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Conselho Científico

Why Do Doctors Leave the National Health Service in Portugal? State of Play and Possible Solutions

Porque É que os Médicos Deixam o Serviço Nacional de Saúde em Portugal? Ponto da Situação e Possíveis Soluções

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Keywords: Internship and Residency; National Health Programs; Physicians
Palavras-chave: Internato Médico; Médicos; Serviço Nacional de Saúde

Over the last 40 years, Portugal has established a solid healthcare system. Through the establishment of a public National Health Service (NHS), as well as medical career pathways and medical training schemes through an organized medical residency program, we have a system that has served, although with identified deficits, the ultimate purpose of providing a good quality medical assistance to the population.

Recently, many specialist physicians have left the NHS. If many did retire, many more are doctors at the peak of their knowledge and technical skills. They are those who would be the trainers and mentors of the new medical generation. They are those who, given the possibility of remaining in the comfort of the familiar environment in which they were trained, prefer to exchange it for uncertainty, opting for a path of adaptation and challenge, usually outside the NHS. Why do they leave? Why will they continue to leave? On a two-sided scale that balances job instability with less peer training, we have the salary, working conditions, and personal living conditions as the main, but not the only, reasons for Portuguese doctors to leave the NHS.[1-3]

It is known that the remuneration and working conditions of physicians are not the best and that they have not improved in a comparable (and fair) way to other professions. In fact, the medical profession is one of the few cases in the Organization for Economic Co-operation and Development (OECD) where remuneration has decreased in real terms in the last decade.[4] Therefore, is it surprising that doctors seek better working conditions?

There are several entities involved in the medical residency program that try to overcome the growing difficulties to increase the number of training posts. In a system with known deficits, this situation becomes possible by resorting to medical centers with partial training capacity, in places with identified structural deficits but with overspecialized activities that are themselves an appeal to the new generation. And this, resulting in the need for additional training, necessarily alters the training and work dynamics of resident physicians and of course the different departments.

Within the scope of the 2021 medical residency application scheme, while more training posts were made available, and even though there were more candidates than posts, 51 posts were unfilled and 24% of candidates did not choose any post. Most vacant posts were in or near the capital, Lisbon, which contradicts the idea that the unfilled posts are in the countryside, far from large urban centers.

Candidates at this stage are looking for placements that, primarily, ensure the quality of training within the scope of the chosen specialty and, secondarily, have prospects for continuing their professional activity within the expectations they have for their future.

Looking in particular at the unfilled training posts, we do not think that this situation is only because of local problems of the departments. There will surely be a reason for a similar tertiary university hospital next door to have all its posts filled to the detriment of another whose training positions remain to be chosen; or for older, less well-paid family health units in the countryside to have all training posts filled to the detriment of a new family health unit in Lisbon. In general, we feel that posts are not filled when the binomial quality of training *versus* cost of living (and therefore prospects as well) is simply not worth it.

Yes, there were already known difficulties in retaining new specialist physicians, but now there is also a difficulty in attracting resident physicians for various specialties.

Focusing on the current situation, we suggest the following solutions to address the current problems:

1) Specialty training posts with overall training capacity close to the limit:
   - Specific mandatory internships see their annual

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training capacity being insufficient due to its lack of technical and material resources.
- The different specialties face difficulties in human resources due to the increasing resignation of many senior physicians in search of better opportunities,[1] which further limits existing capacities.
- Partial posts (those that cannot offer full training) must be opened only after the training needs for completion of the residency program are obtained from other institutions. Overloading capacity because of a lack of central planning will not be good for anyone in the long term.
- The NHS's future human resource needs plan is not known. It is only by measuring that it is possible to manage and plan the training pathways of physicians in the best possible way.

2) Insufficient salary for the cost of living:
   - A position in a location with a higher cost of living is unaffordable on a physician's basic salary. It is also not sustainable for a physician who constantly works overtime (in many cases not adequately paid) but suffers much more wear and tear with consequent unavailability for other activities, as well as significant constraints for his/her personal life. Furthermore, the European Working Time Directive limits may not be respected in those cases.
   - Even the best trainers do not have the capacity to offer their residents all the essential training activities to ensure up-to-date medical training. Expensive courses are needed every year. The Portuguese Government has discouraged and limited industry funded medical education, while not fulfilling its role in the training of its professionals, which is, legally, its own inherent role. It is often physicians themselves, especially resident physicians, who invest in their training within their financial possibilities. The Portuguese Government seems to be increasingly discouraging medical specialization even though specialist care appears to be better and less expensive in the long term. On the other side, non-specialization can often be more profitable for non-specialized physicians because working contracts for emergency departments in both the private and public sector offer better remuneration when compared with the salaries of specialists and residents.

3) Protected time and quality standards for medical training:
   - There is no protected time for residents to study, integrate, reflect, and incorporate the knowledge that makes Medicine the complex science it is. We have 48 medical residency programs and only one (Family Medicine) allocates specific time for it in its training program. In addition to protected time, the existence of structured and instructive training is essential to improve the overall quality of training.[5]
   - The multiple cases of suicide, burnout,[6-8] and the use of psychotherapy and/or pharmacological therapies among residents may be justified by their working conditions.
   - There is often no protected time for trainers. The care burden and all the bureaucratic workload that falls on physicians greatly limit their training capacity, leading to less concern for those who end up doing it as an additional task on top of their clinical activity.
   - In short, protected time will allow a major improvement in the training activity and, consequently, in the future health care activity.

Medicine, in general, does not seem like a well-paid, prestigious, or appealing career anymore.

Medicine is serving as a wake-up call to the entire system, foreshadowing a potential large-scale problem concerning the future maintenance of a minimum number of specialist physicians and of medical trainers in the NHS.

Many doctors are leaving the NHS, the country, and, perhaps worse, Medicine.

Very soon, more than discussing the quality of healthcare, we may be discussing whether there is access to healthcare.

AUTHOR CONTRIBUTIONS

CM, JCR, MLL: Draft, conception, critical review and approval of the manuscript.

IGM: Conception, critical review and approval of the manuscript.

COMPETING INTERESTS

CM: Leadership or fiduciary role in Conselho Nacional do Médico Interno and Conselho Nacional do Internato Médico (Consultant Board of the Ordem dos Médicos).

IGM: Leadership or fiduciary role in Conselho Nacional do Médico Interno, Comissão Regional do Internato Médico da Zona Centro, Assembleia Geral da Secção Regional do Centro da Ordem dos Médicos and Gabinete de Formação Médica da Secção Regional do Centro da Ordem dos Médicos.

MLL: Leadership or fiduciary role in Comissão Regional do Internato Médico, Internato Médico de Medicina Geral e Familiar and Conselho Nacional do Internato Médico.

JCR: Leadership or fiduciary role in Conselho Nacional do Internato Médico, Comissão Regional Internato Médico do Centro.

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Portuguese Version of the Stigma Scale: Preliminary Psychometric Characteristics

Versão Portuguesa da Escala de Estigma: Caraterísticas Psicométricas Preliminares

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ABSTRACT

Introduction: Stigma is associated with poor prognosis of illness and reduced help-seeking behavior, self-esteem and treatment compliance. The aims of this study were to study the reliability and construct validity of the King's *et al* Stigma Scale, and its association with Illness and Help-Seeking Behaviors scale (IHSBS) scores.

Material and Methods: One hundred and forty mental health patients filled out the Stigma scale and the Illness and Help-Seeking Behaviors scale. The exploratory factor analysis of the stigma scale was performed, and its reliability studied. The correlation analysis was used and mean differences in Stigma Scale scores among IHSBS groups were explored.

Results: The exploratory factor analysis indicated four factors (F): F1-Disclosure, F2-Discrimination, F3-Acceptance and F4-Personal Growth, which showed acceptable/good internal consistency (α from 0.70 to 0.91). Help-seeking behaviors were not associated with stigma. The levels of Discrimination were high in the group with global high-IHSB and in patients with medium/high illness behavior (IB) and health-related worries (HW). Additionally, Disclosure and overall stigma levels were higher in groups with high-HW and with medium-IB scores (when compared with the group with low-IB). The group with low-IB also had lower levels of Acceptance and Personal Growth when compared with the groups with medium-IB and high-IB, respectively.

Conclusion: The Stigma Scale (27 items) is a valid, reliable instrument and useful tool to assess stigma in mental health patients.
Keywords: Dementia; Mental Health; Psychometrics; Social Stigma; Surveys and Questionnaires

RESUMO

Introdução: O estigma está associado a pior prognóstico de doença e redução da procura de ajuda, autoestima e adesão ao tratamento. Os objetivos deste estudo foram estudar a fidedignidade a validade de construto da Escala de Estigma de King *et al* e a sua associação com as pontuações da Escala de Comportamento de Procura de Ajuda e de Doença (ECPAD).

Material e Métodos: Cento e quarenta doentes psiquiátricos preencheram a Escala de Estigma e a ECPAD. Foi realizada a análise fatorial exploratória da escala de estigma e a sua fidelidade estudada. Foram realizadas análises de correlação e exploradas as diferenças nas médias das pontuações da escala de estigma nos grupos de ECPAD.

Resultados: A análise fatorial exploratória indicou quatro fatores (F): F1-Divulgação, F2-Discriminação, F3-Aceitação e F4-Crescimento Pessoal (α de 0.70 a 0.91). Os comportamentos de procura de ajuda não se associaram ao estigma. Os níveis de Discriminação foram altos no grupo com CPAD total-elevado e nos grupos com comportamentos de doença (CD) e com preocupações com a saúde (PS) médios/elevados. Adicionalmente, os níveis de Divulgação e Estigma total foram superiores no grupo com PS-elevado e no grupo com CD-médio (quando comparado com o grupo CD-baixo). O grupo com CD-baixo também revelou níveis inferiores de Aceitação e Crescimento Pessoal em comparação com os grupos com CD-médio e CD-elevado, respectivamente.

Conclusão: A escala de estigma (27 itens) é um instrumento válido, fidedigno e útil para avaliar o estigma em doentes psiquiátricos.
Palavras-chave: Demência; Estigma Social; Inquéritos e Questionários; Psicometria; Saúde Mental

INTRODUCTION

Stigma can be defined as a person's negative appreciation or discrimination, based on features such as mental illness, ethnicity, drug abuse, or physical disabilities[1] and it can have negative consequences on a social, political, economic, and psychological level.[2]

The concept can be divided into felt stigma, when mentally ill people expect, fear or perceive discrimination/stigma from others or from society (for example, loss of job opportunities and/or renting opportunities and disregard for one's feelings/opinions), and enacted stigma (similar to experienced stigma), when actual episodes of discrimination against a person are experienced or, if not, the person fears they might occur in case his/her disease is exposed.[3] The latter may or may not be associated with internal stigma as one may not feel discriminated but still fear what others might think of his/her mental disease and avoid uncomfortable situations that might trigger discrimination. Felt stigma includes perceived stigma aspects, such as personal thoughts about the views and beliefs people or society have about the stigmatized group. Felt stigma is also frequently used to describe the internalized negative view of being mentally ill, and its associated feelings.[4] In this way,

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the construct of felt stigma is similar to self-stigma, which reflects the reaction of stigmatized people towards themselves, the acceptance and internalization of stigma as a result of the experience of episodes of discrimination and rejection perpetrated by people from the general population (public stigma), and can go along with feelings of loss of self-esteem, fear, guilt, and shame.[4]

Illness behavior (IB), which may be passive or active, refers to the way individuals feel, evaluate or act upon their symptoms.[5,6]

Help-seeking behavior (HSB) refers to the patient's decision to act on his/her symptoms by seeking help (medical or otherwise). This behavior is influenced not only by multiple sociodemographic and cultural factors, but also by the patient's past experiences.[5] Stigma may also have an influence in IB and HSB, leading patients to postpone seeking help and delay their treatment, which negatively influences the prognosis of the disease.[5,7]

The association between stigma, IB and HSB was studied in multiple samples, such as mental health patients,[8] university students[9] and the general population[10]; almost all showed similar results – stigma is associated with less help-seeking.

The negative consequences of stigma are worse among people with mental health disorders,[2] with higher levels of psychological distress (e.g., depression and anxiety symptoms).[8,11] Also, stigma can lead to less treatment compliance,[8] worse prognosis,[12] lower self-esteem[8,7] and worse occupational and social outcomes.[8,13] The stigma barriers to help-seeking include the patients' beliefs that mental illness might have a negative impact on employment opportunities and the way they would be treated or seen by others, including coworkers.[14]

Knowing that stigma has such deleterious consequences for mental health patients, and that, in Portugal, the studies on mental illness stigma are scarce and most of them focused on public stigma rather than personal stigma (i.e., the subjective experience of stigma) it is imperative to have a valid instrument to evaluate this construct in the Portuguese population in order to characterize stigma, study its influence on the quality of life of patients and on the different steps of the mental treatment: help-seeking, treatment, and prognosis. It can also be helpful for the development of specific intervention programs to reduce stigma and for the evaluation of their effectiveness and in clinical practice, thus improving the efficiency of mental health care, namely setting in motion processes that can counteract or reduce the effects of both types of stigma – patients with more severe disease are also the ones that experience more stigma.[11]

To our knowledge, there are only fifteen measures to assess personal stigma.[15] Among the three that evaluate both experiential stigma and self-stigma, only the Internalized Stigma of Mental Illness scale (ISMI)[16] and SS[7] have shown content and construct validity, acceptable internal consistency, and test-retest reliability,[4,15] and only ISMI was translated to European Portuguese and has its psychometric characteristics studied.[4,15] The aim of this study was to assess the King's *SS*[7] reliability and construct validity and its association with the Illness and Help-Seeking Behavior scale (IHSBS)[5] in a sample of Portuguese mental health patients. We predicted that the scores of these two will be inversely correlated.

