Operationalisation for Portugal of the EU(7)-PIM List for Identification of Potentially Inappropriate Medicines in Older Adults

Operacionalização para Portugal da Lista EU(7)-PIM para Identificação de Medicamentos Potencialmente Inapropriados nos Idosos

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ABSTRACT
Introduction: In 2015, the EU(7)-PIM List was published, which identifies potentially inappropriate medicines in older patients and resulted from a consensus of experts from seven European countries. Portugal was not part of this group, so it was not originally adapted to the Portuguese reality. With this work, we intend to elaborate a list of potentially inappropriate medicines adapted to the reality of medicines marketed in Portugal, through the operationalization of the EU(7)-PIM List for the national reality and to evaluate the adequacy of its use for clinical practice.
Material and Methods: Search, in INFARMED's Infomed database, of drugs that are included in the EU(7)-PIM List that have marketing authorization, and analysis of possible new drugs for inclusion in the list. The tool adapted to the Portuguese reality was applied to a sample of 1089 outpatient, polymedicated older patients from 38 primary care units in Central Portugal.
Results: The final PIM list adapted to the Portuguese reality includes 184 potentially inappropriate medicines (from these, 178 are active substances, five are classes of drugs, and one corresponds to the sliding scale therapeutic scheme used in insulin therapy). Of 1089 polymedicated older patients, 83.7% took at least one drug included in the final potentially inappropriate medicines list or belonging to one of the groups included in the list, and, on average, each patient took 1.74 (IQR 1 – 2).
Discussion: Even though the availability of drugs on the market is quite diverse, the EU(7)-PIM List has been used in several European countries. With this study, we operationalized the European list for the Portuguese reality, which will enable its application in clinical practice.
Conclusion: The list drawn up is a useful tool for the identification of potentially inappropriate medicines, easy to use in clinical practice and research.
Keywords: Aged; Inappropriate Prescribing; Portugal; Potentially Inappropriate Medication List

RESUMO
Introdução: Em 2015 foi publicada a lista EU(7)-PIM, que identifica medicamentos potencialmente inapropriados na população idosa e resultou de um consenso de peritos de sete países europeus. Portugal não fez parte deste grupo, pelo que na sua origem não foi adaptada para a realidade portuguesa. Com este trabalho pretendemos elaborar uma lista de medicamentos potencialmente inapropriados adaptada à realidade dos medicamentos comercializados em Portugal, através da operacionalização da lista EU(7)-PIM para a realidade nacional, avaliar a adequabilidade do seu uso na prática clínica.
Material e Métodos: Pesquisa, na base de dados Infomed do INFARMED, dos medicamentos incluídos na lista EU(7)-PIM que apresentam autorização de introdução no mercado, e análise de possíveis novos medicamentos para inclusão na lista. A ferramenta adaptada para a realidade Portuguesa foi aplicada a uma amostra de 1089 idosos polimedicados não institucionalizados, utentes de 38 unidades de cuidados de saúde primários da região centro.
Resultados: A lista final adaptada para a realidade portuguesa inclui 184 medicamentos potencialmente inapropriados (dos quais 178 são substâncias ativas, cinco são classes de medicamentos e um corresponde ao esquema terapêutico *sliding scale* usado nas insulinas). Dos 1089 idosos polimedicados, 83,7% tomavam pelo menos um fármaco incluído na lista final de medicamentos potencialmente inapropriados ou pertencente a um dos grupos incluídos na lista e, em média, cada doente tomava 1,74 (IQR 1 – 2).
Discussão: Apesar da disponibilidade de fármacos no mercado ser bastante diversa, a lista EU(7)-PIM tem sido utilizada em vários países europeus. Com este estudo operacionalizamos a lista europeia para a realidade portuguesa, facilitando assim a sua aplicação na prática clínica.
Conclusão: A lista elaborada apresenta-se como uma ferramenta útil para a identificação de medicamentos potencialmente inapropriados, de fácil utilização na prática clínica e em investigação.
Palavras-chave: Idoso; Lista de Medicamentos Potencialmente Inapropriados; Portugal; Prescrição Inapropriada

