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Conselho Científico

A Transição de Serviços de Saúde de Crianças e Jovens para Serviços de Saúde de Adultos: Uma Realidade com Impacto no Prognóstico

The Transition of Children and Adolescent Healthcare Services to Adult Healthcare Services: A Reality with Impact on Prognosis

José SALGADO✉[1]

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Palavras-chave: Acesso aos Serviços de Saúde; Adolescente; Criança; Encaminhamento e Consulta
Keywords: Adolescent; Child; Health Services Accessibility; Transition to Adult Care

Aos 18 anos, as pessoas com patologias de evolução prolongada mudam do serviço que os acompanhavam, por vezes desde há muito tempo, para um novo serviço. Esta mudança ou transição, parecendo trivial, tem um impacto significativo no curso da doença, sendo importante haver um plano consistente para a fazer.[1]

Todavia, constata-se que uma boa transição é rara mesmo em sistemas de saúde bem organizados, dado que este processo deve ser intencional e planeado, considerando as necessidades médicas, psicossociais e educacionais / vocacionais de adolescentes e jovens adultos com doenças crónicas de qualquer tipo.

Este processo torna-se complexo porque envolve geralmente jovens com doenças crónicas que sabem que a doença fará parte das suas vidas para sempre.[2]

Podem assim reagir com raiva, tristeza ou negação, embora a maioria aprenda a conviver com isso, se o processo for conduzido adequadamente.

Nos Estados Unidos, cerca de 750 000 jovens com "necessidades de saúde especiais" distintas, (por exemplo, diabetes, transplantes, doenças cardíacas, psiquiátricas, reumatológicas, hepáticas e oncológicas, entre outras), transitam anualmente para serviços de adultos porque completam 18 anos, mas só menos de metade têm acesso a serviços e apoios adequados nesta passagem.[3]

Esta mudança pode ser feita numa lógica de transferência ou de transição.

Transferência implica o encerramento de cuidados no serviço pediátrico e o início de cuidados no serviço de adultos, enquanto que a transição é um processo desenvolvido com propósitos terapêuticos.[4] Na primeira situação o jovem chega aos 18 anos e passa para um serviço de adultos, por vezes com um relatório para entregar no novo serviço ou apenas com alta para o Médico de Família. Não existe qualquer comunicação direta entre os dois serviços ou os médicos envolvidos. Na transição, a passagem de um serviço para outro é assumida pelos dois serviços em articulação, com preparação de uma estratégia conjunta para que não haja rotura na continuidade de cuidados. Esta estratégia será mais consistente, se incluir um período de consultas com a participação de médicos dos dois serviços envolvidos (Fig. 1).

Considerar que os dois conceitos são semelhantes, sendo a transferência uma versão menor da transição, produz resultados com impacto negativo.[5]

As dificuldades que persistem nesse processo, na maioria das especialidades médicas,[3] demonstram que devemos prestar maior atenção à transição, para que não constitua um entrave na continuidade de cuidados, por roturas, hiatos ou interrupções no tratamento.

A transição/processo terapêutico deve incluir a preparação da pessoa envolvida, um período de atendimento conjunto, reuniões de planeamento e partilha de informações clínicas, e ser entendido como um processo de continuidade de cuidados.[4]

Um mau planeamento e implentação deste processo, , pode levar a que jovens de 16 a 20 anos não recebam os cuidados apropriados, e como tal, deixem de estar apoiados por uma rede de cuidados.

McDonagh e Viner[6] apontaram várias dificuldades que surgem na transição, tais como: falta de treino dos profissionais envolvidos, dificuldades na obtenção dos recursos necessários, má coordenação entre as organizações de saúde e falta de apoio institucional, de planeamento e de especialistas com experiência.

O estabelecimento de normas de orientação clínica que diminuam o impacto da transição influencia positivamente o prognóstico da doença. Devemos avaliar os programas / processos de transição e seu impacto numa base contínua.[7]

Estas normas de orientação clínica podem incluir equipas de transição autónomas dentro do sistema de saúde[2] e uma abordagem multidisciplinar com envolvimento do paciente e pessoas significativas. A avaliação deve incluir outros parâmetros além da idade, produzindo uma transição partilhada, maior cooperação entre os serviços e en-

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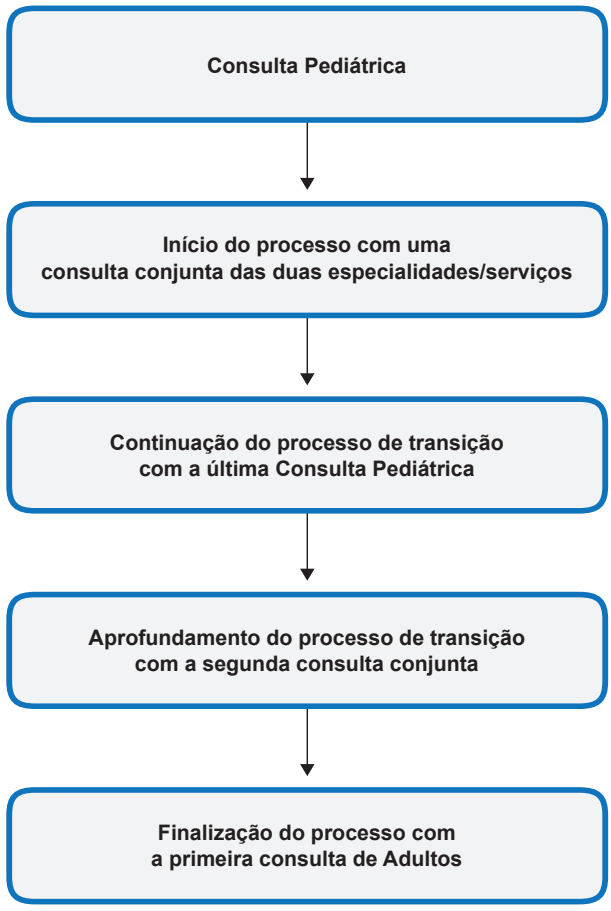

Figura 1 – Fluxograma de colaboração entre serviços no processo de transição

volvimento de profissionais de saúde pediátrica e adulta. É frequente os jovens terem alta dos serviços pediátricos e é o Médico de Família que articula e concretiza a passagem para os serviços de adultos.

Nas últimas décadas, o debate sobre as melhores estratégias para uma transição mais eficiente tem aumentado, mas os resultados não conseguiram superar problemas como a dificuldade de comunicação entre os serviços e a rígida barreira dos 18 anos.

Mesmo quando existem protocolos de transição, o resultado do processo é muitas vezes insatisfatório.[8] Contudo, isso não diminui a sua importância antes reafirma a necessidade de aperfeiçoamento, porque planeamento e operacionalização são elementos essenciais na organização e prestação dos serviços de saúde.

O estudo TRACK[8] analisou as transições em Saúde Mental na região de Londres, envolvendo jovens na 'idade de transição', com patologia psiquiátrica. Os autores concluíram que menos de 10% fizeram uma transição adequada. Noutras especialidades, embora a taxa de sucesso seja maior, geralmente não chega aos 50%,[3] isto é, mais de metade sofre um impacto negativo para a sua doença nessa fase da vida.

É redutor pensar que a transição é um processo que deve ser realizado porque o doente chegou à maioridade, independentemente das condições para tal passagem de testemunho[9] (cooperação entre os serviços, proximidade geográfica e colaboração da família, etc.).

Como tal, o doente não deve mudar de serviço porque tem 18 anos, mas porque tem condições para o fazer, num processo que pode começar aos 16 ou aos 20, e considerando: maturidade da personalidade, gravidade e consciência da doença e consistência do suporte familiar e social, e capacidade dos serviços pediátricos e de adultos para se envolverem no processo de transição (reconhecendo a vantagem de estratégias de comunicação assertivas e/ou desenvolvendo protocolos para essa mudança).

Existem resistências que podem assumir contornos diversos, tanto por parte dos serviços de adolescentes como de adultos quando a fronteira dos 18 não é rigorosamente cumprida. Antes dos 18, os serviços de adolescentes consideram que são mais capazes de manter o acompanhamento, enquanto que os segundos consideram que não têm experiência suficiente em lidar com adolescentes, podendo ser perigoso para o jovem por não estarem preparados para lidar com esta faixa etária.[10]

Quando atingem a idade adulta, os serviços de adolescentes podem ter relutância em largar os pacientes pelo receio de estes não tolerarem a rotura dos laços terapêuticos estabelecidos e os serviços de adultos pensam que a intervenção deve ser diferente da que tem sido seguida até então. Podem não acautelar, quer uns quer outros, que a abordagem terapêutica evolua com o crescimento do doente, sem solavancos.

Se os serviços funcionarem em continuidade de cuidados, com um mínimo de perturbações, reduz-se o número de jovens que se perdem nesta transição,[7] e dessa forma o processo será mais pacífico, de acordo com a pessoa específica e não com a idade.

Um compromisso flexível sem perder rigor, poderá traduzir-se num protocolo de seguimento partilhado pelas duas equipas/especialidades não inferior a seis meses, como mostra o fluxograma (Fig. 1), mas não devendo ultrapassar um ano para não se perpetuar. O número de consultas partilhadas poderia variar, dependendo da avaliação conjunta, caso a caso.

Assim, poderia haver uma transição progressiva e 'obrigatória' de uma especialidade para outra, agilizando a comunicação entre equipas e conduzindo ao estabelecimento de pontes. O paciente e sua família não se sentiriam desapoiados pelo serviço que conhecem e seria mais fácil entrar no novo serviço.

Embora possa haver alguma subjetividade no processo de transição,[4] a simples transferência comporta mais riscos, porque não sabemos como será a chegada do jovem ao novo serviço.

Acreditamos que um processo de transição, discutido e organizado em colaboração, não é a única forma de passar de um serviço pediátrico para um de adultos, mas será aquela que trará maiores benefícios para os pacientes e para a dinâmica dos serviços envolvidos.

CONFLITOS DE INTERESSE

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ARTIGO ORIGINAL

Colorectal Screening Program in Northern Portugal: First Findings

Programa de Rastreio de Cancro Colo-Rectal no Norte de Portugal: Primeiros Resultados

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ABSTRACT

Introduction: In Portugal, a colorectal cancer screening program based on faecal immunochemical test followed by colonoscopy was shown to be cost-effective for individuals between 50 and 74 years old. We report the first findings of the implementation of a population-based program In Northern Portugal.

Material and Methods: In the pilot phase, eligible subjects were allocated either to a direct mailing invitation or to primary care centers. In the first year of program implementation, we assessed the uptake rate, the faecal immunochemical test -positivity rate, the diagnostic yield of advanced neoplasia, and the quality parameters for post-faecal immunochemical test + colonoscopy.

Results: We invited 100 501 eligible subjects (49% male with a median age of 55 years). Of these, 5228 participated in the pilot phase and 95 273 participated in the first year of the program. In the first year of the program, the adherence was 29%, with a positivity rate of 5% and a 60% compliance to colonoscopy. The faecal immunochemical test-detection rate of advanced neoplasia was 0.35/1000 subjects, and the positive predictive value at post- faecal immunochemical test + colonoscopy was 44% and 2% for advanced adenoma and invasive cancer, respectively. No major adverse events were reported after colonoscopy.

Conclusion: A centralized invitation system based on direct mailing was feasible and both colonoscopy quality and diagnostic yield were adequate antecipating the success of the programme.

Keywords: Colonoscopy; Colorectal Neoplasms; Early Detection of Cancer; Mass Screening; Occult Blood; Portugal

RESUMO

Introdução: Em Portugal, foi demonstrado que o rastreio do cancro colo-rectal, baseado no teste imunoquímico fecal seguido de colonoscopia, seria custo-efetivo para indivíduos entre os 50 e 74 anos. Neste artigo reportamos os primeiros resultados da implementação do programa de base populacional na região Norte de Portugal.

Material e Métodos: Na fase piloto, os sujeitos elegíveis foram alocados a dois métodos, por convite através do correio ou por meio de entrega direta nos centros de saúde. No primeiro ano de implementação do programa avaliámos a taxa de adesão, a taxa de positividade de teste imunoquímico fecal, o rendimento diagnóstico de neoplasia avançada e os parâmetros de qualidade da colonoscopia pós- teste imunoquímico fecal positivo.

Resultados: Foram convidados 100 501 indivíduos elegíveis (49% do sexo masculino com idade mediana de 55 anos). Destes, 5228 participaram na fase piloto e 95 273 participaram no primeiro ano do programa. No primeiro ano do programa, a adesão foi de 29%, com taxa de positividade de 5% e adesão de 60% às colonoscopias. A taxa de deteção de teste imunoquímico fecal de neoplasia avançada foi de 0,35/1000 indivíduos, e o valor preditivo positivo na colonoscopia pós-teste imunoquímico fecal positivo foi de 44% e 2% para adenoma avançado e cancro invasivo, respetivamente. Não foi relatado nenhum evento adverso após colonoscopia.

Conclusão: Um sistema de convite centralizado foi viável, a qualidade das colonoscopias realizadas e o rendimento diagnóstico adequados antecipando o sucesso do programa.

Palavras-chave: Colonoscopia; Detecção Precoce de Cancro; Neoplasias Colorrectais; Portugal; Programas de Rastreio; Sangue Oculto

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide, accounting for one out of 10 cancer cases and deaths in the world.[1] In Portugal, approximately 30 new CRC cases are diagnosed every day, representing the most common type of cancer and the main oncological cause of premature death in individuals between 50 and 74 years old.[2,3] Moreover, survival of CRC is as low as 58% at five years.[4]

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Colorectal Cancer Screening should be a population-based organized screening program aimed at covering all eligible individuals, regardless of gender, from the 50 - 74 years of age cohort.[5-7] Two main strategies, namely Fecal Immunochemical test (FIT) with post-FIT+ colonoscopy and primary screening colonoscopy, are currently used in different countries. In particular, FIT has shown superior accuracy and acceptability when compared with previous guaiac-based faecal tests.[8,9] In Portugal, a Markov cost-utility analysis comparing biennial FIT *versus* primary screening colonoscopy every 10 years showed the higher cost-effective profile of the former option.[10]

The Northern Portugal Regional Health Administration (ARSN) recommended a systematic approach while implementing a CRC screening program.[11] A team was created to coordinate the screening program, centralized at ARSN, and targeting the 1 100 000 inhabitants aged between 50 and 74 years old. In December 2016, ARSN launched a pilot-program aimed at to comparing two different methodologies for invitation, i.e. centralized invitation based on direct mailing *versus* capillary invitation through organized visits to Primary Care Centers (PCC). Early in 2018, the program was expanded to the regional level.

Our aim is to report the results of the pilot program and of the first year of regional implementation concerning adherence and detection rate of advanced neoplasia, as well as to assess the quality of post-FIT+ colonoscopy and surveillance.

MATERIAL AND METHODS

Coordination team and organizational strategy

A coordination team of healthcare professionals was created to implement a CRC screening program. This team concentrated all executive decisions and was responsible for the monitoring and evaluation of the program. Briefly, a centralized information system [System for Monitoring and Evaluation of Health Programs, (SiiMA)] managed all the relevant outcomes, including adherence rate to FIT and post-FIT+ colonoscopy invitations, diagnostic yield for advanced neoplasia, and quality assessment. SiiMA was also linked to the national health databases for invitation of the population, to PCC, and to electronic health records through the endoscopic units. All FIT were performed in the same laboratory with a cut-off of 100 ng/ml (equivalent to 20 µ/gr),[12] (OC-Auto Sampling 3 Eiken Chemical Co., Ltd.). Finally, all individuals eligible for screening were included in this screening and both FIT and colonoscopy were offered free of charge.

Pilot program

In December 2016, the *pilot-program* was aimed at testing the uptake rate of two different invitation strategies for FIT (Fig. 1). For that, each method was applied in two different areas:

- Method A with a direct invitation and FIT test sent to citizen by regular mail. Individuals were first presented with an awareness letter, inviting, and informing about the importance of screening and what would happen next. All individuals could self-exclude themselves from the screening program by calling or emailing the coordination team. A few days later, a second letter was sent with the FIT, explaining how to do the test and where to deliver it. A third letter was sent to promote delivery of the kit to those who had not yet delivered the FIT at their PCC. In this case, the endoscopic unit was 30 km away from the unit.

- Method B where the relationship between the individuals and their health team was explored. Briefly, Portuguese PCC are organized as 'health teams' where all healthcare professionals align their actions in order to treat every patient within a certain 'list' of patients. In this case, after the invitation letter, the FIT was delivered by a nurse. Finally, for those accepting, they would deliver the FIT at the physical space of the primary care centers (a specific box was designed for this pilot and placed at the entrance of the primary care centers) and were transported to a regional laboratory to be analyzed. In this case, the endoscopic unit was close to the inhabitants' residence.

Each method (A and B) was tested in specific areas and colonoscopies performed in two different centers (colonoscopy center 1 and 2, respectively). Both centers were public hospitals and also provided the histopathological assessment and the post-colonoscopy and diagnosis care if needed (endoscopic and/or surgery).

The inclusion criteria considered all individuals between 50 and 74 years of age, a residence registry with a match to a local primary care center inside the Northern Regional Health Administration (ARSN) catchment area, no previous family history of gastrointestinal diseases, no previous personal history of gastrointestinal diseases (identified through a search in the ARSN patient records using International Classification of Primary Care two (ICPC-2) codes) and no previous colonoscopy done in the last 10 years prior to the pilot-screening project (identified through a search in the national database).

The Portuguese National Health Service (SNS) has a centralized information system, and most citizens have an electronic health record run by the Ministry of Health. Also, most colonoscopies are paid by the NHS and there is, consequently, a registry of when the individuals had a colonoscopy.

The two colonoscopy centers used the digital platform for relevant clinical data registry. Information about colon or/and rectum lesions were introduced by the gastroenterologist responsible for the endoscopic procedure (morphology and other histopathological data included).

First year of FIT program at regional level

In 2018, the program was expanded, corresponding to an estimated number of 250 000 eligible patients to consider for invitation in the first year. In order to find the eligible patients, we performed a linkage process with the electronic health records of individuals, according to certain inclusion criteria, and close to 1 100 000 individuals were selected. Due to estimated operational challenges, the population

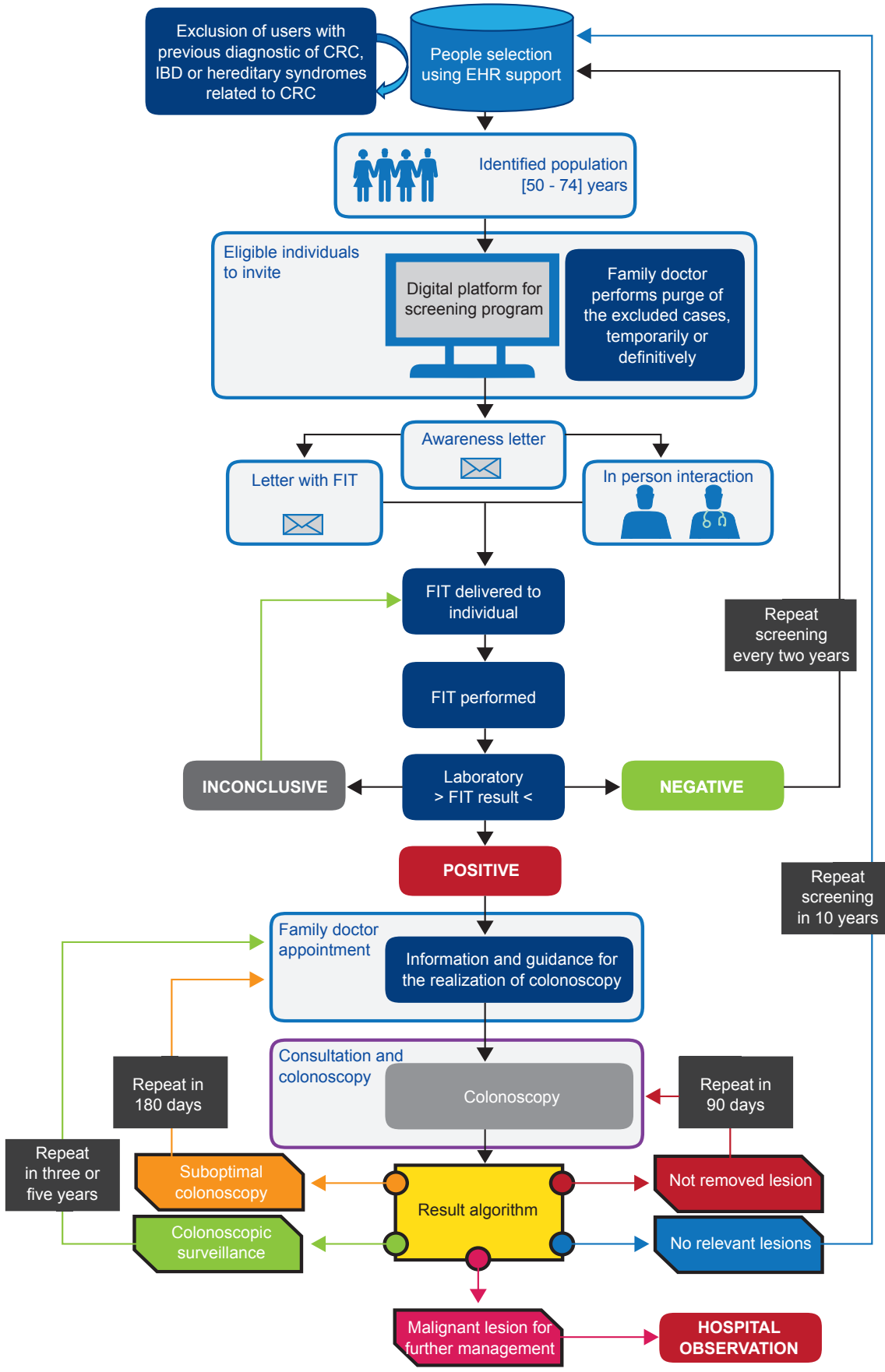

Figure 1 – Algorithm for the pilot study. After assessment the invitation by letter was decided.

was divided in half for a two-year period of screening. After that period, all individuals were estimated to have been invited to the program and had the chance to participate. Therefore, a cycle would end, and a new cycle of selection would start. The workflow was kept according to the pilot program and opportunities for improvement were considered during the regional implementation. The coordination team decided that two mail letters should be sent, the first to invite for screening and a second one delivering the FIT test, including instructions on how to proceed. All FITs were taken to a central regional laboratory (ARSN, Regional Laboratory of Public Health) where all analysis was centered, and results published in the same digital platform. Results were automatically available to the Primary Care physicians of the individuals participating. Moreover, the closest public hospitals to the inhabitants' residence were used.

The main outcomes of FIT and post-FIT+ colonoscopy were collected, including various relevant operational variables (like refusal for colonoscopy orientation – positive cases, time values for laboratory reception and publication of results and time values for different appointment phases before and post hospital referral). In this paper we present the results of data from individuals that were invited up to June 2019 – meaning that only individuals below 70 years of age were selected. The exclusion criteria for invitation would be previous endoscopic procedures (colonoscopy in the past 10 years or sigmoidoscopy in the past five years) or surveillance due to familiar syndromes or inflammatory bowel disease (IBD).

Analysis was based on databases without any identification of specific individual data thus not requiring specific ethics committee approval.

Statistical analysis

Statistical analysis involved simple descriptive results regarding general traits of the individuals invited to participate and their results in key moments of the screening workflow. The results presented here focus on key metrics relevant for the screening project: participation rates, positive FIT rates, primary care consultation and management of positive cases, Hospital center response to referrals, adenoma detection rates after colonoscopy and neoplasm detection rates.[13] The chi-square test was performed to compare different main variables related to the screening process in relation to method A and B (p-value < 0.05) - rejecting the null-hypothesis suggests there is a difference between groups. We also performed a simple trend analysis to compare different key operational processes, between key moments of the screening program. The positive predictive value (PPV) determined for this study provided the probability that subjects with a positive screening test truly have the disease or certain stages of disease once detected. In practice, PPV is a key performance indicator for screening programs, in particular the FIT test use, because sensitivity and specificity cannot be derived without every patient going through a colonoscopy. Thus, a high PPV allows to infer high capacity of the screening test to detect positive cases.

RESULTS

Pilot study

Eligible individuals for screening were selected from two lists allocated to two primary care center groups. After linkage of the data referring to exclusion criteria with the electronic health records of individuals in the lists, a total of 5287 individuals were selected and divided according to the above groups. Method B presented higher adherence rates to FIT invitation (45% *vs* 37%, p < 0.010) and post-FIT+ colonoscopy (66% *vs* 40%, p < 0.010; see Table 1). However, the costs were significantly higher namely if adherence would be above 50%. Both units provided high-quality key performance measures for colonoscopies.

First year

Eligible individuals for screening were selected from lists allocated to PCC groups and 95 573 individuals were invited by mail to participate in the screening program – see Table 2. In terms of population demographics, this first year covered 85% of individuals of the 50 - 59 years of age range (15% from 60 to 69 years of age) and 51% were female. There were no noticeable age differences regarding adherence and diagnostic accuracy.

The main cause for exclusion (over 70%) was the performance of a colonoscopy in the past 10 years or sigmoidoscopy in the past five years. A total of 27 779 tests were

Table 1 – Overall results and per centers/methods the pilot phase

	Overall pilot	Centers / Methods		
		Method A	Method B	p-value
Invitees [n (%)]	5228	2640	2588	
Adherence to FIT [n (%)]	2143 (41.0)	970 (37.0)	1173 (45.0)	< 0.001
Positivity rate [n (%)]	127 (5.9)	47 (4.8)	80 (6.8)	0.002
Colonoscopies [n (%)]	72 (57.0)	19 (40.0)	53 (66.0)	< 0.001
ADR [n (%)]	62 (86.0)	12 (63.0)	40 (75.0)	0.256
Advanced phenotype rate* [n (%)]	35 (49.0)	10 (52.0)	25 (47.0)	0.606
Carcinoma** [n (%)]	2 (2.0)	1 (5.0)	1 (2.0)	

ADR: adenoma detection rate; n: absolute value; %: proportion in relation to total value in context
* Advanced phenotype - 3 or more adenomas or one adenoma > 10 mm or villous component or high-grade dysplasia
** Advanced carcinoma

Table 2 – First year results: main results

	Overall 1st year	Centers				
		1	2	3	4	5
Invitees [n (%)]	95 273	17 086	21 855	13 472	22 031	20 829
Primary care centers/units (n)	76	16	15	12	19	14
Adherence to FIT [n (%)]	27 779 (29.0)	4 176 (24.0)	6 035 (28.0)	4 859 (36.0)	7 309 (33.0)	5 400 (26.0)
Positivity rate [n (%)]	1 343 (4.8)	214 (5.1)	282 (4.7)	251 (5.2)	352 (4.8)	244 (4.5)
Colonoscopies [n (%)]	807 (60.0)	186 (87.0)	165 (58.0)	139 (55.0)	175 (50.0)	142 (69.0)
Cecal intubation [n (%)]	753 (93.0)	179 (96.0)	162 (98.0)	128 (92.0)	153 (87.0)	131 (92.0)
BBPS < 6 or 0 - 1 [n (%)]	60 (8.0)	17 (9.0)	14 (8.0)	14 (10.0)	6 (3.0)	9 (6.0)
Adverse events (%)	0	0	0	0	0	0
ADR [n (%)]	328 (41.0)	79 (42.0)	74 (45.0)	66 (47.0)	61 (35.0)	48 (34.0)
Advanced phenotype rate [n (%)]	179 (22.0)	57 (30.0)	35 (21.0)	29 (21.0)	24 (14.0)	34 (24.0)
Carcinoma [n (%)]	3 (0.4)				2	1

performed resulting in a FIT participation rate of 29%. The average turnaround time of a test was 53 days (29 SD). Less than 1% (0.6%) of laboratory tests had inconclusive results, and in this case a new FIT test was sent to the individual.

Simple trend analysis by trimester of the median days between FIT result and a family doctor appointment show a trend of smaller and smaller periods of time. As the programme advanced, there was a clear effort in improving time-to-appointment, between result and primary care consultation. A summary is presented as text 21 days (1st trimester), 46 days (2nd semester), 32 (3rd), 19 (4th), 22 (5th) and 18 (6th).

There were 1343 positive tests (4.8%), with a compliance of 60% (807/1343) to post-FIT+ colonoscopy. There were no adverse events across all centers in the period of observation. Also, cecal intubation and bowel preparation was above standard (e.g., adequate). Among those that underwent colonoscopy, the positive predictive value (PPV) for any adenoma was 80%, whereas the PPV for advanced adenoma and invasive cancer was 44% and 2%, respectively. The overall detection of advanced adenoma and invasive cancer was 179/95 273 (1.9 per 1000) and 10/95 273 (0.1 per 1000), respectively.

DISCUSSION

According to our study, a strategy to direct invitation to the target population is effective when inviting eligible subjects to FIT screening. However, a low uptake for FIT and a suboptimal compliance to post-FIT colonoscopy were recorded, suggesting the need for additional adjustments.

In the pilot study, the superiority of a Primary Care physician-filtered invitation over direct invitation was different from other countries. In Italy, a randomized trial on the same interventions led to opposite outcomes – Table 3. This may be due to the differences in interest or awareness of PCP for such activity, especially when considering the substantial burden of clinical activity they need to perform. Nevertheless, invited subjects may be likely to discuss the pros and cons of FIT screening with their PCPs. Thus, PCPs should be adequately informed about the FIT program and possibly informed when their patients receive the invitation. In our case, the differences are also the distance between place of residence and the endoscopy unit (also favoring PCPs invitation). However, overall expected costs would be significantly higher, and thus the option for both 'approaching' the endoscopic unit of the place of residence and also using the direct invitation.

The selection of a direct invitation strategy for our national program is not unexpected. All the European countries eventually came to adopt such an intervention that also simplifies the centralization of data and a timely use of limited resources. The fact that adherence in the pilot phase was only 30% should not discourage the healthcare system. Adherence to any screening intervention is known to grow over a mid- to long-term horizon, requiring the loyalty and trust of the general population regarding the screening program. In addition, it cannot be excluded that opportunistic screening mainly by primary colonoscopy is still competing with the organized approach in the short-term. However, the suboptimal adherence rate might bring the consideration of a more conservative approach. For instance, instead of wasting 70% of the FIT kits, other innovative means for promoting adherence to screening and colonoscopy will be considered in the future as full regional coverage for the program is reached and reasons behind non-adherence investigated.

Table 3 – Comparison with Zorzi M *et al*

	Current report	Zorzi M *et al*
Invitees (n)	92 573	178 828
Invitation method	Mailing	Mailing
Adherence to FIT (%)	29.0	69.0
Positivity rate (%)	4.5	5.7
Colonoscopies adherence (%)	60.0	91.5
ADR (%)	41.0	-
Advanced adenoma (%)	22.0	15.9
Carcinoma (%)	2.0	3.34

Our pilot implementation of a direct mailing invitation has shown the feasibility of a population-based program in Portugal. However, an unexpected suboptimal adherence to post-FIT colonoscopy was also disclosed. This is a critical problem as efficacy of a FIT program depends on the post-FIT+ removal of advanced neoplasia. Any loss of colonoscopy compliance directly translates into a loss of efficacy of FIT program in the first place. Possible alternatives can be explored. For instance, direct contact between the screening/endoscopic center and the patient may be proposed rather than to defer the positive patient to PCP as implemented in several European countries.

It is important also to highlight the high-quality parameters for the colonoscopies performed in all centers, namely the cecal intubation and bowel preparation, but more importantly, the adenoma detection rate were above standard.[13] This is crucial to assess and to continuously monitor. These first results are very promising and allow us to think that those procedures performed within this context will guarantee long term results for the screening programme.

There are limitations to our study. We limited our analysis to the first round of FIT. It is well known that uptake of FIT is much higher at subsequent rounds in those who previously accepted. On the other hand, PPV for AN tends to decrease. We did not perform subgroup-analyses according to age and sex. It is known that female and older subjects tend to have a higher yield of uptake. We did not test different cut-off values of positivity for FIT. This is known to alter the detection rate as well as the PPV of colonoscopy. However, this is now secondary to the increase in uptake rate of FIT.

CONCLUSION

We showed the effectiveness of a centralized, direct FIT invitation in a Portuguese setting, resulting in a high feasibility of the program enabling PCPs to be allocated to other components of the programme (e.g., pre- and post-colonoscopy management). Further interventions are needed to increase uptake with FIT and compliance with post-FIT colonoscopy.

AUTHORS CONTRIBUTIONS

HM, FT, JR, MDR: Conception of the work, critical review and final approval of the version to be published.

GF: Conception of the work and final approval of the version to be published.

MJC, SC, LC, JC, IP, JS, RH, MJB, CH: Critical review and final approval of the version to be published.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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18F-FDG PET/CT in Patients with Vulvar and Vaginal Cancer: A Preliminary Study of 20 Cases

18F-FDG PET/TC em Doentes com Carcinoma da Vulva e Vagina: Estudo Preliminar de 20 Casos

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ABSTRACT

Introduction: Despite the growing evidence supporting the use of 2-[F-18]-fluor-2-desoxi-D-glucose positron emission tomography/computed tomography in cervical and ovarian malignant tumours, data on vulvar and vaginal cancer is sparse. Our aim was to assess the role of 2-[F-18]-fluor-2-desoxi-D-glucose positron emission tomography/computed tomography in patients with vulvar and vaginal cancer.

Material and Methods: A retrospective study was conducted on a cohort of 20 patients with biopsy-proven vulvar (n = 17) and vaginal (n = 3) cancer who performed 2-[F-18]-fluor-2-desoxi-D-glucose positron emission tomography/computed tomography, between January 2013 and April 2018. We collected the clinical data of all patients, as well as the indication for 2-[F-18]-fluor-2-desoxi-D-glucose positron emission tomography/computed tomography, its results, and the main lesion maximum standard uptake value (SUVmax). In addition, we correlated the results of 2-[F-18]-fluor-2-desoxi-D-glucose positron emission tomography/computed tomography with other diagnostic modalities, namely histological findings, computed tomography and magnetic resonance imaging. Patients were divided into two groups, one with newly diagnosed disease and another with recurrent disease.

Results: Six patients had newly diagnosed disease and 14 had recurrent disease. The main lesion was detected by 2-[F-18]-fluor-2-desoxi-D-glucose positron emission tomography/computed tomography in five out of six patients with newly diagnosed disease and in all 14 patients with recurrent disease. Additional sites of 2-[F-18]-fluor-2-desoxi-D-glucose uptake were identified in inguinal and iliac lymph nodes and in distant lesions. Magnetic resonance imaging and computed tomography were performed in 12 cases. In four patients with recurrent disease, abnormalities (main lesion/ metastatic lymph nodes) identified by 2-[F-18]-fluor-2-desoxi-D-glucose positron emission tomography/computed tomography were not detected as suspicious by computed tomography.

Conclusion: In this preliminary study, 2-[F-18]-fluor-2-desoxi-D-glucose positron emission tomography/computed tomography demonstrated it can be a useful method in patients with vulvar and vaginal cancers, namely in defining the extent of disease and contributing to accurate staging and restaging.

Keywords: Fluorodeoxyglucose F18; Positron Emission Tomography Computed Tomography; Vaginal Neoplasms/diagnostic imaging; Vulvar Neoplasms/diagnostic imaging

RESUMO

Introdução: Apesar da crescente evidência que suporta o uso da tomografia por emissão de positrões/ tomografia computorizada com 2-[F-18]-fluor-2-desoxi-D-glucose em tumores malignos do colo do útero e do ovário, os dados sobre o carcinoma da vulva e da vagina são escassos. O nosso objetivo foi avaliar o papel da tomografia por emissão de positrões/ tomografia computorizada com 2-[F-18]-fluor-2-desoxi-D-glucose em doentes com carcinoma da vulva e da vagina.