MATERIAL AND METHODS

This study was approved by the Ethics Committee of the Faculty of Medicine of the University of Coimbra. The patients were invited (by investigators or by their physician) to join the study and participating subjects signed an informed consent form. The Inclusion criteria were the ability to understand the purpose and method of the research project and to be over 18 years old. No exclusion criteria were used. Recruitment was conducted from November/2017 to February/2018 and from September/2018 to January/2019.

Sample

A data set from 140 mental health patients (70% women), followed in an outpatient clinic at the Psychiatry Department of Coimbra and Baixo Vouga's Hospitals (62.9%) and six primary healthcare units in the Center region (37.1%), was collected using a non-probability convenience sampling method. The sample was made up of patients with a mean age of 39.49 years old (SD = 15.71, range: 18 – 78), and that were mostly single (48.9%) or married (36.7%) and were mostly born in Portugal (94.3%). Most of them finished elementary / high school (66.7%: 35.5% elementary school; 31.2% high school) and college (23.9%); 8.6% had a master or PhD degree. Of all patients, 57.9% reported their profession – most of them were specialists, working in intellectual or scientific activities (30.9%) and in personal services (23.5%) and a minority were unqualified workers (14.8%). We also registered that 38.7% of the patients were currently working, 21.2% unemployed and 11.7% were on sick leave/medical certificate. The psychiatric diagnoses (which could be more than one per patient) were reported by each physician whose patients participated in the study and comprised depression (43.6%), anxiety (27.1%), bipolar disorder (11.4%), schizophrenia (10.7%), disorders related with trauma/stress (5%), personality disorders (4.3%), obsessive compulsive disorder (4.3%), addictive behaviors (2.1%), eating disorders (2.1%), dissociative disorders (2.1%) and sleep disorders (1.4%).

Instruments

The SS was created by Michael King *et al*[7] to evaluate the personal stigma in mental health patients and consists of 28 items that are answered according to a Likert scale of five points, from "Strongly disagree" (1) to "Strongly agree" (5). Nine items are reversely scored (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/14623/Appendix_01.pdf), so that a higher SS total score means higher levels of stigma. The scale originally had 42 items and arose from a pilot study, based on the qualitative analysis of the answers from an interview of the patients followed in mental health care facilities.[7]

Using the exploratory factor analysis (EFA) in a sample of 193 psychiatric patients with a wide range of diagnosis and from many psychiatric services located in London (north), a set of 35 items was reduced to 28 items (α = 0.87), divided into three factors: F1-Discrimination (α = 0.87), F2-Disclosure (α = 0.85) and F3-Positive Aspects (α = 0.64) and had good psychometric qualities.[7]

The cultural adaptation of the SS followed the standard procedures (translation into European Portuguese; back-translation; expert panel to check for equivalent meaning of the versions; pilot test of the initial SS version; final *SS* version with the inclusion of information obtained from pilot test participants).

The IHSBS was created by Macedo *et al*[5] and consists of 17 items that are answered according to a Likert scale of five points, from "Strongly disagree" to "Strongly agree". The items 2, 3, 6, 7, 12, and 14 are reversely scored so that a higher IHSBS total/dimensional scores are associated with more proactive illness and help-seeking behaviors. The study of the reliability and construct validity of the scale, performed in a sample of psychiatric patients for the first time during this study, suggested the scale was divided into three factors: F1-HSB (α = 0.69), F2- Health Worries (HW) (α = 0.76) and F3- Illness Behavior (IB) (α = 0.68). Both the scale and its factors showed adequate psychometric qualities.

Statistical analysis

Descriptive and inferential statistical analysis was performed using SPSS, for windows (25th version).

The parametric tests were applied when the distribution of the variables was close to the normal distribution (-1 < skewness and kurtosis < 1),[17] and if not, the non-parametric tests were used.

Pearson's and Spearman's correlations were used for analyzing the associations between the variables.[17] The Student's *t*-test, one-way ANOVA test with Bonferroni´s post hoc tests, Mann-Whitney U test and Kruskal-Wallis test were used, appropriately. The significance level was $p < 0.05$.

Firstly, some practical procedures were applied to assess the adequacy of the data for factor analysis. The sample size, the intercorrelations between the items (r > 0.30), the Kaiser–Meyer–Olkin measure of sampling adequacy (KMO) (value = / > 0.60), and Bartlett's test of sphericity with $p < 0.05$.

Secondly, the factor extraction was performed. To make an initial decision on the number of factors to retain for further investigation, the principal components analysis method (PCA)[17] was performed, as well as the Horn´s parallel analysis,[18] using the Watkins statistical program.[19] The components with eigenvalues over one were considered (Kaiser criterion)[20] and compared with the average eigenvalues for 100 randomly generated samples.[18] Additionally, the percentage of explained variance (EV) was considered, and the scree plot was inspected.[21] Lastly, the factors were rotated (factors' orthogonal varimax rotation) and only the items with a loading over 0.4 in each factor were retained in it.

To explore the discriminative power of the items,[22] the corrected item total/dimensional correlations were computed. The internal consistency estimation of reliability, Cronbach's alpha (α), was computed for SS (and dimensions).[22] The contribution of each SS item to the scale's internal consistency was assessed exploring what would be the α if that item was deleted from the scale/subscale.

The SS association with the IHSBS was assessed, using correlation analysis, and the analysis of SS scores by groups with different levels of illness and help-seeking behaviors. These groups were arranged based on the mean and standard deviation (SD) scores of IHSBS: low, the group with scores 1 SD below the mean; high, the group with scores 1 SD above the mean; medium, the group with scores between 1 SD under and above the mean.

RESULTS

Distribution of the items' answers

All items covered the scale of values, from the minimum value (1) to the maximum value (5), showed skewness and kurtosis values that do not indicate serious deviations from normality and medians very close to the mean value (Table 1). Thus, the items did not present relevant problems of sensitivity and normality.

Exploratory factor analysis procedures to assess the adequacy of the data for factor analysis

The size of the sample matched the criterion of five participants for each item, allowing the factorial analysis of the data, according to some authors.[17] Most of the correlations between the items were more than 0.30 but less than 0.90.[22] The Keiser-Meyer-Olkin measure (KMO) value of 0.861[23] and the statistical significance ($p < 0.05$) of the Bartlett's test of sphericity[24] proved the ability of factorization of the correlation's matrix.[17,22]

Principal analysis, parallel analysis and number of factors

The PCA method for the extraction of the initial factors indicated seven components with eigenvalues-greater-than-one (EV = 68.44%). The Cattell's scree plot[21] analysis showed a slope after ¾ components (Fig. 1).

The Horn's[17] parallel analysis indicated four components with eigenvalues exceeding the corresponding values for a randomly generated matrix's data of the same size, which suggested that the scale should be divided into four factors instead of the seven suggested by PCA.The parallel analysis has been shown to be among the most accurate methods, as PCA and the Cattell's scree test tend to overestimate the number of components,[17] and therefore we considered that the 4-factor solution was more suitable than the 3-factor solution, which was subsequently explored.

Factors' orthogonal varimax rotation

Table 1 shows the items' descriptive statistics, the

Table 1 – Descriptive statistics, rotated four factors matrix for 28-items Stigma Scale and the factor loadings in the four factors

Item	Mean (SD) Median	F1 D‡	F2 Dcr†	F3 A‖	F4 PG§	Original scale factor‡
SS28	2.69 (1.37) 3	**0.851**				F2-D
SS27	2.35 (1.31) 2	**0.779**				F2-D
SS25	3.06 (1.33) 3	**0.774**				F2-D
SS17	2.74 (1.34) 3	**0.697**	(0.315)			F1-Dcr
SS5	2.69 (1.38) 3	**0.681**				F2-D
SS12	2.70 (1.38) 3	**0.653**	(0.432)			F2-D
SS16	2.55 (1.33) 3	**0.637**	(0.409)			F2-D
SS26	2.93 (1.38) 3	**0.627**	(0.396)			F1-Dcr
SS24	2.94 (1.35) 3	**0.544**				F2-D
SS11	2.91 (1.43) 3	**0.537**	(0.485)			F1-Dcr
SS9	1.95 (1.14) 1.5		**0.773**			F1-Dcr
SS8	1.70 (0.94) 1		**0.723**			F1-Dcr
SS22	1.58 (0.94) 1		**0.695**	(0.344)		F1-Dcr
SS21	1.74 (0.98) 1		**0.684**	(0.441)		F1-Dcr
SS18	2.56 (1.28) 3	(0.372)	**0.673**			F1-Dcr
SS1	1.89 (1.16) 1		**0.615**			F1-Dcr
SS2	2.27 (1.34) 2	(0.367)	**0.610**			F1-Dcr
SS13	2.81 (1.43) 3	0.476	**0.527**			F1-Dcr
SS19	2.79 (1.40) 3			**0.660**		F1-Dcr
SS4	2.76 (1.35) 3			**0.615**		F2-D
SS14	3.16 (1.43) 3	(0.326)		**0.595**		F2-D
SS15	3.39 (1.39) 4	(0.398)		**0.515**		F2-D
SS20	1.71 (1.01) 1		(0.382)	**0.492**		F1-Dcr
SS7	2.54 (1.10) 2		(0.358)	**0.487**		F3-PA
SS23	3.01 (1.28) 3				**0.753**	F3-PA
SS3	2.75 (1.19) 3				**0.752**	F3-PA
SS10	2.89 (1.19) 3				**0.751**	F3-PA
SS6	3.48 (1.14) 4	0.169	-0.055	0.086	-0.189	F3-PA

F: factor; SS: Stigma Scale; ‡F1 D: Disclosure; †F2 Dcr: Discrimination; ‖ F3 A: Acceptance; §F4 PG: Personal Growth
‡Original scale[7]: F1 Dcr: Discrimination; F2 D: Disclosure ; F3 PA: Positive Aspects; factor loadings in brackets: acceptable loading values also in this factor
SD: standard deviation

rotated four-factor matrix for 28-items SS.

The four factors (4F) explained 55.88% of the total variance – explained variance (EV: F1 = 32.02%, F2 = 9.02%, F3 = 8.24%, F4 = 6.59%).

The items with a loading over 0.40 in the factor were retained in it. F1 and F2 are Disclosure and Discrimination; F3 evaluates the disease's Acceptance, not only by the patient but also by others, and F4 evaluates each patient's personal growth, boosted by their mental illness, so we defined it by Personal Growth.

The item number six of the factor Positive Aspects of the original scale[7] had an unacceptable factorial weight in all the factors (< 0.40).

The mean (SD) scores were the following: SS 70.61 (SD = 14.19); Disclosure 27.66 (SD = 8.90), Discrimination 16.51 (SD = 6.71), Acceptance 17.09 (SD = 4.21) and Personal Growth 9.35 (SD = 2.95).

Reliability

The item six did not contribute to the internal consistency of *SS* (28 items) (Table 2). Regarding the 27 items of the SS, they are representative of the construct measured by the subscale they're a part of and contribute to their internal consistency; the exceptions were items number 23 (Personal Growth) and number 24 (Disclosure) (Table 2). Despite that, the content of these two items was related with the construct measured by their corresponding subscale, they had acceptable correlations (both > 0.26) with the corrected total score of the SS (27 items) and they contributed to its internal consistency or to its maintenance; therefore, those items were kept in the SS.

The total scale consists of 27 items (the sixth item was excluded from the scale) and both the scale (α = 0.91) and its subscales had acceptable/high internal consistency (α: F1 = 0.91; F2 = 0.87; F3 = 0.70; F4 = 0.72).