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INTRODUCTION

World population ageing is a reality of this century. For the first time in history, the number of people aged 65 and older exceeded the number of children under the age of five in 2018 and it is estimated that the number of adolescents and young adults in 2050 will be exceeded by the number of elderly people.[1] The increasing average life expectancy of population is undoubtedly one of the main achievements. However, ensuring that the increasing years of life corresponds to years of health and life quality has emerged as a new challenge.[2]

Ageing is often associated with increasing multimorbidity, with more than half of the elderly population suffering from several pathologies simultaneously, with an impact on quality of life and well-being.[3-5] Therefore, more medication is used by the elderly population than the younger population.[6,7] A recent Portuguese study among the population aged 65 or older, carried out in primary care units, showed that 77% of the participants were simultaneously on more than five medications.[8] On the one hand, the improved access to healthcare and medication, especially for the chronically ill, has contributed to an increase in the average life expectancy of population while, on the other hand, there is a growing concern that many older adults could be taking an inappropriately high number of medications.[7-12]

With the physiological changes related to ageing, different pharmacokinetics and pharmacodynamics of many drugs can be found in the elderly, changing the expected pharmacological response to some medications.[13-16] These changes are associated with the presence of comorbidities and polypharmacy, with an increasing susceptibility to adverse drug reactions and a relevant impact on health and well-being.[13,17] The inappropriate use of medicines in the elderly with multiple diseases is a public health concern due to its impact on morbidity, quality of life and increasing utilisation of health resources.[12,15-18] Potentially inappropriate medications (PIMs) in the elderly include those with a potential risk outweighing the potential benefit, especially when there are more effective alternatives available.[19] The use of PIMs is a public health concern due to the high prevalence rates in different healthcare settings and has been associated with a higher risk of adverse reactions.[20]

Classification criteria have been developed to assess the prevalence of the use of PIM in this population and were aimed at the development of strategies to reduce their use.[20,21] The criteria can be ranked as explicit, implicit or mixed.[21] The explicit criteria include lists of drugs that can be applied with minimal information and clinical judgment, not addressing the individual differences between patients, whereas the implicit criteria consider the patient's therapeutic regimen and are based on the judgment of a health professional, being specific to each patient.[21]

Although there are no national criteria, the operationalisation of Beers' criteria for Portugal was published by Soares *et al.* in 2008.[22] Beers' criteria are an explicit criteria tool developed by the American Geriatrics Society and have been updated several times over the years, the latest

in 2019.[23]

The EU(7)-PIM list was launched in 2015 [an explicit criteria tool developed by experts from seven European countries (Germany, Finland, Estonia, the Netherlands, France, Spain and Sweden) aimed at the identification and comparison of PIM in older people in these countries].[19] The development of the EU(7)-PIM list involved participants (different European experts) in consecutive rounds of a Delphi survey. The final list consists of 282 PIMs, including 275 corresponding to active substances (seven-digit Anatomical Therapeutic Chemical Classification (ATC) code) and seven medication classes (five-digit ATC code), from 55 therapeutic classes and 34 therapeutic groups. Some inclusion criteria have been defined taking into account the dose, time of use or therapeutic scheme. Two drug categories were included: category A including PIMs that should be avoided in the elderly population under any circumstances and category B including active substances that are only considered PIMs in the presence of specific clinical conditions or comorbidities.

Although there are few Portuguese studies on PIM, the published data show the relevance of research in this area. There were no other studies on the use of the EU(7)-PIM list in the Portuguese population. Therefore, the implementation for the Portuguese reality is crucial, taking into account the medicines with national marketing authorisation (MA). This study was aimed at the development of a PIM list adapted to the reality of medicines within the Portuguese market through the implementation of the EU(7)-PIM list for the Portuguese reality and at the assessment of the suitability of its use for the identification of possible PIMs in clinical practice.

MATERIAL AND METHODS

Operationalisation of the EU(7)-PIM list for the Portuguese market

1.1 Search for medicines included in the EU(7)-PIM list and available in the Portuguese market

All the medicines from the EU(7)-PIM list with AIM in Portugal were identified, using the ATC code, by searching the *Infomed* database (the database of INFARMED - *Autoridade Nacional do Medicamento e Produtos de Saúde, IP*).[24] The search was performed in May 2019 and was updated in January 2020.

