidados de saúde são indiretas, e o consumo de energia é responsável por mais de metade das emissões totais devido à extensa utilização de combustíveis fósseis na sua obtenção.[5]

O impacto dos diferentes produtos e equipamentos também pode ser quantificado, recorrendo a análises do ciclo de vida (*life cycle assessment*, LCA). Um LCA é uma abordagem padronizada (International Organization for Standardization - ISO 14040-44) que avalia o impacto ambiental de um produto ou processo ao longo do seu ciclo de vida: extração de matérias-primas, processamento, transporte, utilização, reutilização e eliminação. Este impacto é reportado frequentemente em 'equivalentes de CO_2', mas podem ser acrescentadas outras métricas, como gasto energético, consumo de água, poluição dos solos ou depleção de ozono. Esta abordagem é ideal para conhecer, comparar e escolher as melhores práticas, mas, devido à sua complexidade, ainda se encontra disponível num número reduzido de contextos, existindo (no caso da anestesia) apenas algumas comparações na área dos anestésicos inalatórios, intravenosos e anestesia locorregional.[6]

O PAPEL DA ANESTESIOLOGIA

O bloco operatório (BO) é um local com particular impacto, estimando-se que consuma três a seis vezes mais energia que os restantes serviços hospitalares e constitui uma fonte muito significativa de resíduos. A aplicação de LCA neste contexto identificou os gases anestésicos, equipamentos de uso único, aquecimento e ventilação como as principais fontes de emissões.[7] De salientar que a Anestesiologia contribui com 25% dos resíduos provenientes do BO, ocupando uma posição particular por ser responsável

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Tabela 1 – Quantificação da emissão de equivalentes de dióxido de carbono segundo os Âmbitos do *Greenhouse Gas Protocol*

	Definição	Exemplos
Âmbito 1	Emissões diretas de GEE[a] com origem em fontes controladas pela instituição de saúde.	Combustão de combustíveis fósseis (caldeiras, frota de veículos), gases medicinais.
Âmbito 2	Emissões indiretas resultantes da aquisição de energia pela instituição.	Aquisição de eletricidade.
Âmbito 3	Emissões indiretas resultantes de atividades da instituição não incluídas no Âmbito 2.	Gestão de resíduos, consumo de água, aquisição de produtos e serviços, deslocações de trabalhadores e utentes.

[a]GEE: gases com efeito estufa

pela emissão direta de GEE: os anestésicos inalatórios. Estes fármacos são responsáveis por até 5% da 'pegada de carbono' dos cuidados hospitalares, representando frequentemente a maioria das emissões diretas (Âmbito 1).[6,8]

Os gases halogenados (ex. isoflurano, sevoflurano e desflurano) e o N_2O são administrados por via inalatória e, sendo a sua metabolização negligenciável, a eliminação ocorre por via pulmonar com todo o gás a ser libertado para a atmosfera. Todos estes gases absorvem radiação IV dentro do espectro que em condições normais seria 'transparente', o que os torna potentes GEE. Na Tabela 2 é possível observar as propriedades dos diferentes gases referidos.[9] As diferenças principais entre estes encontram-se no tempo de vida atmosférico e na eficiência radiativa, que por sua vez lhes conferem diferentes potenciais de aquecimento global (*global warming potential*, GWP). O GWP é uma medida específica de cada gás que compara a acumulação de energia provocada por este em relação a uma massa semelhante de CO_2, num determinado período. Além das propriedades físicas, existem particularidades clínicas que também influenciam o impacto destes gases. Os anestésicos inalatórios têm diferentes potências, descritas como concentração alveolar mínima. O desflurano, sendo menos potente que o sevoflurano, implica a utilização de concentrações maiores para o mesmo efeito, tornando o seu efeito ambiental cerca de 50 vezes superior. O N_2O, ainda menos potente, é utilizado em concentrações 10 a 20 vezes superiores aos anteriores.

Com o objetivo de reduzir o impacto dos gases anestésicos, sociedades como a American Society of Anesthesiologists e a European Society of Anaesthesiology destacaram algumas atitudes: preferir sevoflurano sobre desflurano, evitar N_2O, utilizar baixo fluxo de gases frescos e optar por técnicas de anestesia regional ou intravenosa. Desconhece-se o impacto ambiental total das técnicas alternativas, tal como os consumíveis associados, mas é improvável que tenham maior emissão de GEE. O propofol, por exemplo, apresenta 1% do GWP do sevoflurano ao longo do seu ciclo de vida, mas é incerta a magnitude da poluição aquática.[6]

A crescente consciencialização desta problemática por parte dos profissionais impulsionou também a indústria a desenvolver tecnologias de adsorção de halogenados, eliminando o impacto das emissões diretas.[10] O processamento dos gases capturados poderá seguir diferentes vias: eliminação, transformação noutros compostos ou reaproveitamento para anestesia veterinária ou humana. O reaproveitamento está já a dar os primeiros passos, devendo este processo ser mais eficiente que a sua produção *de novo*, diminuindo ainda mais o seu impacto e funcionando como um exemplo de economia circular.

CONCLUSÃO

Os anestesiologistas podem otimizar a sua prática, de forma a diminuir o seu impacto ambiental sem comprometer a qualidade e a segurança dos cuidados prestados, um princípio chave na aplicação destas medidas. Nesta especialidade, como em todas as outras, vale a pena relembrar e reforçar um conceito útil e transversal para guiar outras atitudes: o dos cinco "**R**". **R**educir os consumos; **R**eutilizar material e equipamentos; **R**eciclar os resíduos; **R**epensar práticas e circuitos; Investigar (***R**esearch*) o impacto dos diferentes equipamentos e técnicas, bem como das tecnologias que ajudem na sua redução.

As questões ambientais ultrapassam a atividade assistencial. É necessário que haja consciencialização a todos os níveis da estrutura de decisão em saúde relativamente ao impacto ambiental da sua atividade, e de como muitas das medidas de sustentabilidade ambiental acarretam também vantagens económico-financeiras. Com as métricas e conhecimento atual, podemos desde já repensar a nossa prática de forma a selecionar as intervenções comprovadamente mais úteis, mais sustentáveis e que minimizam gastos desnecessários. A nível institucional, apenas com

Tabela 2 – Caraterísticas do protóxido de azoto e gases halogenados que contribuem para o seu efeito estufa

	CO_2	N_2O	Isoflurano	Sevoflurano	Desflurano
Tempo de vida atmosférico (anos)	120	114	3,2	1,1	14
Pico absorção IV (μm)	12 - 19	4,5; 7,8; 12,5 - 17,0	7,5 - 9,5	7 - 10	7,5 - 9,5
Eficiência radiativa (W m^{-2} ppb^{-1})	0,0000676	0,00303	0,453	0,351	0,469
GWP_{100}[a]	1	298	510	130	2540
Depleção de ozono	Não	Sim	Sim	Não	Não
MAC[b] (%)	-	104	1,17	1,8	6,6

[a]GWP_{100}: *global warming potencial* a 100 anos. [b]MAC: concentração alveolar mínima. Adaptado de Sulbaek *et al*.[9]

processos rigorosos e abrangentes de medição da 'pegada de carbono', bem como um plano para a sua gestão, conseguiremos identificar e implementar as medidas necessárias com vista à tão desejada neutralidade carbónica.

CONTRIBUTO DOS AUTORES

Ambos os autores contribuíram de igual forma para a conceptualização, pesquisa bibliográfica, escrita e revisão crítica do trabalho.

CONFLITOS DE INTERESSE

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

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Cross-Cultural Adaptation and Validation of the European Portuguese Version of the Western Ontario Shoulder Instability Index (WOSI)

Adaptação Cultural e Validação da Versão Portuguesa do Western Ontario Shoulder Instability Index (WOSI)

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ABSTRACT

Introduction: The Western Ontario Shoulder Instability Index (WOSI) is a self-administered questionnaire specifically used to determine the impact of shoulder instability on quality of life. The aim of this study was to translate the WOSI into European Portuguese and analyze its validity and reliability in a population with shoulder instability.

Material and Methods: The WOSI was translated and culturally adapted from its original version into European Portuguese (WOSI-PT). Internal consistency and test-retest analyses were conducted to determine the level of reliability of the scale. WOSI-PT, QuickDASH, and SF-12 questionnaires were applied to 81 patients with symptomatic shoulder instability to assess validity, and reliability was tested by randomly selecting 50 patients within 72 hours using a test-retest design.

Results: The reliability of the WOSI-PT was very high, with Cronbach´s alpha equal to 0.97 and an intraclass correlation coefficient of 0.98. Regarding the construct validity, the correlation between the WOSI-PT and QuickDASH was high and negative (-0.79). The correlations between WOSI-PT and SF-12 were positive, respectively, moderate with physical (0.66) and low with mental (0.34) health.

Conclusion: WOSI-PT is a reliable and valid instrument for assessing the functional impact of shoulder joint instability on quality of life.

Keywords: Cross-Cultural Comparison; Patient Outcome Assessment; Portugal; Quality of Life; Shoulder Dislocation; Shoulder Joint; Surveys and Questionnaires; Translations

RESUMO

Introdução: O *Western Ontario Shoulder Instability Index* (WOSI) é um questionário de autopreenchimento utilizado especificamente para determinar o impacto da instabilidade do ombro na qualidade de vida. O objetivo deste estudo foi traduzir o WOSI para português e analisar a sua validade e fiabilidade para a população portuguesa com instabilidade do ombro.

Material e Métodos: O WOSI foi traduzido e adaptado culturalmente da sua versão original para Português (WOSI-PT). Foram efetuadas as análises de consistência interna e teste-reteste para determinar o seu nível de fiabilidade. Os questionários WOSI-PT, QuickDASH, and SF-12 foram aplicados a 81 pacientes com sintomas de instabilidade para avaliar a validade, enquanto a fiabilidade foi testada usando 50 desses pacientes selecionados de modo aleatório, num estudo do tipo teste-reteste com 72 horas de intervalo.

Resultados: A fiabilidade do WOSI-PT foi excelente com alfa de Cronbach de 0,97 e um *intraclass correlation coeficiente* de 0.98. Relativamente à validade de constructo, a correlação entre o WOSI-PT e a QuickDASH foi alta e negativa (-0,79). A correlação entre o WOSI-PT e o SF-12 foi positiva e moderada para a componente física (0,66) e positiva e baixa para a componente de saúde mental (0,34).

Conclusão: O WOSI-PT é um instrumento fiável e válido para avaliar o impacto da instabilidade do ombro na qualidade de vida.

Palavras-chave: Articulação do Ombro; Avaliação de Resultados da Assistência ao Paciente; Comparação Transcultural; Inquéritos e Questionários; Luxação do Ombro; Portugal; Qualidade de Vida; Traduções

INTRODUCTION

Shoulder instability can be described as the inability to maintain the correct positioning of the humeral head in the scapular glenoid cavity during functional movements of the upper limb. This disability usually causes pain or discomfort and has an incidence of about 2% in the general population.[1] Shoulder instability may be classified as anterior, posterior, or multidirectional, and it may have a traumatic or non-traumatic origin. However, anterior traumatic instability is the most commonly described origin, and is predominant in middle and senior age individuals.[2]

The stability of the glenohumeral joint depends on the interaction of both static and dynamic-stabilizing structures. Static stabilizers include the bony anatomy, negative intra-articular pressure, the glenoid labrum, and the glenohumeral ligaments along with the joint capsule. The dynamic-stabilizing structures comprise the rotator cuff muscles and the other muscular structures surrounding the shoulder joint. The combined effect of these stabilizers is to support multiple degrees of motion within the glenohumeral joint.[3]

Several extrinsic risk factors are well described in

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shoulder instability, namely, those related to work or activity using the upper limbs above the head, impact sports, either in direct contact with other athletes or on the playing field, and intrinsic factors such as age and hypermobility of the joint complex.[2]

Traumatic dislocation of the glenohumeral joint is the most common injury among young athletes.[4] In fact, traumatic shoulder instability, such as subluxation and dislocation, is commonly associated with rugby players and wrestlers due to collisions between athletes, while instability resulting from repetitive microtrauma is usually associated with tennis, baseball, and volleyball players, as well as swimmers.[5] Nevertheless, this problem may also be job-related, such as painters and decorators or carpenters.

According to Perrin *et al,*[6] the subjective symptoms that predominate in shoulder instability are apprehension and lack of confidence to perform activities of daily living and sports.[7] These subjective symptoms lead to a decrease in participation in activities by patients, resulting in a negative impact on their quality of life.[6] Therefore, subjective clinical evaluation methods are important when used along with physical examination, having in mind the patient's opinion about his or her condition.[8] Moreover, these methods could provide relevant information about function and quality of life.[3]

However, instruments validated for the Portuguese population, such as the Shoulder Pain and Disability Index (SPADI)[9] and the Disabilities of the Arm, Shoulder and Hand (DASH),[10] aim essentially to measure the function and pain scores.[6] Furthermore, the DASH is not a shoulder-specific instrument, i.e., it is a tool to assess disabilities of the arm, shoulder, and hand.

The Western Ontario Shoulder Instability Index (WOSI), developed by Kirkley *et al*,[11] is a simple questionnaire designed for self-assessment of shoulder function in patients with instability problems and the impact of the condition on quality of life, and it has been suggested as being more effective due to its responsiveness.[12] It is also claimed to be one of the best self-reported measurement methods for patients with shoulder joint dysfunction.[13]

The WOSI aims to measure functionality and the impact of shoulder instability on quality of life. In comparison with the aforementioned questionnaires, WOSI is a more specific shoulder instability questionnaire as it contains twenty-one questions across four domains. The first domain contains 10 items on 'physical symptoms'; the second domain consists of four items directed to 'sports, recreational activities and work'; the third domain has four items related with 'lifestyle'; and finally, the fourth domain has three items on 'emotions'. Each item can be scored from 0 to 100 on the Visual Analog Scale. Thus, according to the authors of the original version, the results from the questionnaire range from 0 to 2100, where 0 means that the patient has 'no decrease in quality of life' relative to shoulder symptomatology, and 2100 means the patient has an extreme decrease in quality of life related with shoulder symptoms. However, a score ranging from 0 (worst) to 100 (best) was used to be comparable with other instruments, as the Short Form 36.[14]

Knowing that WOSI had not yet been validated for the Portuguese population, the aim of this work was to translate the WOSI into European Portuguese, to culturally adapt it, and to verify its reliability and validity.

MATERIAL AND METHODS

Permission to develop the Portuguese version of WOSI was obtained from the authors, who provided the original version. The study was approved by the Ethics Committee of the School of Health of the Polytechnic Institute of Porto (nº CE 0926).

Cross-cultural adaptation

The translation and cross-cultural adaptation process of the original WOSI questionnaire for the Portuguese population was performed according to the guidelines proposed by Reeve *et al*[15] and Mokkink *et al*.[16]

Translation of the WOSI questionnaire was performed independently by two native Portuguese professional translators. Thus, two different versions of the questionnaire were obtained. The obtained translations were discussed in an initial consensus panel that was comprised of both translators and members of this research team study, and a consensus was reached on a Portuguese translation.

This version was back-translated to English by two independent English translators. The translation and back-translations were compared by a second consensus panel composed of the last two translators and the same members of the research team who took part in the first panel.

In order to obtain a clinical perspective and to learn the most appropriate manner in which to communicate with Portuguese patients with shoulder instability, this last version was submitted to an orthopedic surgeon, an expert in shoulder assessment and surgery with over thirty years of experience in the field, and a physiotherapist with more than ten years of experience in shoulder rehabilitation.

Therefore, ten patients with shoulder instability completed the questionnaire, aiming to test its clarity, comprehension, and acceptability.

Validation study

Patients

The study was carried out with 103 patients with shoulder instability (anterior, posterior, multidirectional instability) who were selected from three local healthcare institutions. Twenty-two patients were later excluded as they did not meet the inclusion criteria or declined to participate in the study. The number of patients in the sample was determined following the recommendation of Altman, who states that the minimum number of patients must be 50 for methodological comparison.[17] The inclusion criteria were as follows: (1) eighteen years old or older; (2) diagnosed with shoulder symptomatic instability, whether anterior, posterior, or multidirectional, traumatic or non-traumatic; (3) a native Portuguese speaker and able to read Portuguese; and (4) receiving no treatment between test-retest

assessments. The exclusion criteria were as follows: (1) inability to complete the form due to significant psychiatric or psychological disorder; (2) having a neurological disease; (3) having systemic inflammatory conditions; and (4) having neoplastic disorders or cervical radiculopathy and thoracic outlet syndrome.

The study consisted of completing a questionnaire for demographic and disease characteristics, the WOSI-PT, the Quick Disabilities of the Arm, Shoulder and Hand Score (QuickDASH), and the Short Form 12 Health Survey (SF-12) questionnaires. However, in order to determine test-retest reliability, 50 of the 81 patients were randomly selected to repeat the WOSI-PT 72 hours later. This period of time was defined with the aim of avoiding the "memory effect" and ensure that patients remained in a stable clinical condition.

For the validation process the following instruments were used:

The QuickDASH, developed by Beaton *et al*[18] and validated for the Portuguese population by the authors Santos and Gonçalves, aims to measure the impact of a health condition on upper limb function and to measure the impact of healthcare provided after upper limb injury.[10]

The SF-12 was developed by Ware *et al*[19] and validated for the Portuguese population by Ferreira.[20] This questionnaire aims to measure and evaluate the general health status of subjects with and without disease.

Statistical analysis

The non-normality of distribution of values was verified with the Shapiro-Wilk test. Therefore, quantitative variables were described using the median and interquartile range (IQR) values, whereas the categorical variables were presented by frequency and percentage values.

Test-retest reliability of the WOSI-PT was assessed by intraclass correlation coefficient (ICC) and internal consistency analysis using Cronbach's alpha. Standard

Table 1 – Demographics and baseline characteristics of patients

Characteristics	**Total sample** (n = 81)	**Test-retest group** (n = 50)
Gender n (%)		
Male	37 (45.5)	17 (34.0)
Female	44 (54.3)	33 (66.0)
Age (years; X ± SD)	37.3 ± 17.6	42.4 ± 18.1
Body Mass Index (Kg/m^2; X ± SD)	25.7 ± 4.3	26.7 ± 4.7
Average duration of complaints (months; X ± SD)	27.1 ± 32.2	31.4 ± 35.4
Handedness n (%)		
Right	74 (91.4)	46 (92.0)
Left	7 (8.6)	4 (8.0)
Affected side n (%)		
Dominant	39 (48.1)	24 (48.0)
Non-dominant	15 (18.5)	7 (14.0)
Both	27 (33.4)	19 (38.0)
Type of Shoulder Problems n (%)		
Anterior Instability	58 (71.6)	40 (80.0)
Posterior Instability	2 (2.5)	1 (2.0)
Multidirectional instability	21 (25.9)	9 (18.0)
Questionnaire Score (Median ± IQR)		
WOSI total	60.1 ± 38.8	49.8 ± 27.9
WOSI Physical symptoms	61.0 ± 28.3	53.6 ± 18.5
WOSI Sports/recreation/work	56.1 ± 53.6	39.9 ± 27.4
WOSI Lifestyle	73.0 ± 50.7	51.9 ± 40.9
WOSI Emotional well-being	49.6 ± 41.7	33.7 ± 33.7
QuickDASH Total	31.8 ± 34.1	47.7 ± 30.1
QuickDASH Work	43.7 ± 43.7	62.5 ± 37.5
QuickDASH Sports	31.3 ± 39.1	43.7 ± 31.3
SF-12 Physical component	39.6 ± 14.4	36.8 ± 9.0
SF-12 Mental component	51.3 ± 46.3	46.1 ± 16.7

Values of WOSI and QuickDASH are expressed as percentage; Values of SF-12 physical component range from 24.0 to 56.6 points; Values of SF-12 mental component range from 19.1 to 60.9 points

measurement error (SEM) as well as minimal detectable change at the individual and group levels were calculated in the WOSI-PT total score and in all four domains. Regarding the sensitivity of the scale, floor and ceiling effect were measured.

For construct validity, three predefined analyses were performed: the correlations between WOSI-PT (and its domains) and QuickDASH total score, with QuickDASH modules and with SF-12.

The construct validity was analyzed using Spearman correlation, and the values were interpreted as follows: very high positive (or negative) correlation when greater than or equal to 0.90; high positive (or negative) correlation when between 0.70 to 0.89; moderate positive (or negative) when between 0.50 and 0.69; low positive (or negative) when between 0.30 and 0.49; and negligible correlation when less than 0.30.[21] The *p* values of 0.01 and 0.05 were taken as the reference level of significance. Due to the transformation of WOSI-PT to 100, ranging from "0 = Worst" to "100 = Best", as suggested by Angst *et al*,[14] a negative correlation with QuickDASH is expected, and a positive one with SF-12.

Statistical analyses were performed using the Statistical Package for Social Sciences Software (SPSS) version 24.0 (IBM Corporation, Chicago, IL, USA).

RESULTS

Cross-cultural adaptation

Some differences in sentence composition were found between the two translation versions. After the first consensus panel discussion, the translated version of WOSI was finalized. The back translation was then carried out and two back-translated versions were produced. Both were confirmed to have retained the questionnaire's original meaning. Turning to the process undertaken by the expert committee, the meaning of the words and expressions 'snapping', 'looseness', 'How much loss', and 'How much do you feel' in Portuguese were discussed, and words or expressions were selected that fit better with the original questions. As there were minor aspects in the comprehensibility test that were 'not well understood', they were replaced by other words within the same context. This version was again applied to 10 other participants, and, as there were no significant changes in the structure and evaluation properties, this final version was used for the validation study (WOSI-PT). Therefore, this version was used in the validation study without any additional modification, and no item was left blank.

Validation study

Demographic and disease-descriptive characteristics of patients are presented in Table 1. A total of 81 patients with clinical diagnosis of shoulder instability were included in the internal consistency and validity assessments, and 50 of them were randomly selected and included in the reproducibility and measurement error assessment. There were no missing data for any individual items on the WOSI-PT, QuickDASH, or SF-12.

Table 2 – Internal consistency, test-retest, standard error of measure, minimal detectable change and floor-ceiling effect analysis

WOSI-PT (Number of items)	Cronbach's alpha (n = 81)	Intraclass correlation coefficient (ICC) (n = 50)	Standard error of measure (n = 50)	Minimal detectable change: individual level (n = 50)	Minimal detectable change: group level (n = 50)	Floor–ceiling effect (%) (n = 50)
Physical symptoms (10)	0.93	0.97 (0.90 - 0.99)	3.73 (2.38 - 7.04)	10.35 (6.61 - 19.51)	1.46 (0.93 - 2.76)	0.0 - 0.0
Sports/recreation/work (4)	0.93	0.98 (0.93 - 0.99)	4.39 (2.89 - 7.49)	12.16 (8.02 - 20.75)	1.72 (1.13 - 2-94)	0.0 - 6.2
Lifestyle (4)	0.93	0.99 (0.98 - 0.99)	3.37 (2.47 - 4.48)	9.35 (6.86 - 12.43)	1.32 (0.97 - 1.76)	0.0 - 6.2
Emotional well-being (3)	0.77	0.97 (0.95 - 0.98)	4.52 (3.42 - 5.92)	12.53 (9.48 - 16.41)	1.77 (1.34 - 2.32)	1.2 - 1.2
Total (21)	0.97	0.98 (0.94 - 0.99)	3.10 (1.99 - 5.92)	8.60 (5.52 - 16.42)	1.22 (0.78 - 2.32)	0.0 - 0.0

Confidence interval of 95%

Reliability and sensitivity

The results of internal consistency, reproducibility, as well as standard error of measure, minimal detectable change (individual and group levels), and the floor and ceiling effects are presented in Table 2. Cronbach´s alpha coefficient (0.97) indicates a high level of internal consistency in the WOSI-PT questionnaire. When analyzing Cronbach´s alpha coefficient for each domain, 'emotional well-being' had the least internal consistency (0.77). Nevertheless, this value was still not found to be below the cut-off value.

The test-retest analysis of the total score of the WOSI-PT showed very high ICC (0.98). In the same manner, high ICC values were verified in 'physical symptoms', 'sports/recreation/work', 'life-style', and 'emotional well-being', ranging from 0.97 - 0.99. Therefore, the WOSI-PT, as well as each domain, are stable over time. Additionally, the SEM recorded was 3.1 points, and the minimal detectable change at individual and group levels was 8.60 and 1.22 points, respectively.

Regarding to the floor-ceiling effects, the analysis of the worst-best status values revealed no floor-ceiling effect (less than 15%) [29] in total score (0%) nor in the different modules (0-6.2%).

Construct validity

In order to analyse the convergent validity, a correlation analysis of WOSI-PT with QuickDASH and SF-12 questionnaires was conducted (Table 3).

The total score of WOSI-PT had a high negative correlation with the total score of QuickDASH (-0.798), as did WOSI-PT with the module 'work' in QuickDASH (-0.733); while the correlation between WOSI-PT and the module 'sports' in QuickDASH was positive and moderate (0.544). Moreover, a good correlation was found between WOSI-PT and the Physical component of SF-12 (0.666), and a moderate correlation was found between WOSI-PT and the mental component of SF-12 (0.354).

DISCUSSION

The aim of this study was to translate and culturally adapt the WOSI Index into European Portuguese and to verify its reliability and validity.

The WOSI questionnaire is an instrument to specifically measure functionality and the impact of shoulder instability on quality of life, in contrast with other validated scales for the Portuguese population which are not specific for shoulder instability. Therefore, it was important to have a tool to determine, for example, the effect of treatment on shoulder instability and/or the impact of this disorder on quality of daily life. The results of the present study showed that WOSI-PT is a reliable and valid instrument; consequently, it can be used for this specific shoulder disability, thus fulfilling the purposes of the original version.

In fact, the Cronbach's alpha analysis showed a high level of internal consistency in the WOSI-PT. The value of 0.97 was comparable to that of other validation studies.[1,3,6,12] The extremely high value of Cronbach's alpha suggests that the Portuguese version of WOSI could have certain items with some redundancy. However, when analyzing the four different domains of WOSI-PT, the Cronbach's alpha ranged from 0.77 to 0.93, confirming the good consistency of each domain of the scale. In examining the internal consistency of WOSI validated for other countries, a Cronbach's alpha of 0.91 in the Turkish version,[3] 0.92 in the Dutch version,[22] and 0.95 in the Sweden version[12] were found.

The results also demonstrated excellent reproducibility for the WOSI-PT, with an ICC of 0.98 (IC 0.94 - 0.99), and all four domains ranged from 0.97 to 0.99, being in agreement with several other WOSI validations.[3,12,22]

Our results recorded a SEM of 3.1% (65 out of 2100 points) and an MDC of 8.6% (180 out of 2100 points), for a 72 hours interval, indicating that an improvement in the WOSI-PT of at least 181 points between two different assessment moments could be considered significant, independently of measurement error. These results agreed with several others, such as those found by Cacchio *et al* (2012) (SEM of 3.4% and MDC 95% of 9.3%),[23] Van der Linde *et al* (SEM of 8.3% and MDC 95% of 23%),[24] and Wiertsema *et al* (SEM of 6.2% and MDC95% of 17.2%).[22]

Descriptive statistical analysis showed that there are no floor nor ceiling effects in the WOSI-PT (*n* 81 0–0%). According to Arafat et al. (2016),[25] the floor-ceiling effect is present when over 15% of the subjects obtained the lowest or highest possible scores on the scale, which indicates the proportion for whom no meaningful deterioration or improvement in their condition could be detected since they are already at the extreme of the range. Therefore, it is possible to determine changes in the clinical conditions of

Table 3 – Spearman correlation analysis of WOSI-PT with QuickDASH and SF-12 questionnaires

WOSI-PT	QuickDASH			SF-12	
	Total	Work	Sports	Physical	Mental
Physical symptoms	-0.768**	-0.738**	-0.489*	0.631**	0.347*
Sports/recreation/work	-0.794**	-0.758**	-0.638**	0.681**	0.364**
Lifestyle	-0.761**	-0.709**	-0.453*	0.654**	0.339*
Emotional well-being	-0.541**	-0.374*	-0.532**	0.379**	0.262*
Total	-0.798**	-0.733**	-0.544**	0.666**	0.354**

WOSI -PT: Western Ontario Shoulder Instability index of the Portuguese version; QuickDash: The Quick Disabilities of the Arm, Shoulder and Hand score; SF-12: Short Form 12 Health Survey

*: correlation is significant at $p < 0.05$; **: correlation is significant at $p < 0.01$

patients more precisely.

Regarding validity, the WOSI-PT reported a high negative correlation (- 0.798) with QuickDASH, which is in agreement with results found in the validation process for the Turkish (0.67)[3] and Dutch (0.81) versions.[22] It is important to stress that both WOSI-PT and QuickDASH scored "0" as 'no limitations'. Nevertheless, the negative correlation in our study is attributed to the inversion of the scale.

After analyzing the correlations between the domains of WOSI-PT and QuickDASH, high negative correlations with 'physical symptoms' (-0.768), 'sports/recreation/work' (-0.794), and 'life-style' (-0.761) were found; in contrast, the correlation of the WOSI 'emotional well-being' domain with QuickDASH showed a moderate negative correlation (- 0.541).

The physical and mental components of SF-12 were also correlated with WOSI-PT, and a moderate positive correlation was found for the Physical component (0.666); as expected, a low positive correlation with the mental component (0.354) was found.

One limitation of our study was the fact that the responsiveness analysis, which is important to understand the sensitivity of the scale to detect clinically important changes over time, was not executed, even when the changes were small.

CONCLUSION

The Portuguese version of WOSI questionnaire is a reliable and valid tool to measure shoulder-related quality of life in patients with symptomatic shoulder instability.

AUTHORS CONTRIBUTION

All the authors had an equal contribution to the literature research, draft and distribution of the questionnaire, analysis of the results and draft 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

The authors have declared that no competing interests exist nor any form of support.

INFORMED CONSENT

Informed consent was obtained from all patients included in the study.

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Real-World Characterization of the Portuguese Population Living with HIV who Initiated Raltegravir Based-Regimens: The REALITY Study

Caracterização da População Portuguesa com VIH que Iniciou um Regime Baseado em Raltegravir: O Estudo REALITY

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ABSTRACT

Introduction: Although raltegravir has been available since 2007, data are lacking on the Portuguese population living with HIV who initiated this antiretroviral therapy. Hence, this study aimed to characterize the patients who initiated raltegravir-based regimens between January 2015 and December 2017, on sociodemographics, clinical features, and treatment satisfaction.

Material and Methods: Observational, retrospective, multicentre study conducted at 11 reference sites. Sociodemographic and clinical data were collected retrospectively from hospital medical records. For participants continuing raltegravir at study inclusion, the HIV Treatment Satisfaction Questionnaire was administered to assess satisfaction with raltegravir-based therapy. Descriptive statistics were performed. Treatment-naïve and treatment-experienced subgroups were compared for demographic and clinical variables.

Results: A total of 302 patients were included; mostly men (69.5%) with a mean age of 49 years old. Approximately half of the patients had at least one non-AIDS-related comorbidity at baseline (53.3%), such as hypercholesterolemia, arterial hypertension, diabetes mellitus, and depression. Moreover, 52.3% were treatment-experienced patients with up to two treatments prior to raltegravir. Across the study time points, there was a reduction in the viral load and improvement in CD4 counts in both the treatment-naïve and treatment-experienced subgroups. Continuing users of raltegravir reported high treatment satisfaction (55.4 ± 7.2 points).

Conclusion: Raltegravir-based regimens seem like a valid therapeutic option in heterogeneous populations of HIV-infected patients, in patients with previous ART experience and as part of first-line therapeutic options alongside with the latest generation of drugs from its class.

Keywords: Anti-Retroviral Agents; HIV Infections/complications; HIV Infections/drug therapy; Portugal; Raltegravir Potassium/therapeutic use

RESUMO

Introdução: Apesar de o raltegravir estar disponível desde 2007, os dados na população portuguesa com VIH que iniciou esta terapêutica antirretroviral são escassos. Deste modo, este estudo teve por objetivo caracterizar os doentes que iniciaram um regime terapêutico baseado em raltegravir entre janeiro de 2015 e dezembro de 2017, relativamente a dados sociodemográficos, características clínicas e satisfação com o tratamento.

Material e Métodos: Estudo observacional, retrospetivo, multicêntrico conduzido em 11 centros de referência. Os dados sociodemográficos e clínicos foram recolhidos retrospetivamente nos processos clínicos. Os participantes que continuaram o regime com raltegravir após a inclusão no estudo preencheram o *HIV Treatment Satisfaction Questionnaire* para avaliar a satisfação com a terapêutica. Foram efetuadas análises de estatística descritiva e comparações para as variáveis sociodemográficas e clínicas nos subgrupos de doentes *naïve* de tratamento e de doentes com experiência terapêutica.

Resultados: Foram incluídos 302 doentes, maioritariamente do sexo masculino (69,5%) com idade média de 49 anos. Aproximadamente metade dos doentes tinha pelo menos uma comorbilidade não relacionada com SIDA no início do estudo (53,3%), tais como hipercolesterolemia, hipertensão arterial, diabetes *mellitus* ou depressão. Adicionalmente, 52,3% eram doentes com experiência terapêutica com até dois tratamentos anteriores ao raltegravir. Ao longo do estudo verificou-se uma redução na carga viral e uma melhoria nas contagens de CD4 em ambos os subgrupos de doentes (doentes *naïve* de tratamento e doentes com experiência terapêutica). Os doentes com uso continuado de raltegravir reportaram uma elevada satisfação com o tratamento (55,4 ± 7,2 pontos).

Conclusão: Os regimes terapêuticos baseados em raltegravir parecem ser uma opção terapêutica válida em populações

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heterogéneas de doentes infetados com VIH, em doentes com experiência em ART e como tratamento de primeira linha, em paralelo com outras terapêuticas de última geração.

Palavras-chave: Antirretrovirais; Infecções por VIH/complicações; Infecções por VIH/tratamento farmacológico; Portugal; Raltegravir Potássico/uso terapêutico

INTRODUCTION

The human immunodeficiency virus (HIV) infection is currently a chronic disease, for which new challenges arise, such as the search for life-long, effective, and safe treatments.[1] New available antiretroviral therapies (ART) show similar high efficacy rates in clinical trials.[2] Real-world data can provide a comprehensive characterization of different patients and an understanding of how to achieve an individualized care plan for specific subgroups of HIV-infected individuals.[3,4]

Raltegravir (RAL) is an HIV-1 integrase inhibitor that demonstrates potent antiretroviral activity and well-tolerated oral administration, with few drug-drug interactions.[5,6] Several clinical trials support the efficacy and safety profile in both treatment-naïve and experienced adults infected with HIV-1.[7-13] Real-world cohort studies confirm the effectiveness and tolerability of RAL in clinical practice, and the potential use of this drug in different subsets of patients (e.g., with previous treatment for HIV / non-naive, pregnant, co-infected).[14-16]

Between 1983 and 2019, 61 433 individuals had HIV in Portugal [2020 data from the Directorate-General of Health (DGS)] and, in late 2018, there were 41 305 people living with HIV (prevalence of 0.40%).[17] In this study, we aimed to characterize, for the first time, patients treated with RAL in clinical practice, the sociodemographics, and the satisfaction with treatment among those receiving treatment with RAL. Furthermore, in an exploratory analysis, treatment-naïve and treatment-experienced patients were compared for the viral, immunological, and clinical variables.

MATERIAL AND METHODS

This was an observational, retrospective study conducted at 11 Portuguese reference centers with structured HIV Units in the Portuguese mainland. All study procedures were performed under routine clinical practice. The study was approved by each site's Ethics Committee.

Between July 2018 and April 2019, written informed consent was obtained during a routine medical appointment and patients were included in the study if they were HIV-1, aged ≥ 18 years old at baseline, and initiated RAL between January 2015 and December 2017. Baseline was defined as the time of initiation of RAL-based therapy. Both treatment-naïve and treatment-experienced patients were included. The participant's medical records must have had, at least, the following information: age, sex, date of diagnosis of HIV infection, date of RAL initiation, CD4 counts, and viral load (VL) at baseline. Patients were excluded if enrolled in a clinical trial during the observation period with or without RAL, or if unable/unwilling to comply with study requirements according to the investigator's opinion. In order to minimize selection bias, patients were enrolled in a consecutive manner.

Considering the expected number of patients under treatment with RAL-based regimens (2880 medical records screened), the minimal possible sample established to achieve a precision ≈ 5% for any estimated proportion of the patient's characteristics, with 95% CI, was a sample size of 296 patients. By the time of RAL initiation in this study (between 2015 and 2017), only RAL 400 mg (BID) was available in Portugal. RAL 600 mg was granted reimbursement by the Portuguese medicines agency (INFARMED, I.P.) in December 2018 and, therefore, all study participants were on RAL 400 mg. Treatment switch between RAL formulations was not collected in this study.

Measures

Sociodemographic and clinical characteristics

Sociodemographic and clinical data were collected retrospectively from hospital medical records. Demographics included age at baseline, sex, and country of origin; addictive behaviors included smoking (current or past smoker, or never smoked), diagnosis of chronic alcoholism,[18] and illicit drug use (current or past user, or never used).

Clinical data related with HIV infection covered the following: duration of HIV infection, mode of transmission, CDC stage 1993 Revision[19] (classified in A—clinical categories; B—symptomatic conditions or C—AIDS diagnosis), hepatitis B or C co-infection, plasma HIV RNA (viral load), and CD4 counts at diagnosis (i.e., date of diagnosis of HIV infection), at baseline (i.e., initiation of RAL-based therapy), and at last measurement (i.e., last laboratory value reported in the patients' chart regardless of ART regimen—patients could be or not on RAL). Duration of HIV infection was defined as the time between diagnosis and baseline (i.e., initiation of RAL-based therapy).

Non-AIDS-related comorbidities

Non-AIDS-related comorbidities (NARC) were obtained from the medical records, including hypercholesterolemia, arterial hypertension, anxiety/depression, chronic hepatitis C, diabetes mellitus, nephrolithiasis, emphysema/bronchitis, renal failure, malignancy, osteoporosis, and chronic hepatitis B. The number and type of non-AIDS-related comorbidities were calculated based on the number of patients with at least one reported non-AIDS-related comorbidity (n = 161 patients). These variables were considered of interest based on their high prevalence in the Portuguese population and clinical relevance in the HIV-infected population, as described in a previous population-based study.[20]

Antiretroviral treatment

For treatment-experienced patients, data on previous ART regimens were collected, namely the therapeutic class of last ART, before RAL-based therapy, and the number of

previous treatments. RAL-based regimens were described for treatment duration (i.e., start date to the last visit reporting RAL-based therapy), and continuing use at the study visit.

The number and type of previous ART regimens were calculated based on the number of treatment-experienced patients (n = 199 patients).

Treatment satisfaction with RAL-based regimen

For those patients who were RAL-continuing users, a patient-reported questionnaire was administered during the study visit, to assess the satisfaction with RAL treatment (HIV treatment Satisfaction Questionnaire, HIVTSQs©).[21-23] The Portuguese version of the HIVTSQs© (version 8.4.10) used in this study has been linguistically validated, including review by a clinician and pilot testing in Portuguese patients.

Statistical analysis

All patients fulfilling the selection criteria were included for statistical analysis. Descriptive statistics were performed. Continuous variables were summarized as mean ± standard deviation (SD), median, range, and interquartile range (IQR); categorical variables were summarized as absolute and relative frequencies. CD4 counts were presented by thresholds (≤ 200 cells/mm^3; 201 - 500 cells/mm^3; > 500 cells/mm^3), as well as for VL (≤ 50 copies/mL; > 50 copies/mL).

The HIVTSQs© score derived from two subscales (General Satisfaction and Lifestyle) grouped together to produce the treatment satisfaction total score (range: 0 - 60 points).[20-22] The higher the score, the greater the treatment satisfaction. Internal consistency reliability of the 10-item treatment satisfaction scale (HIVTSQs©) was assessed using Cronbach's alpha coefficient.

As part of the exploratory objectives of this study, treatment-naïve and treatment-experienced subgroups were compared for quantitative variables (CD4 counts, VL) by *t*-test or Mann-Whitney nonparametric test, according to the assumption validations of the statistical test. Comparisons between subgroups regarding categorical variables were tested through Chi-square test or Fisher exact test, when assumptions of Chi-square test were not met.

Associations of independent variables of interest with time to discontinuation of RAL-based regimens were explored based on Kaplan-Meier survival analyses and log rank test. Treatment maintenance was estimated according to RAL treatment duration in months (dependent variable). Hazard ratios (HR) were estimated through Cox regression method to measure the magnitude of risk differences between comparative subgroups. Associations of RAL-based treatment satisfaction (total score and items) with independent variables of interest were assessed by Spearman's rank correlation (quantitative variables) and Mann-Whitney/Kruskal-Wallis (categorical variables).

No imputation of missing data was performed. All comparisons were two-tailed and statistical significance was set at 5%. All analyses were conducted with SAS software (version 9.4; SAS Institute Inc, Cary, USA).

RESULTS

Sociodemographic characteristics

Table 1 summarizes the baseline sociodemographics of the 302 patients included in this study. At baseline, 69.5% patients were males, with a mean age of 49 years;-and approximately half of the patients were above 50 years old (47.0%).