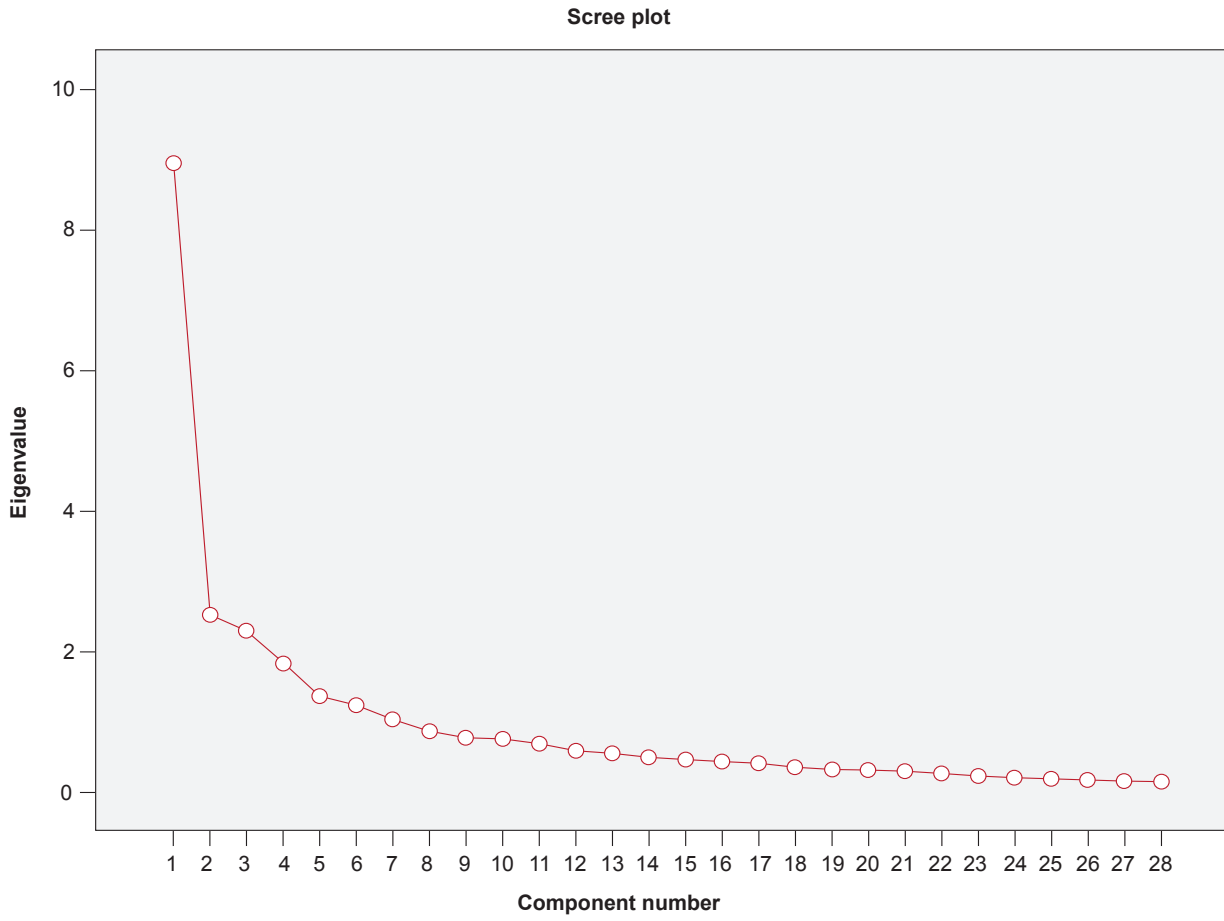

Figure 1 – Scree plot

Correlations between the scores of the SS

The score of the SS was highly and positively correlated with the factors Disclosure and Discrimination (r = 0.88/0.80, $p < 0.01$) and moderately correlated with the Personal Growth factor (r = 0.32 $p < 0.01$). The correlation between Disclosure and Discrimination was also high and positive (r = 0.65, $p < 0.01$). The factor Acceptance was not correlated with the SS score but was inversely correlated with Disclosure and Discrimination (r = -0.25/-0.29, $p < 0.01$).

Stigma asssociation with IHSBS

Correlations between the scores of the SS and the scores of IHSBS

Both total Stigma and Discrimination correlated positively and modestly or moderately with IHSBS (r = 0.22, $p < 0.05$/r = 0.26, $p < 0.01$), IB (r = 0.19, $p < 0.05$/r = 0.32, $p < 0.01$), and especially with HW (r = 0.37/.035, $p < 0.01$).

Also, Disclosure correlated positively with HW (r = 0.38, $p < 0.01$) and with IB (r = 0.19, $p < 0.05$); and Acceptance (low) correlated negatively with IB (r = -0.17, $p < 0.05$), meaning that the more IB the patients have, the more he accepts it.

The Personal Growth (PG) subscale did not correlate with any of the IHSBS subscales.

Differences in SS scores by IHSB groups.

Table 3 describes the levels of the stigma by groups of patients with low, medium and high IHSB scores.

Only the group with high-IHSB (versus low and medium-IHSB groups) showed higher levels of Discrimination.

There are no significant differences in stigma scores among HSB groups.

The group with high-HW had significantly higher levels of Disclosure and total stigma (versus low and medium-HW groups) and of Discrimination (versus low-HW group). Moreover, the group with medium-HW (versus low-HW) also showed higher scores of Discrimination.

The group with high-IB (versus low-IB group) had significantly higher scores of Discrimination and a trend towards higher Disclosure. The scores of Disclosure, Discrimination and total stigma were still significantly higher in the group with medium-IB (versus low-IB group).

The groups with medium and high-IB (versus also Low-IB) showed significantly more adequate Acceptance and PG.

DISCUSSION

The Portuguese version of King's *et al*[7] SS revealed construct validity and good reliability in Portuguese psychiatric patients, and its scores distinguished those with different levels of IHSB.[5]

Table 2 – The corrected item-total correlations and α if the item was deleted for the Stigma Scale - 28 items, and the corrected item-total dimensional correlations and dimensional α if the item was deleted for the Stigma Scale - 27 items (4-factors factorial solution).

	Stigma Scale - 27 items		Stigma Scale - 28 items	
F1 Disclosure items	Corrected item-total dimensional correlations	α if item deleted	Corrected item-total correlations	α if item deleted
SS28	0.813	0.894	0.686	0.894
SS25	0.700	0.901	0.599	0.896
SS27	0.769	0.897	0.711	0.894
SS5	0.678	0.903	0.620	0.896
SS17	0.723	0.900	0.651	0.895
SS12	0.750	0.898	0.708	0.894
SS16	0.737	0.899	0.683	0.895
SS26	0.582	0.908	0.553	0.897
SS11	0.571	0.909	0.514	0.898
SS24	0.469	0.915	0.541	0.897
F2 Discrimination items	Corrected item-total dimensional correlations	α if item deleted	--	--
SS9	0.699	0.843	0.546	0.898
SS21	0.638	0.851	0.595	0.897
SS22	0.663	0.849	0.576	0.898
SS8	0.576	0.857	0.434	0.900
SS18	0.658	0.847	0.639	0.896
SS2	0.651	0.848	0.597	0.896
SS1	0.574	0.856	0.441	0.899
SS13	0.575	0.860	0.616	0.896
F3 Acceptance items	Corrected item-total dimensional correlations	α if item deleted	--	--
SS4	0.491	0.635	0.330	0.902
SS19	0.506	0.629	0.411	0.900
SS14	0.444	0.652	0.381	0.901
SS15	0.442	0.652	0.403	0.900
SS7	0.346	0.681	0.259	0.902
SS20	0.334	0.684	0.421	0.900
F4 Personal Growth items	Corrected Item-total dimensional correlations	α if item deleted	--	--
SS3	0.638	0.504	-0.022	0.907
SS23	0.431	0.761	0.263	0.903
SS10	0.555	0.607	-.040	0.908
SS6	--	--	0.093	0.905

α Stigma Scale (28 items) = 0.902;
Stigma Scale (27 items): α F1 Disclosure = 0 .912; α F2 Discrimination = 0.867; α F3 Acceptance = 0.697; α F4 Personal Growth = 0.717

The SS comprises 27 items which evaluate Disclosure, Discrimination, Acceptance and Personal Growth (α from 0.70 to 0.91). This 4-factor solution is new and does not correspond to that found by King *et al*.[7] Using a sample of psychiatric patients from the north of London, they found that SS evaluated three factors, namely F1-Discrimination, F2-Disclosure and F3-Positive Aspects (PA). Contrasting to our findings, Discrimination was the factor that explained the largest amount of the variability, followed by Disclosure. The 3-factor solution of the SS was also found by other authors, using samples of patients with mental disorders from several different countries, such as Switzerland,[25] Iran,[26] Chine,[27] and Japan.[28]

The items with acceptable loading in Disclosure (F1) corresponded almost completely to those of this factor in the original version,[7] except for three items that are part of Discrimination and that involve feelings of isolation/loneliness (item 11), feelings about the injustice of life (item 26) due to the fact of having a mental illness, and non-disclosure of mental health problems due to the fear of people's reactions (item 17).

Regarding Discrimination (F2), all of its items had an

Table 3 – The SS scores (Mean, SD) by groups with low, medium and high levels of Illness and Help-Seeking Behaviors (IHSBS)¥

	IHSBS_T Groups			Test	*p*	Multiple comparisons
	Low‖ (n = 15) 1	Medium§ (n = 99) 2	High†† (n = 26) 3			
SS scores	**M (SD)**	**M (SD)**	**M (SD)**			
SS_F2	14.60 (3.92)	15.86 (6.79)	20.07 (6.62)	F (2,137) = 5.03	0.008**	3 > 1*, 2*†
	HW groups			**Test**	***p***	**Multiple comparisons**
	Low‖ (n = 11) 1	Medium (n = 105) 2	High†† (n = 24) 3			
SS scores	**M (SD)**	**M (SD)**	**M/SD**			
SS_ F1	22.55 (10.48)	26.81 (8.48)	33.71 (7.20)	H = 14.77	0.001**	3 > 1*, 2**‡
SS_F2	11.45 (4.30)	16.47 (6.66)	19.96 (6.69)	H = 10.76	0.005*	2 > 1*‡; 3 > 1**‡
SS_T	63.18 (12.34)	69.50 (14.50)	78.83 (9.89)	H = 13.18	0.001**	3 > 1*, 2**‡
	IB groups			**Test**	***p***	**Multiple comparisons**
	Low‖ (n = 45) 1	Medium (n = 79) 2	High†† (n = 16) 3			
SS scores	**M (SD)**	**M (SD)**	**M (SD)**			
SS_F1	24.31 (9.43)	29.20 (7.84)	29.44 (10.22)	H = 9.54	0.009*	2 > 1**‡
SS_F2	13.53 (5.94)	17.61 (6.08)	19.44 (8.88)	H = 15.48	< 0.001***	2 > 1**‡, 3 > 1*‡
SS_F3	18.38 (4.27)	16.46 (3.92)	16.63 (4.86)	F (2,137) = 3.20	0.044*	1 > 2*†
SS_ F4	9.73 (3.18)	9.47 (2.61)	7.69 (3.24)	F (2,137) = 3.14	0.047*	1 > 3*†
SS_T	65.96 (12.85)	72.73 (13.49)	73.19 (18.42)	H = 7.61	0.022*	2 > 1*‡

*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$; M: mean; SD: standard deviation; ¥: Only the statistically significant differences between groups were described; †: Bonferroni´s test; ‡: Mann-Whitney U test; F: one-way ANOVA test; H: Kruskal-Wallis test

F: factor; IHSBS: Illness and Help-Seeking Behavior scale; IHSBS_T: IHSBS total score; HW: Health Worries; IB: Illness Behaviors; ‖Low: group of subjects with IHSBS total or dimensional scores 1 SD under the mean; ††: High - group of subjects with IHSBS total or dimensional scores 1 SD above the mean; §: Medium - group of subjects with IHSBS total or dimensional scores between 1 SD under and above the mean.

SS: Stigma scale; SS_T: SS total score; SS_F1: Disclosure; SS_F2: Discrimination; SS_F3: Acceptance; SS_F4: Personal Growth

acceptable loading on this same factor of the original version.[7]

The items of the factor PA were distributed in the factors Acceptance and, in particular, in PG. All the items of PG are part of PA dimension of the original version. The Acceptance includes items that have acceptable loadings in PA (item 7), Discrimination (items 19, 20) and Disclosure (items 4, 14,15) dimensions of the original version, which are associated with the acceptance of the mental illness and to the perception that others also accept it, and with the intention of revealing the mental health problems.

The SS total score correlated with high levels of Disclosure and Discrimination, and with the low PG, therefore these dimensions evaluate the total stigma construct. The Discrimination and Disclosure were strongly associated, suggesting that patients who feel discrimination may also conceal their mental health problems to avoid negative stereotyping, labeling, stigmatization, which may not only hamper their social and vocational integration, but also interfere with help-seeking and effective treatment.

The Discrimination and Disclosure dimensions correlated with high levels of Acceptance. Thus, the results showed that, even though stigma is correlated with low PG, it was also shown that the Discrimination and Disclosure dimensions may create more Acceptance of the disease. This means that, for some patients, there might be a bright side in having a mental illness, as it can promote positive changes.[29] It may be possible that patients who better accept their mental illness or perceive acceptance of it by others may become more open to making positive changes[7] and more prone to disclosure,[27] which may promote better adjustment.[29]

Regarding the association between SS and IHSBS[5] scores, the results showed that neither the total stigma nor its subscales were significantly associated with the HSB. They also didn't differentiate the groups with low, medium and high HSB which means that the help-seeking is independent from the stigma in this population.

The levels of Disclosure, Discrimination and total Stigma were positively associated with HW and were significantly higher in the groups with more HW, which suggests that the patients with these cognitive characteristics can find it difficult to disclose their condition and are afraid of discrimination due to their illness and high levels of global stigma.

On one hand, the mean values of Disclosure, Discrimination and total Stigma increased gradually between the groups with low, average and high IB. On the other hand, the Acceptance and PG gradually became more adequate. These results suggest that patients with higher IB, meaning more proactive, show higher levels of total Stigma and Discrimination and tend to feel more afraid of the Disclosure, but also have more positive feelings towards their illness, more Acceptance and more PG compared to patients with less proactive IB.

High levels of Discrimination were positively associated with higher levels of total IHSB. Therefore, the results suggest that the greater the Discrimination, the greater the patient's proactivity regarding IHBS.