1.2 Identification of possible PIMs available in the Portuguese market and not included in the EU(7)-PIM list

Medicines with MAs in Portugal and with similar mechanisms of action to those included in the EU(7)-PIM list, which not included there were searched for and then checked on whether these had MA in any of the seven participant countries in the development of the EU(7)-PIM list, based on the official databases of the regulatory agencies in each country. The information was discussed among the researchers and whenever no consensus was reached, this

was validated by a third researcher.

2. Assessment of the applicability of the EU(7)-PIM list to the Portuguese reality

The PIM list for the Portuguese reality was applied to a sample of 1,089 elderly patients, whose medicine consumption data came from the previously developed MedElderly project [SAICT-POL/23585/2016] [non institutionalised patients aged 65-99 attending primary care clinics.[25] The project obtained a favourable opinion from the Ethics Committee of the Central Regional Health Administration [*Administração Regional de Saúde do Centro*) (Report no. 105/2017) and was approved by the National Data Protection Commission (Authorisation no. 13028/ 2017). Data collection on the medicines used by the elderly population took place between April and August 2019 in 38 primary healthcare clinics within the Central region of Portugal.

Table 1 – Active substances available in the Portuguese market, included in the medicine classes considered as PIM

ATC Code	Potentially inappropriate medications (INNs)
A02AB	**Antacids aluminium compounds**
A02AB01	Aluminium hydroxide
A02AB03	Aluminium phosphate
A02AB04	Aluminium and sodium di-hydroxide carbonate
A02AD	**Combinations and complexes of Al, Ca and Mg**
A02AD02	Magaldrate
A02BC	**Proton pump inhibitors**
A02BC01	Omeprazole
A02BC02	Pantoprazole
A02BC03	Lansoprazole
A02BC04	Rabeprazole
A02BC05	Esomeprazole
A02BC06	Dexlansoprazole
B03AA	**Iron bivalent, oral preparations**
B03AA03	Ferrous gluconate
B03AA07	Ferrous sulfate
G03C	**Oestrogen**
G03CA03	Estradiol
G03CC07	Bazedoxifen + conjugate oestrogen
G03CX01	Tibolone
N02CC	**Selective serotonin (5HT1) agonists**
N02CC01	Sumatriptan
N02CC02	Naratriptan
N02CC03	Zolmitriptan
N02CC04	Rizatriptan
N02CC05	Almotriptan
N02CC06	Eletriptan
N02CC07	Frovatriptan

RESULTS

1. Operationalisation of the EU(7)-PIM list for the Portuguese reality

Out of the 275 active substances in the EU(7)-PIM list, 173 are available in Portugal. The seven drug classes in the EU(7)-PIM list include a total of 59 active substances in the ATC classification, 22 of which are available in Portugal (Table 1). Quinine and derivatives (M09AA) drug class does not include medicines with MA in Portugal.

A total of 111 active substances were identified as possible PIMs to be added to the 173 with MA in Portugal that were on the initial list, as they present similar mechanisms of action. Only seven of these 111 active substances had no MA in at least one of the participants countries included in the development of the EU(7)-PIM list. From the final round of evaluation, only five active substances remained as new PIMs to be added to the EU(7)-PIM List (Table 2).

The final PIM list adapted for the Portuguese reality includes 184 PIMs, of which 178 correspond to active substances (seven-digit ATC code), five are drug classes (four-or five-digit ATC code) and one corresponds to sliding scale insulin therapy. A comprehensive table of PIM with justification for classification as PIM, as well as a proposal of therapeutic alternatives for each case, is shown in Appendix 1 (see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13618/Apendice_01.pdf); 47 therapeutic classes (four-digit ATC code) and 30 therapeutic groups (three-digit ATC code) are included in this list.

According to the ATC classification, group N - nervous system (n = 72), group C - cardiovascular system (n = 29), A - digestive system, insulins, antidiabetics and glucagon (including insulins in sliding scale therapeutic scheme) (n = 28) were the anatomical groups with the highest number of PIM.

2. Assessment of the applicability of the EU(7)-PIM list to the Portuguese reality

Out of the 1,089 study participants, 83.7% were at least on one active substance included in the final list of PIM and, on average, each patient took 1.74 possible PIM (IQR 1 - 2). It is worth mentioning that 43.9% of our group of patients took at least one medicine included in the proton pump inhibitors (PPIs) group, 35.9% took at least one benzodiazepine included in the PIM list and 14.4% were on alprazolam. The 10 drugs that are possibly the most prevalent PIMs in the study sample are shown in Fig. 1.