Material e Métodos: Entre janeiro de 2013 e abril de 2018 foi realizado um estudo retrospetivo numa coorte de 20 doentes com carcinoma da vulva (n = 17) e da vagina (n = 3), comprovados por biópsia, que efetuaram tomografia por emissão de positrões/ tomografia computorizada com 2-[F-18]-fluor-2-desoxi-D-glucose. Recolheram-se os dados clínicos de todos os doentes, bem como a indicação clínica para a realização da tomografia por emissão de positrões/ tomografia computorizada com 2-[F-18]-fluor-2-desoxi-D-glucose, os seus resultados e o valor de captação padronizado máximo da lesão principal (SUVmax). Para além disso, correlacionaram-se os resultados da tomografia por emissão de positrões/ tomografia computorizada com 2-[F-18]-fluor-2-desoxi-D-glucose com os de outras modalidades diagnósticas, nomeadamente com os achados histológicos, a tomografia computadorizada e a ressonância magnética. Os doentes foram divididos em dois grupos, um com doença recém diagnosticada e outro com doença recorrente.

Resultados: Seis doentes tinham doença recém diagnosticada e 14 tinham doença recorrente. A lesão principal foi detetada em cinco dos seis doentes com doença recém diagnosticada e nos 14 com doença recorrente. Foram identificados outros locais de captação de 2-[F-18]-fluor-2-desoxi-D-glucose, nomeadamente gânglios linfáticos ilíacos e inguinais, e lesões à distância. Em 12 casos foram realizadas ressonância magnética e tomografia computorizada. Em quatro casos com doença recorrente, as anomalias (lesão principal / gânglios linfáticos metastáticos) identificadas na tomografia por emissão de positrões/ tomografia computorizada com 2-[F-18]-fluor-2-desoxi-D-glucose não haviam sido descritas como suspeitas pela tomografia computorizada.

Conclusão: Neste estudo preliminar, a tomografia por emissão de positrões/ tomografia computorizada com 2-[F-18]-fluor-2-desoxi-D-glucose demonstrou poder ser um método útil em doentes com carcinoma da vulva e da vagina, nomeadamente na definição da extensão da doença e na contribuição para o estadiamento e restadiamento precisos.

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Palavras-chave: Fluordesoxiglucose F18; Neoplasias Vaginais/diagnóstico por imagem; Neoplasias Vulvares/diagnóstico por imagem; Tomografia Computorizada com Tomografia por Emissão de Positrões

INTRODUCTION

Vaginal and vulvar cancers are rare, accounting for 1% – 4% of all gynaecological malignancies.[1] The majority of cases are seen in postmenopausal elderly women and the most common histological subtype is squamous cell carcinoma.[2,3] These tumours are staged according to the International Federation of Obstetrics and Gynaecology (FIGO) staging system.[4,5] Typical patterns of disease spread include local invasion and lymphatic dissemination.[6,7]

There is growing evidence supporting the use of 2-[F-18]-fluor-2-desoxi-D-glucose positron emission tomography/computed tomography (18F-FDG PET/CT) in gynaecologic malignancies. This technique is already used to stage, to monitor response and to detect recurrent disease in patients with cervical and ovarian cancer.[8] However, data on the role of 18F-FDG PET/CT in vulvar and vaginal cancer is sparse.

The aim of this study was to assess 18F-FDG PET/CT role in patients with vulvar and vaginal cancers.

MATERIAL AND METHODS

Study design and participants

We retrospectively analysed 20 patients with biopsy-proven vulvar (n = 17) and vaginal (n = 3) cancer who underwent 18F-FDG PET/CT in an oncology center, between January 2013 and April 2018. Demographic and clinical data of patients was collected, namely age when undergoing 18F-FDG PET/CT, histological findings, FIGO staging and previous treatments. The indication for 18F-FDG PET/CT, main lesion maximum standard uptake value (SUVmax) and final results were registered. In addition, 18F-FDG PET/CT results were correlated with computed tomography (CT) and magnetic resonance imaging (MRI). CT or MRI scans were performed within three months of the 18F-FDG PET/CT and no therapeutic interventions were carried out between these tests. Patients were divided into two groups, one with newly diagnosed disease and other with recurrent disease.

This study was approved by the Ethics Committee of Instituto Português de Oncologia do Porto (CES IPO: 373R/019).

PET imaging

Images were acquired on a Biograph 6 True Point in 14 patients and on a Biograph 20 mCT Flow with added time-of-flight technology (Siemens Healthcare, Erlangen, Germany) in six patients. Patients were instructed to fast for six hours prior to the intravenous administration of 18F-FDG (median administered activity 343.3 MBq, IQR 97.03). Blood glucose levels were lower than 200 mg/dL at the time of the tracer injection. All patients were orally hydrated and asked to empty their bladder before image acquisition. Images were acquired 60 minutes after radiopharmaceutical injection, from mid-thigh to vertex. Image acquisition was performed in supine position. CT was performed first, with no breath-hold, a section width of 3 mm and standard window reconstruction. Exposure factors were modulated automatically, using 120 KeV as reference and 30-60 mAs. PET was performed in 3D mode. 'Step-and-shoot' PET images were acquired on the Biograph 6 system (15 cm beds, 3 min/bed, 7 - 8 beds) and continuous table motion PET acquisition was performed on the Biograph 20 system (1.1 - 1.5 mm/s). Image reconstruction procedures included attenuation and scatter correction, ordered subset expectation maximization (OSEM) and Gaussian filter application.

Image analysis

18F-FDG PET/CT images were evaluated by two nuclear medicine physicians. In case of lack of agreement, a third element was consulted.

The PET images were analysed visually and semi-quantitatively by measuring the SUVmax. Suspicious abnormal focus of 18F-FDG uptake were considered 'positive' for lesions (main lesion/secondary lesion). Main lesions SUVmax was measured by drawing a region of interest (ROI) over the area of maximum activity and was calculated as the highest SUV of the pixels within the ROI.

RESULTS

Seventeen vulvar cancer patients and three vaginal cancer patients were studied. All patients had squamous cell carcinoma. The mean age of the sample was 69.1 ±

Table 1 – Clinical data, histologic findings, 18F-FDG PET/CT, CT and MRI of newly diagnosed patients

			Primary tumour					Metastasis				
Patient number	Test indication	Figo stage	Biopsy	PET	CT	MRI	Location	Biopsy	PET	CT	MRI	Location
1	Staging	I	(+)	(-)	ND	ND	Vulva	ND	(-)	ND	ND	
2	Staging	II	(+)	(+)	ND	ND	Vulva	ND	(+)	ND	ND	IN
3	Staging	IV	(+)	(+)	(+)	ND	Vulva	(+)	(+)	(+)	ND	IL, IN
4	Staging	II	(+)	(+)	ND	(+)	Vagina	ND	(-)	ND	(-)	
5	Staging	IV	(+)	(+)	(+)	(+)	Vagina	ND	(+)	(+)	(+)	IL, IN
6	Staging	II	(+)	(+)	ND	(+)	Vagina	ND	(-)	ND	(-)	

PET: positron emission tomography; CT: computed tomography; MRI: magnetic resonance imaging; (-): negative for malignancy; ND: not done; (+): positive for malignancy; IL: iliac lymph nodes; IN: inguinal lymph nodes

11.7 years old. Six patients had newly diagnosed disease and 14 had recurrent disease.

Newly diagnosed cancer

Six patients were evaluated as part of pre-treatment assessment and18F-FDG PET/CT was requested to stage these patients.

Clinical data, histological findings, 18F-FDG PET/CT, CT and MRI of newly diagnosed patients are displayed in Table 1.

The six patients with newly diagnosed disease were clinically classified as FIGO I, II and IV. Histological confirmation of the primary tumour was obtained in all patients. Histological confirmation of metastatic disease was obtained in one patient.

The primary tumour was detected by 18F-FDG PET/CT in five out of six patients (median SUVmax 6.5 [min = 6.0; max = 18.7]) – Figs. 1 and 2. The patient with negative 18F-FDG primary cancer had a clinical stage of I and performed the technique on Biograph 6 True Point. 18F-FDG PET/CT identified suspicious metastatic lymph nodes in three cases (inguinal and iliac).

CT studies were performed in two patients. CT detected the primary tumour and positive lymph nodes in the two cases.

Three patients underwent MRI. The primary tumour was identified in all three MRI studies and positive lymph nodes (inguinal and iliac) in one case.

CT was in agreement with 18F-FDG PET/CT in both cases (2/2) and MRI in all cases (3/3), in the evaluation of the primary tumour and metastasis.

Recurrent disease

Fourteen patients had previously underwent surgery: hemivulvectomy (n = 4), radical vulvectomy (n=6) and vulvectomy with pelvic lymph node dissection (n = 4). Four of these patients were being treated with chemotherapy.

18F-FDG PET/CT was requested to restage 10 patients (nine patients had vulvar recurrence on routine follow-up examination and one had clinically suspected metastatic disease) and to evaluate treatment response in four patients under chemotherapy.

Table 2 describes the clinical data, histologic findings, 18F-FDG PET/CT, CT and MRI of patients with recurrent disease.

The original clinical stage of the 14 patients with recurrent disease was FIGO I, II and III, respectively. Histological confirmation of the recurrent tumour was obtained in all patients. Histological confirmation of metastatic disease was obtained in three patients.

The recurrent main lesion was detected by 18F-FDG PET/CT in all patients [median SUVmax 9.3 (min = 6.2; max = 50.6)]. 18F-FDG PET/CT identified suspicious metastatic lymph nodes (exemplified on Fig. 3) in five studies (inguinal and iliac) and distant metastases (lung and subcutaneous tissue of the thigh) in two.

CT studies were performed in four patients. CT detected recurrent disease in three cases. Suspicious metastatic

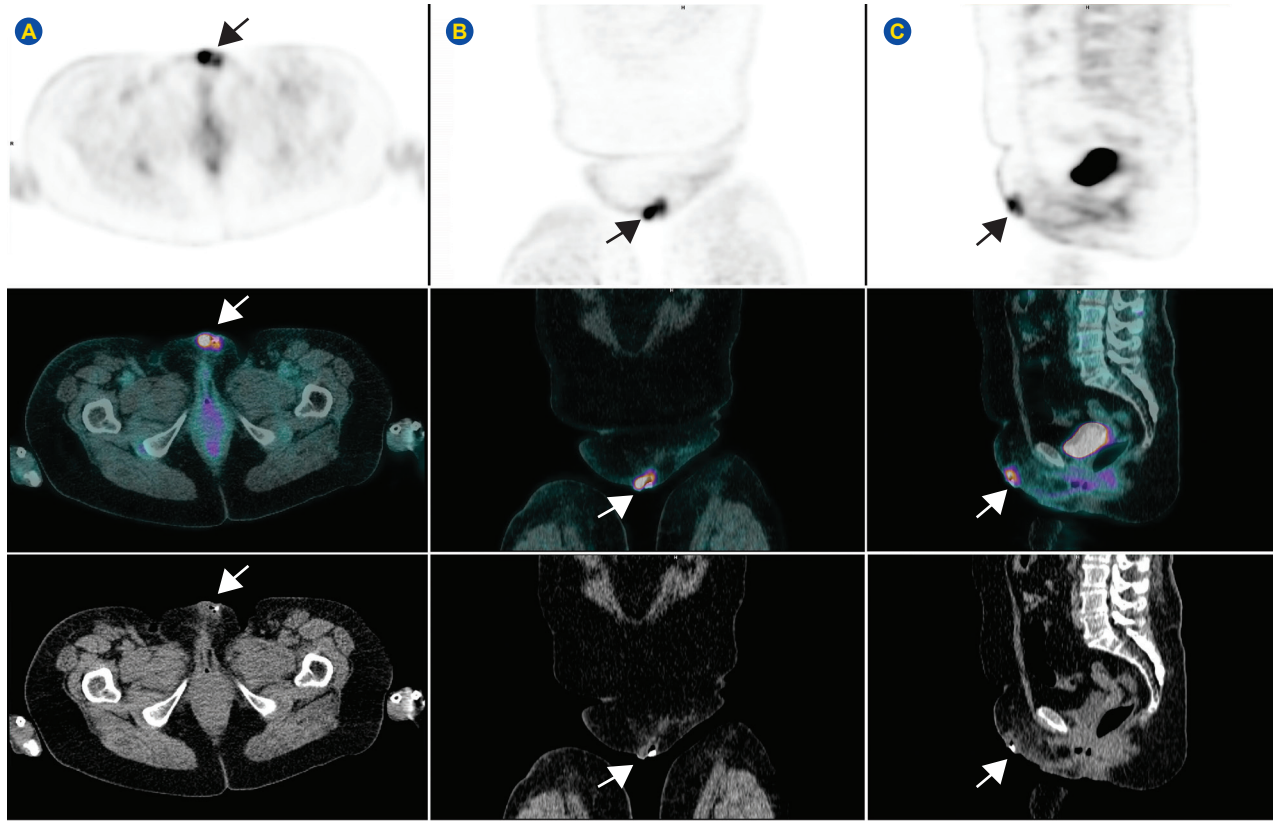

Figure 1 – Intense 18F-FDG activity in primary vulvar cancer (arrows on PET, PET/CT and CT in axial A, coronal B, and sagittal C planes)

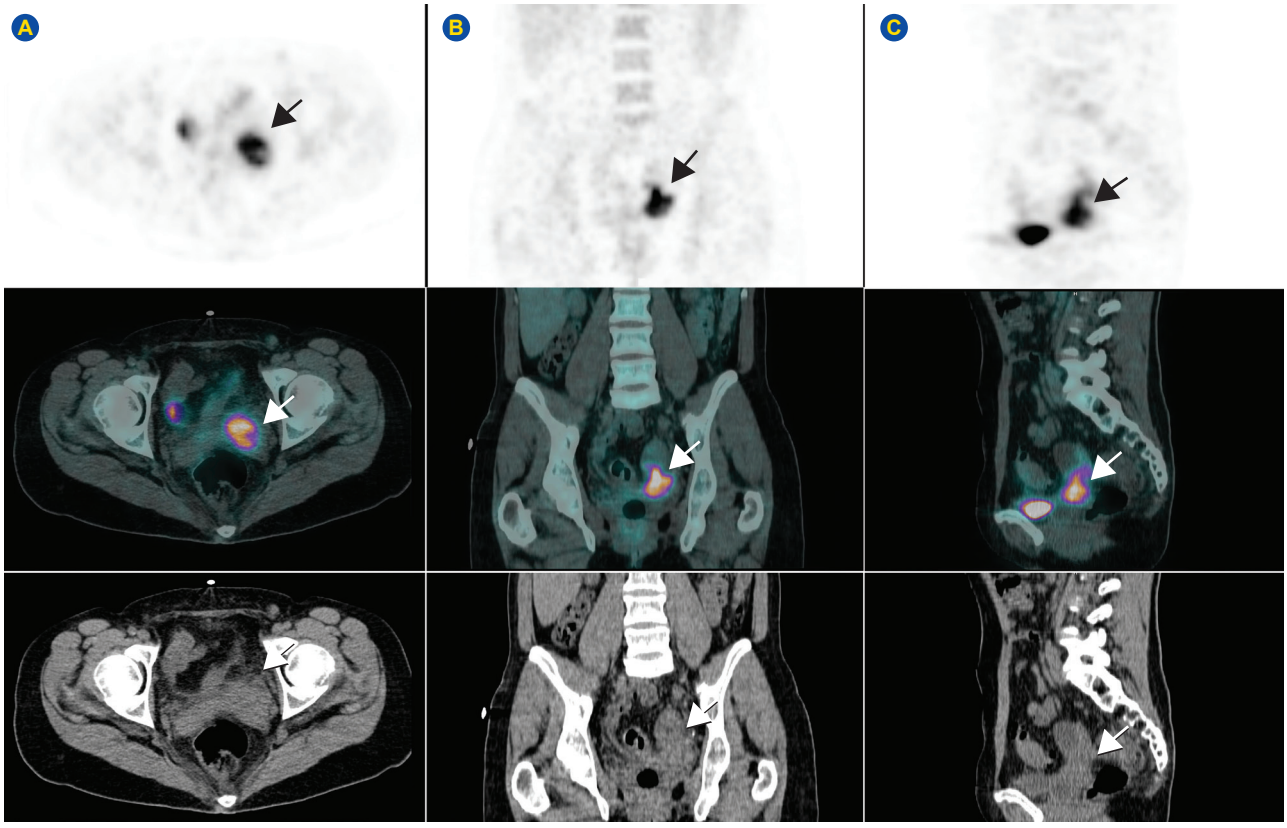

Figure 2 – Increased 18F-FDG uptake in primary vaginal cancer (arrows on PET, PET/CT and CT in axial A, coronal B, and sagittal C planes)

disease was not detected by CT.

Three patients underwent MRI. The recurrent tumour was identified in three MRI studies. Suspicious metastatic disease was not identified on MRI.

Regarding the recurrent main lesion, CT was in agreement with 18F-FDG PET/CT in three cases (3/4). In one case, the recurrent tumour detected on 18F-FDG PET/CT was not considered suspicious in CT. MRI was in agreement with 18F-FDG PET/CT in all cases (3/3).

Regarding the detection of metastasis, CT was in agreement with 18F-FDG PET/CT in 1 case (1/4). In the other three cases, metastatic lymph nodes identified by 18F-FDG

Table 2 – Clinical data, histologic findings, 18F-FDG PET/CT, CT and MRI of patients with recurrent disease

Patient number	Test indication	Figo stage	Recurrent tumour					Metastasis				
			Biopsy	PET	CT	MRI	Location	Biopsy	PET	CT	MRI	Location
7	R	III	(+)	(+)	ND	ND	Vulva	ND	(-)	ND	ND	
8	R	III	(+)	(+)	(+)	ND	Vulva	ND	(+)	(-)	ND	IL
9	R	I	(+)	(+)	ND	(+)	Vulva	ND	(-)	ND	(-)	
10	R	III	(+)	(+)	(-)	(+)	Vulva	ND	(-)	(-)	(-)	
11	R	II	(+)	(+)	ND	ND	Vulva	ND	(-)	ND	ND	
12	R	I	(+)	(+)	ND	ND	Vulva	ND	(-)	ND	ND	
13	R	I	(+)	(+)	ND	ND	Vulva	ND	(-)	ND	ND	
14	R	I	(+)	(+)	ND	(+)	Vulva	ND	(-)	ND	(-)	
15	R	III	(+)	(+)	ND	ND	Vulva	ND	(-)	ND	ND	
16	R	I	(+)	(+)	ND	ND	Vulva	ND	(-)	ND	ND	
17	TR	III	(+)	(+)	ND	ND	Vulva	ND	(+)	ND	ND	IL, IN, ST (thigh)
18	TR	III	(+)	(+)	(+)	ND	Vulva	(+)	(+)	(-)	ND	IL, IN
19	TR	III	(+)	(+)	ND	ND	Vulva	(+)	(+)	ND	ND	IL, IN, lung
20	TR	III	(+)	(+)	(+)	ND	Vulva	(+)	(+)	(-)	ND	IN

R: restaging; TR: treatment response; PET: positron emission tomography; CT: computed tomography; MRI: magnetic resonance imaging; (-): negative for malignancy; ND: not done; (+): positive for malignancy; IL: iliac lymph nodes; IN: inguinal lymph nodes; ST: subcutaneous tissue

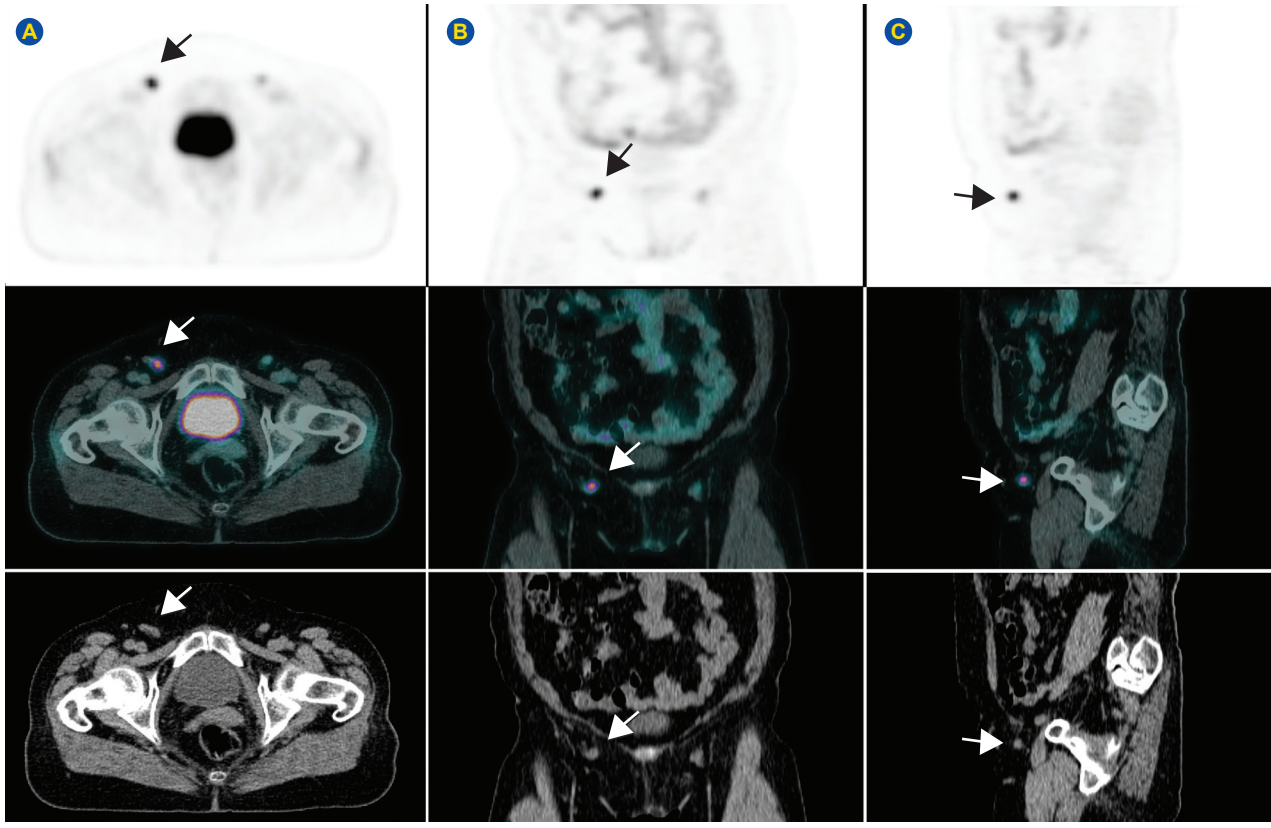

Figure 3 – 18F-FDG-avid metastatic inguinal lymph node (arrows on PET, PET/CT and CT in axial A, coronal B, and sagittal C planes)

PET/CT were not detected as suspicious by CT. Biopsy was carried out in two of these patients and confirmed malignancy in both. MRI studies were in agreement with 18F-FDG PET/CT in all cases (3/3).

DISCUSSION

In our study, 18F-FDG PET/CT identified abnormalities (main lesion/metastatic lymph nodes) more often than conventional CT scans in recurrent disease. In comparison with histology, 18F-FDG PET/CT had a sensitivity of 95% and a positive predictive value (PPV) of 100% in identifying the primary tumour and the recurrent main lesion. The sensitivity and PPV of 18F-FDG PET/CT in detecting metastasis was not determined because of the lack of histology data.

In the current literature, there is scarce data available on the usefulness of 18F-FDG PET/CT in the management of vulvar and vaginal cancer.

Cohn *et al* reported that 18F-FDG PET/CT had 80% sensitivity, 90% specificity and a PPV of 80% in identifying vulvar cancer lymph node metastasis.[9] Given the high specificity, it is postulated that 18F-FDG PET/CT can be used to locate metastatic nodes and assess response to radiation prior to groin dissection. Furthermore, 18F-FDG PET/CT has the potential of identifying metastatic disease in pelvic lymph nodes, which can be useful to prevent extensive groin dissection and treat alternatively with chemoradiation.[10] Kamran *et al* found that 18F-FDG PET/CT had 50% sensitivity, 100% specificity, a PPV of 100%, and a negative predictive value (NPV) of 57% in detecting metastatic groin lymph nodes in patients with vulvar cancer.[11] The high PPV supports the notion that 18F-FDG PET/CT imaging can be used for treatment planning preceding surgical staging and to adequately plan preoperative chemoradiation therapy. However, owing to low sensitivity, a negative scan result does not preclude surgical resection. On the other hand, Dolanbay *et al* demonstrated a sensitivity, specificity, PPV and a NPV of 100% in identifying inguinofemoral lymph node metastases in patients with vulvar cancer.[12] In a prospective study of 23 patients, Lamoreaux *et al* demonstrated that 18F-FDG PET/CT detected all metabolically active primary vaginal tumour with a sensitivity of 100% and detected metastatic lymph nodes more often than conventional CT scans.[13]

Lin *et al* studied 23 women with vulvar cancer and concluded that 18F-FDG PET/CT imaging may have a positive impact on patient management.[14] A recent study in patients with vulvar cancer reported that preoperative 18F-FDG PET/CT changed the therapeutic management in 61.5%, although inflammatory lymph nodes may also be 18F-FDG avid on 18F-FDG PET/CT scanning and can result in false-positive results, whereas necrotic lymph nodes may not be metabolically active and can cause false-negative results.[15] Robertson *et al* reported a change in patient management in 36% of patients with primary or recurrent vaginal and vulvar cancer after 18F-FDG PET/CT.[16]

Our findings reinforce the usefulness of this technique in vulvar and vaginal cancer.

There are a number of limitations in our study. The

retrospective cross-sectional design of this study precludes causal inference. The small sample size and the lack of comparative imaging tests (due to the rarity of vulvar and vaginal cancer) represent additional limitations. In an ideal comparison, all patients would have undergone 18F-FDG PET/CT and whole-body conventional CT imaging and/or MRI, using histopathology data as the reference standard. The sensitivity, specificity, PPV and Negative Predictive Value (NPV) of 18F-FDG PET/CT in identifying metastasis could then be evaluated. Finally, the use of two PET/CT systems could have interfered in image analysis and influenced the SUVmax calculation concerning the main lesion.

CONCLUSION

Our study showed that 18F-FDG PET/CT can be a useful tool in patients with vulvar and vaginal cancers, namely in defining the extent of disease and contributing to an accurate staging and restaging. However, further studies, namely prospective multicenter studies, are necessary to define this role.

AUTHORS CONTRIBUTIONS

PG: Data acquisition and analysis, literature research, draft of the manuscript.

ASP, SN: Data acquisition, critical review of the manuscript.

LV: Data acquisition, draft and critical review of the manuscript.

RT: Data analysis, critical review of the manuscript.

AP, LHD: Critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

CONFLICTS OF INTEREST

All authors report no conflict of interest.

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Therapeutic Plasmapheresis: Seven Year Experience of an Intensive Care Unit in Portugal

Plasmaferese Terapêutica: Experiência de Sete Anos de um Serviço de Medicina Intensiva em Portugal

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ABSTRACT

Introduction: Therapeutic plasmapheresis is a therapeutic procedure in which the patient's blood is passed through a medical device which separates out plasma from other components of blood. The plasma is removed and replaced with a replacement solution. Studies on the use of plasmapheresis in critically ill patients are scarce. The aim of this study was to review all therapeutic plasmapheresis sessions carried out in the Hospital Beatriz Ângelo intensive care unit.

Material and Methods: An observational retrospective study was conducted between April 2012 and March 2019. All patients who underwent therapeutic plasmapheresis in the intensive care unit were included, and plasmapheresis sessions held outside the intensive care unit were excluded.

Results: Of 46 patients, 63% were men (n = 29), with a median age of 53 years. The most frequent diagnoses were hypertriglyceridemia-induced pancreatitis, vasculitis, autoimmune haemolytic anaemia, and atypical haemolytic-uremic syndrome. A total of 198 plasmapheresis sessions were carried out in the intensive care unit. Most of the used replacement solutions were fresh frozen plasma (34.4%), albumin/crystalloid (24.2%), and albumin/fresh frozen plasma (19.2%). The most common complications were hydroelectrolytic changes (84; 42.4%) and coagulation disorders/thrombocytopenia (65; 32.8%). There was no need to interrupt any plasmapheresis session due to complications related to the patient.

Conclusion: Therapeutic plasmapheresis is a complex technique that requires specific training. The indications are diverse, and some are not consensual. Complications were frequent, but they did not increase morbidity.

Keywords: Critical Illness/therapy; Plasma Exchange/methods; Plasmapheresis/adverse effects; Plasmapheresis/methods; Plasmapheresis /therapeutic use

RESUMO

Introdução: A plasmaferese terapêutica é um procedimento em que o sangue passa por um circuito extracorpóreo que separa o plasma dos outros componentes do sangue. O plasma removido é substituído por soluções de reposição. Os estudos sobre a utilização de plasmaferese terapêutica no doente crítico são escassos. O objetivo do estudo foi rever todas as sessões de plasmaferese realizadas no serviço de Medicina Intensiva do Hospital Beatriz Ângelo.

Material e Métodos: Estudo observacional retrospetivo de todos os doentes admitidos no serviço de Medicina Intensiva entre abril de 2012 e março de 2019. Foram selecionados os doentes submetidos a plasmaferese e excluídas as sessões realizadas fora do serviço de Medicina Intensiva.

Resultados: No período de estudo foram incluídos 46 doentes. A maioria eram homens (n = 29; 63%) com uma idade mediana de 53 anos. Os diagnósticos mais frequentes foram pancreatite secundária a hipertrigliceridemia, vasculite, anemia hemolítica autoimune e síndrome hemolítica urémica atípica. Foram realizadas 198 sessões de plasmaferese no serviço de Medicina Intensiva. As soluções de substituição mais utilizadas foram plasma fresco congelado (34,4%), albumina/cristalóide (24,2%) e albumina/plasma (19,2%). As complicações mais comuns foram alterações hidroeletrolíticas (84; 42,4%), e distúrbios da coagulação/plaquetas (65; 32,8%). Em nenhum dos casos a técnica teve que ser interrompida por complicações relacionadas com o doente.

Conclusão: A plasmafere terapêutica é uma técnica complexa que requer treino específico. As indicações são diversas e algumas não consensuais. As complicações foram frequentes, mas não condicionaram morbilidade associada.

Palavras-chave: Estado Crítico/tratamento; Plasmafere/efeitos adversos; Plasmafere/métodos; Plasmafere/uso terapêutico; Troca Plasmática/métodos

INTRODUCTION

Therapeutic plasmapheresis (PX) is a therapeutic procedure in which blood of the patient passes through a medical device which separates out plasma from other components of blood in order to remove high molecular weight compounds. These compounds may be antibodies, toxins, and other disease specific molecules. The plasma is removed and replaced with a replacement solution such as colloid solution (e.g., albumin and/or plasma) or a combination of crystalloid/colloid solution.[1] The body's inability to clear these molecules, as well as renal replacement techniques increase the need for PX in order to change the course of the disease, thus reducing its morbidity and mortality.

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The plasma-separation methods can be centrifugation or filtration. Centrifugation was the first method used for PX and relies on the variation in the specific gravity of blood components These systems are often large and complicated and suffer from contamination of the separated plasma with platelets and other cellular components. This method has a high plasma extraction ratio (80%), so a low blood flow rate is required, which can be achieved by peripheral venous access (up to 80 mL/min). Filtration is a membrane-based separation method, which relies on particle size. With advances in membrane technology, it has become more biocompatible, safer, and more adaptable to conventional haemodialysis and hemofiltration machines. The membranes used for PX have significantly larger pores (0.2 - 0.3 μm) than the membranes used in hemofiltration, allowing macromolecules, but not cellular components, to convectively cross the membrane. The advantages of this method are operational simplicity, lower cost, more reliability, and potentially no loss of cellular components as can be seen with centrifuge-based plasma removal. However, as the plasma extraction ratio is lower, it requires a higher blood flow rate (50 – 200 mL/min) to achieve the same plasma separation. In order to do so, a double lumen central venous catheter must be inserted, which has some specific complications.[2]

At our hospital, both in the intensive care unit (ICU) and the Medical Day Hospital (MDH), we apply the filtration method, using the haemodialysis monitor Multifiltrate (Fresenius®) and the filter PlasmaFlux (PSU 2S). Plasma is removed and replaced with a solution that can be fresh frozen plasma (FFP), albumin, crystalloid, or combinations of these.

There are scarce published data about the applicability and safety of PX in a critical care environment, despite the higher probability of complications in this group of patients.[3-6]

According to the latest guidelines of the American Society for Apheresis (ASFA) 2019, indications for PX may be divided into categories, according to the level of scientific evidence. Category I includes indications for PX as the first-line therapeutic option, and category II includes indications for PX as the second-line therapeutic option. In categories III-IV, the benefit has not been well established.[1]

PX has been carried out in our ICU since its opening in 2012, but there has never been a systematic analysis of the procedure. For that reason, in order to improve daily clinical practice, and because studies on the use of PX in critically ill patients are scarce,[7-10] we developed this study. The aim of this study was to review all PX sessions that were held at the ICU of Beatriz Ângelo Hospital (HBA), including the total number of sessions, diagnosis and indication for PX, characteristics of each session, and associated complications.

MATERIAL AND METHODS

This single-centre, retrospective observational study was conducted at HBA's ICU (Loures, Portugal). This is a type-C ICU consisting of 22 beds (levels 2 and 3). Of all the patients admitted to the ICU in the period between April 2012 and March 2019, those undergoing PX were selected, and sessions held outside the ICU were excluded. Data were collected from clinical records and recorded in a specific database. The collected data included the following: demographic data, diagnosis and indication for PX, total number of PX sessions, number of sessions per patient and their frequency, characteristics of each PX session, including replacement solution, volemic replacement, type of anticoagulation, complications associated with PX session, need for invasive mechanical ventilation (IMV) and renal replacement therapy (RRT), length of stay (LOS) in the ICU and in the hospital, and mortality in the ICU and in the hospital.

The Ethics Committee of HBA approved the study. Informed consent was waived given the characteristics of the study.

Statistics

The pseudoanonimized database was created using the program FileMaker Pro Advanced version 17.0.4. Statistical analysis was performed using Excel version 16.28.

Categorical and discrete variables are presented as frequency or number and percentage (%). Continuous variables with normal distribution are expressed as mean ± standard deviation and continuous variables without normal distribution as median and interquartile range (Q1 - Q3).

RESULTS

The retrospective analysis identified 46 patients for inclusion [0.4% of all patients admitted to the ICU (n = 11 232) and 0.6% of patients admitted at level 3 (n = 7518)]. Most patients were men (29; 63%), and 37% were women (n = 17) with a median age of 53 years (43 – 68), median body mass index of 26 (23 – 29), and median APACHE score of 13 (6 – 18). The total number of PX sessions performed during patients' ICU stay was 227. Of these, 29 sessions were excluded from the analysis as they were held outside the ICU at the MDH Therefore, we only analysed the 198 PX sessions performed by the ICU staff. Thirteen patients (28.2%) maintained the need for PX after discharge from the UCI.

Diagnosis and indication

The most frequent initial diagnoses with an indication for PX included the following: hypertriglyceridemia-induced pancreatitis (13; 28.2%), vasculitis (8; 17.4%), autoimmune haemolytic anaemia (5; 10.9%), atypical haemolytic-uremic syndrome (aHUS) (5; 10.9%), and Guillain-Barré syndrome (GBS) (4; 8.7%) (Fig. 1).

The initial diagnosis was confirmed in 40 patients (87%). It was confirmed before initiating PX in 63% (n = 29). However, in 17 patients (37%), PX was initiated before the definitive diagnosis due to clinical severity and a high degree of clinical suspicion. In the six cases in which the initial diagnosis was not confirmed, two maintained an indication for plasmapheresis.