We thus concluded that, in this sample, contrary to what we had predicted, stigma did not correlate with HSB. Even though it is not the expected result, other studies have similar findings. For example, a study showed that stigma did not prevent patients from seeking their GP's for their health problems,[30] and two meta-analysis concluded that stigma was not always significantly associated with active HSB and that they can even be inversely associated.[10,31] It is possible that differences in the methodology of the studies accounted for these dissonant results.[31] Additionally, the possibility that these results may be justified by regular follow-up and have a higher mean age. In fact, some studies show that the negative effect of stigma is stronger in adolescents,[10] in younger patients[32] and in the beginning of the treatment.[8] The period from adolescence to early adulthood shows a higher incidence of most mental disorders[33] and therefore the first contact with a healthcare professional help may occur at this time. The beginning of the treatment is the period when the patients have to accept their illness and the need for receiving psychiatric treatment (first appointment, being diagnosed with a psychiatric illness and beginning treatment).[34,35] It has also been shown that seeking help one time changes the way each patient perceives help-seeking behavior.[31]

The high representativeness of women in the sample may also contribute to the lack of association between stigma and HSB, as women reveal less stigma-related barriers to help-seeking[10] and higher mental health literacy,[36] both of which may promote adjusted help-seeking behaviors. There is also high representativeness of graduates and post-graduates in the sample and education is associated with reduced stigma and high levels of mental health literacy,[10] namely a high level of knowledge about mental health, awareness, and health-seeking attitudes.[36] Besides stigma, there are many predictive factors of help-seeking behavior such as the normalization of mental health problems, knowing they are not the only ones with these kind of problems, having friends that also have psychiatric problems, the knowledge that the appointments are confidential, the lower caregiver stigma, the respect and non-judgment of healthcare professionals, higher physical dysfunction and the belief that the doctor will help.[10,30] Regarding the factors that negatively influence the HSB besides stigma, there are, for example, the desire to solve the problem by themselves, the patients' belief that they do not need help, a feeling of embarrassment to talk about their problems, the patients' concerns about hospitalization and the treatments available, poor knowledge about the available services and how to contact them, difficulties in taking time off work and having financial problems.[14,31,33] Therefore, patients that have a higher level of mental health literacy and a more positive attitude regarding seeking professional help are the ones that do it the most.[30,36]

Therefore, patients that are already followed in regular appointments because of their psychiatric problems, such as those who participated in the present study, probably know that they cannot solve the problems by themselves and that they need the help of healthcare professionals. As the appointments are in public institutions and Portugal has a high governmental financial participation in healthcare costs, it seems less likely that low HSB is associated with financial problems. Despite this, a study performed with most patients of the sample of the present study[14] revealed that the financial concerns figure among the top instrumental barriers for help-seeking.

Even though stigma in the present sample of psychiatric patients was not associated with HSB regarding the illness itself, it was associated with HW and IB, which can have an impact on the patients' quality of life and treatment outcomes.

The development of campaigns to eradicate or, at least, to decrease social negative judgments and rejection of people with psychiatric problems (including professionally)[37] is of the utmost importance. These campaigns should also target the shame that the patients feel for having psychiatric problems and contribute to the abolishment of stereotypes, such as that patients with mental health problems are dangerous, weak or unable to contribute to the society in which they live in.[10] Interventions to reduce stigma must also focus on the promotion of personal growth and acceptance of the mental illness.

A point in favor of the SS and its factorial solution is that it allows us to evaluate not only the two major components of the personal stigma – Discrimination and Disclosure, but also positive aspects such as Acceptance and PG related with the stigma.

The sample of the present study was a non-probability convenience sample of out-patients from two hospitals and family health units of the center area of Portugal and might not be representative of all people with mental disorders, which limits the generalizability of the results to all mental health patients. The validation of the scale in other populations of psychiatric patients, from several areas of Portugal, can be an important contribution to the knowledge of the psychometric characteristics of the scale.

Although the sample size of 140 participants is acceptable for the EFA,[17] that size did not allow us to perform, in addition to it, the confirmatory factorial analysis, which we intend to carry out in future studies. Future studies with two assessments may allow the study of the temporal stability of

the SS scores.

There is preliminary evidence of criterion-related validity and convergent validity of SS. The SS factor structure explains stigma differences among the diagnoses of participants in the present sample, and differences were found in Acceptance and PG.[38] Another study with most participants of the present sample showed that total SS score was positively associated with stigma-related barriers.[14]

CONCLUSION

The Stigma scale showed good psychometric qualities in this sample of psychiatric patients including reliability, and construct validity, meaning it is a useful instrument to measure stigma from the perspective of the person with mental illness. In particular, the SS items evaluate Disclosure and Discrimination, and the lower levels of Acceptance and PG associated with the disease. Its scores distinguished the patients with different IHSB. The scale can be particularly helpful not only for evaluating stigma per se, but also the Acceptance and PG that emerges from the disease and can be a valuable instrument to assess the impact of stigma on IHSB. The SS can be a useful tool for research and clinical purposes in Portuguese patients with mental disorders.

OBSERVATIONS

Part of this work was presented in the European Congress of Psychiatry, Madrid, Spain, on 4-7 July 2020, as a poster presentation.

AUTHORS CONTRIBUTION

CS: Participated in data collection; design of the study; statistical analysis; contributed to the writing of the manuscript: draft of the paper; final approval of the manuscript.

MJS: Participated in data collection; design of the study; orientation of the work; statistical analysis; critically reviewed of the different versions of the paper and contributed to its correction; final approval of the manuscript.

NM, IR, AA: Coordinated of the sites where the assessment was conducted; participated in the data collection of most of the participants; critically reviewed the paper; final approval of the manuscript.

AFM: Participated in data collection of most of the participants; constructed the database; critically reviewed the paper; final approval of the manuscript.

ATP: Participated in the research project elaboration and submission to the Ethics Committee of the Faculty of Medicine of the University of Coimbra; critically reviewed the paper; final approval of the manuscript.

CC: Critically reviewed the paper; final approval of the manuscript.

AM: Directs the team and coordinates the research project in which the present study is framed. Participated in the research design and in the orientation of the work; critically reviewed the paper and contributed to its correction; final approval of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

IR: Personal fees for training/oral communications from Boehringer Ingelheim; Novartis Farma - Produtos Farmacêuticos S.A.; Merck Sharp & Dohme, Lda; Astra Zeneca. Support for the attendance of courses or congresses: Ferrer Portugal, S.A.; Merck Sharp & Dohme, Lda; Pfizer Biofarmacêutica Sociedade Unipessoal Lda; Novo Nordisk Portugal, Lda. Advisory board: Novo Nordisk Portugal, Lda.

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Translation and Cultural Adaptation to European Portuguese of the "Measure of Moral Distress – Healthcare Professionals" Scale: A Cross-Sectional Multicenter Study

Tradução e Adaptação Cultural para Português Europeu do Instrumento "Medida do Sofrimento Moral – Profissionais de Saúde": Um Estudo Transversal Multicêntrico

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ABSTRACT

Introduction: Moral distress occurs when one knows the morally correct action to take but is constrained from taking that action. The aims of this study were to translate into European Portuguese and culturally adapt the "Measure of Moral Distress – Healthcare Professionals" questionnaire to the context of the Portuguese healthcare system and to explore the frequency and intensity of moral distress occurring among medical students.

Material and Methods: The "Measure of Moral Distress – Healthcare Professionals" questionnaire was translated and culturally adapted to European Portuguese, following the internationally accepted "COnsensus-based Standards for the selection of health Measurement INstruments". Afterwards, a web-based survey was conducted, following the "Checklist for Reporting Results of Internet E-Surveys" guidelines. Medical students were asked to rate potentially morally distressing situations on frequency and intensity.

Results: Of approximately 4300 medical students, 939 (22%) completed the survey. Participants experienced, on average, 16 morally distressing situations. Median of composite score of moral stress was 79 (IQR 44 - 118). Only 31% of the students felt well prepared to handle a morally distressing situation, 26% considered leaving medical school and 28% thought about choosing a non-clinical specialty due to moral distress.

Conclusion: Despite a plethora of studies on this topic, the results suggested that moral distress is still a common phenomenon among medical students with a cumulative effect over time. These results emphasize the importance of a critical review of medical education, reducing the harmful effects of preventable psychological phenomena in clinical practice and in the lives of future healthcare professionals.

Keywords: Health Personnel/psychology; Morals; Occupational Stress; Portugal; Psychometrics/instrumentation; Stress, Psychological; Students, Medical; Surveys and Questionnaires; Translating

RESUMO

Introdução: O sofrimento moral ocorre quando um profissional de saúde sabe qual a ação moralmente correta a adotar, mas identifica um obstáculo que o constrange de realizar. Os objetivos deste estudo foram traduzir para Português Europeu e adaptar culturalmente para o contexto do sistema de saúde Português o questionário "Measure of Moral Distress – Healthcare Professionals" e explorar a frequência e intensidade deste fenómeno entre estudantes de medicina.

Material e Métodos: Primeiro, traduzimos e adaptámos culturalmente para português Europeu o questionário "Measure of Moral Distress – Healthcare Professionals", seguindo o protocolo "COnsensus-based Standards for the selection of health Measurement INstruments". Depois, elaborámos um questionário seguindo as normas de orientação "Checklist for Reporting Results of Internet E-Surveys". Os estudantes de Medicina identificaram situações potencialmente causadoras de sofrimento moral em frequência e intensidade.

Resultados: De aproximadamente 4300 participantes, 939 (22%) completaram o questionário. Os estudantes experienciaram, em média, 16 situações causadoras de sofrimento moral. A mediana da cotação composta de sofrimento moral foi 79 (IQR 44 - 118). Apenas 31% dos estudantes se sentem bem ou muito bem preparados para lidar com estas situações, 26% já consideraram deixar o curso de Medicina e 28% já pensaram escolher uma especialidade não clínica por este motivo.

Conclusão: Apesar de vários estudos na área, os resultados sugerem que o sofrimento moral é um fenómeno comum entre alunos de medicina e a sua experiência mostra um efeito cumulativo ao longo do tempo. Estes resultados enfatizam a importância de rever criteriosamente o currículo de educação médica, de forma a reduzir os danos de um fenómeno evitável na prática clínica e nas vidas dos futuros profissionais de saúde.

Palavras-chave: Estudantes de Medicina; Inquéritos e Questionários; Moral; Pessoal de Saúde/psicologia; Portugal; Psicometria/instrumentação; Stress Ocupacional; Stress Psicológico; Tradução

INTRODUCTION

Moral distress was first described as a situation that occurs when a healthcare professional knows the morally correct action to take but is constrained in some way from taking that action.[1] Currently, a broader approach of moral

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distress has been adopted and can be considered as a psychological response to morally challenging situations, including moral conflict, dilemma, or uncertainty.[2]

Moral distress is frequent among healthcare professionals and seems to be increasing.[3] It may cause physical and emotional symptoms[4] and contribute to many undesirable effects, including burnout, decrease of wellbeing, lack of empathy and, ultimately, decrease of quality of care.[5] Among healthcare professionals, those with more clinical experience face the "crescendo effect" phenomenon,[6] meaning they have higher levels of moral distress due to the negative effects which have built up over time.

Medicine has undergone many changes over time and the doctor-patient relationship has gained relevance as one of the main subjects of medical discussions.[7] This relationship requires a moral conduct from the physician to deal with moral issues and to do the right choices considering all circumstances.[8,9] Many aspects of our lives influence the way we define ethical clinical practice, namely religion, philosophy and culture.[7] A code of ethics helps healthcare professionals to deal with situations when they find barriers preventing them from fulfilling their duties, supporting them in their practice and reducing their moral distress.[10]

Medical students are vulnerable to moral distress due to their low position in the hospital hierarchy and their underdeveloped professional identity,[11-13] but this is not widely recognized by medical educators,[14] which may overwhelm medical schools' efforts to advance student's levels of empathy and contribute to the persistent lack of efficacy of ethics and humanities curricula.[15]

The Moral Distress Scale-Revised (MDS-R)[16] was used by most recent studies evaluating moral distress in healthcare professionals.[17-20] In a recent revision of the "Measure of Moral Distress – Healthcare Professionals (MMD-HP)" questionnaire, the authors recommended replacing the MSD-R as a measure for moral distress among healthcare professionals in order to include more sources of moral distress and simplify its use.[21]

The aims of this study were to translate into European Portuguese and culturally adapt the MMD-HP questionnaire[21] to the context of the Portuguese healthcare system, and to explore the frequency and intensity of moral distress occurring among medical students in seven Portuguese medical schools.

MATERIAL AND METHODS

Study design

A cross-sectional, multicenter study was conducted in medical students attending clinical years (fourth to sixth) using a web-based survey, as per the Checklist for Reporting Results of Internet E-Surveys (CHERRIES checklist).[24] The study was approved by the ethics committees of seven medical schools: Faculdade de Medicina da Universidade do Porto (FMUP), Faculdade de Medicina da Universidade de Lisboa (FMUL), Faculdade de Medicina da Universidade de Coimbra, Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Nova Medical School | Faculdade de Ciências Médicas (NMS|FCM), Faculdade de Ciências da Saúde da Universidade da Beira Interior (UBI), Escola de Medicina da Universidade do Minho (UM).