DISCUSSION

A list of explicit criteria, divided into three categories, was obtained from the operationalisation of the EU(7)-PIM list for the Portuguese reality: (i) active substances (seven-digit ATC code) with 178 PIMs, (ii) drug classes (four or five-digit ATC code) with five PIM and (iii) sliding scale insulin therapy, identified as a PIM. This tool, published in Portuguese and adapted to the Portuguese market, was aimed at health professionals and research studies, allowing for the

Table 2 – Active substances classified as new PIM to be added to the EU(7)-PIM

ATC code	New potentially inappropriate medication (INN)	Reason for inclusion as PIM	Dose adjustment / special considerations	Alternative therapy/medicine
J01MA17	Prulifloxacin[a,b]	Half-life time could be extended with high serum concentrations in elderly patients; increase risk of *torsade de pointes* and tendinitis or tendon rupture.	Increased risk of aortic aneurysm and dissection with the use of fluroquinolones, particularly in the elderly population. Tendinitis, which is rarely associated with the use of quinolones, may occasionally lead to rupture, mainly involving the Achilles tendon. Elderly patients are more prone to tendinitis. Elderly and female patients may be more sensitive to medicines related to QT interval prolongation.	Other antibiotics, according to susceptibility and resistance tests.
M01AB08	Etodolac[b]	High risk of potentially fatal gastrointestinal bleeding, ulceration or perforation.	Elderly patients have a higher frequency of adverse reactions with NSAIDs, mainly potentially fatal gastrointestinal bleeding and perforation.	Acetaminophen; ibuprofen (≤ 3 x 400 mg/d or for less than one week); naproxen (≤ 2 x 250 mg/d or for less than one week). Opioids involve a lower risk of delirium (e.g. naloxone, morphine, oxycodone, buprenorphine, hydromorphone).
M01AX17	Nimesulide[c]	High risk of hepatotoxicity. No therapeutic advantage or improved gastrointestinal safety compared with other NSAIDs, while exposing patients to an increased risk of fatal liver disorders.	Nimesulide is associated with a slightly increased risk of hepatotoxicity, increasing with time of exposure and dosage. It is recommended a restriction of its use to the treatment of acute pain, symptomatic treatment of painful osteoarthritis and primary dysmenorrhoea.	Acetaminophen; ibuprofen (≤ 3 x 400 mg/d or for less than one week); naproxen (≤ 2 x 250 mg/d or for less than one week). Opioids involve a lower risk of delirium (e.g. naloxone, morphine, oxycodone, buprenorphine, hydromorphone).
N05BA22	Cloxazolam[b]	Risk of falling, with hip fracture; prolonged reaction times; psychiatric reactions (paradoxical, e.g. agitation, irritability, hallucinations, psychosis); cognitive impairment; depression.	Dose reduction is recommended in elderly patients. Psychiatric and paradoxical reactions occur more frequently or more severely in elderly patients, who are more susceptible to the effect of benzodiazepines, as regards falls and hip fractures.	Non-pharmacological treatment; low doses of short-acting benzodiazepines (≤ 0.5 mg/day), brotizolam (≤ 0.125 mg/day); antidepressants with anxiolytic profile (SSRIs). If used as hypnotic/sedative: zolpidem (≤ 5 mg/d), zopiclone (≤ 3.75 mg/d); trazodone.
N06BX02	Pyritinol[d]	No proven efficacy; poor benefit-risk balance.	Clinical use is not recommended.	Non-pharmacological treatment; consider pharmacotherapy for Alzheimer's disease: acetylcholinesterase inhibitors, memantine.