Non-AIDS-related comorbidities

Percentage of NARC was determined in the group of patients reporting any baseline comorbidity (n = 161) and in all study participants (n = 302). More than half of the patients (53.3%) had at least one NARC at baseline (time of initiation of RAL for each patient) (Fig. 1A).

Among those patients who reported baseline comorbidities (n = 161), the most frequent were hypercholesterolemia (44.1%), arterial hypertension (42.2%), diabetes mellitus (17.4%), and depression (17.4%). The same pattern was observed for baseline comorbidities in all participants (n = 302): hypercholesterolemia (23.5%), arterial hypertension (22.5%), diabetes mellitus (9.3%), and depression (9.3%).

Renal failure was also common (11.8% in patients with any comorbidity and 6.3% in all participants). Other comorbidities were described in 70 patients (43.5% of patients with any comorbidity and 23.2% of all participants), including chronic hepatitis C (three patients), cirrhosis (four patients), epilepsy (four patients), and obesity (six patients). Participants with any comorbidity had a mean of 2.0 comorbidities, while 50 reported three or more comorbidities (Fig. 1B).

Clinical HIV characteristics

Clinical characteristics related with HIV infection were described for all study time points (Table 2). The main transmission mode was heterosexual sex (58.0%), followed by men who have sex with men (MSM, 23.0%), and intravenous drug use (IDU, 18.0%). At diagnosis, most patients were at CDC stage A (68.7%). Additionally, 57.3% had a late diagnosis (i.e., CD4 counts < 350 cells/mm^3). Plasma HIV RNA levels (viral load) decreased to viral suppression in most patients (96.0% with ≤ 50 copies/mL at last measurement). The CD4 count increased from diagnosis until last measurement, with 24.8% of the patients having > 500 cells/mm^3 at diagnosis, followed by 46.7% at baseline, and 67.5% at last measurement. Most participants reported no hepatitis B or C co-infection throughout the study time points.

Antiretroviral treatment

Overall, 103 patients (34.1%) were treatment-naïve and 199 (65.9%) were treatment-experienced before initiation of RAL-based therapy. Fig. 2 depicts the number and therapeutic class of last ART. Protease inhibitors (PI)-based therapy (50.8%) and non-nucleoside reverse transcriptase inhibitors (NNRTI)-based therapy (40.2%) were the most

Table 1 – Sociodemographic characteristics of study participants at baseline

Sociodemographic characteristics	n (302)
Sex, n (%)	
Male	210 (69.5%)
Female	92 (30.5%)
Age at baseline*, years	
Mean ± SD	49.1 ± 12.7
Median (min. – max.)	48.0 (19.0 – 92.0)
IQR (Q3 – Q1)	16.0 (57.0 – 41.0)
Geographic origin, n (%)	
Portugal	251 (83.1%)
Brazil	12 (4.0%)
Cape Verde	12 (4.0%)
Other	27 (8.9%)
Smoking status, n (%)	
Current smoker	110 (39.6%)
Former smoker	45 (16.2%)
Never smoker	123 (44.2%)
Unknown	24
Diagnosis of chronic alcoholism, n (%)	
Yes	20 (6.6%)
No	282 (93.4%)
If yes, duration of chronic alcoholism, years (n = 14)	
Mean ± SD	8.6 ± 6.1
Median (min. – max.)	8.0 (0.1 – 17.8)
Missing values	6
Illicit drug use, n (%)	
Never used	230 (76.2%)
Past use	65 (21.5%)
Current use	7 (2.3%)
If past use, substance†, n (%)	
Heroin	50 (76.9%)
Cocaine	32 (49.2%)
Cannabis	9 (13.8%)
Ecstasy	3 (4.6%)
LSD	1 (1.5%)
Other	4 (6.2%)
If current use, substance*, n (%)	
Cocaine	4 (57.1%)
Cannabis	3 (42.9%)
Heroin	2 (28.6%)
Ecstasy	1 (14.3%)
LSD	1 (14.3%)

min.: minimum; max.: maximum: LSD: lysergic acid diethylamide; SD: standard deviation
*: baseline was defined as the time of initiation of RAL-based therapy
†: patients could report more than one option

common ART classes prior to RAL (Fig. 2A). For treatment-experienced patients, the mean duration of previous ART regimens was 4.2 ± 3.2 years (median: 3.7; range: 0.003 - 14.9 years). The number of previous ART regimens ranged between 1 and 11, and 52.3% of the patients received up to two ART regimens (Fig. 2B).

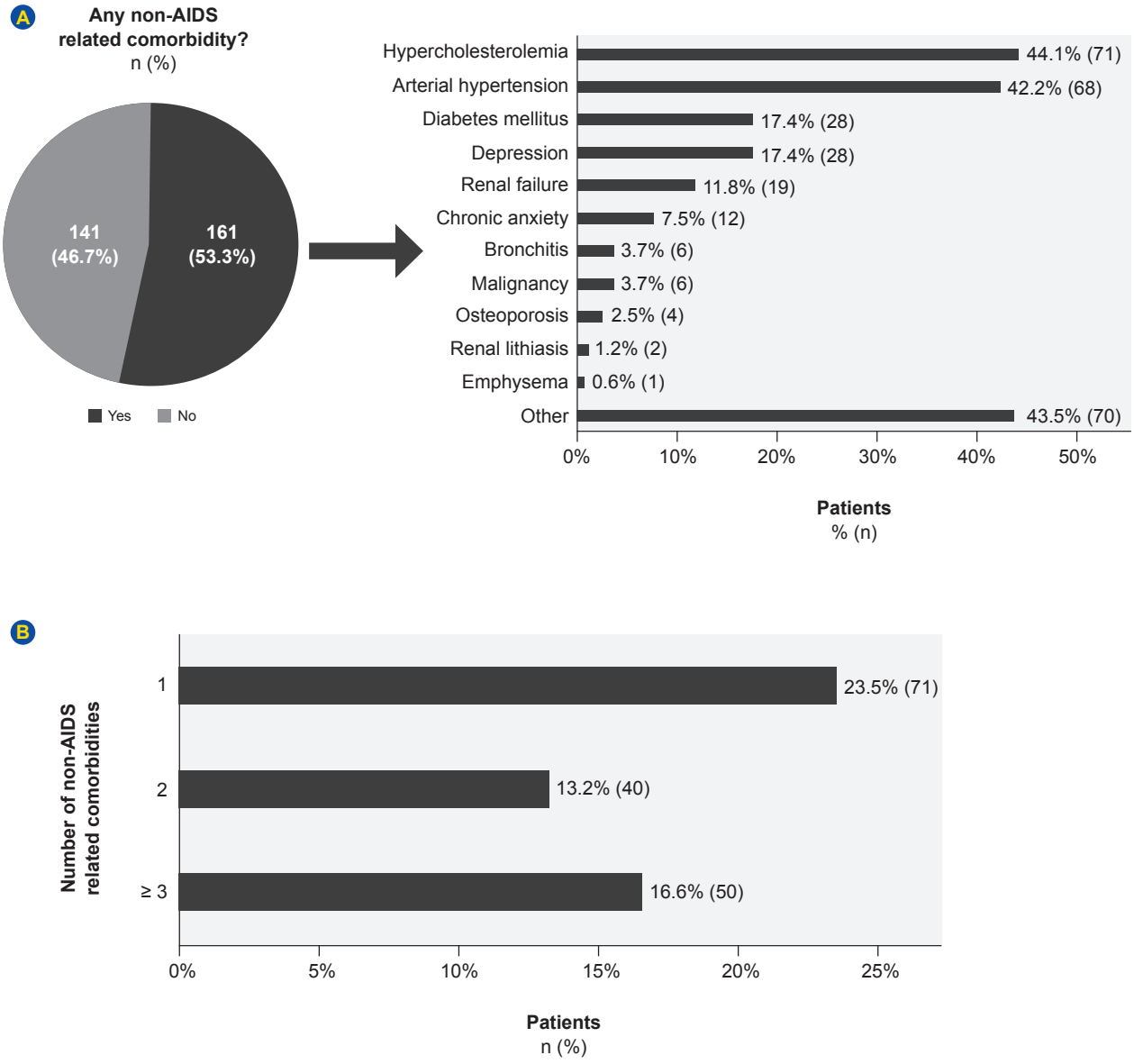

Figure 1 – Non-AIDS-related comorbidities of study participants at baseline: (A) Type of Non-AIDS-related comorbidities; (B) Number of Non-AIDS-related comorbidities

The median time between diagnosis and initiation of the first ART regimen was 6.8 years (i.e., 82.0 months). Most participants (80.8%; 244/302) continued to take RAL at the inclusion visit and the median duration of RAL-based therapies was 2.1 years, considering the time of the study visit as the cut-off.

Treatment satisfaction with RAL-based regimen

In our study, Cronbach's alpha coefficient showed an excellent internal consistency (> 0.9)[24] for reliability of the total score (0.9175). Participants who continued RAL-based therapies at the inclusion visit reported a high satisfaction with a total mean score of treatment satisfaction of 55.4 ± 7.2 points.

Treatment-naïve *versus* treatment-experienced patients

Treatment-experienced patients had a higher median age than treatment-naïve patients (50 years *vs* 43 years, $p < 0.0001$) (S1 Table in Appendix 1: https://www.actamedica-portuguesa.com/revista/index.php/amp/article/view/16785/Appendix_01.pdf).

HIV infection-related characteristics were also described for the two subgroups (Table 3). As expected, treatment-naïve patients had a shorter median duration of HIV infection that was statistically significant, compared to treatment-experienced patients (0.21 years *vs* 12.37 years, $p < 0.0001$). Furthermore, 75.8% of treatment-naïve and 64.8% of treatment-experienced patients were diagnosed at CDC stage A ($p = 0.036$). The proportion of non-co-infected patients at baseline was lower in the treatment-experienced subgroup than in the treatment-naïve subgroup (78.2% *vs* 92.2%, $p = 0.009$). At baseline (RAL initiation), treatment-naïve patients showed a lower median value of CD4 count (336.0 cells/mm^3 *vs* 573.0 cells/mm^3, $p < 0.0001$) and all had a

Table 2 – Clinical characteristics associated with HIV infection, at diagnosis, baseline (RAL initiation) and last measurement

Clinical characteristics associated with HIV infection	At diagnosis*	At baseline†	Last measurement§
Duration of HIV infection at baseline, years			
n	302	-	-
Mean ± SD	8.5 ± 7.5		
Median (min. – max.)	8.0 (0.0 – 28.5)	-	-
IQR (Q3 – Q1)	14.2 (14.7 – 0.5)	-	-
Mode of transmission, n (%)			
Men who have sex with men (MSM)	69 (23.0%)	-	-
Heterosexual sex	174 (58.0%)	-	-
Intravenous drug use (IDU)	54 (18.0%)	-	-
Parenteral	1 (0.3%)		
Other	2 (0.7%)		
Total	300	-	-
Unknown	2	-	-
CDC HIV stage of disease, n (%)			
A	189 (68.7%)	-	-
B	33 (12.0%)	-	-
C	53 (19.3%)	-	-
Total	275	-	-
Unknown	27	-	-
CD4 counts, cells/mm^3			
n	262	302	302
≤ 200 cells/mm^3, n (%)	96 (36.6%)	52 (17.2%)	13 (4.3%)
201 - 500 cells/mm^3, n (%)	101 (38.5%)	109 (36.1%)	85 (28.1%)
> 500 cells/mm^3, n (%)	65 (24.8%)	141 (46.7%)	204 (67.5%)
Late diagnosis (< 350 cells/mm^3)	150 (57.3%)	-	-
Non-late diagnosis (≥ 350 cells/mm^3)	112 (42.7%)	-	-
Plasma HIV – RNA, viral load, copies/mL			
n	238	302	302
≤ 50 copies/mL, n (%)	2 (0.8%)	154 (51.0%)	290 (96.0%)
> 50 copies/mL, n (%)	236 (99.2%)	148 (49.0%)	12 (4.0%)
Co-infection, n (%)			
Hepatitis B	8 (2.7%)	8 (2.7%)	8 (2.7%)
Hepatitis C	58 (19.7%)	43 (14.4%)	12 (4.0%)
No co-infection	228 (77.6%)	248 (82.9%)	279 (93.3%)
Unknown	8	3	3

min.: minimum; max.: maximum; IDU: intravenous drug use; IQR: interquartile range; HIV: human immunodeficiency virus; MSM: men who have sex with men; SD: standard deviation
*: diagnosis was defined as the date of diagnosis of HIV infection.
†: baseline was defined as the time of initiation of Raltegravir-based therapy.
§: last measurement was defined as the last laboratory value reported in patient's chart, regardless of the antiretroviral regimen (patients could or not be on RAL).

detectable VL, compared to treatment-experienced patients. At diagnosis and last measurement, no statistically significant differences were observed between the two subgroups.

The mean duration of RAL-based therapy was very similar between treatment-naïve and treatment-experienced patients [25.0 vs. 25.5 months, $p = 0.747$ (*t*-test)].

The proportion of treatment-naïve patients with no comorbidities was significantly higher than for the treatment-experienced subgroup (63.1% *vs* 38.2%; $p = 0.0001$). Moreover, the median number of comorbidities was lower in treatment-naïve compared to treatment-experienced patients (1 NARC *vs* 2 NARCs, $p = 0.0077$) (S2 Table in Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16785/Appendix_01.pdf). However, a statistically significant higher proportion of patients with hypercholesterolemia was found in the group of treatment-experienced patients (48.8% *vs* 28.9% in treatment-naïve patients, $p = 0.0314$).

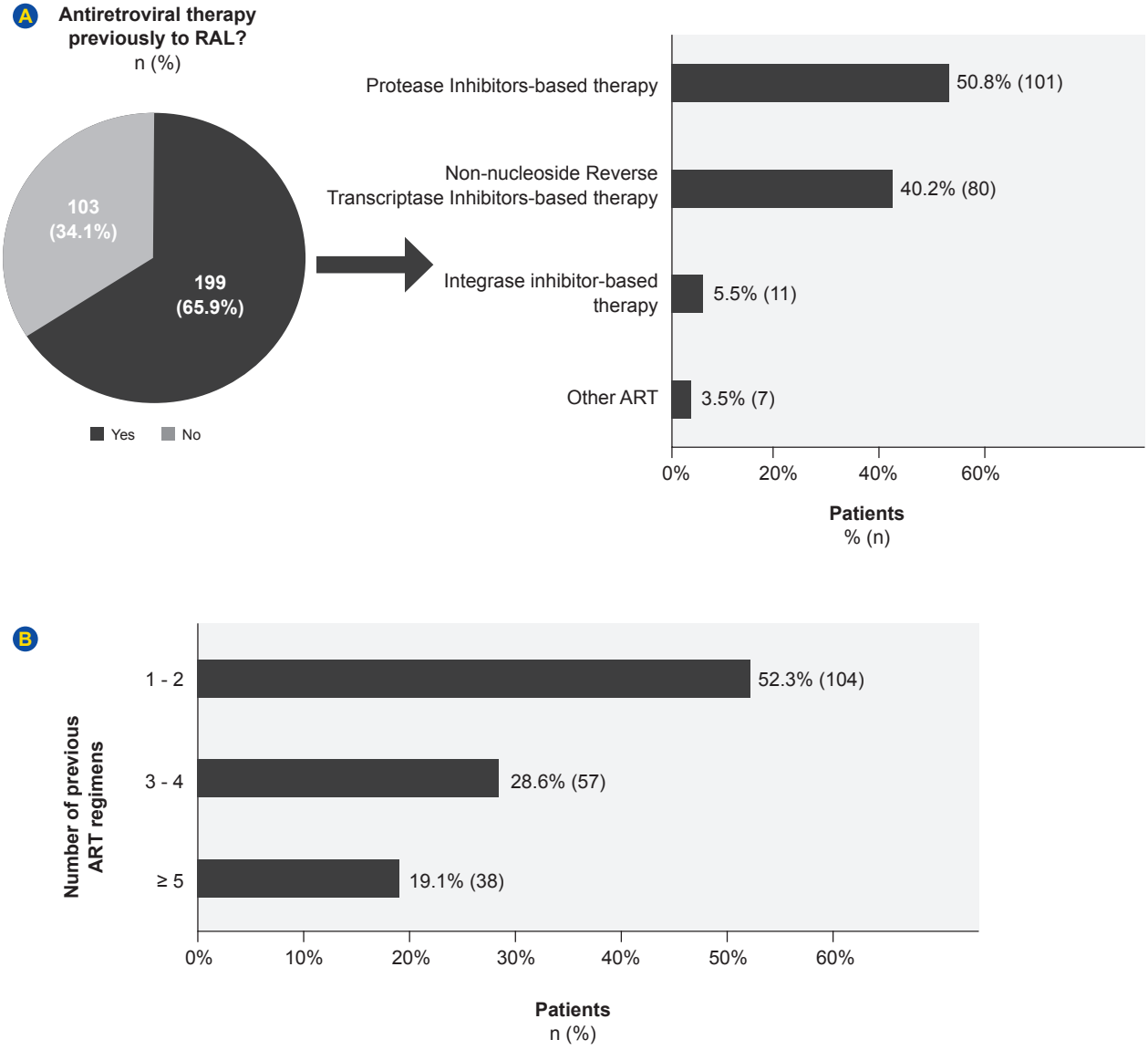

Figure 2 – Characteristics of previous ART regimens in treatment-experienced patients: (A) Type of ART regimen; (B) Number of ART regimens

Associations of independent variables of interest with time to discontinuation of RAL-based treatment and with RAL-based treatment satisfaction

The associations of time to discontinuation of RAL-based regimens and treatment satisfaction of RAL-continuing users assessed for independent variables are shown in Appendix 1, S3 and S4 Tables, respectively (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16785/Appendix_01.pdf).

Kaplan-Meier estimates for treatment maintenance at 48 months were determined based on the proportion of patients who continued RAL-based regimens. The results suggested that patients with longer time between previous ART regimen and RAL initiation had a slightly higher risk of discontinuation [HR = 1.016, (95%CI: 1.002 to 1.030)], meaning an increase of 1.6% per month in the time between last ART and initiation of RAL therapy.

Significant differences were found for score items in subgroups according to sex, viral load at baseline and co-infection (S5 to S7 Tables in Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16785/Appendix_01.pdf).

DISCUSSION

The REALITY study characterized a large and representative sample of Portuguese HIV-infected patients who initiated RAL-based regimens, between January 2015 and December 2017, and investigated potential differences in specific subgroups. Almost half of the participants were aged 50 years old, and most were born in Portugal (83.1%). As expected, most patients were men (69.5%); however, the proportion of HIV-infected women in this study was higher than that in most EU/EEA countries in 2019.[25] More than half of the patients were current or past smokers (55.8%)

Table 3 – HIV infection characteristics of treatment-naïve versus treatment-experienced patients

Clinical characteristics associated with HIV infection	Treatment-naïve patients (n = 103)	Treatment-experienced patients (n = 199)	*p*-value
Duration of HIV infection, years			
n	103	199	MW: < 0.0001
Median (min – max)	0.2 (0.0 – 15.1)	12.4 (0.1 – 28.5)	
IQR (Q3 – Q1)	0.7 (0.8 – 0.1)	9.9 (17.2 – 7.3)	
Missing values	206	398	
CDC HIV stage of disease, n (%)			
A	75 (75.8%)	114 (64.8%)	CS: 0.0364
B	13 (13.1%)	20 (11.4%)	
C	11 (11.1%)	42 (23.9%)	
Total	99	176	
CD4 counts, at diagnosis* , cells/mm^3			
Median (min. – max.)	336.0 (6.0 – 1621.0)	286.0 (0.0 - 1165.0)	MW: 0.0511
≤ 200 cells/mm^3, n (%)	28 (29.5%)	68 (40.7%)	CS: 0.1621
201 - 500 cells/mm^3, n (%)	39 (41.1%)	62 (37.1%)	
> 500 cells/mm^3, n (%)	28 (29.5%)	37 (22.2%)	
Missing values	8	32	
Late diagnosis (< 350 cells/mm^3)	50 (52.6%)	100 (59.9%)	CS: 0.2542
Non-late diagnosis (≥ 350 cells/mm^3)	45 (47.4%)	67 (40.1%)	
CD4 counts, at baseline†, cells/mm^3			
Median (min. – max.)	336.0 (6.0 – 1147.0)	573.0 (2.0 – 2067.0)	TT: < 0.0001
≤ 200 cells/mm^3, n (%)	29 (28.2%)	23 (11.6%)	CS: < 0.0001
201 - 500 cells/mm^3, n (%)	46 (44.7%)	63 (31.7%)	
> 500 cells/mm^3, n (%)	28 (27.2%)	113 (56.8%)	
CD4 counts, last measurement§, cells/mm^3			
Median (min. – max.)	641.0 (136.0 – 1598.0)	675.0 (43.0 – 2060.0)	MW: 0.6655
≤ 200 cells/mm^3, n (%)	2 (1.9%)	11 (5.5%)	CS: 0.2643
201 - 500 cells/mm^3, n (%)	27 (26.2%)	58 (29.1%)	
> 500 cells/mm^3, n (%)	74 (71.8%)	130 (65.3%)	
Plasma HIV – RNA, viral load, at diagnosis*, copies/mL			
Median (min. – max.)	96144.0 (94.0 – 7795576)	56881.0 (50.0 – 5000000)	MW: 0.1403
≤ 50 copies/mL, n (%)	1 (1.1%)	1 (0.7%)	FS: > 0.9999
> 50 copies/mL, n (%)	94 (98.9%)	142 (99.3%)	
Missing values	10	61	
Plasma HIV – RNA, viral load, at baseline†, copies/mL			
Median (min. – max.)	88877.0 (156.0 – 7795576)	417.0 (0.0 – 5606415)	MW < 0.0001
≤ 50 copies/mL, n (%)	0 (0.0%)	154 (77.4%)	CS: < 0.0001
> 50 copies/mL, n (%)	103 (100.0%)	45 (22.6%)	
Missing values	1	130	
Plasma HIV – RNA, viral load, last measurement§, copies/mL			
Median (min. – max.)	31.0 (0.0 – 197.0)	26.5 (0.0 – 137000.0)	MW: 0.8828
≤ 50 copies/mL, n (%)	98 (95.1%)	192 (96.5%)	FS: 0.5510
> 50 copies/mL, n (%)	5 (4.9%)	7 (3.5%)	
Missing values	84	169	

min.: minimum; max.: maximum; CS: Chi-square test; FS: Fisher exact test; HIV: human immunodeficiency virus; IQR: interquartile range; MW: Mann-Whitney test; TT: T-test
*: diagnosis was defined as the date of diagnosis of HIV infection.
†: baseline was defined as the time of initiation of Raltegravir-based therapy.
§: last measurement was defined as the last laboratory value reported in patient's chart regardless of the antiretroviral regimen (patients could or not be on RAL).

but reported low percentages of current or past history of drug or alcohol disorders. The AGING POSITIVE study — an observational study conducted in the Portuguese HIV-infected population — reported similar rates of chronic alcoholism (7.7%), past or current use of tobacco (47.6%) and of illicit drugs (17.2%).[20] The rate of current smokers in HIV-infected patients is two to three times higher than in the general population, increasing the risk of NARC.[26]

In our study population, the most common comorbidities were hypercholesterolemia, arterial hypertension, diabetes mellitus, and depression. Most participants had no hepatitis B or C co-infection during the study period, which could have reflected the high cure rates in HCV patients resulting from the treatment program implemented in Portugal.[27] The AGING POSITIVE study described consistent results on the comorbidities of Portuguese HIV-infected patients, which are comparable to those reported here and for the general population.[20] The proportion of patients with hypercholesterolemia was lower in the REALITY study when considering the overall study population (23.5% *vs* 60% in the AGING POSITIVE study).[20] This proportion is closer to that described in HIV-infected populations from other regions, such as Brazil and the United States (US).[28,29] However, it should be highlighted that participants of the AGING POSITIVE study were older (all patients were ≥ 50 years) and had longer duration of HIV infection.[20]

The MSM mode of transmission in Portuguese patients is reported to be low (9% - 18%),[17,20] compared to those from other European studies (31% - 41%).[15,30,31] Low MSM transmission may be associated with cultural factors and is less common in older HIV-infected individuals. Heterosexual transmission appears to be more frequent in men who present high-risk behaviours (e.g., IDU or commercial sex) and travel abroad.[25,32] This transmission route is also the most common one in patients with late HIV diagnosis (CD4 counts < 350 cells/mm^3).[25] In fact, 57.3% of the study participants had a late HIV diagnosis. Both the European Centre for Disease Prevention and Control (ECDC) annual report for Europe and national data from Portugal's Directorate-General of Health (DGS) in 2019 agreed in determining that almost half of the patients had a late HIV diagnosis (49.7% in EU/EEA and in Portugal).[17,25] The median time between diagnosis and initiation of the first ART regimen was approximately seven years. In our study, 81 patients had a delay of more than eight years between HIV diagnosis and the start of ART. This gap has been associated with multiple patient-level reasons (e.g., patient's concerns about treatment, prolonged adjustment periods, or IDU),[33] or structural reasons (e.g., access barriers, lower socioeconomic status), especially among migrants.[34] Although these patients were diagnosed with HIV many years ago - between 1987 and 2006 - and were later referred for treatment, early interventions in patient perception and decision to start ART are still of foremost importance nowadays. In 2015, clinical guidelines were amended to recommend treatment of all patients regardless of the infection stage.[35] Therefore, knowing that over 50% of the study patients were treatment-experienced and the duration of the infection is long, this might also help explain the delay in treatment initiation.

A reduction in plasma HIV RNA and an improvement in CD4 counts were observed from diagnosis until last measurement.[36] Two patients had reported undetectable VL at diagnosis. One of these patients was treatment-naïve and was born in another country, while the second was treatment-experienced and had a VL of 50 copies/mL at diagnosis. Both patients had CD4 counts > 500 cells/mm^3 and it took several months before initiating ART. These cases could be either patients who were already receiving HIV treatment at another clinic (and whose information was not transferred to the current centre), or HIV controllers that maintain suppressed VL for years without ART.[37,38]

Approximately half of the treatment-experienced patients (52.3%) received up to two prior treatments, with the previous ART regimen lasting, on average, 4.2 years. PI-based therapies (50.8%) and NNRTI-based therapies (40.2%) were the most frequently administered ART, as reported in the AGING POSITIVE study.[20] A similar pattern in ART prescribing was found for other large population-based studies in the US and Europe (e.g., UK, Germany, and France).[14,15,31,39,40] Switching from a prot-based to a RAL-based regimen has been associated with a decrease in plasma lipids (e.g., total cholesterol, LDL cholesterol, and triglycerides), which might confer long-term cardiovascular protection to patients.[41] This effect of treatment switch was also described in a cohort of older HIV-infected patients (aged 60 years and older).[42] Furthermore, as regimens containing tenofovir alafenamide (TAF) were only available with reimbursement in Portugal by December 2017, it is unlikely that the patients were taking this drug known to increase lipid levels.

Around 81% of the patients were RAL-continuing users at the time of the inclusion visit. The HIVTSQs© was administered to these participants, who reported high satisfaction with RAL-based therapy (55.4 ± 7.2 points). The well-established low drug-drug interaction profile[43] and tolerability of RAL might explain the satisfaction for this regimen in a setting of high burden of comorbidities and co-medications. As patients could have started other ART regimens several weeks before study inclusion, satisfaction with RAL was not assessed in patients who discontinued this therapy. However, this fact might have contributed to the high level of satisfaction obtained with RAL in this study. Reasons for discontinuing RAL-based regimens were also not collected in this study; nonetheless, those reasons most frequently reported for RAL switch are patient/physician choice and treatment simplification.[44,45] Considering that RAL 600 mg was approved in Portugal in December 2018, it is unlikely that participants switched from RAL 400 mg to 600 mg during the recruitment period (July 2018 – April 2019). Although this information was not collected, most participants were expected to be on RAL 400 mg (BID) at study inclusion.

As expected, treatment-experienced patients were older and had longer duration of HIV infection than treatment-naïve patients. More patients in the treatment-experienced

subgroup had at least one NARC at baseline. At RAL initiation, treatment-experienced patients had higher CD4 counts and a higher proportion of undetectable VL than treatment-naïve patients ($p < 0.0001$). And, at the last measurement, both subgroups had a CD4 count increase and a reduction of viral load. These similar clinical outcomes appear to support the effect of RAL-based regimens on immune restoration (particularly in treatment-naïve patients),[9] considering that most patients (80.8%) were RAL-continuing users. In other real-world studies evaluating RAL-based regimens, increasing CD4 counts[16,46] and high rates of viral suppression (over 80%)[14] were observed in both groups.

Exploratory analyses suggest that a longer time between discontinuation of previous ART regimens and initiation of RAL might increase the risk of treatment discontinuation. Patients with a history of ART interruption were reported to have the highest rates of RAL discontinuation (23.7%), while those with suppressed VL at baseline had the lowest (13.2%).[47] However, several other patient-related factors –such as treatment perception and expectations or personal reasons– can lead to early treatment discontinuation.[48]

The main limitations of this study are related with its observational and retrospective design, relying mainly on routine clinical records with laboratory results (viral load and CD4 count) collected by different laboratories. Of notice, the HIVTSQs® was only applied as a cross-sectional survey instrument in order to assess the level of satisfaction in patients who were continuing users of RAL at the inclusion visit. Therefore, treatment satisfaction for those who discontinued RAL prior to the enrolment period could not be appraised. To overcome these limitations, prospective studies should be conducted to assess causal relationships between patient-related factors, adherence to ART, treatment satisfaction over time and discontinuation rates among specific subgroups.

CONCLUSION

RAL-based regimens are a valid therapeutic option in heterogeneous populations of HIV-infected patients. To the best of our knowledge this is the first study in Portugal to evaluate real world data in patients treated with RAL and satisfaction among those remaining on RAL. This therapy can be used in patients with previous ART experience and as part of first-line therapeutic options considered in clinical guidelines,[49] alongside with the latest generation of drugs from its class.

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AUTHORS CONTRIBUTION

RS, KM, FM, NM, AC, RP, AZ, JM, IN, JO, PP, RCA, ACM, PC, LP, JA: All the authors had an equal contribution to the literature research, draft and distribution of the questionnaire, analysis of the results and draft of the paper.

PROTECTION OF HUMANS AND ANIMALS

The authors have followed the protocols of their work center on the publication of data. The data was anonymized and none of the authors had access to patient identification. The study was conducted in accordance with the Helsinki Declaration updated in 2013.

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

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Readmissions to a Pediatric Ward: An Eleven-Year Experience in a Portuguese Hospital

Reinternamentos numa Enfermaria de Pediatria: A Experiência de Onze Anos de um Hospital Português

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ABSTRACT

Introduction: Pediatric readmissions have received increased attention in the past few years. Distinguishing between planned and unplanned readmissions and between preventable and unpreventable ones constitutes an important target to better understand this thematic. The aim of this study was to analyze the readmission rate and characterize the population readmitted within a 30-day period after discharge in the pediatric ward of a level II hospital.

Material and Methods: Observational retrospective single center study of the pediatric patients who were discharged from a level II hospital, between 2009 and 2019, and had at least one readmission within 30 days after discharge. Clinical and demographic data were obtained from the analysis of the patient's medical records. We considered as potentially preventable all the unplanned readmissions that were related with the index admission.

Results: From the 6879 admissions during the study period, 4.8% resulted in readmissions within the next 30 days. Excluding the planned readmissions, the seven, 15 and 30-day readmission rates were respectively 1.7%, 2.7% and 3.9%. Most of the unplanned readmissions (77%) were considered as potentially preventable. Patients reevaluated in the Pediatric Day Hospital after discharge had shorter intervals to readmission. Readmissions due to decompensation of chronic disease were more likely related with the index admission. Patients with chronic disease, as well as patients with neurological impairment were more likely to have multiple readmissions.

Conclusion: We found a low overall readmission rate, but a higher percentage of potentially preventable readmissions, when compared with the available literature.

Keywords: Child; Hospitals, Pediatric; Patient Discharge; Patient Readmission

RESUMO

Introdução: Nos últimos anos, os reinternamentos pediátricos têm sido alvo de atenção crescente. Distinguir reinternamentos programados de não programados, e os que podem ou não ser evitados constituem aspetos importantes para a melhor compreensão desta temática. O objetivo deste estudo foi analisar a taxa de reinternamentos e caracterizar a população reinternada até 30 dias após a alta numa enfermaria de Pediatria de um hospital de nível II.

Material e Métodos: Estudo observacional retrospetivo dos doentes com alta da enfermaria de Pediatria de um hospital de nível II, entre 2009 e 2019, e que tiveram pelo menos um reinternamento até 30 dias após a alta. Dados clínicos e demográficos foram obtidos a partir da análise dos processos clínicos. Considerámos potencialmente evitáveis os reinternamentos não programados relacionadas com o internamento índex.

Resultados: Das 6879 admissões durante o período de estudo, 4,8% resultaram em reinternamento até 30 dias. Excluindo os reinternamentos programados, a taxa de reinternamento até sete, 15 e 30 dias foi, respetivamente, 1,7%, 2,7% e 3,9%. A maioria dos reinternamentos não programadas (77%) foi considerada potencialmente evitável. Os doentes reavaliados em Hospital de Dia após a alta apresentaram um menor intervalo até ao reinternamento. Os reinternamentos devido à descompensação de doença crónica apresentaram maior probabilidade de estarem relacionados com o internamento índex. Doentes com doença crónica e com compromisso neurológico apresentaram maior probabilidade de terem múltiplos reinternamentos.

Conclusão: Em comparação com a literatura disponível, foi identificada uma baixa taxa global de reinternamentos, mas uma percentagem superior de reinternamentos potencialmente evitáveis.

Palavras-chave: Alta do Doente; Criança; Hospitais Pediátricos; Readmissão do Doente

INTRODUCTION

The impact of hospital readmissions has been an object of study for the last six decades, especially in the adult population.[1] Although pediatric patients have, in general, lower readmission rates than adults, a growing attention has been given to this subject in the past few years.[1–3] However, the information available on pediatric readmissions remains relatively sparse and derives mainly from studies on specific age groups or medical conditions.[3–5]

A hospital readmission can be defined as a new admission within a certain period after discharge, from seven days to one year. The most common definition considers a 30-day period after discharge. Readmissions within 15-days of a previous discharge are usually considered early readmissions.[6,7] In children, readmissions rates vary among different studies, but are usually low, with about 6.5% of hospitalized children experiencing an unplanned readmission to an acute care hospital within 30-days.[7,8]

In adults, it has been established that high hospital readmission rates are associated with an increase in healthcare costs, psychosocial burden and higher hospital

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mortality rates.[9] Therefore, readmission rates are increasingly being used as a measure of healthcare quality, assuming they may result from substandard quality of care delivered during the initial hospital stay, such as incomplete treatment of the underlying condition or inadequate discharge planning.[3,8,10] However, it is also recognized that many other factors before and after the hospitalization, which are beyond the hospital's direct control, contribute to the risk of readmission. Therefore, using readmission rates as a single quality measure remains controversial.[11,12] On the other hand, and for some medical conditions, high readmission rates can result from low mortality rates and a good access to hospital care.[11]

Hospital readmissions in children also constitute a complex event influenced by multiple factors, including not only the hospital care during the index admission, but also factors associated with the patient and his family, such as the presence of an underlying chronic disease and the socioeconomic resources, and external factors such as the access to primary medical care and social support.[6,10,13] Known risk factors for readmission in children include the presence of a chronic health condition, complex care needs and a fragile social support network.[14,15]

The experience of worsening health after discharge and returning for another hospitalization is generally undesirable and disruptive for both the child and the family.[1,12] As such, reducing readmission rates not only contributes to decreasing healthcare costs, but can also influence the children's well-being. To accomplish this goal, multiple interacting factors must work efficiently, including the process of discharge, family education, social support system and primary health care in the community.[16]

Some readmissions are expected, necessary and unpreventable, whereas others are not. Distinguishing between planned and unplanned readmissions and between preventable and unpreventable ones in children constitutes an important target in order to better understand this subject.[1,15]

The main aim of this study was to analyze the readmission rate and characterize the population readmitted within a 30-day period after discharge in the pediatric ward of a level II hospital, during an eleven-year period. A secondary aim was to identify possible differences in the time to readmission in groups with different clinical and demographical variables and to find a possible association between these variables and the occurrence of multiple readmissions and readmissions associated with the index admission. The authors expect that studying this population might help to improve clinical practice and reduce pediatric hospital readmissions.

MATERIAL AND METHODS

The authors performed an observational retrospective study of the pediatric patients (aged zero to 17 years and 365 days) who were discharged from our hospital's pediatric ward between the 1st January 2009 and the 31st December 2019 and had at least one readmission within that period and up to the 31st January 2020. We considered a readmission when the patient was readmitted to the pediatric ward until 30 days after the discharge from the index admission (original admission). Additional admissions within 30 days were not considered as readmissions or index admissions. An additional admission after 30 days was considered as a new index admission.

The pediatric department where the study was carried out is part of a level II hospital located in the Greater Lisbon area. It is mainly a general pediatric department, but is also a reference in Neonatology and Pediatric Neurology. It is a department that has a very active day hospital and privileges ambulatory care, working in great proximity with both primary care and long-term care units.

Data was obtained from the analysis of the electronic medical records of patients. We analyzed demographic data (sex, age at index admission, area of residence, assignment of a family doctor) and data from the index admission and the readmission (length of stay, primary diagnosis - categorized by the International Statistical Classification of Diseases and Related Health Problems 10th Revision, ICD-10 -, existence of an underlying chronic medical condition, destination after discharge, time between discharge and readmission, readmission planning and, if so, with what purpose). The reasons for readmission were classified as related or unrelated with the index admission and, in the ones related with the index admission, were further categorized as worsening or recurrence of symptoms, or complication of procedures. We considered all the non-programmed readmissions that were related to the index admission as potentially preventable. We defined as a complex chronic disease any medical condition for which it is reasonable to expect a duration of at least 12 months (except in the case of death) and which affects several different systems or an organ in a sufficiently severe manner to require specialized pediatric care and probably some period of admission to a tertiary medical center.[17] We considered as neurological impairment the presence of intellectual disability, limitations in mobility and/or communication difficulties. A permanent catheter was considered as any central vascular line or ventriculoperitoneal or atrial shunt.

The authors performed a descriptive analysis to characterize the studied population and a statistical analysis using independent *t*-student test (after applying a normality test) to compare means of readmission times between groups of variables and chi-square test to access possible associations between categorical variables, calculating the odds ratio for the statistically significant associations. The statistical work was carried out in SPSS® Statistics 24 (IBM Corp., 2016, United States of America); *p* values of 0.05 were considered statistically significant. The study was approved by the hospital's Ethics Committee. The need for informed consent was waived as this was a retrospective non-interventional study.

RESULTS

Characterization of the studied population (Table 1; n = 267)

During the study period, there were a total of 6879 admissions in our pediatric ward; 333 (4.8%) were followed by a readmission within 30 days of discharge. These 333 readmissions occurred in 267 patients, meaning that 28 patients (10.5%) had two or more readmissions. From the total of patients readmitted, 138 were male and 129 were female. The mean age at the index admission was 4 ± 5 years (range from 0 to 17 years). About half of the patients were younger than one year old (45.7%) and more than two thirds of patients (68.9%) were younger than five years of age at the index admission. About half of the patients (46.4%) had an underlying chronic disease, the most frequent being nervous system diseases (27.4%), congenital malformations (26.6%) and hematologic diseases (12.1%). Around 91% of chronic diseases were complex chronic diseases. About 10% of patients had medical devices and approximately 23% had some degree of neurological impairment (cognitive and/or motor impairment). Most patients (77.1%) lived in the hospital area and had an assigned family doctor (77.2%).

Characterization of the index admissions (Table 2; n = 333)

Most patients concerning index admissions (60.9%) were admitted through the pediatric emergency department. There were several primary diagnoses, the most frequent ones belonging to the respiratory system group (23.1%). About 15.6% of index admissions involved surgical intervention. The duration of the index admission was 9 ± 16 days (range from 0 to 175 days). The destination after discharge was mostly to the patient's home (92.8% - four of these patients with home support). About one third of discharges (33.9%) were evaluated in the pediatric day hospital. Most of the admissions (70.9%) were referred to pediatric ambulatory hospital care at discharge.

Characterization of the readmissions (Table 3; n = 333)

There was an average interval time of 11 ± 9 days between the index admission discharge and the readmission (range from zero to 30 days). Most of the readmissions occurred until 15 days after discharge (68.5%).

The length of stay in the readmission was 10 ± 42 days (range from zero to 746 days). The total length of hospital stay (index admission plus readmission) was 18 ± 45 days (range of one to 757 days).

Most patients had an unplanned readmission (81.4%) and were admitted through the pediatric emergency department (60%). Regarding the planned readmissions, most (79.3%) were for medical or surgical treatment or diagnostic assessment. The most frequent primary diagnosis, excluding the group of symptoms and signs not elsewhere classified, were the ones belonging to the respiratory and nervous system groups (24% and 12.3%, respectively).