Measures

The author of the MDS-R[16] was contacted and recommended the use of the MMD-HP version of the questionnaire.[21] Following the COSMIN checklist[25] and guidelines and principles of good practice for this process,[26,27] the original questionnaire was linguistically translated and culturally adapted to the context of the Portuguese healthcare system.

The initial translation of the MMD-HP from English into Portuguese was made by a physician and a researcher who was aware of the concepts used in this context and by an English teacher, with no experience in the subject. Afterwards, we created a final common version.

A retroversion to English of the translated Portuguese version was made in order to ensure content equivalence between the versions. It was performed by two physicians and a nurse, who were blind to the original version and fluent in English. We compared the versions and created a prefinal version.

The final Portuguese version was discussed in a focus group comprised of seven medical students and the first author, in order to ascertain the validity of the interpretation and achieve consensus on the best way to formulate each item and ensure there were no divergent interpretations. The interview guide used by the focus group is available as Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16531/Appendix_01.pdf).

Cronbach's alpha, α, revealed a good internal consistency (α = 0.89). The α value of the original instrument was 0.98.[21] Any issues were identified after evaluating item-to-item correlations and changes to alpha calculations if certain items were deleted.

The Portuguese version of the questionnaire presented 27 potential distress situations. Students were asked to rate each situation in terms of the frequency and intensity on a 5-point numerical rating scale. If a student had never experienced a situation described in one or more items, we still asked them to rate the items by selecting zero regarding frequency and indicate how distressed they think they would feel if they had experienced it. There were free text boxes to allow addition of new situations. The Portuguese version of MMD-HP is available as Appendix 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16531/Appendix_02.pdf).

Furthermore, we asked participants if they ever considered leaving medical school or if they ever considered choosing a non-clinical specialty due to moral distress and how well prepared they felt to handle a morally distressing situation. We also asked if such issues had been addressed during their medical education. One last free text item allowed participants to write any comments about the theme if they wished. The instrument included a definition of moral

distress at the beginning.

The final questionnaire was made available online and the link sent by email to the participants, who were informed about the volunteer nature of the study; there were no incentives offered. Free, informed consent was obtained by each potential participant in the form of clicking a square next to the statement declaring the aim of the study, which also included their right to withdrawal at any point with no consequences. The questionnaire had 38 items sequentially presented and could only be submitted if all items were answered, except for the free text items. Data were collected between the 6th March 2020 and the 3rd April 2020. The complete survey is available as Appendix 3 (Appendix 3: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16531/Appendix_03.pdf).

Analysis

Descriptive analysis was used to look at distribution of sociodemographic and categorical response data.

Analysis was performed using the two-tailed significance level set at $\alpha = 0.05$. The frequency and intensity for each situation were first analyzed individually and then a composite item of moral distress (the product between the frequency and intensity of each factor), that ranged from 0 to 16, was created in order to compare it with other variables. The resulting composite score based on 27 items has a range of 0 - 432.

If data related with the composite score showed a skewed right distribution, the logarithm of the variable would be used to normalize it and to perform the statistical tests. T tests were performed to compare the composite score in different groups of participants. One-way ANOVA tests were performed when more than one group were being compared at the same time. The IBM SPSS software, version 26 (IBM corp., Armonk, N.Y.) was used.

Table 1 – Demographics of the population

Number of participants, n	939
Age, median (IQR)	23 (22 – 24)
Gender, n (%)	
Female	739 (79)
Male	200 (21)
Year of study, n (%)	
4th	186 (20)
5th	308 (33)
6th	445 (47)

RESULTS

Demographics of the population

Of approximately 4300 medical students (students from the fourth to the sixth year attending the academic year 2019/2020 in seven Portuguese medical schools), 939 (22%) completed the survey. As shown in Table 1, 739 (79%) of 939 participants were female, which is close to the gender division of the medical students in Portugal (about 70% female) and the median age was 23 [interquartile

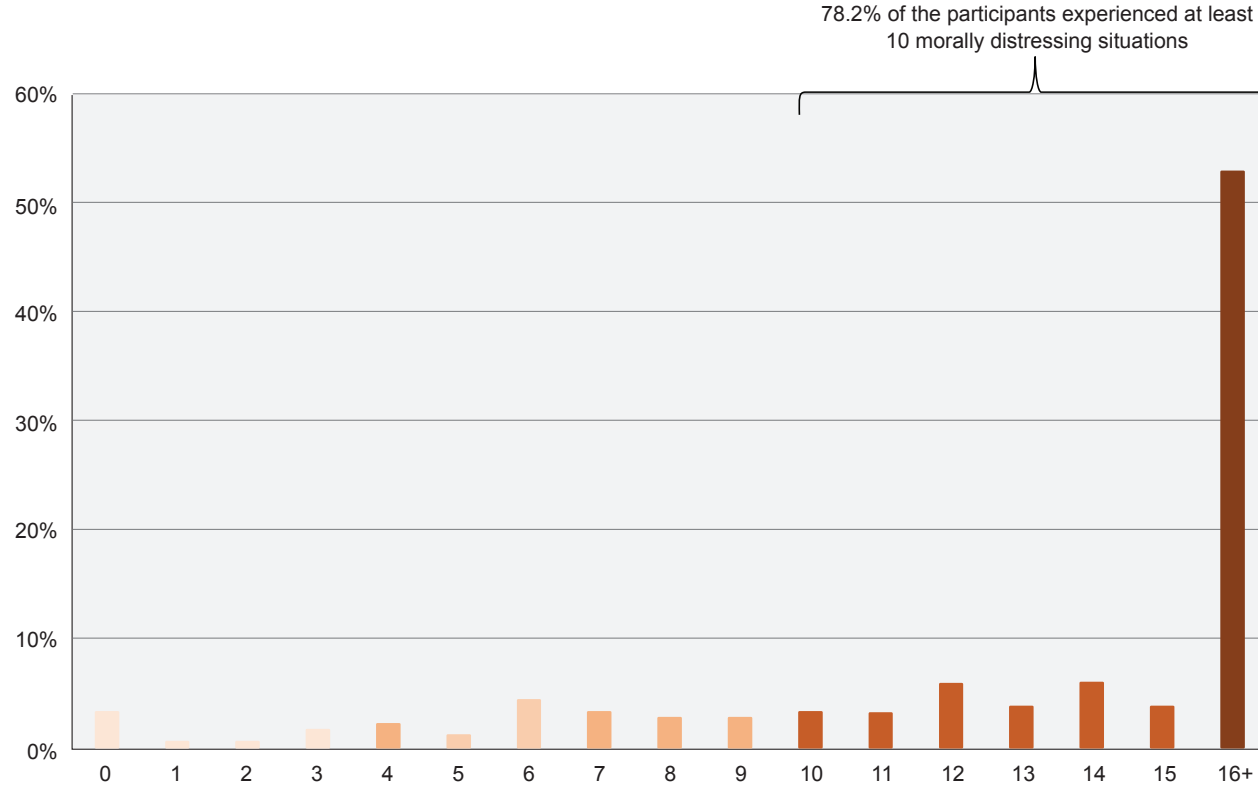

Figure 1 – Frequency of the number of morally distressing situations experienced by participants

range (IQR) 22 - 24]. Of all participants, 186 (20%) were from the fourth year, 308 (33%) from the fifth and 445 (47%) from the sixth year.

Morally distressing situations: frequency and intensity

Students experienced, on average, 16 morally distressing situations (minimum 0; maximum 27). Most students (n = 496, 53%) experienced at least 16 situations. Only 30 (3%) of them never experienced any situation (Fig. 1).

Table 2 presents the occurrence rates and intensity scores for each situation, including experienced and anticipated situations.

Less than 1% of all respondents (n = 5) reported other situations of moral distress concerning situations such as participation in abortion appointments and witnessing a patient suffering during diagnostic procedures.

The average composite score of moral distress was 79 (IQR 44-118).

Handling a morally distressing situation

Only 295 (31%) of 939 respondents felt well or very well prepared to handle a morally distressing situation, 540 (58%) felt poorly prepared and 99 (11%) of the students did not feel prepared at all (Fig. 2). The majority, 583 (62%), reported that such issues had never been addressed during their medical education.

Potential consequences of experiencing moral distressing situations

Of all participants, 247 (26%) considered leaving medical school and, among these, 33 (13%) were considering leaving it at present due to moral distress. At some point, 258 (28%) of 939 students thought about choosing a non-clinical specialty due to moral distress.

The composite score of moral distress among students who considered leaving medical school (median 97; IQR 58 - 142) was higher than in students that never thought about that (median 77; IQR 38 - 108) ($p < 0.001$). Among students who were considering leaving, the composite score of moral

Table 2 – Occurrence rates and intensity scores for potentially morally distressing situations

	Potentially morally distressing situations	Frequency % (n)	Experienced Intensity median (IQR)	Anticipated Intensity median (IQR)
3	*Sentir-se pressionado a pedir ou cumprir um pedido de exames e tratamentos que considera serem desnecessários ou inadequados.* Feel pressured to order or carry out orders for what I consider to be unnecessary or inappropriate tests and treatments.	**75 (705)**	2 (1 – 3)	2 (0 – 3)
4	*Estar impossibilitado de prestar os melhores cuidados possíveis devido a pressões da administração ou seguradoras para reduzir custos.* Be unable to provide optimal care due to pressures from administrators or insurers to reduce costs.	69 (644)	**3 (3 – 4)**	**3 (1 – 4)**
5	*Continuar a prestar um tratamento agressivo a uma pessoa que muito provavelmente morrerá, independentemente deste tratamento, quando ninguém toma a decisão de o suspender.* Continue to provide aggressive treatment for a person who is most likely to die regardless of this treatment when no one will make a decision to withdraw it.	55 (517)	3 (2 – 4)	**3 (0 – 4)**
8	*Participar em cuidados que causam sofrimento desnecessário ou não aliviam adequadamente a dor ou outros sintomas.* Participate in care that causes unnecessary suffering or does not adequately relieve pain or symptoms.	50 (473)	3 (2 – 4)	**4 (0 – 4)**
9	*Observar os cuidados ao doente serem afetados devido à falta da sua continuidade.* Watch patient care suffer because of a lack of provider continuity.	**74 (695)**	3 (2 – 4)	2 (0 – 3)
17	*Vivenciar comprometimento dos cuidados ao doente devido a falta de recursos/equipamento/capacidade de camas.* Experience compromised patient care due to lack of resources/equipment/bed capacity.	**84 (785)**	**3 (3 – 4)**	3 (0 – 4)
19	*Sentir os cuidados ao doente comprometidos por excesso de burocracia.* Have excessive documentation requirements that compromise patient care.	**84 (784)**	3 (2 – 4)	3 (0 – 3)
20	*Temer represálias se falar com franqueza.* Fear retribution if I speak up.	**73 (684)**	3 (2 – 4)	2 (0 – 3)
27	*Trabalhar com membros da equipa que não tratam doentes vulneráveis ou estigmatizados com dignidade e respeito.* Work with team members who do not treat vulnerable or stigmatized patients with dignity and respect.	58 (544)	**4 (3 – 4)**	**3 (0 – 4)**

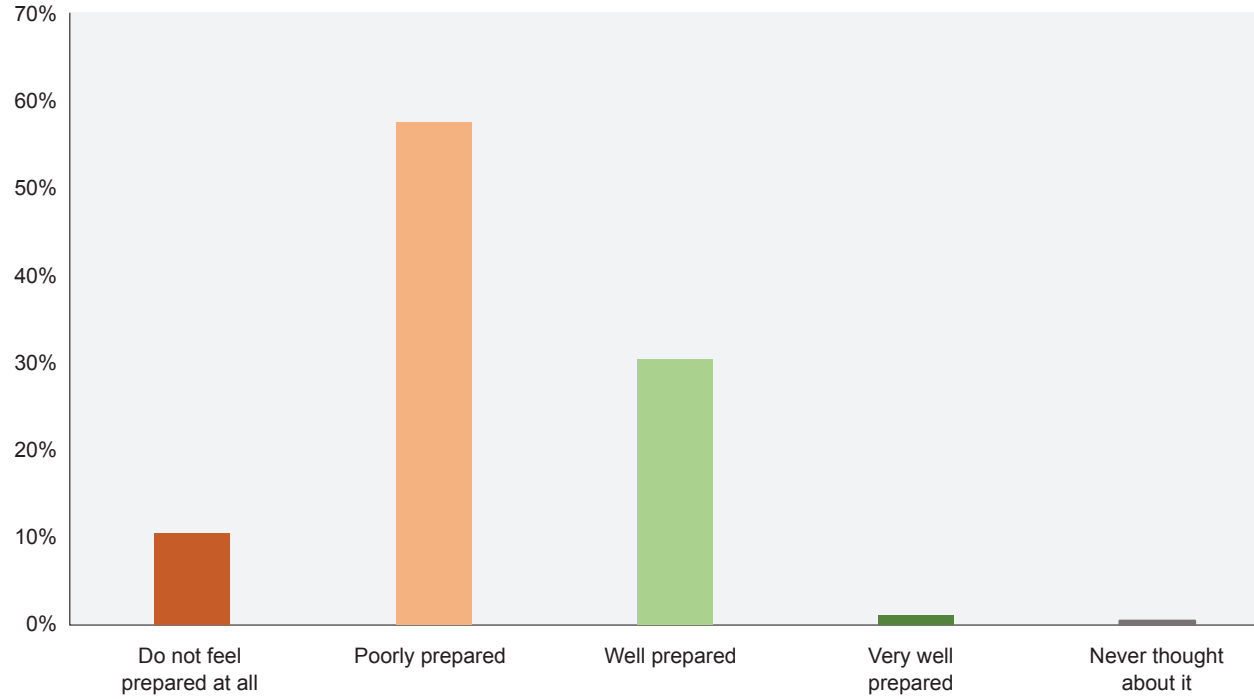

Figure 2 – How well-prepared participants felt handling a morally distressing situation

distress was also statistically significantly higher (median 118; IQR 92 – 169.5) than in students who were not considering it at the present time (median 78; IQR 41.75 - 115) ($p < 0.001$).