a Pasternak B, Inghammar M, Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: Nationwide cohort study. *BMJ* 2018.360:k678.
b INFARMED. Infomed: Resumo das Características do Medicamento. [consultado 2020 fev 03]. Disponível em: https://extranet.infarmed.pt/INFOMED-fo/index.xhtml.
c Donati M, Conforti A, Lenti MC, Capuano A, Bortolami O, Motola D, *et al.* Risk of acute and serious liver injury associated to nimesulide and other NSAIDs: data from drug-induced liver injury case–control study in Italy. Br J Clin Pharmacol. 2016;82:238-248.
d INFARMED. Prontuário Terapêutico Online. [consultado 2020 fev 03]. Available at: https://app10.infarmed.pt/prontuario/index.php

comparison with studies and populations from other European countries using the same criteria. It is worth mentioning that a high number (around 39.7%) of PIM on the operationalised list include drugs associated with effects on the nervous system, most probably due to their anticholinergic properties, leading to dizziness, difficulty in concentration, loss of memory, confusion, cognitive function impairment, delirium and balance disorders in the elderly.[13,26,27]

Different market availabilities of active substances have been found throughout the different European countries and therefore different lists of MA can be found depending on the reality of each country. A recent study assessed the availability of medicines included as PIM in the EU(7)-PIM list and showed that the number of medicines with MA, listed as PIM, is quite different in each country, ranging from 42.8% in Serbia to 71.4% in Spain.[28] In a Belgian study,[29] the authors showed that out of 275 active substances included in the original list, only 157 were available on the market. Within the seven drug classes, 21 active substances were available in the Belgian market. In the same study, the authors reached the conclusion that the prevalence of PIM was 72.8% according to the operationalised list. In our study, we found that 83.7% of the participants took at least one medicine included in the operationalised list for the Portuguese reality. However, in some cases, no PIM could have been described, as data on the period of administration of the drugs were not available. Although 43.9% of the participants were taking PPIs, we could not conclude that they were taking a PIM, as the period of administration could be less than eight weeks. However, recent studies have shown that PPIs are overused and that 25% to 70% of prescriptions have no indication for use.[30] Indications for use as chronic therapy include[31]: (i) gastro-oesophageal

reflux disease (GERD) with esophagitis, (ii) GERD without esophagitis but with persistent symptoms, (iii) Barrett's oesophagus; (iv) peptic ulcer with recurrent episodes and (v) Zollinger-Ellison syndrome. A recent meta-analysis[32] has reached the conclusion that, although the use of PPIs has short-term therapeutic benefits, their long-term use is associated with adverse events that can be potentially severe. In the different studies included in this meta-analysis the possible association between the use of PPIs and chronic kidney disease, pneumonia, cancer, dementia, fracture, anaemia, hypomagnesemia and cardiac disorders was reported. Thus, in the elderly population, an increasing careful monitoring of the prescription of PPIs and their use as a chronic therapy is even more relevant, due to the increasing risk of potentially serious adverse events.

The EU(7)-PIM list has been used as a tool to search for PIMs in some European studies. In Finland, 73% of elderly patients took at least one PIM.[36] In Northern Sweden, a study of medical records of elderly patients found that 40.9% of patients were prescribed with at least one PIM according to the EU(7)-PIM list.[37] In Lithuania 57.2% of PIMs were found and the authors found that only 45% of medicines listed on the EU(7)-PIM list were available on the market.[38]