Concerning the unplanned readmissions, 209 (77.1%)

Table 1 – Demographic and clinical characterization of the studied population (n = 267)

	n (%)
Sex	
Male	138 (51.7)
Female	129 (48.3)
Age (years)	
< 1	122 (45.7)
1 – 4	62 (23.2)
5 – 9	40 (15.0)
10 – 14	23 (8.6)
≥ 15	20 (7.5)
Chronic disease	
No	143 (53.6)
Yes	124 (46.4)
Complex chronic disease	113 (91.1)
Non-complex chronic disease	11 (8.9)
Nervous system	34 (27.4)
Congenital malformations	33 (26.7)
Hematologic	15 (12.1)
Perinatal period	15 (12.1)
Respiratory system	7 (5.6)
Endocrine and metabolic	5 (4.0)
Digestive system	5 (4.0)
Neoplasms	4 (3.2)
Musculoskeletal system and connective tissue	3 (2.4)
Mental and behavioral	2 (1.6)
Genitourinary system	1 (0.8)
Neurological impairment	
Yes	62 (23.2)
Motor	26 (41.9)
Cognitive	7 (11.3)
Both	29 (46.8)
No	205 (76.8)
Medical devices	
Yes	26 (9.7)
Permanent catheter	18 (69.2)
Gastrostomy	4 (15.4)
Tracheostomy	2 (7.7)
Other	2 (7.7)
No	241 (90.3)
Residence	
Hospital's referral area	206 (77.2)
Outside hospital's referral area	61 (22.8)
Family physician	
Yes	206 (77.2)
No	51 (19.1)
Unknown	10 (3.7)

Table 2 – Characterization of the index admissions (n = 333)

	n (%)
Source of admission	
Pediatric emergency department	203 (60.9)
Pediatric outpatient care	44 (13.2)
Neonatal and pediatric intensive unit	29 (7.7)
Other outpatient care	24 (7.2)
Other hospital	24 (7.2)
Pediatric day hospital	7 (2.1)
Other	2 (0.6)
Surgery	
Yes	52 (15.6)
No	281 (84.4)
Primary diagnosis (ICD-10)	
Respiratory system	77 (23.1)
Symptoms and signs not elsewhere classified	47 (14.1)
Nervous system	33 (9.9)
Hematologic	30 (9.0)
Perinatal period	28 (8.4)
Congenital malformations	20 (6.0)
Neoplasms	14 (4.2)
Infectious	12 (3.6)
Circulatory system	11 (3.3)
Digestive system	11 (3.3)
Musculoskeletal system and connective tissue	10 (3)
Skin and subcutaneous tissue	8 (2.4)
Genitourinary system	8 (2.4)
Injury and poisoning	7 (2.1)
Ear and mastoid process	5 (1.5)
Endocrine and metabolic	4 (1.2)
Eye and adnexa	3 (0.9)
External causes of morbidity and mortality	3 (0.9)
Mental and behavioral	1 (0.3)
Factors influencing health status and contact with healthcare services	1 (0.3)
Length of stay (days)	
0 – 2	77 (23.1)
3 – 7	168 (50.5)
8 – 14	45 (13.5)
≥ 15	43 (12.9)
Destination after discharge	
Home	305 (91.6)
Home with outpatient support	4 (1.2)
Inpatient institution	2 (0.6)
Other hospital	22 (6.6)
Evaluation in Pediatric Day Hospital after discharge	
Yes	113 (33.9)
No	220 (66.1)
Referral to pediatric ambulatory hospital care	
Yes	236 (70.9)
No	97 (29.1)

were considered by the authors to be related with the index admission and most of them occurred after clinical worsening or symptomatic recurrence (90.4%). The remaining unplanned readmissions related with the index admission (9.6%) happened due to complications of procedures performed in the index admission.

Considering the overall number of admissions in the study period, which was 6879, the overall 30-day readmission rate in our study was 4.8% (n = 333). When excluding the programmed readmissions, the seven, 15 and 30-day readmission rates were, respectively, 1.7% (n = 119), 2.7% (n = 186) and 3.9% (n = 267). As for the potentially preventable readmissions only, the readmission rate was 3% (n = 209).

Statistical analysis (Tables 4, 5 and 6)

There were no statistically significant differences between time to readmission and sex, assignment of a family physician or presence of chronic disease.

Planned and unplanned readmissions had also similar

Table 3 – Characterization of the readmissions (n = 333) (initial section)

	n (%)
Origin of readmission	
Pediatric emergency department	200 (60.0)
Pediatric day hospital	37 (11.1)
Other specialty outpatient care	26 (7.8)
Pediatric outpatient care	25 (7.5)
Other hospital	25 (7.5)
Neonatal and pediatric intensive unit	8 (2.4)
Other	12 (3.6)
Type of readmission	
Unplanned	271 (81.4)
Planned	62 (18.6)
Medical treatment	18 (29.0)
Surgical treatment	21 (34.0)
Diagnostic investigation	17 (27.4)
Caregiver's rest	3 (4.8)
Other	3 (4.8)
Primary diagnosis	
Respiratory system	80 (24.0)
Symptoms and signs not elsewhere classified	68 (20.4)
Nervous system	41 (12.3)
Hematologic	27 (8.1)
Congenital malformations	18 (5.4)
Musculoskeletal system and connective tissue	14 (4.2)
Skin and subcutaneous tissue	11 (3.3)
Digestive system	10 (3.0)
Injury and poisoning	9 (2.7)
Circulatory system	9 (2.7)
Genitourinary system	8 (2.4)
Infectious	8 (2.4)
Neoplasms	7 (2.1)
Perinatal period	7 (2.1)
Factors influencing health status and contact with healthcare services	4 (1.2)
Endocrine and metabolic	4 (1.2)
Ear and mastoid process	3 (0.9)
Eye and adnexa	2 (0.6)
External causes of morbidity and mortality	2 (0.6)
Mental and behavioral	1 (0.3)

Table 3 – Characterization of the readmissions (n = 333) (final section)

	n (%)
Length of stay (days)	
0 – 2	77 (23.1)
3 – 7	168 (50.5)
8 – 14	49 (14.7)
≥ 15	39 (11.7)
Interval from discharge to readmission (total readmissions)	
Up to 7 days	147 (44.1)
Up to 15 days	228 (68.5)
Interval from discharge to readmission (unplanned readmissions)	
Up to 7 days	119 (43.9)
Up to 15 days	186 (68.6)
Relation to the index admission (unplanned readmissions)	
Unrelated	62 (22.9)
Related (potentially preventable)	209 (77.1)
Clinical worsening or recurrence of symptoms	189 (90.4)
Complication of procedures	20 (9.6)
- Surgical wound infection (n = 6)	
- CSF fistula (n = 6)	
- Post-surgery meningitis (n = 5)	
- Urinary tract infection after cystography (n = 1)	
- Post-catheterization hematuria (n = 1)	
- Incarceration of PEG (n = 1)	
Chronic disease (unplanned readmissions)	
No	112 (41.5)
Yes	158 (58.5)
Readmission due to decompensation of chronic disease	98 (62)
Readmission unrelated to chronic disease	60 (38)

intervals of time to readmission. Readmissions that were considered to be related with the index admission had shorter times to readmission, but without statistical significance (11 *vs* 13 days, *p* value = 0.10). When the patients were assessed in the pediatric day hospital after discharge from the index admission, the time to readmission was significantly shorter (9 *vs* 12 days, *t*-test - 2.662; gl 331; *p* value = 0.008).

In unplanned readmissions, there was no statistically significant difference between the age groups and the association with the index admission.

When there was an underlying chronic disease, we found that the presence of decompensation of chronic disease was more frequent in the readmissions related with the index admission (*p* value < 0.001) with an odds ratio of 6.0 (95% IC, 2.7 to 13.0).

Patients with chronic disease were more likely to have multiple readmissions (*p* value < 0.001) with an odds ratio of 11.8 (95% IC, 3.5 to 40.1) as well as patients with neurological impairment, (*p* value = 0.002) with an odds ratio of 3.4 (95% IC, 1.5 to 7.5). The same was not demonstrated in the group with medical devices.

DISCUSSION

As far as we know, and even though there are previous studies on readmissions to pediatric emergency departments,[18–20] this is the first Portuguese study on readmissions to a pediatric ward, The all-cause 30-day readmission rate in our study was 4.8%, which is similar to the results of Feudtner *et al*[14] and lower than the 6.1% readmission rate obtained by Sills *et al*.[21] When excluding the planned readmissions, the seven, 15 and 30-day readmission rates were respectively 1.7%, 2.7% and 3.9%. These numbers are lower than what was reported in most pediatric studies. The largest study on pediatric readmissions to date is the one developed by Berry *et al*, involving 72 children's hospitals and more than 568 000 readmissions. These authors found an overall 30-day unplanned readmission rate of 6.5%,[7] the same rate reported by Toomey *et al*.[8] In 2011, Gay *et al* reported a 15-day readmission rate of 8.4%[5] and in a different study four years later, found all-cause readmission rates at seven, 15 and 30 days of 5%, 8.7%, and 13.3%, respectively.[6] The most similar results to our study were those reported by Wallace *et al* in 2015 and by Pérez *et al* in 2019, with an overall 30-day unplanned readmission rate of 3.1% and

Table 4 – Comparison of the time to readmission between different groups of demographic and clinical variables

	Time to readmission (average ± standard deviation, in days)	*p* value*
Sex (n = 333)		
Male	11 ± 9	0.901
Female	11 ± 9	
Chronic disease (n = 333)		
Yes	12 ± 8	0.333
No	11 ± 9	
Family physician (n = 323)		
Yes	11 ± 9	0.468
No	12 ± 9	
Planned readmission (n = 333)		
Yes	11 ± 9	0.936
No	11 ± 9	
Readmission related with index admission/ potentially preventable (n = 271)		
Yes	11 ± 9	0.100
No	13 ± 9	
Surgery in index admission (n = 333)		
Yes	12 ± 9	0.602
No	11 ± 9	
Neurologic impairment (n = 333)		
Yes	12 ± 9	0.264
No	11 ± 9	
Presence of medical devices (n = 333)		
Yes	10 ± 9	0.355
No	11 ± 9	
Assessment in pediatric day hospital after index admission discharge (n = 333)		
Yes	9 ± 8	0.008
No	12 ± 9	

* Independent *t*-student test

4.1%, respectively.[22,23]

As for Portuguese references, a recent national study on general hospital readmissions found an overall 30-day readmission rate of 6.8%, with lower rates in children and young people (2.6% in zero to 14 years and 3.8% in 15 to 24 years), which is also consistent with our results.[9]

One possible explanation for our lower readmission rates, almost half when compared to most studies in the pediatric population, might be the fact that our study was carried out in a pediatric ward of a level II hospital, as opposed to most studies presented, which involved children's hospitals, which are mostly level III. These hospitals usually have a population with a higher degree of medical complexity, who are prone to more readmissions.

One could speculate that the fact that our department privileges ambulatory care and, therefore, usually discharges children as early as possible, would be associated with a high rate of readmissions. However, we demonstrated this wasn't the case. In the light of these results, we could say that our department's general approach is fairly safe.

In the study of readmissions, many authors highlight the importance of primarily distinguishing between planned and unplanned readmissions, and most exclude planned readmissions from their analyses.[24] We found a percentage of planned readmissions of 18.6%, mostly for medical or surgical treatment or diagnostic investigation. There weren't any measures to reduce this kind of readmissions and they were often helpful, beneficial and related with the prevention of further health issues.[25]

After distinguishing planned from unplanned readmissions, it is critical, although challenging, to differentiate preventable from unpreventable ones in order to better design methods to reduce readmission rates and to possibly use them as a quality metric.[6,15] Sometimes, even though it is assumed that all unplanned readmissions are preventable, one can't plan measures to prevent readmissions in which the cause isn't related with the index admission.[25] In our study, we assumed as potentially preventable every unplanned readmission that was related with the index admission. Most of the unplanned readmissions (77%, corresponding to 63% of all readmissions and 3% of total hospital admissions) were related with the index admission

Table 5 – Comparison between demographic and clinical variables and the association with the index admission (unplanned readmissions)

	Readmission related with index admission / potentially preventable	Readmission non-related with index admission	*p* value*	Odds ratio
Age group (n = 271)	**(n = 209)**	**(n = 62)**		
< 1 year (n = 109)	76 (70%)	33 (30%)		
1 – 4 years (n = 76)	60 (65%)	16 (35%)	0.139	
5 – 9 years (n = 46)	40 (87%)	6 (13%)		
10 – 14 years (n = 25)	20 (80%)	5 (20%)		
≥ 15 years (n = 15)	13 (87%)	2 (13%)		
Decompensation of chronic disease (n = 158)#	**(n = 117)**	**(n = 41)**		
Yes (n = 99)	86 (87%)	13 (13%)	**< 0.001**	**6.0** (95% IC, 2.7 to 13.0)
No (n = 59)	31 (53%)	28 (47%)		
Surgery in index admission (n = 271)	**(n = 209)**	**(n = 62)**		
Yes (n = 37)	32 (86%)	5 (14%)	0.144	
No (n = 234)	177 (76%)	57 (24%)		
Neurologic impairment (n = 271)	**(n = 209)**	**(n = 62)**		
Yes (n = 86)	68 (79%)	18 (21%)	0.603	
No (n = 185)	141 (76%)	44 (24%)		
Presence of medical devices (n = 271)	**(n = 209)**	**(n = 62)**		
Yes (n = 26)	20 (77%)	6 (23%)	0.980	
No (n = 245)	189 (77%)	56 (23%)		

*: Chi-square test; # Number of unplanned readmissions in patients with chronic disease

Table 6 – Comparison between patients with a single readmission and patients with multiple readmissions (n = 267)

	Patients with multiple readmissions	Patients with a single readmission	*p* value*	Odds ratio
Chronic disease	**(n = 28)**	**(n = 239)**		
Yes (n = 124)	25 (20%)	99 (80%)	**< 0.001**	**11.8** (95% IC, 3.5 to 40.1)
No (n = 143)	3 (2%)	140 (98%)		
Presence of medical devices	**(n = 28)**	**(n = 239)**		
Yes (n = 26)	5 (19%)	21 (81%)	0.126	
No (n = 241)	23 (10%)	218 (90%)		
Neurological impairment	**(n = 28)**	**(n = 239)**		
Yes (n = 62)	13 (21%)	49 (79%)	**0.002**	**3.4** (95% IC, 1.5 to 7.5)
No (n = 205)	15 (7%)	190 (93%)		

*: Chi-square test

and thus deemed as potentially preventable. When compared with most studies, which found rates of preventable readmissions ranging from 20% to 30%,[3,8,23] we obtained a higher percentage of potentially preventable readmissions which can, in part, be explained by the different methodologies used to assess preventability.

Several authors perceived that, preventable readmissions, or readmissions related with the index admission, occurred earlier after hospital discharge than unpreventable or unrelated ones,[8] which was also the case in our study, although without statistical significance.

To the best of our knowledge, our study was the first to assess the interference of clinical reevaluation at a Pediatric Day Hospital after discharge on readmissions. We found that when patients were evaluated at the Pediatric Day Hospital, the time to readmission was significantly shorter. We might argue that this happened because pediatricians schedule children with more severe disease or with clinical conditions not completely resolved after discharge or with the potential to regress or stagnate for evaluation at the day hospital. These children usually require close follow up shortly after discharge and sometimes it is not possible to maintain care exclusively ambulatory. A possible premature discharge of these patients is also a possibility to consider but was not further investigated in this study.

Several studies reported on the impact of chronic diseases in pediatric readmissions. Markham *et al*[4] reported that 79% of readmissions were in patients with an underlying chronic illness, which was similar to the percentage presented by Gay *et al*.[5] Comparably, in our study, about half

the readmissions (56.2%) occurred in patients with an underlying chronic disease, almost all being considered complex chronic diseases. We also found that readmissions due to decompensation of a chronic disease were more likely related with the index admission and therefore, more likely to be preventable, thus differing from the study of Toomey *et al* which found no relation between these variables.[8] In our study, we also found that children with a chronic disease and children with neurological impairment were more likely to have multiple readmissions. Our results support the idea that the presence of chronic disease in pediatric patients may have a significant influence on readmissions.

Although in our study there was a significant dispersion in groups of diagnoses in both the index admission and the readmission, the most frequent diagnoses in the readmission were respiratory and nervous system diseases. The predominance of respiratory diseases is expected as they are some of the most common diseases in childhood, and thus some of the most common diseases that cause readmissions. The prevalence of nervous system diseases is, in part, explained by the existence of a pediatric neurodevelopment center in our hospital, where many children with nervous system conditions are followed. These kinds of conditions may imply a higher rate of readmissions, since they are mainly chronic diseases, with many associated with cognitive or motor impairment and some with the need for the support of medical devices.

Many authors contest the use of readmission rates as an acceptable quality measure of hospital care and claim that it should only be used as a marker of healthcare use. It is argued that we need more research to better determine the proportion of readmissions that are due to poor hospital quality of care *versus* other reasons for readmissions (such as complex social environments and difficulties in access to primary ambulatory care) and how many are preventable. Until then, one should not consider pediatric readmission rates as a quality indicator of single hospitals but as a quality indicator of the entire healthcare system.[8,16,25–28]

Whether or not they should be considered a suitable measure of hospital quality, knowledge of pediatric hospital readmission rates and the characterization of this population is essential to help reduce preventable readmissions. In particular, parental perception of the child's health and discharge conditions has been associated with the risk of readmission, with both parents and healthcare care providers identifying communication difficulties and lack of shared understanding as potential causes for readmission.[29–32] Optimization of discharge planning, including family education and care coordination with ambulatory and outpatient providers is essential, especially for children with complex medical needs.[30] Some authors suggest an optimized process of discharge, including a team with specialized knowledge of the child's condition to assume responsibility for the inpatient-to-outpatient transition and that offers ongoing support to the family following discharge.[30,33]

This study has several limitations. First, it is a retrospective study, so information related with the index admissions and readmissions might have been missing. Furthermore, it was a single institution study of a level II hospital, with a relatively small sample, and therefore the results may not be generalizable to the Portuguese pediatric population. This study did not consider patients readmitted to a different hospital, so the overall true readmission rate in this population is probably higher. Our hospital's pediatric emergency department has an observation area that admits patients from the emergency room who will predictably have a short length of stay (usually up to 48 hours), thus preventing an admission in the pediatric ward. In this study, we did not consider these patients, which might also have underestimated the overall readmission rate. Finally, our study did not attempt to compare patients with and without readmissions, which would have been essential to try to find risk factors for readmissions.

The general use of readmission rates as a quality measure of hospital care is still very controversial and even more so in the pediatric population. As such, a national multicenter prospective cohort study is crucial in order to better characterize pediatric readmissions, to assess their preventability and possible risk factors to ultimately understand how to better prevent them. The contributions of external factors such as the family's social and economic conditions, access to ambulatory care and social support in the community after discharge also warrant further study.

CONCLUSION

In our study, we found a low overall readmission rate, but a higher percentage of potentially preventable readmissions, when compared with the available literature. We also found that the patients assessed in the pediatric day hospital after discharge from the index admission, had significantly shorter times until readmission. When there was an underlying chronic disease, readmissions due to decompensation of chronic disease were considered more likely to be preventable. On the other hand, the existence of chronic disease and neurological impairment were identified as risk factors for multiple readmissions.

AUTHORS CONTRIBUTION

JSM: Design of the work, data acquisition, interpretation and management, draft of the paper.

RS: Design of the work, data acquisition, data management, draft of the paper.

JM, PC: Design of the work, critical review and major contribution for the final version of the paper.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

publication.

COMPETING INTERESTS

The authors declare that no competing interests exist nor any form of support.

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Advanced Maternal Age as an Obstetric Risk Factor: Current Experience in a Hospital from Northwestern Spain

A Idade Materna Avançada como Fator de Risco Obstétrico: Experiência Atual num Hospital do Noroeste de Espanha

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ABSTRACT

Introduction: Studies updating the evidence in advanced maternal age as an independent factor of obstetric risk are needed. The aim of this study was to determine the prevalence of ≥ 35-years-old pregnant women who give birth in a Spanish hospital in Northwestern Spain, and to describe the incidence of maternal and perinatal morbidity and mortality.

Material and Methods: Retrospective follow-up observational study including women ≥ 20 years-old who gave birth over one year (n = 1378). Data were collected from medical records, including socio-demographic characteristics, comorbidities, gestational conditions, variables related with the delivery and perinatal outcomes. Multivariable logistic regression analysis was performed to determine the association of advanced maternal age with obstetric and perinatal outcomes.

Results: Forty-two percent of pregnant women were ≥ 35 years old. In the multivariable analysis, advanced maternal age was associated with the likelihood of gestational diabetes (OR = 1.84; 95% CI = 1.10 - 3.07), hypothyroidism (OR = 2.11; 95% CI = 1.17 - 3.80), lower probability of an eutocic delivery (OR = 0.74; 95% CI = 0.56 - 0.98), and a hospital admission > four days (OR = 2.91; 95% CI = 1.95 - 4.35). An association with the rate of C-sections was not found (OR = 1.24; 95% CI = 0.89 - 1.72).

Conclusion: A high prevalence of pregnant women of advanced maternal age was confirmed. There was a higher rate of comorbidities and longer hospital admissions in older women but not a higher rate of higher C-sections and other complications.

Keywords: Cesarean Section; Delivery, Obstetric; Labor, Obstetric/complications; Maternal Age; Pregnancy

RESUMO

Introdução: São necessários estudos que atualizem as evidências sobre a idade materna avançada como fator independente de risco obstétrico. O objetivo deste estudo foi determinar a prevalência de mulheres grávidas com idade igual ou superior a 35 anos admitidas para o parto num hospital espanhol do Noroeste da Espanha, e descrever a incidência de morbilidade e mortalidade materna e perinatal.

Material e Métodos: Estudo observacional retrospetivo que inclui mulheres com idade igual ou superior a 20 anos admitidas para o parto ao longo de um ano (n = 1378). Os dados foram recolhidos em prontuários médicos, incluindo características sociodemográficas, comorbilidades, patologia gestacional, variáveis relacionadas com o parto e resultados perinatais. Foi realizada uma análise de regressão logística multivariada para determinar a relação da idade materna avançada com os resultados obstétricos e perinatais.

Resultados: Quarenta e dois por cento das mulheres grávidas tinham idade igual ou superior a 35 anos. Na análise multivariada, a idade materna avançada estava associada com maior probabilidade de diabetes gestacional (OR = 1,84; 95% CI = 1,10 - 3,07), hipotiroidismo (OR = 2,11; 95% CI = 1,17 - 3,80), menor probabilidade de parto eutócico (OR = 0,74; 95% CI = 0,56 - 0,98), e hospitalização superior a quatro dias (OR = 2,91; 95% CI = 1,95 - 4,35). Não foi encontrada uma associação com a taxa de cesarianas (OR = 1,24; 95% CI = 0,89 - 1,72).

Conclusão: A elevada prevalência de mulheres grávidas com idade materna avançada foi confirmada. As mulheres mais velhas apresentaram maior número de comorbilidades e maior tempo de hospitalização, mas não apresentaram uma maior ocorrência de cesarianas e outras complicações.

Palavras-chave: Cesariana; Gravidez; Idade Materna; Parto Obstétrico/complicações

INTRODUCTION

Advanced maternal age has been a constant in delivery rooms in developed countries for the last couple of decades.[1–3] Some authors,[4–10] including those of a recent meta-analysis,[7] have observed that advanced age entails an increased risk of obstetric and perinatal morbidity and mortality. However, other known factors that can contribute to an abnormal pregnancy also have to be taken into account, such as assisted reproduction techniques[4,5] or previous conditions,[10,11] Improved control and monitoring of pregnancy, delivery, and postpartum, especially in women of advanced age, could contribute to improved results. Therefore, it is necessary to carry out new studies that update the available evidence in advanced maternal age as an independent factor of obstetric risk.

Already in 1958, the International Federation of Gynaecology and Obstetrics (FIGO), defined 'advanced maternal age' (AMA), 35 years of age and over.[4,8,11–14] Nowadays, there is no consensus on where to establish this age limit[4]: 35, 38, 40, or even 45 years of age.[5,9,15] The optimal reproductive age is considered to be between 18 and 34 years of age, after

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finishing the pubertal development, growth, and maturation.

In Spain, the average age of first-time mothers is 30.79 years of age, and the global average is 31.3 years.[2] Spain is the only country in Europe after Italy on this list.[3] This average has been increasing since the 1980s, when mothers had their first child at the age of 25.[2] This was due to the social changes that occurred during this time, especially more women entering the workforce and receiving a higher level of education.[2,3] In America, there is also a trend towards a higher maternal age. In Brazil, 30-year-old (or older) women deliveries comprise up to 31.3% of the total. In the USA in 2016, the average age of first-time mothers was 26.6 years.[1]

Despite the advanced age at which Spanish women have their first child, few studies have analysed the obstetric and perinatal results,[16–19] as well as comorbidities of women older than the optimal pregnancy age during pregnancy. In addition, it is interesting to analyse if, despite the improved quality of healthcare available to pregnant women in recent years and the early detection of conditions, there is still a high incidence of maternal and neonatal morbidity and mortality.

The objectives of this study are to determine the prevalence of pregnant women aged 35 and overwho gave birth in a hospital in the Northwestern Spain (Lugo, Galicia), and to describe the incidence of maternal and perinatal morbidity and mortality in these pregnant women as well as in newborns, in comparison with younger women.

MATERIAL AND METHODS

Retrospective follow-up observational study of all the deliveries at the Lucus Augusti University Hospital (also known as HULA) (Lugo, Northwest of Spain) over one year. This hospital was inaugurated in 2011 and is the hospital of reference for a province of approximately 355 000 inhabitants.

From an initial sample of 1420 pregnant women who gave birth over the period of the study, 11 were excluded for being uncontrolled pregnancies, and 31 as women were younger than 20 years old. Therefore, the sample of the study includes 1378 pregnant women. This sample size allows to estimate the incidence rate of obstetric and perinatal outcomes with a relative precision of ± 2.7% and a 95% confidence level.

The analysed data was taken from the patients' medical records, after receiving consent to access it, thus preserving data confidentiality according to current legislation. The study was performed after obtaining approval from the ethics committee (Committee of Research Ethics of Santiago-Lugo), code 2015/258).

The following variables were collected from each pregnant woman:

• **Characteristics of pregnant women**: maternal age at the time of birth and place of residence (urban/rural areas). Comorbidities before pregnancy (thyroid disease, arterial hypertension, diabetes, obstetric or gynaecological surgeries, autoimmune diseases, cancer, and heart disease), and obstetric history (full-term pregnancies, labour, abortions, C-sections, and pregnancies by assisted reproduction).

• **Related with pregnancy**: pregnancy complications (gestational diabetes, hypertension, gestational age < 37 weeks, intrauterine growth restriction) and weight gain during pregnancy. Threatened premature delivery was defined by the presence of regular uterine contractions associated with cervical changes that occurred after 20 weeks and before 37 weeks of gestation. The body mass index (BMI) was calculated at the beginning of the pregnancy and the weight gain during the pregnancy was classified according to the recommendations of the WHO[20]:

- BMI < 18.5: should aim to gain 13 - 18 kg, underweight women
- BMI 18.5 - 24.9: should aim to gain 11.5 - 16 kg
- BMI 25 - 29.9: should aim to gain 7 - 11 kg
- BMI ≥ 30: should aim to gain 5 - 9 kg

• **Related with the delivery**: gestational age at the time of delivery, type of onset (spontaneous, induced, programmed C-section) type of delivery (eutocic, instrumental, or C-section) and total number of admission days. An admission is considered prolonged if it lasts for more than four days.

• **Newborn measurements**: weight (small for gestational age, large for gestational age or normal weight) and Apgar at minute 1 and 5 after birth, gestational age (< 37 weeks/ ≥ 37 weeks) and destination of the newborn after birth.

Statistical analysis

Advanced maternal age is considered to be 35 years of age and over (according to FIGO), and these pregnant women were compared to women younger than 35.[4,8,11–14] So in order to explore differences in the risk of complications depending on the maternal age (< 40 or ≥ 40 years old), and following other authors, a comparison between three age groups was performed (20 - 34 years old, 35 - 39 years old and ≥ 40 years old).

A descriptive study of all the variables was performed, both globally and according to maternal age (< 35 and ≥ 35 years of age). The quantitative variables are shown as mean ± standard deviation. Qualitative variables are shown as absolute value and percentage, with an estimation of its 95% confidence interval (CI).

The baseline characteristics of pregnant women were compared according to their age, development of pregnancy, delivery, and perinatal results. In order to compare the quantitative variables, the Student's *t*-test or the Mann-Whitney test were used, after checking normality with the Kolgomorov-Smirnov test. In order to compare the percentages, the statistic chi-square test or Fisher's exact test were used.

The *odds ratio* (OR) values related to advanced maternal age were calculated for the different obstetric and perinatal results obtained, both crude and adjusted, with multivariable logistic regression models. The multivariable analysis was adjusted for each case using a direct approach,

including as covariates those variables that were associated ($p < 0.20$) with each obstetric or perinatal outcome in the bivariate analysis, along with other potential confounding factors according to the results reviewed in the literature.

Additionally, we examined the strength and shape of the relationship of maternal age with the log odds of of the different obstetric and perinatal outcomes studied using restricted cubic splines, using the 50th percentile (age = 34 years) as reference point. This approach allows for a flexible association between age and the incidence of the complications studied, without assuming a linear association. Therefore, it could be useful to identify the age at which the risk of a determined adverse outcome starts to increase.

All tests were performed with a bilateral approach. *P* - values < 0.05 were considered statistically significant.

RESULTS

During the period of the study, 1378 women gave birth, of which 581 (42.2%) were between 35 and 50 years old at the moment of the birth (n = 126, 9.1% were ≥ 40 years-old), with a global average age of 37.8 ± 2.5 years (Table 1). We identified 60.9% of women as being first-time mothers (53.0% in the AMA group), with 40 (2.9%) twin pregnancies (26 in the AMA group).

AMA pregnant women had a higher proportion of previous conditions (42.2 % *vs* 20.2%, $p < 0.001$), with a higher prevalence of both obstetric-gynaecological surgical interventions (26.5% *vs* 19. %, $p = 0.001$) and hypothyroidism (10.2% *vs* 6.1%, $p = 0.006$). On the other hand, smoking habits were more frequently observed in younger women (18.1% *vs* 11.4%; $p = 0.001$). The use of assisted reproduction techniques was significantly higher in older women (11.4% *vs* 2.1%, $p < 0.001$). Differences in the prevalence of hypertension, diabetes, overweight, or obesity were not observed (Table 1).

Regarding pregnancy complications and obstetric outcomes, the presence of gestational diabetes was more frequent in AMA pregnant women (7.4% *vs* 4.3%; $p = 0.012$), as well as gestational hypothyroidism, although in this case without statistical significance (5.5% *vs* 3.4%; $p = 0.055$).

Table 1 – Maternal demographic, medical background data and obstetric characteristics on the study population

	Total (n = 1378)	**20 - 34 age** (n = 797)	**35 - 39 age** (n = 455)	**≥ 40 age** (n = 126)		
	n (%)	**n (%)**	**n (%)**	**n (%)**	***p*§**	***p*‖**
Maternal age at delivery, Mean ± SD	33.2 ± 5.2	29.7 ± 3.7	36.7 ± 1.4	41.7 ± 2.0	< 0.001	< 0.001
Parity, Mean ± SD	1.4 ± 0.5	1.3 ± 0.5	1.5 ± 0.5	1.5 ± 0.5	< 0.001	< 0.001
nulliparous	839 (60.9)	531 (66.6)	239 (52.5)	69 (54.8)		
multiparous	539 (39.1)	266 (33.4)	216 47.5)	57 (54.2)		
Previous CS	122 (8.9)	57 (7.2)	48 (10.5)	17 (13.5)	0.020	0.014
Nº abortions, Mean ± SD	0.4 ± 0.7	0.3 ± 0.7	0.4 ± 0.8	0.6 ± 0.9	---	0.001
0	1005 (72.9)	605 (75.9)	318 (69.9)	82 (65.1)		
1	272 (19.7)	148 (18.6)	100 (2.0)	24 (19.0)		
≥ 2	101(16.4)	44 (5.5)	37 (8.1)	20 (15.9)		
	n (%)	**n (%)**	**n (%)**	**n (%)**	***p*§**	***p*‖**
Region					< 0.001	< 0.001
urban	938 (68.1)	493 (61.9)	351 (77.1)	94 (74.6)		
rural	440 (31.9)	304 (38.1)	104 (22.9)	32 (25,4)		
Chronic illness[a]	485 (35.2)	241 (30.2)	183 (40,2)	61 (48,4)	< 0.001	< 0.001
Previous gynaecological surgery	306 (22.2)	152 (19.1)	118 (25.9)	36 (28.6)	0.004	0.001
Assisted reproduction	83 (6.0)	17 (2.1)	34 (7.5)	32 (25.4)	< 0.001	< 0.001
Hypothyroidism	108 (7.8)	49 (6.1)	39 (8.6)	20 (15.9)	0.001	0.006
Chronic hypertension	14 (1.0)	9 (1.1)	3 (0.7)	2 (1.6)	---	0.623
Pre-gestational diabetes	8 (0.6)	4 (0.5)	1 (0.2)	3 (2.4)	---	0.653
Smoking	210 (15.2)	144 (18.1)	57 (12.5)	9 (7.1)	0.001	0.001
BMI (kg/m^2)					0.308	0.235
underweight (< 18.5 kg/m^2)	18 (1.5)	7 (1.0)	10 (2.5)	1 (0.9)		
normal (18.5 – 24.9 kg/m^2)	680 (55.6)	398 (56.1)	226 (55.9)	56 (51.9)		
overweight (25 – 29.9 kg/m^2)	358 (29.3)	202 (28.5)	124 (30.7)	32 (29.6)		
obese (≥ 30 kg/m^2)	166 (13.6)	103 (14.5)	44 (10.9)	19 (17.6)		

CS: caesarean section; BMI: body mass index
a: diabetes, hypertension, hypothyroidism, cancer and autoimmune diseases
§: *p*-value for the comparison of three age groups: 20 - 34 *vs* 35 - 39 *vs* ≥ 40 years old
‖: *p*-value for the comparison of two age groups: 20 - 34 *vs* ≥ 35 years old

On the other hand, no difference was observed as regards preeclampsia, premature delivery threat, gestational hypertension, or intrauterine growth restriction. Weight gain during pregnancy was similar in both groups. A percentage of 40.9% of women had gained weight within the recommended limits, 32.7% did not gain enough weight, and 26.4% had excessive weight gain (Table 2).

Regarding delivery onset, completion, and duration of the hospital admission, labour started spontaneously more frequently in younger women (60.2% *vs* 54.9%, $p = 0.048$), and more scheduled C-sections were performed in older women (9.6% *vs* 5.4%) ($p = 0.003$). An eutocic delivery was more frequent in young women (56.5% *vs* 50.4% $p = 0.027$) and emergency C-sections were more frequent in older women (30.1% *vs* 24.3%) ($p = 0.017$), without any significant differences in the duration of labour. In addition, AMA women stayed longer in the hospital (42.3% *vs* 27.9% $p < 0.001$).

We recorded 1436 births (56.2 % males), of which 92.9 % were full-term births, without differences in maternal age. No significant differences were observed in the newborn weight across the maternal age range, with 82.9% of the newborns being within the normal percentile. Fetal unfavourable results, such as APGAR < 7 at minute 1 and 5 (both in single and twin pregnancies) or fetal death, were infrequent, without differences between both age groups (Table 3).

The multivariable analysis, after being adjusted for different variables, showed that AMA women had a significantly higher risk of developing gestational diabetes (OR = 1.84; 95% CI = 1.10 - 3.07), gestational hypothyroidism (OR = 2.11; 95% CI = 1.17 - 3.80), a longer hospital admission (OR = 2.91; 95% CI = 1.95 - 4.35). A decrease in the rate of eutocic deliveries was also observed (OR = 0.74; 95% CI = 0.56 - 0.98) (Table 4). On the other hand, AMA was not associated with weight gain during the pregnancy, threatened premature delivery, or with the admission of the newborn to the NICU. Intrauterine growth restriction, Small for gestational age, a lower probability of having a spontaneous labour, or a higher rate of C-sections were not associated with AMA either. The analysis based on cubic regression splines is shown in Fig. 1. The results suggested that age around 35 years can be a good cut-off point from which both the risk of gestational diabetes and gestational hypothyroidism increases, as well as the probability of a prolonged hospital admission. On the other hand, the chances of having a

Table 2 – Pregnancy and delivery outcomes for the study population

	Total (n = 1378)		**20 - 34 age** (n = 797)	**35 - 39 age** (n = 455)	**≥ 40 age** (n = 126)		
	n (%)	**95% CI**	**n (%)**	**n (%)**	**n (%)**	***p*§**	***p*‖**
Gestational diabetes	77 (5.6)	4.3 – 6.8	34 (4.3)	30 (6.6)	13 (10.4)	0.011	0.012
Gestational hypothyroidism	59 (4.3)	3.2 – 5.4	27 (3.4)	4 (5.3)	8 (6.3)	0.138	0.055
Pre-eclampsia	22 (1.6)	0.9 – 2.3	15 (1.9)	5 (1.1)	2 (1.6)	---	0.322
Gestational hypertension	28 (2.0)	1.3 – 2.8	15 (1.9)	12 (2.6)	1 (0.8)	---	0.644
Premature contractions	67 (4.9)	3.7 – 6.0	35 (4.4)	24 (5.3)	8 (6.3)	0.562	0.341
IUGR	43 (3.1)	2.2 – 4.1	25 (3.1)	15 (3.3)	3 (2.4)	---	0.967
Weight gain in pregnancy (WHO recommendations)						0.184	0.123
low gestational weight	335 (32.7)	29.8 – 35.6	198 (32.4)	101 (31.4)	36 (39.1)		
normal gestational weight	419 (40.9)	37.8 – 43.9	238 (39.0)	145 (45.0)	36 (39.1)		
excessive weight gain	271 (26.4)	23.7 – 29.2	175 (28.6)	76 (23.6)	20 (21.7)		
Delivery characteristics						0.003	0.006
spontaneous onset	799 (58.0)	55.3 – 60.6	480 (602)	261 (57.4)	58 (46.0)		
induction of labour	480 (34.8)	32.3 – 37.4	274 (34.4)	151 (33.2)	55 (43.7)		
caesarean section (elective)	99 (7.2)	5.8 – 8.6	43 (5.4)	43 (9.5)	13 (10.3)		
Mode of delivery						0.007	0.039
natural delivery	743 (53.9)	51.3 – 56.6	450 (65.5)	240 (52.7)	53 (42.1)		
instrumental delivery[a]	266 (19.3)	17.2 – 21.4	153 (19.2)	90 (19.8)	23 (18.3)		
caesarean section (emergency)	369 (26.8)	24.4 – 29.2	194 (24.3)	125 (27.5)	50 (39.7)		
Length of hospitalization (days)						< 0.001	< 0.001
< 2 days	8 (0.6)	0.1 – 1.0	8 (1.0)	0 (0.0)	0 (0.0)	---	
2 - 4 days	901 (65.4)	62.9 – 68.0	566 (71.1)	272 (59.8)	63 (50.0)	< 0.001	
≥ 4 days	468 (34.0)	31.5 – 36.5	222 (27.9)	183 (40.2)	63 (50.0)	< 0.001	

IUGR: intrauterine growth restriction
a: vaginal delivery where either thongs or vacuum extraction was used
§: *p*-value for the comparison of three age groups: 20 - 34 *vs* 35 - 39 *vs* ≥ 40 years old
‖: *p*-value for the comparison of two age groups: 20 - 34 *vs* ≥ 35 years old

Table 3 – Neonatal outcomes in women 20 - 34 years and AMA

	Total (n = 1378)		20 - 34 age (n = 797)	35 - 39 age (n = 455)	≥ 40 age (n = 126)		
	n (%)	CI 95%	n (%)	n (%)	n (%)	p§	p‖
Singleton gestation							
APGAR 1' < 7	23 (1.7)	1.0 – 2.5	12 (1.6)	11 (2.0)	0 (0.0)	0.145	0.532
APGAR 5' < 7	6 (0.5)	0.1 – 0.9	3 (0.4)	3 (0.6)	0 (0.0)	---	0.698
Gestational age at delivery						0.712	0.427
< 37 weeks	81 (6.1)	4.7 – 7.4	44 (5.6)	28 (6.7)	8 (6.7)		
≥ 37 weeks	1255 (93.8)	92.5 – 95.1	738 (94.4)	406 (93.3)	111 (93.3)		
Neonatal birthweight:						0.357	0.466
small for gestational age	92 (6.9)	5.5 – 8.3	51 (6.5)	29 (6.7)	12 (10.1)		
normal birth weight	1132 (84.6)	82.6 – 86.6	670 (85.7)	363 (83.3)	99 (83.2)		
fetal macrosomia	113 (8.5)	6.9 – 10.0	61 (7.8)	44 (10.1)	8 (6.7)		
Intrauterine fetal death	3 (0.2)	0.1 – 0.7	1 (0.1)	2 (0.4)	0 (0.0)	---	0.573
NICU admission	122 (9.1)	7.5 – 10.7	63 (8.2)	46 (10.7)	13 (11.1)	0.261	0.102
Multiple gestation							
APGAR 1' < 7	3 (4.2)	0.9 – 11.9	2 (7.4)	1 (2.9)	0	---	0.553
APGAR 5' < 7	1 (1.4)	0.0 – 7.6	0 (0.0)	1 (2.9)	0	---	1.00
Gestational age at delivery						0.813	0.608
< 37 weeks	15 (37.5)	21.3 – 53.8	6 (42.9)	7 (36.8)	2 (28.6)		
≥ 37 weeks	25 (62.5)	46.3 – 78.8	8 (57.1)	12 (63.2)	5 (71.4)		
Neonatal birthwight:						---	0.676
small for gestational age	10 (18.8)	6.1 – 26.1	3 (21.4)	9 (25.0)	0 (0.0)		
normal birth weight	52 (81.3)	73.9 – 93.8	11 (78. 6)	27 (75.0)	14 (100.0)		
Fetal macrosomia	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)		
Intrauterine fetal death	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	-	-
NICU admission	31 (40.8)	29.1 – 52.5	14 (50.0)	12 (35.3)	5 (35.7)	0.459	0.212

NICU: neonatal intensive care unit
§: *p*-value for the comparison of three age groups: 20 - 34 *vs* 35 - 39 *vs* ≥ 40 years old
‖: *p*-value for the comparison of two age groups: 20 - 34 *vs* ≥ 35 years old

eutocic delivery do not seem to start to decline until a slightly older age.