There were similar findings with students who thought about choosing a non-clinical specialty due to moral distress, presenting a higher score of moral distress (median 98; IQR 58 - 145) than students who never considered that (median 77; IQR 38 - 108) ($p < 0.001$).

Group differences

There was no statistically significant difference ($p = 0.52$) in composite score of moral distress among genders [female - median 80 (IQR 42 - 120); male - median 77 (IQR 47.5 - 104)].

Sixth year medical students (median 96; IQR 58 - 136) showed a statistically significantly higher score of moral distress than students from the fourth ($p < 0.001$) and the fifth ($p < 0.001$) years. There was no statistically significant difference among fourth (median 77; IQR 26 - 112) and fifth (median 67; IQR 36.25 - 102) year students ($p = 0.86$).

Some statistically significant differences in composite score of moral distress were observed between the different medical schools (Table 3). The three medical schools in northern Portugal reported lower levels of experienced moral distress when compared with the remaining ones. UBI medical school did not show levels that were statistically significantly different compared to other schools.

Participants who addressed this topic, (n = 357, 38%) during their medical education did not show scores of moral distress that had statistically significant differences ($p = 0.20$) compared to participants who had never addressed it.

DISCUSSION

One of the most relevant findings of this study was that most medical students had already experienced a significant number of morally distressing situations.

The most frequent situations reported by participants include root causes at all levels (patient, team and system are the three main identified sources of moral distress[21]).

Patient-level causes were not reported as causing high levels of moral distress. This may be explained by the fact that all participants were students. They may have witnessed patient-level situations, considering it frequent, but those did not occur directly with them since they are not yet responsible for medical decisions at this level.

New root causes were not identified in this study as write-in items added by participants reported situations that can be included in items already considered in the questionnaire.

Patient, team and system-level root causes

Situations regarding futile care and inadequate pain control were already identified by other studies as one of the main causes of moral distress,[28-30] reinforcing the view that moral distress often describes an ethical issue and its psychological consequences.[6,14] Students seem to be more vulnerable in situations where they recognize a direct negative impact on patient care even when these situations occur with low frequency. The expectations of students that medicine can always cure may contribute to this source of distress. Physicians should share their ethical issues with their students and reveal their concerns, even if a solution for more complex problems is not found.[31]

Table 3 – Composite score of moral distress by medical school

Medical school	Composite score of moral distress Median [IQR]		*p* value
ICBAS	78 (25 – 122.25)		
		FMUC	**0.02**[a]
		U. Minho	0.86
		FMUL	**0.01**[a]
		NMS | FCM	**0.01**[a]
		UBI	0.47
		FMUP	0.98
FMUC	97 (58 – 113)		
		ICBAS	**0.02**[a]
		U. Minho	0.06
		FMUL	0.89
		NMS | FCM	0.96
		UBI	0.33
		FMUP	0.07
U. Minho	67 (58 – 136)		
		ICBAS	0.86
		FMUC	0.06
		FMUL	**0.02**[a]
		NMS | FCM	**0.02**[a]
		UBI	0.58
		FMUP	0.91
FMUP	67 (38 – 132)		
		ICBAS	0.98
		FMUC	0.07
		U. Minho	0.91
		FMUL	**0.03**[a]
		NMS|FCM	**0.03**[a]
		UBI	0.54
FMUL	89 (67 – 132)		
		NMS | FCM	0.92
		UBI	0.25
NMS|FCM	92 (61.25 – 115)		
		UBI	0.28
UBI	79 (64 – 90)		

[a]: Statistically significant difference.
FMUP: Faculdade de Medicina da Universidade do Porto; FMUL: Faculdade de Medicina da Universidade de Lisboa; FMUC: Faculdade de Medicina da Universidade de Coimbra; ICBAS: Instituto de Ciências Biomédicas Abel Salazar; NMS|FCM: Nova Medical School | Faculdade de Ciências Médicas; UBI: Universidade da Beira Interior; U. Minho: Universidade do Minho.

The lack of cooperation and good communication between team members seems to be a source of moral distress for students. Due to their low position in the hierarchy, they may remain silent because they fear that voicing concerns could negatively impact their evaluations or make instructors feel their authority is being questioned.[32] Promoting equal participation of the different elements in the discussion of clinically challenging situations, helping to create an environment that encourages the willingness of students to speak up,[11,13] can help not only students but all healthcare professionals to address morally distressing situations.

Our institutions, with well-defined hierarchical and bureaucratic organizational models, seem to contribute to this phenomenon. Students may feel restrictions to their freedom in providing the best care to patients.[3,33,34] Therefore, creating mechanisms that allow adequate flexibility and reduction of time spent with bureaucratic processes may be an effective approach to reduce levels of moral distress.[32,35] At the same time, the inability to provide the best care due to lack of resources could be prevented by improving

working conditions,[36] namely ensuring there are no shortages of material and all the means for treating patients are guaranteed.

Handling a morally distressing situation

Our data showed that most students felt poorly prepared to handle morally distressing situations. Indeed, there were no differences in levels of moral distress between students who stated addressing this topic in classes and those who did not. One could argue that although some schools recognize it is important to address this issue, the approaches used do not seem to have a protective effect on their students. Once morally distressing situations have occurred, a moral wound may remain as a result from the violation of moral values – "moral residue".[6,37] Therefore, it may be important to do more than discuss the topic and provide students with skills to deal with these situations.

Potential consequences of experiencing moral distressing situations

Moral distress was higher in participants who considered leaving medical school and in participants who thought about choosing a non-clinical specialty. This is well aligned with the current literature that shows higher MMD-HP scores for those considering leaving their position.[4,21] Medical school dropouts constitute a direct economic loss to society, may compromise healthcare and represent a loss of useful contributions to the medical profession.[38] Moreover, student dropout may be symptomatic of preventable malfunctioning in medical education.[39]

These data, along with the poor preparation reported by students, represent new and valuable knowledge to the literature, reporting how students feel about the theme, the lack of/ineffective approaches to the topic by medical schools and exposing the potencial consequences of continued moral distress over time.

Differences between year of attendance

Higher levels of moral distress in students from the sixth year seem to support the concepts of 'crescendo effect'[21] and 'moral residue'.[6,28] The latter contributes to a higher baseline level of distress to which subsequent situations add their distress.[15] Consequently, the phenomenon of moral distress may have a cumulative effect over time.[28] Nonetheless, due to the nature of its curriculum, the students in the final year are more exposed to patients, which, along with their greater clinical knowledge compared to younger students, can contribute to and magnify this effect.

Differences between medical schools

Differences between medical schools are not explained by the approach or lack of approach to the theme, so other causes should be considered. Ethics curricula are widespread, reflecting the prevalence of ethical issues in clinical practice,[39] but its content and distribution is not homogeneous across schools. The main difference observed is that in the medical schools in northern Portugal, the ethics subjects are integrated in the first clinical years, while in other schools the same subjects are part of the first years of medical education. This could have a protective effect towards students in northern Portugal and could potentially cause deficits in skills that may leave the other students more vulnerable to the impact of moral distress.[15]

Our data seem to support that all medical schools could consider creating a strong ethics and humanities curricula alongside clinical practice, including didactic programs on normative ethics. This could potentially increase not only self-confidence but also the willingness to speak up and engage in morally responsible actions.[11,15]

Strengths and limitations

The participation of students from seven out of eight Portuguese medical schools included in the study enabled a robust assessment of this issue at a national level, but also a robust comparison with the international literature.

The retrospective design of the study is a limitation, since the participants had to resort to memory in order to score each situation.

The response rate of 22% is quite reasonable considering the web-based design but can limit the generalizability of results. Perhaps students who participated in the study have different levels of moral sensitivity than those who did not participate. However, the widespread distribution of participants is a strength of this study.

The last two weeks of data collection period coincided with the notification of the first cases of COVID-19 in Portugal. All medical schools suspended their activity since the first case was notified, so these extraordinary circumstances should not have affected the results of the study.

CONCLUSION

Our study showed that most Portuguese medical students had already experienced morally distressing situations as early as during the first years of clinical practice. These experiences may promote school dropouts and may affect the way future healthcare professionals deal with clinical challenging situations.

The recognition of this phenomenon by medical educators might be the first step to mitigate its effects. Approaches to reduce moral distress may include strategies to help medical students identify and use their inner resources (i.e., emotional intelligence), increasing their empowerment and self-confidence.

The curricula of medical schools might benefit from the promotion of a strong mentoring program for students in their clinical years, which can help to promote trust and open communication and may have a strong positive effect on the level of empathy among medical students. Including ethics subjects alongside clinical ones and promoting their interaction may also be a good approach to reduce moral distress.

Despite the extensive literature showing high levels of moral distress among healthcare professionals, this study shows that the phenomenon occurs early in medical school.

This emphasizes the importance of a critical review of medical education, particularly in ethics and humanities curricula, reducing the harmful effects of preventable psychological phenomena in clinical practice and in the lives of healthcare professionals all over the world.

Future research should address the differences in the curricula adopted by different medical schools in order to assess which model(s) might have the best effect on reducing moral distress. It should also address if students who experienced high levels of moral distress are at higher risk of burnout, especially considering these unprecedented times.

OBSERVATIONS

This study was developed as a master's thesis, and it was presented by the first author of the study to obtain a master's degree in Medicine.

AUTHORS CONTRIBUTION

MD: Design of the study; data acquisition and statistics process; draft and critical review of the paper.

CT, BA: Design of the study; draft and critical review of the paper.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

COMPETING INTERESTS

The authors had no competing interests.

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Síndrome Metabólica em Portugal: Prevalência e Fatores Associados

Metabolic Syndrome in Portugal: Prevalence and Associated Factors

ARTIGO ORIGINAL

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RESUMO

Introdução: A síndrome metabólica consiste num conjunto de fatores que, quando associados, conferem maior risco de desenvolver doenças cardiovasculares e diabetes tipo 2, constituindo um importante problema de saúde pública. O objetivo deste estudo foi estimar a prevalência desta síndrome na população portuguesa, e avaliar possíveis associações com determinantes demográficos e socioeconómicos.

Material e Métodos: Com base no primeiro Inquérito Nacional de Saúde com Exame Físico de 2015, realizou-se um estudo epidemiológico transversal numa amostra representativa da população portuguesa (n = 4797) entre os 25 e 74 anos. A prevalência foi estimada na população total e em cada sexo, estratificada por grupo etário, região de saúde, tipologia de área urbana, estado civil, escolaridade, situação profissional e risco de pobreza. A magnitude das associações foi medida pelas razões de prevalências ajustadas.

Resultados: A prevalência estimada foi de 33,4% (IC 95%, 31,7 – 35,1) na população portuguesa [35,6% nos homens (IC 95%, 31,9 – 39,2) e 31,3% nas mulheres (IC 95%, 28,5 – 34,2)]. Em ambos os sexos, a maior prevalência estava significativamente associada ao aumento da idade, a indivíduos viúvos/casados/unidos de facto e com menor escolaridade. Não se verificou associação com sexo, região de saúde, tipologia de área urbana, situação profissional ou risco de pobreza.

Conclusão: A síndrome metabólica estava independentemente associada a grupos específicos. Este conhecimento reforça a importância de uma avaliação holística dos determinantes de saúde associados à síndrome metabólica.

Palavras-chave: Portugal; Prevalência; Síndrome Metabólica/epidemiologia

ABSTRACT

Introduction: The metabolic syndrome consists of a set of factors that, when associated, are associated with a higher risk of developing cardiovascular diseases and type 2 diabetes, and is thus an important public health problem. The objective of this study was to estimate the prevalence of this syndrome in the Portuguese population, and to evaluate possible associations with demographic and socioeconomic determinants.

Material and Methods: Based on the 1st National Health Survey with Physical Examination of 2015, a cross-sectional epidemiological study was conducted on a representative sample of the Portuguese population (n = 4797) aged between 25 and 74 years old. The prevalence was estimated for the total population and each gender, stratified by age group, health region, type of urban area, marital status, education, professional status, and risk of poverty. The magnitude of the associations was measured with adjusted prevalence ratios.

Results: In the Portuguese population the estimated prevalence was 33.4% [95% CI, 31.7 – 35.1] [35.6% in men (95% CI, 31.9 – 39.2) and 31.3% in women (95% CI, 28.5 – 34.2)]. In both genders, the highest prevalence was significantly associated with increasing age, widowed/married/de facto partners and those with lower levels of education. There was no association with gender, health region, type of urban area, professional status or risk of poverty.

Conclusion: Metabolic syndrome was independently associated with specific groups. This knowledge reinforces the importance of a holistic assessment of the health determinants associated with the metabolic syndrome.