In Portugal, there are no previous studies on the assessment of the prevalence of PIM using the EU(7)-PIM list. However, in a recent study using the Beers 2015 criteria, it was found that 68.6% of the elderly included in the sample were taking at least one PIM and that 46.1% were taking more than two.[8] Other Portuguese studies found a 75.4% prevalence of PIM in institutionalised elderly patients, applying the STOPP (Screening Tool of Older Person's Prescriptions) criteria[33] and that in primary healthcare, using
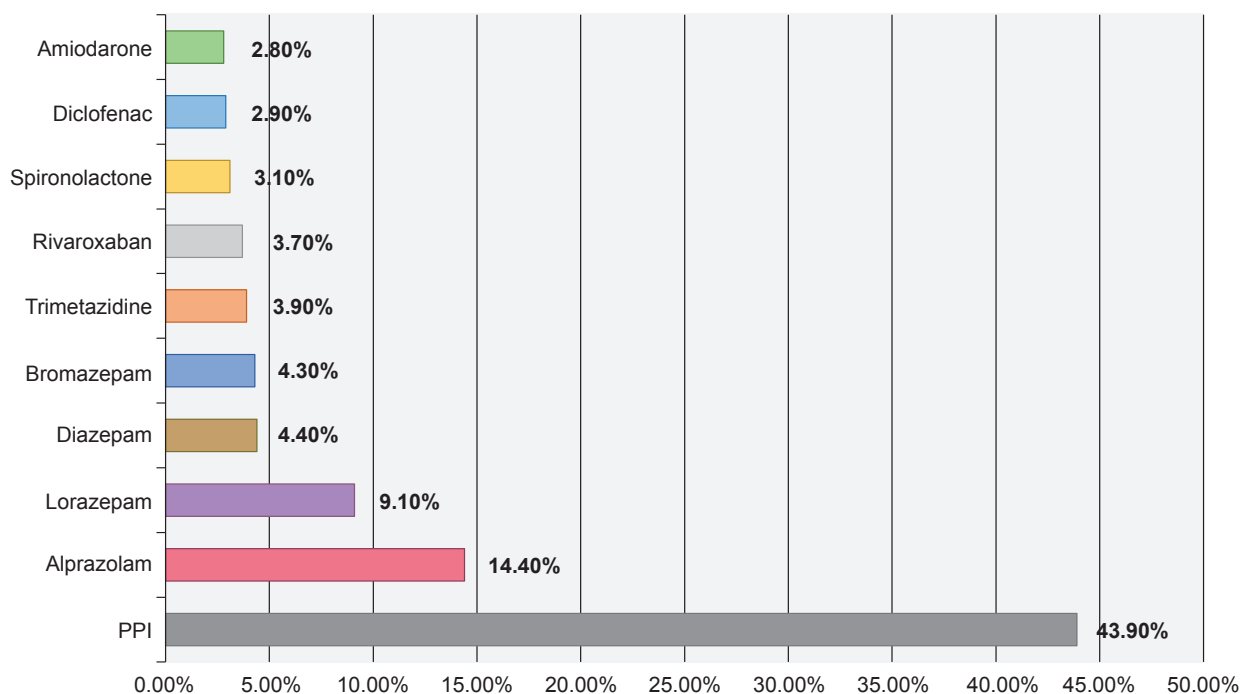

Figure 1 – Possible PIM that are more prevalent in our group of patients

2012 Beers' criteria, a 37% prevalence of PIM was found.[34] A 27.7% and 38.5% prevalence rate was found in an older study, carried out in community pharmacies, using 1997 and 2003 Beers' criteria, respectively.[35]

In PIM prevalence studies comparing results obtained by using different tools, it has been found a higher number of PIM with the application of the EU(7)-PIM list.[39-42]

The use of common criteria between countries, but with the operationalisation for the reality of each country, allows the development of a crucial tool that may help healthcare professionals in their clinical practice, ensuring an increased safety and therapeutic efficacy. Furthermore, this type of tool is also relevant in research studies, enabling comparisons between countries. The table in the appendix (see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13618/Apendice_01.pdf), with the operationalisation of the EU(7)-PIM list, is a tool available in Portuguese that may be used by all professionals and researchers for epidemiological studies in Portugal.

The sample used to assess the applicability of the operationalised list was an important limitation of this study, due to the fact that it is a non-random sample from a specific region of Portugal, not allowing for the extrapolation of the results to other regions. On the other hand, the available data did not allow for the application of all criteria. However, the assessment of the prevalence of PIM in Portugal was not the main purpose of the study and rather to provide a useful tool for its identification and to reach the conclusion that it is an easy tool to be used in clinical practice and research.

CONCLUSION

The exposure of the elderly population to PIM medicines is a reality, showing a high consumption of medicines mainly from the PPIs and benzodiazepine groups. The use of PIM identification tools, with information on therapeutic alternatives during clinical practice will certainly become relevant in the prescription decision and could contribute to discourage the prescription of some of these drugs, according to the guidelines of the Directorate-General for Health.

This study was based on a comprehensive analysis of the MAs of all medicines ranked as PIM by the EU(7)-PIM list, in order to best match the operationalisation adapted to the national reality and is therefore a useful tool for health professionals. The integration of this list, adapted to the Portuguese reality, into clinical decision support systems will be an important tool to support prescribing decisions in the elderly population and to improve healthcare safety.

HUMAN AND ANIMAL PROTECTION

The authors declare that this project complied with the regulations that were established by the Ethics and Clinical Research Committee, according to the 2013 update of the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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