DISCUSSION

The objective of this study was to describe the characteristics of pregnant women aged 35 and over, and the problems associated with these women in a hospital in Northwestern Spain. These data may be usefulto adapt current guidelines and provide healthcare centres with the necessary resources in order to treat those pregnancies formerly considered high-risk.

It is worth highlighting that in this study there was a high prevalence of AMA pregnant women (42.4 %) and the higher risk these women had of developing diabetes and hypothyroidism during pregnancy, the decrease in the rate of eutocic deliveries, and the probability of having a longer hospital admission. However, despite having a higher number of previous conditions, no differences were observed in terms of other another pregnancy complications, threatened preterm labour, orperinatal outcomes.

As stated, this study stands out due to the high percentage of AMA women. AMA has become common in Spain in recent years due to several factors: the economic crisis of the last decade, a higher percentage of women educated at university level, job positions with more responsibilities, etc. This makes maternity something more likely to be postponed to a period of greater economic and professional stability. Despite these factors being common throughout Spain, the percentage of AMA in this hospital in Northwestern Spain is even higher compared to other Spanish regions by almost eight points.[16] If we compare this data internationally, we observe a lower prevalence of AMA in other studies: 8.5%,[15] 14%,[21] 15%,[9] 21%[8] and 35.8%.[4] These may be influenced by the current uncertainty of the job market (lack of stability), the high housing prices, and a lack of rental market, which delays emancipation. This high prevalence rate shows the importance of studying the obstetric and perinatal outcomesin this age group, which is increasingly growing.

During pregnancy, advanced maternal age entails risks, one of them being the increased proportion of previous conditions, as shown in this study (42.0 % *vs* 30.2 %).

Table 4 – Crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) for advanced maternal age and risk of the most frequent obstetric, perinatal and fetal outcomes

	OR crude	95% CI	OR adjusted	95% CI
Gestational diabetes (n = 77)	1.80	1.13 – 2.86	1.84†	1.10 – 3.07
Gestational hypothyroidism (n = 59)	1.66	0.99 – 2.81	2.11†	1.17 – 3.80
Gestational hypertension (n = 28)	1.19	0.56 – 2.53	1.40†	0.6 – 3.28
Weight gain (n = 271 above recommended range)	0.75	0.56 – 1.00	0.81‡	0.58 – 1.12
Premature contractions (n = 67)	1.27	0.78 – 2.06	0.96‡	0.53 – 1.74
Intrauterine growth restriction (IUGR) (n = 43)	0.99	0.53 – 1.83	1.19‡	0.59 – 2.40
Spontaneous onset (n = 799)	0.80	0.65 – 0.99	0.77§	0.59 – 1.01
Natural delivery (n = 743)	0.78	0.63 – 0.97	0.74§	0.56 – 0.98
Caesarean section (n = 369)	1.34	1.05 – 1.70	1.24§	0.89 – 1.72
Prolonged hospital admission (≥ 4 days) (n = 468)	1.90	1.52 – 2.38	2.91‖	1.95 – 4.35
Preterm birth (n = 98)	1.29	0.85 – 1.94	0.96‡	0.57 – 1.60
NICU admission (n = 153)	1.36	0.94 – 1.98	1.25‡	0.82 – 1.89

†: adjusted for: BMI, smoking habit, parity, assisted reproduction and chronic illness. Gemelarity was included in the model when sample size requirements were met.
‡: adjusted for: BMI, smoking habit, parity, assisted reproduction, chronic illness, gestational diabetes, gestational hypertension and gestational hypothyroidism. Gemelarity was included in the model when sample size requirements were met.
§: adjusted for: BMI, smoking habit, parity, assisted reproduction, chronic illness, gestational diabetes, gestational hypertension, gestational hypothyroidism, gemelarity and weight gain during pregnancy.
‖: adjusted for: BMI, smoking habit, parity, assisted reproduction, chronic illness, gestational diabetes, gestational hypertension, gestational hypothyroidism, gemelarity, weight gain during pregnancy and C-section delivery.

The prevalence of previous co-morbidities was higher than that shown in other studies (between 8% and 39 % in older pregnant women, and between 1% and 25% in women younger than 35 years old).[4,5,9,22,23] Similarly, there is also a higher prevalence of conditions as maternal age increases.[5,22,23]

Our findings also support a greater need for the use of reproduction techniques in the case of AMA (11.4% *vs* 2.1%, $p < 0.001$), as shown in Ankarcroma *et al*[15] and Macías Villa *et al*[4] and even higher than other studies: 4.3% *vs* 0.2%.[9] These assisted reproduction treatmentsare associated with an increase in the number of twin pregnancies, which are more frequent in AMA, in addition to spontaneous pregnancies, as the study by Rydahl *et all*[9] shows.

Even though 5.6% of patients were diagnosed with gestational diabetes, that percentage increased to 7.4% in women of advanced maternal age. This finding showed the increasing trend of diabetes related to maternal age, which is similar to the study by Ben-David et *al*. Shan *et al* also observed an increased risk of 2.78 times in women older than 35.[24]

Thyroid disease is frequent in the Northern Spain, especially in Galicia. Before the inclusion of the intake of iodized salt in the general population, there was a deficit of this element and, as a consequence, a high number of patients with thyroid disease. This is the reason why thyroid disease is assessed during pregnancy in this region. The results show that AMA women suffer from gestational hypothyroidism twice as much as young women. Since this is not a frequent condition, other hospitals are less likely to include these checks in routine care and they are only performed if there are symptoms. Therefore, we do not have other data with which to compare.

Regarding high blood pressure (HBP) present during pregnancy, the tendency is the same, although the difference is minimal. (2.3% *vs* 1.9%). This may be due to the low number of cases found, since HBP tends to increase as maternal age increases. Other authors have observed greater differences.[8,9,13,25,26] but in general all studies show a tendency of HBP increasing with age.[5,10,21,24]

Regarding threatened premature labour, other studies have found a bigger tendency in AMA, although the differences are not always significant.[6,9,13,27] In this study, the rate of threatened premature labour is slightly higher in the AMA group (5.5 % *vs* 4.4 %), although this association cannot be confirmed (OR = 0.94; 95% IC: 0.52 - 1.70).

Given that the observed conditions are frequent, it is not always possible to wait for women to start labour spontaneously, but it may be necessary to terminate the pregnancy due to medical causes. Sometimes, elective C-sections are necessary. Several studies associate an advanced maternal age with a higher number of C-sections[4,6,8,11,16,21] and instrumental deliveries.[5] In this sample, the probability of an eutocic delivery was significantly lower in the AMA group (OR = 0.75). However, the risk of C-section was not associated with maternal age OR = 1.24 IC (0.89 - 1.72) after adjusting, among other variables, for previous and gestational conditions.

Something similar happens with prematurity: the number increases slightly with age (8.1 % *vs* 6.4 %), but these results are not associated with advanced age OR = 0.96 IC (0.57 - 1.60). In other studies, the percentages of premature births are much higher, and this may be because the age of these patients is also higher: they consider older pregnant women to be between 40 and 45 years old. This may also be due to less monitoring of threatened premature lbour.[5,6,8,10,16,26,28] It is also very important to take into account that prematurity is influenced by other factors like smoking,

HBP during pregnancy, and the quality of healthcare and monitoring during pregnancy.

It is especially noteworthy that AMA is associated with longer hospital admissions, even after considering C-sections in the analysis, and despite the absence of significant differences in obstetric events in both groups, such as previous comorbidities and gestational diseases. We cannot discard that this difference could be explained due to other confounding variables not included in this study. In the hospital where the data was gathered, pregnancies are not finalised depending on the maternal age, it is only finalised if there is an obstetric pathology or a prolonged pregnancy regardless of the age of the pregnant woman, but it is possible that there is a bias that leads to believe that pregnant women with AMA can develop more diseases after labour and therefore end up extending hospital admissions without justification, which will mean more hospital expenses in this age group.

As for neonatal results, we found a slightly higher percentage of AMA newborn admissions to NICU, and this is supported by studies like the one conducted by Schwartz *et al* and the one by Kahveci *et al*.[6,13] However, after performing a multivariable analysis, a significant association with AMA was not obtained OR = 1.25 IC (0.82 - 1.89).

Low weight at birth is more frequent in AMA children,[5,11,14–16] and this matches the results observed, although the differences are not statistically significant.

The results of this study have to be interpreted of a number of possible limitations.

One of the main limitations is the lack of statistical power to detect differences in the incidence of less frequent obstetric or perinatal events. For the same reason, this study was not designed to analyse the differences in the rates of complications in the subgroups aged 35-39 and ≥ 40, as other studies did.[29] This is a study carried out in a specific geographical area during oneyear, and therefore these results may not be generalisable. The data could also vary between a public hospital (like the one in this study) and a private hospital, especially in terms of C-section rates, since they are only performed under justified circumstances.

In addition, one must also consider that this study is retrospective and based on information from medical records, which can be subject to bias. Only one person was responsible for collecting the data from the medical records, which minimized biases. As opposed to other studies, a multivariable analysis adjusted for previous and gestational conditions was performed, which minimized confounding. The thoroughness of the information collected allowed the adjustment of this analysis for multiple variables, which could explain the differences in the results obtained in other papers that did not perform this adjustment.

It is important to be aware tha women's role in society is changing and that this leads to a higher maternal age. This seems to be a tendency that will carry on over time. A consequence of this fact will be increased healthcare expenses, especially due to long hospital admissions and to less favourable obstetric-perinatal outcomes. Therefore, it is necessary to adapt guidelines to this new reality especially in terms of both the number of consultations of pregnant women and the moment when they take place, and the training of healthcare professionals. It is important to 'normalize' AMA in pregnancies and not to over-diagnose or perform unnecessary tests only due to an advanced maternal age.

CONCLUSION

This study brings to light the high prevalence of AMA pregnant women in Spain and partly confirms its impact on obstetric and perinatal outcomes. Although older women tended to have worse outcomes, the differences in many cases were not as substantial as shown in previous studies. We can conclude that it is important to continue studying older pregnant women in order to prevent or identify, at an early stage, potential problems during pregnancy.

AUTHORS CONTRIBUTION:

LPM: Conception and design of the work, data acquisition and analysis, draftof the paper, critical review and approval of the final version.

SBL, NLC, RNA: Conception and design of the work, data acquisition, critical review and approval of the final version.

TSP, SPD: Conception and design of the work, data analysis, critical review and approval of the final version.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper.

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A Real-World Analysis of Anti-Atherosclerotic Medical Treatment and Risk Factor Control in a Cohort of Vascular Surgery Patients in Portugal

Tratamento Médico Anti-Aterosclerótico e Controlo de Fatores de Risco numa Coorte de Doentes Vasculares em Portugal

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ABSTRACT

Introduction: The aim of this study was to assess the pattern of anti-atherosclerosis medicines in patients admitted to a vascular surgery department, the effective control of the target values and its subsequent modification by the vascular surgery team.

Material and Methods: A retrospective single-center cohort study of prospectively collected data was performed between May 2017 and May 2018 in a tertiary center. The STROBE guidelines were followed. All patients undergoing a primary elective surgery for carotid disease, aortic aneurysm and peripheral arterial disease were included. 'Best medical treatment' was defined as treatment with both anti-thrombotic and lipid-lowering treatment and, when appropriate, antihypertensive and anti-diabetic drugs. Both baseline and post-discharge best medical treatment were recorded. Blood work-up was performed at admission and 'adequately controlled patient' was defined if all blood test values were in agreement with the guidelines.

Results: A total of 279 patients (78% male; mean age 69 years-old) were included. Optimal medical therapy was registered in 58.8% upon admission but improved to 73.8% (95% CI, 2.197 – 7.781; $p < 0.001$) after discharge. At baseline, a total of 65.4% of patients were on lipid-lowering agents and of these, only 37% had LDL-C values within the targets. Likewise, only 34.6% of the 78 patients with diabetes had glycated hemoglobin within the normal range. Additionally, 8.5% of the remaining cohort had undiagnosed diabetes.

Conclusion: In our current practice, only 75% of the patients receive best medical treatment. Although the admission in a Vascular Surgery department was an opportunity to optimize medical therapy, treatment remains suboptimal in one-quarter of patients. Further efforts should be carried out to alert vascular surgeons to this problem and to find future multidisciplinary solutions that can improve the cardiovascular risk profiles of these patients.

Keywords: Atherosclerosis/treatment; Cardiovascular Diseases/treatment; Risk Factors; Vascular Surgical Procedures

RESUMO

Introdução: Este estudo pretendeu avaliar o padrão de tratamento médico antiaterosclerótico em doentes internados num serviço de cirurgia vascular, o controlo efetivo dos valores-alvo e a sua posterior modificação pela equipa vascular.

Material e Métodos: Foi realizado um estudo de coorte retrospetivo com dados coletados prospectivamente entre maio de 2017 e maio de 2018 num centro terciário. Foram seguidas as *guidelines* da STROBE e incluídos todos os doentes submetidos a cirurgias primárias eletivas para correção de doença carotídea, aneurisma de aorta e doença arterial periférica. Definiu-se como 'tratamento médico otimizado' o tratamento com fármacos anti-trombóticos e hipolipemiantes e, quando apropriado, com agentes anti-hipertensivos e antidiabéticos. Foi registado tratamento médico otimizado à entrada bem como após a alta. À admissão foi igualmente realizado um controlo analítico e os doentes foram classificados como 'adequadamente controlados' se todos os valores analíticos estivessem de acordo com as normas de orientação clínica.

Resultados: Foram incluídos 279 pacientes (78% homens; idade média de 69 anos). O tratamento médico otimizado foi registado em 58,8% à data de admissão, tendo melhorado para 73,8% (IC 95%, 2,197 – 7,781; $p < 0,001$) após alta da enfermaria vascular. No início do estudo, 65,4% dos doentes estavam sob agentes hipolipemiantes e, destes, apenas 37% tinham valores de LDL-C dentro dos valores-alvo estabelecidos pelas normas de orientação clínica. Da forma semelhante, apenas 34,6% dos 78 doentes com diabetes tinham hemoglobina glicada dentro da normalidade. Da restante coorte, 8,5% tinha diabetes não diagnosticada.

Conclusão: Na nossa prática atual apenas 75% dos pacientes seguem o tratamento médico otimizado. Apesar do internamento num serviço de Cirurgia Vascular ser uma oportunidade única para otimizar o tratamento médico, este permanece abaixo do ideal em cerca de um quarto dos doentes. Devem ser realizados esforços adicionais no sentido de alertar os cirurgiões vasculares para esse problema e encontrar soluções multidisciplinares futuras que permitam melhorar o perfil de risco cardiovascular destes doentes.

Palavras-chave: Aterosclerosis/tratamento; Doenças Cardiovasculares/tratamento; Factores de Risco; Procedimentos Cirúrgicos Vasculares

INTRODUCTION

Atherosclerotic disease (AD) is the leading cause of morbidity and mortality worldwide and is the most prevalent condition in vascular surgery patients.[1] As a polyvascular disease, it affects not only the peripheral territories but may simultaneously involve the coronary and cerebral arteries resulting in exceedingly high mortality from stroke and myocardial infarction.[2-7] Therefore, it is essential to focus on the prevention of general cardiovascular complications beyond

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the treatment of the specific vascular condition. The current medical management of cardiovascular risk factors, such as anti-thrombotic, lipid-lowering, anti-hypertensive and anti-diabetic medication [commonly designated as best medical therapy (BMT)], have shown to be effective in lowering overall and cause-specific related mortality in patients with coronary disease as well as other vascular disorders like extra-coronary atherosclerotic occlusive disease and aneurysms.[2,8-12] In observational studies, BMT has shown to be effective in reducing the risk of stroke in patients with asymptomatic carotid stenosis leading to ample discussions in the vascular and neurology communities regarding the risk of asymptomatic stenosis and the indications for intervention.[13,14] However, it remains questionable how these results from very controlled populations can be extrapolated to the real-world setting and some publications[6] suggest that a significant number of patients are not well controlled. Furthermore, being medicated does not mean adequately controlled [i.e., target LDL value, target blood pressure (BP)], an issue that has not been considered in previous studies.

Therefore, the aim of this study was to assess the medical management of a real-world cohort of vascular surgery patients, in order to: 1) assess the pattern of anti-atherosclerosis medicines in patients admitted to a vascular surgery department; 2) evaluate how adequately treated patients are effectively controlled, considering the therapeutic targets suggested by guidelines[2,3,8,10] and 3) assess the impact of the admission to the vascular surgery Department on the improvement of medical treatment for atherosclerosis. We hypothesized that most patients admitted to the hospital were not adequately medicated and not adequately controlled either. Moreover, we hypothesized that admission to the Vascular Surgery department would improve the medical treatment of these patients.

MATERIAL AND METHODS

Study design

A retrospective single-center cohort study of prospectively collected data was performed. The STROBE (StrengThening the Reporting of Observational Studies in Epidemiology) guidelines for reporting cohort studies were followed.[15]

Setting

The study was conducted from May 2017 to May 2018 in the Vascular Surgery Department of Centro Hospitalar Universitário Lisboa Norte (CHULN), a tertiary University Hospital in the center of Lisbon and one of the largest hospitals in Portugal. Data was collected prospectively using a pre-specified case report form.

Participants

All consecutive patients admitted for a primary elective surgery during the study period were included. Re-admissions, emergency cases and patients admitted through the emergency department were excluded.

Variables, data sources and measurement

A complete medical history was recorded upon admission. Patients were assessed regarding medication use (active drug, dose, duration of treatment and compliance), previous medical history (smoking, hypertension, diabetes, lower limb peripheral artery disease, carotid disease, aneurysmal disease, dyslipidemia, coronary artery disease, heart failure and chronic renal disease) and past surgical history. Past medical history was assessed by consulting the patients' clinical records. Regarding *de novo* diagnoses based on laboratory values, guideline target values[2,3,5,10] were used: hypertension was defined as office systolic BP values ≥ 140 mmHg and/or diastolic BP (DBP) values ≥ 90 mmHg; dyslipidemia was considered in patients with LDL-C > 70 mg/dL and diabetes with HbA1c > 7%. The diagnosis leading to admission and the details of the surgery were also registered.

Any modifications to the baseline medical therapy following admission in the Department were registered.

Blood work-up was performed including complete blood cell count, coagulation test including fibrinogen, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, creatinine, urea, AST, ALT, glycated hemoglobin (HbA1c), fasting glucose, C-reactive protein (CRP) and uric acid.

Vascular procedures were divided into four groups according to the diagnosis (Index Procedures): carotid disease, abdominal aortic aneurysm (AAA), intermittent claudication (IC) and chronic limb-threatening ischemia (CLTI).

'Best medical treatment' was defined as a baseline treatment with both anti-thrombotic drugs (ATD) and statins and, when appropriate, antihypertensive and anti-diabetic agents.

A patient was considered 'adequately controlled' when the risk factor variables met the guideline target values (BP < 140/90 mmHg and in patients with diabetes DBP < 85 mmHg; LDL-C < 70 mg/dL and HbA1c < 7%).[2,3,5,10]

The effective control of ambulatory arterial hypertension was found to be difficult to assess during hospital admissions for surgery or for critical conditions and it was not included in the analysis.

Major adverse cardiovascular events (MACE) including nonfatal stroke, nonfatal myocardial infarction and cardiovascular death, were registered during the study period.

Bias

In order to lower the possibility for performance bias, only two physicians were involved in the study and collected data without interfering in day-to-day practice. Data was collected prospectively in order to deal with reporting bias. The study focused on patients with different diagnoses in order to account for some selection bias.

Statistical methods

Descriptive statistics are presented for demographic and baseline variables as absolute and relative frequencies. Continuous variables are presented as mean (standard deviation – SD) if normally distributed and median

(interquartile range – IQR) if not. Category variables are presented as frequency (percentage).

To study which variables could influence a patient to be in BMT, univariate comparisons of preoperative comorbidities were performed using the Pearson χ^2 and Fisher exact tests, the latter when the event rates were low (< 10 events). The same statistical analysis was used to study in-hospital mortality and MACE. In addition, variables with potential influence on preoperative BMT were also included in a multivariable logistic regression model. BMT rate was analyzed using a McNemar's test to compare the study group before and after admission to the Vascular Surgery Department. Statistical significance was set at $p < 0.05$. Analyses were performed using Stata version 14.0 for Mac (Stata Corp® 2015, *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Ethics

Informed consent was obtained from all individual participants included in the study. Due to the sensitive nature of the questions asked in this study, survey respondents were assured the raw data would remain confidential and would not be shared. This article does not contain any studies with human participants performed by any of the authors and so the Ethic Committee approval was waived.

RESULTS

Participants and descriptive data

A total of 291 patients were electively admitted to the Vascular Surgery department during the study period for Index Procedures. Twelve patients were excluded for having missing data regarding pre-hospitalization medication. The final cohort included a total of 279 patients, 78% male

Table 1 – Baseline characteristics of 279 patients undergoing index elective procedures

		Total (n = 279)	Carotid disease (n = 74)	Intermittent claudication (n = 16)	Critical limb ischaemia (n = 129)	Aortic aneurysm (n = 60)
Gender	Female	62 (22.2%)	18 (24.3%)	2 (12.5%)	37 (28.7%)	5 (8.3%)
	Male	217 (77.8%)	56 (75.7%)	14 (87.5%)	92 (71.3%)	55 (91.7%)
Mean age, years		69.03	71.59	64.53	67.11	72.87
Smoking status	Never	117 (41.9%)	33 (44.6%)	6 (37.5%)	54 (41.9%)	24 (40.0%)
	Current	79 (28.3%)	22 (29.7%)	6 (37.5%)	40 (31.0%)	11 (18.3%)
	Former	83 (29.8%)	19 (25.7%)	4 (25.0%)	35 (27.1%)	25 (41.7%)
Hypertension	No	55 (19.7%)	13 (17.6%)	4 (25.0%)	28 (21.7%)	10 (16.7%)
	Yes	224 (80.3%)	61 (82.4%)	12 (75.0%)	101 (78.3%)	50 (83.3%)
Dyslipidemia	No	137 (49.1%)	31 (41.9%)	4 (25.0%)	81 (62.8%)	21 (35.0%)
	Yes	142 (50.9%)	43 (58.1%)	12 (75.0%)	48 (37.2%)	39 (65.0%)
Coronary artery disease	None	206 (73.8%)	58 (78.4%)	11 (68.7%)	96 (74.4%)	41 (68.3%)
	Recent MI / unstable angina	4 (1.4%)	0	0	3 (2.3%)	1 (1.7%)
	Prior MI	66 (23.7%)	15 (20.3%)	5 (31.3%)	29 (22.5%)	17 (28.3%)
	Stable angina	3 (1.1%)	1 (1.3%)	0	1 (0.8%)	1 (1.7%)
Coronary revascularization	None	228 (81.7%)	63 (85.1%)	11 (68.7%)	108 (83.7%)	46 (76.7%)
	PTCA	25 (9.0%)	5 (6.8%)	3 (18.8%)	9 (7.0%)	8 (13.3%)
	CABG	26 (9.3%)	6 (8.1%)	2 (12.5%)	12 (9.3%)	6 (10.0%)
Cerebrovascular disease	No	207 (74.2%)	27 (36.5%)	14 (87.5%)	111 (86.1%)	55 (91.7%)
	Stroke	64 (22.9%)	42 (56.8%)	2 (12.5%)	15 (11.6%)	5 (8.3%)
	TIA	8 (2.9%)	5 (6.7%)	0	3 (2.3%)	0
Diabetes	No	167 (59.9%)	48 (64.9%)	12 (75.0%)	61 (47.3%)	46 (76.7%)
	Yes - OAD	76 (27.2%)	22 (29.7%)	3 (18.7%)	39 (30.2%)	12 (20.0%)
	Yes- Insulin	36 (12.9%)	4 (5.4%)	1 (6.3%)	29 (22.5%)	2 (3.3%)
COPD	No	252 (90.3%)	65 (87.8%)	15 (93.7%)	118 (91.5%)	54 (90.0%)
	Yes	27 (9.7%)	9 (12.2%)	1 (6.3%)	11 (8.5%)	6 (10.0%)
Chronic kidney disease	No	238 (85.3%)	67 (90.5%)	16 (100.0%)	102 (79.1%)	53 (88.3%)
	Yes	24 (8.6%)	7 (9.5%)	0	11 (8.5%)	6 (10.0%)
	Yes - dyalisis	17 (6.1%)	0	0	16 (12.4%)	1 (1.7%)
Cancer	No	256 (91.8%)	69 (93.2%)	15 (93.7%)	119 (92.2%)	53 (88.3%)
	Yes	23 (8.2%)	5 (6.8%)	1 (6.3%)	10 (7.8%)	7 (11.7%)

MI: myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; CABG: coronary artery bypass graft; OAD: oral antidiabetic drugs

and the median age was 70 years old. The admission diagnosis was carotid disease in 26.5%, intermittent claudication in 5.8%, critical limb ischemia in 46.2% and aortic aneurysm in 21.5%. The prevalence of risk factors was as follows: arterial hypertension (80.3%), smoking habits (58.1%), dyslipidemia (50.9%) and diabetes (40.1%). Coronary artery disease was present in 26.2% and cerebrovascular disease in 25.8%. Demographic data and previous medical history are described in Table 1.

Main results

Preoperative medical therapy

Only 58.8% of our cohort was under BMT upon admission. The BMT rate varied according to the admission diagnosis. Patients with intermittent claudication had the highest rate of adequate treatment use with 75% of patients under BMT. All other subgroups had similar rates, between 55 and 60% (Fig. 1).

Effective control of risk factors according to guideline targets

Regardless of the subgroup, only 65.4% of patients were on statin therapy and of these, only 37% had LDL-C values within the targets set by the guidelines for very high-risk patients.[8] In the remaining 34.6% of the patients that were not on statins, high LDL levels, ≥ 70 mg/dL, were observed in 71.4%.

In the group of patients with diabetes, only 34.6% of the 78 patients had HbA1c within the normal range. Additionally, in the remaining patients, 8.5% showed HbA1c values ≥ 7 mg/dL meaning patients were unaware of their diabetic condition.

Postoperative medical therapy and impact of Vascular Surgery admission

After discharge, the number of patients under BMT increased from 58.8% to 73.8% (95% CI, 2.2 – 7.8; $p < 0.001$), mostly attributed to the carotid disease group where this improvement was 25.6% (from 56.8% at baseline to 82.4% after intervention; 95% CI, 2.6 – 92.4; $p = 0.001$). There was also a significant improvement in the CLTI group, from 55.8% to 71.3% (95% CI, 2.1 – 23.8; $p = 0.002$). In the IC group, the difference between the pre and postoperative BMT was not statistically significant (75% *vs* 87.5% 95% CI, 0.2 – 157.5; $p = 0.317$) neither was the AAA group (63.3% *vs* 65% (95% CI, 0.4 – 3.7; $p = 0.796$) (Fig. 1; Table 2).

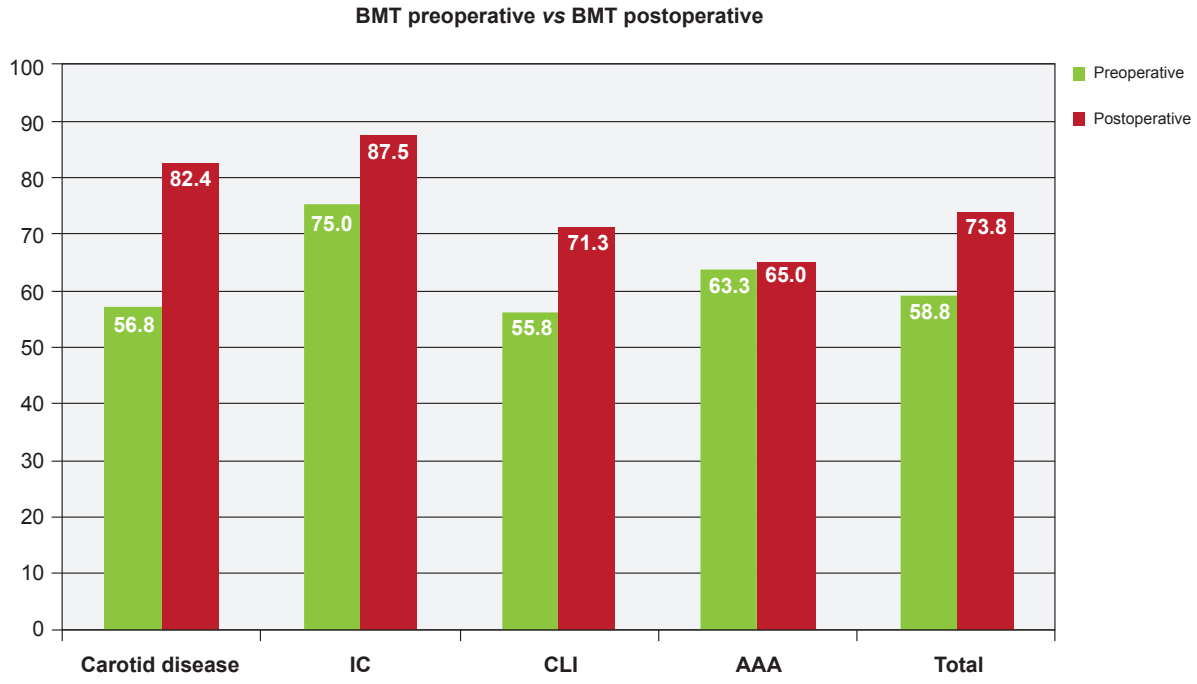

Figure 1 – Treatment demographics with percentage of patients on optimal medical therapy across procedures on admission and upon discharge (n = 291)
IC: intermittent claudication; CLI: critical limb ischemia; AAA: abdominal aortic aneurysm

Table 2 – Variation in best medical treatment's rate on admission and upon discharge across procedures

	BMT				
	Preoperative, %	**Postoperative**, %	**OR**	**95% CI**	***p*-value**
Carotid disease	42 (56.8)	61 (82.4)	10.5	2.5 – 93.4	0.001
Intermittent claudication	12 (75.0)	14 (87.5)	3.0	0.25 – 157.5	0.317
Critical limb ischemia	72 (55.8)	92 (71.3)	6.0	2.1 – 23.8	0.002
Aortic aneurysm	38 (63.3)	39 (65.0)	1.1	0.36 – 3.7	0.796

Nevertheless, IC remained the best-medicated subgroup, with 87.5% of patients under BMT postoperatively.

Other analyses

Preoperative medical therapy

When analyzing the prevalence of BMT based on risk factors and associated disorders, coronary artery disease ($p = 0.025$), previous coronary revascularization ($p = 0.001$), dyslipidemia ($p < 0.001$) and chronic kidney disease ($p = 0.043$) showed a positive association (Table 3) with better treatment.

In a multivariable logistic regression model, previous coronary revascularization, dyslipidemia, chronic kidney disease and cerebrovascular disease were significantly associated with BMT upon admission (Table 4).

MACE and mortality

During this study, 16 patients (5.8%) suffered major adverse cardiovascular events as defined previously. All cause in-hospital mortality was 3.2%, but only 1.1% (three patients) was attributed to MACE. CKD was the only comorbidity that was significantly associated with mortality ($p = 0.005$).

Although there was no statistically significant difference between MACE or mortality rates and preoperative BMT (MACE under BMT 46.6% *vs* MACE without BMT 53.3%, $p = 0.790$ / mortality under BMT 44.4% *versus* mortality without BMT 55.6%, $p = 0.050$, respectively), there was a clear trend towards an association.

DISCUSSION

Atherosclerosis is a polyvascular condition underlying most vascular surgery patients, from peripheral arterial disease to aortic aneurysms.[1] Despite advances in perioperative care, clinically significant cardiovascular complications remain frequent and result in an exceedingly high mortality rate, mainly from stroke and myocardial infarction.[2-7] Consequently, the European Society of Vascular Surgery (ESVS) and the European Society of Cardiology (ESC) guidelines support aggressive risk reduction therapies for secondary prevention in patients with atherosclerotic disease including PAD, aortic aneurysms and carotid artery disease. Those guidelines recommend pharmacological treatment with anti-thrombotic and lipid-lowering agents as well as antihypertensive and anti-diabetic drugs, when appropriate. Blood pressure should be < 140/90 mmHg (in patients with diabetes, diastolic BP should be < 85 mmHg), LDL-C < 70 mg/dl and HbA1c < 7%. Non-pharmacological therapies with

Table 3 – Univariate analysis of baseline characteristics potentially associated with BMT upon admission

	Preoperative BMT		
	Yes, %	**No**, %	***p*-value**
Male	126 (58.1)	91 (41.9)	0.649
Smoking history	90 (55.5)	72 (44.5)	0.198
Arterial hypertension	135 (60.3)	89 (39.7)	0.309
Dyslipidemia	99 (69.7)	43 (30.3)	< 0.001
Diabetes	68 (60.7)	44 (39.3)	0.591
Coronary artery disease	51 (69.9)	22 (30.1)	0.025
Coronary revascularization	40 (78.4)	11 (21.6)	0.001
Cerebrovascular disease	37 (51.4)	35 (48.6)	0.139
Chronic kidney disease	30 (73.2)	11 (26.8)	0.043
COPD	14 (51.9)	13 (48.1)	0.441
Cancer	13 (56.5)	10 (43.5)	0.818

COPD: chronic obstructive pulmonary disease

Table 4 – Multivariable logistic analysis of factors potentially associated with BMT upon admission

	95% CI	***p*-value**
Hypertension	-81 – 0.53	0.685
Diabetes	-0.49 – 0.61	0.827
Dislypidemia	0.50 – 1.56	< 0.001
Smoking history	-0.98 – 0.15	0.151
Coronary artery disease	-1.30 – 0.61	0.475
Coronary revascularization	0.19 – 2.46	0.023
Cerebrovascular disease	-1.27 – (-0.49)	0.034
Chonic kidney disease	0.01 – 1.63	0.049
Cancer	-0.78 – 1.04	0.776
Age	-1.63 – 1.65	0.641

lifestyle modifications such as smoking cessation, weight reduction and improvement of physical activity are equally important.[2,3,5,8,10]

The RCT's by Durazzo[16] and Schouten[17] also confirmed that peri-operative statin therapy reduced adverse cardiovascular events after AAA surgery.

Evidence from the UK Heart Protection Study revealed a 25% relative risk reduction in MACE with statin therapy in a subset of patients with PAD.[18] Randomized control trials on the effect of antithrombotic drugs in PAD patients, such as CAPRIE and more recently COMPASS and VOYAGER, identified a reduction of adverse effects, such as stroke and cardiovascular mortality, especially in high-risk groups.[19-21] De Martino further suggested, in a cohort-study of 14 489 patients, that anti-platelet and statin therapy was associated with reduced 30-day mortality and a 18% absolute improvement in 5-year survival after vascular surgery.[6]

Regarding carotid artery disease, observational studies showed that BMT was an effective strategy to reduce the stroke risk in patients with asymptomatic carotid stenosis.[13,14, 22]

However, despite the well-known benefits, the present study highlights a gap between the recommendations and 'real-world' practice. Upon admission to our department, only 58.8% of patients were on BMT. These findings are in line with those of previous randomized controlled trials like the bypass *versus* angioplasty in severe ischemia of the leg (BASIL) where only 54% of patients were on ATD and 34% on statins and the AAA OVER trial where there was also a low rate of patients on ATD.[23,24]

Moreover, we observed that patients with intermittent claudication were, upon admission, better treated compared to the other groups. This was already recognized in the literature[6] and may be due to higher awareness of t family doctors regarding the importance of good control of cardiovascular risk factors in avoiding cardiac and cerebral events.

In patients with carotid stenosis best medical treatment alone is associated with a reduced risk of stroke and may spare some interventions.[13,14] This contemporary concept emerged from population based studies where a strict risk factor control was achieved.[13,14] The importance of medical treatment was also recognized in randomized controlled trials like the revascularization *versus* Stenting trial (CREST) or the asymptomatic carotid surgery trial (ACST-1) where 85% – 90% were under BMT.[25-27] Notwithstanding, it remains questionable how these results from very controlled populations can be extrapolated to the real-world setting and some publications suggest that a significant number of patients remain under-treated.[6]

The analysis according to the risk factors, showed that coronary patients were under more comprehensive anti-atherosclerotic treatment than what was expected due to the surveillance protocols after events and intervention. Additionally, doctors seem to be aware of the impact of treating dyslipidemia and most patients are in fact under proper treatment and finally, CKD patients are usually under close surveillance with positive implications on BMT.

One of the strengths of our study was the assessment, not only of the pattern of anti-atherosclerosis medicines, but also of its effectiveness, considering the therapeutic targets suggested by the guidelines.

In our cohort, only about a third of patients on lipid lowering medication had LDL-C within the target values. Similarly, in the group of patients with diabetes, approximately a third of patients had HBA1c < 7 mg/dL. Additionally, 8.5% of the remaining patients had undiagnosed diabetes. This means that the number of patients that are not effectively controlled is much higher than just the ones that were not on BMT upon admission (41.2%).

Although the main goal of our study was to assess the pharmacological patterns and its real effectiveness, we also analyzed the impact of hospitalization on the improvement of medical treatment for atherosclerosis. Overall, the rate of patients on BMT increased by 15% (from 58.8% to nearly 75%). Despite the positive association, this moderate increase emphasizes the missed opportunities to improve medical therapy after admission in a Vascular Surgery ward.

A comment should also be added regarding the lack of impact of the BMT on MACE. A positive association is, however, well established in the literature and our results are influenced by the sample size. Nevertheless, mortality was higher in patients without BMT and this trend almost reached significance ($p = 0.05$).

Our study has some limitations. The sample used is relatively small, the dosage of each drug wasn't always recorded, and previous hypertension was documented but the ambulatory blood pressure measurements were not consistently reported. The effective control of arterial hypertension was not included as it seemed difficult to assess the ambulatory control based on measurements during hospital admissions for surgical procedures or for critical conditions. We also acknowledge that, if some of the major benefits of BMT were likely to be obtained in the long term, follow-up data and information regarding adherence to treatment should be included in a subsequent prospective study. Despite these limitations, our results highlight the gap between the 'real world' setting and the guideline recommendations and offer an opportunity to rethink the way we manage our patients.

As atherosclerosis is increasingly viewed of as a systemic disease, it may be advisable in the future to devise a multidisciplinary approach to improve the treatment of these patients. Improving overall awareness of the need for cardiovascular risk factor control and adequate anti-atherosclerotic medication in the primary care setting, and a specialized consultation and dedicated outpatient clinic for risk factor control would probably be beneficial in order to improve our results.

Future studies are needed in order to address some key questions. A follow-up study, with mid to long-term data, would be necessary in order to analyze a continued benefit of our interventions and to draw further conclusions regarding long-term risk factor control, adherence to treatment

protocols and long-term results regarding MACE. Furthermore, comparative studies with other non-vascular surgery patients, would also be useful in order to understand if this is general problem or a specific issue regarding vascular surgery patients.

CONCLUSION

Despite the current recommendations, the rate of patients on BMT only increased by 15% (from 58.8% to nearly 75%) after admission in a Vascular Surgery Department. Although this suboptimal treatment did not show significant differences in MACE or mortality, we strongly believe that the admission to a vascular surgery ward should be an opportunity to optimize medical treatment in order to improve outcomes and the cardiovascular risk profiles. Therefore, these results are an opportunity to alert physicians to this problem and to find future multidisciplinary solutions that can improve the treatment of these patients.

AUTHORS CONTRIBUTION:

AL: Responsible for conception and design of the study. Collected, analyzed and interpreted the patient data. read and approved the final manuscript.

LMP: Responsible for conception and design of the study. Read and approved the final manuscript.

RM, LMP: Major contributors in writing the manuscript. Read and approved the final 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 declare that there is no conflict of interests regarding the publication of this paper.

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Consecutive Ankle Sprain Classification and Injury Systematization (CASCaIS), Uma Nova Classificação de Entorse Lateral do Tornozelo Baseada no Teste de Pivot: Estudo Prospetivo de Coorte

Consecutive Ankle Sprain Classification and Injury Systematization (CASCaIS), A New Lateral Ankle Sprain Classification Based on the Pivot Test: A Prospective Cohort Study

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RESUMO

Introdução: O maior desafio no tratamento da entorse aguda do tornozelo é a indefinição do prognóstico. As classificações clássicas têm várias interpretações e pouca correlação com o prognóstico. Com este trabalho propomos uma nova classificação baseada apenas em critérios clínicos.