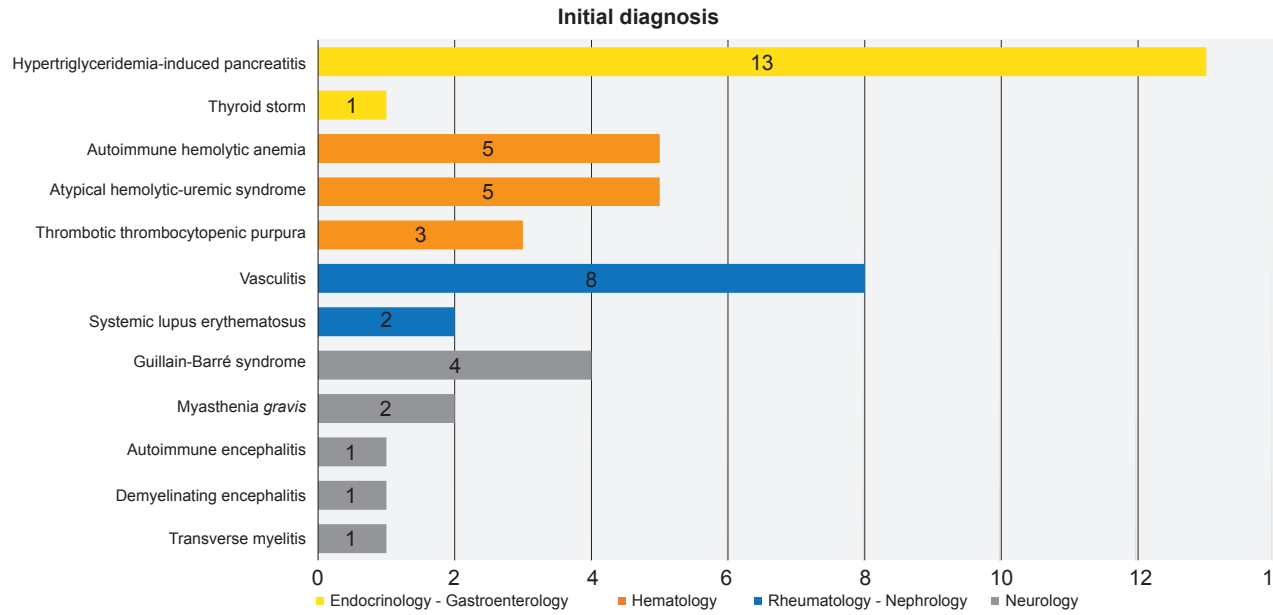


Figure 1 – Distribution of the number of patients requiring therapeutic plasmapheresis during admission to the intensive care unit, according to the initial diagnosis

As for to the initial diagnosis, the main indications for PX were triglycerides over 1000 mg/dL in hypertriglyceridemia-induced pancreatitis (13; 28.3%), clinical severity in different conditions (13; 28.3%), as a first-line therapeutic option (8; 17.4%), diffuse alveolar haemorrhage (7; 15.2%), refractoriness to the first therapeutic line (4; 8.7%) and dialysis dependence (1; 2.1%) (Table 1).

Plasmapheresis and associated therapy

Plasmapheresis was used as an isolated therapy in 19 patients (41.3%), associated with corticosteroids or other type of immunosuppression in 17 patients (36.9%), with immunoglobulin in five patients (10.9%) and in combination with all aforementioned therapies in five patients (10.9%).

Organ support: renal replacement therapy and invasive mechanical ventilation

Regarding the need for organ support, most patients did not require IMV (29; 63%). In the group of patients undergoing IMV (17; 37%), the most common diagnoses were GBS (4; 23.5%) and vasculitis (4; 23.5%). RRT was required in 17 patients (37%). In this group, RRT was intermittent in

Table 1 – Indication for therapeutic plasmapheresis, according to the diagnosis

Disease	Indication	Category	n (46)
Hypertriglyceridemia-induced pancreatitis	Triglyceridemia > 1000 mg/dL	III	13
Vasculitis	Diffuse alveolar hemorrhage	I	7
	Dialysis dependence	I	1
Atypical hemolytic-uremic syndrome (thrombotic microangiopathy)	Severe	I - III (according to etiology)	5
Autoimmune hemolytic anemia (warm antibodies)	Severe	III	4
Guillain-Barré syndrome	First-line therapeutic option	I	1
	After immunoglobulin	III	3
Thrombotic thrombocytopenic purpura	First-line therapeutic option	I	3
Myasthenia *gravis*	First-line therapeutic option	I	2
Systemic lupus erythematosus	Severe	II	2
Autoimmune hemolytic anemia (cold antibodies)	Severe cold agglutinin disease	II	1
Transverse myelitis	First-line therapeutic option	I	1
Autoimmune encephalitis	First-line therapeutic option	I	1
Demyelinating encephalitis	Refractoriness	II	1
Thyroid storm	Severe	II	1

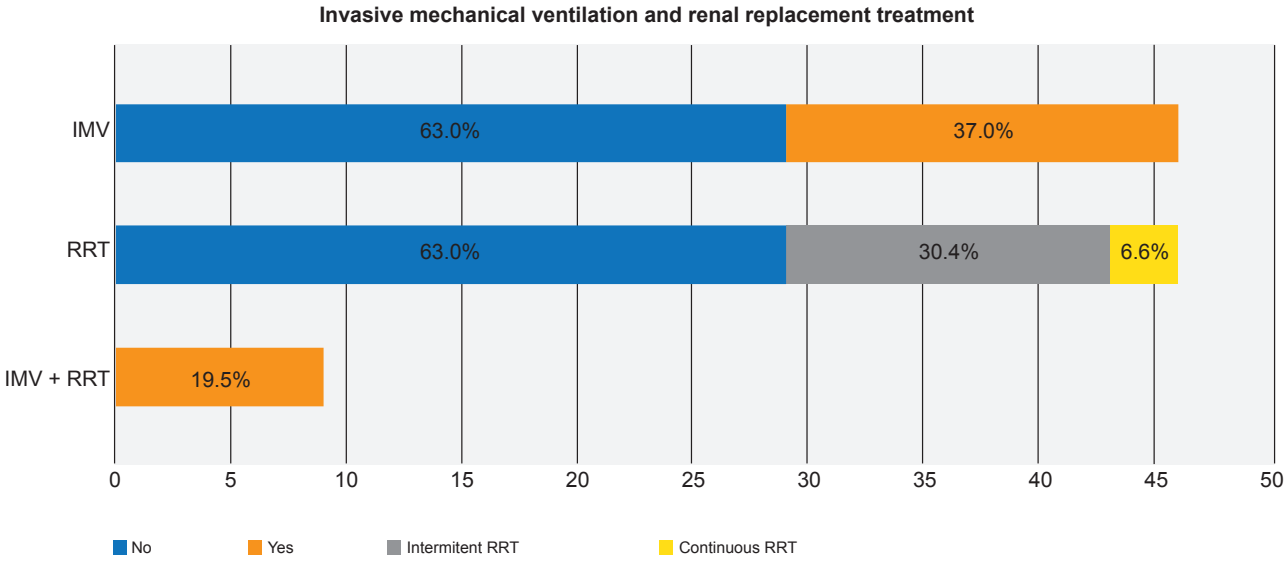


Figure 2 – Description of the percentage of patients that needed invasive mechanical ventilation and renal replacement therapy, in addition to plasmapheresis

IMV: invasive mechanical ventilation; RRT: renal replacement therapy

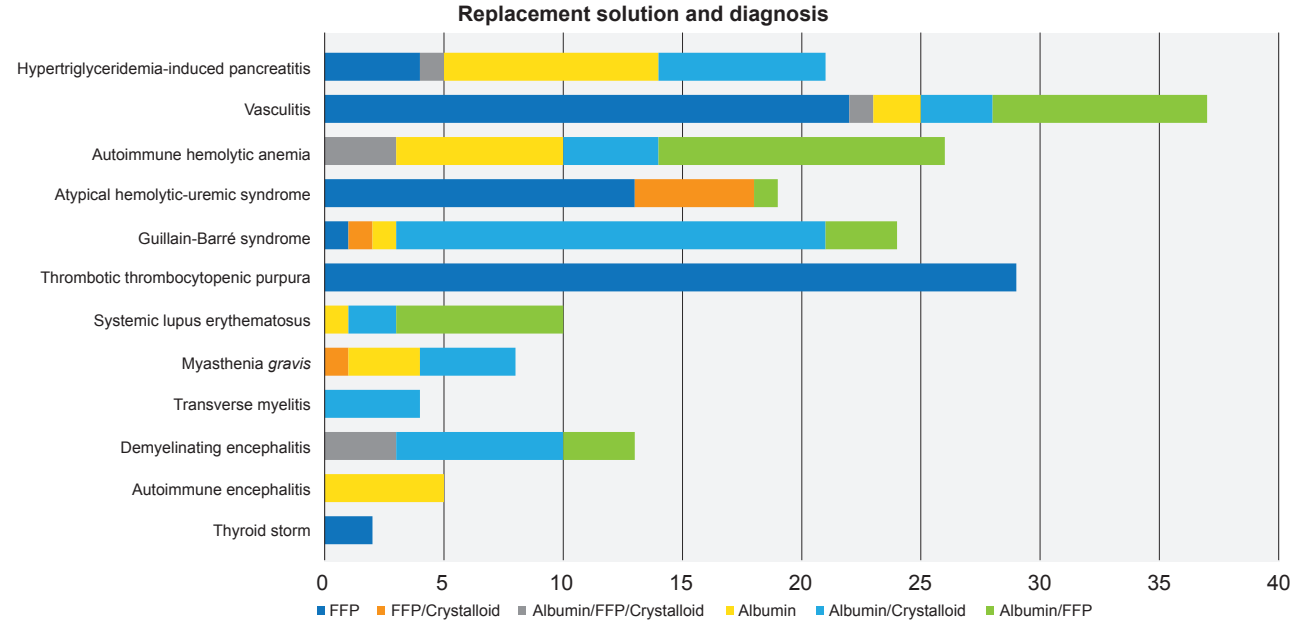


Figure 3 – Replacement solution combinations used for all therapeutic plasmapheresis sessions, according to initial diagnosis

TTP: thrombotic thrombocytopenic purpura; Ahus: atypical hemolytic-uremic syndrome; FFP: fresh frozen plasma

14 cases (82.4%) and continuous in 3 (17.6%). The most frequent diagnoses were vasculitis (7; 50%) and aHUS (4; 28.5%). In 19.5% (n = 9) of all cases, IMV and RRT were required. In this group, vasculitis was the most common diagnosis (4; 44.4%) (Fig. 2).

Characteristics of the plasmapheresis sessions

The mean replacement volume used was 3,600 ml, corresponding mostly to 1 volemic replacement (136; 68.7%) and 1.5 volemic replacement in 31.3% (n = 62). The mean duration of sessions was 3.4 hours (2 – 7); however, in many cases (37; 18.6%), the duration of the PX could not be determined due to a lack of registration in the clinical records.[1]

FFP was the most used replacement solution (68; 34.4%), followed by the albumin/crystalloid combination (48; 24.2%), albumin/FFP (38; 19.2%), albumin (28; 14.1%), FFP/crystalloid (7; 3.5%), and albumin/FFP/crystalloid (9; 4.6%).

When comparing the type of replacement solution with the diagnosis, FFP was the predominant choice in cases of vasculitis, thrombotic thrombocytopenic purpura (TTP), and haemolytic-uremic syndrome. In these cases, replacement with FFP is indicated because its components are indispensable for treatment, such as the replacement of ADAMTS13 in TTP, or also due to the high bleeding risk, such as in alveolar haemorrhage. The only case of thyroid storm was also treated using FFP given the advantage of

increasing the concentration of thyroglobulin (Fig. 3).

Regarding anticoagulation, heparin was used in 65.2% (n = 129) of PX sessions, and regional citrate anticoagulation was used in 28.8% (n = 57). In 6%, it was not possible to ascertain the type of anticoagulation instituted from the clinical records. The dose of heparin (bolus and infusion) did not always reach the recommended value. The mean bolus dose was 2062 UI (min 0; max 5000), and the mean infusion dose was 836 UI/h (min 0; max 5000).

Number and periodicity of PX sessions

The following figure represents the number of PX sessions performed, stratified by condition. In most cases, the median of sessions was between five and seven sessions per patient. The diagnosis requiring fewer PX sessions per patient was hypertriglyceridemia-induced pancreatitis (Fig. 4).

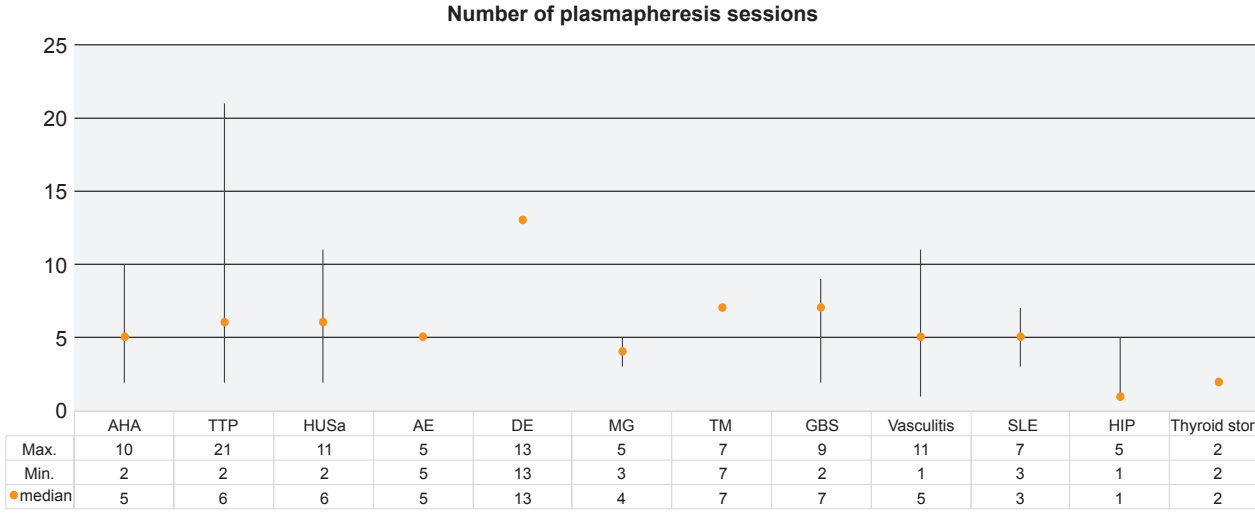
The frequency of sessions per patient and condition is more variable. The following figure illustrates this periodicity according to a colour gradient. It is difficult to establish a pattern as it appears that most patients had daily sessions at an early stage, with the interval increasing over time (Fig. 5).

Complications

a) Interruption of sessions

Twenty per cent of the PX sessions (n = 40) were interrupted at least once (30; 75%), and the remainder were discontinued two (5; 12.5%), three (4; 10%) or six times (1; 2.5%).

The technique was interrupted mainly due to filter rupture (15; 37.5%), elevated transmembrane pressure (TMP) (14; 35%), and circuit clotting (7; 17.5%). These events



	AHA	TTP	HUSa	AE	DE	MG	TM	GBS	Vasculitis	SLE	HIP	Thyroid storm
Max.	10	21	11	5	13	5	7	9	11	7	5	2
Min.	2	2	2	5	13	3	7	2	1	3	1	2
median	5	6	6	5	13	4	7	7	5	3	1	2

Figure 4 – Graphical representation of the number of therapeutic plasmapheresis sessions required, per each diagnosis
AHA: autoimmune hemolytic anemia; TTP: thrombotic thrombocytopenic purpura; aHUS: atypical hemolytic-uremic syndrome; AE: autoimmune encephalitis; DE: demyelinating encephalitis; MG: myasthenia gravis; TM: transverse myelitis; GBS: Guillain-Barré syndrome; SLE: systemic lupus erythematosus; HIP: hypertriglyceridaemia-induced; Max.: maximum; Min.: minimum

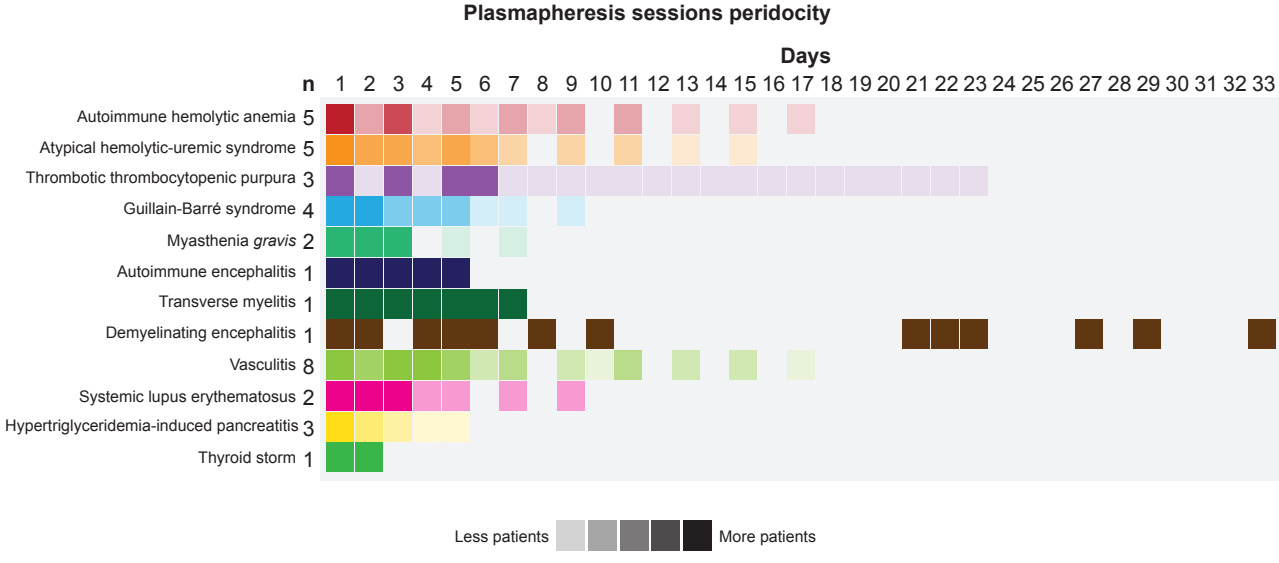


Figure 5 – Heatmap of plasmapheresis sessions. For each diagnosis, the intensity of the color for each day is proportional to the number of patients with that diagnosis that have done plasmapheresis in that day.
aHUS: atypical hemolytic-uremic syndrome; TTP: thrombotic thrombocytopenic purpura; SLE: systemic lupus erythematosus

occurred more frequently when heparin was the anticoagulation chosen. On the other hand, the diagnoses in which sessions were more often interrupted were pancreatitis (12; 30%) and vasculitis (8; 20%).

b) Other complications

Hydroelectrolytic changes, namely hypokalaemia, hypocalcaemia, and metabolic alkalosis, were the most frequent complications (84; 42.4%), in which 36.9% had more than one hydroelectrolytic change simultaneously. Hypocalcaemia occurred in 31.3% of the PX sessions, most often associated with regional citrate anticoagulation (38.6% of the citrate sessions had hypocalcaemia, compared with 26.4% of the heparin sessions). Metabolic alkalosis (27; 13.5%) was also more frequent with citrate (36.9% of sessions with citrate and 4.6% of sessions with heparin).

Coagulation and platelet disorders occurred in 32.8% (n = 65), most of them thrombocytopenia (n = 51).

We also highlight hypotension (9; 4.5%), arrhythmias (4; 2%), acute pulmonary oedema (2; 1%), hypersensitivity reaction in a PX session with FFP (1; 0.5%) and problems related with the central venous catheter (4; 2%).

Outcome

The ICU LOS was four days (3 - 15), and the hospital LOS was 24 days (12 - 35). Hospital mortality was 21.7% (n = 10), with 90% of these patients dying in the ICU. Thirty-two patients were discharged home (69.6%), three (6.5%) were transferred to another hospital, and one (2.2%) was admitted to the National Integrated Continuing Care Network.

DISCUSSION

PX is an urgent procedure that can change the clinical course of a disease and reduce morbidity and mortality of critically ill patients. This justifies that 37% of the patients started the technique before the diagnostic confirmation.

There are several diagnoses and indications for plasmapheresis with different recommendations.[1]

In this study group, plasmapheresis was more frequently performed in patients with hypertriglyceridemia-induced pancreatitis with triglycerides over 1000 mg/dL, although it is a category-III indication (ASFA).[11,12] In pancreatitis, complications occur more often in the cases of hypertriglyceridemia-induced pancreatitis compared to other causes.[13] Morbidity and mortality are also higher in that group of patients.[14] In this case, the rapid and efficient reduction in serum triglyceride levels has a significant impact on clinical outcomes, considering that plasmapheresis is both effective and safe.[15]

Ramírez-Bueno *et al* demonstrated that 72.7% of these patients needed only one session of PX, 18.2% received two sessions, and only 9.1% had three sessions. They obtained an 81% reduction of the initial level of triglycerides.[16] Other studies have also shown that a single session of PX reduces triglyceride levels by 66.3% to 70%.[15,17] An additional exchange increased the triglyceride removal rate to 83.3%.[17] In our study, the median of PX sessions in this group of patients was also one session per patient. The benefits of PX in these cases are broader than just the decrease in triglyceridaemia, which also contributes to the removal of excess proteases and the replacement of the protease inhibitors that are consumed.[15]

In pancreatitis, the indicated replacement solution is albumin or crystalloid, and FFP may be associated at the end of the session if there is a high bleeding risk, which was recorded in one session. In most sessions (16; 76.2%), albumin or crystalloid/albumin was used according to the recommendations.

Anti-neutrophil cytoplasm antibodies (ANCA) vasculitis is a frequent cause of rapidly progressive glomerulonephritis and may be associated with alveolar haemorrhage. The pulmonary-renal syndrome increases mortality significantly.[6,18]

PX is recommended by international guidelines for the treatment of ANCA vasculitis with pulmonary hemorrhage, based on evidence that shows a faster recovery in most patients, without much impact on kidney function. The efficacy of PX seems to be related with the rapid removal of autoantibodies and proinflammatory mediators that perpetuate the increased permeability of the alveolar–capillary barrier.[8] However, a recently published randomized controlled trial (PEXIVAS trial) involving 704 patients with severe ANCA associated vasculitis compared the efficacy of plasma exchange with no plasma exchange in terms of mortality or end-stage kidney disease. The use of plasma exchange did not reduce the incidence of death or end-stage kidney disease.[19]

According to the ASFA 2019 guidelines,[1] alveolar haemorrhage and/or dialysis dependence are indications for PX (category I). In our study, the main indication was alveolar haemorrhage (87.5%), also justifying that the FFP was the most used replacement solution (59.5%). The other combinations of albumin, crystalloid, and FFP were used when the indication was dependent on dialysis and after resolution of alveolar haemorrhage.

Autoimmune haemolytic anaemia may be due to cold or warm antibodies. PX is indicated when the disease is severe or unresponsive to immunosuppression (categories II and III).[20,21] The recommended replacement solution is albumin. In this study, albumin was used in all sessions, alone or as the main element in a combination with crystalloid or FFP.

Guillain-Barré syndrome is an immuno-mediated, acute inflammatory demyelinating polyneuropathy, which can cause respiratory failure requiring mechanical ventilation.

Recovery is spontaneous; however, recovery can be slow in the most patients with severe disease requiring mechanical ventilation. PX accelerates motor recovery and reduces the number of days of mechanical ventilation.[22] PX is recommended as the first-line therapeutic option (category I) and in cases refractory to intravenous immunoglobulin (category III).[1] Scientific evidence shows that immunoglobulin and PX are equivalent in terms of effectiveness.[23,24]

In our study, only one (25%) patient underwent PX as the first-line therapeutic option. The majority (75%) had PX after refractoriness to immunoglobulin. The recommended replacement solution is albumin, used in 91.6% of the sessions, alone or in combination with crystalloid or FFP.

The atypical haemolytic-uremic syndrome is a disused concept, which classifies a thrombotic microangiopathy (TMA); however, in the absence of better etiological characterization of the TMA type in our patients (mediated by complement, drugs, metabolism, or coagulation), we kept this terminology.[25,26] Atypical haemolytic-uremic syndrome has a poor prognosis, with a mortality rate around 25% and a progression to end-stage renal disease in 50% of cases.[27,28] PX may achieve full haematological and renal recovery in up to 50% of cases, although its impact on mortality is not so clear. It is recommended that PX must be started empirically and early in the course of TMA until the definitive diagnosis is clarified. The recommended replacement solution is FFP.[28,29]

TTP is distinguished by the severe deficiency of ADAMTS13, more severe thrombocytopenia, and the more extensive target organ damage, with the exception of the kidney, which is less affected.[30]

Regarding organ support, it is easy to understand that the need for IMV was more frequent in GBS due to ventilatory failure and in ANCA vasculitis due to alveolar haemorrhage.

The need for RRT was more common in aHUS due to the predominant renal impairment, as well as in ANCA vasculitis, regardless of whether the indication for PX was dependent on dialysis or worsened kidney function in patients with pulmonary-renal syndrome.

In most sessions, we chose the replacement solution in agreement with the guidelines. However, we performed some PX sessions with FFP without a clear bleeding risk. We also recorded cases with a combination of albumin and FFP at the end of the session. We believe this decision was aimed at making up for the loss of clotting factors due to the technique.[31] The depletion of clotting factors is more evident after three to five sessions in the same week, when the replacement solution used is albumin. The bleeding risk can be minimized with the administration of FFP at the end of the PX session.[32] Despite changes in coagulation, the incidence of bleeding complications is low. In this study, no complications of this nature were registered.

Heparin was the most used type of anticoagulation, probably due to staff experience. Our ICU only started regional anticoagulation with citrate in PX in 2015. Most of the complications with the extracorporeal circuit occurred with heparin, which seems to be related to the infra-therapeutic dose administrated in many cases.[33]

The dose required for anticoagulation with heparin in PX is higher than that required for other techniques such as RRT, due to the significant extraction of the molecule during PX. This fact, as well as the perception of the risk of coagulation factor depletion during PX, can lead doctors to prescribe doses of heparin closer to those used for RRT, not always reaching the required target.

Citrate ensures a more effective regional anticoagulation of the extracorporeal circuit, minimizing the risk of circuit clotting and systemic effects.[33] Circuit clotting also occurred in sessions with citrate. This could be attributed to technical issues; however, it was not possible to assess it with the available data. Filtration, when compared with the centrifugation technique, is associated with an increased risk of circuit clotting. Moreover, inadequate pump flow can increase the risk of clotting and elevation of TMP, leading to filter failure.[34]

The interruption of sessions due to filter rupture, clotting or clogging was overcome by replacing the circuit and restarting the PX session. Optimization of both the blood flow rate and the heparin infusion dose were pursued.

Hydroelectrolytic changes were the most frequent complications. Hypokalaemia is partly explained by the low potassium concentration of 5% albumin (2 mmoL/L). Potassium chloride was not routinely or prophylactically administered during PX sessions, but hypokalaemia was monitored and corrected with potassium chloride as needed. Metabolic alkalosis occurred mainly when anticoagulation with citrate was used due to its metabolic conversion to bicarbonate.[35,36] Hypocalcaemia was more frequent with citrate than with heparin, but not as expressively as metabolic alkalosis, probably due to the tight control of calcaemic and correction with continuous infusion of calcium gluconate. Citrate and calcium gluconate infusion rates were titrated according to an established protocol.

Hypotension was corrected with fluids, while arrhythmias and acute pulmonary oedema were treated as usual. A hypersensitivity reaction to FFP was overcome with administration of intravenous antihistamines and corticosteroids and did not lead to interruption of PX.

Limitations

This is a single-centre retrospective study. Some of the missing data in the electronic health records compromised data collection and a more complete analysis.

CONCLUSION

PX is a complex technique that requires specific training. There are several indications, and some are not consensual. Given the urgency of instituting PX, the initial diagnosis is not always confirmed before starting the technique.

Due to its infrequency, the staff experience on PX prescribing and maintenance particularities is not always optimal. This can lead to errors in anticoagulation prescribing, selection of the adequate replacement solution, and frequency of sessions.

For this reason, we consider that training the team and defining a PX action protocol may be important in standardizing the prescribing technique and improving clinical practice. Since complications were frequent but did not affect morbidity or mortality, PX can be considered a safe technique in patients admitted to the ICU.

AUTHORS CONTRIBUTION

RF: Design of the study protocol. Data acquisition and registration. Statistics analysis. Draft and critical review of the article.

AB: Design of the study protocol. Data acquisition and registration. Critical review of the article.

AG: Design of the study protocol. Data acquisition and registration. Statistics analysis. Critical review of the article.

LF, AC, SF: Design of the study protocol. Data acquisition and registration. Critical review of the article.

JC: Design of the study protocol. Database conception and design. Statistics analysis. Critical review of the article.

CMO, AM: Design of the study protocol. Draft and critical review of the article.

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 of Hospital Beatriz Ângelo and by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENCIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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What Leads to a Patient Refusal for Ambulatory Surgery? A Logistic Regression Prediction Model Based on a Five Year Retrospective Analysis of Patients with Abdominal Wall Hernia

O que Leva à Recusa de um Doente Para Cirurgia de Ambulatório? Um Modelo Preditivo de Regressão Logística Baseado numa Análise Retrospetiva de Cinco Anos de Doentes com Hérnia da Parede Abdominal

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ABSTRACT

Introduction: Ambulatory surgery has proven benefits in patient wellbeing and cost reduction in healthcare systems. However, some patients referred for ambulatory surgery are refused and directed instead towards inpatient care, which generates several drawbacks. The reasons for this refusal have not been yet studied. The aim of this study is to identify, retrospectively, significant variables associated with patient refusal for ambulatory surgery and develop a mathematical tool able to predict with strong accuracy those who will be rejected.

Material and Methods: Over a 5-year period (2014 - 2018), all patients that underwent abdominal hernia repair in our hospital in an inpatient setting, and that had been previously refused for ambulatory surgery, were analysed for a total of 94 variables. A multivariate logistic regression model was developed to identify risk factors associated with refusal using data from 136 patients (65 refused *vs* 71 accepted). A prediction index for refusal in ambulatory surgery (IRAS), was derived and tested (n = 62 patients).

Results: The risk index included five significant risk factors: type 2 diabetes mellitus [OR 14.669 (2.982; 72.154)], physical status [OR 49.155 (15.532; 155.555)], prior malignancy [OR 14.518 (2.653; 79.441)], prior abdominal surgery [OR 3.455 (1.006; 11.866)] and usage of antiplatelet agents [OR 25.600 (4.309; 152.066)]. All risk factors were associated with a high risk of refusal (OR between 3.455 for history of prior abdominal surgery and 49.155 according to the American Society of Anaesthesiologists physical status classification). Defining five points as the maximum IRAS score that predicts suitability for ambulatory surgery resulted in a positive predictive value of 93.55% and negative predictive value of 87.10%.

Conclusion: IRAS is a useful tool that can contribute to reduce time to surgery and improve patients' quality of life.

Keywords: Ambulatory Surgical Procedures; Logistic Model; Patient Selection

RESUMO

Introdução: A cirurgia de ambulatório tem benefícios comprovados no bem-estar dos doentes e na redução de custos dos sistemas de saúde. Porém, alguns doentes referenciados para cirurgia de ambulatório são recusados e encaminhados para internamento. Os motivos desta recusa ainda não foram estudados. Neste trabalho identificámos, retrospectivamente, variáveis significativas na recusa dos doentes e fornecemos uma ferramenta matemática capaz de prever de forma precisa aqueles que serão rejeitados.

Material e Métodos: Ao longo de cinco anos (2014 - 2018), todos os doentes submetidos a correção cirúrgica de hérnia abdominal em regime de internamento no nosso centro hospitalar previamente recusados para cirurgia de ambulatório foram analisados para um total de 94 variáveis. Um modelo de regressão logística multivariada foi desenvolvido para identificar os fatores de risco para recusa usando dados de 136 doentes (65 recusados *vs* 71 aceites). Um índice preditivo para recusa de cirurgia em ambulatório (IRAS), foi criado e testado (n = 62 doentes).

Resultados: O IRAS incluiu cinco fatores de risco significativos: diabetes *mellitus* tipo 2 [OR 14,669 (2,982; 72,154)], estado físico [OR 49,155 (15,532; 155,555)], neoplasia maligna prévia [OR 14,518 (2,653; 79,441)], cirurgia abdominal prévia [OR 3,455 (1,006; 11,866)] e uso de agentes antiplaquetários [OR 25,600 (4,309; 152,066)]. Todos os fatores de risco foram associados a elevado risco de recusa (OR entre 3,455 para história de cirurgia abdominal prévia e 49,155 de acordo com a classificação do estado físico segundo a American Society of Anaesthesiologists). A definição de cinco pontos como a pontuação máxima do IRAS que prevê adequação para cirurgia de ambulatório resultou num valor preditivo positivo de 93,55% e um valor preditivo negativo de 87,10%.

Conclusão: O índice IRAS é uma ferramenta útil que pode contribuir para a redução dos tempos de espera e melhorar a qualidade de vida dos doentes.

Palavras-chave: Modelos Logísticos; Procedimentos Cirúrgicos Ambulatórios; Selecção de Doentes

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INTRODUCTION

Ambulatory surgery has grown in developed countries in the last 50 years and it has increasingly become more established in developing countries as well.[1-3] It is considered a safe, efficient and cost-effective level of care contributing to patient satisfaction and improved quality of life.[4-6] Patients initially proposed for ambulatory surgery across the different medical specialties can be rejected and redirected to inpatient care. This imposes a delay in the resolution of the patients' condition with added days of morbidity, increased loss of both working days and healthcare costs.

Refusal of a given patient is a medical decision and relies mostly on anaesthesiologists or surgeons that conduct the preliminary medical assessment. Although efforts have been made to conduct a pre-operative assessment and patient preparation prior to ambulatory surgery, there are no defined guidelines to reject a patient based on his/her clinical information.[7]

A tool that can predict with a reasonable amount of accuracy which patients will be accepted or refused for surgery in the outpatient setting, can be an important aid for the initial referral by both primary care specialties or other medical specialties that can also refer patients. In this way, the clinician would be more supported and empowered in deciding if the initial referral should be made to either outpatient or inpatient care, which is beneficial to both the patient and the healthcare system. The possibility to take a more informed decision would deliver quicker and safer solutions to all patients, thus decreasing the burden of disease and improving the clinical management.

The aim of this study is to propose a statistical methodology to identify which variables best predict whether a patient is likely to be rejected or accepted for ambulatory surgery and to develop a risk score to predict the refusal of a given patient by using a registry of patients that have been referred for ambulatory surgery.

MATERIAL AND METHODS

Database and study population

A retrospective observational study was conducted at our centre from the 1st January 2014 to 31st December 2018 (five years) in accordance with the specifications and approval from the local ethics committee. During this period, all the adult patients (age ≥18 years) undergoing elective abdominal wall hernia surgery in inpatient care were analysed 1593 patients). The authors implemented a 1:1 study consisting of an equal size between refused and non-refused patients for ambulatory surgery.

Based on the clinical records, those that were initially proposed for ambulatory surgery and refused, and ultimately undergoing surgery in inpatient care (78 patients), were selected for further analysis. Among these, 13 patients were excluded due to social reasons and were rejected from further analysis. Therefore, a total of 65 patients were included in our study sample in the refusal group.

Among the group of patients that underwent elective abdominal wall hernia surgery in the ambulatory setting during the same 5-year period, a control group (n = 71 patients) were selected by random number generation.