Keywords: Metabolic Syndrome/epidemiology; Portugal; Prevalence

INTRODUÇÃO

A síndrome metabólica (SM) tem elevada prevalência a nível global, constituindo um problema atual de saúde pública pela morbilidade e mortalidade associadas.[1] Esta síndrome duplica o risco potencial de desenvolvimento de doenças cardiovasculares nos cinco a 10 anos seguintes e está associado a um aumento de cinco vezes no risco de desenvolver diabetes tipo 2 ao longo da vida quando comparados com indivíduos sem SM.[2]

Diferentes organizações propuseram critérios distintos para a definição da SM. Contudo, um consenso entre várias sociedades internacionais foi estabelecido em 2009, criando uma definição harmonizada. Segundo esta definição, a SM consiste na presença em simultâneo de três ou mais das seguintes componentes: hiperglicemia, hipertensão arterial (HTA), hipertrigliceridemia, níveis baixos de colesterol de lipoproteína de alta densidade (c-HDL) e perímetro da cintura aumentado.[2]

A SM é comum e tem uma prevalência crescente em todo o mundo, que se relaciona em grande parte com o aumento da obesidade e com os estilos de vida sedentários.[2–4] Estima-se que a sua prevalência a nível global seja de 20% - 25%.[5–7] O estudo *Portuguese Metabolic Syndrome* (PORMETS), realizado em 2007/2009 na população com 18 ou mais anos de idade, estimou uma prevalência da

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SM de 43,1% (39,8% nos homens e 45,7% nas mulheres) em Portugal Continental, utilizando a definição harmonizada.[8] O Estudo Epidemiológico de Prevalência da Síndrome Metabólica na População Portuguesa (VALSIM), realizado em 2006/2007, analisou os utentes com 18 ou mais anos de idade frequentadores dos cuidados de saúde primários (CSP) em Portugal Continental e Ilhas e, aplicando critérios semelhantes à definição harmonizada, estimou uma prevalência da SM de 27,5% (26,0% nos homens e 28,7% nas mulheres).[9] Por outro lado, em 2015, segundo o 1º Inquérito Nacional de Saúde com Exame Físico (INSEF) a prevalência de obesidade ou excesso de peso em Portugal correspondia a cerca de dois terços da população adulta (67,6%).[10]

Uma recente meta-análise mostrou um aumento da prevalência de SM em indivíduos com vulnerabilidade socioeconómica [OR 1,15 (IC 95%, 1,12 - 1,18)].[11] Os determinantes demográficos e socioeconómicos foram abordados por vários estudos que mostraram consistentemente o aumento da prevalência da SM nos grupos etários com mais idade,[7–9] menor escolaridade[12–14] e situação laboral e financeira desfavorecida.[15]

Dado que as últimas estimativas da prevalência da SM na população portuguesa reportam a 2007/2009,[8] o objetivo do presente estudo foi determinar a prevalência da SM e seus fatores associados na população residente em Portugal em 2015, com idades entre os 25 e os 74 anos.

MATERIAL E MÉTODOS

Fonte dos dados

Este estudo epidemiológico observacional transversal descritivo com componente analítica teve como base o INSEF de 2015.[16] O INSEF foi desenvolvido, entre 2013 e 2016, pelo Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA) em colaboração com as cinco administrações regionais de saúde do Continente, as secretarias regionais de saúde e dos assuntos sociais das regiões autónomas dos Açores e da Madeira e o Instituto Norueguês de Saúde Pública. Todos os procedimentos foram realizados segundo as recomendações do Inquérito Europeu de Saúde com Exame Físico (EHES).[17] O INSEF incluiu três componentes: exame físico, colheita de sangue para análises clínicas e entrevista com um questionário geral de saúde. O trabalho de campo decorreu entre fevereiro e dezembro de 2015 e foi realizado por equipas formadas e treinadas especificamente para o INSEF, num total de 117 profissionais de saúde. O exame físico (medição da tensão arterial, altura, peso e perímetros da cintura e anca) foi realizado por enfermeiros e seguiu todos os procedimentos e recomendações do EHES. A tensão arterial foi medida, após repouso de cinco minutos na posição sentada, por três vezes no braço direito com um minuto de intervalo entre medições. As colheitas de sangue para análises clínicas [perfil lipídico, hemoglobina glicada A1c (HbA1c) e hemograma] foram realizadas por um técnico de análises clínicas ou um enfermeiro e decorreram durante todo o dia, sem jejum obrigatório. O questionário, baseado em instrumentos padronizados e amplamente testados, foi aplicado por *Computer-Assisted Personal Interview* e incluiu 23 secções (relativas a caraterização sociodemográfica e socioeconómica, estado de saúde, determinantes de saúde e cuidados de saúde).

População em estudo

A população alvo do INSEF foi constituída por indivíduos entre os 25 e 74 anos, que em 2015 residiam em Portugal há pelo menos 12 meses antes da data da entrevista, não-institucionalizados, e que falavam a língua portuguesa. Os participantes do INSEF foram selecionados em duas etapas, através de amostragem probabilística estratificada por região (Norte, Centro, Lisboa e Vale do Tejo, Alentejo, Algarve, Madeira e Açores) e tipologia de área urbana (rural e urbana). Numa primeira etapa, em cada região foram selecionadas aleatoriamente sete unidades primárias de amostragem (PSU), geralmente definidas por áreas geográficas correspondentes à área de influência dos antigos centros de saúde do Serviço Nacional de Saúde, com probabilidade de seleção proporcional à dimensão da população residente com idade elegível. Na segunda etapa, em cada unidade primária de amostragem foram selecionados indivíduos por amostragem aleatória simples, que constituem as unidades secundárias de amostragem, a partir das listas de utentes do Serviço Nacional de Saúde. A dimensão da amostra foi estabelecida de forma a ser possível estimar uma prevalência esperada de 50%, com uma precisão absoluta de 5% para um intervalo de confiança a 95%, em cada região de saúde do Continente ou Região Autónoma, considerando um efeito do desenho da amostra de 1,5. O cálculo da dimensão da amostra mínima necessária resultou em 600 indivíduos a nível regional e 4200 a nível nacional, sendo que a amostra final obtida no INSEF correspondeu a 4911 indivíduos.[18]

Para o presente estudo foram excluídos os indivíduos cujas respostas omissas não permitiam determinar a presença ou ausência de SM (n = 114), correspondendo a uma amostra final de 4797 indivíduos.

Variáveis em estudo

As caraterísticas demográficas e socioeconómicas incluíram o sexo, grupo etário (25 - 44; 45 - 54; 55 - 64; 65 - 74), região de residência (Norte, Centro, Lisboa e Vale do Tejo, Alentejo, Algarve, Região Autónoma da Madeira e Região Autónoma dos Açores), tipologia de área urbana (rural e urbana), estado civil (solteiro; casado ou em união de facto; divorciado; viúvo), nível de escolaridade (analfabeto/1º ciclo do ensino básico; 2º ciclo/3º ciclo do ensino básico; secundário; ensino superior), condição perante o trabalho e risco de pobreza. Para a variável tipologia de área urbana, as áreas de influência das PSU foram analisadas a partir de informação dos Censos (2011) e da tipologia de área urbana (TIPAU), tendo uma PSU sido classificada como urbana quando o peso da população residente com idade elegível nas freguesias com classificação TIPAU de área predominantemente urbana era superior a 50% da população total da PSU; caso contrário, a PSU seria

classificada como rural. A condição perante o trabalho foi definida em três categorias - trabalho remunerado, desempregado e sem atividade profissional remunerada (inclui reformados, domésticas e estudantes). O risco de pobreza foi aferido com a questão: "Se surgisse uma despesa inesperada de cerca de 434 euros, conseguiria o seu agregado familiar pagá-la de imediato sem recorrer a empréstimos?". Este item utiliza uma percentagem do ordenado mínimo, e faz parte dos itens de privação material na população total do *European Union Statistics on Income and Living Conditions* (EU-SILC) 2014 - 2015 para avaliar o risco do limiar da pobreza.[19]

As variáveis do exame físico incluíram o perímetro da cintura (cm) e tensão arterial sistólica e diastólica (mmHg).

As variáveis em estudo obtidas através da colheita de sangue para análises clínicas foram a trigliceridemia (mg/dL), o c-HDL (mg/dL) e a HbA1c (%).

Considerou-se SM presente quando um indivíduo tinha simultaneamente três ou mais das cinco componentes seguintes: perímetro da cintura aumentado (homens ≥ 94 cm e mulheres ≥ 80 cm), trigliceridemia ≥ 175 mg/dL, c-HDL diminuído (homens < 40 mg/dL e mulheres < 50 mg/dL), HTA (sistólica ≥ 130 mmHg, diastólica ≥ 85 mmHg ou terapêutica anti-hipertensora) e HbA1c ≥ 5,7% ou terapêutica para glicemia elevada. Devido ao jejum não estar garantido, o ponto de corte considerado para trigliceridemia elevada foi de ≥ 175 mg/dL (em vez de ≥ 150 mg/dL como indicado na definição harmonizada). Não foi realizada qualquer correção ao valor do c-HDL, pois este não é afetado pelo estado de jejum/não jejum.[20] Nas variáveis trigliceridemia e c-HDL não se considerou a toma de medicação, uma vez que esta informação era omissa no questionário geral de saúde. A HbA1c substituiu a componente da definição harmonizada 'Glicemia em jejum ≥ 100 mg/dL', tendo-se selecionado o ponto de corte de ≥ 5,7%.

Análise estatística

É consensual a existência de diferenças entre sexos em termos de estado de saúde e comportamentos relacionados com saúde. Estas diferenças podem dever-se a aspetos biológicos ou determinantes comportamentais.[21,22] Dada a etiologia multifatorial da SM, considerou-se mais adequada a análise das estimativas estratificada por sexo.

A população em estudo foi caraterizada segundo as variáveis demográficas, socioeconómicas, analíticas e do exame físico. Para as variáveis nominais e ordinais foram criadas tabelas de distribuição de frequências com as contagens e as respetivas percentagens. Para as variáveis numéricas foram determinadas medidas de tendência central como a média e mediana, e medidas de dispersão, como o desvio padrão, amplitude, mínimo e máximo.

A prevalência da SM, e respetivos intervalos de confiança a 95% (IC 95%), foi estimada para o total da população e separadamente para homens e mulheres, estratificada por grupo etário, região de saúde, tipologia de área urbana, estado civil, escolaridade, condição perante o trabalho e risco de pobreza. A versão de Rao-Scott do teste qui-quadrado ajustada ao desenho amostral foi utilizada para comparar as prevalências estimadas entre as categorias das variáveis de estratificação.[23]

Para identificar fatores associados à SM foram estimadas as razões de prevalência bruta (RP), de acordo com grupo etário, região de saúde, tipologia de área urbana, estado civil, escolaridade, condição perante o trabalho e risco de pobreza, usando a regressão de Poisson. Estimaram-se também as razões de prevalências ajustadas com respetivos IC 95% [aRP (IC 95%)]: ajustadas, no total da população, para sexo e grupo etário; ajustadas para grupo etário no sexo; as variáveis 'trabalho' e 'risco de pobreza' foram também ajustadas para o nível de escolaridade. Optou-se pelo modelo de regressão de Poisson devido à expectável elevada prevalência da SM (> 10%), que utilizando a *odds ratio* (OR) obtida através de regressão logística poderia levar à sobrestimação das magnitudes de associação.[24] Foi considerado o nível de significância de 5%.

Todas as estimativas pontuais foram ajustadas utilizando pesos amostrais calibrados para a distribuição da população portuguesa, por sexo e grupo etário, em cada uma das sete regiões de saúde, para a estimativa da população residente em 2014.

A análise estatística foi realizada com recurso ao *software* R (versão 1.1.463)[25] e módulo *survey* (versão 3.36)[26] para análise de amostras complexas.

Questões éticas

Este estudo utilizou a base de dados do INSEF, que foi criada seguindo um protocolo autorizado pela Comissão Nacional de Proteção de Dados e pelas Comissões de Ética para a Saúde do INSA, Administrações Regionais de Saúde do Norte, Centro, Lisboa e Vale do Tejo, Alentejo e Algarve, Serviço de Saúde da Região Autónoma da Madeira, Hospital da Horta e Centro Hospitalar de Lisboa Ocidental. Todos os participantes no INSEF assinaram uma declaração de consentimento informado referente ao exame físico, colheita de sangue e entrevista de saúde.

Foi obtido o parecer positivo da Comissão de Ética para a Saúde do INSA para a realização do presente estudo.

RESULTADOS

Caraterização da amostra em estudo

A amostra em estudo compreendeu 4797 indivíduos, sendo 52,1% do sexo feminino (Tabela 1). A maioria dos indivíduos da amostra tinha menos de 55 anos (64,6%), era casada ou unida de facto (70,1%), residia em área urbana (71,5%), tinha trabalho remunerado (61,0%) e conseguia suportar uma despesa inesperada (60,9%). Cerca de um terço tinha o 2º ou 3º ciclo do ensino básico (32,7%) e apenas 17,3% frequentou ou completou o ensino superior.