Material e Métodos: Foram prospectivamente avaliados doentes entre os 18 e os 45 anos com entorse aguda do tornozelo, admitidos numa instituição durante 24 meses. O seguimento mínimo teve uma duração de 12 meses. Estes doentes foram classificados nos primeiros dias após a entorse (CASCaIS-Inicial) com base na valorização da capacidade de marcha autónoma, inspeção do quadro inflamatório e palpação. Passadas algumas semanas (CASCaIS-Diferida) complementou-se com a avaliação ligamentar pelo teste de *pivot* do tornozelo.

Resultados: Dos 49 doentes que completaram o seguimento, nenhum dos que tinha um teste *pivot*-negativo evoluiu para instabilidade crónica do tornozelo (ICT). Nove dos 33 doentes (27%) com um *pivot*-positivo evoluíram para ICT (p = 0,022). A avaliação da CASCaIS-Diferida demonstrou uma associação com a ICT (p = 0,018).

Conclusão: Esta classificação demonstrou ser uma ferramenta simples, não dispendiosa e fiável que os clínicos poderão usar para determinar o prognóstico da entorse.

Palavras-chave: Lesões do Tornozelo; Ligamentos Laterais do Tornozelo; Prognóstico

ABSTRACT

Introduction: The biggest challenge in the treatment of acute ankle sprain is the uncertainty of the prognosis. The traditional classifications have several interpretations and little correlation with prognosis. In this study we propose a new classification for acute ankle sprain only based on clinical criteria.

Material and Methods: We prospectively evaluated all patients with an ankle sprain, aged between 18 and 45 years, admitted to a hospital during a 24 month period. The minimum follow-up period was 12 months. The sprains were classified, in the first few days (CASCaIS-Initial), according to autonomous gait capacity, inspection and palpation. After a few weeks (CASCaIS-Deferred), it was complemented with the mechanical evaluation of ligaments through the ankle pivot test.

Results: Among the 49 patients who completed the follow-up, none of those who had a pivot-negative test progressed to chronic ankle instability (CAI). Nine of the 33 patients (27%) with a positive pivot progressed to CAI (p = 0.022). The evaluation of CASCaIS-Deferred demonstrated an association with CAI (p = 0.018).

Conclusion: This classification proved to be a simple, inexpensive, and reliable tool that clinicians can use to determine the prognosis of the sprain.

Keywords: Ankle Injuries; Ankle Lateral Ligament; Prognosis

INTRODUÇÃO

As entorses agudas do tornozelo são a lesão mais frequente deste segmento e têm uma elevada incidência nos principais desportos coletivos.[1] Correspondem a cerca de 20% de todas as lesões desportivas,[2,3] não sendo exclusivamente tratadas por médicos da área ortopédica ou fisiátrica.[4]

Há três grupos de ligamentos que podem ser lesados no tornozelo: os laterais, os mediais (deltoide) e os sindesmóticos. As entorses agudas ocorrem, em 85% das vezes, por supinação,[2,5] o que condiciona uma lesão do complexo ligamentar lateral (Fig. 1). Devido a esta predominância, as entorses laterais são frequentemente designadas apenas

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como 'entorses', enquanto as lesões dos ligamentos deltoide e sindesmóticos são especificadas, respetivamente, como 'entorse medial' e 'entorse alta'.

A maioria das entorses evolui para uma recuperação funcional completa.[2,5] Uma percentagem considerável, na ordem dos 35%, manterá algum tipo de sintomas e

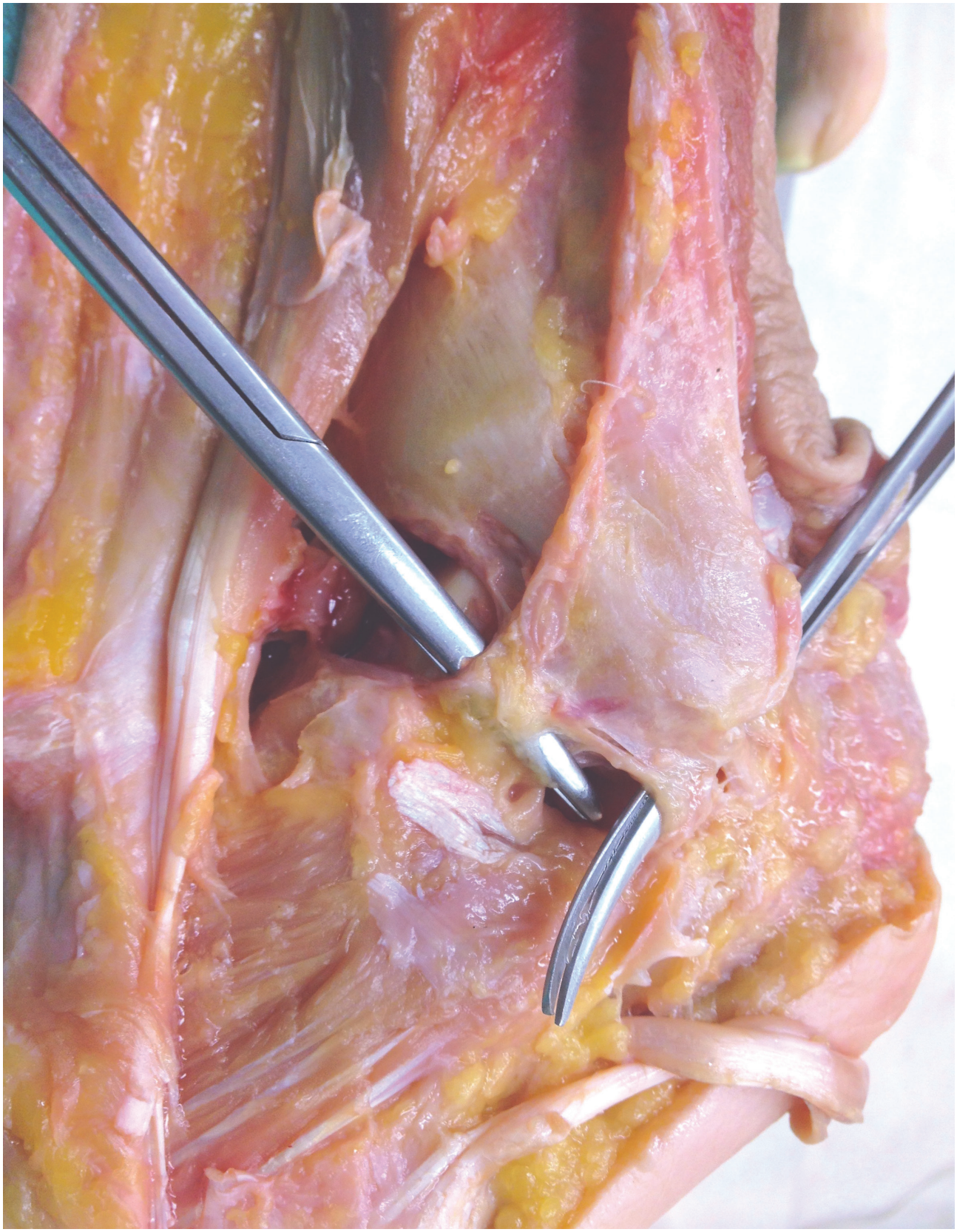

Figura 1 – Dissecção da face lateral do tornozelo (esquerdo), com identificação dos ligamentos peroneo-astragalino anterior e peroneo-calcaneano

limitações crónicas. Isto tem um elevado impacto sócio-económico e mudou o paradigma desta doença, sendo palavra corrente que 'não há entorses do tornozelo simples'.[5]

A instabilidade crónica do tornozelo definir-se-á assim, como limitação funcional persistente após entorse do tornozelo devido a dor, entorses de repetição, sensação de instabilidade ou instabilidade objetiva.[6-8] A dor crónica é um critério de instabilidade crónica do tornozelo (ICT).[6,9]

Se considerarmos a elevada incidência das entorses e a percentagem de doentes que não ficam curados compreendemos que o grande problema da entorse aguda do tornozelo é a indefinição do seu prognóstico. Nos primeiros dias após a entorse não sabemos quem são os doentes que vão evoluir para ICT.

Durante o movimento de entorse ocorre uma supinação do tornozelo que lesiona primeiro o ligamento peroneo-astragalino anterior, (LPAA)[10] fazendo deste ligamento o fator de prognóstico mais relevante. Os doentes que não rompem este ligamento, ou sofrem apenas uma distensão do mesmo, vão evoluir favoravelmente em poucas semanas.[11]

Quando um doente sofre uma rotura completa do LPAA (Fig. 1) tem, por definição, uma entorse severa. A partir desta lesão está aberto o caminho para várias outras lesões ligamentares, tendinosas, do osso e da cartilagem.[12] Estudos prospetivos reportam uma lesão completa do LPAA em 60% - 75% das entorses podendo, no entanto, haver um viés de seleção causado pela referenciação preferencial dos doentes com rotura ligamentar completa aos centros de referência.[13,14] Os doentes com entorses ligeiras têm queixas ligeiras e autolimitadas e sem necessidade de acompanhamento médico.

Seria útil um sistema de classificação que orientasse os clínicos na abordagem das entorses severas do tornozelo. Uma classificação só é relevante quando orienta no tratamento e no prognóstico, e não há nenhuma classificação que nos permita aferir, nos primeiros dias, qual será o resultado clínico final do doente.[7]

A clássica divisão em três graus é, ela própria, ambígua. Alguns autores usam uma classificação 'anatómica',[15] enquanto outros aplicam uma classificação 'funcional'.[16]

Nesta última, as entorses são classificadas como grau I quando ligeiras, grau II quando moderadas e grau III quando o quadro inflamatório observado é severo. Esta classificação tem uma utilidade duvidosa, na medida em que o grau I e II têm o mesmo prognóstico e porque agrupa, no seu grau III, vários prognósticos diferentes. Mantêm-se, assim, as dúvidas relativamente ao prognóstico dos doentes com entorses de grau III, presumivelmente severo.[17] A adesão a este clássico organigrama mental resulta da tradição, em Medicina, de agrupar os casos clínicos em ligeiros, moderados e severos, mesmo que essa distinção não tenha impacto prognóstico confirmado.

O objetivo desta investigação é a proposta de uma nova classificação de entorses agudas do tornozelo, baseada apenas em critérios clínicos, que permita uma correlação prognóstica. Tem como base os pontos fortes de vários trabalhos prévios, nomeadamente a avaliação diferida dos doentes, da capacidade de marcha e a avaliação da laxidez dos ligamentos laterais do tornozelo.[3,18-21]

Este sistema procura diagnosticar uma rotura do LPAA através do teste do *pivot*[21] (Fig. 2 e Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13804/Apendice_01.mov) e inferir outras lesões concomitantes através de duas avaliações clínicas sucessivas, eventualmente confirmadas por exames auxiliares de diagnóstico. Permite englobar as lesões resultantes de entorse

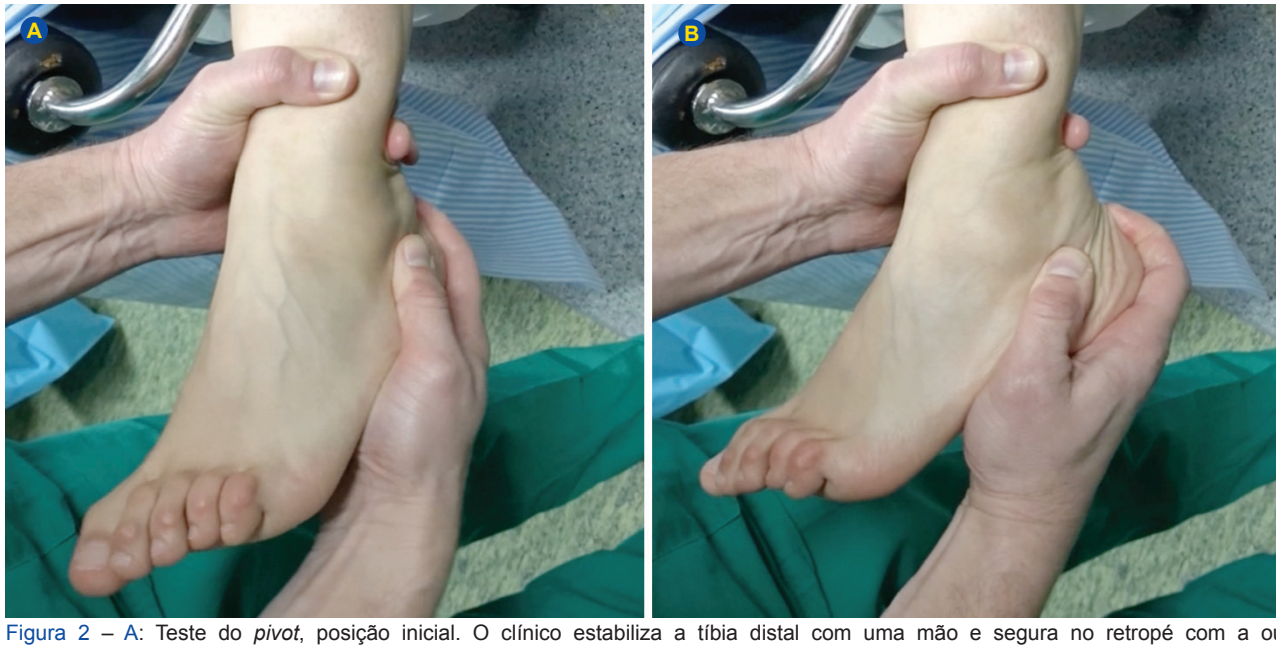

Figura 2 – A: Teste do *pivot*, posição inicial. O clínico estabiliza a tíbia distal com uma mão e segura no retropé com a outra mão, num posicionamento com o pé pendente em ligeira flexão plantar; B: Teste do *pivot*, posição final. Ao aplicar uma força rotatória no calcanhar aplica rotação interna do medio e antepé, com um fulcro no maléolo interno. Deve sempre ser realizado inicialmente no membro são para que o doente não sinta apreensão e para aferir qual é a laxidez fisiológica nesse doente. (captura de imagens do Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13804/Apendice_01.mov)

do tornozelo num modelo compreensivo que auxilia o clínico, valorizando todos os elementos com potencial interesse prognóstico. Por fim, procura relacionar as queixas e limitações do doente com o grau de lesão tecidular desta articulação.[22,27]

As hipóteses colocadas são de que o teste de *pivot* positivo e a classificação em quatro graus progressivos de gravidade permitem prever quais os doentes que irão evoluir desfavoravelmente para instabilidade crónica.

MATERIAL E MÉTODOS

Este trabalho é baseado num estudo prospetivo observacional de coorte com aprovação pela Comissão de Ética do Hospital Dr. José de Almeida, Cascais, tendo sido aplicadas as *guidelines* STROBE (*STrengthening the Reporting of OBservational studies in Epidemiology,* em Apêndice 2 (Apêndice 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13804/Apendice_02.pdf).

Foi criada uma Consulta de Entorses de Tornozelo (CET) direcionada para esta investigação. Esta CET recebeu referenciação dos casos de entorse do serviço de urgência do mesmo Hospital num período de 24 meses (entre 1 de janeiro de 2017 e 31 de dezembro de 2018). Trata-se, assim, de uma amostra de conveniência que inclui todos os doentes referenciados neste período. A CET teve lugar duas vezes por semana, de modo a que todos os entorses pudessem ser reavaliados menos de cinco dias após a observação no Serviço de Urgência.

Os critérios de referenciação e inclusão foram:

- primeiro entorse do tornozelo ocorrido há menos de 48 horas;
- sem comorbilidades do mesmo membro;
- doentes com idades compreendidas entre os 18 e os 45 anos;
- consentimento no seguimento por um período mínimo de 12 meses.

Os critérios de exclusão foram:

- outro diagnóstico que não o entorse agudo lateral do tornozelo;
- entorse da sindesmose (com dor nos testes de *stress* em rotação externa);
- cirurgia prévia neste ou no outro tornozelo;
- fratura atual ou recente (menos de seis meses) de algum segmento dos membros inferiores;
- eventual instabilidade crónica:
  - entorse prévio com edema importante ou recuperação superior a duas semanas;
  - história prévia de entorses de repetição, dor ou sensação de instabilidade;
- patologia reumatoide, terapêutica com corticoides ou algum tipo de imunomodulador.

Na primeira CET, após confirmação dos critérios de inclusão e exclusão, foi feito um registo detalhado do exame clínico e aplicada a *Consecutive Ankle Sprain Classification and Injury Systematization* (CASCaIS) Inicial. (Tabela 1). Esta variante tem especial foco na capacidade de marcha do doente, inspeção – descrição de edema, hematoma e sua localização – e palpação do tornozelo, com a localização dos pontos dolorosos. Por exemplo: um doente que consegue fazer carga, mas tem dor severa em toda a face lateral do tornozelo será classificado como um C. Se esse doente tiver dor antero-medial do tornozelo (que sugere uma lesão da cartilagem no momento do entorse) será classificado como C2.

A segunda CET teve lugar entre as três e as seis semanas após o entorse. Nesta foi aplicada a classificação 'Diferida' (Tabela 2). Baseia-se na marcha, inspeção, palpação e testes mecânicos de instabilidade (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13804/Apendice_01.mov). Por exemplo: um doente que, algumas semanas após a entorse, consegue fazer marcha autónoma com dores limitantes e com queixas atrás do maléolo peroneal (sobre os tendões peroneais) será classificado como B2. Um outro doente com marcha normal, com dores apenas sobre o LPAA e com um teste de *pivot* positivo será classificado como um B1.

Em ambos os momentos, os doentes foram classificados em quatro graus de gravidade (A, B, C ou D) e a interpretação da lesão foi seguida de acordo com a *Consecutive Ankle Sprain Classification and Injury Systematization.* A classificação em subtipos ajuda o registo clínico de lesões associadas. Deste modo a gravidade inicial e os demais achados ficam em destaque.

Após estas CET os doentes foram acompanhados a cada seis semanas, com uma avaliação objetiva através dos *scores Cumberland Ankle Instability Tool* (CAIT) e *Foot and Ankle Ability Measure* (FAAM) preenchidos pelo médico por entrevista ao doente.[23,24]

Para análise estatística foi utilizada a última avaliação de cada doente.

O *outcome* primário foi a incidência de instabilidade crónica do tornozelo. Os *outcomes* secundários são a pontuação nas classificações CAIT, FAAM e FAAM Desportivo.

Para minimizar o viés da variância inter-observador as primeiras duas consultas, em que foram aplicadas as classificações CASCaIS Inicial e Diferida, foram realizadas sempre pelo primeiro autor. As restantes avaliações, bem como a colheita de *scores*, foram realizadas por cinco co-autores. A última avaliação, telefónica, foi realizada no último mês de 2019.

Análise estatística

A análise de dados foi realizada com o programa STATA v13.1 (StataCorp, College Station, USA). Numa fase inicial, as variáveis contínuas foram avaliadas quanto à sua simetria e curtose por via de histogramas e quanto à normalidade pelo teste de Shapiro-Wilk. Foram utilizados testes não paramétricos (Mann-Whitney e Kruskal-Wallis) para a associação das variáveis contínuas com variáveis nominais, com dois grupos e mais de dois grupos, respetivamente. Para analisar a associação entre as variáveis categóricas foi utilizado o teste exato de Fisher. A avaliação da concordância entre o resultado da classificação CASCaIS Inicial e CASCaIS Diferida foi realizada com o coeficiente kappa

Tabela 1 – *Consecutive Ankle Sprain Classification and Injury Systematization* - Inicial

CASCaIS Inicial (1ºs dias):	**Tipo A**		**Tipo B**	**Tipo C**		**Tipo D**
Marcha	Possível, quase normal		Difícil, mas possível; consegue fazer carga	Muito difícil		
Inspeção: hematoma ou edema?	Ligeiro ou ausente		Presente, anterolateral	Exuberante, anterolateral ou lateral		
Palpação do tornozelo	Dor na face AL	Dor na face AL e dor sobre outras estruturas*	Dor severa na face AL	Dor severa na face AL e dor sobre outras estruturas*	Dor severa na face AL e sob a ponta do maléolo externo	Dor severa na face AL e sob a ponta do maléolo externo acrescida de outras lesões Lesões de alta energia Luxações
Testes de instabilidade (p.e., *pivot*)	Normais e não dolorosos		Não os aplicar nos primeiros dias se houver qualquer dor na manipulação			
Qual é a lesão provável?	Lesão parcial ou distensão do LPAA	Lesão parcial ou distensão do LPAA e outras lesões *minor*	Rotura completa do LPAA	Rotura completa do LPAA e outras lesões	Rotura completa do LPAA e lesão parcial do LPC, possível lesão subtalar	…e outras lesões Rotura completa do LPAA e do LPC, com lesões associadas
Subtipos:	**Tipo A1**	**Tipo A2**	**Tipo B1**	**Tipo B2**	**Tipo C1**	**Tipo C2** / **Tipo D**
Classificação "clássica"	**Grau I ou II**		**Grau III**			
Interpretação da lesão	Entorse ligeiro	Entorse ligeiro, Focar atenção nas outras lesões	Entorse severa	Entorse severa Com outras lesões relevantes	Entorse severa com atingimento subtalar	Entorse severa com atingimento subtalar Com outras lesões relevantes Entorse muito severa, atingimento subtalar. Lesões associadas significativas
Exames sugeridos	Nenhum**		Ecografia na primeira ou segunda semanas**			
Tratamento proposto	**RICE**	**RICE; Tratamento funcional / Ortótese**		**RICE; Imobilizar por um curto período para controlo da dor e quadro inflamatório**		
Próxima avaliação	Dentro de 4 a 6 semanas		Dentro de uma ou duas semanas			
Comentários ao seguimento	O objetivo é verificar o prognóstico favorável assim que a contusão e distensão resolver		Entorse severa, realizar todos os testes clínicos nas semanas seguintes	Remover a imobilização e realizar todos os testes clínicos nas semanas seguintes. Baixo limiar para pedir ressonância magnética.		
Riscos clínicos	-	Negligenciar lesões associadas	Perder o seguimento ou negligenciar lesões associadas	Roturas complexas, multiligamentares, com outras lesões associadas. Provável lesão da cartilagem.		

LPAA: ligamento peroneo-astragalino anterior; LPC: ligamento peroneo-calcaneano; AL: antero-lateral; RICE: *rest, ice, compression and elevation* (repouso, crioterapia, compressão e elevação do tornozelo)
*: outras estruturas passiveis de lesão durante um entorse: cartilagem; tendões peroneais; ligamento deltoide; sindesmose.
**: realização de radiografias de acordo com critérios de Ottawa.

de Cohen. O nível de significância utilizado para decisões sobre a hipótese nula foi de 5%.

RESULTADOS

Foram inicialmente referenciados 67 doentes, dos quais 49 (73%) completaram o seguimento e constituem a nossa amostra. A idade média foi de 27,7 (DP 8,5) anos. Observámos a progressão das entorses para a instabilidade crónica do tornozelo (ICT) em 18% dos doentes. A análise estatística de todos os dados fez-se de acordo com a associação ao *outcome* primário, ou seja, a ocorrência de instabilidade crónica do tornozelo (ICT). Os resultados estão apresentados na Tabela 3.

Na primeira CET foram avaliados os sinais inflamatórios, a marcha e a localização da dor à palpação.

Nesta consulta, 39 doentes conseguiam andar com dores e oito doentes não conseguiam andar. Vinte e cinco por cento dos doentes que não conseguiam fazer qualquer tipo de marcha nos primeiros dias após o entorse evoluíram para ICT. Dezassete por cento dos doentes que

conseguiam fazer marcha (normal ou possível) nos primeiros dias após o entorse evoluíram para ICT.

Na inspeção inicial não houve nenhum doente sem equimose ou hematoma, 41 doentes tinham edema ou hematoma ligeiro a moderado, e oito doentes tinham hematoma severo.

Todos os doentes tinham dores à palpação do LPAA, e 20% dos doentes evoluiu para ICT. Nos doentes com dores também noutros locais, a evolução para ICT ocorreu em 17%.

A avaliação da *Consecutive Ankle Sprain Classification and Injury Systematization* Inicial demonstrou uma tendência estatística com ICT (p = 0,088).

Na segunda CET foram avaliados os sinais inflamatórios, a marcha, a localização da dor e a estabilidade, pelo teste de *pivot*.

Nesta segunda consulta, metade dos doentes conseguia andar normalmente.

Tabela 2 – *Consecutive Ankle Sprain Classification and Injury Systematization* - Diferida

CASCalS Diferida	**Tipo A**		**Tipo B**		**Tipo C**		**Tipo D**
Marcha	Normal		Marcha autónoma com alguns sintomas		Melhoria ligeira nas primeiras semanas, ainda precisa de auxiliares de marcha		
Inspeção: hematoma ou edema?	Ausente ou resolvido		Resolvido ou ligeiro, hematoma frequente		Hematoma e edema ainda em resolução		
Palpação do tornozelo	Dor ligeira ou ausente	Dor AL ligeira ou ausente Dor eventual sobre outras estruturas*	Dor na face AL	Dor na face AL e dor sobre outras estruturas*	Dor na face AL e sob a ponta do maléolo externo	... e dor sobre outras estruturas*	Dor na face lateral do tornozelo e sobre as outras estruturas
Testes de instabilidade (p.e., *pivot*)	Normais e não dolorosos		*Pivot test* positivo, com laxidez de vários milímetros		Instabilidade grosseira. *Pivot test* positivo, sem *end-point*		
Qual é a lesão provável?	Lesão parcial ou distensão do LPAA	Lesão parcial ou distensão do LPAA e outras lesões *minor*	Rotura completa do LPAA	Rotura completa do LPAA e outras lesões	Rotura completa do LPAA e lesão parcial do LPC, possível lesão subtalar	…e outras lesões	Rotura completa do LPAA e do LPC, com lesões associadas
Subtipos:	**Tipo A1**	**Tipo A2**	**Tipo B1**	**Tipo B2**	**Tipo C1**	**Tipo C2**	**Tipo D**
Classificação "clássica"	**Grau I ou II**		**Grau III**				
Interpretação da lesão	Entorse ligeira resolvido	Prognóstico favorável, dependente das lesões associadas	Entorse severa, 30% de hipóteses de queixas crónicas	…além do prognóstico das lesões associadas	Prognóstico mais reservado pela lesão multiligamentar e pelas lesões associadas		
Exames sugeridos	Nenhum	De acordo com as lesões associadas	Ecografia	Ressonância magnética A presença de derrame articular detetado na ecografia traduz uma alta percentagem de lesão multiligamentar ou da cartilagem			
Tratamento proposto			Tratamento funcional com ortótese e apoio da Medicina Física e de Reabilitação		Remover imobilização. Colocar ortótese. Reabilitação precoce. Possível necessidade de cirurgia.		
Próxima avaliação	Necessário de acordo com alguma queixa residual		A cada 4 a 6 semanas				
Comentários ao seguimento			Observações seriadas para monitorizar a resposta à reabilitação, verificar cicatrização ligamentar com os testes de instabilidade e acompanhar a evolução das lesões associadas				
Riscos clínicos	-	Negligenciar lesões associadas	Negligenciar uma instabilidade objetiva ou a ausência de progressão clínica favorável Ter sempre presente o diagnóstico de Instabilidade Crónica do Tornozelo				

LPAA: ligamento peroneo-astragalino anterior; LPC: ligamento peroneo-calcaneano; AL: antero-lateral

*: outras estruturas passiveis de lesão durante um entorse: cartilagem; tendões peroneais; ligamento deltoide; sindesmose.

Tabela 3 – Dados obtidos na primeira e segunda avaliações na Consulta de Entorses, agrupados pelo prognóstico final dos doentes num seguimento mínimo de 12 meses

n = 49	*Outcome*: Bom prognóstico	*Outcome*: Instabilidade crónica do tornozelo	(Soma)	*p-value*
Sexo				0,868
Mulheres	19 (47,5%)	4 (44,4%)	23	
Homens	21 (52,5%)	5 (55,6%)	26	
Idade				0,486+
mediana	25,9	30,9		
AIQ	13,1	15,9		
Primeira CET				
Marcha				0,760
Marcha normal	2 (5,0%)	0 (0,0%)	2	
Marcha possível	32 (80,0%)	7 (77,8%)	39	
Marcha impossível	6 (15,0%)	2 (22,2%)	8	
Edema / hematoma				0,322
Ausente	0 (0,0%)	0 (0,0%)	0	
Presente	32 (80,0%)	9 (100,0%)	41	
Severo	8 (20,0%)	0 (0,0%)	8	
Dor sobre LPAA				> 0,990
Sem dor	0 (0,0%)	0 (0,0%)	0	
Dor sobre LPAA	28 (70,0%)	7 (77,8%)	35	
...e outro local	12 (30,0%)	2 (22,2%)	14	
CASCaIS Inicial				0,088
A	14 (35,0%)	0 (0,0%)	14	
B	17 (42,5%)	7 (77,8%)	24	
C	6 (15,0%)	1 (11,1%)	7	
D	3 (7,5%)	1 (11,1%)	4	
Segunda CET				0,289
Marcha				
Marcha normal	22 (55,0%)	3 (33,3%)	25	
Marcha possível	18 (45,0%)	6 (66,7%)	24	
Marcha impossível	0 (0,0%)	0 (0,0%)	0	
Edema / hematoma				> 0,990
Ausente	18 (45,0%)	4 (44,4%)	22	
Presente	21 (52,5%)	5 (55,6%)	26	
Severo	1 (2,5%)	0 (0,0%)	1	
Dor sobre LPAA				0,340
Sem dor	16 (40,0%)	2 (22,2%)	18	
Dor sobre LPAA	15 (37,5%)	3 (33,3%)	18	
...e outro local	9 (22,5%)	4 (44,5%)	13	
Teste de *pivot*				**0,022**
Negativo	16 (40,0%)	0 (0,0%)	16	
Positivo	24 (60,0%)	9 (100,0%)	33	
CASCaIS Diferida				**0,018**
A	18 (45,0%)	0 (0,0%)	18	
B	12 (30,0%)	7 (77,8%)	19	
C	6 (15,0%)	1 (11,1%)	7	
D	4 (10,0%)	1 (11,1%)	5	
MCDTs evidenciam rotura ligamentar				0,094
Ausência	10 (25,0%)	0 (0,0%)	10	
Rotura parcial	5 (12,5%)	0 (0,0%)	5	
Rotura total	8 (20,0%)	4 (44,4%)	12	
(sem exames)	17 (42,5%)	5 (55,6%)	22	

AIQ: amplitude interquartil; +: teste de Mann-Whitney; n: dimensão total da amostra
O teste *pivot* foi realizado apenas na segunda CET e apresentou associação com a ICT (p = 0,022).

À inspeção, 22 doentes já não tinham qualquer evidência de edema ou hematoma. Quatro destes 22 doentes (18%) evoluíram para ICT. Cinco dos 26 doentes (19%) em que estes sinais inflamatórios persistiram evoluíram para ICT.

Relativamente à dor na palpação, 18 dos doentes estavam já assintomáticos. Destes, 11% evoluíram para ICT. Entre os doentes com queixas persistentes, 16% também evoluíram para ICT, o mesmo acontecendo com 30% dos que tinham dor do LPAA e noutro local, sendo que a diferença não é estatisticamente significativa (p = 0,34).

Em relação ao teste de *pivot*, nenhum dos doentes com *pivot* negativo evoluiu para ICT. Nove dos 33 doentes (27%) com um teste de *pivot* positivo evoluiu para ICT. Observamos assim que existe uma relação entre o resultado no teste de *pivot* e posterior evolução para ICT (p = 0,022).

Ao avaliar a relação entre a *Consecutive Ankle Sprain Classification and Injury Systematization* diferida e a evolução para ICT (Tabela 3) encontramos uma diferença com significado estatístico na frequência de evolução para ICT entre os diferentes grupos desta classificação (p = 0,018).

Foi analisada a concordância entre as classificações Inicial e Diferida. Dos 24 doentes classificados como tipo B na CASCaIS Inicial verificou-se que três deles foram reclassificados como tipo A após a realização do teste de *pivot*, que apurou integridade ligamentar. Os restantes 21 tinham um teste de *pivot* positivo e foram classificados como B, C ou D de acordo com a gravidade do quadro clínico e a laxidez ligamentar. Constatamos uma forte concordância entre a avaliação CASCaIS Inicial e CASCaIS Diferida (Tabela 4) tendo sido apurada uma concordância na classificação em 87,8% dos casos (coeficiente kappa de Cohen 0,82, p < 0,001).

Os resultados das avaliações dos doentes utilizando os questionários com sistema de pontuação *Cumberland Ankle Instability Tool* (CAIT) e *Foot and Ankle Ability Measure* (FAAM) são apresentados na Tabela 5.

Não foram apuradas associações significativas entre CASCaIS e as pontuações finais, o que pode ser atribuído ao baixo número de doentes nas categorias mais graves.

Nos questionários (Tabela 5) os doentes com entorses tipo A tinham, ao final de um ano, uma melhor pontuação com qualquer dos questionários de avaliação. Isto ilustra o valor preditivo, tranquilizador, de uma classificação CASCaIS – A logo nos primeiros dias após a entorse.

Se compararmos a evolução para ICT dos doentes com entorse tipo A com todos os outros agrupados (B,C e D) (Tabela 6), encontramos uma associação com significado estatístico, quer na avaliação inicial (p = 0,045), quer na avaliação diferida (p = 0,018).

DISCUSSÃO

Na nossa amostra, demonstrámos que a classificação proposta tem capacidade prognóstica na identificação dos doentes que irão desenvolver ICT após entorse do tornozelo. Neste estudo, a incidência de ICT foi de 18%, o que está em concordância com a literatura.[2,7,25]

Encontrámos na amostra uma capacidade prognóstica significativa no teste de *pivot* (p = 0,022) e na classificação CASCaIS Diferida (p = 0,018). Apurámos também uma tendência estatística entre a classificação CASCaIS Inicial e o *outcome* primário (p = 0,088). Há, ainda, uma correlação significativa entre as classificações Inicial e Diferida (p = 0,001), pelo que a avaliação clínica tem uma elevada probabilidade de se confirmar algumas semanas depois. Isto sugere que a intensidade do quadro clínico inflamatório inicial pode dar uma boa perceção sobre a ocorrência de lesões ligamentares graves do tornozelo. Esta perceção poderá ser confirmada, passadas algumas semanas, com o teste de *pivot*.

A aplicação dos testes de instabilidade, alguns dias após um entorse do tornozelo, foi considerada uma técnica válida para o diagnóstico das entorses severas, ou seja, aquelas em que ocorre uma rotura ligamentar completa do LPAA.[13,18] Aplicámos o mesmo organigrama cronológico mas evitámos a realização de testes de instabilidades na primeira CET para minimizar o desconforto dos doentes. Aplicámos estas manobras na segunda CET. Identificou-se um teste de *pivot* positivo,[21] o que traduz uma rotura completa do LPAA, em 33 (67%) dos doentes. Esta incidência está em concordância com a literatura.[13,14]

Nenhum doente com um teste de *pivot* negativo evoluiu para um prognóstico desfavorável. Nove (27%) dos 33 doentes com teste *pivot* positivo evoluíram para ICT. De acordo com a nossa hipótese, o teste de *pivot* teve um correlação com o prognóstico desfavorável dos doentes, demonstrando-se assim o seu interesse prognóstico.

Classificar os doentes conforme os diferentes graus de gravidade e prognóstico é de extrema importância. Nos casos ligeiros poder-se-ão poupar recursos e os casos

Tabela 4 – Número de doentes de acordo com o tipo de classificação nos primeiros dias (CASCaIS Inicial) e nas primeiras semanas (CASCaIS Diferida)

Concordância entre CASCaIS Inicial e Diferida						
		CASCaIS Diferida				Soma
CASCaIS Inicial		A	B	C	D	
	A	14 (100,0%)				14
	B	3 (12,5%)	19 (79,1%)	1 (4,2%)	1 (4,2%)	24
	C	1 (14,0%)		6 (86,0%)		7
	D				4 (100,0%)	4

Coeficiente *kappa* de Cohen 0,82, p < 0,001
A avaliação clínica inicial tem uma elevada probabilidade de se verificar algumas semanas depois.

Tabela 5 – Relação entre a classificação e o resultado final nos questionários *Cumberland Ankle Instability Tool* (CAIT, onde uma pontuação de 30 significa a melhor função) e *Foot and Ankle Ability Measure* (FAAM, onde o 100% significa a melhor função)

		Média	DP		Mediana	IQR	*p, two sided test*
CASCaIS Inicial	**CAIT**			**CAIT: A *versus* não-A**			
	A (n = 14)	29,4	1,3	A (n = 14)	30	0	**0,0438+**
	B (n = 24)	26,8	5,7				
	C (n = 7)	27,3	3,9	B, C, D (n = 35)	29	5	
	D (n = 4)	26,8	3,8				
		p = 0,197§					
	FAAM em %			**FAAM: A *versus* não-A**	Mediana	IQR	
	A (n = 14)	99,6	1,3	A (n = 14)	100	0	**0,0446+**
	B (n = 24)	95,0	11,4				
	C (n = 7)	99,3	1,9	B, C, D (n = 35)	100	5	
	D (n = 4)	92,5	15,0				
		p = 0,724§					
		Média	DP		Mediana	IQR	*p, two sided test*
CASCaIS Diferido	**CAIT**			**CAIT: A *versus* não-A**			
	A (n = 18)	29,5	1,2	A (n = 18)	30	0	**0,0137+**
	B (n = 19)	26,2	6,2				
	C (n = 7)	27,3	3,9	B, C, D (n = 31)	29	6	
	D (n = 5)	26,8	3,3				
		p = 0,0884§					
	FAAM em %			**FAAM: A *versus* não-A**	Mediana	IQR	
	A (n = 18)	99,7	1,2	A (n = 18)	100	0	**0,0362+**
	B (n = 19)	93,7	8,2				
	C (n = 7)	99,3	1,9	B, C, D (n = 31)	100	7,7	
	D (n = 5)	94,0	13,4				
		p = 0,0531§					

Nas colunas da esquerda estão as pontuações médias nos 4 tipos de entorse. Nas colunas da direita está a discretização em A *versus* não-A.
DP: desvio padrão; IQR: *interquartile range*; §: teste de Kruskal-Wallis; +: teste de Mann-Whitney

severos serão tratados mais agressivamente, o que se traduzirá num melhor resultado clínico e menor absentismo laboral.

As entorses em inversão do tornozelo são frequentemente classificadas em três graus de gravidade.[11,17] A classificação funcional, da qual nos aproximamos neste trabalho, classifica como grau I as entorses com dor e repercussão funcional ligeira a moderada e pouco edema. O grau III diz respeito aos doentes com grande hematoma ou edema e incapacidade para a marcha. O grau II corresponde a um quadro clínico intermédio entre estes dois. A evidência demonstra que os doentes com lesão grau I têm, invariavelmente, um bom prognóstico. Nos doentes com lesão grau III e rotura ligamentar completa do LPAA, o prognóstico é mais incerto. Um detalhe que retira valor a esta classificação é a inclusão, no mesmo grau III, dos doentes com roturas isoladas do LPAA e dos doentes com roturas multiligamentares, do LPAA e LPC.

Há alguma evidência na pesquisa de fatores prognósticos após uma entorse. Debie analisou o seguimento a curto prazo em 31 doentes, através de um sistema de pontuação funcional que combina dor, instabilidade, capacidade para a carga e padrão de marcha.[19]

Wilson avaliou 21 atletas com entorses de grau I ou II três dias após as entorses, excluindo as aparentemente severas. Este investigador mediu o arco de mobilidade, o edema, escala visual analógica de dor e tarefas funcionais (como saltar num membro afetado), concluindo que a incapacidade funcional inicial tinha o melhor interesse prognóstico.[26]

Cross utilizou, em 20 atletas, o número de dias de retorno ao desporto como o *outcome* primário. Encontrou capacidade preditiva nos questionários de autoavaliação, mas não na avaliação do arco de movimento ou da força muscular.[27]

Em 38 doentes, Langner procurou relacionar o resultado de ressonância magnética com o resultado final. Este exame foi realizado nas primeiras 48 hora após a entorse, apurando-se rotura ligamentar em 63% dos doentes. Os doentes com rotura retornaram às suas funções desportivas mais tarde. No final de seis meses só sete doentes não conseguiam fazer marcha autónoma e cinco destes tinham uma lesão multiligamentar, do LPAA e LPC, com significado estatístico.[28]

Wees, num estudo com 33 doentes, desenvolveu o *Ankle Function Score* baseado na dor, estabilidade, marcha e capacidade de carga. Este autor reporta que os doentes com lesão severa tinham uma menor probabilidade de recuperar nas duas semanas após o incidente, sendo que o valor preditivo positivo para este valor de *cutoff* foi de 86%.[29]

Van Middelkoop acompanhou 102 doentes com idades compreendidas entre os 18 e os 60 anos com entorse aguda observado na primeira semana. Não apurou qualquer relação entre o prognóstico aos 12 meses e a idade, sexo, IMC, tipo de tratamento ou classificação em três graus.[30]

A *Consecutive Ankle Sprain Classification and Injury Sistematization* procurou distinguir as entorses benignas, sem rotura ligamentar (tipo A), das roturas completas do LPAA (tipo B).