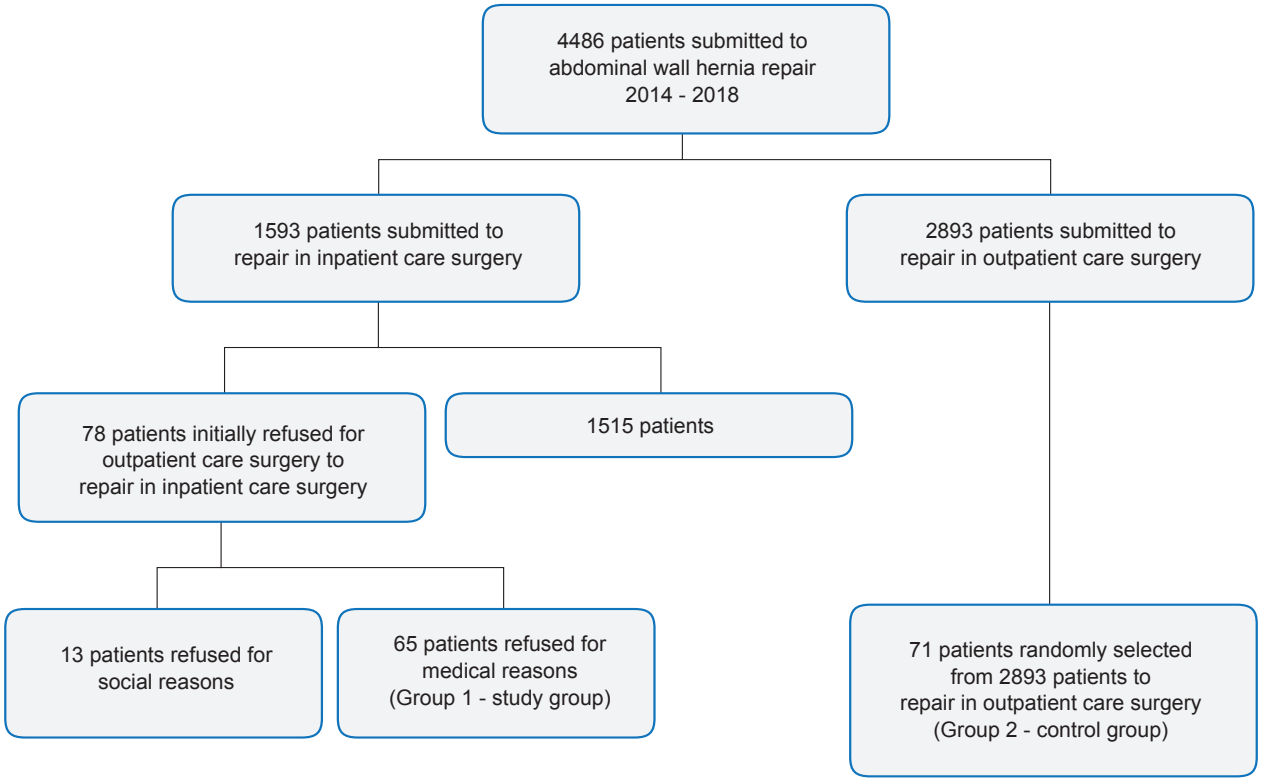

Figure 1 – Flow diagram from the initial time of patient selection to the composition of the final patient samples

Fig. 1 shows the flow diagram from the initial time of patient screening to the establishment of the final patient sample.

A total of 94 parameters, which included data on comorbidities, daily habits, anthropometry, prior surgical record, anaesthetic complications, and other considered relevant were collected from the patient medical record and clinical registries, in both the study and control groups. Additionally, both the reason and the medical specialty responsible for refusal of ambulatory surgery in the study group were gathered.

The reasons for refusal of the 78 patients that had initially been proposed for surgery in the ambulatory setting, and subsequently redirected to inpatient care, were scrutinised. Thirteen patients (16.7%) were rejected due to social reasons, mainly associated with a considerable degree of dependency on others for the daily tasks, in patients that lived alone or that had reduced home support. These patients were excluded from further analyses. Sixty-five (83.3%) patients [50 males (76.9%)] were rejected after being evaluated by the anaesthesiologist (81.9%) or the surgeon (18.1%) and these patients constituted our study group (Group 1)].

The reasons for refusal due to medical reasons were gathered through analysis of the medical records and are presented in Fig. 2. A threshold of 5% was defined, and only reasons that were represented above this limit are shown. In this sense, those who represented more than 5% were: cardiac conditions (21.8%), respiratory conditions (19.2%), obstructive sleep apnoea (13.9%), cardiovascular risk factors (9.9%), difficult orotracheal intubation (7.7%), previous post-operative hemodynamic instability (6.8%) and chronic kidney disease (5.8%). The hernia size was the single reason specified by the surgeon for patient rejection for ambulatory surgery, with the remaining reasons being attributed to the anaesthesiologist.

Afterwards, and for each patient refused, the selected 94 variables were analysed and coded.

By means of a random number generator, a random sample of 71 patients among the population of adult patients undergoing elective abdominal wall hernia surgery in outpatient care from the 1st January 2014 to 31st December 2018 (n = 2893 patients) was selected. This group of patients - Group 2, was analysed and coded for the same variables chosen for those refused for ambulatory surgery.

Statistical analysis

A multivariate logistic regression model was developed to predict refusal in ambulatory surgery using a training-test strategy. Logistic regression models can be used to identify potential risk factors for refusal of ambulatory surgery. The patient's total risk index is the result of a simple linear function of the risk factors, which are previously quantified and weighed.

In order to identify and remove features with little or no predictability of the target to prevent overfitting and to identify highly correlated or redundant features while suppressing the negative impacts towards the model without losing important information, the first stage of the proposed methodology consisted of a bivariate analysis to investigate the presence of a relationship between refusal and each potential risk factor based on the hospital's training data. In this bivariate analysis, whenever possible, the chi-square test or Fisher's exact test (only for 2 x 2 contingency tables) for nominal variables and the *t* test or the Z-test for

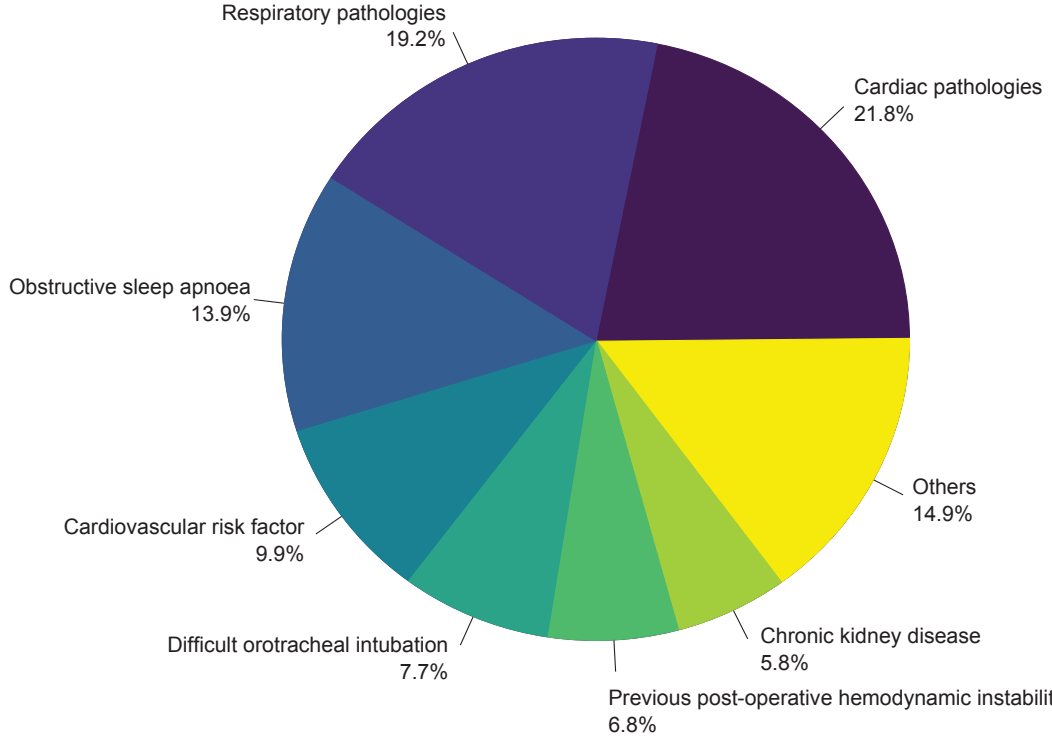

Figure 2 – Medical reasons presented for refusal of patients referred to ambulatory surgery

continuous variables were applied.

The potential risk factors examined included comorbidities, daily consumption of alcohol and tobacco habits, anthropometric indicators, prior surgical record, anaesthetic complications, and other relevant considerations. The risk factors that were significantly related with refusal of ambulatory surgery were considered as a natural candidate for independent variables in the multivariate logistic regression model.

In order to identify which variables best predicted whether a patient was likely to be rejected, a multivariate logistic regression model with stepwise forward variable selection method was then estimated. All variables with $p < 0.10$ were included in the final model. The discrimination power of the final predictive model was evaluated with the C-statistic (also called as area under the receiver operating characteristic curve, AUC) and the Hosmer-Lemeshow test was used to evaluate the goodness of the fit (calibration).

The third step of the proposed methodology included the prediction index for refusal in ambulatory surgery (IRAS) derivation. This index was developed as a score system that is easy to use and that requires simple calculations. IRAS is given by the sum of points assigned to each category of the significant risk factors. The point value for the j-th category of the i-th risk factor was defined as the ratio between the respective regression coefficient, $\beta_{i,j}$, and its standard error $se_{i,j}$ (normalization), and this ratio was rounded to the nearest integer.

Finally, the risk score was validated using a test group (n = 62 patients) - validation cohort - consisting of patients that underwent elective abdominal wall hernia surgery in random time points during 2019, in either inpatient or ambulatory setting.

All the data analysis was performed in R, version 3.5.2 (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Among the candidate predictors, based on 94 different clinical parameters, there are 15 significant risk factors. Table 1 presents the univariate frequencies and prevalence (%) for all significant candidate predictors in both groups. Data is presented as frequencies (prevalence in percentage) for categorical variables and as mean ± standard deviation for the age variable.

Multivariable analysis

The 15 significant risk factors identified in bivariate analysis were considered as potential predictors in a multivariate logistic regression model, with stepwise forward variable selection method.

Table 2 presents the results of a logistic regression model that was developed to predict refusal for ambulatory surgery.

From these 15, and using a stepwise strategy, only five were considered significant namely, the presence of type 2 diabetes mellitus, presence of higher physical status classification according to the American Society of Anaesthesiologist [(ASA) 3/4], history of prior malignancy, history of prior abdominal surgery and usage of antiplatelet agents. All risk factors were associated with a very high risk of refusal for ambulatory surgery (odds ratio – OR - range between 3.455 for history of prior abdominal surgery and 49.155 for the presence of higher physical status classification ASA 3/4). The predictive performance of the refusal prediction model was assessed by calibration and discrimination. The model fit the data well in terms of discrimination (AUC = 0.806) and

Table 1 – Significant risk factors for refusal of ambulatory surgery

Risk factor	Group 1 (n = 65)	Group 2 (n = 71)	*p* value*
Age (years)	65.50 ± 12.93	53.86 ± 11.75	< 0.001
High blood pressure	37 (57.0)	16 (23.0)	< 0.001
Dyslipidemia	31 (48.0)	11 (15.0)	< 0.001
Type 2 diabetes mellitus	18 (28.0)	3 (4.0)	< 0.001
Atrial fibrillation	9 (14.0)	1 (1.0)	0.007
Obstructive sleep apnoea under Ci-PAP	11 (17.0)	1 (1.0)	0.002
Chronic kidney disease	9 (14.0)	0 (0.0)	0.001
History of prior malignancy	12 (18.0)	3 (4.0)	0.013
Prior abdominal surgery	22 (34.0)	11 (15.0)	0.012
Previous acute coronary syndrome	6 (9.0)	0 (0.0)	0.028
Cardiac ischemia	13 (20)	0 (0.0)	< 0.001
Chronic obstructive pulmonary disease	14 (21.2)	2 (2.7)	< 0.001
Severe physical status classification (ASA 3/4)	56 (86.0)	9 (13.0)	< 0.001
Usage of hipocoagulants	9 (14.0)	1 (1.0)	0.008
Usage of antiplatelet agents	27 (42.0)	2 (3.0)	< 0.001

Group 1: refused patients; Group 2: non-refused patients.
ASA: American Society of Anesthesiologists; ASA ¾: severe physical status (class 3 and class 4).
* With the exception of the age variable, whose *p*-value is associated with a t-test, the remaining p-values are associated with the chi-square test of independence.

Table 2 – Logistic regression model to predict refusal of ambulatory surgery.

Risk factor	Coefficient	OR [90% CI]	*p* value
Type 2 diabetes mellitus	2.686	14.669 [2.982, 72.154]	0.006
Severe physical status classification (ASA 3/4)	3.895	49.155 [15.532, 155.555]	< 0.001
History of prior malignancy	2.654	14.518 [2.653, 79.441]	0.009
Prior abdominal surgery	1.240	3.455 [1.006, 11.866]	0.098
Usage of antiplatelet agents	3.243	25.600 [4.309, 152.066]	0.003

Intercept: -3.455. OR: odds ratio; CI: confidence interval

Table 3 – Score associated with refusal of ambulatory surgery

Risk factor	Category	IRAS
Type 2 diabetes mellitus	No (reference) Yes	0 3
Severe physical status classification (ASA 3/4)	No (reference) Yes	0 6
History of prior malignancy	No (reference) Yes	0 3
Prior abdominal surgery	No (reference) Yes	0 2
Usage of antiplatelet agents	0 (reference) ≥ 1	0 3
Risk index		0 - 17

calibration (p = 0.113 in Hosmer-Lemeshow goodness-of-fit test).

Refusal probability for ambulatory surgery using IRAS

Depending on the power of the selected predictors measured by regression coefficients and corresponding precision, an index for refusal in ambulatory surgery (IRAS) was developed as a score system that is easy to use and that requires simple calculations. All factors included in the index are categorical with two categories. The point value for the i-th risk factor was defined as the ratio between the regression coefficient, β_i, and its standard error (normalization), and this ratio was rounded to the nearest integer.

Table 3 and Appendix 1 (see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15733/Appendix_01.pdf) present the point values for all significant risk factors identified in the logistic regression model. Excluding reference categories, which were given zero points, point values ranged from two for the history of prior abdominal surgery to six for the presence of severe physical status classification (ASA 3/4). The index IRAS ranges from 0 to 17 points, 0 for a patient without any risk factors and 17 for a patient with all the five risk factors.

In order to estimate a probability of refusal $(\hat{p})$, a new univariate logistic model was adjusted using the value of the IRAS index as predictor and the refusal (binary variable) variable as dependent variable. The estimated logistic regression equation may be written as:

$$\hat{p} = \frac{1}{1 + e^{(-3.216 + 0.687 \times IRAS)}}$$

where - 3.216 is the intercept of the univariate logistic regression model and 0.687 is the constant of the scoring system.

Table 4 and Fig. 3 show the estimated risk (predicted probabilities) of refusal for ambulatory surgery for each risk score. The estimated risk ranged from 3.855% for a patient with a score of 0 and 99.979% for patients with score 17.

Table 4 – Risk estimation (%) associated with refusal of ambulatory surgery

IRAS score	Estimated risk	IRAS score	Estimated risk
0	3.855	9	95.095
2	13.672	11	98.711
3	23.939	12	99.347
5	55.419	14	99.833
6	71.185	15	99.916
8	90.704	17	99.979

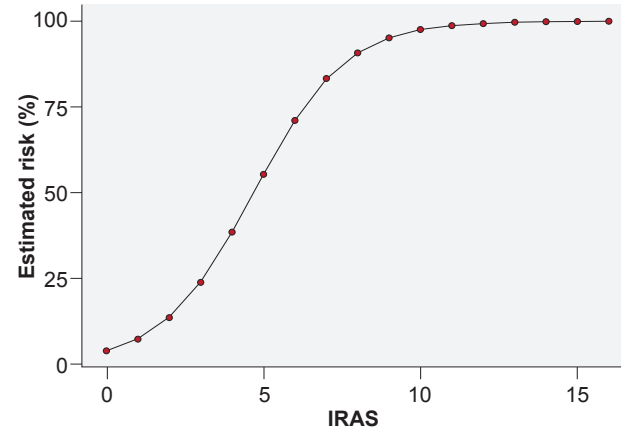

Figure 3 – Estimated probability (estimated risk) of refusal of ambulatory surgery using IRAS

Table 5 – IRAS associated with refusal of ambulatory surgery for test patients

Refused patients (n = 31)			**Non refused patients** (n = 31)		
IRAS	**Estimated risk**	**Number of patients**	**IRAS**	**Estimated risk**	**Number of patients**
0	3.855	1	0	3.855	16
2	13.672	1	2	13.672	4
5	55.419	3	3	23.939	7
6	71.185	7	6	71.185	2
8	90.704	5	8	90.704	1
9	95.095	4	12	99.347	1
11	98.711	2			
12	99.347	1			
14	99.833	5			
17	99.979	2			

In order to use the IRAS in clinical practice, a threshold must be defined in order to rule out the refusal for ambulatory surgery. This threshold may be adjusted in order to obtain certain pre-requisites, for example, to obtain a certain positive predictive value (IRAS makes a positive prediction – refusal – and the patient is really refused) or a certain negative predictive value (IRAS makes a negative prediction – no refusal – and the patient isn't refused). We can also choose a threshold to rule out refusal for ambulatory surgery that ensures a certain probability of refusal. For example, defining five points as a threshold - that is, patients who score less than five should be proposed for ambulatory surgery - implies that, for a patient with a predicted risk less than 50% (Table 4), the model will not refuse him for ambulatory surgery.

The model was tested in a group of randomly chosen 62 patients undergoing abdominal wall hernia surgery during 2019. Within the 62 patients, 31 had been initially refused for ambulatory surgery based on the clinical registries.

Table 5 presents the value of IRAS for the 62 test patients. IRAS ranged from 0 (estimated risk = 3.855%) to 11 (estimated risk = 98.711%) in the non-refused patient group, and from 0 (estimated risk = 3.855%) to 17 (estimated risk = 99.979%) in the refused patients group.

A threshold equal to five points meant a positive predictive value (or true positive) of 93.550% and negative predictive value (or true negative) of 87.100%, as detailed in Table 6.

DISCUSSION

Outpatient or ambulatory surgery is established nowadays in most western societies as a safe and effective way to perform certain surgical protocols. Its implementation is also advancing in developing countries as well.[8,9]

Outpatient surgery allows reduced hospital stays with lower rates of hospital-acquired infections and associated comorbidities and improved cost effectiveness. Overall, and based on the literature, patients are satisfied with outpatient procedures.[10,11]

Table 6 – Positive and negative predictive values for the model

Real\Model	Not refused	Refused
Non refused	87.10%	12.90%
Refused	6.45%	93.55%

The progress in terms of anesthetical and minimally invasive surgical protocols has allowed the inclusion of clinically more complex patients in an ambulatory setting in a wider range of medical specialties. Given the technical evolution regarding equipment and procedures, it is expected that this trend will continue in the coming future.[12-15]

Due to the current demand for ambulatory procedures by both patients and institutions, an efficient management of enrolled patients is of utmost importance to ensure the adequate sustainability of the ambulatory surgery process, allowing more patients to be operated with progressively shorter surgery waiting lists.

We observed that a percentage of patients initially proposed for outpatient surgery are rejected and redirected to inpatient care where they have to enrol in another waiting list, which leads to additional morbidity time and loss of active days, until undergoing surgery. This study determined which variables are relevant to the physician in order to reject or accept a patient for ambulatory surgery and developed a mathematical model using data from patients with abdominal wall hernia that predicts the probability of acceptance/rejection of a given patient. Furthermore, we tested the model in a random group of new patients with good results. One should bear in mind, however, that the variables and methodology chosen are applied to abdominal wall hernia. Although the same principles and methods may apply to other conditions, these are valid in this specific context.

This 5-year retrospective analysis shows that the majority of patients refused for ambulatory surgery were declined due to medical reasons. The reasons for this refusal, as described in clinical records and individual registries), are not entirely objective for defining a standard profile of a patient to be rejected.

Due to this observation, a randomly selected group of patients that was referred and underwent abdominal wall hernia surgery in ambulatory setting was used for comparison with the group of rejected patients. After

analysing both groups, it was observed that patients refused for ambulatory surgery were older, had a higher proportion of cardiovascular risk factors such as high blood pressure, dyslipidemia and type 2 diabetes mellitus. This group also had a significantly higher proportion of atrial fibrillation, ischemic cardiopathy, history of acute coronary syndrome, chronic kidney disease, chronic obstructive pulmonary disease, obstructive sleep apnea under Ci-PAP, and prior abdominal surgery. Finally, they also presented higher ASA Physical Status scores and had a significantly higher use of hypocoagulant and antiplatelet drugs.

Overall, one can state that the rejected patients were older patients with more conditions and more comorbidities and that, although the reasons for refusal are not objectively defined in the medical registries, these are in fact related with the specific pathological conditions and comorbidities. Such a detailed analysis is, to our knowledge, novel considering the current state of the art.

Using logistic regression analysis, a predictive model based on AUROC was built. It considers each individual patient based on his/her profile for the 94 variables studied for the conception of the model and estimates the probability of rejection/acceptance for ambulatory surgery.

Testing of a randomly selected group of patients out of our study group was performed in order to assess the accuracy of the model. A total of 62 patients that underwent abdominal wall hernia surgery during 2019 were randomly selected and evaluated. The model presented a concordance statistic (C-statistic) of 0.86. The C-statistic for a logistic regression model, a measure of goodness of fit for binary outcomes in a logistic regression model, is a commonly used statistic that measures discrimination. It generally lies between 0.5 and 1 with values close to 0.5 representing poor discrimination between patients (in this case rejected/accepted) and values closer to 1 representing good discrimination. Based on the literature, our model is considered a strong predictive model.[16,17] It can be a valid tool to aid in the medical decision of referral of a given patient to either inpatient or ambulatory care. Due to its construction, the input of data on conditions and comorbidities of a specific patient can be converted to a user-friendly tick box algorithm, which instantly delivers a probability of rejection/acceptance. In primary care for example, physicians can consider this information in their decision to direct a patient with an abdominal wall hernia to outpatient or inpatient care. In this way, a more informed decision is made on whether to send a patient, in order to more rapidly and effectively solve his/her medical issue.

Based on the analysed data, a patient proposed for ambulatory surgery that was declined, has a statistically significant additional waiting period of 11 months until surgery (571 ± 324 days), as compared with a similar patient undergoing surgery in outpatient care (240 ± 169 days) ($p < 0.05$). This represents an added burden in terms of morbidity time and loss of working days. Moreover, a more precise and informed referral might save human and financial resources if one considers the enrolment in medical and nursing appointments, in both outpatient and inpatient scenarios.

There are inherent limitations to this study. Firstly, the study describes the reality of a third line specialised central hospital in Western Europe. The habits and conditions of patients may not necessarily be generalizable to other populations although, in the authors' perspective, the results are expected to reflect the trends at a similar societal level.

Secondly, the model was built based on a 'template' of abdominal wall hernia surgery which constitutes a limitation in terms of broadness. However, this study shows that the reasons for refusal are mostly related with the individual profile of patients rather than the underlying condition itself. Therefore, it is reasonable to assume that its use can be adjusted to other surgical conditions not only within General Surgery but also in other medical specialties where ambulatory surgery is an alternative.

Moreover, the attribution of a level index based on the beta coefficient of the logistic regression model might overlook some aspects related with the clinical value of each particular variable. Finally, some limitations in the clinical application of the current model might be present due to the lack of external validation.

Focusing on future improvements of the healthcare system, strategies to cope with the reasons for refusal of a given patient in an outpatient setting can be described. For example, if one considers obstructive sleep apnea, a protocol and supportive guidelines to be followed can be developed for managing such patients. Ultimately, it would enable their inclusion as successfully treated patients in an ambulatory setting.

CONCLUSION

We analysed the reasons of refusal of a series of patients in an outpatient setting using five year-retrospective data from patients with abdominal wall hernias. When comparing these with patients that successfully underwent ambulatory surgery because of the same condition, we observed that certain comorbidities and conditions are significantly more prevalent in the refused population. Based on this observation, a mathematical model was developed by means of a logistic regression analysis and successfully tested in a group of new patients. It predicts, with good accuracy, which patients have a higher likelihood of being rejected or accepted for ambulatory surgery. Such a tool can be made accessible by a user-friendly interface that can aid in the decision of referring a specific patient to either inpatient or outpatient care. Indeed, the trend in most western societies is to reinforce ambulatory care in medical institutions while maintaining the possibility for either inpatient or outpatient care. This study can contribute to a reduction in waiting time until surgery, with less morbidity time and improved quality of life for patients, along with added efficacy in terms of healthcare management.

AUTHORS CONTRIBUTIONS

JO, SR, MC: Conception and draft. Data acquisition and

analysis. Writing and reviewing the paper. Final approval of the manuscript.

IN, CM, MS: Writing and reviewing the paper. Final approval of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENCIALITY

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

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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Retrospective Study of 114 Free Flaps for Head and Neck Oncological Reconstruction in a Portuguese Tertiary Cancer Center

Avaliação Retrospetiva da Reconstrução Oncológica da Cabeça e Pescoço com 114 Retalhos Livres num Centro Oncológico Terciário Português

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ABSTRACT

Introduction: The Portuguese experience in microsurgical reconstruction of the head and neck after oncological surgery is scantly described. The primary aim of this study was to characterize the use of microvascular reconstruction after head and neck tumor resection in a Portuguese tertiary oncological center

Material and Methods: The authors retrospectively evaluated 114 microvascular free flap procedures performed for head and neck reconstruction after oncological resection in a department of Head and Neck Surgery of a Portuguese tertiary oncological center. Patients were operated on from January 2012 to May 2018. Data on patient demographic features, tumour characteristics, perioperative complications, postoperative aesthetic and functional results, survival time and time to recurrence were extracted.

Results: Most tumours mandating microsurgical reconstruction were mucosal squamous cell carcinomas (85%) and were located in the oral region (95.6%). Around 45% of the patients had a T4a tumour and 30% a T2 tumour. Cervical metastases were present in 45.6% of the cases. The radial forearm flap and the fibular flap were the most commonly used microsurgical reconstructive options (58% and 41%, respectively). More than 80% of patients had no post-operative complications. Partial necrosis of the flap occurred in 6.1% of patients, while total flap necrosis occurred in 3.5% of cases. Aesthetic and functional results were considered at least satisfactory in all patients in which the flaps survived.

Conclusion: Microvascular reconstruction seems like a reliable treatment option in head and neck oncological surgery at our institution.

Keywords: Free Tissue Flaps; Head and Neck Neoplasms/surgery; Postoperative Complications; Reconstructive Surgical Procedures

RESUMO

Introdução: A experiência portuguesa na reconstrução microcirúrgica da cabeça e pescoço após cirurgia oncológica está escassamente descrita. O objectivo deste estudo foi caracterizar a reconstrução microcirúrgica da cabeça e pescoço num centro de referência terciário português.

Material e Métodos: Os autores avaliaram retrospetivamente 114 procedimentos de retalhos livres microvasculares realizados para reconstrução de cabeça e pescoço após ressecção oncológica num departamento de Cirurgia de Cabeça e Pescoço de um centro oncológico terciário português. Os doentes foram operados no período de janeiro de 2012 a maio de 2018. Foram registadas as características demográficas dos doentes, as características do tumor, as complicações peri-operatórias, os resultados estéticos e funcionais pós-operatórios, bem como o tempo de sobrevida e o tempo de recorrência.

Resultados: A maior parte dos tumores estava localizada na região oral (95,6%), sendo o carcinoma de células escamosas o tipo histológico mais frequente. Os retalhos antebraquial radial e fibular foram as opções reconstrutivas mais usadas (58% e 41%, respetivamente). Mais de 80% dos doentes não apresentaram complicações pós-operatórias. A necrose parcial do retalho ocorreu em sete doentes (6,1%), enquanto a necrose total do retalho ocorreu em apenas quatro casos (3,5%). Os resultados estéticos e funcionais foram considerados pelo menos satisfatórios em todos os doentes em que os retalhos sobreviveram.

Conclusão: A reconstrução microvascular parece ser uma opção fiável e eficaz no âmbito da cirurgia oncológica de cabeça e pescoço na nossa instituição.

Palavras-chave: Complicações Pós-Operatórias; Neoplasias de Cabeça e Pescoço/cirurgia; Procedimentos Cirúrgicos Reconstrutivos; Retalhos de Tecido Biológico

INTRODUCTION

Head and neck cancers represent the sixth most common malignant neoplasms in most developed countries.[1] Even today, reconstruction of major defects after head and neck oncological resection continues to be a vexing problem.[2-8] The literature is unanimous in stating that head and neck cancer has a major negative impact on patients' quality of life and socio-economic status.[9,10]

The head and neck regions are anatomically and

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histologically complex. Most malignant neoplasms in these regions arise from the mucosa of the upper aerodigestive tract, including the oral cavity, pharynx, larynx, nasal cavity, and sinuses. Other locations such as the salivary glands, thyroid, and parathyroid glands, soft tissue, bone, and skin are less frequent origins. The most common malignant neoplasms of the head and neck consist of squamous cell carcinoma and papillary thyroid cancer. Salivary gland cancers and sarcomas of the soft tissue and bone are less frequent.[5,11-13]

Although surgery has been the mainstay of therapy for these neoplasms, it can result in severe defects associated with aesthetical and functional impairment. Functional deficits range from difficulties in speech and swallowing to changes in eyelid function, oral competence, and maintenance of nasal and oral permeability.[5,8] Speech and swallowing impairment are particularly troublesome and are related with tumor dimension. In this context, tumors of the tongue and floor of the mouth have a poorer functional outcome.[8]

Reconstructive solutions are usually thought of in terms of aesthetic and functional units which are rebuilt starting from the underlying bony framework, and subsequently replacing the overlying integument. A spectrum of reconstructive options exists, ranging from allowing wounds to heal by secondary intention or primary closure of relatively small defects, to extensive reconstruction, involving pedicled and/or microvascular free flaps.[14-18] The appropriate option depends on the location and type of the defect, the patient's overall health, available donor sites, the status of the tissue adjacent to the defect (taking into consideration, for example, prior irradiation, infection and/or surgery), and on the function of the area to be reconstructed. Not only must the reconstructive surgeon choose which option is best suited for a given defect, but also secondary and tertiary options should be planned in case of flap failure or recurrent disease.[8,19]

Microvascular free flaps are increasingly performed worldwide in head and neck surgery departments since the 1970s, and are associated with better functional and aesthetical outcomes compared to those of more conservative treatments, while ensuring high flap survival rates.[20,21] They are reportedly reliable in achieving successful reconstruction of the head and neck regions, with the incidence of postoperative complications being largely related with preoperative comorbidities.[22] According to most authors, surgical re-exploration due to vascular insufficiency is necessary in less than 10% of the flaps, and necrosis of the flap occurs in only about 5% of cases. The American Society of Anesthesiology (ASA) class and age are considered the best predictors of post-operative morbidity.[23] However, as indications are progressively being widened, even advanced age has been questioned as an indicator of increased risk of perioperative complications, such as flap failure.[24,25] In fact, there are series of selected patients over 90 years old that are subjected to head and neck microsurgical reconstruction with no apparent increase in complications.[26] Prior radiotherapy, on the other hand, seems to have a particularly deleterious effect on free flap survival in the realm of head and neck oncological reconstruction.[27] Similarly, oral cavity and pharyngeal free flap reconstruction have also been associated with a greater complication rate.[28]

Surprisingly, despite this vast international experience, the information regarding the Portuguese reality in head and neck microvascular reconstruction after oncological resection is scant at best.[29-34]

The primary aim of this study was to characterize the use of microvascular reconstruction after head and neck tumor resection in a Portuguese tertiary oncological center over an extended period of time. Secondarily, the authors evaluated the influence of risk factors, such as tumor staging and therapy choice, in locoregional recurrence and patient survival.

MATERIAL AND METHODS

The authors retrospectively reviewed the clinical records of all patients subjected to reconstruction of the head and neck regions after tumour ablation in the department of Head and Neck Surgery of Instituto Português de Oncologia de Lisboa Francisco Gentil (Lisbon, Portugal), between January 2012 and May 2018. Only those patients with at least two post-operative follow-up visits were included in the study.

Data on the following variables were extracted: demographic features, co-morbidities, current immunosuppression status, antiaggregation, anticoagulation, smoking and alcohol drinking habits, clinical, histological and staging features of the primary tumour, reconstructive option, concomitant neck dissection, immediate and/or postoperative complications (occurring during and after hospital discharge, respectively),[35] need of adjuvant chemotherapy and/or radiotherapy, presence of recurrence and time to recurrence. Functional and aesthetical results were qualitatively evaluated by the surgical team as: poor, fair, good, or excellent. The authors used the seventh edition of the American Joint Committee on Cancer TNM Staging of Head and Neck Cancer and Neck Dissection Classification for tumor staging and neck dissection classification.[36]

The authors declare that they acted in accordance with the regulations established by the Ethics Committee of their institution and in accordance with the Helsinki Declaration of the World Medical Association that was updated in 2013.[37] Moreover, the authors confirm that they followed their institution's regulations on publishing data. Being a retrospective descriptive study, no formal ethical committee review was required.[38]

Statistical analysis

The Statistical Package for the Social Sciences (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) was used for statistical analysis. A significance level of 0.05 was considered. Values were expressed as means and standard deviation (SD) for continuous variables and as percentages for

categorical variables. We evaluated frequency differences using the chi-square test. The Yates's correction for continuity was applied in order not to overestimate chi-square test values. Differences between means were evaluated using the Student's *t*-test. The association between specific characteristics and the recurrence of squamous cell carcinoma after surgery was assessed via a logistic regression approach using the Firth procedure.[39] For odds ratios (OR), 95% confidence intervals (CI) were used.

RESULTS

The authors identified 114 patients subjected to head and neck reconstruction using free flaps (Table 1). In each case, the choice of a microsurgical reconstruction was made by the surgical team based on the potential superiority of this option compared to more traditional techniques. Most patients were male (n = 84; 74%). The average age of patients at the time of surgery was 54.0 ± 10.6 years. Mean follow-up time was 43.2 ± 3.1 months, ranging from 12 to 85 months. Almost half of the patients (44%) were considered healthy prior to the diagnosis of neoplasia. Interestingly, the single most frequent pre-operative comorbidity was a prior malignant neoplasm diagnosis in another location, which was present in 27% of patients. In 15% of all patients there was a history of a previous squamous cell carcinoma of the lip, oral cavity or nasal-oro-hypopharynx regions. These latter patients had been subjected to prior surgery in the head and neck region. Hypertension was present in 16% and asthma or chronic obstructive pulmonary disease (COPD) in 8% of the cases (Table 1).

Around a quarter of patients were immunosuppressed. and the most important causes were identified as neoadjuvant chemoradiotherapy (7.9%), neoadjuvant radiotherapy (7.0%), diabetes mellitus (3.5%), corticosteroid therapy (2.6%) and HIV infection (1.8%) (Table 1). However, this was not considered an exclusion criteria to perform a microvascular free flap. Only 8% were anti-aggregated, and no patient was hypo-coagulated. Prior to the surgery, three quarters of the patients had a history of cigarette smoking, and around 60% reported regular alcohol consumption (Table 1).

Regarding the primary tumour histopathologic features, the most common tumour types were mucosal squamous cell carcinoma (85%), and cutaneous squamous cell

Table 1 – Clinical data analysis of the patients who underwent microvascular free flap

Variables	**n** (%)
Gender	
Male	84 (73.7)
Female	30 (26.3)
Age (mean ± standard deviation [years])	54.05 ± 10.6
Comorbidities	
None	50 (43.9)
Malignant neoplasm	29 (27.3)
Squamous cell carcinoma of the lip, oral cavity or nasal-oro-hypopharynx region	17 (14.9)
Other tumors, except the head and neck region	6 (5.3)
Other carcinomas of head and neck region	4 (3.7)
Lymphoproliferative disease	2 (1.8)
Hypertension	18 (15.8)
Asthma or Chronic obstructive pulmonary disease	9 (7.9)
Other	6 (5.4)
Immunosuppression	
None	86 (75.4)
Neoadjuvant chemoradiotherapy	9 (7.9)
Neoadjuvant radiotherapy	8 (7.0)
Diabetes mellitus	4 (3.5)
Corticosteroid therapy	3 (2.6)
HIV infection	2 (1.8)
Other	2 (1.8)
Antiaggregation	9 (7.9)
Anticoagulation	0 (0.0)
Consuming habits	
Smoking	85 (74.6)
Alcohol	67 (58.8)

carcinoma (4%). The tongue and the floor of the mouth were the most frequent primary tumour sites (Table 2). Histologically, around 45% of the patients had a T4a tumour, and 30% a T2 tumour. The histopathological examination showed that cervical metastases were present in 45.6%, whereas 46.5% presented a N0 neck staging. More than three quarters (76%) possessed a moderate or an undifferentiated carcinoma (Table 3).

Concerning tumour histopathological features, ominous characteristics were present in around half of the patients and these were considered an indication for adjuvant chemotherapy. Amongst these negative histopathological characteristics, perineural invasion was present in 16.7%, lymphovascular invasion in 14.0% and simultaneous invasion of nerves and vessels in 14.0%. Only 10.5% of patients had a tumour resection margin below 1 mm (Table 3).

As for the choice of free flap used for the oncological reconstruction, the radial antebrachial fasciocutaneous flap was used in 58% of patients, particularly when thin soft tissue was required to reconstruct the defect (Table 4). Fibular bone flaps were used in 41% of patients. The latter flap was especially useful to reconstruct subtotal segmental mandibular defects. Its thick cortical plates proved ideal to resist to mastication forces and allow a smooth posterior fixed oral rehabilitation. All flaps were connected to the recipient site with at least one arterial and two venous anastomoses.

In most cases, microvascular reconstruction was performed immediately after tumour removal in the same operative time (89%). In less than 3%, reconstruction was performed within one to two years after tumour extirpation, and in 4% microvascular reconstruction was deferred to at least five years after tumour ablation. Concerning concomitant neck dissection, 55% had a unilateral modified radical dissection, 25% had a bilateral modified radical dissection and 11% did not have a neck dissection (Table 4).

In the postoperative period, free flap reconstruction patients were admitted to the intensive care unit for the first 24 to 48 hours. Even though more than 80% of the patients had an uneventful post-operative period, 11.4% experienced an immediate post-operative complication (psychomotor agitation, and poor flap vascularization). In the late postoperative period, there were four cases of tumour progression (3.5%) with two cases culminating in patient death. Partial or total flap necrosis occurred only in seven (6.1%) and four (3.5%) cases, respectively. Fibula and radial forearm free flaps showed no significant differences in terms of viability. Patients with flap suffering (9.6%) underwent microvascular

Table 2 – Clinical and staging features of the primary tumour

Variables	n (%)
Site	
Tongue	36 (31.6)
Floor of the mouth	27 (23.7)
Gum	17 (14.9)
Retromolar trigone	15 (13.2)
Mandible (intra-osseous)	8 (7.0)
Skin	5 (4.4)
Hard palate	2 (1.8)
Other	4 (3.6)
Histology	
Squamous cell carcinoma of oral cavity	97 (85.1)
Skin carcinoma	4 (3.5)
Ameloblastoma	3 (2.6)
Malignant odontogenic tumour	3 (2.6)
Salivary gland carcinoma	3 (2.6)
Melanoma	2 (1.8)
Other	2 (1.8)
Tumour staging	
T	
Not applicable[a]	8 (7.0)
Carcinoma *in situ*	0 (0.0)
T1	9 (7.9)
T2	34 (29.8)
T3	11 (9.6)
T4a	52 (45.6)
N	
Not applicable[b]	9 (7.9)
N0	53 (46.5)
N1	10 (8.8)
N2a	0 (0.0)
N2b	34 (29.8)
N2c	8 (7.0)
M0	114 (100)

[a]: odontogenic tumours; [b]: odontogenic tumours and basal cell carcinomas

Table 3 – Histopathologic features of the primary tumour

Variables	n (%)
Histological differentiation (G)	
Not applicable	12 (10.5)
G1	15 (13.2)
G2	62 (54.4)
G3	25 (21.9)
Negative histological characteristics	
None	57 (50.0)
Perineural invasion	19 (16.7)
Lymphovascular invasion	16 (14.0)
Both	16 (14.0)
Not applicable	6 (5.3)
Histological margins	
≥ 5 mm	48 (42.1)
1 - 4 mm	52 (45.6)
< 1mm	12 (10.5)
Not applicable	2 (1.8)

Histological differentiation of the tumour: G1 Well differentiated (low grade); G2 Moderately differentiated (intermediate grade); G3 Poorly differentiated (high grade)

Table 4 – Surgical data

Variables	n (%)
Free flap	
Fibula	47 (41.2)
Antebrachial	66 (57.9)
Other	1 (0.9)
Reconstructive surgery	
Same operating time	101 (88.6)
≤ 1 year	2 (1.8)
> 1 - 4 years	6 (5.5)
> 5 years	5 (4.4)
Neck dissection	
No	13 (11.4)
Unilateral radical modified	63 (55.3)
Bilateral radical modified	28 (24.6)
Ipsilateral radical modified and contralateral supraomohyoid neck dissection	6 (5.3)
Unilateral supraomohyoid neck dissection	3 (2.6)

anastomosis revision and/or local surgical debridement. In cases of full-thickness flap necrosis, a contralateral free flap or local pedicled flap were used. There was no statistically significant association between flap failure and specific demographic or clinical features.

Aesthetic and functional results were considered at least satisfactory in all patients in which the flaps survived. Most patients were subjected to adjuvant therapy with either radiotherapy or a combination of chemotherapy and radiotherapy (Table 5). No flap complications were observed as a consequence of these treatments.

The degree of tumour histological differentiation was statistically different in males, smokers, as well as in patients with alcohol drinking habits: more G2 tumours (moderately differentiated) than G1 or G3 tumours (well differentiated and poorly differentiated, respectively) were observed in males (67% *vs* 39% $p = 0.028$), smokers (68% *vs* 35% $p = 0.004$) and alcohol consumers (69% *vs* 46%, $p = 0.016$) (Table 6).

Female patients presented a lower incidence of smoking (33.3% *vs* 89.3%, $p < 0.001$) and alcohol drinking habits (13.3% *vs* 75%, $p < 0.001$) compared to male patients.

Table 5 – Postoperative period

Variables	n (%)
Postoperative complication	
None	95 (83.3)
Psychomotor agitation	2 (1.8)
Flap partial necrosis	7 (6.1)
Flap total necrosis	4 (3.5)
Progression of tumoral disease	4 (3.5)
Death	2 (1.8)
Adjuvant radiotherapy	85 (74.6)
Adjuvant chemoradiotherapy	67 (58.7)

Female patients had a lower tumour recurrence (30%) compared to male patients (40%), even though the difference was not statistically significant. Locoregional tumor recurrence was observed in 32.5% of patients, with the majority being diagnosed in the first 6 months after the oncological surgery (18.4%). Afterwards, recurrences were increasingly rare (7.9% between six to 12 months postoperatively, 5.3% from one to three years, and 0.9% after more than three years). In fact, most of recurrent cases were associated with the persistence of the primary tumor. Metastases were detected in only five cases (4.4%).

Comparing patients' survival time or time to recurrence based on their surgical margins on histopathology examination (> 5 mm; 1 - 5 mm; < 1 mm), there were no statistically significant differences ($p = 0.143$ and $p = 0.157$, respectively). Moreover, none of the tested characteristics (tumour margin size, T and N staging, and type of neck dissection) was associated with tumour recurrence (no recurrence versus any recurrence).

DISCUSSION

Although microsurgical reconstruction of the head and neck regions has been described for half a century, the inherent technical difficulty of the procedures has discouraged many large volume centres of adopting these techniques for the majority of patients.[21] As far as the authors could determine, this is by far the largest series of microsurgical head and neck reconstruction after oncological surgery reported by a single tertiary centre in Portugal.[29-34]

As most authors, in our series two flaps were mainly used for microsurgical reconstruction: the fasciocutaneous radial antebrachial flap was used in 58% of patients when thin soft tissue was required, and a fibular bone flap was raised to reconstruct subtotal segmental mandibular defects. The thick cortex of this bone allows the insetting of reconstruction plates that are ideal to resist mastication forces

Table 6 – Tumour histological differentiation by patient' characteristics

Variables				
Gender, n (%)	G1	G2	G3	*p*-value
Female	7 (30.4)	9 (39.1)	7 (30.4)	
Male	8 (10.1)	53 (67.1)	18 (22.8)	**0.028**
Immunosuppression, n (%)				
No	13 (16.3)	48 (60.0)	19 (23.8)	
Yes	2 (9.5)	14 (66.7)	5 (23.8)	0.712
Smoking habits, n (%)				
No	8 (34.8)	8 (34.8)	7 (30.4)	
Yes	7 (8.9)	54 (68.4)	18 (22.8)	**0.004**
Alcohol consumption, n (%)				
No	10 (27.0)	17 (45.9)	10 (27.0)	
Yes	5 (7.7)	45 (69.2)	15 (23.1)	**0.016**

Histological differentiation of the tumour: G1 Well differentiated (low grade); G2 Moderately differentiated (intermediate grade); G3 Poorly differentiated (high grade)
Frequency differences were evaluated using the chi-square test. The Yates's correction for continuity was applied.

and to permit a smooth posterior fixed oral rehabilitation.[40,41]

The authors performed reconstructive surgery at the same time of tumour ablation in about 87% of the cases. In less than 3%, the reconstruction was deferred to one to two years after removing the tumour and in about 4% only after five years of follow up. In the present series, tumour recurrence had no relationship with the timing of the microsurgical reconstructive procedure. These data vindicate those who defend immediate microsurgical reconstruction, in order to minimize functional and aesthetical limitations while ensuring oncological safety.[41-43]

Regarding neck dissection, a unilateral modified radical dissection was performed in 55% of the cases, a bilateral modified radical dissection in 25%, and in 11% of the patients no neck dissection was done (benign tumours, *in situ* tumours and basal cell carcinomas). Even in T1 patients (7.9%), with no clinical neck metastasis, a selective neck dissection was performed, that in conjunction with adjuvant radiotherapy has been shown to increase survival rate.[11-13] The authors endorse the view that prophylactic neck dissections are warranted for clinically negative head and neck tumors that have a significant probability of having occult metastasis in the neck.[44-46] In the case of large tumours mandating microsurgical reconstruction, as the ones described in this series, the authors do not regularly perform sentinel node biopsy, due to the risk of overlooking skip metastases.[44]

More than 80% of patients presented an eventful postoperative period. Flap partial and total necrosis only occurred in seven (6.1%) and four (3.5%) cases, respectively. These data lend support to the safety of microsurgical reconstruction in the realm of head and neck oncological reconstruction.[2,5,6,8,19,20,23,42]

Probably due to the small number of cases in which partial or total flap necrosis occurred, it was not possible to associate flap failure with specific demographic or clinical features in the present series. However, according to the literature, technical errors and certain pre-existing conditions are associated with a higher tendency to flap failure, namely alcohol abuse, radiotherapy and diabetes mellitus.[6,7,47] Other characteristics, such as advanced age and gender, have not been linked to an increased risk of free flap failure.[24,48-50] Nevertheless, the importance of meticulous attention to perioperative management of comorbidities, hemoglobin and albumin levels, anticoagulation, fluid and electrolytes, as well as flap monitoring cannot be overstated.[47,48]

It is known that negative histopathologic features can help to predict a higher tumour recurrence rate. Among those, extracapsular ganglion dissemination, perineural and vascular invasion, poor tumour differentiation and positive margins seem to be crucial to patient prognosis, and indicate whether a patient should be directed or not to adjuvant chemotherapy.[51] Extranodal extension was introduced in the eight edition of the American Joint Committee on Cancer (AJCC) staging manual TNM staging for both clinical and pathologic N staging of tumours not associated with high-risk Human Papillomavirus. In fact, extranodal extension has been increasingly recognized as important independent prognostic factor.[52] However, for the duration of most of this patient series the seventh edition of the AJCC TNM staging was in place, in which this variable was not explicitly included.[36] Therefore, the authors did not assess this variable in the present study. Further studies are warranted to evaluate if extranodal extension status has an impact on free flap reconstruction of the head and neck.

Half of patients had at least one negative histopathologic feature with perineural invasion being predominant (14%). The authors observed that the degree of tumor histological differentiation was statistically different in smokers *versus* non-smokers, males *versus* females, as well as in patients with alcohol drinking habits (Table 6). Smoking habits and alcohol drinking habits were more prevalent in male patients, whereas tumour recurrence was less frequent in female patients, although this latter difference was not statistically significant.

It is known that histological margins in squamous cell carcinoma are the most important survival indicator. By following the National Comprehensive Cancer Network®

guidelines, the authors considered a free margin if the resected specimen included a cuff of at least 5 mm of non-invaded tissue, even when accounting for tumour shrinkage as result of histopathology preparation.[53] In this context, free margins were obtained in almost half of the patients. The authors feel that this finding was due to the advanced stage of many of the tumours. In fact, around 45% of the patients had a T4a tumour and 45.6% cervical metastasis at the time of surgery. These data highlight the importance of an early diagnosis, in order to prevent growth and histological mutations, which carry a worse prognosis.[19]

It is widely accepted that free flap reconstruction does not preclude adjuvant therapy.[2,24] In the present series, the majority of patients (74.6%) were treated with radiotherapy, and 58.7% with combined chemoradiotherapy. No significant flap complications were noted after these treatments, which lends further support to the use of free flaps in the realm of head and neck oncological resection.

It is widely accepted that squamous cell carcinoma is a generalized mucosal disease.[54] Long-term follow up of squamous cell carcinoma is mandatory and distinguishing a new primary tumour from a persistence or recurrence of the same tumour is paramount in order to ensure an adequate treatment.[54,55] The authors observed locoregional tumor recurrence in 32.4% of the patients with the majority having a diagnosis in the first six months post-operatively. In fact, most of these cases probably resulted from the persistence of the primary tumor.[56] Remote metastases were found in only five cases (3.55%).

These data are well aligned with those generally described in the literature for tertiary oncological centers. It is well established that complete resection of malignant tumors in the head region is frequently more difficult than that of other anatomical regions, due to the high density of functional and aesthetically relevant structures in the former regions.[57-59]

The authors observed that neither the survival time nor the time until recurrence were statistically different according to surgical margins. Similarly, the authors did not associate any of the tested characteristics (surgical margins, T and N staging or neck dissection) with recurrence. However, the prognostic value of TNM staging in head and neck cancer has been thoroughly documented. The lack of association in the present study is probably the result of the relatively small number of patients, and of the limited follow up time.

This study provides a single institution and retrospective analysis with cumulative surgical experience over eight years. During this period, different surgeons intervened, but only one senior surgeon (M.V) executed the microvascular anastomoses, which could be a potential source of bias. Further studies are warranted to confirm or rebut these findings in smaller institutions, and in places where surgeries are performed more often by junior doctors.

Another potential limitation of this study is that the experience reported refers exclusively to that of the Head and Neck Surgery Department of Instituto Português de Oncologia de Lisboa Francisco Gentil (Lisbon, Portugal). It does not include the experience of other Departments of this institution namely of the Otorhinolaryngology and Plastic and Reconstructive Surgery Departments, that also perform free flap reconstruction on a regular basis. Hence, 95.6% of the oncological defects mandating microvascular reconstruction in the present series were located in the oral region. Future studies based on prospective hospital wide or even nationwide registries may allow the inclusion of data pertaining to different anatomical regions and various medical specialties.[60]

CONCLUSION

The authors believe that this sizeable experience of microvascular reconstruction seems to be a reliable treatment option in the context of head and neck oncological reconstructive surgery in a Portuguese tertiary centre. In this realm, microvascular flaps provided adequate aesthetic and functional results, with no compromise of the start of adjuvant therapy.

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AUTHORS CONTRIBUTION

AS, PC: Conception and design of the work. Acquisition, analysis, and interpretation of data for the work. Drafting.

MV: Conception and design of the work. Acquisition, analysis, and interpretation of data for the work. Drafting the work and revising it critically as far as format and contents are concerned.

CS, MM: Conception and design of the work. Analysis and interpretation of data for the work. Critical review of the work as far as format and contents are concerned.

CZ, DC: Conception or design of the work. Analysis and interpretation of data for the work. Drafting.

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 CONFIDENCIALITY

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

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Fatores de Risco Associados à Recusa de Notas de Transferência e Vales Cirurgia: O Caso da Região Centro em Portugal

Risk Factors Associated with the Refusal of Surgery Vouchers: The Case of Central Portugal

ARTIGO ORIGINAL

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RESUMO

Introdução: Em Portugal, a recusa de Notas de Transferência e Vales Cirurgia é elevada, dificultando o cumprimento dos tempos máximos de resposta garantidos para cirurgias eletivas. Os objetivos deste estudo foram analisar a evolução de notas e vales emitidos/recusados para o período compreendido entre o terceiro trimestre de 2016 e o quarto trimestre de 2019 e os fatores de risco associados à sua recusa, na Região Centro, em Portugal.

Material e Métodos: Os dados provêm da base de dados de notas/vales cancelados e da lista de inscritos para cirurgia a 31 de dezembro de 2019. Na análise dos fatores de risco recorremos à regressão logística múltipla.

Resultados: A emissão de notas/vales aumentou após 2018 e as taxas de recusa de transferência mantiveram-se acima dos 55% a partir do terceiro trimestre de 2018. A *chance* de recusa foi maior para idades superiores a 55 anos (OR = 1,136; IC = 1,041 – 1,240; OR = 1,095; IC = 1,005 – 1,194; OR = 1,098; IC = 1,002 – 1,203, para as faixas etárias 55 - 64, 65 - 74 e 75 - 84, respetivamente) para a cirurgia convencional, quando comparada com ambulatório (OR = 2,498; IC = 2,343 – 2,663) e para a especialidade de Ortopedia, quando comparada com Cirurgia Geral (OR = 1,123; IC = 1,037 – 1,217). A *chance* de recusa variou também entre hospitais (por exemplo OR = 3,853; IC = 3,610 – 4,113; OR = 3,600; IC = 3,171 – 4,087; OR = 2,751; IC = 3,383 – 3,175 e OR = 1,337; IC= 1,092 – 1,637, para os hospitais de origem identificados como HO_2, HO_7, HO_4 e HO_6, respetivamente).

Conclusão: Neste estudo confirmou-se que a emissão de notas de transferência/vales cirurgia aumentou após a redução legal dos tempos máximos de resposta garantidos em 2018 e que as taxas de recusa de transferência vinham já a registar uma tendência de aumento desde 2016, tendo-se mantido acima dos 55% a partir do terceiro trimestre de 2018. Alguns fatores para os quais se encontrou uma associação positiva com a recusa são a idade, a cirurgia convencional (em comparação com ambulatório) e a especialidade de Ortopedia (em comparação com Cirurgia Geral).

Palavras-chave: Acesso aos Serviços de Saúde; Fatores de Risco; Listas de Espera; Portugal; Procedimentos Cirúrgicos; Procedimentos Cirúrgicos Eletivos

ABSTRACT

Introduction: In Portugal, the rate of refusals regarding transfer between hospitals through surgery vouchers is high, which makes it difficult to meet maximum waiting times for elective surgeries. The objectives of this study are to examine how many vouchers were issued and refused between the third quarter of 2016 and the fourth quarter of 2019 and the risk factors associated with their refusal, in Central Portugal

Material and Methods: Data was obtained in the database of cancelled vouchers and the waiting list for surgery on the 31st December 2019. Multiple logistic regression was used to investigate risk factors.

Results: The number of issued vouchers increased after 2018 and the rate of refusals has been above 55% since the 3rd quarter of 2018. Refusal was more likely for individuals aged 55 years or above (OR = 1.136; CI = 1.041 – 1.240; OR = 1.095; CI = 1.005 – 1.194; OR = 1.098; CI = 1.002 – 1.203, for the age bands 55 - 64, 65 - 74 and 75 - 84, respectively), for inpatient surgery when compared to ambulatory (OR = 2.498; CI = 2.343 – 2.663) and for Orthopaedics when compared to General Surgery (OR = 1.123; CI = 1.037 – 1.217). The *odds* of refusal also varied across hospitals (for example OR = 3.853; CI = 3.610 – 4.113; OR = 3.600; CI = 3.171 – 4.087; OR = 2.751; CI =3.383 – 3.175 e OR = 1.337; CI = 1.092 – 1.637, for hospitals identified as HO_2, HO_7, HO_4 and HO_6, respectively).

Conclusion: In this study, we have confirmed that the number of issued surgery vouchers increased after the administrative reduction of maximum waiting times in 2018 and that the rate of transfer refusals has been increasing since 2016 and has remained above 55% from the third trimester of 2018 onwards. Some of the factors for which we obtained a positive association with refusal are age, inpatient surgery (compared to ambulatory) and Orthopaedics (compared to General Surgery).

Keywords: Elective Surgical Procedures; Health Services Accessibility; Portugal; Risk Factors; Surgical Procedures; Waiting Lists

INTRODUÇÃO

As listas e os tempos de espera para cuidados de saúde em geral, e para cirurgias eletivas em particular, constituem uma importante questão da política de saúde na maioria dos países da Organização para a Cooperação e Desenvolvimento Económico (OCDE).[1] Em alguns países da OCDE os tempos de espera para cirurgias eletivas estagnaram na última década mas em outros começaram a subir mesmo antes da pandemia por COVID-19.[2] Embora possam existir vários constrangimentos e tempos de espera nos diversos contactos do utente com os serviços de

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saúde, a interpretação mais comum de tempo de espera para cirurgia eletiva corresponde ao tempo que medeia a data em que o utente é adicionado à lista de espera, para um determinado procedimento e após a avaliação de um especialista, e a data em que é admitido num serviço para a realização do procedimento em causa.[3] Esta é também a interpretação subjacente ao presente trabalho.

Os tempos de espera ocorrem quando há um desequilíbrio entre a oferta e a procura de serviços de saúde. Num cenário de mercado tradicional, o preço ajusta-se promovendo o encontro entre a oferta e a procura. No setor da saúde e em países onde existe cobertura universal, combinada com copagamentos nulos ou diminutos e recursos limitados, os tempos de espera emergem como um mecanismo de racionamento alternativo ao preço e independente da capacidade de pagar.[4] Tendências como o aumento da esperança de vida da população, do número de cidadãos com doença crónica e do aparecimento de novos medicamentos e tecnologias em saúde contribuem para aumentar as listas de espera, enquanto o aumento da oferta de serviços e da produtividade dos prestadores concorrem para a redução dessas listas.[1]

Do ponto de vista da eficiência, os tempos de espera são relevantes para evitar a subutilização da capacidade instalada[5] e podem mesmo pressionar os hospitais a aumentarem a sua produtividade.[1,3] No entanto, longos tempos de espera podem acarretar aumento de custos para os prestadores devido à gestão das listas de espera.[6] Da perspetiva dos utentes são várias as desvantagens associadas aos tempos de espera como sejam a deterioração do seu estado de saúde e eventualmente da sua autonomia, prolongamento do sofrimento e a ansiedade, todos confluindo na redução da qualidade de vida.[3,7-9] Adicionalmente, existe evidência ao nível dos países da OCDE de tempos de resposta desiguais para cuidados prestados mesmo no setor público. Esta desigualdade tende a ser favorável aos indivíduos com estatuto socioeconómico mais elevado.[10,11]

Em face destes problemas, têm sido adotadas algumas medidas de política para combater tempos de espera considerados excessivos. Algumas são direcionadas para a oferta como o aumento temporário dos serviços oferecidos com financiamento extra, aperfeiçoamento da gestão das listas, subcontratação aos setores privado e social ou pagamentos baseados na atividade por forma a incentivar maior eficiência. Do lado da procura existem exemplos, tais como normas para priorizar doentes e subsidiação de seguros privados. Pela sua maior eficácia reconhecida, temos assistido nos países da OCDE a um enfoque crescente em políticas combinadas como por exemplo os tempos máximos de resposta garantidos (TMRG), associados ou não a sanções, e à escolha dos utentes e concorrência entre prestadores.[1,12] O objetivo dos TMRG é assegurar a prestação do serviço requerido dentro de um período de tempo, previamente definido de acordo com o que é considerado clinicamente aceitável em cada caso tipo.

Em muitos países, os TMRG têm sido cada vez mais associados à escolha de prestador por parte dos utentes como forma de impor efetivamente os tempos máximos que se pretendem garantir.[1] Em teoria, espera-se que a possibilidade de escolha conduza ao aumento da qualidade dos serviços prestados e da produtividade devido à concorrência entre instituições no intuito de atrair utentes e consequentemente o financiamento respetivo.[13] Por sua vez, a qualidade dos cuidados percebida pelos utentes dependerá de diversas determinantes como por exemplo a reputação do hospital, a competência dos profissionais e o relacionamento interpessoal.[14,15] Não obstante a influência previsível da qualidade dos serviços sobre a escolha dos utentes, este processo é complexo, envolvendo outros fatores. Desde logo a escolha fica sujeita à condição do procedimento ser oferecido pela instituição pretendida. Adicionalmente, a escolha pode ser influenciada pela recomendação de conhecidos ou de profissionais de saúde bem como pela localização, existindo uma preferência por instituições próximas da área de residência sobretudo no caso de utentes idosos.[16]

Em Portugal, os tempos de espera têm também constituído motivo de preocupação no âmbito da política de saúde ao longo das últimas décadas. Deste modo, foram sendo adotadas medidas, destinadas, não só mas essencialmente, ao combate às listas de espera cirúrgicas. O programa mais antigo, o Programa Específico de Recuperação de Listas de Espera, teve uma duração de três anos entre 1995 e 1998; outros lhe seguiram.[1,17] Em 2004, foi implementado o Sistema Integrado de Gestão de Inscritos para Cirurgia (SIGIC), ainda em vigor, e que tem por objetivo gerir, de forma integrada e continuada, a lista de inscritos para cirurgia nos estabelecimentos do Serviço Nacional de Saúde (SNS). A Lei n.º 41/2007 de 24 de agosto[18] veio introduzir o conceito de TMRG no quadro da Carta dos Direitos de Acesso aos Cuidados de Saúde no SNS, sendo os tempos específicos definidos mais tarde em 2008 pela Portaria n.º 1529/2008 de 26 de dezembro.[19] Também em 2008, foi instituída a liberdade de escolha do utente, pela Portaria n.º 45/2008 de 15 de janeiro.[20] De acordo com este modelo, em Portugal, quando 50% do TMRG é atingido é emitida uma Nota de Transferência (NT) que permite ao utente realizar a sua cirurgia noutro hospital público com disponibilidade. Aos 75% do tempo é emitido um Vale Cirurgia (VC) que permite ao utente realizar a sua cirurgia num conjunto mais alargado de instituições do setor público, privado e social. Os utentes têm o direito de recusar a transferência do processo, tendo a circunstância de um elevado número de recusas sido identificada há mais de uma década.[21] No triénio 2014 - 2016 a taxa de utilização de NT/VC continuava muito baixa, situando-se nos 20%.[22] A Portaria n.º 153/2017 de 4 de maio,[23] com efeitos a partir de 1 de janeiro de 2018, veio implementar a redução dos TMRG, o que significa que os utentes passam a receber as NT/VC mais cedo, o que pode aumentar ainda mais a já elevada recusa destes mecanismos.

Neste contexto, torna-se pertinente perceber quais os fatores de risco associados à recusa de NT/VC com vista a delinear estratégias que aumentem a sua eficácia,

contribuindo desse modo para um melhor cumprimento dos TMRG.

Tanto quanto é do nosso conhecimento, o único estudo sobre recusa de transferência usa dados de 2007,[21] baseando-se numa metodologia e amostra diferentes das que são utilizadas neste trabalho.

Os objetivos deste estudo são assim investigar esses fatores de risco para o caso da Região Centro e analisar a evolução de NT e VC emitidos e recusados entre o terceiro trimestre de 2016 e o quarto trimestre de 2019.

MATERIAL E MÉTODOS

Para o presente estudo foram recolhidos dados relativos à Região Centro e referentes a: i) número de NT/VC emitidos mensalmente, extraídos pela Administração Central do Sistema de Saúde (ACSS, IP), para o período entre 1 de julho de 2016 e 31 de dezembro de 2019; ii) NT/VC cancelados, por motivo, extraídos do Sistema Integrado de Gestão da Lista de Inscritos para Cirurgia (SIGLIC), para o período entre 1 de julho de 2016 e 31 de dezembro de 2019; iii) lista de inscritos para cirurgia (LIC) em 31 de dezembro de 2019, extraída do SIGLIC. A extração da informação do SIGLIC foi efetuada pela Administração Regional de Saúde do Centro (ARSC, IP).

A base de dados de NT/VC cancelados continha inicialmente 87 215 observações com informação acerca do hospital de origem (HO), especialidade cirúrgica no HO, número da posição que ocupa na LIC do HO, motivo de cancelamento e data de cancelamento do vale. Para analisar a evolução trimestral de NT/VC emitidos e cancelados, apenas se considerou o motivo 'Recusa de Transferência', sendo neste caso a amostra constituída por 71 504 observações.

A base de dados da LIC continha inicialmente 50 382 episódios. Cada episódio compreende informação respeitante a todo o processo clínico do utente: número do processo de origem, número do processo de destino, data de inclusão, prioridade, idade do utente, sexo, HO, número da LIC de origem, número da LIC de destino, especialidade cirúrgica, código de intervenção e sua respetiva designação, modalidade de cirurgia (convencional ou ambulatório), código da patologia, patologia, tempo de espera (em meses), estado atual do utente, data de agendamento, localidade do utente, código do grupo de extração e sua respetiva descrição, código do grupo nosológico e sua respetiva descrição, e médico proponente.

Na análise dos fatores de risco associados à recusa de NT/VC, este estudo apenas considera os utentes maiores de idade, no pressuposto de não serem os menores a decidir sobre a recusa, ou não, de NT/VC. Por conseguinte, foram eliminadas 3291 observações da base de dados inicial.

Face aos novos valores dos TMRG definidos para cada patologia e nível de prioridade, e perante o tempo de espera e nível de prioridade para cada episódio clínico indicado na LIC, determinou-se em que estádio de tempo de espera se encontrava cada episódio: inferior a 50%, igual ou superior a 50% e inferior a 75%, igual ou superior a 75% e inferior a 100%, ou superior a 100% do TMRG. Para a análise dos fatores de risco associados à recusa, assumiu-se que todos os episódios com tempos de espera inferiores a 50% não se qualificavam para NT ou VC pelo que foram eliminados da base de dados. Deste modo, a amostra final utilizada na análise de regressão corresponde a 33 153 observações.

Nesta análise, considerou-se como variável dependente a variável binária 'Recusa' que assume o valor 1 se o utente recusou NT/VC e 0, caso contrário. Para construir esta variável, comparou-se o número da LIC de origem presente na base de dados de NT/VC cancelados com o número da LIC de origem presente na base de dados dos episódios que aguardavam resolução cirúrgica em 31 de dezembro de 2019. Quando os números das LIC coincidem, significa que houve cancelamento de NT/VC por recusa de transferência. Assim, nos casos em que os números das LIC coincidem, a variável 'Recusa' toma o valor um, e nos casos em que o número da LIC dos episódios em espera em 31 de dezembro não tem correspondência na base de dados dos NT/VC cancelados a variável 'Recusa' toma o valor zero.

Como variáveis explicativas e tendo em conta a informação disponível na base de dados, selecionaram-se variáveis sociodemográficas e variáveis relativas ao processo clínico do utente. Para o efeito, consideraram-se o sexo e a idade dos utentes, o HO, o nível de prioridade, a modalidade, a especialidade da cirurgia e o período de inscrição na lista de espera (se antes ou após a redefinição dos TMRG). A Tabela 1 apresenta a categorização destas variáveis, a respetiva descrição e a sua representatividade na amostra.

Para analisar a associação entre os diversos fatores considerados neste estudo e a recusa de NT/VC, recorremos à regressão logística múltipla. As análises foram realizadas com o programa SPSS 26.0®. Os resultados são relatados sob a forma de razão de *chances* (*odds ratio*), também designado de razão de possibilidades. A razão de *chances* resulta da razão da *chance* de exposição (neste caso, a recusa de NT/VC) num determinado grupo dividido pela *chance* de exposição noutro grupo, tomado como categoria de referência. Por sua vez, a *chance* é também uma razão: da probabilidade de sucesso (recusa de NT/VC) e da probabilidade de insucesso (não recusa de NT/VC). A *chance* é assim um conceito diferente da probabilidade. Considerando por exemplo a variável sexo (tomando como referência o sexo 'feminino'), se 80 em 100 indivíduos do sexo masculino recusarem NT/VC, então a sua probabilidade de recusa é 0,8 e a sua probabilidade de não recusa é 0,2. A *chance* de recusa entre os homens será de 80 para 20, ou seja, 4 (= 0,8/0,2). Se, no caso das mulheres, 75 em 100 recusarem NT/VC, então, a sua probabilidade de recusa é 0,75 e a sua probabilidade de não recusa é 0,25. A *chance* de recusa entre as mulheres será de 3 (= 0,75/0,25). Deste exemplo resulta uma razão de chances de 1,33 (= 4/3). Conclui-se que a *chance* ou possibilidade de recusa de NT/VC entre os homens é 1,33 vezes superior à *chance* de recusa de NT/VC entre as mulheres.

Tabela 1 – Variáveis usadas na análise de regressão

Variável	Número de observações (n = 33 153)	Frequência relativa (%)
Variável dependente		
Recusa	10 372	31,3
Variáveis explicativas		
Sexo		
Masculino	14 240	43,0
Idade		
Idade_18_44§	5165	15,6
Idade_45_54	4163	12,6
Idade_55_64	6058	18,3
Idade_65_74	8267	24,9
Idade_75_84	7577	22,8
Idade_85+	1923	5,8
Hospital de origem		
HO_1§	*	*
HO_2	*	*
HO_3	*	*
HO_4	*	*
HO_5	*	*
HO_6	*	*
HO_7	*	*
HO_8	*	*
HO_9	*	*
HO_outros	*	*
Nível de prioridade da cirurgia		
Normal§	30 536	92,1
Prioritário_MP	2617	7,9
Modalidade da cirurgia		
Cir_ambul§	16 371	49,4
Cir_convenc	16 782	50,6
Especialidade da cirurgia		
Cir_geral§	5586	16,8
Oftalmologia	10 938	33,0
Ortopedia	7977	24,1
Outras_esp	8652	26,1
Período posterior/anterior à redefinição dos TMRG		
Ano_inclusão†	31 406	94,7

§: Categoria de referência
†: Inscrição em lista de espera foi realizada em 2018 ou em 2019
*: Por forma a garantir a não identificação dos hospitais omitiram-se estas estatísticas. Há três hospitais de origem de maior dimensão que perfazem 79% da amostra.

Relativamente a questões éticas, foi solicitada à ARSC, IP autorização para usar os dados com vista a submeter um artigo a uma revista científica. O pedido foi reencaminhado para o Ministério da Saúde. Na sequência do Despacho N.º 6741/2019 de 29 de julho,[24] a autorização foi concedida, tendo sido rececionada por uma das autoras, via *email*, no dia 23 de agosto de 2019. Na solicitação supramencionada, foi manifestado o compromisso de não revelar a identificação dos hospitais. Consequentemente, os hospitais estão identificados apenas com números e suprimiram-se as estatísticas descritivas que de algum modo poderiam permitir a sua identificação.

RESULTADOS

A percentagem de recusas foi de 31 (Tabela 1). Existiu uma maior proporção de utentes do sexo feminino (57%) e a idade mais prevalente corresponde à faixa 65 - 74 anos com 25% da amostra, seguida da faixa 75 - 84 anos com 23%. Existiu equilíbrio entre o número de utentes à espera de cirurgia em ambulatório e o número à espera de cirurgia convencional e Oftalmologia é a especialidade que sobressai na amostra com uma prevalência de 33%. Apenas 8% dos utentes em lista de espera configuraram uma situação prioritária ou muito prioritária. Em termos de hospitais de origem, há três hospitais que conjuntamente foram responsáveis por 79% das inscrições em LIC. Por fim, a esmagadora maioria dos utentes inscritos, apresentaram 2018 ou 2019 como ano de inclusão na lista.