A rotura completa do LPAA define uma entorse severa, e a suspeita clínica deve ser assinalada nos primeiros dias (CASCaIS Inicial) ou nas primeiras semanas (CASCaIS Diferida). É útil realizar uma interpretação clínica das entorses segundo um contínuo de gravidade em que as tipo A têm bom prognóstico, as tipo B são entorses severas que merecem seguimento, e as tipos C ou D constituem lesões multiligamentares que justificam referenciação precoce para um especialista.

Consideramos que a suspeita da rotura do ligamento peroneo-calcaneano é um ponto fulcral a ser identificado, classificando-o como um C, já que as roturas parciais podem estar associadas a lesões ligamentares da articulação subtalar. Por último, classificamos como tipo D as entorses muito severas com rotura completa da LPAA e LPC. Para além de todas as considerações anteriores estes doentes podem ter lesões importantes da cartilagem de outros ligamentos (como o deltoide) ou dos tendões peroneais. Derivam, frequentemente, de lesões de alta energia e não devem estar agrupadas com as demais entorses.

Extinguimos, assim, o conceito de entorse 'moderada', ou grau II, que consideramos uma zona cinzenta que deve ser interpretada como entorse severa (tipo B) até prova em contrário. As roturas parciais do LPAA têm um prognóstico semelhante às distensões, na medida em que a integridade de parte do ligamento vai orientar favoravelmente o processo cicatricial.[31]

Neste sistema há ainda uma classificação em subtipos (Tabelas 1 e 2), segundo a qual se acrescenta o número 1 após a letra quando a única suspeita é de lesão do complexo ligamentar externo ou o número 2 quando suspeitamos da existência de lesões associadas.

Analisámos ainda, especificamente, o valor preditivo favorável da classificação tipo A. Todos os doentes com classificação no CASCaIS Inicial mantiveram-na na CASCaIS Diferida (Tabela 4). Para além desta concordância, estes doentes obtiveram melhores resultados clínicos finais na medição com CAIT e FAAM, e nenhum doente classificado como A evoluiu para ICT. Do ponto de vista clínico isto sugere que, nos doentes com pouca limitação funcional e sinais inflamatórios ligeiros (ou ausentes) podemos realizar um teste de *pivot* alguns dias após uma entorse do tornozelo , que será presumivelmente indolor e normal dada a manifestação de integridade tecidular. Estes doentes têm um prognóstico favorável, se forem clinicamente excluídas as lesões associadas.

As principais limitações deste trabalho são a taxa de abandono e o tamanho da amostra.

De uma amostra inicial de 67 doentes, apenas 49 mantiveram o seguimento mínimo de 12 meses. Isto corresponde a uma taxa de abandono de 29%, semelhante às descritas por Cross (32%) e Middelkoop (22%).[27,30]

Para este estudo foi utilizada uma amostra de conveniência, composta por todos os doentes observados na nossa instituição durante o período temporal do estudo e que cumpriam os critérios. Embora o tamanho total da amostra seja de dimensão semelhante à maioria dos trabalhos publicados neste tópico, uma análise *post-hoc* mostra que tem um poder estatístico de 0,406 na relação entre a classificação inicial e o *outcome* principal. Sendo assim, as conclusões apresentadas não são uma certeza absoluta. No entanto, os dados recolhidos apontam a direção para estudos futuros e ajudam na definição da dimensão da amostra.

O número de doentes com roturas multiligamentares (ou seja, tipos C e D) na CASCaIS Diferida foi de 12, o que corresponde a 39% dos entorses não-A. Estes valores são sobreponíveis a toda a literatura, desde a mais antiga à mais recente.[14,28,32] Foi efetuada uma análise de poder *post-hoc* para as diferenças médias nos testes CAIT e FAAM, discretizando em tipo A versus não-A. O poder desta amostra (verdadeiro positivo) para o CAIT é 0,75 e para o FAAM é de 0,66.

Outra fraqueza potencial é o facto de todas as avaliações iniciais terem sido realizadas pelo mesmo autor, não permitindo a avaliação da concordância inter-observador. Por outro lado, como já referido, houve uma boa concordância entre as CASCaIS Inicial e Diferida.

Por último, não foi feita uma correlação com os exames de imagem por motivos logísticos.

O desenho deste estudo não contemplou a realização de exames de imagem a todos os doentes, dadas as limitações impostas pela orgânica funcional do sistema de saúde em que estamos inseridos. A concordância com a imagiologia evidenciaria a sensibilidade dos testes clínicos utilizados, o que não diminui a validade das nossas hipóteses, mas possivelmente ainda as reforça.

Os pontos de maior destaque deste trabalho estão relacionados com toda a estrutura clínica (Consulta de Entorses) organizada para acompanhar os doentes com entorse do tornozelo que recorreram à respetiva urgência hospitalar. O acompanhamento prospetivo permitiu uma avaliação seriada de todos estes doentes com critérios clínicos e avaliação objetiva por intermédio de *scores*. Observou-se uma elevada significância estatística entre a classificação CASCaIS semiológica diferida e o prognóstico final dos doentes.

Este tipo de avaliação não requer outra logística para

além da disponibilidade de observação clínica durante alguns dias ou semanas após um entorse agudo, e é possível que seja facilmente generalizável nos cuidados de saúde primários.

CONCLUSÃO

Este estudo propõe uma nova classificação de entorses agudos do tornozelo. É baseada na identificação de uma rotura do LPAA através do teste do *pivot* e procura inferir outras lesões subsequentes através de duas avaliações clínicas sucessivas, eventualmente sustentadas em exames auxiliares de diagnóstico. Acima de tudo, procura englobar as lesões resultantes de entorses do tornozelo num modelo compreensivo que auxilia o clínico e o ajuda a valorizar todos os elementos com potencial interesse prognóstico.

Observámos que existe uma relação com significado estatístico entre a classificação CASCaIS Diferida e a evolução para instabilidade crónica do tornozelo. Esta relação foi observada na classificação CASCaIS Inicial quando esta foi abreviada em dois grupos (A *versus* não A).

Há uma correlação significativa entre as classificações Inicial e Diferida (p = 0,001) o que sugere que basta uma avaliação para orientar o tratamento e informar sobre a possibilidade de desenvolver um resultado desfavorável. A classificação CASCaIS Diferida (p = 0,018) e o teste de *pivot* (p = 0,022) demonstraram capacidade prognóstica para a ocorrência de instabilidade crónica do tornozelo.

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CONTRIBUTO DOS AUTORES

FGP, TAS: Conceção do estudo, planeamento, aquisição e interpretação de dados. Redação do artigo, aprovação da versão final.

JC, RA: Aquisição e interpretação de dados. Redação do artigo, aprovação da versão final.

ABC: Tratamento estatístico, análises e interpretação dos dados. Redação do artigo, aprovação do mesmo.

JP, DL: Análise e interpretação de dados. Redação do artigo, aprovação da versão final.

NC-R: Conceção do estudo, planeamento. Redação do artigo, aprovação da versão final.

JGC: Conceção do estudo. Redação do artigo, aprovação da versão final.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFIDENCIALIDADE DOS DADOS

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

CONFLITOS DE INTERESSE

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

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Anisakis Allergy: Raising Awareness

Alergia ao Anisakis: Sensibilizar para o Seu Diagnóstico

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ABSTRACT

Introduction: Ingestion of *Anisakis* is a common cause of allergic reactions to seafood in countries in which undercooked/raw seafood is part of gastronomic traditions. Despite current trends for the ingestion of raw/marinated/undercooked fish, the prevalence rate of anisakiasis and allergy to *Anisakis* is still considered to be low in Portugal. We aimed to review the current pathogenic mechanisms, the clinical and diagnostic approach of *Anisakis* allergy, and *Anisakis*-related eviction measures, while raising awareness to this problem.

Material and Methods: Literature search in the MEDLINE and Scopus databases, regarding *Anisakis* allergy.

Conclusion: Assessment of sensitization to *Anisakis* should be included in the workup study of urticaria/angioedema and anaphylaxis, as there is a rise in consumption of raw and undercooked fish. Ingestion of previously frozen and properly cooked fish appears to be safe for most patients who are allergic to *Anisakis*.

Keywords: Anaphylaxis; Anisakiasis; Anisakis; Food Hypersensitivity; Hypersensitivity; Urticaria

RESUMO

Introdução: A ingestão de *Anisakis* é uma causa frequente de alergia a pescado, em países onde o hábito de ingerir estes alimentos crus/pouco cozinhados faz parte das tradições gastronómicas. Apesar do aumento na frequência de ingestão de peixe cru/marinado/pouco cozinhado que se verifica em Portugal, a prevalência de anisaquíase e alergia ao *Anisakis* continua a ser considerada como sendo baixa. O nosso objectivo foi rever os mecanismos fisiopatológicos da alergia a *Anisakis*, a abordagem clínica e diagnóstica, e as medidas de evicção de *Anisakis*. Em simultâneo, pretendemos consciencializar para este problema de saúde crescente.

Material e Métodos: Foi efetuada uma pesquisa e revisão bibliográfica nas bases de dados MEDLINE e Scopus, sobre alergia ao *Anisakis* e anisaquíase.

Conclusão: A avaliação da sensibilização ao *Anisakis* deve ser incluída no estudo inicial da urticária/angioedema e anafilaxia, dado que o consumo de peixe cru e malcozinhado está a aumentar. A ingestão de peixe previamente congelado e sujeito a uma cocção correta parece ser segura para a grande maioria dos doentes alérgicos ao *Anisakis*.

Palavras-chave: Anafilaxia; Anisakis; Anisaquíase; Hipersensibilidade; Hipersensibilidade Alimentar; Urticária

INTRODUCTION

The ingestion of *Anisakis* is a common cause of allergic reactions to seafood in countries with high fish consumption, particularly in those in which ingestion of undercooked/raw seafood is part of their gastronomic traditions.[1,2] Even though the specific prevalence and incidence rates are unknown, gastro-allergic anisakiasis (parasitosis caused by nematodes of the genus *Anisakis*). *Anisakis* allergy and asymptomatic sensitization are particularly common in countries in which raw fish (e.g. Japan), or undercooked/marinated fish (e.g. Italy and Spanish Basque Country) are an important part of the traditional gastronomy.[1] Despite having one of the highest fish consumption rates *per capita* in the European Union (EU), Portugal is currently considered as having a low prevalence rate of *Anisakis* allergy.[3] Whether this results from a reduced awareness/underdiagnosis, or a low prevalence rate granted by the 2004's EU regulations on hygiene of foodstuffs,[4] remains largely unknown. Nonetheless, the growing trend of ingestion of raw fish (i.e. *sushi* and *sashimi*), undercooked (e.g. *tataki*) and marinated fish (e.g. *ceviche*) may require a paradigm shift, namely one that moves towards a more thorough evaluation of idiopathic allergic reactions that may be related, even if remotely, to the ingestion of fish.

We aimed to review current pathogenic mechanisms, the clinical and diagnostic approach to *Anisakis* allergy, and *Anisakis*-related eviction measures, while raising awareness to this problem.

MATERIAL AND METHODS

A literature search was made in the MEDLINE® and Scopus® databases using the PubMed and Google Scholar search engines. Conjugated keywords used included: '*Anisakis*', 'Anisakiasis', 'Gastro-allergic anisakiasis', 'urticaria', 'anaphylaxis'. The search was limited to articles published during the past 10 years, but relevant clinical and observational studies published before, and those regarding oral provocations with *Anisakis* extracts and allergen components were also cited. No language restrictions were included. A narrative review was performed based on all relevant literature encountered.

DISCUSSION

Microbiology and life cycle

Most allergic reactions related to *Anisakis* have been

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found to be caused by the so called *Anisakis simplex* complex, which includes *A. simplex*, *A. pegreffii* and *A. berlandi*.[5] However, other members of the *Anisakidae* family, such as the *Pseudoterranova* genus, may also induce disease.[6] Humans are accidental hosts for these nematodes. Infection occurs following ingestion of viable larvae present in raw, or even undercooked seafood. The life cycle of *Anisakis* is summarized in Fig. 1. While fish are quite often parasitized, cephalopods [the taxonomic group (class) that includes for instance octopuses, squids and cuttlefishes] are infrequent hosts for *A. simplex*.[7]

Humans may suffer from different diseases caused by the *A. simplex* complex. Anisakiasis is a parasitic infection that may involve gastric, intestinal or extra-gastrointestinal mucosae and that may or may not include allergic symptoms, depending on the patient's immune response.[5] Patients with no evidence of current infection may also display allergic symptoms.[5]

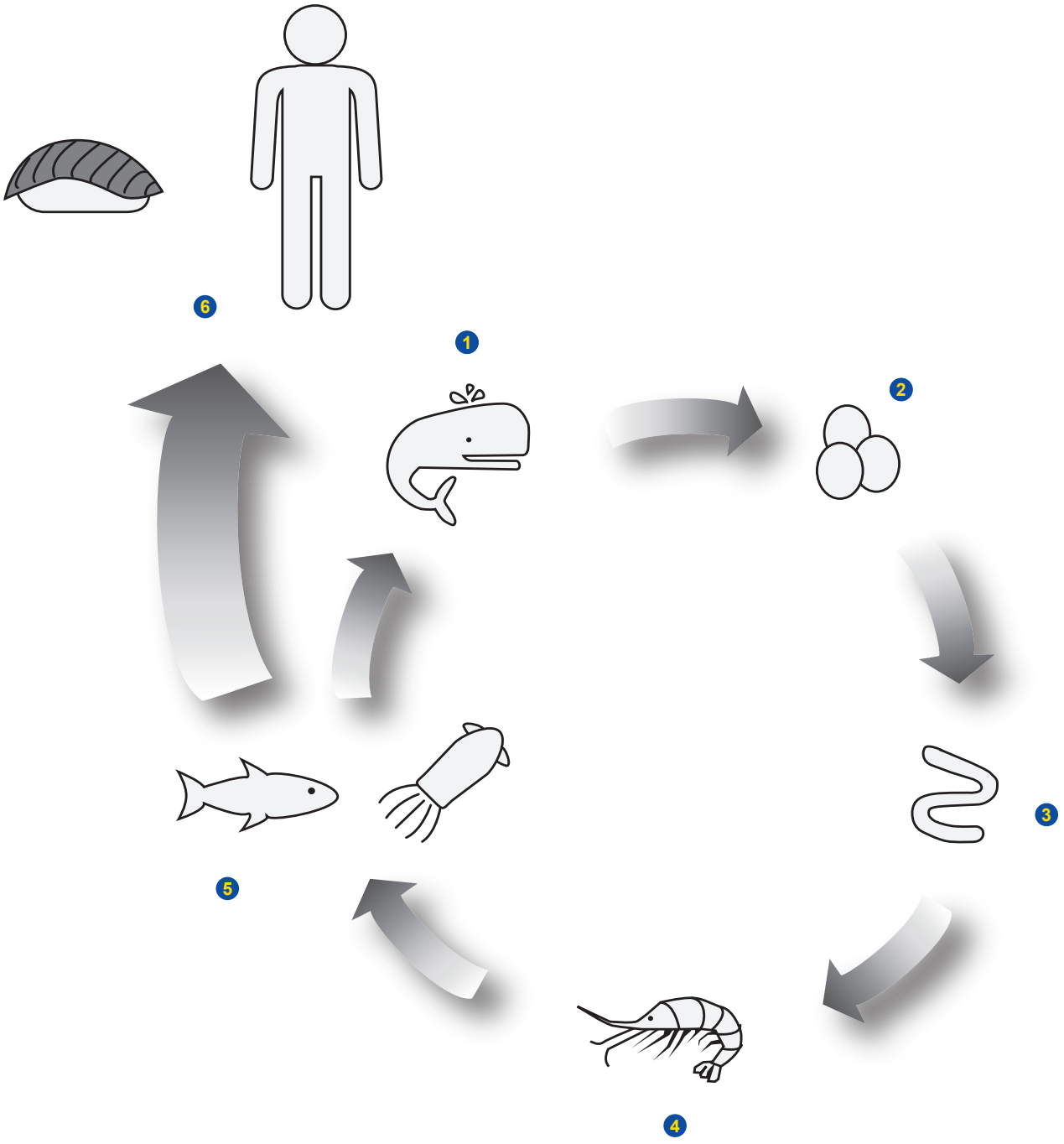

Figure 1 – Life cycle of Anisakis. 1: Eggs are released into the gastric lumen of the definitive host and are later excreted with faecal matter; 2: Hatching occurs at the ocean floor, where stage 2 larvae emerge; 3: Stage 2 larvae are ingested by planktonic crustaceans (e.g. krill) and other invertebrates, and develop into L3; 4: Infested zooplankton is ingested by fish, cephalopods and cetaceans (which may also ingest the former); 5: Stage 3 larvae (L3) of the Anisakis complex reach the adult stage at the gastric mucosae of large marine mammals such as cetaceans or pinnipeds; 6: Humans ingest viable larvae, present in raw or undercooked seafood.

Epidemiology

Little is known about the true global burden of anisakiasis. Sensitization rates seem to be increasing worldwide, reaching a seroprevalence of 27.4%[2] and 29.8%[8] in the Spanish general population and in patients showing urticaria and/or food allergy in Japan, respectively. These numbers are even more significant among chronic urticaria patients, ranging between 14% and 63%.[9,10] True allergy to *Anisakis* may be more prevalent than seafood allergy *per se* in countries with a high burden,[8] ranging from 4.5% to 15% of cases of suspected seafood allergy.[9,11] Nevertheless, these results should be interpreted with caution as they report data from different populations.

In Portugal, a study by Falcão *et al* showed a sensitization prevalence rate of 5.5% among children with relapsing acute urticaria[12] but studies on the actual prevalence rate among both children and adults are lacking. In fact, Portugal is considered a low burden country as far as allergy to *Anisakis* is concerned, notwithstanding the fact that cod and most of the fish on Portuguese shores are often parasitized[13-15] and that the notification of *Anisakis* in fish has been increasing.[16] This may be due to the absence of gastronomic traditions involving the ingestion of undercooked/raw fish but also due to compliance with the aforementioned EU regulations. However, at least two clinical cases of anisakiasis diagnosed during gastroscopy have been reported by Portuguese authors, in the last few years. These have been associated with the ingestion of undercooked scabbard (*Aphanopus carbo*)[17] and *sushi*.[18] Whether the increased exposure of the Portuguese population to parasitized fish is actually associated with an increase in the incidence of sensitization and allergy to *Anisakis* is still unknown. This surely results from a lack of studies on this matter but awareness of the issue may also be lacking.

Pathophysiology

Both gastrointestinal anisakiasis and ectopic anisakiasis (i.e., involving the oral cavity, lungs, peritoneal cavity) may present without allergic symptoms. Pure gastrointestinal anisakiasis usually presents with mild-to-severe abdominal pain, hours to days following ingestion of live larvae.[19] *Anisakis* can penetrate the mucosal lining through release of proteases.[20] Local innate immune responses induce the formation of an eosinophilic and/or neutrophilic granuloma surrounding the larvae. Eosinophilic inflammation sustained by local mastocytosis leads to abdominal pain. Parasites usually perish after a few days, due to the deleterious effects of eosinophil major basic protein, inducible nitric oxide synthase, peroxidases and eosinophil-derived neurotoxin.[19]

Adaptive immunity and namely the Th1/Th2 balance plays a vital role in the course of the disease. As it seems, patients with pure gastrointestinal disease present with a less adapted strictly Th1-driven immune response,[21] often requiring surgical, or endoscopic removal of parasites.[17-19] On the other hand, a more Th2-driven immune response induces release of polyclonal immunoglobulin (Ig) E, which further activates mast cells. Mast cell mediators induce massive and quick constriction of gastrointestinal and bronchial smooth muscle leading to intense vomiting, profuse diarrhea and cough, which may, by itself, eliminate larvae.[21] However, patients in which the Th2 response lacks proper regulation may also display urticaria, angioedema or even anaphylaxis due to massive mast cell activation. Such acute manifestations may recur on reexposure, creating the false impression that patients suffer from chronic rather than relapsing acute urticaria/angioedema, or anaphylaxis.[21, 22]

Clinical manifestations

Gastrointestinal anisakiasis may involve the gastric and/or intestinal mucosae. Strict gastric involvement usually presents with acute epigastric pain, nausea and vomiting, with or without fever within 24 hours following the ingestion of undercooked/raw fish.[23] Presentation of intestinal anisakiasis is usually delayed from 48 hours up to until one week following exposure, and usually includes abdominal pain, diarrhea with mucus and/or blood, and fever.[24] More severe cases may present with intestinal obstruction, appendicitis or peritonitis.[25] The latter may occur due to migration through the intestinal wall and into the peritoneal cavity and such migration may also occur into the pleural cavity.[26]

Allergic manifestations from exposure to *Anisakis* may occur because of ingestion, cutaneous or even respiratory exposure.[1] Gastroallergic anisakiasis presents with similar gastrointestinal manifestations but may be associated with urticaria/angioedema, bronchospasm or even anaphylactic shock.[25] Occupational cutaneous or respiratory exposure may induce urticaria, rhinitis and conjunctivitis, or even anaphylaxis.[27-29]

Diagnosis

Diagnosis of urticaria or anaphylaxis related with *Anisakis* may be underreported in countries in which the prevalence rate is unknown, as many of those allergic to *Anisakis* may display symptoms only once or twice a year, despite having a high fish consumption.[30,31] Moreover, clinical manifestations may appear more than 24 hours following ingestion of infested fish, which makes it more difficult to recognize in low prevalence areas.[32]

When approaching patients with suspected allergy to *Anisakis*/gastro-allergic anisakiasis, one should keep in mind that the patient may be currently infected. These patients usually present significantly higher total IgE levels during the acute reaction.[17] Physical removal of the worm through endoscopy or surgery is usually curative.[17,23] In spite of the absence of international consensus, a reasonable approach for patients presenting with urticaria/angioedema or anaphylaxis with accompanying gastrointestinal manifestations and acutely high total IgE with a recent history of ingestion of undercooked/raw fish may include an endoscopic study. A larger proportion of patients may display only recurrent urticaria with/without angioedema upon exposure, mimicking chronic urticaria, or even bronchospasm or anaphylaxis following exposure to the live parasite, in the absence of evidence of gastrointestinal infection.[1] In fact,

the prevalence rate of allergy to *Anisakis* has been reported in some series to be around 67%[1] and 10%[20] of patients suffering from chronic idiopathic urticaria and idiopathic anaphylaxis, respectively. Both specific IgE and skin prick tests (SPT) for *Anisakis* may be used for the assessment of sensitization and display similar sensitivities.[1] Nonetheless, a positive specific IgE or a positive SPT do not make the diagnosis of allergy to *Anisakis*, as asymptomatic sensitization should be considered.

Asymptomatic sensitization has been associated with *Anisakis* specific IgE (sIgE) below 3.5 kU/L.[33] However, patients with values above that cutoff may not be truly allergic and the opposite may also occur.[34] Elevated specific IgE for *Anisakis* may occur due to cross-sensitization with other invertebrates, due to the presence of panallergens (i.e. allergens which are present in closely related organisms from a phylogenetic point of view; examples: casein in mammalian milk, tropomyosin from the exoskeleton of arthropods and crustaceans.) - tropomyosin (*Ani s 3*), present in mites and crustaceans,[35, 36] or paramyosin (*Ani s 2*), present in *Ascaris* - that are usually present in allergenic extracts.[37]

Several methods have been proposed to avoid misdiagnosing true allergy. In order to exclude cross-reactivity with *Ascaris*, Brusca and col. have proposed a diagnostic algorithm based on a ratio between sIgE for Anisakis over sIgE for Ascaris above 4.2, as diagnostic of true sensitization to *Anisakis*, following exclusion of sensitization to tropomyosin.[34] Besides *Ani s* 3, *Ani s* 1 is also commercially available in Portugal, while other allergen components have been extensively used for research purposes.[33,35,38] Serine proteases (i.e. *Ani s* 1, and *Ani s 7*), paramyosin (i.e. *Ani s 2*), a protein with unknown function (*Ani s 12*) and hemoglobin (i.e. *Ani s 13*) are considered major allergens, as they are found in 85%, 100%, 88%, 57% and 64% of *A. simplex* infections, respectively.[39-41] *Ani s* 13 seems to be more sensitive and specific than *Ani s* 1 or *Ani s* 7, while showing absence of cross-reactivity with Ascaris hemoglobin.[42]

Until this moment, no double-blind oral food challenge trials have shown that ingestion of individualized allergens/dead larvae lead to symptoms. In fact, previous studies have shown that truly allergic patients tolerate the ingestion of dead/unviable larvae, displaying no allergic reactions.[43-45] Such reports were based in oral challenges with 11[43] to 20[45] previously frozen encapsulated larvae that had been obtained from gastroscopic procedures, or from 20 to 40 mg (equivalent to 105 to 201 larvae, respectively) of previously frozen lyophilized encapsulated larvae obtained from parasitized fish.[44] However, self-reported reactions on patients under eviction measures have cast a potentially reasonable doubt on the ability of allergens to penetrate through highly permeable gastrointestinal mucosae, causing recurrent acute urticaria.[46] In fact, *Ani s* 1, *Ani s* 4, *Ani s* 5[47] and *Ani s* 11-like protein (*Ani s 11.0201*)[38] do retain *in vitro* IgE-binding ability following prolonged exposure to high temperatures. Nonetheless, strong *in vivo* evidence of reactions following ingestion of properly frozen and cooked fish is still lacking. There is, however, evidence that transcutaneous and airborne exposure to allergens of *Anisakis* may induce cutaneous, respiratory, or even multisystemic reactions, as mentioned above.[27-29]

Management

Several *Anisakis* eviction measures have been proposed and are currently regulated by the EU.[4] Different recommendations have been proposed for patients with anisakis allergy, with varying degrees of restrictiveness.

Viable larvae are not usually found in frozen fish.[48] As such, less restrictive measures include ingestion of fish that has been frozen at -35ºC for more than 24 hours, or -20ºC for more than 72 hours - preferably deep-frozen at deep-sea.[45] This simple measure seems to be enough to ensure that patients with previous gastro-allergic anisakiasis and, or urticaria remain symptom-free.[5,31] While strict eviction of non-frozen and undercooked fish may be enough to avoid reactions in most patients,[49] ingesting only fish that has been cooked for at least 10 minutes at a 60ºC temperature is strongly recommended. Smoked, or marinated fish should also be avoided since these are not usually previously frozen, nor heated, nor processed in a way that would kill live larvae. Ingestion of portions nearest to the tail of large specimens should be preferred, as muscle nearest to the digestive system often possesses larvae.[20] Concerning canned fish, reports on safety are ambiguous as the presence of larvae depends of the specific process of conservation – those heated before canning seem to be safe, however industrial tuna in olive oil preparations have been associated with self-reported reactions.[11] Moreover, some authors propose lowering the risk of exposure to *Anisakis* through consumption of farmed fish,[7,50] or species that are usually not heavily parasitized (e.g. wild gilthead seabream, *Sparus aurata*),[51] while following the aforementioned preventive measures, after making it clear to the patient that it may be impossible to predict whether allergic reactions will recur.

Restrictive measures for the prevention of allergic reactions may include avoidance of all seafood, regardless of fish processing methods, with obvious deleterious effects to general health and wellbeing of those allergic to *Anisakis*. This option is based on self-reported cases of allergic reactions following ingestion of previously frozen, aquaculture fish and, or canned fish,[52] which have been purportedly explained by the ability of *Anisakis* allergens to retain IgE-binding abilities, even following freezing and treatment with high temperatures.[47] Nonetheless, compliance with restrictive eviction recommendations may be low in patients that appreciate seafood, as most present a low frequency of allergic reactions.[30]

Recommendations for the prevention of allergic reactions require an individual risk-benefit assessment, since most patients remain reaction-free when less restrictive preventive measures are followed but may be required for those that sustain recurrent reactions.[49] Oral food challenges may support the diagnosis and may help to establish specific recommendations. This procedure seems to be

safe, since the large majority of patients do not display positive challenges following the ingestion of non-viable/dead larvae.[44] However, standardization is still lacking.

Standardization is also lacking in the proper approach to acute gastric and intestinal infection. Nevertheless, endoscopic and surgical approaches have been successfully used.[23] Moreover, some authors also suggest a course of albendazole (400 - 800 mg qd, during six to 21 days) but evidence on its efficacy is also lacking.[26]

CONCLUSION

Anisakis allergy may be an underdiagnosed cause for urticaria/angioedema and anaphylaxis in Portugal, due to a rise in consumption of undercooked, raw or marinated fish. The authors recommend that patients presenting allergic symptoms related to the ingestion of fish – especially if undercooked or raw – be studied for IgE mediated sensitization to *Anisakis*. The correct approach to acute infection by *Anisakis* lacks a broad consensus but performing endoscopic studies on patients presenting with urticaria, gastrointestinal symptoms and high total IgE hours to days after the ingestion of undercooked/raw fish might be reasonable approach.

While ingestion of previously frozen and properly cooked fish seems to be safe in the vast majority of patients in whom IgE mediated allergy was confirmed, better diagnostic markers may be needed in order to prevent potential systemic reactions in the remainder few.

AUTHORS CONTRIBUTION

TAR: Main author. Literature research, conception and draft of the paper.

DS: Contributed to the draft and critical review of the paper.

PROTECTION OF HUMAN SUBJECTS

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 issued by the World Medical Association and 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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Diagnosis of Statin-Induced Necrotizing Myopathy: Contribution of Anti-HMGCR Antibodies

Diagnóstico da Miopatia Necrotizante Induzida por Estatinas: Contribuição dos Anticorpos Anti-HMGCR

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ABSTRACT

Over the last few years, several cases of statin-induced necrotizing myopathy have been described. This myopathy is characterized by the necrosis of muscle fibers and the presence of anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) antibodies. Although the diagnosis of myopathies relies on muscle biopsy, which is considered the gold-standard, the search for autoantibodies has proved to be an essential contribution to the diagnosis of immune-mediated myopathies. The detection of anti-HMGCR antibodies in the patient's serum can be performed by enzyme immunoassays, and more recently, by imunofluorescence. As for the latter, the detection of anti-HMGCR antibodies is performed on tissue sections by indirect immunofluorescence and is characterized by a typical fluorescence pattern called "HMGCR Associated Liver IFL Pattern". The authors present two case reports that show the importance of diagnosing statin-induced necrotizing myopathy as quickly as possible and the contribution of anti-HMGCR antibody detection for the diagnosis.

Keywords: Autoimmune Diseases/chemically induced; Hydroxymethylglutaryl CoA Reductases; Hydroxymethylglutaryl-CoA Reductase Inhibitors/adverse effects; Muscular Diseases/chemically induced

RESUMO

Nos últimos anos foram descritos vários casos de miopatia necrotizante induzida por estatinas. Esta miopatia caracteriza-se por necrose das fibras musculares e pela presença de anticorpos anti-3-hidroxi-3-metilglutaril-coenzima A redutase (anti-HMGCR). Apesar do diagnóstico das miopatias depender da biópsia muscular, considerada o *gold-standard*, a pesquisa dos auto-anticorpos tem-se revelado uma contribuição fundamental para o diagnóstico das miopatias imuno-mediadas. A pesquisa dos anticorpos anti-HMGCR no soro do doente pode ser efetuada por recurso a imunoensaios enzimáticos e mais recentemente foi descrita a possibilidade da sua deteção por imunofluorescência. Neste caso, a pesquisa de anticorpos anti-HMGCR é efetuada em seções de tecido, por imunofluorescência indireta e caracteriza-se pela deteção de um padrão de fluorescência típico denominado "HMGCR Associated Liver IFL Pattern". Os autores apresentam dois casos-clínicos que evidenciam não só a importância de diagnosticar o mais rapidamente possível a miopatia necrotizante induzida por estatinas como também a contribuição da deteção de anticorpos anti-HMGCR para o diagnóstico desta miopatia.

Palavras-chave: Doenças Autoimunes/induzidas quimicamente; Doenças Musculares/induzidas quimicamente; Hidroximetilglutaril-CoA Redutases; Inibidores de Hidroximetilglutaril-CoA Redutases/efeitos adversos

INTRODUCTION

Immune mediated necrotizing myopathy (IMNM) is characterized by progressive and disabling proximal muscle weakness, high serum levels of creatine kinase (CK) and the presence of necrotic fibers with minimal inflammatory cell infiltrate on muscle biopsy.[1,2] The European Neuromuscular Centre has recognized three serologically different subtypes of IMNM: autoantibody negative, anti-signal recognition particle and anti-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) myopathy. Recently, several cases of anti-HMGCR myopathy associated with statins exposure were described, which raised the profile of this IMNM and the need to diagnose it as soon as possible.

Statins competitively inhibit HMGCR and have a well-established role in the secondary prevention of cardiovascular events.[3] However, clinical data suggests that the adverse reactions of statins may affect at least 30% of patients.[4] Among the several possible adverse reactions, statin-associated myopathy is the most common, with anti-HMGCR IMNM being the most severe subtype.[5] The exact incidence of statin associated myopathy is not known. However, recent studies reported that the incidence may vary from 15% to 72% depending on age, geographic location and eating habits as anti-HMGCR could be associated with both the medicine and natural statins occurring in food such as red yeast rice.[6]

The diagnosis of myopathy relies on muscle biopsy, which is considered the gold-standard. Nevertheless, in IMNM, the screening of serum antibodies is changing the diagnostic algorithm. Serology studies are now considered as important as histological studies, with the detection of anti-HMGCR antibodies considered the hallmark in the diagnosis of anti-HMGCR IMNM.

During a 24-hour period, the detection of antibodies could be achieved by immunoassays such as immunoblot and enzyme linked immunosorbent assay. In 2016, Alvarado-Cardenas *et al* used indirect immunofluorescence in rat tissue sections to evaluate serum antibodies of IMNM patients and identified a new specific pattern which was

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called HMGCR Associated Liver IFL Pattern (HALIP).[7] This pattern is characterized by the presence of stained hepatocytes (no more than 10%) with a centro-lobular distribution. Moreover, the staining was limited to the cytoplasm and spared the nuclei.[7]

In order to emphasize that anti-HMGCR IMNM may present a rapid and fatal course, as well as to highlight the role of antibody detection in the diagnosis of this myopathy, we present two patients with anti-HMGCR statin-induced IMNM.

CASE REPORTS

Patient 1 was a 72-year-old man admitted to the emergency department due to a 4-week history of myalgia and decrease of muscle strength in the lower limbs, without other neuromuscular symptoms. One month before the onset of symptoms the patient started taking pitavastatin 4 mg, in addition to atorvastatin 40 mg. The patient had been taking atorvastatin for a few months but since he was not achieving the therapeutic goal, atorvastatin was switched to pitavastatin. Due to a misunderstanding, the patient kept taking both statins. The patient had a clinical history of dyslipidemia, arterial hypertension, and type 2 diabetes mellitus. As for family history, the patient's daughter had a multiminicore congenital myopathy. At the time of the daughter's myopathy diagnosis, the patient did not undergo genetic testing since he presented normal CK values. On admission, he was found to have CK levels of 9764 U/L (reference range (rf) < 171 U/L), lactic dehydrogenase (LDH) of 1046 U/L (rf < 248 U/L), aspartate transaminase (AST) of 376 U/L (rf < 35 U/L), alanine transaminase (ALT) of 444 U/L (rf 45 U/L) and increased inflammatory parameters, (Table 1).

Table 1 – Summary of patient characteristics and diagnostic test results

	Patient 1	Patient 2
Patient's characteristics		
Age	72	59
Sex	Male	Male
Symptoms	Myalgia and decrease of muscle strength in the lower limbs	Decrease of muscle strength and episode of rhabdomyolysis
Statin	Pitavastatin 4 mg + Atorvastatin 40 mg[1]	Atorvastatin 20 mg
Medical history	Dyslipidemia, arterial hypertension, type 2 diabetes mellitus, benign prostatic hyperplasia	Dyslipidemia, knee osteoarthritis
Family history	Daughter with multiminicore congenital myopathy	Irrelevant
Blood tests		
Leucocytes[2]	15.2 x 10^9/L	9.5 x 10^9/L
Neutrophils[2]	14.14 x 10^9/L	5.45 x 10^9/L
CK[2]	9764 U/L	8635 U/L
LDH[2]	1046 U/L	908 U/L
AST[2]	376 U/L	217 U/L
ALT[2]	444 U/L	196 U/L
C-reactive protein (CRP)[2]	11.46 mg/dL	0.49 mg/dL
Anti-HMGCR antibodies[3]	HMGCR antibodies detected	HMGCR antibodies detected
Other autoimmune myositis autoantibodies[4]	Not detected	Not detected
Other diagnostic tests		
EMG	Acute signs of muscle fiber injury	Acute signs of muscle fiber injury
Muscle biopsy	Extensive necrotic areas	Muscle cell necrosis
Treatment and evolution		
Treatment	Prednisolone and immunoglobulin	Prednisolone
Evolution	Infectious complications that led to death	Good; maintenance of low dose corticosteroid therapy

[1] Due to misunderstanding the patient kept taking atorvastatin concomitantly with pitavastatin.
[2] Levels at admission; Leucocytes reference range (rf) 4.0 – 10.0 x 10^9; neutrophils rf 2.0 - 7.0 x 10^9; CK rf < 171 U/L; LDH rf < 248 U/L; AST rf < 35 U/L; ALT rf 45 U/L; CRP rf < 0.50 mg/dL.
[3] IgG antibodies detection by immunodot assay. Detection of IgG antibodies against Jo-1, PL-7, PL-12, EJ, SRP, Mi-2, MDA-5, TIF1γ, HMGCR, SSA/Ro-52, SAE1/2 and NXP-2. BlueDot Myositis[12] IgG – D-tek®.
[4] IgG antibodies detection by immunoblot assay. Detection of IgG antibodies against Mi-2α, Mi-2β, TIF1γ, MDA-5, NXP-2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ and Ro-52 antigens. EUROLINE Autoimmune Inflamatory Myopaties 16 Ag - EUROIMMUN®.

The patient was admitted for diagnostic investigation. Electromyography (EMG) revealed acute signs of muscle fiber injury and the muscle biopsy showed extensive necrotic areas. The study of specific myositis antibodies revealed the presence of anti-HMGCR antibodies, and immunofluorescence revealed the presence of HALIP (Figs. 1A, 2A), ten days after hospital admission. The patient started treatment with methylprednisolone with a slight improvement in symptoms and in analytical parameters. Due to clinical worsening, methylprednisolone was replaced by prednisolone and 31 days after hospital admission he started treatment with immunoglobulin. Nevertheless, 39 days after hospital admission, the patient died due to infectious complications.

Patient 2 was a 59-year-old male outpatient admitted for diagnostic investigation after an episode of rhabdomyolysis with increased levels of CK (8635U/L), LDH (908 U/L), AST (217 U/L) and ALT (196 U/L); normal inflammatory parameters; and complaints of muscle strength weakness, (Table 1). He had been taking atorvastatin 20 mg in the previous month and had a medical history of dyslipidemia and knee osteoarthritis. The EMG revealed acute muscle fiber injury, and the muscle biopsy showed muscle cell necrosis. The diagnostic investigation of specific myositis antibodies revealed the presence of anti-HMGCR antibodies and immunofluorescence revealed the presence of HALIP (Figs. 1B, 2B). The patient started treatment with prednisolone one year after the first appointment, with clinical and analytical improvement.

In both patients, the presence of anti-HMGCR antibodies was evaluated by immunoblot (D-tek®) followed by indirect immunofluorescence in rat triple tissue sections (EUROIMMUN®). A pattern of stained hepatocytes with centrilobular-distribution, confined to the cell's cytoplasm, similar to the one described by Alvarado-Cardenas *et al*,[7] was observed in both patient samples (Fig. 2) but not in the internal control sample. This pattern was observed in less than 10% of the stained hepatocytes.

DISCUSSION

These case reports highlighted the role of serological screening whenever the patients are taking statins and present complaints suggestive of myopathy. Although the detection of serum autoantibodies is not the gold-standard in the diagnosis of myopathies, it has several advantages over muscle biopsy such as being less invasive, faster (muscle biopsy has a turnaround time of approximately one week), easier to perform, and most immunology laboratories already use the lab-testing methodologies. Since immunofluorescence is less expensive and faster compared to immunoblot, and HMGCR is highly expressed in liver tissue,[7] immunofluorescence seems to be adequate to screen for the presence of HMGCR antibodies. Both case reports showed that the detection of HALIP by immunofluorescence is a useful test to screen for anti-HMGCR myopathy in statin-exposed patients. Since anti-HMGCR antibodies are highly associated with statin-induced IMNM,[1] their presence is a warning that statin dose should be evaluated and eventually be discontinued. It is also important to emphasize that in a patient taking statins and complaining of myalgia one of the first procedures is to evaluate serum CK level. If CK levels rise to more than 10 times the upper limit, the risk and benefit of statin withdrawal should be assessed.[8]

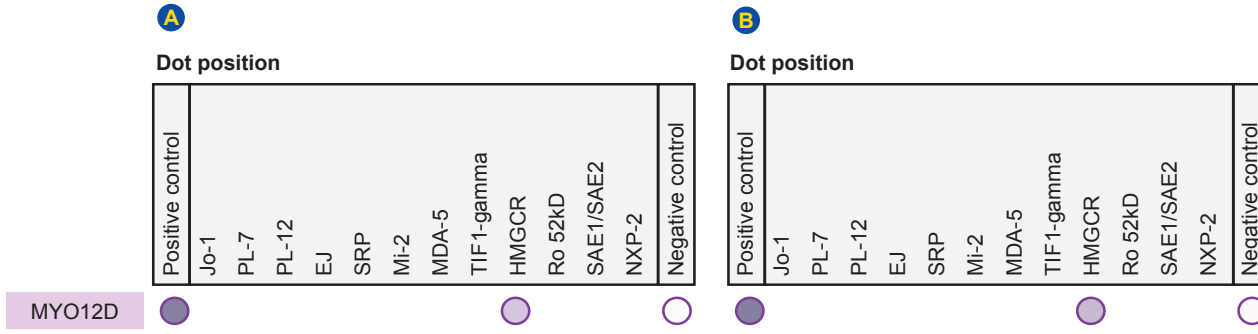

Figure 1 – Anti-HMGCR antibodies detected by immunodot assay. BlueDot Myositis12 IgG – D-tek® (A) Patient 1; (B) Patient 2.

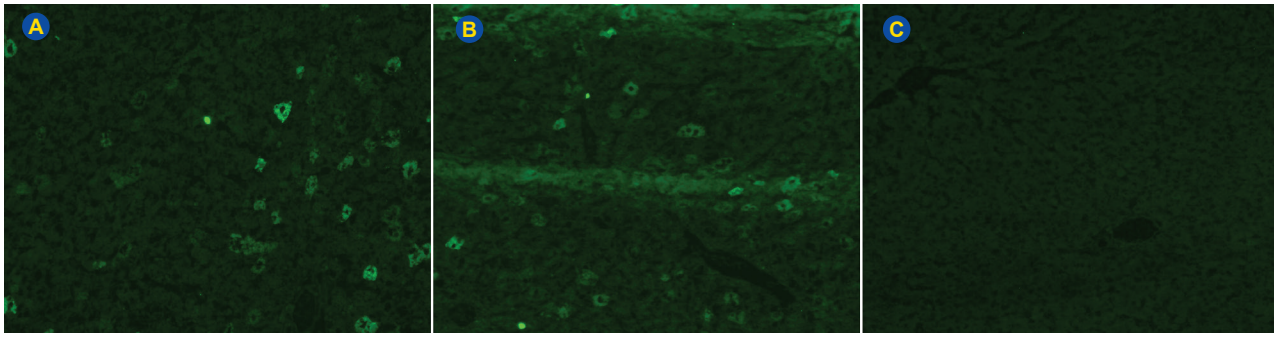

Figure 2 – HALIP pattern in rat liver sections. Indirect immunofluorescence using triple rat tissue. No fluorescence was observed in kidney and stomach sections. (A) Patient 1; (B) Patient 2; (C) Internal control sample.
Images captured by EUROPattern (EUROIMMUN®).

CONCLUSION

Statin-induced IMNM is an autoimmune disease associated with the presence of anti-HMGCR antibodies that may present with a rapid, aggressive and fatal clinical course if not rapidly diagnosed. The clinical course of this myopathy seems to be associated with the statin dose, which is in agreement with previous studies.[6,9] The detection of anti-HMGCR antibodies may contribute to the early diagnosis of this IMNM and to the development of a successful therapeutic strategy.[7]

AUTHORS CONTRIBUTION

CF: Case description and discussion.

AM, RC, FR: Critical review of the work.

PROTECTION OF HUMANS AND ANIMALS

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DATA CONFIDENTIALITY

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A Rare Case of Unilateral Tongue Edema with Angiotensin Converting Enzyme Inhibitors

Um Caso Raro de Edema Unilateral da Língua com Inibidores da Enzima de Conversão da Angiotensina

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ABSTRACT

Angiotensin converting enzyme inhibitors (ACEi) are widely used for the treatment of multiple conditions such as hypertension, heart failure and chronic kidney disease. Angioedema is a rare but potentially fatal complication of ACEi use and unilateral tongue edema is a very rare presentation. We report a case of a 55-year-old man, with a history of hypertension, on enalapril for three years, who presented to the hospital with unilateral tongue swelling, without airway compromise. Other causes were excluded and the diagnosis of angioedema due to enalapril was established. The patient was discharged with discontinuation of ACEi with total resolution of symptoms and without relapse after several months. Although very rare, unilateral tongue swelling should be considered in the presentation of angioedema associated with ACEi. Tight surveillance is important to prevent fatal complications such as airway obstruction. ACEi discontinuation is crucial to avoid clinical relapse.

Keywords: Angioedema; Angiotensin-Converting Enzyme Inhibitors; Enalapril

RESUMO

Os inibidores da enzima de conversão da angiotensina (iECAs) são amplamente usados no tratamento de várias patologias como a hipertensão arterial, insuficiência cardíaca e doença renal crónica. O angioedema é uma complicação rara mas potencialmente fatal desta medicação e o edema unilateral da língua é uma apresentação rara desta condição. Reportamos o caso de um homem de 55 anos com hipertensão, medicado há três anos com enalapril, que à admissão hospitalar apresentava edema unilateral da língua sem compromisso da via aérea. Outras etiologias foram excluídas, tendo-se assumido o diagnóstico de angioedema associado ao enalapril. Após suspensão do iECA os sintomas diminuíram progressivamente, sem recorrência do quadro após vários meses. Ainda que raro, o edema unilateral da língua deve ser considerado na apresentação do angioedema associado a iECA. É importante uma vigilância apertada para prevenir complicações fatais, tais como a obstrução da via aérea. A descontinuação do iECA é fundamental para evitar recidiva.

Palavras-chave: Angioedema; Enalapril; Inibidores da Enzima de Conversão da Angiotensina

INTRODUCTION

Angiotensin converting enzyme inhibitors (ACEi) are widely used in the management of several diseases. Angioedema is a self-limited, localized subcutaneous or submucosal swelling, resulting from the increased capillary permeability due to accumulation of bradykinins by ACEi. Unilateral tongue edema is an atypical and rare presentation. In a large clinical trial, angioedema occurred in approximately 0.6% of patients treated with enalapril, and its occurrence decreased over time.[1]

We present the case of a 55-year-old man with unilateral tongue edema associated with ACEi.

CASE REPORT

A 55-year-old man with chronic hypertension and receiving treatment with enalapril presented for the first time in the emergency department (ED) with a one-hour history of sudden onset tongue edema. He noticed the edema after waking up with breathing discomfort. Upon admission in the ED, he had left unilateral non tender soft tongue swelling, without lip or palate involvement (Figs. 1 to 3). He was hemodynamically stable, without any abnormal findings in the pulmonary evaluation. The remaining physical observation was normal, including the neurological examination. The patient denied history of tongue trauma and recent changes in any hygiene products. He had no history of allergies. He also denied dysphagia, hoarseness, rash, fever or pruritus. In the ED, blood tests were performed, without any changes. Cranial computed tomography was normal. During several hours of medical observation, the edema progressively resolved without any complications, such as airway compromise. Due to daily treatment with ACEi for almost three years and given the absence of other causes, the diagnosis of enalapril angioedema was assumed and the patient was discharged with indication to stop enalapril.

A few months after the discontinuation of enalapril, at follow-up, he had a normal volume tongue with no history of angioedema relapse (Figs. 4 and 5).

DISCUSSION

Angioedema is one of the well-known side effects of ACEi treatment. ACEi inhibit angiotensin converting enzyme (kininase II), which is responsible for the degradation

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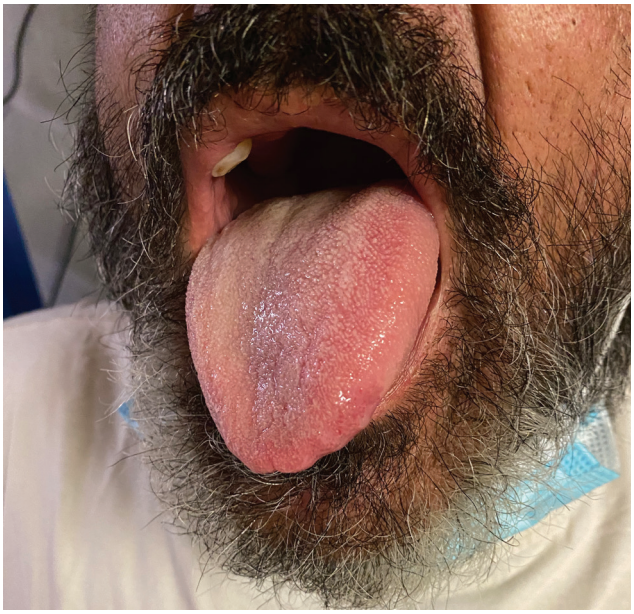

Figure 1 – Unilateral left tongue edema, left lateral view

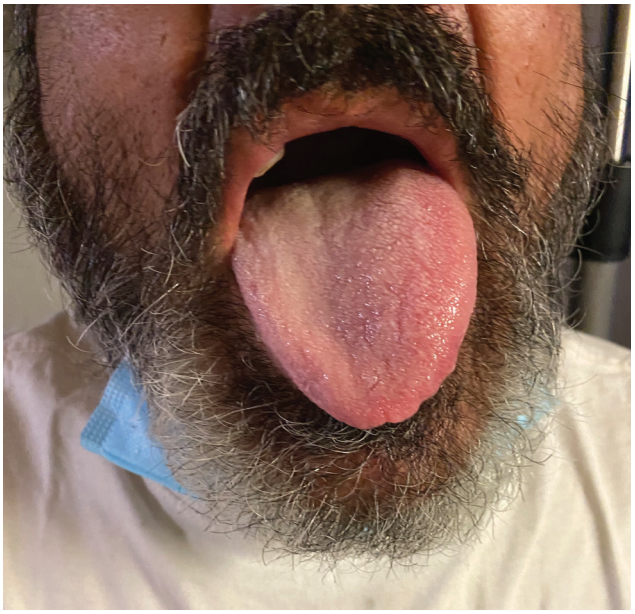

Figure 2 – Unilateral left tongue edema, frontal view

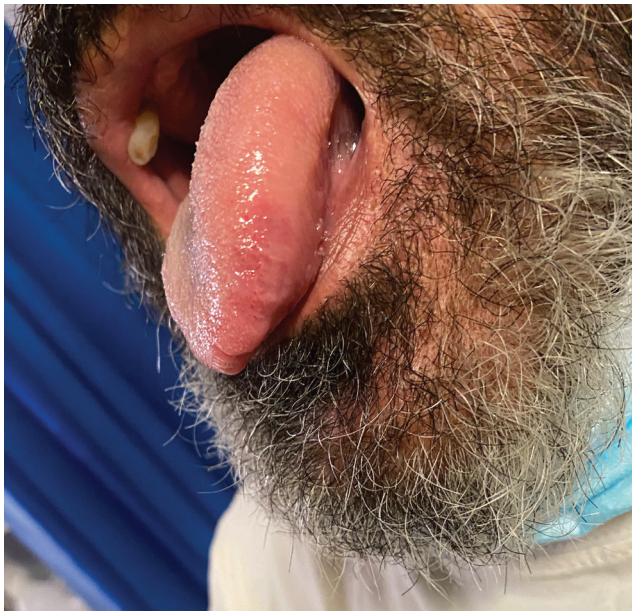

Figure 3 – Unilateral left tongue edema, lateral perspective

of bradykinin. The increased concentration of this peptide increases capillary permeability, with fluid extravasation and swelling of tissues, resulting in angioedema.

Angioedema due to ACEi usually occurs in the initial months after starting therapy, although there are described cases when the effect only appears after several years, with a greatly decreasing risk over time.[1,2] According to the literature, it can develop over minutes to hours, resolving over 24 to 72 hours after medication discontinuation.[2,3] Previous angioedema history, smoking, age above 65 years, use of non-steroidal anti-inflammatory drugs or female sex are risk factors for angioedema development.[1,4-6] Our patient only presented a history of smoking and was treated for almost three years with enalapril, which reveals the importance of considering ACEi side effects during the course of treatment.

In this patient, we observed unilateral tongue edema involvement. This is a very rare angioedema presentation with few cases reported in the literature.[7-13] The cause of this specific involvement remains uncertain, but one theory states that unilateral edema might be the progression over time to bilateral edema.[14] Although rare, this presentation should be considered in this diagnosis due to the risk of progression to airway obstruction. The management of these patients involves tight surveillance, with immediate airway evaluation, since its compromise could be potentially fatal. Although there is no specific targeted therapy for angioedema, some patients may require corticosteroids and antihistamines.[14] The effective long-term treatment is ACEi discontinuation. In this case report, after enalapril discontinuation, symptoms resolved without angioedema relapse.

Regardless of the time of use, considering this case with the appearance of angioedema after several years on enalapril, clinicians should always be aware of the possibility of this side effect in patients under treatment with ACEi, no matter how long ago the drug was introduced.

AUTHORS CONTRIBUTION

BGB: Draft of the article.

MC, PN: Draft and critical review of the article.

FP, CM: Critical review of the article.

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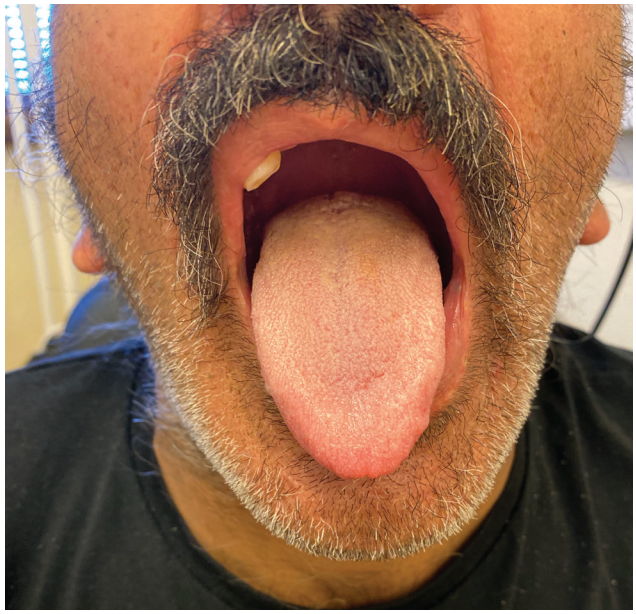

Figure 4 – Follow-up, one and a half months later, frontal perspective

Figure 5 – Follow-up, one and a half months later, left side perspective

DATA CONFIDENTIALITY

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

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Digital Mucous Cyst: An Unusual Presentation of Osteoarthritis

Quisto Mucóide Digital: Uma Manifestação Improvável de Osteoartrose

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Keywords: Fingers; Ganglion Cysts; Osteoarthritis; Primary Health Care
Palavras-chave: Dedos; Cuidados de Saúde Primários; Osteoartrite; Quistos Glanglionares

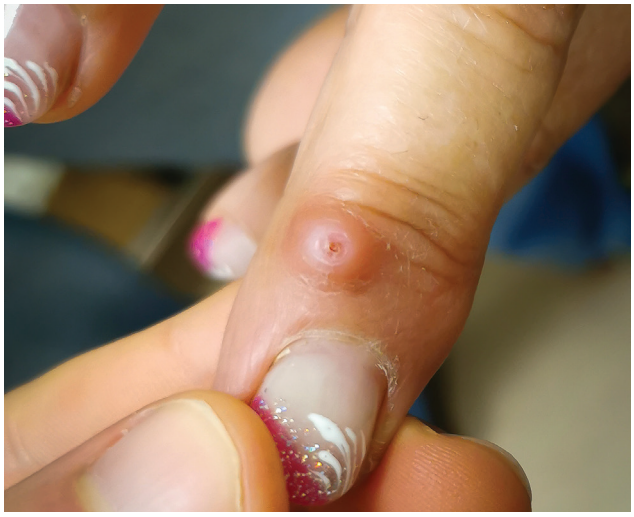

Figure 1 – Round, transilluminated and dome-shaped cyst on the distal dorsal aspect of the third finger of the right hand

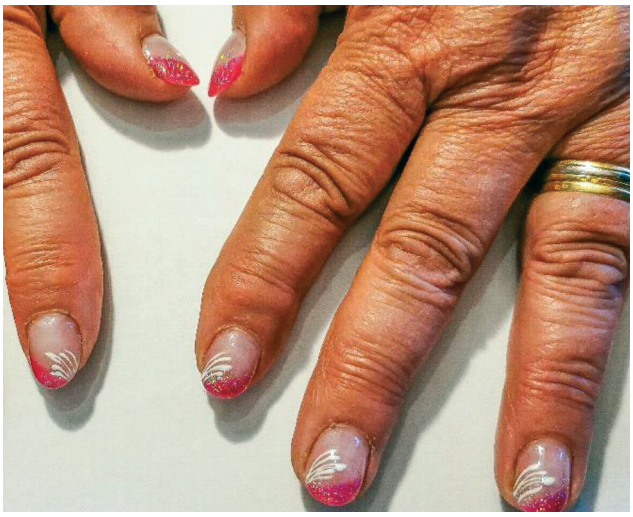

Figure 2 – Evidence of osteoarthritic hands. *Heberden* nodes are marked by blue arrows.

A 61-year-old female patient, with obesity and distal interphalangeal joint (DIPJ) osteoarthritis (OA) radiologically documented, presented with a painful and insidious swelling on the third finger (Fig. 1) that had appeared 15 days ago. She described significant pain only when touched, decreased range of motion, and denied spontaneous drainage, previous trauma, colour changes, or insect bite. Moreover, she reported a similar presentation in the past. On palpation, the swelling was painful, firm and not mobile. *Heberden* nodes were visible (Fig. 2). Given the past medical history, the diagnosis of digital mucous cyst (DMC) was made.

DMC are benign and recurrent lesions of the fingers associated with OA,[1] which usually develop in older patients, and more frequently in women. Its diagnosis may be unsuspected in Primary Care without being aware of past medical history. *Heberden* nodes, despite being strong markers of OA, are a common and challenging differential diagnosis. These also appear in the DIPJ, but unlike DMCs, these are bony nodes, are usually not painful and present with multiple dorsolateral nodes in the same finger.[2] A conservative approach is commonly advised, although it can require surgical treatment.[3,4] The major risk of DMC is rupture, which will require other treatment approaches in order to prevent joint infection.[5]

AUTHORS CONTRIBUTION

JS: Drat of the case description and discussion.
CP, LA: Critical review of the work.

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Protocolo Intra-Hospitalar para Abordagem da Doença COVID-19 no Adulto

Intrahospital Protocol for the Management of COVID-19 Disease in Adults

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RESUMO

A pandemia de COVID-19 é, atualmente, responsável por mais de 526 milhões de infeções e mais de 6,3 milhões de mortes. Como nova doença, é extenso o número de publicações sobre o tema, motivando uma considerável heterogeneidade na sua abordagem. Apesar de existirem terapêuticas com benefício comprovado, continuam a ser propostas novas intervenções e estratégias, algumas das quais carecendo ainda de suporte científico, dificultando assim uma abordagem uniforme e consensual. Este documento tem como objetivo uniformizar, baseando-se na melhor e mais atualizada evidência científica disponível, a prestação de cuidados aos doentes adultos com COVID-19 moderada a crítica, desde o serviço de urgência até à hospitalização, quer em enfermarias gerais, quer em enfermarias de cuidados intensivos de nível 2 e 3. Este protocolo apresenta recomendações para a estratificação da doença COVID-19, critérios de hospitalização, meios complementares de diagnóstico adequados à admissão e durante a hospitalização, medidas terapêuticas gerais e terapêutica farmacológica dirigida, gestão de complicações como pneumonia organizativa e sobreinfeção bacteriana, tromboprofilaxia, considerações especiais na gravidez e amamentação, e possíveis opções terapêuticas futuras.

Palavras-chave: COVID-19/complicações; COVID-19/tratamento; Hospitalização; Protocolos Clínicos

ABSTRACT

The COVID-19 pandemic is currently responsible for over 526 million infections and over 6.3 million deaths. As a new disease, the number of papers on the subject is extensive, motivating considerable heterogeneity in its approach. Despite some medicines having sound evidence of benefit, new interventions and strategies continue to be proposed, and some still lack scientific evidence, which hinders a uniform and consensual approach. This article aims to standardize healthcare to adult patients with moderate-to-critical COVID-19, from the emergency department to hospitalization, either in a general ward or in level 2 or level 3 intensive care units, based on the best and most updated scientific evidence available. This protocol presents recommendations for the stratification of adult patients with COVID-19 disease, adequate workup at admission and during hospitalization, inpatient treatment criteria, general treatment measures, pharmacological treatment, management of complications such as organizing pneumonia and bacterial superinfection, thromboprophylaxis, special considerations on pregnancy and breastfeeding and possible future therapies.

Keywords: Clinical Protocols; COVID-19/diagnosis; COVID-19/therapy; Hospitalization

INTRODUÇÃO

A COVID-19, acrónimo de *coronavirus disease* 2019, é uma doença causada por um novo coronavírus denominado *severe acute respiratory syndrome coronavirus* 2 (SARS-CoV-2). As infeções originadas por este vírus cursam desde doença totalmente assintomática até pneumonia bilateral grave com síndrome de dificuldade respiratória aguda (ARDS) e insuficiência respiratória com necessidade de suporte ventilatório mecânico.

A 11 de março de 2020, a COVID-19 foi classificada como pandemia pela Organização Mundial de Saúde (OMS). Até à data de redação deste documento, estão descritos mais de 526 milhões de casos e mais de seis milhões de mortes.[1]

Como resposta a esta pandemia, assistimos a uma produção massiva de pesquisa científica sem precedentes, direcionada sobretudo para a abordagem da doença e a determinação de tratamento dirigido com impacto significativo na mortalidade. Apesar de já existirem opções terapêuticas com benefício comprovado em ensaios randomizados, continuam a ser propostas alternativas – novas classes farmacológicas, posologias ou esquemas terapêuticos – que carecem ainda de suporte científico, dificultando uma abordagem uniforme e consensual a nível mundial.

Este documento foi redigido com base na evidência científica disponível mais atualizada, no intuito de melhorar a prestação de cuidados aos doentes adultos, desde a sua abordagem inicial até ao internamento a nível hospitalar, quer em enfermarias gerais, quer em enfermarias de medicina intensiva de níveis 2 e 3.

Apesar do contexto inicial intra-hospitalar, este documento pode aplicar-se a qualquer hospital que preste cuidados ao doente com COVID-19 e as recomendações aqui apresentadas poderão ser adaptadas às realidades de outros hospitais.

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A evidência estudada é relativa à população adulta com infeção por COVID-19, pelo que a informação e as recomendações contidas neste documento são aplicáveis apenas a esta população e não deverão ser extrapoladas para a população pediátrica, dadas as particularidades desse grupo etário.

MATERIAL E MÉTODOS

Este protocolo foi redigido após revisão da literatura publicada na PubMed, sendo excluídos os estudos não disponíveis em inglês ou português. Foram também consultados os resumos de características do medicamento de todos os fármacos referidos, bem como os alertas e recomendações da Agência Europeia do Medicamento (EMA).

O protocolo divide-se em recomendações para o diagnóstico e estratificação do doente COVID-19; medidas gerais em doente hospitalizado por COVID-19; tratamento dirigido à COVID-19, incluindo nesta secção recomendações específicas para corticoterapia (quer na doença COVID-19 aguda, quer na pneumonia organizativa secundária à COVID-19), anacinra, tocilizumab, remdesivir e tromboprofilaxia; abordagem do doente com suspeita de sobreinfeção bacteriana; considerações especiais na gravidez e amamentação; e futuras modalidades terapêuticas.

A versão integral deste documento pode ser consultada no Apêndice 1 (Apêndice 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18236/Apendice_01.pdf).

Protocolo de atuação em doentes hospitalizados por COVID-19

A Fig. 1 sistematiza, em fluxograma, todas as recomendações presentes neste protocolo, para uma fácil interpretação e consulta em qualquer contexto clínico.

Diagnóstico e estratificação da doença COVID-19

A abordagem inicial de qualquer adulto com suspeita de infeção por SARS-CoV-2 deve seguir as orientações da Norma nº 004/2020 da Direção Geral de Saúde.[2]

Após confirmação da infeção, deverá proceder-se à estratificação de gravidade da doença conforme os critérios de gravidade de apresentação clínica, tendo igualmente em conta os fatores de risco para progressão de doença grave (Tabela 1).

A indicação para hospitalização deve basear-se na apresentação clínica e fatores de risco:

- Todos os doentes com doença ligeira ou assintomática deverão realizar isolamento no domicílio – e rapidamente reavaliados presencialmente em serviço de urgência caso haja qualquer sinal de agravamento clínico;
- Ponderar hospitalização em doentes com doença moderada, especialmente perante a existência de múltiplos fatores de risco, saturação periférica em ar ambiente entre 92% e 94% ou pneumonia radiologicamente comprovada;
- Todos os doentes com doença grave devem ser hospitalizados – doentes com múltiplos fatores de risco ou necessidade de suporte de órgão deverão ser sinalizados/admitidos precocemente em unidades de nível 2 ou 3;
- Todos os doentes com doença crítica devem ser hospitalizados em unidades de nível 3.

Nos doentes com critérios de hospitalização recomenda-se a realização dos exames complementares explicitados na Tabela 2. Estes exames permitem monitorizar a evolução da doença, constituindo marcadores independentes de gravidade ou de prognóstico, avaliando a indicação para tratamento ou despistando complicações ou comorbilidades potencialmente tratáveis.[3]

Os doentes com doença grave ou crítica devem realizar angiografia por tomografia computorizada (angio-TC) torácica para despiste de tromboembolia pulmonar e estratificação imagiológica da doença. Esta deverá ser feita antes da admissão nas unidades de nível 2 e 3.

Medidas gerais em doente hospitalizado por COVID-19

Devem, conforme avaliação clínica individualizada, ser realizadas as seguintes medidas gerais de suporte:

- Tratamento sintomático, de suporte e das comorbilidades e doenças crónicas descompensadas;
- Oxigenoterapia suplementar para SpO_2 alvo entre 92% e 96%, administrada de forma convencional; em alto fluxo por cânula nasal; por sistemas de administração por pressão positiva no final da expiração; ou pressão positiva expiratória na via aérea com válvula de resistência calibrada;
- Terapêutica por via inalatória, sem nebulização;
- Suporte ventilatório precoce, nos casos selecionados, com falência da oxigenoterapia;
- Suporte vital por oxigenação por membrana extracorporal em casos selecionados de insuficiência respiratória aguda grave refratária a suporte ventilatório otimizado.

Os doentes devem realizar estudo analítico seriado regularmente, caso a situação clínica o justifique, com:

- Hemograma com leucograma;
- Creatinina, ureia e ionograma completo;
- ALT; AST; FA e GGT;
- Bilirrubina total, direta e indireta;
- Troponina T e mioglobina, se alteradas à admissão;
- PCR;
- Ferritina;
- Fibrinogénio, D-dímeros;
- Gasometria arterial.

Em caso de agravamento clínico ou ausência de qualquer resposta favorável ao tratamento após sete dias de terapêutica, as seguintes três medidas devem ser realizadas:

- Sinalização para admissão em unidade de cuidados intensivos de nível 2 - 3, se aplicável;
- Repetição de controlo imagiológico com angio-TC tórax, para exclusão de tromboembolia pulmonar e/ou evolução para pneumonia organizativa;
- Exclusão de qualquer outra patologia que possa

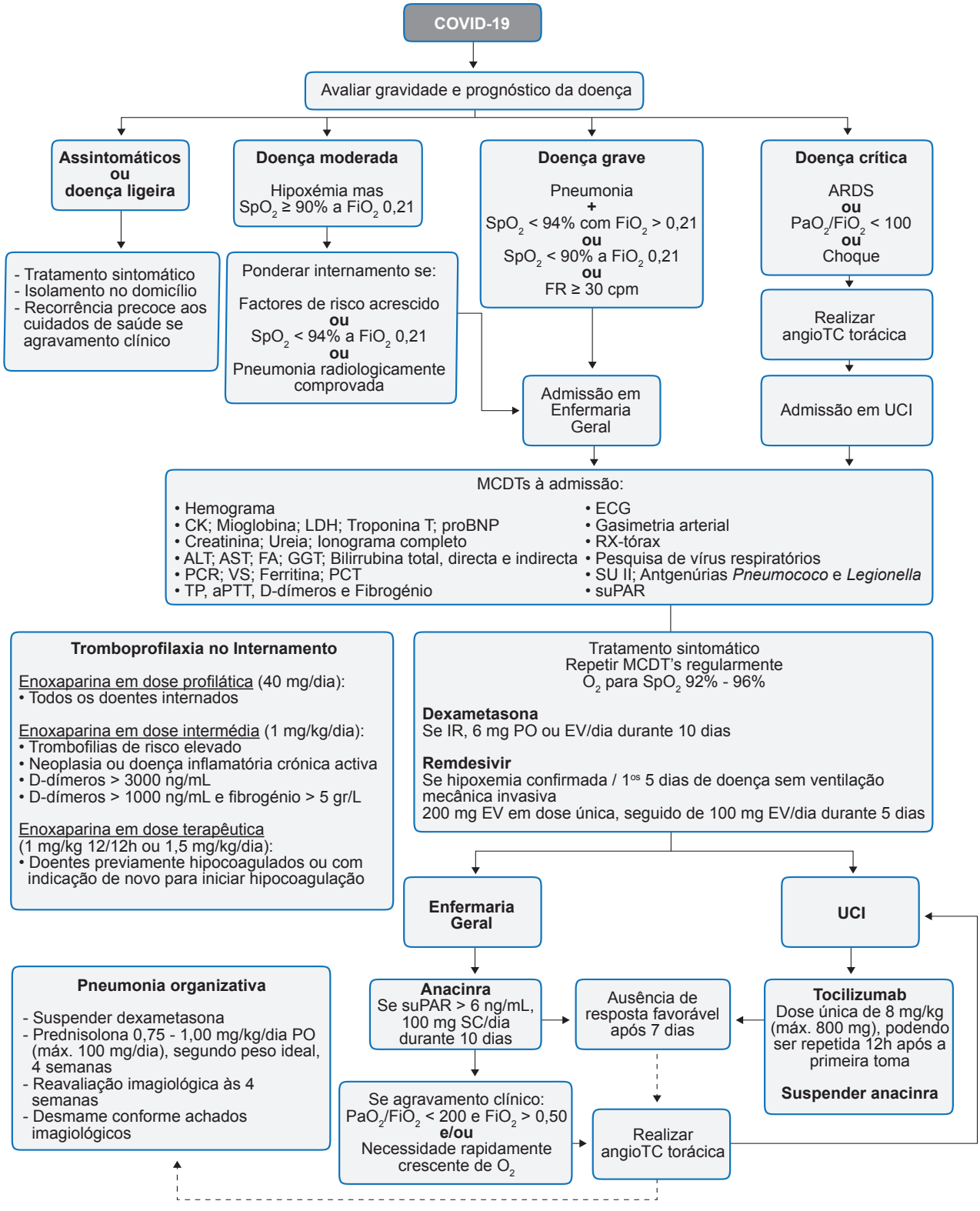

Figura 1 – Fluxograma de atuação na abordagem do doente COVID-19

ALT: alanina aminotransferase; angioTC: angiotomografia computorizada; aPTT: tempo de tromboplastina parcial ativado; ARDS: síndrome de dificuldade respiratória aguda; AST: aspartato aminotransferase; CK: creatinina kinase; ECG: electrocardiograma; EV: endovenoso; FA: fosfatase alcalina; FiO_2 fração inspirada de oxigénio; FR: frequência respiratória; GGT: gama glutamil transferase; INR: rácio internacional normalizado; IR: insuficiência respiratória; LDH: lactato desidrogenase; MCDTs: meios complementares de diagnóstico e terapêutica; PaO_2: pressão arterial de oxigénio; PCR: proteína C reativa; PCT: procalcitonina; PO: *per os*; ProBNP: péptido natriurético tipo B; SC: subcutânea; SpO_2: saturação periférica de oxigénio; SU II: exame sumário de urina II; suPAR: recetor do ativador do plasminogénio da uroquinase solúvel; TEV: tromboembolismo venoso; TP: tempo de protrombina; UCI: unidade de cuidados intensivos; VS: velocidade de sedimentação

contribuir para o agravamento do quadro e iniciar tratamento dirigido, se aplicável.

Tratamento dirigido à COVID-19

O tratamento dirigido à COVID-19 baseia-se em quatro fármacos principais: a corticoterapia (com dexametasona ou prednisolona de acordo com a situação clínica), o anacinra, o tocilizumab e o remdesivir. Na Tabela 3 estão descritas as posologias, indicações, contraindicações e advertências de cada um dos fármacos recomendados.

Dexametasona em doentes hospitalizados por COVID-19

Entre todas as terapêuticas disponíveis, a corticoterapia é aquela cujo benefício no doente com COVID-19 está mais bem estabelecido, sendo por isso o fármaco mais utilizado na prática clínica,[4,5] em particular nos doentes que requerem oxigenoterapia (incluindo ventilação mecânica invasiva ou não invasiva ou oxigenação por membrana extracorpórea). Pode ser administrado por via endovenosa em caso de impossibilidade por via oral. Não há evidência

Tabela 1 – Critérios de gravidade de apresentação clínica e fatores de risco para progressão de doença COVID-19 grave

Gravidade da apresentação clínica	Critérios
Doença ligeira ou assintomática	Ausência de sintomas ou sintomas ligeiros sem evidência de pneumonia ou hipoxemia
Doença moderada	Pneumonia (febre, tosse, dispneia, taquipneia) ou hipoxemia mas SpO_2 superior a 90% em ar ambiente
Doença grave	Pneumonia e, pelo menos, um dos seguintes critérios: ● Taquipneia superior a 30 ciclos por minuto ● SpO_2 inferior a 90% em ar ambiente ● SpO_2 inferior a 94% sob oxigenoterapia suplementar
Doença crítica	Síndrome de dificuldade respiratória aguda ou PaO_2/FiO_2 <100 ou instabilidade hemodinâmica/choque

Fatores epidemiológicos	Fatores clínicos	Fatores laboratoriais
Idade superior a 60 anos	Taquipneia com FR > 24 cpm	D-dímeros > 1000 ng/mL
Gravidez	Taquicardia com FC > 125 bpm	CK > 2x LSN
Imunodepressão	SpO_2 < 94% em FiO_2 21%	LDH > 245 UI/L
Doença ou condição crónica: DPOC, asma, insuficiência cardíaca, diabetes, cirrose hepática, doença renal crónica em hemodiálise, drepanocitose, obesidade	PaO_2/FiO_2 < 300	Linfócitos < 800/µL
Neoplasia maligna ativa, particularmente sob quimioterapia, radioterapia ou imunoterapia/biológicos		Ferritina > 500 ng/mL
		Elevação de MNM

Adaptado a partir da Norma nº 004/2020 da Direção Geral de Saúde

CK: creatinina kinase; DPOC: doença pulmonar obstrutiva crónica; FiO_2: fração inspirada de oxigénio; FC: frequência cardíaca; FR: frequência respiratória; LDH: lactato desidrogenase; LSN: limite superior ao normal; MNM: marcadores de necrose miocárdica; PaO_2: pressão arterial de oxigénio; SpO_2: saturação periférica de oxigénio

Tabela 2 – Exames complementares recomendados à admissão para todos os doentes hospitalizados com COVID-19

Exames complementares
Hemograma com leucograma
Creatinina; ureia; ionograma completo
Bilirrubina total, direta e indireta, ALT, AST, FA, GGT
suPAR
Gasimetria arterial
Pesquisa de vírus respiratórios (influenza A e B; VSR; adenovírus; metapneumovírus; enterovírus; vírus parainfluenza 1-4; bocavírus; binovírus e outros coronavírus)
CK; mioglobina; LDH; troponina T; proBNP
PCR; VS; ferritina; PCT
Eletrocardiograma
TP; INR; aPTT; fibrinogénio; D-dímeros
Radiografia do tórax
Exame sumário de urina II; antigenúrias *Pneumococo* e *Legionella*

ALT: alanina aminotransferase; aPTT: tempo de tromboplastina parcial ativado; AST: aspartato aminotransferase; CK: creatinina kinase; FA: fosfatase alcalina; GGT: gama glutamil transferase; INR: rácio internacional normalizado; LDH: lactato desidrogenase; PCR: proteína C reativa; PCT: procalcitonina; ProBNP: péptido natriurético tipo B; suPAR: recetor do ativador do plasminogénio da uroquinase solúvel; TP: tempo de protrombina; VS: velocidade de sedimentação; VSR: vírus sincicial respiratório

de benefício em dose baixa de corticoterapia em doentes sem necessidade de oxigenoterapia suplementar.

Em doentes hospitalizados com COVID-19 com insuficiência respiratória, com contraindicação para dexametasona, podem ser utilizadas alternativas à dexametasona, nomeadamente:

- Hidrocortisona 50 mg EV 8/8 horas
- Metilprednisolona 32 mg PO ou EV de 24/24 horas
- Prednisolona 40 mg PO ou EV de 24/24 horas

Doses alternativas de corticoterapia em doentes hospitalizados por COVID-19

Têm sido publicados múltiplos estudos sobre outros esquemas de tratamento com outros corticóides sistémicos.

Edalatifard *et al*[6] publicou um ensaio clínico randomizado que comprovou impacto significativo na mortalidade com esquema de metilprednisolona, 250 mg/dia, durante três dias, em comparação com doentes não tratados com corticoterapia, ao contrário dos estudos GLUCOVID[7] e METCOVID,[8] que utilizaram doses mais baixas de metilprednisolona.

Após a divulgação deste estudo, outros foram publicados com diferentes esquemas de altas doses de metilprednisolona.[9-15] Contudo, nenhum conseguiu demonstrar diminuição da mortalidade em comparação com o esquema de dexametasona recomendado. Em setembro de 2021, Yakoob *et al*[16] comparou retrospetivamente esquemas de 1 - 2 mg/kg/dia de metilprednisolona *versus* esquemas com 1000 mg/dia *versus* 0 mg de corticóide, onde foram verificados melhores *outcomes* nos doentes tratados com doses de 1 - 2 mg/kg/dia que nos doentes tratados com doses mais elevadas, onde se verificaram mais complicações associadas ao tratamento. O mesmo se verificou nos restantes estudos com doses superiores a 250 mg/dia de metilprednisolona – sem benefício adicional pelo aumento marcado de complicações.

Tabela 3 – Resumo de posologia, indicação clínica e principais advertências dos fármacos recomendados para o tratamento dirigido à COVID-19

Fármaco e posologia	Indicação clínica	Contraindicações	Notas/ advertências
Dexametasona 6 mg PO ou EV/dia 10 dias ou até alta clínica	Doentes hospitalizados com doença COVID-19 grave que requerem oxigenoterapia	• Doença ligeira-moderada, sem oxigenoterapia a não ser que exista outra indicação • Hipersensibilidade prévia • Infeção fúngica não controlada	• Risco de reativação de infeções latentes • Risco de hiperglicemia • Ver recomendações para grávidas
Prednisolona 0,75 - 1 mg/kg/dia PO durante 4 semanas, depois reduzir para 0,5 - 0,75 mg/kg/dia PO se melhoria durante 6 semanas	Doente com pneumonia organizativa comprovada por TC torácica	• Hipersensibilidade prévia • Infeção fúngica não controlada • Estados psicóticos não controlados • Vacinação com agentes vivos atenuados	• Vigiar efeitos secundários de corticoterapia de longa duração • Desmame conforme melhoria clínica e imagiológica
Anacinra 100 mg SC/dia 10 dias ou até alta clínica	COVID-19 com pneumonia (mesmo se sem insuficiência respiratória) com necessidade de hospitalização e suPAR ≥6 ng/mL (medido no SU ou na admissão à enfermaria)	• Associados ao RCM do fármaco • PaO_2/FiO_2 inferior a 150 • Necessidade de ventilação mecânica (não crónica) • Terapêutica anti-citocina nos últimos 30 dias • Falência hepática • Doença renal crónica terminal ou sob diálise • Gravidez ou amamentação	• Início em enfermaria geral e de forma precoce • Se necessidade de tocilizumab, suspender anacinra
Tocilizumab Dose única 8 mg/kg EV até máximo de 800 mg Possível repetir nova toma com a mesma posologia 12h após a primeira dose	Doentes com agravamento clínico rápido, sob dexametasona, com pelo menos um dos seguintes: • PaO_2/FiO_2 < 200 com FiO_2> 50% • Necessidade rapidamente crescente de O_2	• Associadas ao RCM • Infeção bacteriana não controlada	• Risco de reativação de infeções latentes • Administrar o mais precocemente possível (em enfermaria geral, se necessário) • Ponderar admissão em Unidade de Cuidados Intensivos
Remdesivir 200 mg EV em dose única seguida por 100 mg EV/dia 5 dias	Doentes sob oxigenoterapia suplementar, apenas nos primeiros cinco dias de doença e em risco de progressão para doença grave	• Doentes com mais de cinco dias de sintomas • TFG inferior a 30 mL/min/1,73m^2 • ALT superior a 5x o LSN • Necessidade de ventilação mecânica invasiva • ARDS	• Obter níveis basais de TFG e de AST/ALT previamente à administração • Necessária avaliação diária das transaminases

ALT: alanina aminotransferase; ARDS: síndrome de dificuldade respiratória aguda; AST: aspartato aminotransferase; EV: endovenoso; FiO_2: fração inspirada de oxigénio; LSN: limite superior ao normal; PaO_2: pressão arterial de oxigénio; PO: *per os*; RCM: resumo das características do medicamento; SC: subcutânea; SU: serviço de urgência; suPAR: recetor do ativador do plasminogénio da uroquinase solúvel; TC: tomografia computorizada; TFG: taxa de filtração glomerular

Assim, de acordo com a literatura publicada até à data, não existem ensaios clínicos randomizados ou meta-análises onde se verifique benefício adicional de metilprednisolona na mortalidade em comparação com a dexametasona.