Em relação à evolução trimestral do número de NT/VC emitidos e recusados, de acordo com a Fig. 1, com exceção do primeiro trimestre de 2018, o número de emissões foi sempre superior após a implementação dos novos TMRG comparado com o período anterior a estes novos TMRG. Entre o segundo trimestre de 2018 e o segundo trimestre de 2019, as NT/VC emitidos ultrapassaram as 12 000 unidades, enquanto o valor mais alto atingido antes da redefinição do TMRG foi de 9386 no quarto trimestre de 2016. Em relação à proporção de recusas, o valor mais baixo no período em análise foi registado no primeiro trimestre de 2017 (30%) e o valor mais elevado no quarto trimestre de 2019 (68%). Em geral, as proporções de recusas foram superiores no período após a implementação dos novos TMRG comparado com o período anterior. A única exceção corresponde aos 51% do segundo trimestre de 2018, que ficou abaixo dos 55% do quarto trimestre de 2017. Todavia, é de sublinhar que, com exceção do quarto trimestre de 2016 (que foi atípico no período anterior a 2018 - no âmbito de um Relatório do Tribunal de Contas, a ACSS relatou constrangimentos no processo de impressão de NT/VC em 2016,[22] e assim, este valor atípico no último trimestre poderá dever-se à recuperação de atrasos nos trimestres anteriores), a proporção de recusas vinha a aumentar de modo muito marcante mesmo antes dos novos TMRG. Entre o primeiro trimestre de 2017 e o quarto trimestre de 2017 observou-se um aumento em todos os períodos, passando-se de 30% para 55% de recusas; após o primeiro trimestre de 2018, as percentagens de recusas alcançaram uma estabilização relativa embora a níveis elevados (sensivelmente entre 55% - 65%). De facto, nos três primeiros trimestres de 2019 a percentagem de recusas ficou aquém dos 60%, sugerindo uma redução face a 2018. Contudo, no último trimestre de 2019, assistiu-se a duas alterações significativas face à evolução anterior - o número de emissões diminuiu

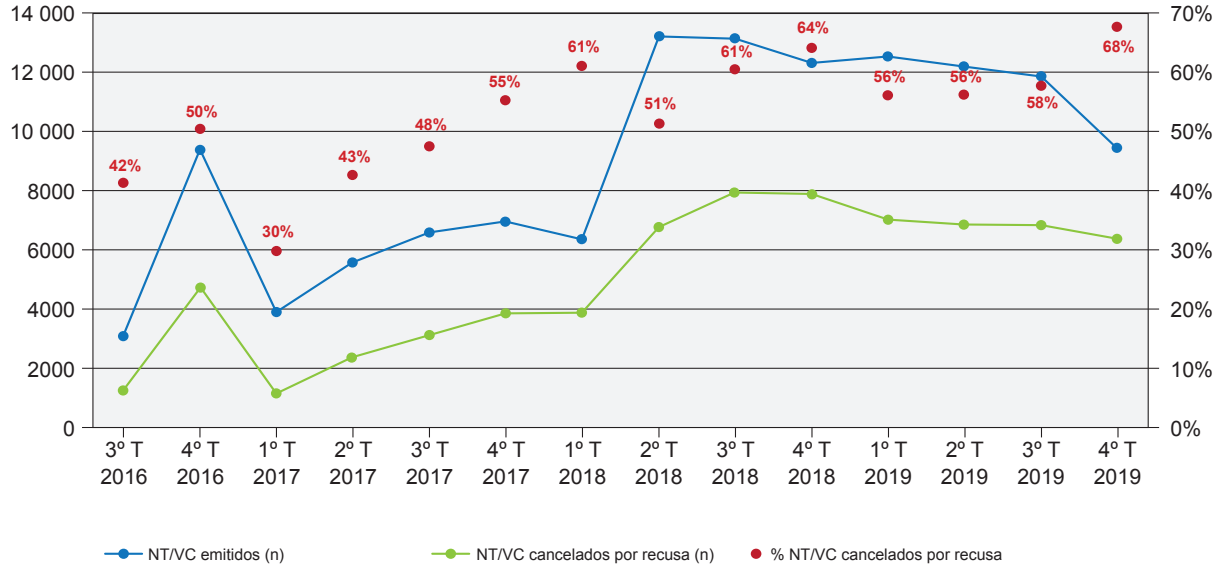

Figura 1 – Notas de transferência (NT) e vales cirurgia (VC) emitidos e cancelados por recusa de transferência entre 1 de julho de 2016 e 31 de dezembro de 2019 na Região Centro

em um quinto enquanto a percentagem de recusas foi no sentido inverso e aumentou 10 pontos percentuais (o que representa no caso em questão um aumento de 17%).

Em relação à análise de regressão, o teste Omnibus mostrou que a diferença entre o modelo apenas com a constante e o modelo adicionado das variáveis explicativas é estatisticamente significativa ($p < 0,001$). Os resultados para a razão de *chances* encontram-se na Tabela 2.

Os resultados não evidenciaram uma associação entre o sexo do utente e a recusa de NT/VC mas esta aumentou com a idade – para a faixa etária 55 - 64 a *chance* de recusa foi 1,14 vezes superior e para as faixas etárias 65 - 74 e 75 - 84 esta *chance* foi 1,10 vezes superior, todas em comparação com a faixa etária dos mais novos (18 - 44 anos). Em relação aos hospitais de origem, comparados com o HO_1, em três hospitais a *chance* de recusa foi inferior e nos restantes foi superior. No caso de se tratar de uma cirurgia classificada com nível superior de prioridade, a *chance* de recusa foi menor face à prioridade normal. Os utentes à espera de cirurgia convencional apresentaram uma *chance* de recusa 2,5 vezes superior à dos utentes à espera de cirurgia em ambulatório. Os utentes na especialidade de Oftalmologia correspondem ao grupo com maior peso e apresentaram uma *chance* de recusa inferior face aos utentes na Cirurgia Geral. Já para a especialidade de Ortopedia os resultados sugeriram uma *chance* de recusa superior por comparação com Cirurgia Geral. Por fim, a *chance* de recusa foi duas vezes inferior entre os utentes inscritos em 2018 ou depois em comparação com quem foi inscrito antes de 2018.

DISCUSSÃO

Os TMRG constituem um mecanismo utilizado em Portugal, como em vários países, com vista a reduzir os tempos de espera para cirurgia. Quando são atingidos os 50% do TMRG é emitida uma NT e aos 75% do tempo é emitido um VC. Contudo, a taxa de utilização das NT/VC tem sido muito baixa (na ordem dos 20% no triénio 2014 - 2016).[22] Note-se que neste estudo analisámos os cancelamentos por recusa de transferência, mas a este motivo acrescem outros (por exemplo, desistência, já operado e erro administrativo). Assim, o total de cancelamentos é superior aos apresentados nos nossos resultados. Os TMRG foram redefinidos em 2017, com efeitos a partir de 1 de janeiro de 2018. Um dos objetivos deste trabalho foi analisar a evolução dos NT/VC emitidos e recusados desde 2016 até 2019, por forma a perceber se se perceciona uma mudança de comportamento após 2018. Pelos nossos resultados, houve um aumento notório na emissão de NT/VC após 2018 e uma relativa estabilização da proporção de recusas a níveis mais elevados face ao período anterior a 2018. Em todo o caso, registava-se uma tendência de subida da percentagem de recusas antes mesmo dos novos TMRG.

Em julho de 2018, o grupo técnico independente (GTI), constituído para avaliar os sistemas de gestão do acesso a cuidados no SNS, alertava para o facto da redução legal dos TMRG, sem o aumento da capacidade de resposta das instituições do SNS, acarretar o aumento das emissões de NT/VC mas com pouco impacto na redução de listas de espera devido à baixa taxa de utilização.[22] Os nossos resultados confirmam este aumento das emissões e a persistência de taxas de recusas muito elevadas. O relatório do GTI aponta algumas lacunas a todo o processo das NT/VC, tais como a carência de informação transparente sobre a qualidade dos resultados de desempenho das unidades hospitalares (não chega saber os tempos de espera) e os problemas de informação por parte dos prestadores ou das entidades responsáveis aos doentes/utentes, incluindo a informação sobre NT/VC. O problema da informação foi identificado logo nos anos iniciais do SIGIC. Um estudo com 570 entrevistas telefónicas,[21] sobre os motivos de recusa no primeiro semestre de 2007, apurou que uma das

Tabela 2 – Análise da associação entre fatores de risco e recusa de NT/VC

Variável	Razão de *chances*	Intervalo confiança (95%)
Sexo		
Masculino	1,017	0,966; 1,071
Idade		
Idade_45_54	1,036	0,941; 1,140
Idade_55_64	1,136***	1,041; 1,240
Idade_65_74	1,095**	1,005; 1,194
Idade_75_84	1,098**	1,002; 1,203
Idade_85+	1,020	0,891; 1,168
Hospital de origem		
HO_2	3,853***	3,610; 4,113
HO_3	0,654***	0,573; 0,746
HO_4	2,751***	3,383; 3,175
HO_5	0,706***	0,583; 0,853
HO_6	1,337***	1,092; 1,637
HO_7	3,600***	3,171; 4,087
HO_8	0,972	0,807; 1,171
HO_9	1,371***	1,266; 1,486
HO_outros	0,007***	0,002; 0,027
Nível de prioridade da cirurgia		
Prioritário_MP	0,638***	0,577; 0,706
Modalidade da cirurgia		
Cir_convenc	2,498***	2,343; 2,663
Especialidade da cirurgia		
Oftalmologia	0,783***	0,714; 0,857
Ortopedia	1,123***	1,037; 1,217
Outras_esp	0,732***	0,675; 0,794
Período posterior/anterior à redefinição dos TMRG		
Ano_inclusão	0,447***	0,400; 0,500

Nota - categorias de referência: sexo feminino; idade_18_44; HO_1; Prioridade normal; Cirurgia de ambulatório; Cirurgia geral; inscrição em lista de espera anterior a 2018.
***: $p < 0,01$; **: $p < 0,05$; *: $p < 0,1$
R^2 Nagelkerke = 0,206

razões de recusa era precisamente o défice de informação (embora tenha sido o motivo com menor expressão). À data em que escrevemos este artigo, as NT/VC foram, entretanto, alvo de um redesenho, com informação melhorada para apoiar o utente na sua decisão. Estudos futuros poderão averiguar o seu impacto sobre a taxa de recusas.

No contexto de uma tão baixa utilização de NT/VC é importante investigar os fatores de risco associados à recusa e este é outro objetivo do presente estudo. Pelos nossos resultados, eventuais medidas políticas não necessitam de discriminar os utentes por sexo uma vez que não se encontraram diferenças a este nível. Os mais novos também parecem ser menos propensos à recusa, e portanto os esforços para melhorar a utilização de NT/VC devem centrar-se nos utentes com idades superiores a 55 anos. Merecem particular atenção os utentes à espera para cirurgia convencional e na especialidade de Ortopedia, onde a *chance* de recusa parece ser superior. Em termos de unidades hospitalares, os resultados sugerem a existência de algumas diferenças, em alguns casos, bastante acentuadas. O compromisso da não identificação dos hospitais não nos permite, no entanto, formular recomendações a este respeito.

Pela natureza dos dados usados, não é possível apurar as razões que levaram à recusa. O único estudo sobre esse tema utilizou dados de há mais de 10 anos.[21] A principal razão para a recusa de transferência foi a preferência pela equipa médica e hospital com quem o utente já se sente familiarizado, seguido da indisponibilidade para usar a NT/VC dentro do prazo de validade e a relutância em mudar de área de residência. O cruzamento desta informação com as características dos utentes/cirurgias identificados no nosso estudo poderá ser útil no desenho de medidas para aumentar a eficácia das NT/VC, sob pena de estar a ser realizada despesa com todo este processo sem retorno.

Limitações

O presente estudo vem preencher uma lacuna na literatura, dada a quase total ausência de análises sobre a baixa utilização de NT/VC. Dois pontos fortes do nosso trabalho prendem-se com o uso de dados administrativos e de um elevado número de observações. No entanto, existem algumas limitações. Assumiu-se que para tempos de espera para cirurgia iguais ou superiores a 50% houve emissão de NT/VC. Tal poderá não ser o caso, pelo que a nossa amostra pode incluir episódios em que a variável 'Recusa' toma o valor zero, quando efetivamente essas observações deveriam ser eliminadas. Por outro lado, a base de dados de NT/VC cancelados inclui recusas ocorridas no máximo até 31 de dezembro de 2019. Consequentemente, é provável que alguns utentes à espera de cirurgia a 31 de dezembro tenham recusado as respetivas NT/VC após esta data e, como tal, não estão contemplados no nosso estudo. Estas duas razões poderão explicar a discrepância entre a taxa de recusas que emergiu da análise de regressão e as taxas na Fig.1. A informação em relação à associação entre a recusa e o hospital de origem é limitada pela impossibilidade de revelar a identificação dos hospitais. Contudo, a análise foi desenvolvida e consideramos ser em todo o caso relevante alertar para este achado. Os nossos resultados sugerem que a *chance* de recusa foi menor para inscrições em LIC a partir de 2018, apesar da esmagadora maioria dos utentes em espera a 31 de dezembro terem sido inscritos após 2018 e os inscritos anteriormente poderão ter atingido 50% do TMRG já em 2018. Assim, este resultado deve ser lido com cautela. Os nossos dados aplicam-se apenas à Região Centro, pelo que outros estudos serão necessários em relação às restantes regiões do país. Os resultados da análise de regressão mostraram que a diferença entre o modelo usado e o modelo apenas com a constante é estatisticamente significativa. Contudo, a percentagem de observações corretamente previstas foi, no total, de 71,3%,

tendo sido consideravelmente mais baixa nos casos de recusa. Por outro lado, não foi possível obter através das fontes de dados utilizadas neste estudo informação relativa às alternativas dos hospitais de destino oferecidas ao utente. Esta informação é potencialmente relevante para melhor investigar a decisão de recusa, nomeadamente, no que tem que a ver com a distância entre os hospitais de destino e o de origem, um fator já identificado na literatura como tendo impacto na escolha do hospital.[16] Efetivamente, pela natureza dos dados utilizados, a nossa análise restringiu-se ao impacto de fatores administrativos e de gestão, tendo elementos como a confiança na equipa médica e amenidades da entidade escolhida ficado de fora. Apesar destas limitações, é nossa convicção que os resultados alcançados são pertinentes e poderão informar a política de saúde sobre um problema que persiste. Chama-se ainda a atenção que, caso os utentes não sejam inscritos em LIC na data da consulta em que foi verificada a necessidade de cirurgia,[22] os tempos de espera, mesmo com base em dados administrativos, poderão estar subestimados.

CONCLUSÃO

Os tempos de espera para cirurgia continuam a ser uma preocupação de política em Portugal e nos países da OCDE, a qual deverá agravar-se com os cancelamentos devido à pandemia de COVID-19. Neste estudo confirmou-se que a emissão de NT/VC aumentou após a redução legal dos TMRG em 2018 e que as taxas de recusa de transferência vinham já a registar uma tendência de aumento desde 2016, tendo-se mantido acima dos 55% a partir do terceiro trimestre de 2018. Alguns fatores para os quais se encontrou uma associação positiva com a recusa são a idade, a cirurgia convencional (em comparação com ambulatório) e a especialidade de Ortopedia (em comparação com Cirurgia Geral). São necessários mais estudos em outras regiões do país que também analisem os motivos de recusa de transferência, de modo a desenhar estratégias para aumentar a taxa de utilização das NT/VC e reduzir o atual desperdício de recursos com a emissão de milhares de NT/VC que vêm posteriormente a ser cancelados.

CONTRIBUTO DOS AUTORES

SC, CQ, PA: Conceção do estudo, análise/interpretação de dados, elaboração do manuscrito e aprovação da versão submetida.

PROTECÇÃO DE PESSOAS E ANIMAIS

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

CONFIDENCIALIDADE DOS DADOS

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

CONFLITOS DE INTERESSE

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

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Endocrinopatias Associadas ao Tratamento com Inibidores do Checkpoint Imunológico

Endocrinopathies Associated with Immune Checkpoint Inhibitors

ARTIGO DE REVISÃO

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RESUMO

Introdução: Os inibidores do *checkpoint* imunológico (ICI) são anticorpos monoclonais que permitem aumentar a eficiência do sistema imunitário na destruição das células neoplásicas. Nos últimos anos, estes fármacos têm sido cada vez mais utilizados no tratamento de muitas neoplasias em estadios avançados. Contudo, a alteração da regulação do sistema imunitário induzida por estes fármacos tem como potencial efeito adverso o aparecimento de autoimunidade em praticamente todos os órgãos. As endocrinopatias são um dos eventos adversos autoimunes mais frequentes com estes fármacos.

Material e Métodos: Revisão não sistemática sobre as endocrinopatias reportadas em contexto de tratamento com ICI. Foram pesquisados artigos publicados na PubMed até 31 de janeiro de 2020, selecionados com base na sua relevância e excluídos em caso de conteúdo redundante. Foram utilizados os seguintes termos de pesquisa: "immune checkpoint inhibitor" e "endocrinopathy" / "endocrine system diseases" / "pituitary" / "thyroid" / "diabetes" / "adrenal" / "parathyroid".

Resultados: Foram já reportadas endocrinopatias com todas as classes de ICI (anti-CTLA-4, anti-PD-1, anti-PD-L1). A disfunção tiroideia é a endocrinopatia mais frequentemente reportada, principalmente sob anti-PD-1 e anti-PD-L1. A hipofisite é a mais prevalente sob anti-CTLA-4. É crescente a incidência de diabetes autoimune neste contexto, principalmente sob anti-PD-1 e anti-PD-L1. Foram reportados também casos raros de insuficiência suprarrenal primária, doença de Graves e hipoparatiroidismo primário.

Conclusão: O conhecimento do espectro de endocrinopatias desencadeadas pela terapêutica com ICI, assim como as suas manifestações clínicas, critérios de diagnóstico e tratamento, é essencial, dada a sua elevada prevalência e o cada vez maior número de doentes oncológicos tratados com estes novos fármacos.

Palavras-chave: Antineoplásicos Imunológicos; Doenças do Sistema Endócrino; Inibidores de Checkpoint Imunológico; Receptor de Morte Celular Programada 1

ABSTRACT

Introduction: Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that increase the efficiency of the immune system in the destruction of neoplastic cells. In recent years, these drugs have been increasingly used in the treatment of many neoplasms in advanced stages. However, the change in the regulation of the immune system induced by these drugs has the potential adverse effect of inducing autoimmunity in practically all organ systems. Endocrinopathies are one of the most common autoimmune adverse events of these drugs.

Material and Methods: Non-systematic review of endocrinopathies reported in the context of treatment with ICIs. A search was carried out on PubMed until January 31st, 2020, and articles were selected based on their relevance and excluded in case of redundant content. The following search terms were used: "immune checkpoint inhibitor" and "endocrinopathy" / "endocrine system diseases" / "pituitary" / "thyroid" / "diabetes" / "adrenal" / "parathyroid".

Results: Endocrinopathies with all classes of ICIs (anti-CTLA-4, anti-PD-1, anti-PD-L1) have been reported. Thyroid dysfunction is the most frequently reported endocrinopathy, mainly with anti-PD-1 and anti-PD-L1. Hypophysitis is the most prevalent with anti-CTLA-4. The incidence of autoimmune diabetes in this context is increasing, mainly with anti-PD-1 and anti-PD-L1. Rare cases of primary adrenal insufficiency, Graves' disease and primary hypoparathyroidism have also been reported.

Conclusion: Knowing the spectrum of endocrinopathies triggered by ICI, as well as their clinical features, diagnosis and treatment criteria is essential, given its high prevalence and the increasing number of cancer patients treated with these new drugs.

Keywords: Antineoplastic Agents, Immunological; Endocrine System Diseases; Immune Checkpoint Inhibitors; Programmed Cell Death 1 Receptor

INTRODUÇÃO

Os *checkpoint* imunológicos são mecanismos essenciais para a regulação da resposta do sistema imunitário a antigénios estranhos. Podem ser estimuladores ou inibidores, levando à destruição de antigénios estranhos ao organismo ou supressão da resposta autoimune.[1] Muitas células neoplásicas conseguem induzir o aumento da expressão de *checkpoint* imunológicos inibitórios, o que lhes permite evadirem-se da ação antitumoral das células T citotóxicas. A descoberta deste mecanismo de sobrevivência das células tumorais, revolucionou o tratamento de muitas neoplasias, levando ao desenvolvimento de uma nova classe farmacológica: os inibidores do *checkpoint* imunológico (ICI).[1]

Inibidores do *checkpoint* imunológico

Os inibidores do *checkpoint* imunológico são anticorpos monoclonais que bloqueiam a atividade inibitória dos mecanismos de resposta imunológica a antigénios tumorais, reativando desta forma os linfócitos T citotóxicos contra as células tumorais.[1] Os ICI não atuam diretamente nas células tumorais, mas nos recetores dos linfócitos ou seus ligandos, estimulando a atividade destas células.[1] Têm um

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efeito antitumoral eficaz e duradouro num amplo espectro de neoplasias em estadio avançado e têm tido uma utilização crescente desde a aprovação do primeiro fármaco da classe, em 2011.[1-3]

Existem, atualmente, três classes de ICI aprovadas pela Food & Drug Administration (FDA) e pela Agência Europeia do Medicamento (EMA): os anti-CTLA-4, os anti-PD-1 e os anti-PD-L1 (Tabela 1).[4]

O CTLA- 4 (*cytotoxic T-lymphocyte-associated protein* 4) inibe a ativação precoce das células T citotóxicas nos gânglios linfáticos, diminui a atividade cas células T *helper* e aumenta a atividade imunossupressora das células T reguladoras.[1-3] O seu bloqueio impede a indução de anergia das células T, aumentando a atividade das células T CD8+ e CD4+ efetoras e inibindo a ação das células T reguladoras.[1,2] O primeiro ICI aprovado pela FDA, em 2011, foi o ipilimumab, um anti-CTLA-4.

O PD-1 (*programmed cell death protein* 1) é expresso numa maior variedade de células: células T citotóxicas, células T reguladoras, células B, células *natural killer*, macrófagos e células dendríticas.[1,2] Limita a atividade pró-inflamatória destas células e previne a autoimunidade. No microambiente tumoral, a ativação da via do PD-1 é um importante mecanismo de escape das células tumorais à destruição pelo sistema imunitário. A exposição crónica dos linfócitos T a antigénios tumorais promove a expressão persistente de PD-1 nos linfócitos e a sua anergia/exaustão.[1,2] A segunda classe de ICIs aprovada foi a dos anti-PD-1. Ao bloquearem a via PD-1, estes fármacos aumentam a ação das células T efetoras e diminuem a ação das células T reguladoras nos tecidos e microambiente tumoral.

O PD-1 possui dois ligandos (PD-L1 e PD-L2). O PD-L1 é expresso em muitos tipos de células linfóides e não linfóides, sendo um importante mecanismo de proteção contra a autoimunidade.[2] O PD-L2 é principalmente expresso nas células apresentadoras de antigénios e diminui a resposta imune induzida pelas células Th2.[2] O PD-L1 e o PD-L2 existem em grande quantidade à superfície de muitos tumores. Através deles, as células tumorais ligam-se aos recetores de PD-1 na superfície dos linfócitos, levando à inativação dos linfócitos T. Os anti-PD-L1, anticorpos monoclonais que se ligam aos ligandos do PD-1 na superfície das células tumorais, foram a terceira classe de ICI aprovada pela FDA (Tabela 1).[4]

MATERIAL E MÉTODOS

Foi feita uma revisão não sistemática sobre endocrinopatias em contexto de tratamento com ICI. Para esse efeito, foi feita uma pesquisa na PubMed de todos os artigos publicados até 31 de janeiro de 2020, tendo por base as seguintes palavras-chave: "immune *checkpoint* inhibitor" e "endocrinopathy" / "endocrine system diseases" / "pituitary" / "thyroid" / "diabetes" / "adrenal" / "parathyroid". Todos os artigos foram lidos e posteriormente selecionados com base na sua relevância. Foram incluídos todos os tipos de artigos, incluindo relatos de caso. Foram excluídos artigos cujo conteúdo fosse considerado redundante.

RESULTADOS

Eventos adversos autoimunes por ICI

A desinibição do sistema imunitário obtida pelo bloqueio de vias inibitórias dos *checkpoint* imunológicos tem um potencial inerente de autoimunidade.[2] Foram já descritos numerosos eventos adversos autoimunes em contexto de

Tabela 1 – Inibidores do *checkpoint* aprovados pela FDA[4]

Classe de ICI	Fármaco	Ano de provação	Indicações aprovadas
Anti-CTLA-4	Ipilimumab	2011	melanoma; carcinoma de células renais; carcinoma colorrectal com instabilidade de microssatélite
Anti-PD-1	Pembrolizumab	2014	melanoma; carcinoma do pulmão de não pequenas células; carcinoma do pulmão de pequenas células; carcinoma espinocelular da cabeça/pescoço; linfoma de Hodgkin clássico; linfoma primário do mediastino de grandes células B; carcinoma urotelial; neoplasias com elevada instabilidade de microssatélite; carcinoma gástrico; carcinoma do esófago; carcinoma do colo do útero; carcinoma hepatocelular; carcinoma de células de Merkel; carcinoma de células renais; carcinoma do endométrio
	Nivolumab	2014	melanoma, carcinoma pulmão de não pequenas células; carcinoma do pulmão de pequenas células; carcinoma espinocelular da cabeça/pescoço; linfoma de Hodgkin clássico; carcinoma de células renais; carcinoma urotelial; carcinoma colorrectal com elevada instabilidade de microssatélite; carcinoma hepatocelular
	Cemiplimab	2018	carcinoma espinocelular
Anti-PD-L1	Atezolizumab	2016	carcinoma urotelial; carcinoma do pulmão de não pequenas células; carcinoma do pulmão de pequenas células; carcinoma da mama triplo negativo
	Durvalumab	2017	carcinoma pulmão de não pequenas células; carcinoma urotelial
	Avelumab	2017	carcinoma urotelial; carcinoma de células de Merkel; carcinoma de células renais

FDA: Food and Drug Administration; ICI: inibidor do *checkpoint* imunológico; CTLA-4: antigénio-4 de linfócito T citotóxico; PD-1: proteína de morte celular programada 1; PD-L1: ligando 1 da proteína de morte celular programada 1

ICI [efeitos adversos imunorrelacionados (EAir)]. Os EAir podem atingir qualquer órgão com uma gravidade variável e causar inclusivamente morte/risco de morte.[2] O tratamento combinado com duas classes de ICI associa-se a maior incidência e gravidade de EAir.[2,5] Estes eventos adversos podem surgir a qualquer momento após o início do tratamento, até meses depois da sua suspensão.[5] Vários estudos sugerem a existência de uma associação positiva entre a ocorrência de EAir e maior resposta tumoral ao tratamento, com melhor prognóstico da doença oncológica, o que traduz uma maior capacidade do sistema imunitário em reconhecer e destruir as células neoplásicas. No entanto, esta associação não está claramente provada.[2]

Endocrinopatias associadas a ICI

As glândulas endócrinas são dos órgãos mais frequentemente afetados por EAir em contexto de ICI. Numa meta-análise com 38 ensaios clínicos e 7551 doentes, a incidência global de endocrinopatias foi de 6,6%.[6] Contudo, estudos mais recentes apontam para uma incidência entre 4% - 30%.[7] Dados da vida real, obtidos após a introdução dos fármacos no mercado, têm mostrado uma incidência crescente do número de endocrinopatias descritas em contexto de ICI, principalmente nos primeiros quatro anos após a sua comercialização.[8,9] No maior estudo de farmacovigilância sobre endocrinopatias por ICIs publicado até à data, com mais de 6000 doenças endócrinas registadas, verificou-se a ocorrência de 54,5% sob anti-PD-1; o risco de endocrinopatia foi maior sob anti-CTLA-4; a terapêutica combinada de anti-PD-1 e anti-CTLA-4 associou-se a um maior risco e maior frequência destes EAir; 17% das endocrinopatias associaram-se a morte/risco de morte, provavelmente por dificuldade/atraso na sua deteção e tratamento atempados.[8,10] É necessário um elevado grau de suspeição para o diagnóstico de endocrinopatias por ICI, pois alguns dos seus sintomas mais comuns (astenia, anorexia, emagrecimento) são frequentemente observados em doentes oncológicos.[11]

Hipofisite

A hipofisite foi das primeiras endocrinopatias descritas em contexto de ICI e estima-se que atinja cerca de 3% dos doentes.[12] Pode aparecer em qualquer momento após o início do tratamento.[2,13] O seu mecanismo patofisiológico é desconhecido e parece não depender da existência de autoimunidade hipofisária prévia.[13] Foi documentada necrose extensa da adenohipófise com ausência total de gonadotrofos e tireotrofos na única autópsia disponível.[14] Foram propostos dois mecanismos fisiopatológicos: ativação da via clássica do complemento e citotoxicidade mediada por células e dependente de anticorpos (ADCC). O risco de hipofisite parece depender de fatores individuais (polimorfismos na expressão de CTLA-4 na hipófise) e também da classe de ICI (diferente potência relativa para ativar complemento e ADCC).[2,15] Apesar de já ter sido relacionada com as três classes de ICI, a endocrinopatia é mais frequentemente associada aos anti-CTLA-4, com risco dependente da dose, sobretudo em terapêutica combinada.[2,6,15-17] A maior série de hipofisites por ICI publicada até à data, com dados da vida real, incluiu 94 casos em 249 endocrinopatias (37,8% das endocrinopatias reportadas). O fármaco mais associado com hipofisite foi o ipilimumab (43%), mas a incidência com anti-PD-1 foi semelhante (nivolumab 30%, pembrolizumab 14%), mostrando que esta endocrinopatia pode ocorrer com qualquer classe de ICI. O tempo de tratamento até à hipofisite foi menor com ipilimumab (em monoterapia ou associação) do que com anti-PD-1 em monoterapia. A gravidade da hipofisite foi menor com pembrolizumab do que com nivolumab e ipilimumab.[13]

A apresentação clínica consiste em sinais/sintomas inespecíficos devido ao hipopituitarismo, sendo os mais frequentes astenia e cefaleias. Os doentes podem também apresentar náuseas, anorexia, tonturas, hipotensão, diminuição da líbido, intolerância ao frio, emagrecimento, sintomas psiquiátricos (apatia, ansiedade, depressão), febre, hipoglicemia ou dores articulares.[2,11] Pode ocorrer efeito de massa por aumento do volume da hipófise, mas é geralmente ligeiro e transitório.[2] As células hipofisárias mais frequentemente atingidas são os corticotrofos [produtores de hormona adrenocorticotrófica (ACTH)], os tirotrofos [produtores de hormona tiroestimulante (TSH)] e os gonadotrofos [produtores de hormona luteinizante (LH) e de hormona folículo-estimulante (FSH)]. O défice de ACTH está presente em quase todos os doentes, é geralmente persistente e o maior responsável pela morbilidade associada a este tipo de hipofisite.[2] O défice de TSH e FSH/LH é comum e pode ser reversível. Os anti-CTLA-4 parecem associar-se a um maior risco de défice hipofisário múltiplo e os anti-PD-1/PD-L1 parecem associar-se mais a défice isolado de ACTH.[2,11,16] Foram também descritos casos raros de diabetes insípida com ipilimumab e avelumab, traduzindo atingimento da hipófise posterior.[18,19] O diagnóstico de hipofisite é bioquímico, documentando-se os défices hormonais existentes. A ressonância magnética hipofisária, que não é essencial para o diagnóstico, pode mostrar desde hipófise de aspeto normal até aumento ligeiro/moderado do volume da hipófise, que geralmente normaliza após semanas/meses. O tratamento consiste na substituição hormonal das linhas hipofisárias atingidas: hidrocortisona PO 10 – 20 mg/dia e levotiroxina (5 - 7 dias após o início da hidrocortisona) (dose inicial 0,8 ug/kg/dia). Pode ser considerada uma dose inicial menor de levotiroxina em doentes idosos ou com doença cardíaca (12,5 – 25 ug/dia), com ajuste posterior de dose às quatro semanas de tratamento, de acordo com o valor de T4 livre. O tratamento do hipogonadismo pode ser considerado em homens ou mulheres em pré-menopausa. O tratamento com corticóides endovenosos em doses elevadas não está recomendado, exceto em caso de crise adrenal ou aumento marcado do volume da hipófise. O seu uso não aumenta a probabilidade de recuperação de função hipofisária nem a sobrevida global dos doentes.[2,11,22] Após o início do tratamento pode ocorrer recuperação da função hipofisária, nomeadamente do hipotiroidismo e do hipogonadismo, sendo rara a recuperação do

hipocortisolismo. O tratamento com ICI não tem que ser suspenso, exceto nos casos de hipofisite grave, em que poderá ser retomado após estabilização da situação clínica.[2,11] A sua suspensão não altera a probabilidade de recuperação da função hipofisária.[2] Para diagnóstico precoce recomenda-se vigilância da função tiroideia (TSH e T4 livre) antes do início do tratamento e antes de cada ciclo (ou a cada 4-6 semanas), pelo menos nos primeiros cinco ciclos.[2,20] Em caso de sintomas sugestivos de hipocortisolismo deve existir um limiar baixo para doseamento de cortisol/ACTH. Em caso de diagnóstico de hipofisite, devem ser doseados FSH/LH e estradiol/testosterona para documentação de eventual hipogonadismo. É necessário manter vigilância e suspeição mesmo após suspensão de ICI (Tabela 2).[2,15,20]

Tiroidite

A tiroidite é a endocrinopatia mais frequente com ICI e ocorre com maior frequência com os anti-PD-1 (5% - 10%), em monoterapia ou associação com anti-CTLA-4.[2,21] Apesar de descrita como mais rara com os anti-PD-L1, talvez devido à sua aprovação mais recente, um estudo recentemente publicado mostrou uma incidência de 21% de disfunção tiroideia sob anti-PD-L1.[22] A disfunção tiroideia pode ocorrer a qualquer momento após o início do tratamento, mas é mais frequente nas primeiras seis semanas e é mais precoce com a terapêutica combinada.[2,22] O mecanismo fisiopatológico não é totalmente conhecido, mas pensa-se que ocorra uma tiroidite destrutiva mediada por células T citotóxicas. Inicialmente, há uma fase de tireotoxicose (por libertação das hormonas tiroideias armazenadas na tiróide), que pode ser clínica/subclínica e que evolui semanas/meses depois para eutiroidismo ou hipotiroidismo primário, resultante da destruição da tiróide.[2,6] Contudo, há doentes que se apresentam logo com hipotiroidismo (subclínico/clínico), que pode ser transitório ou permanente.[2] A etiologia da tiroidite destrutiva não está estabelecida. Foi proposto que, uma vez que a tiróide expressa PD-L1, o bloqueio da via PD-1 possa levar a autoimunidade tiroideia local.[23] Por outro lado, epítopos tumorais podem possuir sequências de aminoácidos semelhantes a auto-antigénios tiroideus, levando os linfócitos a reagir contra células tiroideias.[3] Tem sido estudada a relação entre este tipo de tiroidite e os anticorpos anti-peroxidase (anti-TPO) e anti-tiroglobulina (anti-Tg). Apesar da sua incidência parecer ser superior em doentes com anticorpos anti-TPO e anti-Tg prévios positivos, também estão descritos casos com anticorpos positivos apenas após o início do tratamento e identificados doentes que nunca apresentam anticorpos positivos. Além disso, nem sempre a positividade dos anticorpos se associa a disfunção tiroideia. Foi proposto que o aparecimento dos anticorpos após o início do tratamento se possa dever a uma resposta humoral perante uma maior exposição de antigénios tiroideus, provocada por tiroidite destrutiva,[2] pelo que não está estabelecido se os anticorpos antitiroideus são fator de risco para este tipo de tiroidite.[2,3,6,11]

Tabela 2 – Manifestações endócrinas autoimunes da terapêutica com inibidores do *checkpoint*