Mais recentemente, foi publicado o estudo COVID STEROID 2[17] que também não demonstrou benefício adicional significativo na sobrevida aos 28 dias em doentes com 12 mg/dia de dexametasona *versus* a dose recomendada de 6 mg/dia.

Assim, face à evidência atualmente disponível, parece não existir benefício na administração de doses mais elevadas ou esquemas alternativos de corticoterapia. A exceção será nos doentes com evolução para pneumonia organizativa.

Tratamento da pneumonia organizativa secundária a COVID-19

A pneumonia por COVID-19 pode evoluir para pneumonia organizativa, havendo, nestes doentes, benefício comprovado de curso prolongado com prednisolona. Dado não existir evidência para tratamento específico de pneumonia organizativa secundária à COVID-19, o tratamento é extrapolado do tratamento da pneumonia organizativa criptogénica.[18]

Anacinra em doentes hospitalizados por COVID-19

Um ensaio clínico randomizado de fase 3 (SAVE-MORE) com mais de 600 doentes hospitalizados evidenciou benefício na utilização de anacinra. Trata-se de uma abordagem através da estratificação de risco via determinação do valor sérico do biomarcador suPAR, cujo aumento é mais precoce que os marcadores clássicos de inflamação (PCR, D-dímeros, ferritina, interleucina-6) e identifica progressão para fase inflamatória da doença.[19,20]

O valor superior a 6 ng/mL permitiu estratificar os doentes de maior risco para progressão da doença, verificando-se que a adição do anacinra ao *standard of care* levou a menor progressão da doença e mortalidade relativa.[21] Face a estes resultados, a EMA emitiu recentemente um parecer a recomendar a aprovação do fármaco para o tratamento da COVID-19 grave.[22]

Deve ser administrado de forma precoce em enfermaria geral.

Tocilizumab em doentes hospitalizados por COVID-19

Os estudos randomizados REMAP-CAP e RECOVERY[23,24] e uma meta-análise publicada no *Journal of the American Medical Association*[25] mostram um claro benefício do uso de tocilizumab, um inibidor da interleucina-6, na redução de progressão para ventilação mecânica invasiva e na redução da mortalidade aos 28 dias, em doentes hospitalizados com COVID-19 grave. Com base nestes estudos, a OMS[26] e múltiplas sociedades científicas (como a Infectious Diseases Society of America)[27] ou entidades oficiais de Saúde (como o NIH)[28] atualizaram recentemente as suas linhas orientadoras para incluir este fármaco.

Apesar de, no ensaio randomizado RECOVERY,[24] uma das indicações consideradas ser um valor de PCR igual ou superior a 75 mg/L, optou-se por não considerar este parâmetro como critério de elegibilidade ou exclusão para instituição de tocilizumab, partindo da assunção de que doentes com doença grave ou crítica com agravamento da doença estarão indissociavelmente em progressão para estado hiper-inflamatório, conforme descrito no REMAP-CAP,[23] onde esta indicação não foi considerada critério de inclusão.

Remdesivir em doentes hospitalizados por COVID-19

Com base na evidência disponível, que inclui uma robusta meta-análise,[29] o benefício do remdesivir parece estar limitado a doentes na fase inicial da doença, não sendo inequívoco o seu impacto na mortalidade avaliada aos 28 dias.

Por esse motivo, a administração do remdesivir tem sido cada vez menos comum, uma vez que o doente com critérios de hospitalização já se encontra habitualmente fora da janela da doença onde tem maior benefício e, consequentemente, o número de doentes que podem beneficiar deste fármaco é muito reduzido. Apesar disso, a sua prescrição não deve ser excluída *a priori*, sendo que, nos doentes com indicação para tal, deve decorrer de uma avaliação clínica individualizada, com ponderação dos riscos e benefícios para o doente e de acordo com o resumo das características do medicamento.

Além disso, com base num estudo randomizado e duplamente cego recentemente publicado,[30] entende-se que o remdesivir poderá ser considerado em doentes com aquisição nosocomial de COVID-19 e fatores de risco para progressão para doença COVID-19 grave.

Abordagem da suspeita de sobreinfeção bacteriana

O diagnóstico de sobreinfeção bacteriana, principalmente a respiratória, em doentes com COVID-19, é um desafio com complexidade. A administração de antibioterapia em doentes sem infeção bacteriana é uma fonte importante de iatrogenia, com custos adicionais e sem benefício para o doente e vai selecionar estirpes mais resistentes de gérmenes patogénicos.

No caso particular da COVID-19, os valores à admissão de proteína C-reativa e a contagem total de leucócitos e neutrófilos são bons marcadores de coinfecção bacteriana,[31] mas é impossível estabelecer *cut-offs* claros por existirem poucos estudos nessa área.

A procalcitonina (PCT) será mais útil para excluir uma infeção bacteriana à admissão. Segundo o PRORATA *Trial*, em doentes críticos com infeções do trato respiratório inferior, níveis de PCT inferiores a 0,25 µg/L indicam etiologia bacteriana como muito improvável, enquanto valores superiores a 1 µg/L indicam elevada probabilidade de etiologia bacteriana.[32]

De acordo com estudos recentes, o SARS-CoV-2, ao contrário de outros vírus, detém proteínas inibidoras do interferão e do STAT-1, ocorrendo uma ativação compensatória do STAT-3 o que leva, por sua vez, à elevação da PCT,

mesmo na ausência de coinfecção bacteriana.[33-35]

Por outro lado, existe evidência de alterações da função monocitária na COVID-19 secundária à sua fisiopatologia, sendo que, de acordo com Martinez *et al*,[36] a perda da função monocitária e a desregulação da sua capacidade secretora resultam num aumento da produção de PCT na COVID-19.

Assim, doentes com COVID-19 têm, habitualmente, níveis baixos de PCT à admissão. No entanto, os seus valores aumentam com a evolução natural da doença, constituindo um bom marcador de gravidade.[32]

As *guidelines* do National Institute for Health and Care Excelence (NICE) advogam que a evidência é escassa no que toca a utilizar a PCT na COVID-19 para guiar o uso de antibioterapia.[37]

Assim, a PCT nos doentes com COVID-19 tem utilidade apenas na admissão hospitalar pelo seu elevado valor preditivo negativo. Não deve ser doseada por rotina durante a hospitalização do doente COVID-19, e o aumento da PCT durante a evolução da doença COVID-19 não deve ser a única justificação para iniciar terapêutica antibiótica.[38] Esta deverá ser iniciada apenas nos casos de forte suspeita clínica de sobreinfeção respiratória bacteriana, nos casos de coinfecção não respiratória e/ou nos casos de isolamento microbiológico em amostras adequadas.

Tromboprofilaxia em doentes hospitalizados por COVID-19

Dados preliminares de fevereiro de 2020 já indiciavam a associação de infeção por COVID-19 a coagulopatia, com alterações analíticas que se traduziam sobretudo no aumento de D-dímeros.[39] As taxas excecionalmente elevadas de tromboembolismo venoso (TEV) levantaram precocemente questões relativas ao estado pró-coagulante inerente a esta infeção face outras infeções, bem como sobre o papel da tromboprofilaxia na redução de eventos trombóticos.

Na infeção por SARS-CoV-2, a coagulopatia é uma complicação frequente que compromete o curso clínico da doença, estando associada a piores *outcomes* e aumento da mortalidade. É reconhecida como um estado pró-trombótico, o que salienta a importância de definição de estratégias de anticoagulação na redução da taxa de mortalidade destes doentes.[40]

A prevalência das complicações trombóticas descritas apresenta grande variabilidade entre estudos. Uma revisão sistemática e meta-análise publicada em outubro de 2020,[41] referente a 33 970 doentes, mostrou uma prevalência global de TEV estimada de 14,1%; a análise de subgrupos mostrou uma prevalência de 22,7% de TEV em doentes hospitalizados em unidade de cuidados intensivos (UCI) e de 7,9% em doentes não hospitalizados neste serviço. Doentes que desenvolveram TEV apresentavam níveis mais elevados de D-dímeros. Embora a prevalência do TEV associada à infeção grave por COVID-19 seja elevada, sobretudo nos doentes em UCI, esta não é, no entanto, superior à prevalência do TEV associada a outras infeções associadas a síndrome de dificuldade respiratória aguda (ARDS) não-COVID.[42]

A profilaxia do TEV por rotina a todos os doentes hospitalizados com infeção COVID-19 é consensual. Esta recomendação é transversal a várias *guidelines* nacionais e de sociedades científicas internacionais.[43-47]

A intensidade da anticoagulação tem sido alvo de amplo debate e as opiniões divergem entre estratégias de prevenção com doses *standard* de profilaxia *(*American College of Chest Physicians, American Society of Hematology*)* ou prevenção com doses intermédias ou mesmo terapêuticas de anticoagulação, com múltiplos estudos a abordarem o uso de doses superiores à dose profilática *standard*. Após mais de dois anos de pandemia, embora alguns estudos apontem um efeito benéfico de doses superiores de profilaxia,[48-50] não existe evidência robusta para o uso generalizado de tromboprofilaxia em doses superiores à *standard.*[51]

Como alternativa, o foco na intensificação da profilaxia deve estar nos doentes com doença grave e potencialmente fatal, que desenvolveram ou estão a desenvolver insuficiência respiratória, sendo importante identificar os doentes em risco e com maior probabilidade de benefício. O aumento dos D-dímeros é um candidato óbvio nessa identificação e, provavelmente, o mais forte preditor de trombose e mortalidade.[42]

A evidência disponível permite emitir as seguintes recomendações:

- Todos os doentes com COVID-19 hospitalizados devem ser avaliados em relação ao seu risco trombótico e risco hemorrágico;
- Se existir contraindicação para profilaxia farmacológica pelo risco hemorrágico, deve ser efetuada profilaxia mecânica;
- Na ausência de risco hemorrágico, deve ser usada de preferência heparina de baixo peso molecular (HBPM)[29,44-46];
- Se existir contraindicação para HBPM (antecedentes de trombocitopenia induzida pela heparina tipo II ou reações de hipersensibilidade à heparina ou álcool benzílico) deve ser usado fondaparinux.

Relativamente à posologia e monitorização da terapêutica anticoagulante (Tabela 4), os doentes com COVID-19 hospitalizados (após exclusão de risco hemorrágico), sem indicação para outras doses, devem realizar profilaxia com enoxaparina na dose *standard* de 40 mg/dia por via subcutânea (SC), com ajuste renal se aplicável e sem necessidade de monitorização da atividade anti-Xa.[29,39-42,44-46,49,50-55]

Doentes com trombofilias de risco elevado (deficiência de antitrombina, proteína C ou proteína S, homozigotias ou duplas heterozigotias para fator V Leiden e PT20210A, síndrome antifosfolipídico, presença de neoplasia ou doenças inflamatórias crónicas ativas) que não faziam previamente anticoagulação; doentes com níveis de D-dímeros superiores a 3000 ng/mL ou doentes com níveis de D-dímeros superiores a 1000 ng/mL e de fibrinogénio superior a 5 g/mL têm indicação para profilaxia com dose intermédia de enoxaparina 1 mg/kg/dia de 24/24 horas SC, com ajuste renal

Tabela 4 – Fatores de risco hemorrágico, doses e monitorização da anticoagulação

Fatores de risco hemorrágico	
Hemorragia ativa	
Acidente vascular cerebral agudo	
Hipertensão não controlada	
Coagulopatias adquiridas	
Trombocitopenia < 50 x 10^9/L	
Doenças hemorrágicas congénitas (hemofilias, doença de von Willebrand, doenças plaquetárias)	
Punção lombar, anestesia epidural ou espinal nas quatro horas prévias ou a efetuar nas 12 horas seguintes	
Heparina de baixo peso molecular: enoxaparina	
Profilaxia standard (40 mg/dia) → atividade anti-Xa 0,1 – 0,3 UI/mL	
Profilaxia intermédia (1 mg/kg/dia) → atividade anti-Xa 0,3 – 0,5 UI/mL	
Dose terapêutica (1 mg/kg 12/12 horas) → atividade anti-Xa 0,5 – 1,0 IU/mL	
Dose terapêutica (1,5 mg/kg/dia) → atividade anti-Xa 0,8 – 1,5 UI/mL	
Quando monitorizar:	
Doença renal: TFG < 30 mL/min/1,73m^2	
Complicações hemorrágicas ou trombóticas	
Como monitorizar:	
4 horas após administração de dose terapêutica de 12/12 horas	
4 – 6 horas após administração de dose terapêutica de 24 horas	
Independentemente da hora de administração se hemorragia grave (despiste de excesso de dose)	
Heparina não fraccionada	
Dose terapêutica:	
Bólus Inicial	80 UI/kg/h (máximo 10 000 UI)
Infusão contínua	18 UI/kg/h
Dose profilática:	
5000 UI por via subcutânea a cada 8 – 12 horas	
Como monitorizar:	
4 – 6 horas após bólus ou após alteração da dose	
Monitorizar com aPTT	
Fondaparinaux	
Dose terapêutica:	
< 50 kg	5 mg/dia
50 – 100 kg	7,5 mg/dia
> 100 kg	10 mg/dia
Dose profilática:	
< 50 kg	Usar agente alternativo
> 50 kg	2,5 mg/dia
Contraindicado	
Doença renal: TFG < 30 mL/min/1,73m^2	
Usar, em alternativa, argatroban	

aPTT: tempo de tromboplastina parcial ativado; TFG: taxa de filtração glomerular; UI: unidade internacional

se aplicável e sem necessidade de monitorização da atividade anti-Xa.[29,44-46,48-55]

Doentes que faziam previamente anticoagulação para prevenção cardioembólica ou tromboembólica [dicumarínicos ou anticoagulantes orais diretos (DOACs)]; doentes com episódio intrahospitalar de trombose *de novo* ou alto grau de suspeição clínica deste apesar de não poder ser documentado[29,44]; ou com trombose de acessos vasculares ou circuitos extracorpóreos, têm indicação para dose terapêutica de enoxaparina, 1 mg/kg/dia de 12/12 horas ou 1,5 mg/kg/dia 24/24 horas SC, com ajuste renal se aplicável, e indicação para monitorização da atividade anti-Xa apenas em casos selecionados.

Apesar da antiagregação plaquetária não estar indicada

como tromboprofilaxia, os doentes previamente medicados com aspirina devem mantê-la durante a hospitalização.[29,44,53,55-57]

COVID-19 na gravidez e amamentação

A gravidez e a amamentação apresentam um especial desafio na abordagem de qualquer patologia grave, pela escassa evidência científica disponível nestes grupos particulares de doentes. No entanto, existem recomendações específicas para a doente grávida com COVID-19.[29]

A abordagem da grávida com COVID-19, além das medidas gerais aplicáveis a todos os doentes, deve seguir as seguintes considerações:

- A hospitalização deve ser realizada num centro que possua meios para realizar monitorização fetal e materna;
- Deve ser realizada monitorização fetal e das contrações uterinas de acordo com a idade gestacional, se apropriado;
- Deve ser estabelecido um plano individualizado, se apropriado;
- Deve envolver uma equipa multidisciplinar, que envolva obstetras, pediatras, infeciologistas e intensivistas, para elaboração do melhor plano terapêutico.

O tratamento farmacológico da grávida com COVID-19 deve ser, no geral, o seguido por qualquer adulto. É recomendado que não se omita ou protele qualquer tratamento farmacológico por preocupações de segurança meramente teóricas, principalmente se o benefício estiver comprovado.

A amamentação, se em contexto de administração de fármacos específicos, deve ser sempre discutida com a doente e a sua família, avaliando benefícios do tratamento farmacológico em curso e o impacto da interrupção da amamentação no lactente e na família.

Grávidas que cumpram critérios para administração de corticoides devido a doença COVID-19 e contemporaneamente em risco de parto prematuro (normalmente entre as semanas 24 e 34) devem cumprir dexametasona 6 mg IM de 12/12 horas durante dois dias e posteriormente transitar para hidrocortisona, metilprednisolona ou prednisolona para reduzir a exposição fetal. Em grávidas que cumpram critérios para administração de corticoides devido a doença COVID-19, mas sem requerimento de corticoterapia para benefício fetal (normalmente até à semana 24 e após a semana 34), estão recomendadas hidrocortisona, metilprednisolona ou prednisolona para minimizar efeitos fetais. A amamentação deve ser evitada nas quatro horas após a toma de corticoide.

A quantidade de dados sobre a utilização de anacinra em mulheres grávidas é limitada, pelo que a sua utilização está, neste momento, contraindicada nesta população. Desconhece-se se o anacinra e os seus metabolitos são excretados no leite humano. Não pode ser excluído o eventual risco para os lactentes, pelo que a amamentação deve ser descontinuada durante o tratamento com anacinra.

Não existem dados adequados de utilização de tocilizumab em mulheres grávidas. Um estudo com alta dose em animais demonstrou um aumento do risco de aborto espontâneo e morte embrionária-fetal. No entanto, o risco para os seres humanos é desconhecido. Assim, o tocilizumab não deve ser utilizado durante a gravidez, exceto se manifestamente necessário. Não se sabe se o tocilizumab é excretado no leite materno humano. A excreção de tocilizumab no leite não foi estudada em animais. A decisão de manter ou não a amamentação após terapêutica com tocilizumab deve ser tomada considerando o benefício da amamentação para a criança e o benefício da terapêutica para a mulher.

O remdesivir apenas deverá ser utilizado em grávidas se os benefícios ultrapassarem os riscos para a mãe e para o feto. Estudos de toxicidade realizados em animais não observaram qualquer efeito adverso no desenvolvimento embrio-fetal. Por outro lado, apesar da presença de remdesivir e dos seus metabolitos no leite de progenitoras em estudos animais ter sido documentada, não existem dados quanto à sua identificação no leite materno humano. Assim, a decisão de suspender a amamentação ou não administrar remdesivir quando indicado deve ser uma decisão tomada em conjunto com a mãe, e baseada nos benefícios do fármaco contra os benefícios da amamentação para a criança e para a mãe.

As recomendações para a tromboprofilaxia no adulto também se aplicam à população de mulheres grávidas.[29] Pela complexidade na gestão destas doentes, recomenda-se a colaboração entre a equipa assistente e as especialidades de Obstetrícia e Imunohemoterapia. Salvaguarda-se que os dicumarínicos e os DOACs estão contraindicados na gravidez, mas durante a amamentação apenas os DOACs estão contraindicados.

Futuras modalidades terapêuticas

Dada a rápida evolução da ciência e a publicação progressiva de novos estudos, existem, à data deste documento, terapêuticas que parecem ser promissoras, mas cujo benefício ainda não foi cientificamente comprovado, não existindo evidência suficiente para serem recomendados. Destas terapêuticas, o baricitinib parece ser o fármaco com maior potencial.

O baricitinib é um imunomodulador cujo benefício em doentes COVID-19 está a ser estudado. O estudo COV-BARRIER,[58] com 1525 doentes, comprovou que o tratamento com baricitinib 4 mg *per os* uma vez por dia durante 14 dias ou até à alta hospitalar, apesar de não atingir o *endpoint* primário combinado de redução da progressão para oxigenoterapia de alto fluxo, ventilação mecânica ou mortalidade aos 28 dias, mostrou um perfil de segurança semelhante ao *standard of care*. Verificou-se igualmente uma mortalidade inferior no braço do baricitinib comparado com o braço do placebo, principalmente no subgrupo de doentes já sob oxigenoterapia de alto fluxo ou ventilação mecânica não invasiva na randomização.

O estudo ACTT-2,[59] com 1033 doentes, comparou o tratamento com baricitinib e remdesivir *versus* a terapêutica com placebo e remdesivir, concluindo que os doentes do

braço com baricitinib apresentaram menor tempo de recuperação e uma melhoria clínica mais célere. Neste estudo, foram excluídos os doentes sob corticoterapia, o que limita a sua aplicabilidade dado o benefício comprovado da corticoterapia nos doentes com COVID-19.

Assim, uma vez que o baricitinib é um imunomodulador como o tocilizumab, e não existem estudos a comprovar a superioridade do baricitinib *versus* o tocilizumab, ou estudos de segurança na administração simultânea ou concomitante destes dois fármacos, não existe, neste momento, evidência suficiente para recomendar o baricitinib em detrimento do tocilizumab. No entanto, o baricitinib está, à data de publicação deste protocolo, aprovado pela Food and Drug Administration (FDA) como uma alternativa ao tocilizumab nos doentes com contraindicações para a sua utilização, não tendo ainda qualquer recomendação pela EMA.

CONTRIBUTO DOS AUTORES

Todos os autores contribuíram de igual forma para o desenho, conceção e revisão do artigo.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFIDENCIALIDADE DOS DADOS

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

CONFLITOS DE INTERESSE

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

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Profilaxia Pré-Exposição para o Vírus da Imunodeficiência Humana e os Cuidados de Saúde Primários

Pre-Exposure Prophylaxis for Human Immunodeficiency Virus and Primary Health Care

Palavras-chave: Cuidados de Saúde Primários; Infecções por HIV/prevenção e controlo; Profilaxia Pré-Exposição
Keywords: HIV Infections/prevention and control; Pre-Exposure Prophylaxis; Primary Health Care

Caro editor,

O artigo "Profilaxia Pré-Exposição para o Vírus da Imunodeficiência Humana no Currículo Médico em Portugal: Uma Análise Transversal" publicado em abril de 2022, demonstrou a necessidade da inclusão desta temática nos planos formativos das escolas médicas. Entre os 64,6% dos estudantes que admitiram saber o que é, a maioria (75,49%) não identificou corretamente/completamente os grupos elegíveis e apenas 34,44% referiram ter conhecimento do método através de uma aula na faculdade.[1] Como parte integrante da estratégia de prevenção da infeção por VIH, a profilaxia pré-exposição (PrEP) constituiu uma importante medida adicional, com redução efetiva (até 90%) da infeção pelo vírus da imunodeficiência humana (VIH).[2]

A infeção por VIH é o problema de saúde pública com maior expressão global.[3] Durante o ano de 2020, 940 000 pessoas de 83 países receberam PrEP pelo menos uma vez, traduzindo um aumento de 49% comparativamente com o ano anterior.[3] Neste mesmo ano, foram notificados 778 novos casos de infeção em Portugal.[4] Ainda que esta seja uma prática exclusiva do meio hospitalar e que os cuidados de saúde primários (CSP) sejam uma das principais portas de entrada para o sistema de saúde, verificámos que em Portugal não existe nenhum estudo que avalie o conhecimento ou sensibilização ao nível dos CSP.

Apesar da sua implementação no SNS,[1] não existem dados sobre o número de utilizadores ou suas características. Apenas se concluiu que ainda existe um grande hiato entre os beneficiários da PrEP e o total dos que dela necessitam.[4] A falta de acessibilidade a esta terapêutica poderá levar à procura deste método através de um meio informal e potencialmente menos fidedigno (por exemplo a Internet ou contactos sociais) como reportado em alguns estudos.[5] A aposta na descentralização das consultas da PrEP deverá constituir uma prioridade nacional, com vista a potenciar-se a máxima eficácia desta estratégia.[4]

Dado o contexto profissional das autoras, o artigo desperta natural curiosidade e expectativa face à realização de estudos futuros relativos à prática e conhecimento deste método pelos profissionais dos CSP. Congratulamos a iniciativa e originalidade do estudo, visto que os estudantes de hoje serão os médicos de amanhã, e que uma formação sólida e consistente poderá traduzir-se numa prática mais segura e empática. Todos os profissionais de saúde deverão estar sensibilizados para os critérios de elegibilidade da PrEP e para as vias de referenciação para consulta hospitalar, dada a boa aceitabilidade do método e uso cada vez mais frequente.

CONTRIBUTO DOS AUTORES

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Consumo de Bebidas Alcoólicas: Um Problema de Saúde Pública em Portugal

Consumption of Alcoholic Beverages: A Public Health Problem in Portugal

Palavras-chave: Consumo de Bebidas Alcoólicas; Cuidados de Saúde Primários; Saúde Pública
Keywords: Alcohol Drinking; Primary Health Care; Public Health

Caro editor,

Foi com interesse que li o artigo de Coimbra Trigo *et al* sobre o consumo de álcool nos estudantes do ensino superior de Coimbra e o impacto das festas académicas.[1] Trata-se de um tema pertinente e de extrema importância tendo em conta não só os resultados do estudo, que fornecem evidência acerca do consumo excessivo de álcool na população portuguesa, neste caso específico nos estudantes do ensino superior, mas também por revelar dados particularmente inovadores. Este é um assunto que me deixa apreensiva, tendo em conta o consumo cultural de bebidas alcoólicas em Portugal e a sua normalização.

O Relatório Europeu da Organização Mundial de Saúde (OMS) de 2021 mostra que o consumo total de álcool *per capita* em adultos em Portugal é de 12,1 L/ano de álcool puro (aumento de 1,6% em relação a 2015), valor este superior à média europeia (9,5 L/ano de álcool puro).[2]

O *binge drinking* corresponde a um consumo igual ou superior a seis bebidas padrão no homem e a cinco bebidas padrão na mulher numa única ocasião, no espaço de duas horas. Este tipo de consumo é considerado um consumo de risco.[3]

O consumo de risco é definido como um padrão de consumo que, se persistir, pode vir a implicar dano físico ou mental. Trata-se de um padrão de consumo com repercussões em termos de saúde pública apesar de ainda não existir perturbação evidente no consumidor.[4]

A evidência sugere que cerca de 20% dos doentes que utilizam os cuidados de saúde primários (CSP) serão consumidores excessivos.[5]

O AUDIT-C é um método de fácil e rápida utilização, pelo que tem uma extrema importância na deteção precoce e no rastreio de problemas relacionados com o consumo de álcool.[1] A sua utilização em CSP é em muitos casos realizada com menor frequência do que o expectável, apesar de estar incorporado em ferramentas informáticas utilizadas durante a consulta, como no caso do sistema SClinico®. Esta subutilização poderá estar relacionada com tempos diminuídos de consulta, com pouca divulgação desta ferramenta nos CSP e expectativas ou crenças desadequadas dos profissionais de saúde relativamente à sua utilização.

Penso, portanto, que é de enorme importância realizar sessões de educação para a saúde nas instituições de ensino, de saúde e outras, de modo a alertar os jovens, de uma forma mais eficaz e precoce, para os malefícios dos consumos de risco, e reforçar a sensibilização dos profissionais de saúde para a utilização do AUDIT-C. Desta forma, estaremos a mitigar as consequências futuras do consumo excessivo e de risco de bebidas alcoólicas, que constitui um verdadeiro problema de saúde pública em Portugal, não só nos jovens, mas também na população geral

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Thoracic Cancers International COVID-19 Collaboration Registry (TERAVOLT) Results in a Tertiary Care Hospital in Portugal

Neoplasias Torácicas e COVID-19: Resultados do Estudo TERAVOLT na Unidade de Tumores Torácicos do Centro Hospitalar Vila Nova de Gaia / Espinho

Keywords: COVID-19; Lung Neoplasms; SARS-CoV-2
Palavras-chave: COVID-19; Neoplasias Torácicas; SARS-CoV-2

Patients with thoracic malignancies have been reported to be at higher risk of COVID-19 infection and may develop severe disease, with increased mortality.[1-4] The Thoracic Cancers International COVID-19 Collaboration Registry (TERAVOLT) is a global consortium that assesses outcomes in this group of patients.[2] The authors aim to describe the results of TERAVOLT in a Portuguese tertiary care hospital through a retrospective cohort study.

Patients diagnosed with COVID-19 at the Thoracic Tumors Multidisciplinary Unit of the Centro Hospitalar Vila Nova de Gaia/Espinho between the 2nd March 2020 and 8th January 2021 were included. Diagnosis was achieved through SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR). Demographic, clinical, pathological and laboratory data were collected. The present population was studied before COVID-19 vaccines were implemented.

The study included 31 patients. From these, 71% were males (n = 22), with median age of 67 years old. Most had Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 (71%; n = 22). Regarding smoking history, all women were non-smokers and most male patients were active smokers (13%; n = 4) or ex-smokers (48%; n = 15). As for histological type, 74.2% (n = 24) had non-small cell lung carcinoma: 19 adenocarcinomas, four squamous cell carcinomas and one large cell carcinoma. The remainder were two small cell lung carcinomas, two carcinoids, one mesothelioma and two cases of thymic hyperplasia. Disease stage was diverse regarding cancer patients (IV - 63%; III – 18.5%; II – 3.7%; I – 14.8%), and 77.4% (n = 24) presented at least one comorbidity, with hypertension being the most frequent. From the overall number of patients, 59.1% (n = 18) were not receiving any treatment: 10 were under surveillance after finishing radical treatment, while the others had not yet started. Twelve were under palliative systemic therapy and one patient was under chemo/radiation therapy. Most patients presented suggestive symptoms, whilst 29% were asymptomatic (Fig. 1). Thirteen patients were hospitalized (41.9%) although none was admitted to the intensive care unit (ICU). Pneumonia was the most frequent complication.

The mortality rate was 16.1% (n = 5). These patients were not eligible for ICU care.

Compared with the published results of TERAVOLT[1] and of a multicenter Spanish study,[2] there was a lower mortality rate in our population (16.1% *vs* 32% and 32.7% respectively). All deaths occurred in stage IV patients with ECOG PS 2-3, who were diagnosed with COVID-19 during hospitalization due to other reasons. Two of these patients had been recently diagnosed and had not yet started any therapy, while one was receiving supportive palliative care, and the remainder were receiving palliative chemotherapy.

The proportion of asymptomatic patients and lower mortality could be due to mandatory SARS-CoV-2 PCR screening tests performed before treatments and invasive procedures. Telephone visits, less frequent immunotherapy

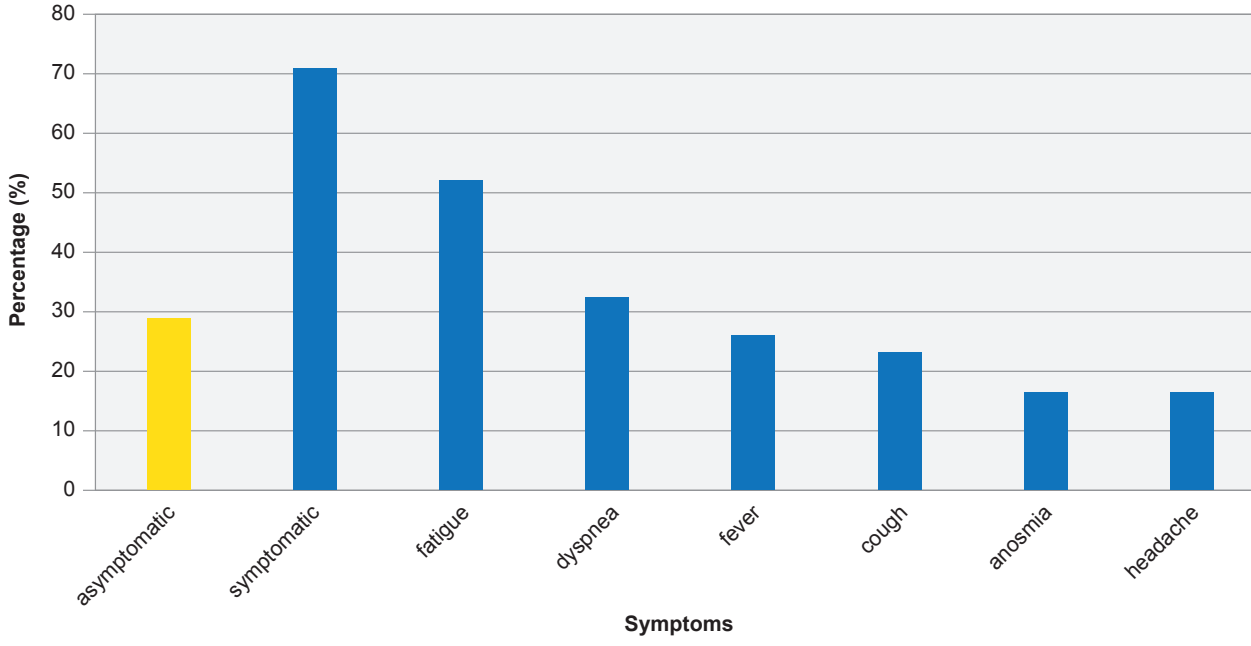

Figure 1 – COVID-19 related symptoms of patients at the Thoracic Tumors Multidisciplinary Unit of the Centro Hospitalar Vila Nova de Gaia/Espinho during the study period

dosing schedules and tyrosine kinase inhibitors administered for a two-month period were measures that were implemented to prevent unnecessary hospital visits. Guidelines on infection control measures and treatment options in this group of patients should be developed. Further outcomes should be considered in future studies.

AUTHORS CONTRIBUTION

RV: Data acquisition. Conception of the work.

ES, DC, MD: Data acquisition.

AB: Data acquisition. Critical review of the work.

COMPETING INTERESTS

DC: Received consulting fees from AstraZeneca, Roche and MSD. Received payment, honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events from AstraZeneca, Roche and MSD. Received payment for expert testimony from MSD. Participates on a Data Safety Monitoring Boars or Advisory Board from AstraZeneca, Roche and MSD. Owns stock or stock options from Teva.

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VIH e o Advento da Imunoterapia no Tratamento do Doente Oncológico: O Caminho é a Inclusão

HIV and the Advent of Immunotherapy in Cancer Treatment: The Path is Inclusion

Palavras-chave: Imunoterapia; Infecções por HIV; Neoplasias
Keywords: HIV Infections; Immunotherapy; Neoplasms

Caros Editores,

Nas últimas quatro décadas, a infeção por VIH passou de uma doença de progressão fatal para uma doença de gestão crónica, mediante adesão sustentada ao tratamento antirretrovírico e ao consequente controlo imunovirológico adequado, acrescida de prevenção e tratamento das doenças associadas e não-associadas ao VIH/SIDA. Talvez sejam poucas as doenças que tenham feito um caminho tão íngreme em tão relativo pouco tempo. É, por isso, uma vitória que estes doentes possam envelhecer. Como corolário, principalmente nos países ditos desenvolvidos, assiste-se pela primeira vez ao fenómeno do doente geriátrico com infeção por VIH.

Como tal, estes doentes acabam por padecer não de doenças oportunistas, mas de outras doenças relacionadas com outros fatores de risco individuais, familiares, ambientais ou relacionados com o envelhecimento. Em infetados por VIH com idades iguais ou superiores a 50 anos, por exemplo, estão referidos aumentos de comorbilidades atribuídas à idade e aos estilos de vida, não-associadas ao VIH/SIDA, mas, também, em consequência da própria infeção vírica, da ativação imunitária persistente, da inflamação crónica e do próprio efeito dos antirretrovíricos. Por isso, a prevalência da doença oncológica não diretamente relacionada com o VIH ou não definidora de SIDA tem crescido, dado que estes doentes terão sempre um risco aumentado de neoplasia em comparação com a população geral.[1,2]

Por outro lado, o arsenal terapêutico disponível para o tratamento oncológico, quer para as neoplasias sólidas, quer para as hematológicas, tem conhecido uma alavancagem significativa, tanto em eficácia como em diversidade, desde a quimioterapia tradicional, à radioterapia, à transplantação de medula óssea, às mais recentes terapias celulares com células T (como as células T com recetor de antigénio quimérico - CAR-T) e à imunoterapia. Principalmente esta última, com os inibidores de *checkpoint* ou a terapêutica molecular dirigida, tem conhecido uma miríade de fármacos aprovados para tratamentos das mais diversas neoplasias.[2-4]

Apesar de vários estudos retrospetivos e prospetivos[2-4] indicarem que as imunoterapias podem ser seguras para as pessoas com infeção por VIH, uma compilação recente[5] de ensaios clínicos registados na base de dados ClinicalTrials.gov concluiu que 72,9% excluíram especificamente esta população nos seus critérios e que uma pequena percentagem (7,3%) admitia doentes com infeção por VIH apenas de forma condicional, de acordo com alguns parâmetros, nomeadamente carga vírica indetetável e contagem mínima de linfócitos T CD4+.[2-5] Sobressaem dúvidas quanto ao grau de imunodeficiência e ao respetivo potencial de resposta, bem como o risco de interações medicamentosas.[2] Contudo, em estudos de vida real, os resultados dos tratamentos nesta população específica não parecem ser piores.[2-4] Arriscamos extrapolar que este mesmo cenário se poderá passar em Portugal.

Assim, e também em jeito de repto, não só os doentes com infeção por VIH devem ser incluídos nos variados ensaios clínicos em curso sobre a utilização de imunoterapia em doentes oncológicos, merecendo uma atenção e gestão de comorbilidade crónica, como, na realidade portuguesa, seria um momento importante para se promover a criação de uma base de dados nacional entre a Associação Portuguesa para o Estudo Clínico do VIH/SIDA e a Sociedade Portuguesa de Oncologia, que no futuro pudesse levar à criação de recomendações conjuntas e a um melhor conhecimento da nossa realidade. Deste modo, beneficiariam os doentes, os profissionais de saúde e a ciência.

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Uso de Antitrombóticos nos Doentes em Fim de Vida

Use of Antithrombotics at the End of Life

Palavras-chave: Anticoagulantes; Cuidados de Fim de Vida; Cuidados Paliativos; Fibrinolíticos; Inibidores da Agregação Plaquetária
Keywords: Anticoagulants; Fibrinolytic Agents; Palliative Care; Platelet Aggregation Inhibitors; Terminal Care

Caro Editor,

Os fármacos antitrombóticos (antiagregantes plaquetários e anticoagulantes) são frequentemente prescritos e mantidos nos doentes em fim de vida como prevenção primária, secundária e terciária.

Em Cuidados Paliativos, um dos principais objetivos é a manutenção do conforto e qualidade de vida dos doentes, pelo que a tomada de decisão no início e/ou manutenção desta terapêutica deve ter em conta que o risco-benefício se altera em função da progressão da doença, da patologia de base, da existência de outras comorbilidades associadas e da preferência do doente e respetiva família.

No estudo de Huisman *et al*[1] foram revistos 180 registos médicos de doentes com esperança média de vida expectável inferior a três meses, que morreram de doença oncológica e não oncológica. Dessa amostra, 60% (n = 108) utilizaram fármacos antitrombóticos nos últimos três meses de vida. Destes, 33,3% morreram no domicílio, 21,3% em unidades de Cuidados Paliativos e 45,4% no hospital. Em 75,9% dos doentes (n = 82), os antitrombóticos foram mantidos até à última semana antes do óbito.[1] Estes dados obrigam-nos a uma reflexão retrospetiva sobre a nossa prática clínica e à revisão de situações e atitudes que experienciamos e em que identificamos potenciais semelhanças, no contexto da manutenção destes fármacos em doentes em fim de vida. Estas atitudes podem estar relacionadas com barreiras desenvolvidas pelos profissionais de saúde, tais como o medo resultante da ausência de estudos de segurança sobre a descontinuação dos fármacos, a inexistência de guias e protocolos de atuação específica desta área, assim como pela complexidade clínica dos casos.

Segundo Romero *et al*,[2] não é aconselhado o uso de anticoagulantes como prevenção primária no fim de vida, e a decisão acerca da sua utilização no tratamento de trombose venosa ou do tromboembolismo dependerá da sintomatologia e prognóstico vital do doente.[2]

Apesar de existirem também algumas ferramentas de apoio à desprescrição, essas ferramentas não especificam alguns destes fármacos, não foram desenvolvidas para utilização nos doentes em fim de vida ou envolvem apenas doentes oncológicos.[3,4]

Assim, este tema deve ser alvo de maior análise pela comunidade científica, levando ao desenvolvimento de mais estudos que considerem a potencial ausência de benefício e riscos associados à utilização destes fármacos e que conduzam a consensos e guias práticos de orientação sobre o seu uso nos doentes com esperança de vida muito limitada, em situação de grande fragilidade e com deterioração física e cognitiva significativas.

Um caso clínico publicado na Acta Médica Portuguesa questiona a necessidade de manutenção da profilaxia do tromboembolismo venoso em doentes terminais.[5] Pretendemos com esta Carta ao Editor lançar uma reflexão mais abrangente, salientando o uso dos antitrombóticos não apenas em doentes com trombose associada ao cancro, mas também na prevenção primária e secundária de eventos cardiovasculares.

É importante salientar que a tomada de decisão não deve ser linear em todos os doentes paliativos, mas ser cautelosa, considerando que estes doentes, sobretudo em fase de fim de vida, têm fragilidades específicas e requerem cuidados diferentes da população que surge na grande maioria dos estudos. Nesse sentido, não devem ser tomadas atitudes estandardizadas.

Devemos manter uma atitude crítica, de forma a promover a discussão e a consciencialização nesta área, sendo também crucial a comunicação com o doente e as famílias, que deverão, sempre que possível, estar envolvidos na decisão final.

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Todos os autores contribuíram de igual forma para o desenho, conceção e revisão do artigo.

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