Endocrinopatia	Classe de inibidor do *checkpoint*	Apresentação	Proposta de protocolo de vigilância
Hipofisite	Anti-CTLA-4	Geralmente, défice de ACTH + défice de TSH e/ou FSH+LH	• Antes de cada ciclo de tratamento: dosear TSH e T4 livre • Se sintomas: dosear ACTH e cortisol matinal
	Anti-PD-1 Anti-PD-L1	Geralmente, défice isolado de ACTH	• Se diagnóstico de hipofisite: dosear FSH e LH + estradiol/testosterona
Tiroidite	Principalmente Anti-PD-1 Anti-PD-L1	Hiper/hipotiroidismo clínico/subclínico	Dosear TSH e T4 livre antes de cada ciclo de tratamento
Diabetes	Principalmente Anti-PD-1 Anti-PD-L1	Hiperglicemia aguda e sintomática de novo ou agravamento de diabetes prévia	Medição de glicemia e vigilância de sinais/sintomas de hiperglicemia antes de cada ciclo durante 12 semanas e depois a cada 3 - 6 semanas
Insuficiência suprarrenal primária	Anti-CTLA-4, anti-PD-1, anti-PD-L1	• Défice de glucocorticoides (cortisol normal/baixo com elevação de ACTH) • Défice de mineralocorticóides (aldosterona baixa e renina elevada, hiponatremia e hipercalemia)	Se sintomas: dosear ACTH e cortisol matinal
Hipoparatiroidismo primário	Anti-PD-1 (em monoterapia ou associação com anti-CTLA-4)	Hipocalcemia, hiperfosfatemia, PTH normal/baixa	Se sintomas: dosear cálcio, fósforo e PTH

CTLA-4: antigénio-4 de linfócito T citotóxico; PD-1: proteína de morte celular programada 1; PD-L1: ligando 1 da proteína de morte celular programada 1; ACTH: corticotrofina; TSH: tireotrofina; FSH: hormona folículo-estimulante; LH: hormona luteinizante; T4: tetraiodotironina; PTH: hormona paratiroideia

A apresentação clínica consiste numa primeira fase de tireotoxicose, geralmente com sintomas inespecíficos e ligeiros. Os mais frequentes são palpitações, emagrecimento, astenia, hipersudorese, diarreia, tremor e intolerância ao calor.[2] Posteriormente, pode surgir uma fase de hipotiroidismo (subclínico/clínico), também muitas vezes com sintomas inespecíficos e ligeiros, como astenia, aumento de peso, obstipação, bradicardia, intolerância ao frio, pele seca.[2] O tempo mediano entre as duas fases é de 4 a 7 semanas.[2] Apesar desta ser a apresentação típica, qualquer alteração de função tiroideia é possível, independentemente da existência ou não de patologia tiroideia prévia.[24] Em doentes com hipotiroidismo primário prévio medicado pode haver alteração da função tiroideia, na maioria com necessidade de aumento de dose de levotiroxina.[24] O diagnóstico é bioquímico, com doseamento de TSH e T4 livre. O doseamento de anti-TPO e anti-Tg não deve ser feito por rotina.[2] A ecografia tiroideia, não necessária para o diagnóstico, pode mostrar achados compatíveis com tiroidite, como estrutura heterogénea ou difusamente hipoecogénica e diminuição da vascularização.[2] A cintigrafia tiroideia mostra diminuição da captação do radiofármaco e apenas é útil para diagnóstico diferencial com doença de Graves.[2] A PET FDG pode mostrar um aumento difuso da captação, típico de tiroidite inflamatória.[2] Na fase tireotóxica, o tratamento tem como objetivo o controlo de sintomas com beta-bloqueantes (ex. propranolol 10 – 30 mg, três vezes ao dia). O tratamento com glucocorticóides não está recomendado, exceto em casos de tireotoxicose grave. O tratamento com antitiroideus de síntese não está recomendado. Deve ser monitorizada a função tiroideia a cada 2 - 3 semanas, pois pode haver rápida progressão para hipotiroidismo. O hipotiroidismo deve ser tratado com levotiroxina caso seja sintomático (independentemente do valor de TSH) ou, sendo assintomático, com TSH persistentemente acima de 10 UI/mL (pelo menos dois doseamentos com quatro semanas de intervalo). A dose inicial de levotiroxina é de 0,8 ug/kg/dia (12,5 – 25 ug/dia em idosos ou doentes com patologia cardíaca), com titulação de dose a cada 4 - 6 semanas.[2,20] Na maioria dos doentes não há necessidade de suspender o tratamento com ICI.[2] Se a disfunção tiroideia for grave, o ICI deve ser suspenso até haver estabilização clínica.[20] Para diagnóstico precoce, recomenda-se dosear TSH e T4 livre antes do início do tratamento e antes de cada ciclo (ou a cada 4 a 6 semanas), pelo menos nos primeiros cinco ciclos.[2,20] Devem fazer-se análises de função tiroideia em qualquer doente (previamente) tratado com ICI e sinais/sintomas sugestivos de hiper/hipotiroidismo. Os doentes com hipotiroidismo primário previamente medicado devem ser regularmente vigiados pois pode haver necessidade de aumento ou redução da dose de levotiroxina (Tabela 2).[2]

Doença de Graves

Há raros relatos de caso de doença de Graves no contexto de tratamento com ICI (anti-CTLA-4: ipilimumab; anti-PD-1: nivolumab). Foi descrita como um quadro de tireotoxicose isolada (sem orbitopatia), mas também como orbitopatia isolada (sem tireotoxicose), com anticorpos anti-recetor da TSH (TRABs) positivos ou negativos, em qualquer uma das formas de apresentação.[2,25]

Pâncreas endócrino: *Checkpoint Inhibitor-Associated Autoimmune Diabetes* (CIADM)

O aparecimento de diabetes *mellitus* (DM) em contexto de ICI foi descrito, pela primeira vez, em 2015, com pembrolizumab.[26] Apesar de ainda ser um evento considerado raro (0,2% – 1,0%), a sua incidência tem vindo a aumentar.[27] O mecanismo fisiopatológico é desconhecido, mas pensa-se que ocorra uma destruição direta das células beta pancreáticas pelas células T citotóxicas.[28-30] Tem sido estudada a relação entre este tipo de DM e haplótipos de risco para diabetes tipo 1 (DM1). Apesar de não haver evidência de uma relação causal, antígenos leucocitários humanos (HLA) de risco para DM1 parecem ser mais prevalentes nestes doentes do que na população em geral.[7] Não se sabe se os autoanticorpos anti-ilhéus pancreáticos estão envolvidos na patogénese ou se predizem aparecimento deste tipo de DM.[2] Cerca de metade dos doentes apresentam positividade para, pelo menos, um anticorpo, sendo o anti-GAD65 o mais frequente. Contudo, os restantes doentes não têm positividade identificada para nenhum dos anticorpos conhecidos, o que sugere que a ativação *major* e súbita de clones de células T CD8+ ocorra sem envolvimento de imunidade humoral.[2,7,31,32] O PD-L1 é expresso nas células de ilhéus pancreáticos e a CIADM ocorre, na maioria dos casos, com anti-PD-1/PD-L1, o que sugere que esta via é importante para a manutenção da auto-tolerância para ilhéus pancreáticos.[2,7,33] O tempo de aparecimento após o início do tratamento é variável (uma semana a 12 meses).[2,11,31,33] A apresentação clínica típica caracteriza-se pelo aparecimento agudo de hiperglicemia grave e sintomática, com rápida progressão para insulinopenia e elevada prevalência de cetoacidose diabética (CAD) e peptídeo C baixo ao diagnóstico (cerca de 70%).[2] Devido à instalação abrupta do quadro, a hemoglobina glicosilada é proporcionalmente mais baixa do que a glicemia, traduzindo a sua sensibilidade limitada para deteção precoce deste tipo de DM.[2,7] A CIADM pode também aparecer em doentes com diagnóstico prévio de diabetes tipo 2 (DM2) ou pré-diabetes. Assim, sugere-se um limiar de suspeição clínica baixo perante um agravamento inexplicado do controlo glicémico nestes doentes.[16,28] Imagiologicamente, o pâncreas pode ter aspetos muito variáveis, desde um aspeto normal, a atrofia ou aumento do volume.[2,7] A maioria dos doentes evolui para insulinopenia permanente, pelo que o tratamento consiste em insulinoterapia com múltiplas administrações diárias de insulina. Perante uma DM *de novo* em contexto de ICI, ou agravamento de DM prévia, a insulinoterapia deve ser precocemente iniciada.[2,20,28] O tratamento com glucocorticóides não tem benefício na reversão deste tipo de EAir e é contraproducente, por agravar o controlo glicémico.[2] Em caso de hiperglicemia marcada ou CAD, o tratamento com ICI deve ser temporariamente suspenso, até que ocorra a estabilização clínica do doente. Para a

realização de um diagnóstico precoce, recomenda-se monitorizar a glicemia e sinais/sintomas de hiperglicemia antes de iniciar o tratamento e antes de cada ciclo, durante as 12 primeiras semanas de tratamento e depois a cada 3 - 6 semanas. Recomenda-se também a educação dos doentes sobre sinais/sintomas de hiperglicemia e CAD (Tabela 2).[2,11,20,28]

Insuficiência suprarrenal primária

Raros casos (0,7%) de insuficiência suprarrenal primária foram descritos em associação com as três classes de ICI.[2,6,17] O mecanismo é desconhecido, presumindo-se que ocorra inflamação e destruição das suprarrenais.[2,11] Estão descritos casos de doentes com níveis elevados de anticorpos ati-suprarrenal (anticorpos anti-21-hidroxilase e anti-córtex suprarrenal), mas desconhece-se se têm papel na patogénese ou valor prognóstico.[2] O tempo de aparecimento após o início do fármaco foi variável (10 semanas com anti-PD-1 e 16 semanas com anti-CTLA-4).[11] A apresentação é típica de insuficiência suprarrenal primária.[2] O diagnóstico é bioquímico, com documentação de défice de glucocorticoides (cortisol normal/baixo com elevação de ACTH) e mineralocorticóides (aldosterona baixa e renina elevada, hiponatremia e hipercalemia).[2] Imagiologicamente, pode haver evidência de inflamação com aumento bilateral difuso e margens regulares das suprarrenais, mas estas podem ter aspeto normal ou sinais de atrofia.[2] A PET-FDG pode mostrar hipercaptação difusa bilateral das suprarrenais. É importante o diagnóstico diferencial com outras causas de insuficiência suprarrenal primária, tais como metastização ou hemorragia bilateral.[2] O tratamento consiste na reposição de gluco e mineralocorticóides. Se a apresentação clínica for ligeira ou moderada, os doentes poderão ser tratados em ambulatório com 10 – 20 mg/dia de hidrocortisona e 0,05 – 2,0 mg/dia de fludrocortisona.[2] Em caso de doença grave, devem ser internados e fazer tratamento inicial endovenoso. Nesta última situação, o tratamento com ICI deve ser temporariamente suspenso até à estabilização clínica[11] A maioria dos doentes permanece com insuficiência suprarrenal, com necessidade de tratamento definitivo (Tabela 2).[2,11]

Hipoparatiroidismo primário

Foram descritos quatro casos de hipoparatiroidismo primário por ICI, todos com sintomas neuromusculares de hipocalcemia aguda grave ao diagnóstico.[34-37] Estes doentes estavam tratados com anti-PD-1 (dois em monoterapia e dois em combinação). O hipoparatiroidismo ocorreu um a quatro meses após o início do tratamento e todos os doentes ficaram com hipoparatiroidismo primário definitivo.[34-37] Desconhece-se o mecanismo subjacente: poderá dever-se a destruição imuno-mediada das paratiroides (hipoparatiroidismo permanente) ou a hiperativação do *calcium-sensor receptor (CaSR)* por anticorpos estimuladores. Estes anticorpos inibem a secreção de paratormona (PTH), mantendo o cálcio abaixo do limiar que estimularia a sua libertação (hipoparatiroidismo funcional).[35-36] O diagnóstico é bioquímico, com evidência de hipocalcemia, hiperfosfatemia e PTH normal ou baixa. O tratamento consiste na toma de cálcio e de formas ativas de vitamina D, para um objetivo de cálcio sérico na ordem dos 7,5 – 8,5 mL/dL.[34-37] Apesar da raridade de casos, uma metanálise sobre alterações eletrolíticas com ICI encontrou uma associação significativa entre o tratamento com anti-PD-1 e o risco de hipocalcemia (RR 10,87; IC 95% 1,4 – 84,16).[38] Assim, nomeadamente com anti-PD-1, a incidência de hipocalcemia ligeira ou assintomática, e eventualmente transitória, poderá ser mais elevada do que o descrito (Tabela 2).

CONCLUSÃO

Nos próximos anos, perspetiva-se uma utilização crescente de ICI no tratamento de muitas neoplasias. As endocrinopatias associadas a ICI possuem um espectro clínico muito variável, podendo haver atingimento simultâneo/sequencial uni/pluriglandular e défices hormonais isolados/múltiplos. Os seus mecanismos fisiopatológicos e fatores de risco permanecem por esclarecer, assim como a sua relação com o prognóstico da doença oncológica. Contrariamente a eventos adversos autoimunes noutros órgãos, as endocrinopatias geralmente não implicam a suspensão de ICI, são maioritariamente irreversíveis e a utilização de glucocorticóides não tem utilidade na sua reversão. A imprevisibilidade da sua ocorrência ou do tempo decorrido após o início do tratamento obrigam a uma vigilância regular dos doentes. Apesar de tratáveis, o maior desafio passa pelo seu diagnóstico e início de tratamento atempados, reduzindo a sua morbilidade e mortalidade. Isto obrigará a uma abordagem multidisciplinar, com participação das várias especialidades médicas envolvidas no tratamento dos doentes oncológicos, em ambulatório, no serviço de urgência ou em internamento hospitalar.

CONFLITOS DE INTERESSE

A autora declara não ter conflitos de interesses relacionados com o presente trabalho.

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Suicide Attempt in a Patient with Sibutramine Associated Psychosis

Tentativa de Suicídio em Doente com Psicose Associada a Sibutramina

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ABSTRACT

Sibutramine is a serotonin-norepinephrine-dopamine reuptake inhibitor, initially developed as a potential antidepressant and later approved for the management of obesity. Sibutramine use is also associated with psychiatric symptoms, namely mania, panic attacks, and, less frequently, psychosis. We report the case of a 32-year-old man, admitted to our hospital due to a suicide attempt in the context of sibutramine-associated psychosis. The symptoms remitted completely after discontinuation of sibutramine and a brief period of antipsychotic medication. The aim of this manuscript is to highlight the importance of the recognition of sibutramine-associated psychosis, to discuss the possible pathophysiology and the proper clinical and therapeutic management.

Keywords: Liaison Psychiatry; Psychotic Disorders; Sibutramine; Suicide

RESUMO

A sibutramina é um inibidor não seletivo da recaptação de serotonina-noradrenalina-dopamina, inicialmente desenvolvido como potencial antidepressivo e posteriormente aprovado para o tratamento da obesidade. O uso de sibutramina está também associado ao aparecimento de sintomas psiquiátricos como mania, ataques de pânico e, com menor frequência, psicose. Relatamos um caso de um homem de 32 anos, internado no nosso hospital devido a uma tentativa de suicídio no contexto de uma psicose associada à sibutramina. Os sintomas remitiram completamente após a descontinuação da sibutramina e um breve período de terapêutica antipsicótica. O objetivo deste artigo é destacar a importância do reconhecimento da psicose associada à sibutramina, discutir a sua possível fisiopatologia e o seu apropriado manejo clínico e terapêutico.

Palavras-chave: Perturbações Psicóticas; Psiquiatria de Ligação; Sibutramina; Suicídio

INTRODUCTION

Sibutramine, a serotonin-norepinephrine-dopamine reuptake inhibitor, was approved by the Food and Drug Administration (FDA) in November 1997 for weight loss and maintenance of weight loss in patients with a body mass index (BMI) greater than or equal to 30 (≥ 30) kg/m^2 or for patients with a BMI over 27 kg/m^2 with other cardiovascular risk factors, after being initially developed as a potential antidepressant.[1] Despite the marketing ban issued by the European Medicines Agency in 2010, due to cardiovascular safety concerns, its use remains common, although illegal, as an anti-obesity medication. Sibutramine can be bought in the black market, usually as a hidden ingredient of some illegal weight-loss products. Sibutramine use is also associated with psychiatric symptoms, namely mania, panic attacks, and, less frequently, psychosis,[2-5] but the real incidence and frequency of these clinical features is difficult to determine because there is no reliable data on its consumption worldwide.

We report a case of suicide attempt in the context of sibutramine-associated psychosis, to highlight the importance of the recognition of this condition and to discuss the possible pathophysiology as well as the proper clinical and therapeutic management.

CASE REPORT

A 32-year-old single man from Brazil, working in Portugal as an elderly caregiver, with no personal history of previous psychiatric or neurological disorders, and with a family history of depressive disorder (namely his mother and a maternal aunt) was admitted to the emergency department due to a suicide attempt where the patient jumped from a 4th-floor window in December 2019. He was initially evaluated by orthopedic surgery, which documented several fractures. His mental status examination revealed perplexity, hyperprosexia (excessive fixity of attention on a stimulus object), anxious mood, behavior indicative of auditory hallucinations, kinesthetic hallucinations, suicide ideation and loss of self-boundaries (the loss of the awareness of the separation between the individual and the environment). Drug scan for amphetamines, cannabis, cocaine and opiates was negative. The patient was then admitted to the orthopedic surgery ward. Besides analgesic drugs, the patient was prescribed olanzapine 10 mg/day. One month following admission, after undergoing major surgical procedures, the patient was reassessed by liaison psychiatry and liaison psychology. The psychotic symptoms and suicide ideation had remitted. The patient disclosed that, since the age of 18, due to being overweight, he had been self-medicating with 15 mg sibutramine for 2-month length cycles. In the

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first of these cycles, at age 18, no associated psychiatric symptoms were reported. The second cycle, when the patient was 21, was associated with overvalued ideas of reference, suspiciousness, sadness, and a feeling of abandonment, and these symptoms were self-limited to the duration of the sibutramine cycle. Between the age of 22 and 32, the patient reported completing one to two cycles of 15 mg sibutramine per year, and all were associated with the same aforementioned symptoms. Eight months before admission, the patient reported a period of overwork, with an increased volume of night shifts and a subsequent inversion of his sleep-wake cycle. During that period, and in the three months before admission, he took a 15 mg sibutramine one-month cycle, followed by a 30 mg two-months cycle with the sibutramine pills that he had brought from Brazil. The patient reported the progressive appearance of overvalued ideas of guilt, reference, elementary auditory hallucinations, somatic anxiety, and mixed insomnia. These symptoms evolved to delusional reference and persecutory ideas, complex auditory hallucinations, accompanied by suicide ideation in early December 2019. Due to these symptoms, the patient abruptly stopped sibutramine a week before the hospital admission. However, the symptoms remained present, and the patient attributed his suicide attempt, a defenestration from his bedroom window to an impulsive, unplanned and desperate act to stop his suffering. Three months after admission, the patient was discharged without any psychotic symptoms, medicated with olanzapine 10 mg/day, and referred to both orthopedic surgery and psychiatric follow-up appointments.

DISCUSSION

There are few reported cases of sibutramine induced psychosis in the literature, and hence the importance of disclosing such clinical cases, in order to promote a better understanding of its clinical features. Clinically, the psychiatric symptoms of our patient are in line with the few reported cases of sibutramine associated psychosis: a case series of 16 patients with sibutramine associated psychosis revealed auditory hallucination in (63%), persecutory ideas (38%), delusions (25%), and suicidal ideation (13%).[6]

Initial reports regarding the receptor-binding properties of sibutramine and its metabolites underestimate the dopaminergic reuptake inhibition of sibutramine compared with the reuptake inhibition of serotonin and noradrenaline. However, more recently, some animal studies suggested a dose-related dopaminergic reuptake inhibition in both the striatal and hypothalamic regions.[2] This finding may explain, at least partially, not only the relationship between sibutramine and psychosis,[7] according with the most accepted dopaminergic theory of psychosis, but also, the fact that our patient only developed psychotic symptoms and suicide ideation under a sibutramine 30 mg cycle and not with the previous 15 mg cycles. Furthermore, using the algorithm of Naranjo *et al*[8] to estimate the probability of an adverse drug reaction, this case report would obtain a probable score of 7 points.

Regarding the delay between sibutramine intake and the onset of psychotic symptoms observed in our patient, some authors argue that it might be the result of a reverse tolerance phenomenon that is similar to the phenomenon described for cocaine and amphetamine abuse, or that sibutramine may act as a precipitating factor in psychosis-predisposed patients.[9]

In terms of the psychopharmacological approach, as in other case reports,[2] the symptoms remitted completely after sibutramine discontinuation and a brief period of antipsychotic medication.

Regarding limitations, we recognize that the absence of a collateral source of information, namely, a close relative, and the fact that the mental state examination had taken place in a liaison psychiatry setting may have limited the accuracy of some clinical elements. However, we tried to mitigate such facts by interviewing the patient in different moments in order to better characterize this case report.

CONCLUSION

Sibutramine may act as a risk factor for psychosis in predisposed patients. Suspension of sibutramine intake and treatment with a low dose antipsychotic, for a short period, appears to be effective in symptom remission. If, in a suspected case of sibutramine induced psychosis, the symptoms persist after those measures are taken, then the case must be reassessed, and another differential diagnosis should be considered. Further studies are required to elucidate the relationship between sibutramine and psychosis and the underlying pathophysiology.

AUTHORS CONTRIBUTION

PCP, CF: Substantial contribution for the draft of the manuscript. Clinical follow-up of the patient and case review.

ALS, JJ, LG: Substantial intellectual contribution. Case review and critical review of the paper.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

PATIENT CONSENT

The authors received consent from the patient to publish the report and the information has been de-identified to protect anonymity.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Granulomas Sarcóides Sobre Cicatriz: Além da Sarcoidose

Sarcoid Granulomas Over Scars: Beyond Sarcoidosis

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RESUMO

Os granulomas sarcóides podem ser encontrados num vasto leque de doenças, pelo que diferenciar a sarcoidose de uma reação tipo sarcóide constituiu um desafio. Apresentamos o caso de uma jovem com lesões papulonodulares eritematovioláceas localizadas nos pavilhões auriculares sobre os locais de aplicação de *piercings*. A biópsia cutânea mostrou um infiltrado constituído por granulomas sarcóides ou focalmente tuberculóides, não excluindo a hipótese de sarcoidose. O estudo complementar, apesar de uma discreta elevação da enzima conversora da angiotensina, excluiu envolvimento ocular ou pulmonar por sarcoidose. Perante a localização das lesões foram realizados testes epicutâneos que revelaram uma reação fortemente positiva ao paládio e ao níquel, apoiando o diagnóstico de dermatite de contacto granulomatosa. Estão descritos escassos casos de dermatite de contacto granulomatosa ao paládio tendo o metal dos *piercings* como fonte de sensibilização. A formação de granulomas sarcóides pode representar quer uma reação tipo sarcóide, quer uma forma de sarcoidose cutânea, e os testes epicutâneos adquirem um papel fundamental no diagnóstico correto.

Palavras-chave: Cicatriz; Dermatite de Contacto; Granuloma; Paládio; Sarcoidose

ABSTRACT

Sarcoid granulomas can be found in a wide range of diseases and differentiating sarcoidosis from a sarcoid-like reaction may be a challenge. We present a woman with erythematoviolaceous papulonodular lesions located on the ears where piercings were placed. A skin biopsy showing an infiltrate of sarcoid and focal tuberculoid granulomas did not exclude sarcoidosis. There was a slight increase in the level of angiotensin-converting enzyme. Systemic involvement due to sarcoidosis was excluded. Epicutaneous tests performed revealed a strong positive reaction to palladium and nickel, supporting the diagnosis of granulomatous contact dermatitis. There are only a few reports of granulomatous contact dermatitis to palladium with piercings as the source of sensitization. The formation of sarcoid granulomas can represent either a sarcoid-like reaction or a form of cutaneous sarcoidosis, and patch tests are essential in order to establish the diagnosis.

Keywords: Cicatrix; Contact Dermatitis; Granuloma; Palladium; Sarcoidosis

INTRODUÇÃO

Os granulomas sarcóides são constituídos por células epitelióides rodeadas por uma escassa coroa linfocitária e sem tendência à caseificação. Podem ser encontrados em lesões de sarcoidose, mas também num vasto leque de outras patologias tais como reações de corpo estranho, sífilis secundária, doença de Crohn, granuloma anular, linfomas e cicatrizes de herpes zoster. Constitui assim um desafio distinguir a sarcoidose de uma reação tipo sarcóide.[1,2]

CASO CLÍNICO

Doente do sexo feminino, 23 anos, saudável e sem medicação habitual, recorreu à consulta de Dermatologia por lesões cutâneas assintomáticas dos pavilhões auriculares com cerca de 1 ano de evolução. Ao nível dos hélices e lóbulos das orelhas, observavam-se lesões papulonodulares, eritematovioláceas, firmes e de superfície lisa (Fig. 1), com distribuição irregularmente linear nos locais de

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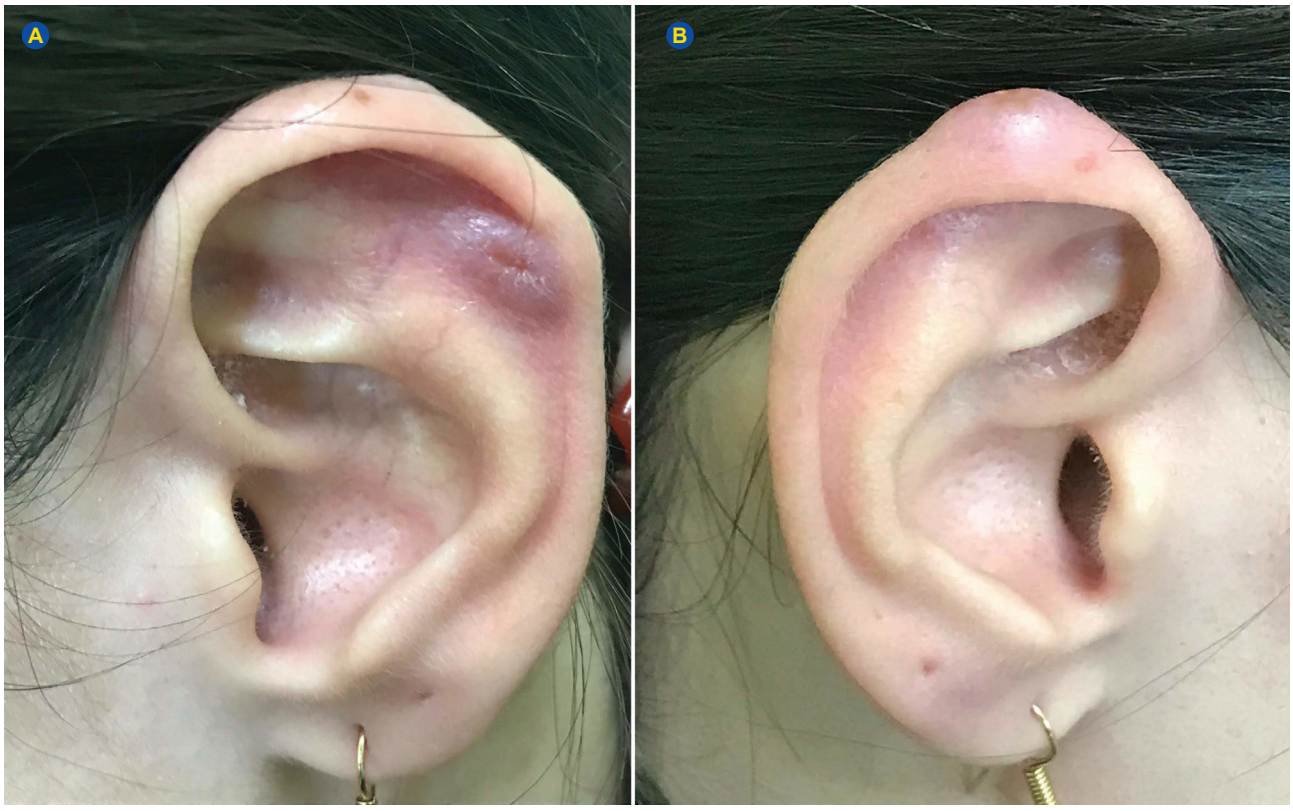

Figura 1 – Lesões cutâneas localizadas sobre os locais de aplicação prévia de *piercings*; (A) pavilhão auricular esquerdo, (B) pavilhão auricular direito

aplicação de *piercings* realizados cinco anos antes (sem prurido ou qualquer reação local nessa data). Ao exame objetivo, além das lesões descritas, não foram encontradas outras alterações mucocutâneas ou de órgãos internos.

A biópsia cutânea de uma lesão do pavilhão auricular mostrou um infiltrado granulomatoso envolvendo a derme superficial e profunda, constituído por granulomas sarcóides ou focalmente tuberculóides, não excluindo a hipótese de sarcoidose (Fig. 2).

As análises laboratoriais mostraram apenas uma discreta elevação da enzima conversora da angiotensina (ECA) (60 U/L, N 8 - 52 U/L). A tomografia computorizada de alta resolução não mostrou alterações no parênquima pulmonar nem adenopatias hilares ou mediastínicas, e a observação pela Pneumologia e Oftalmologia excluiu envolvimento destes órgãos.

Perante um diagnóstico empírico de sarcoidose cutânea a doente iniciou corticoterapia tópica (creme de propionato de clobetasol) sem benefício ao fim de seis meses. A vigilância clínica e realização periódica de radiografia do tórax e análises laboratoriais, incluindo novos doseamentos de enzima conversora da angiotensina (ECA) não revelaram alterações. Dois anos após seguimento, perante a localização das lesões e por suspeita

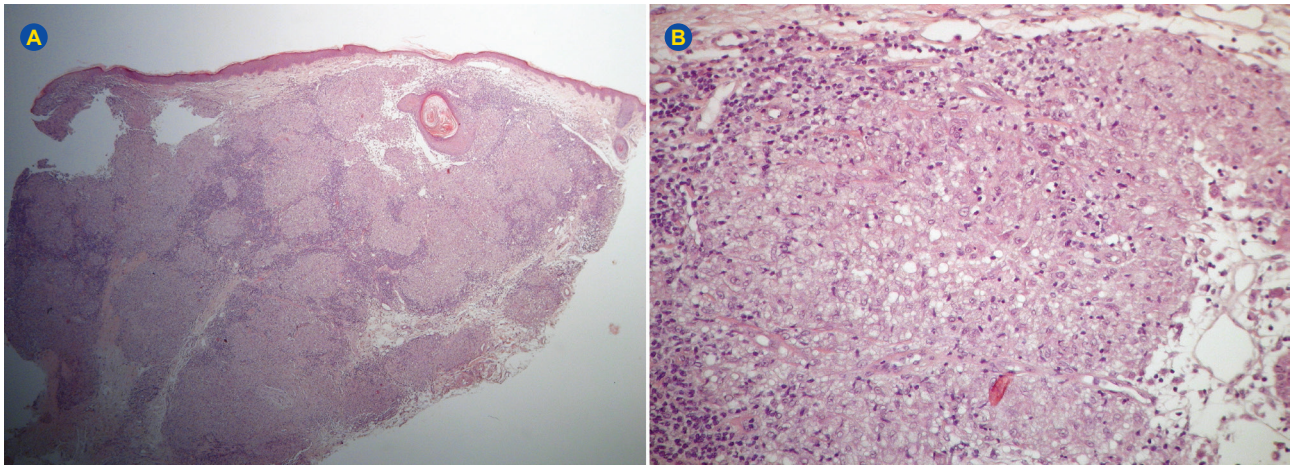

Figura 2 – (A) infiltrado dérmico granulomatoso difuso; (B) granuloma sarcóide: granuloma 'nu', constituído por células epitelióides, sem necrose, com escasso infiltrado linfocitário na periferia.

de dermatite de contacto com padrão granulomatoso, realizou testes epicutâneos de hipersensibilidade retardada. Os alergénios da série básica europeia e das séries de metais (Chemotechnique diagnostics, Vellinge Sweden®) foram aplicados no dorso em Finn-Chambers® e mantidos em oclusão durante 48 horas. As leituras realizadas ao fim de três, cinco e sete dias, de acordo com as normas internacionais, revelaram uma reação fortemente positiva (+++) ao paládio (tetracloropaladato de sódio a 3% vas e cloreto de paládio 2% vas) e ao níquel (sulfato de níquel 5% vas), confirmando hipersensibilidade aos metais, nomeadamente ao paládio, frequentemente presente em bijuteria e descrito como causa de dermatite de contacto (DC) granulomatosa.

Perante este diagnóstico, foi suspensa a realização sistemática de exames complementares de diagnóstico para pesquisa de envolvimento sistémico por sarcoidose e, dada a benignidade da dermatose e por opção do paciente, não foram tentados outros tratamentos, nomeadamente corticosteroides intralesionais ou excisão cirúrgica.

DISCUSSÃO

A sarcoidose cutânea tem um variado espectro de apresentações clínicas e, em cerca de 20% - 30% dos casos, o envolvimento cutâneo precede o envolvimento sistémico.[3] Apesar do exame anatomopatológico apresentar um papel fundamental no diagnóstico, há que ter presente que uma reação granulomatosa não caseosa com granulomas sarcóides não é específico desta doença. Perante este resultado em exames anatomopatológicos de locais de *piercings,* deve ser considerada a possibilidade de uma reação alérgica.

A DC alérgica, uma reação de hipersensibilidade do tipo IV, cursa habitualmente com eczema, mas pode ter outros padrões clínicos, como reações pustulosas, pigmentares, liquenóides, linfomatóides, tipo de eritema multiforme e, como no presente caso, com formação de granulomas, tipicamente sarcóides – DC granulomatosa.

Múltiplos metais podem estar implicados na génese de granulomas de hipersensibilidade, nomeadamente berílio, alumínio, zircónio, titânio, níquel, mercúrio, crómio, cobalto, paládio e ouro. Os dois últimos são os mais frequentemente envolvidos em lesões cutâneas sobretudo em relação com *piercings*, uma causa emergente e crescente de DC granulomatosa.[4,5]

A sensibilização ao paládio é quase tão frequente como a sensibilização ao níquel, sendo comum a reação cruzada entre os dois alergénios, mas a reação cutânea é habitualmente de eczema.[6] A formação de granulomas de contacto alérgico tipo sarcoide é rara e foi descrita pela primeira vez em 1983, estando relatados escassos casos de DC granulomatosa ao paládio relacionada com *piercings*. Ao contrário do eczema, nesta forma de DC as lesões localizam-se de forma exclusiva e desde o início apenas na derme, sem evidência de espongiose e exocitose de linfócitos, típicos das reações de hipersensibilidade de contacto. É possível que a libertação do metal do brinco para a derme possa ocasionar uma reação granulomatosa sem envolvimento da epiderme. Contudo, no teste epicutâneo o paládio induz uma reação eczematosa que, nalguns casos, evolui para um granuloma démico semelhante à reação observada no local de aplicação do *piercing*, o que não se verificou no caso presente.[7]

As lesões da DC granulomatosa ao paládio relacionados com piercings são habitualmente resistentes à corticoterapia tópica e intralesional obrigando por vezes à excisão cirúrgica.[8]

O presente caso clínico pretende demonstrar que a ocorrência de granulomas sarcóides em biópsias cutâneas pode, em casos raros, dever-se a uma reação de hipersensibilidade. Uma história clínica detalhada e a realização de testes epicutâneos com diferentes metais é necessária para revelar a verdadeira natureza destas lesões.

CONTRIBUTO DOS AUTORES

FM; MB: Follow-up do doente, redação do manuscrito.

JCC: Revisão crítica da descrição e discussão histológica.

MG: Revisão crítica do manuscrito.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFIDENCIALIDADE DOS DADOS

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

CONSENTIMENTO DO DOENTE

Obtido.

CONFLITOS DE INTERESSE

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

FONTES DE FINANCIAMENTO

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

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A Curious Case of Dysphagia Due to Osteophytes

Um Curioso Caso de Disfagia Causada por Osteófitos

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Keywords: Cervical Vertebrae; Deglutition Disorders; Osteophyte
Palavras-chave: Osteófito; Perturbações da Deglutição; Vértebras Cervicais

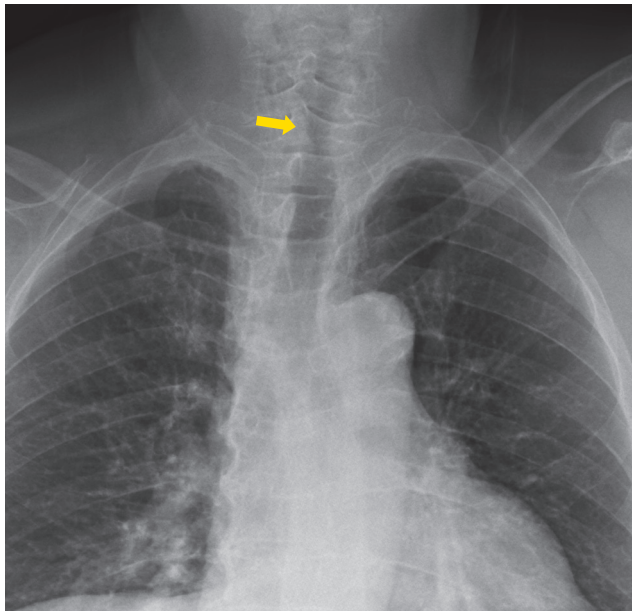

Figure 1 – Posteroanterior chest radiograph revealing a tracheal stricture (arrow)

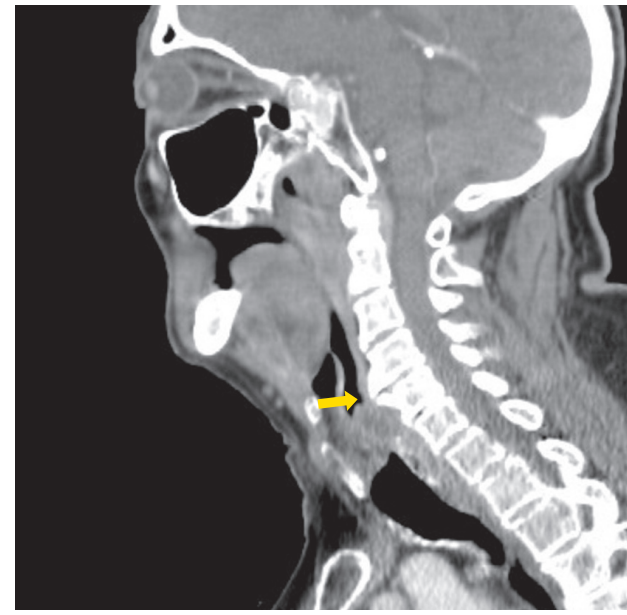

Figure 2 – Contrast-enhanced neck computed tomography with marked anterior osteophytes in the C4-C5 vertebrae (arrow)

An 80-year-old male with Parkinson's disease and partially dependent on activities of daily living (Barthel index 45) was admitted due to a first episode of community-acquired pneumonia. He also complained of long-lasting difficulty in swallowing, which his attending physician attributed to neurogenic dysphagia. Upon closer evaluation, the patient mentioned non-acute onset dysphagia, initially for liquids but now mainly affecting solid foods. The difficulty in swallowing solids was progressive, intermittent, and well-localized to his lower neck. The chest-radiograph revealed a tracheal stricture (Fig. 1), prompting a neck computed tomography that showed an exuberant anterior osteophyte in the C4-C5 vertebrae with soft-tissue and tracheal compression (Fig. 2). The barium esophagram revealed delayed but maintained contrast progression. Although spinal osteophytes are common, occurring in one in every five elderly patients, less than 1% of osteophytes lead to dysphagia.[1-5] This case illustrates how a thorough investigation is essential to evaluate the cause of dysphagia. The patient is currently being managed through a conservative approach due to personal preference.

AUTHORS CONTRIBUTION

SM: Draft of the paper. Data interpretation. Evaluation of the patient. Responsible for the intelectual integrity of the paper.

BC: Evaluation of the patient. Data interpretation. Critical review. Responsible for the intelectual integrity of the paper.

LC: Contribution to the design of the work. Data interpretation. Critical review. Responsible for the intelectual integrity of the paper.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the 2013 Helsinki

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Declaration of the World Medical Association.

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Resposta a "O Impacto da COVID-19 na População Idosa em Portugal: Resultados do Survey of Health, Ageing and Retirement (SHARE)"

Reply to "The Impact of COVID-19 in Older People in Portugal: Results from the Survey of Health, Ageing and Retirement (SHARE)"

Palavras-chave: Avaliação Geriátrica; Brasil; COVID-19; Idoso; SARS-CoV-2; Saúde Mental
Keywords: Aged; Brazil; COVID-19; Geriatric Assessment; Mental Health; SARS-CoV-2

Caro Editor,

Foi com intenso entusiasmo e curiosidade académica que realizámos a leitura do estudo conduzido por Novais *et al*. O artigo supracitado aborda que a pandemia da COVID-19 tornou desafiador a prestação de serviços rotineiros de saúde para as pessoas com mais idade.[1] Por ser um período de recessão e de confinamento, os idosos enfrentaram dificuldades frequentes como de socialização, falta de acompanhamentos multidisciplinares, medicação, transporte, os quais durante a pandemia se restringiram em suas atividades.[2] Por esse prisma, fica realmente evidente a necessidade e o desafio na gestão dessa faixa etária.

Nesse contexto, os idosos ficam mais vulneráveis e no Brasil é possível observar desafios semelhantes na gestão dessa população. Assim, sob a ótica do sistema de saúde brasileiro, apesar do atendimento aos idosos, antes da pandemia, ser realizado de maneira presencial e contínua, a aumento significativo do número de casos de infecção por COVID-19 afastou os doentes dos centros de saúde, e levou a que consequentemente deixassem de procurar e/ou adiaram as suas consultas. Perante as adversidades, acentuaram-se as mudanças na rotina, que no novo contexto revela um défice de hábitos saudáveis e seguros para manutenção favorável das doenças crónicas.[3] Logo, a perturbação na continuidade do tratamento configura um contratempo mundial.

Frente a essa situação, as barreiras impostas pela pandemia urgem ações em saúde, já que manter o atendimento dos idosos é uma forma de prevenir prognósticos indesejados. Nesse intuito, o artigo levou-nos a refletir quais os fatores que teriam impactado o estado de saúde dessa população. Segundo Matheus, para os diabéticos a telemedicina apresenta bons resultados em relação à manutenção dos níveis recomendados de glicémia e, além disso, consegue triar os pacientes que necessitam de atendimento presencial.[4] Essa estratégia também poderia ser aplicada para realizar a triagem dos idosos que necessitam de atendimento contínuo. Por outro lado, a medicina à distância promove as medidas de distanciamento, que são imprescindíveis para diminuir os riscos de infecção por COVID-19. Desse modo, o cuidado aos idosos requer constantes adaptações, a fim de melhor satisfazer as suas necessidades.

Por conseguinte, fica claro que há um grande desafio e necessidade de uma revisão na gestão dos idosos durante a pandemia de COVID-19. Nesse contexto, os profissionais de saúde devem desenvolver novas estratégias de intervenção com o intuito de melhorar e/ou reduzir algumas adversidades durante a pandemia com a população acima de 60 anos.

CONTRIBUTO DOS AUTORES

LRR, JVMP: Elaboração do artigo.
EG, EMS: Orientação 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 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.

FONTES DE FINANCIAMENTO

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William H. Stewart: Quem Persiste na Citação Acrescenta Desinformação

William H. Stewart: Those Who Stand Up for the Quote Add Disinformation

Palavras-chave: Comunicação; Disseminação da Informação
Keywords: Communication; Information Dissemination

Caro Editor,

Quando se discute o panorama das doenças infeciosas ou o uso adequado dos antimicrobianos, é frequente, não apenas na abertura de aulas, de congressos, de colóquios, de debates, em prefácios de livros, como também nas redes sociais e em artigos de imprensa, alguém referir-se à suposta previsão falhada do médico norte-americano William H. Stewart sobre o 'fim' das doenças infeciosas como um problema de saúde para a humanidade.

A citação em causa, que terá sido proferida no final dos anos 1960, e encontrada com pequenas variações, é a seguinte: «*It is time to close the book on infectious diseases, and declare the war against pestilence won*»,[1] que em português (tradução livre) se poderá replicar em algo como «é tempo de encerrar o livro das doenças infeciosas e declarar vitória na guerra contra a pestilência».

O propósito de utilização da frase é o de alertar para o erro de subestimarmos quer a nossa capacidade de solucionar todas as doenças infeciosas que nos afligem, quer a emergência de novos agentes patogénicos para o Homem (poderá facilmente aparecer em várias palestras sobre a pandemia de SARS-CoV-2 que vivemos). De facto, na época em que teria sido proferida, o desenvolvimento de campanhas de vacinação intensas, e o decréscimo significativo, no Ocidente, da incidência e morbimortalidade de doenças como a poliomielite, o sarampo e a varíola, juntamente com o desenvolvimento de várias classes de antibióticos, poderá ter acalentado a ideia de que a erradicação de muitas doenças infeciosas pudesse ter um horizonte largo e tangível.

Contudo, a fonte da referida citação não é verificável, e há mesmo quem se tenha dedicado a fazê-lo de forma exaustiva, numa pesquisa que incluiu desde fontes de artigos médicos, agências noticiosas e registos de discursos oficiais.[1,2] A citação primária não se encontra, sendo que todas as vezes em que surge decorre de citação secundária, no género "de quem conta um conto acrescenta um ponto". Inclusivamente a data e o local são imprecisos (entre 1967 e 1969),[1] como se de um mito urbano se tratasse. A própria revista New Yorker elaborou uma peça jornalística sobre o assunto e a necessidade de reposição da situação apócrifa.[3]

William H. Stewart (1921-2008) foi um médico pediatra e epidemiologista que, entre outros cargos relevantes, foi *Surgeon General* dos Estados Unidos da América (EUA) no período 1965 - 1969, o equivalente, em Portugal, ao cargo de Diretor-Geral da Saúde.[4,5] A ele tem de ser dado o mérito de, como outros médicos de saúde pública, ter percebido e alertado para o crescimento acentuado das doenças cardiovasculares e do metabolismo, até ao lugar mais alto do pódio das causas de morbimortalidade da população, nomeadamente nos países ditos desenvolvidos. Neste sentido, foi um dos primeiros e grandes impulsionadores de políticas de saúde contra o tabagismo, na gestão de doenças crónicas e do acesso justo e não discriminatório aos cuidados de saúde.[3-5]

Assim, não há forma aparentemente credível de atribuir as declarações ao seu suposto autor,[1,2] muito menos com o significado quase jocoso que muitas vezes perpassa, mesmo que o propósito final da citação seja pedagógico e um alerta para o verdadeiro desafio que as doenças infeciosas representam, e sempre representarão, no convívio mais ou menos diplomático com a humanidade.

É provável que a frase continue, ao longo dos tempos, a ser reciclada e republicada, por muito que até o seja pela simples bonomia do ensinamento, mas sê-la-á a expensas do nome de um médico que muito provavelmente nunca a terá proferido. É interessante e ténue a linha que a História traça entre a autoria e a apocrifia.

Num mundo moderno em que a verificação das fontes bibliográficas e a disseminação de *fake news* são problemas diários com que a Medicina (e não só) se tem deparado, de forma externa (e por vezes interna), é responsabilidade de cada um de nós perseverar num rigor suplementar, amiúde difícil, para não ser arrastado para e por elas.

CONTRIBUTO DOS AUTORES

DG, FVS: Ambos os autores contribuíram igualmente para a conceção, recolha dos dados, tratamento e elaboração do manuscrito.

CONFLITOS DE INTERESSE

DG: Recebeu da AARI – Associação de Apoio Às Reuniões de Infecciologia apoio sob a forma de pagamento do *registration fee* no 17º ENAI – Encontro Nacional de Atualização em Infeciologia que teve lugar em 2021 no Porto.

Recebeu da AARI – Associação de Apoio Às Reuniões de Infecciologia honorários pela sua contribuição no Curso de Pós-Graduação em Doenças Infecciosas – 2ª Edição (17/06/2021).

FVS: Recebeu da AARI – Associação de Apoio Às Reuniões de Infeciologia apoio sob a forma de pagamento do *registration fee* no 17º ENAI – Encontro Nacional de Atualização em Infeciologia que teve lugar em 2021 no Porto.

FONTES DE FINANCIAMENTO

Este trabalho foi realizado sem contributo de subsídios ou bolsas.

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Abuso de Álcool na Mulher: Um Problema Subdiagnosticado?

Excessive Alcohol Use in Women: An Underdiagnosed Problem?

Palavras-chave: Alcoolismo; COVID-19; Perturbações Relacionadas com Uso do Álcool; Pandemia; Sexo Feminino
Keywords: Alcohol-Related Disorders; Alcoholism; COVID-19; Female; Pandemics

Os estudos nacionais e internacionais mais recentes[1] mostraram que o confinamento e o isolamento social consequente à pandemia COVID-19 fizeram aumentar os consumos de álcool em 2020, sobretudo em indivíduos que já tinham perturbação do uso de álcool (PUA) prévia.

Historicamente, o consumo etanólico sempre foi mais frequente nos indivíduos do sexo masculino, comparativamente com os indivíduos do sexo feminino. No entanto, o IV Inquérito Nacional ao Consumo de Substâncias Psicoativas[2] revelou um aumento da prevalência do consumo de álcool entre 2012 e 2016/17, especialmente no género feminino. De facto, as mulheres portuguesas registaram o consumo diário de álcool mais elevado na União Europeia (11,8%) segundo dados do Retrato da Saúde publicado pelo Ministério da Saúde em 2018.[3]

Contudo, as mulheres com PUA ainda procuram pouco os cuidados de saúde para tratamento dessa condição.[4] Possivelmente por sentimentos de culpabilização, vergonha e auto-desvalorização, as mulheres com PUA encontram-se pouco representadas nas unidades de tratamento especializadas, nomeadamente quando em comparação com os homens.

Sabe-se também que o consumo excessivo de álcool no sexo feminino apresenta outros desafios na área da Medicina. Do ponto de vista biológico, para a mesma quantidade de álcool consumido, as mulheres apresentam maior probabilidade de aparecimento de lesões orgânicas no organismo.[5] Também do ponto de vista psicológico, as mulheres apresentam maior comorbilidade psiquiátrica associada ao consumo de álcool quando comparadas com os homens.

Os médicos, nomeadamente os médicos de família, que têm o primeiro contacto com os utentes, mas também os médicos das restantes especialidades deverão estar atentos a este fenómeno do aumento do consumo etanólico excessivo em mulheres, que se encontra frequentemente escondido. É sempre importante questionar os hábitos alcoólicos, aconselhar, oferecer ajuda e, caso seja necessário, encaminhar para acompanhamento especializado.[3]

CONTRIBUTO DOS AUTORES

NGR: Contribuição substancial na concepção e desenho do trabalho. Pesquisa bibliográfica e selecção da mesma.

AG, MA: Pesquisa bibliográfica e revisão crítica do trabalho.

JT: Revisão crítica do texto.

CONFLITOS DE INTERESSE

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

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Delirium in Patients with Severe COVID-19: Preliminary Results of the MAPA Longitudinal Study

Delirium em Doentes com COVID-19 Grave: Resultados Preliminares do Estudo Longitudinal MAPA

Keywords: COVID-19; Delirium; Neuropsychiatry; Quality of Life; Risk Factors
Palavras-chave: COVID-19; Delírio; Fatores de Risco; Neuropsiquiatria; Qualidade de Vida

Dear Editor,

We have read a letter published in Acta Médica Portuguesa[1] about delirium in older patients with COVID-19, emphasizing the importance of early detection and therapeutic intervention, in the light of the associated adverse outcomes. Regarding severe COVID-19, the literature indicates that around 65% of patients develop delirium.[2] Several reasons that justify such a high risk have been identified, including direct central nervous system invasion and the effect of sedation or prolonged invasive mechanical ventilation (IMV).[3] However, there are still limited data available on the post-discharge clinical picture of these patients.

We hereby present preliminary data of a longitudinal study focused on predictors and outcomes associated with delirium in patients with severe COVID-19, and which are part of a larger ongoing project: MAPA-Mental health in critically ill patients with COVID-19.

COVID-19 survivors admitted between March and May 2020 (first wave) to the Intensive Care Medicine Department of Centro Hospitalar Universitário São João, were included. Participants were evaluated by telephone in follow-up appointments (median = 106 days), for cognition, depressive and anxiety symptoms, as well as health-related quality of life. Sociodemographic and clinical data (including delirium assessed through clinical observation) were obtained from the hospital's electronic health records and clinical interview.

The sample included 59 patients. None had previous history of cognitive impairment or dementia. Delirium was registered in 49.2% patients, who were significantly older, were more likely to have nosocomial infection, had difficult weaning from IMV, were more likely to have been deeply sedated (propofol, fentanyl and/or midazolam) and require IMV. They also stayed longer in the hospital and after discharge were more likely to report impairments in terms of mobility, self-care and everyday activities (Table 1). Variables that showed statistically significant associations with delirium in the bivariate analyses (age, nosocomial infection, difficult weaning from IMV and deep sedation), or those which are reported in the literature as risk factors for delirium (namely, comorbidities), were selected to enter the logistic regression analysis. In the final model, only age was predictive of an increased risk of delirium (OR = 1.063, 95% CI: 1.006 - 1.125, p = 0.013), while comorbidities (OR = 0.819, 95% CI: 0.600 - 1.117, p = 0.207), nosocomial infection (OR = 1.614, 95% CI: 0.223 - 11.661, p = 0.635), difficult weaning from IMV (OR = 1.313, 95% CI: 0.318 - 5.416, p = 0.706) and deep sedation (OR = 3.561, 95% CI: 0.397 - 31.948, p = 0.257) did not increase the likelihood of developing delirium.

These findings are not only in line with results from previous studies conducted with critically ill non-COVID patients,[4] but also with earlier research on COVID-19,[5] specially concerning the association of delirium with advanced age. We also provide data on health-related effects of severe COVID-19, showing significant differences among those who have also developed delirium.

Through this preliminary analysis, we expect to contribute to the growing understanding of delirium in patients with COVID-19, highlighting distinctive factors and implications for health that are associated with delirium. Such features should draw our attention towards identifying high-risk patients who should be targeted for early routine screening and preventive interventions during hospitalization, and encourage the implementation of follow-up approaches, in order to minimize the associated adverse consequences.

AUTHORS CONTRIBUTION

SM: 1) Contribution to the conception/design of the work, acquisition and analysis of data; 2) Drafting the work and revising it critically for important intellectual content; 3) Final approval of the version to be published and 4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ARF: 1) Contribution to the conception/design of the work and analysis of data; 2) Drafting the work and revising it critically for important intellectual content; 3) Final approval of the version to be published and 4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JF, TV, LFontes, IC: 1) Contribution to the acquisition and analysis of data; 2) Revising it critically for important intellectual content; 3) Final approval of the version to be published and 4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki

Table 1 – Sample characteristics and bivariate analysis

Baseline characteristics	Overall (n = 59)	Delirium (n = 29)	No delirium (n = 30)	*p*-value
Age (years), median (min. - max.)	65 (24 - 81)	72 (30 - 80)	62 (24 - 81)	**0.010**(1)
Male, n (%)	39 (66.1)	18 (62.1)	21 (70.0)	0.520(2)
Education (years), median (min. - max.)	6 (2 - 19)	4 (2 - 19)	6.5 (2 - 17)	0.357(1)
Married, n (%)	37 (62.7)	17 (58.6)	20 (66.7)	0.295(3)
Past psychiatric history, n (%)	25 (42.4)	11 (37.9)	14 (46.7)	0.497(2)
Total number of comorbidities, median (min. - max.)	4 (0 - 11)	4 (0 - 7)	4 (0 - 11)	0.975(1)
Medication (daily), median (min. - max.)	4 (0 - 16)	4 (0 - 11)	4 (0 - 16)	0.771(1)
Hospital clinical data				
Acute illness severity, median (min. - max.)				
APACHE-II score	16 (5 - 36)	17 (6 - 36)	15 (5 - 34)	0.188(1)
SAPS-II score	35 (7 - 77)	41 (10 - 75)	33 (7 - 77)	0.414(1)
Nosocomial infection, n (%)	40 (67.8)	24 (82.8)	16 (53.3)	**0.016**(2)
Difficult weaning from IMV, n (%)	28 (47.5)	18 (62.1)	10 (33.3)	**0.027**(2)
Deep sedation, n (%)	44 (75.0)	26 (89.7)	18 (60.0)	**0.009**(2)
Invasive mechanical ventilation, n (%)	44 (75.0)	26 (89.7)	18 (60.0)	**0.009**(2)
Post-hospital discharge				
Hospital LoS, median (min. - max.)	48 (9 - 255)	67 (13 - 55)	36.5 (9 - 156)	**0.014**(1)
Cognitive impairment (6CIT), n (%)	10 (16.9)	5 (17.2)	5 (16.7)	1.000(4)
Depression (PHQ-9), n (%)	17 (28.8)	7 (24.1)	10 (33.3)	0.436(2)
Anxiety (GAD-7), n (%)	14 (23.7)	4 (13.8)	10 (33.3)	0.078(2)
Health-related quality of life (EQ-5D-5L), n (%) (problems in the following domains)				
Mobility	37 (62.7)	22 (75.9)	15 (50.0)	**0.044**(2)
Self-care	17 (28.8)	14 (48.3)	3 (10.0)	**0.001**(2)
Everyday activities	39 (66.1)	23 (79.3)	16 (53.3)	**0.035**(2)
Pain/discomfort	41 (69.5)	21 (72.4)	20 (66.7)	0.632(2)
Depression/anxiety	35 (59.3)	18 (62.1)	17 (56.7)	0.673(2)

min.- max.: minimum - maximum; APACHE-II: Acute Physiology and Chronic Health Evaluation II; SAPS-II: The Simplified Acute Physiology score; IMV: invasive mechanical ventilation; LoS: length of stay; 6CIT: Six-item Cognitive Impairment test; PHQ-9: Patient Health Questionnaire; GAD-7: General Anxiety Disorder scale: EQ-5D-5L: EuroQol 5-Dimension 5-Level questionnaire; **(1)**: Mann-Whitney test; **(2)**: Chi-square independent test; **(3)**: Chi-square's exact test; **(4)**: Fisher's exact test

Declaration of the World Medical Association updated in 2013. This project was approved by the Ethics Committee for Health of the CHUSJ/FMUP (Ref. nº 218/2020, 05/06/20 – CES, CHUSJ/FMUP).

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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Skills Required of Geriatricians: Why Medical Students Do Not Select Geriatrics as Their Career

Competências Exigidas aos Geriatras: As Razões Porque os Estudantes de Medicina Não Escolhem uma Carreira em Geriatria

Keywords: Geriatricians; Geriatrics/education; Students, Medical
Palavras-chave: Alunos de Medicina; Geriatras; Geriatria/educação

Castro *et al* suggest that family physicians should have mandatory palliative care training during their residency programs.[1] We support this perspective from our interview results.

The aging population continues to grow and is estimated to reach 1.6 billion (16.7%) worldwide by 2050.[2] Although it is necessary to train and increase the number of geriatricians, many young physicians and students are reluctant to pursue a career in this field. Blachman *et al* interviewed fellows in geriatrics training and found that having mentors and adopting early exposure to the field were key for workforce recruitment.[3] Similar results were obtained for the medical faculty. Therefore, we planned our research on the skills required by geriatricians in our educational setting.

We interviewed eight physicians and ten other health care professionals who were involved in geriatrics or home care medicine in a rural area for more than five years. The main question was what kinds of skills did a geriatrician require. We coded and organized the transcribed data and obtained five categories (Table 1). Additionally, we asked 17 medical students about what factors would make them choose to become a geriatrician in the future and divided the responses into three categories: appropriate work-life balance, high financial rewards, and the existence of role models. Some students indicated that geriatrics could be selected as a second career (but not the first).

Similar results were obtained in by Meiboom *et al*; the reasons students did not choose geriatrics as a career were: lack of role models, low financial rewards, low status, and dealing with a chronic illness that cannot be cured.[4] They also found that positive role models and a clear perspective of future professional careers were necessary.[5] Therefore, we need to increase the number of positive role models and clearly convey to students what are the advantages of pursuing a career in geriatrics.

Our findings may also be common to both family physicians and geriatricians. As we mentioned above, we strongly agree with Castro *et al* suggestion,[1] and this might not be limited to family physicians in Portugal but apply globally. If young physicians or students do not have enough knowledge about palliative medicine or geriatrics, they will not aspire to these careers. We hope our results will increase the number of geriatricians in the future globally.

AUTHORS CONTRIBUTION

MM: Research concept, design of the study, prior literature review, data collection, analysis and interpretation, draft of the paper and approval of the final version. Guarantor of the manuscript.

SJ: Research concept, design of the study, prior literature review, data collection, analysis and interpretation, critical review of the paper and approval of the final version.

Table 1 – Summary about aptitude required of geriatricians

Categories	Brief explanation of categories	Example of interviewees' comments
1. Being good at communicating with elderly	To feel comfortable about and empathize with the elderly and communicate from their standpoint.	"In supporting elderly patients and their families at home, we visit their homes and talk with them. If we do not like slow and relaxed communication, we have to have a hard time doing our daily work."
2. Perusing holistic approach of medical care	To be interested in complicated psychosocial issues as well as medical issues and try to understand the elderly as a whole person.	"Because there are patients with various backgrounds, it is important to understand each patient's situation well. The important thing is to provide medical care that suits each patient."
3. Preferring multidisciplinary collaboration and teamwork	Being able to care for the elderly as a team, collaborating with various medical professionals such as nurses and social workers.	"Collaborating with a multidisciplinary team is important. We should show it to our students. When you work in a rural area for the first time and have little experience, experienced nurses will support you, and you can learn a lot from them."
4. Being polite to elderly	Being able to accept the elderly as seniors in their lives and respond with professional courtesy and ethics.	"Some elderly patients are very conservative about etiquette and ethics. Understanding that well, I want our students to meet the elderly with a sophisticated and professional manner."
5. Preferring to foster successors	To be a role model and nurture successors voluntarily without asking for financial compensation.	"It's crucial that there is a culture to raise younger generations in daily medical care. If you want to do so, you should continue to foster an atmosphere in which education is important. That is why I strongly want to cooperate with student education."

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The authors have declared that no competing interests exist.

ETHICAL CONSIDERATIONS

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Reflections on the Relevance of Culture in Psychiatry and Medicine

Reflexões sobre a Relevância da Cultura em Psiquiatria e na Medicina

Keywords: Anthropology; Ethnopsychology/classification; Psychiatry

Palavras-chave: Antropologia; Etnopsicologia/classificação; Psiquiatria

Dear Editor,

A recent article raised relevant questions regarding the specific healthcare needs of vulnerable populations of refugees and migrants in Europe and prompted the authors to briefly reflect on the role of culture in medicine.[1]

Culture is an essential dimension in medicine. Psychiatry is paradigmatic with the exotic nature of certain behaviours in different cultures sparking the interest of early colonial psychiatrists and anthropologists.[2] Despite the recognition of the limitations of the early descriptions, many traces of that aesthetic wonder have persisted throughout the years transpiring into modern psychiatric nosology and medical practice.[2] Over the years, thinkers such as Frantz Fanon voiced their critical view of the colonial origins of psychopathology.[3,4] Disease classification systems (e.g. World Health Organization's International Classification of Diseases) were essential to bring validity and reliability to previously erratic diagnoses. However, some authors question the universality of diagnostic categories, highlighting the importance of recognizing the individual ways in which we express suffering through our personal narratives and the risk of medicalization of behaviours.[4] Cultural syndromes were an intrinsically problematic construct in the sense that they were not in fact culture-bound but rather culture-related; and not true syndromes according to the medical model. These included local explanations or causal attributions of certain behaviours, folk diagnostic labels, different idioms of expression of distress or metaphors.[2] If one wants to develop more robust diagnostic manuals our positivistic third-person approach has to be complemented with phenomenological subjective and intersubjective approaches to inform our research and the way we conceptualize symptoms. Exploration of the self and the basic structures of experience as well as the construction of shared narratives and interpretations allows a more comprehensive understanding of the illness experience of our patients.[5] Every human experience, including illness, is necessarily embedded in social and cultural processes. These processes transform even the most essential biological and physiological disturbances' translation into symptoms and behaviors through the lens of particular cultural codes.[2] The interactions between our own subjectivity and intersubjectivity with culture are essential for a proper understanding of everyday clinical practice.

We hope our work prompts clinicians and researchers to adopt an approach that integrates different frameworks (from genetics to large-scale networks, narrative structures

and social networks) and using different but complementary methods (epidemiology, phenomenology, neurophysiology, neuroimaging, etc.). Otherwise, we risk building knowledge upon increasingly frail foundations, thus hindering the understanding and ultimately the care provided to patients.

AUTHORS CONTRIBUTION

TT: Concept of the work, draft of the manuscript, critical review.

SVBG: Critical review of the paper.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

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Abandoning Old Concepts and Revisiting the Idea of a Diagnostic Hierarchy in Psychiatry

Abandonando Conceitos Antigos e Revisitando a Ideia de uma Hierarquia Diagnóstica em Psiquiatria

Keywords: Mental Disorders/classification; Mental Disorders/diagnosis; Psychotic Disorders; Schizophrenia
Palavras-chave: Esquizofrenia; Perturbações Mentais/classificação; Perturbações Mentais/diagnóstico; Perturbações Psicóticas

To the Editor,

We have read with great interest the letter penned by our fellow psychiatrist Dr Gama Marques published in a recent issue of the Acta Med Port.[1] In his letter, Dr Gama Marques revisits the concepts of pseudo-schizophrenia and secondary schizophrenia. He also emphasises the need for psychiatrists to be vigilant regarding cases of *de facto* organic psychosis misdiagnosed as primary psychosis, namely schizophrenia.

Despite the insightful observations, we diverge from Dr Gama Marques on certain points. The first concerns the concept of pseudo-schizophrenia. Pseudo-schizophrenia is an archaic, ill-defined, concept representing a form of non-diagnosis. The concept goes against the modern notions that any medical diagnostic practice should reside on positive findings, a trend that has received attention in psychiatry and in neurology, particularly in functional disorders.[2] Why use 'schizophrenia' to denote something we suspect is not schizophrenia? If we have reason to believe that a schizophrenia-like syndrome is due to a medical condition, why not just say 'psychosis due to a medical condition'? If a patient with neurosyphilis presents with schizophrenia-like symptoms, they do not have pseudo-schizophrenia or secondary schizophrenia; they simply have neurosyphilis. Despite their historical interest, these concepts are of dubious usefulness and will likely contribute to deteriorated communication among psychiatrists, and between psychiatrists and patients. This first objection leads to our second point of dissent.

During his closing remarks, Dr Gama Marques states that 'schizophrenia is the ultimate diagnosis of exclusion in psychiatry'.[1] Although the spirit of the remark is

understandable, the reference to an exclusion diagnosis brings unwanted noise, as it suggests that every other psychiatric condition is more positively diagnosable than schizophrenia. Thus, we take the opportunity to revisit the concept of diagnostic hierarchy, which is based on the 'organizing principle that polysymptomatic conditions with well-established pathophysiology should rank higher on the diagnostic hierarchy than conditions with fewer symptoms'.[3] The diagnostic hierarchy therefore entails that diagnoses ranked lower in the hierarchy should not be made if diagnoses higher in the hierarchy are present.[3] Despite some controversy, it is hypothesized that this model may improve the performance of clinicians and lead to a reduction of psychotropic prescriptions and misdiagnoses.[3] Famous hierarchies include Fould's hierarchy, with organic and drug-related conditions at its top.[4] Ghaemi[3] adapted the hierarchy for psychiatry, fitting new empirical data regarding psychiatric conditions (first affective, then psychotic, anxious, and personality). With a hierarchical model in mind, particularly the one defended by Ghaemi[3], we are inclined to diverge from the comments of Dr Gama Marques, praising, nonetheless, their ability to elicit discussion.

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COVID-19 em Enfermarias Forenses: O Exemplo do Serviço Regional de Psiquiatria Forense (SRPF-CHPL)

Forensic Units and COVID-19: The Example of the Regional Department of Forensic Psychiatry (SRPF-CHPL)

Palavras-chave: COVID-19; Hospitalização; Pandemia; Portugal; Psiquiatria Forense
Keywords: COVID-19; Forensic Psychiatry; Hospitalization; Pandemics; Portugal

A pandemia de COVID-19 representa um enorme desafio para os serviços de Psiquiatria Forense, particularmente para as enfermarias de segurança, com impacto sobre os indivíduos sujeitos a medida de privação de liberdade (Medida de Segurança). Em 2020 existiam em Portugal, de acordo com dados do Instituto Nacional de Estatística, um total de 159 indivíduos inimputáveis com medidas de segurança aplicadas em hospitais psiquiátricos não prisionais.[1] Os desafios neste contexto são únicos dada a natureza dos doentes e a duração da sua estadia.[2]

Com o início e evolução da situação pandémica em Portugal, a Direção Geral de Reinserção e Serviços Prisionais emitiu uma comunicação a 3 de Abril de 2020, dirigida aos diretores das unidades de internamento de psiquiatria forense. Esta iniciativa teve por objetivo a uniformização de procedimentos nos estabelecimentos onde ocorresse a execução de medidas privativas de liberdade, nomeadamente o internamento de inimputáveis, pela necessidade de evitar riscos e contactos desnecessários com o recluso internado, particularmente vulnerável, face à dupla situação de reclusão e internamento. Entre as medidas implementadas destacaram-se a suspensão de entrada de visitantes, a suspensão de saídas para atividade laboral, formativa ou outras no âmbito do Regime Aberto (medida de execução da pena para o inimputável, semelhante à liberdade condicional. Os pressupostos do Regime Aberto estão detalhados no artigo 14º do Código de Execução de Penas e Medidas Privativas de Liberdade) e a suspensão de atividades de grupo.[3]

Não existia até à data em Portugal qualquer análise do contexto pandémico e do impacto das medidas de controlo sanitário nas unidades de internamento de Psiquiatria Forense. Foi realizada pelos autores uma análise retrospetiva e descritiva das principais intercorrências psiquiátricas ocorridas durante o primeiro período em que decorreu o estado de Emergência Nacional, entre 18 de março e 2 de maio de 2020, da população internada na enfermaria de segurança do Serviço Regional de Psiquiatria Forense do Centro Hospitalar Psiquiátrico de Lisboa. Esta avaliação revelou que 48% dos indivíduos registaram intercorrências (num total de 24 intercorrências), sobretudo (cerca de 50%) em março, potencialmente correspondendo a uma reação de adaptação às restrições implementadas. As situações mais frequentemente reportadas corresponderam a situações de ansiedade, insónia e inquietação, correspondendo a perturbações de adaptação (F43), segundo a Classificação Internacional de Doenças na sua 10ª revisão (CID-10). Houve necessidade de ajustar a terapêutica psicofarmacológica sedativa e ansiolítica, com antipsicóticos atípicos em 71% dos casos, tendo sido reforçado em todas as situações psicoterapia de suporte. Duas queixas foram comumente reportadas "sinto a falta da visita da família" e aumento do pedido de disponibilização de "mais cigarros". Não foi globalmente observado um aumento de hostilidade ou comportamentos violentos.

É necessário alertar para o impacto do contexto pandémico na realidade dos indivíduos internados em enfermarias forenses no âmbito nacional, sendo necessária uma monitorização cuidadosa para prevenir episódios disruptivos comportamentais e diminuir o risco de violência.

CONTRIBUTO DOS AUTORES

IDS: Concepção, revisão e escrita do manuscrito.

FV, PF, MC: Supervisão da interpretação dos dados e revisão crítica.

CONFLITOS DE INTERESSE

FV: Não recebeu nos últimos três anos quaisquer honorários por cursos, apresentações, artigos ou eventos educativos. Recebeu honorários enquanto testemunha pericial na qualidade de consultor forense privado em contexto de acções judiciais de direito civil. Recebeu do Royal College of Psychiatry apoio para participação no Forensic Psychiatry Annual Conference no Reino Unido em março de 2020. É membro da Health and Justice Ministry Group work team on Not Criminally Responsible Patients e do Advisory Board on Civil Commitment Patients.

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