A Tabela 2 apresenta os resultados das caraterísticas analíticas, tensão arterial e medições antropométricas da amostra, segundo os critérios relevantes para a definição da SM. No total da amostra, o perímetro da cintura aumentado foi a componente mais prevalente (64,5%) e o c-HDL diminuído a menos frequente (24,2%). A distribuição das

Tabela 1 – Distribuição das características demográficas e socioeconómicas da amostra de indivíduos entre 25 e 74 anos de Portugal (n = 4797), estratificadas por sexo. (2015)

Variável	Valores	Total		Feminino		Masculino		*p* *
		n	%	n	%	n	%	
Sexo	Feminino	2571	53,6	2571	100,0	-	-	-
	Masculino	2226	46,4	-	-	2226	100,0	-
Grupo etário	25 - 44 anos	1830	42,3	997	38,8	833	37,4	**< 0,001**
	45 - 54 anos	1161	22,3	633	24,6	528	23,7	**0,002**
	55 - 64 anos	1067	19,9	562	21,9	505	22,7	0,081
	65 - 75 anos	739	15,5	379	14,7	360	16,2	0,485
Região	Norte	772	16,1	438	17,0	334	15,0	**< 0,001**
	Centro	695	14,5	358	13,9	337	15,1	0,426
	Lisboa e Vale do Tejo	614	12,8	327	12,7	287	12,9	0,106
	Alentejo	660	13,8	350	13,6	310	13,9	0,120
	Algarve	635	13,2	324	12,6	311	14,0	0,606
	Região Autónoma da Madeira	688	14,3	373	14,5	315	14,2	**0,027**
	Região Autónoma dos Açores	733	15,3	401	15,6	332	14,9	**< 0,001**
Tipologia área urbana	Rural	1368	28,5	735	28,6	633	28,4	**0,006**
	Urbana	3429	71,5	1836	71,4	1593	17,6	**< 0,001**
Estado civil	Solteiro	800	16,7	385	15,0	415	18,6	0,289
	Casado ou união de facto	3365	70,1	1749	68,0	1616	72,6	**0,022**
	Divorciado	396	8,3	235	9,1	161	7,2	**< 0,001**
	Viúvo	236	4,9	202	7,9	34	1,5	**< 0,001**
Escolaridade	Analfabeto / 1º ciclo	1458	30,4	760	29,6	698	31,4	0,104
	2º ciclo / 3º ciclo	1568	32,7	773	30,1	795	35,7	0,578
	Ensino secundário	939	19,6	502	19,5	437	19,6	**0,034**
	Ensino superior	829	17,3	533	20,8	296	13,3	**< 0,001**
Trabalho	Trabalho remunerado	2925	61,0	1501	58,4	1424	64,0	0,154
	Desempregado	536	11,2	298	11,6	238	10,7	**0,010**
	Outra sem atividade profissional	1334	27,8	770	30,0	564	25,3	**< 0,001**
Risco pobreza	Não suporta despesa inesperada	1853	39,1	1103	43,5	750	34,0	**< 0,001**
	Suporta despesa inesperada	2886	60,9	1433	56,5	1453	66,0	0,710

* Comparação de proporções entre sexo feminino e masculino

componentes alteradas diferiu entre sexos, verificando-se as maiores diferenças ao nível da hipertrigliceridemia (37,2% nos homens *vs* 20,9% nas mulheres) e HTA (58,2% nos homens *vs* 41,4% nas mulheres).

Entre os indivíduos da amostra com SM, a componente mais prevalente foi o perímetro de cintura aumentado (95,4%), seguida da hipertrigliceridemia (84,5%), c-HDL diminuído (62,1%) e HTA (61,8%), enquanto a HbA1c aumentada foi a componente menos frequente (50,4%). Mais de metade dos indivíduos cumpria os critérios de SM pela presença de três das cinco componentes (58,1%) e 10,4% apresentava todas as componentes.

Prevalência de síndrome metabólica

A estimativa de prevalência de SM foi de 33,4% (IC 95%, 31,7 - 35,1) (Tabela 3) para a população com idade entre 25 e 74 anos. Não se observaram diferenças estatisticamente significativas entre os sexos, sendo a estimativa pontual da prevalência nos homens de 35,6% (IC 95%, 31,9 - 39,2) e nas mulheres de 31,3% (IC 95%, 28,5 - 34,2). Observou-se um gradual aumento da prevalência dos grupos etários mais jovens para os mais velhos [14,5% *vs* 59,8%; RP = 4,13 (3,51 - 4,90), $p < 0,001$], e o inverso para o nível da escolaridade, com prevalência mais elevada nos indivíduos analfabetos/1º ciclo, e menor prevalência nos indivíduos com o ensino superior [55,1% *vs* 16,5%, RP = 3,34 (IC 95%, 2,80 - 3,99), $p < 0,001$].

Na população total não se verificaram diferenças estatisticamente significativas entre regiões de saúde ou tipologia de área urbana. Relativamente ao estado civil, os solteiros apresentaram menor prevalência de SM que os viúvos [15,1% *vs* 52,3%; RP = 3,46 (IC 95%, 2,79 - 4,30), $p < 0,001$]. A proporção de indivíduos com SM foi menor entre aqueles com trabalho remunerado comparativamente às pessoas sem atividade profissional [24,5% *vs* 54,2%; RP = 2,22 (IC 95%, 1,03 - 2,54), $p < 0,001$]. Os indivíduos que

declararam não conseguir suportar uma despesa inesperada apresentaram valores superiores de prevalência [37,4% *vs* 31,3%, RP = 1,19 (IC 95%, 1,04 - 1,37), *p* = 0,016].

Na estratificação por sexo mantiveram-se as tendências verificadas na população total, a prevalência da SM foi mais elevada nos indivíduos mais idosos, com menor escolaridade, viúvos e sem atividade profissional. Apenas nas mulheres se observou uma maior prevalência entre aquelas incapazes de fazer face a uma despesa inesperada [36,1% *vs* 28,0%; RP = 1,29 (IC 95%, 1,10 - 1,51), *p* = 0,003].

Modelo de regressão multivariável

A análise das razões de prevalências ajustadas (aRP) na Tabela 4 permite verificar que, tanto na população total como em cada um dos sexos, a prevalência foi superior nos indivíduos com mais idade e menor grau de escolaridade. Em comparação com o grupo etário 25 - 44 anos, a maior aRP observou-se no grupo etário 65 - 74 anos [4,15 (IC 95%, 3,51 - 4,91), *p* < 0,001], sendo esta diferença mais pronunciada nas mulheres [6,94 (IC 95%, 5,23 - 9,22), *p* < 0,001] que nos homens [2,71 (IC 95%, 2,31 - 2,19), *p* < 0,001]. Manteve-se também a significância estatística na associação entre SM e nível de escolaridade mais baixo, com uma maior aRP entre os indivíduos analfabetos/1º ciclo [1,76 (IC 95%, 1,46 - 2,11), *p* < 0,001], comparativamente àqueles com o ensino superior. Quanto ao estado civil, tendo como referência os solteiros, a aRP foi superior nas mulheres viúvas [1,31 (IC 95%, 1,06 - 1,62), *p* = 0,018] e nos homens casados ou em união de facto [1,76 (IC 95%, 1,24 - 2,50), *p* = 0,004]. Não se verificaram diferenças estatisticamente significativas entre as categorias das variáveis 'sexo', 'região de saúde', 'tipologia de área urbana', 'trabalho' e 'risco de pobreza'.

Tabela 2 – Distribuição das caraterísticas analíticas, tensão arterial e medições antropométricas da amostra de indivíduos entre 25 e 74 anos de Portugal (n = 4797), estratificadas por sexo. (2015)

Variável	Total n = 4797	Feminino n = 2571	Masculino n = 2226	*p* *
Perímetro da cintura (cm)				
Média	92,8	89,3	96,9	
Desvio padrão	13,4	13,1	12,6	
Mediana	92,1	88,6	96,1	**< 0,001**
Mín - Máx	57,5 - 194,0	57,5 - 148,0	66,0 - 194,0	
Aumentado (♀ ≥ 80 cm; ♂ ≥ 94 cm) (%)	64,5	74,4	57,4	
Tensão arterial sistólica (mmHg)				
Média	125,8	121,4	130,9	
Desvio padrão	16,7	16,5	15,4	
Mediana	124,0	119,0	129,0	**< 0,001**
Mín - Máx	87,5 - 224,0	87,5 - 216,0	88,5 - 224,0	
Tensão arterial diastólica (mmHg)				
Média	74,2	72,4	76,3	
Desvio padrão	9,9	9,4	10,1	
Mediana	73,5	71,5	75,5	**< 0,001**
Mín - Máx	43,5 - 128,0	43,5 - 119,0	47,0 - 128,0	
Aumentada (≥ 130/85 mmHg) (%)	49,2	41,4	58,2	
Trigliceridemia (mg/dL)				
Média	150,7	131,9	172,4	
Desvio padrão	99,9	76,5	117,7	
Mediana	126,0	114,0	144	**< 0,001**
Mín - Máx	17,0 - 1680,0	25,0 - 885,0	17,0 - 1680,0	
Aumentada (≥ 175 mg/dL) (%)	28,5	20,9	37,2	
c-HDL no sangue (mg/dL)				
Média	54,4	58,7	49,25	
Desvio padrão	14,5	13,9	13,6	
Mediana	53,0	57,0	47,0	**< 0,001**
Mín - Máx	17,0 - 171,0	23,0 - 130,0	17,0 - 171,0	
Diminuído (♀ < 50 mg/dL; ♂ <40 mg/dL) (%)	24,2	26,7	21,2	
HbA1c no sangue (%)				
Média	5,5	5,4	5,6	
Desvio padrão	0,8	0,7	0,9	
Mediana	5,4	5,3	5,4	**< 0,001**
Mín - Máx	3,7 - 14,1	4,0 - 12,8	3,7 - 14,1	
Aumentada (HbA1c ≥ 5,7%) (%)	27,4	26,0	29,1	

c-HDL: colesterol de lipoproteína de alta densidade; HbA1c: hemoglobina glicada A1c; IC 95%: intervalo de confiança a 95%

* Comparação de médias entre sexo feminino e masculino

Tabela 3 – Prevalência de síndrome metabólica e respetivos intervalos de confiança a 95% (IC 95%), por caraterísticas demográficas e socioeconómicas, estratificada por sexo e ponderada para a população portuguesa entre 25 e 74 anos. (2015)

Variável	Total			Feminino			Masculino		
	SM (%)	IC 95%	*p*	SM (%)	IC 95%	*p*	SM (%)	IC 95%	*p*
Total	**33,4**	31,7 - 35,1	-	**31,3**	28,5 - 34,2	-	**35,6**	31,9 - 39,2	-
Sexo									
Feminino	**31,3**	28,5 - 34,2	0,140	-	-	-	-	-	-
Masculino	**35,6**	31,9 - 39,2		-	-	-	-	-	-
Grupo etário									
25 - 44	**14,5**	12,3 - 16,6	**< 0,001**	**9,3**	6,7 - 11,9	**< 0,001**	**19,9**	16,2 - 23,7	**< 0,001**
45 - 54	**32,7**	28,5 - 36,9		**28,1**	21,6 - 34,5		**37,6**	29,2 - 49,0	
55 - 64	**53,8**	48,3 - 59,2		**54,2**	48,5 - 60,0		**53,2**	45,9 - 60,6	
65 - 74	**59,8**	55,3 - 64,2		**64,5**	56,3 - 72,6		**54,1**	48,3 - 59,9	
Região									
Norte	**34,2**	35,5 - 36,0	0,207	**34,0**	23,4 - 38,6	0,263	**34,5**	27,8 - 41,3	0,578
Centro	**37,4**	30,6 - 44,1		**34,1**	26,5 - 41,7		**40,9**	33,5 - 48,4	
Lisboa e Vale do Tejo	**31,1**	28,4 - 33,8		**28,3**	22,8 - 33,7		**34,1**	27,1 - 41,1	
Alentejo	**34,3**	27,6 - 41,0		**30,0**	23,7 - 36,3		**38,6**	27,6 - 49,5	
Algarve	**31,1**	25,9 - 36,2		**25,9**	18,5 - 33,3		**36,5**	31,0 - 42,0	
Região Autónoma da Madeira	**28,6**	23,3 - 33,9		**28,1**	22,7 - 33,4		**29,3**	22,9 - 35,6	
Região Autónoma dos Açores	**32,2**	27,8 - 36,7		**29,6**	25,8 - 33,4		**34,9**	25,9 - 44,0	
Tipologia área urbana									
Rural	**36,6**	31,4 - 41,7	0,068	**36,3**	27,3 - 45,4	0,099	**36,8**	25,9 - 47,8	0,731
Urbana	**32,2**	30,7 - 33,6		**29,6**	27,2 - 31,9		**35,1**	32,0 - 38,3	
Estado civil									
Solteiro	**15,1**	12,5 - 17,7	**< 0,001**	**13,6**	8,8 - 16,5	**< 0,001**	**16,4**	10,2 - 22,6	**< 0,001**
Casado ou União de facto	**38,1**	36,3 - 40,0		**34,7**	31,4 - 38,0		**41,8**	37,4 - 46,3	
Divorciado	**26,9**	20,5 - 33,3		**23,1**	12,5 - 33,6		**31,1**	24,0 - 38,2	
Viúvo	**52,3**	41,1 - 63-6		**52,7**	41,9 - 63,5		**50,8**	25,3 - 76,3	
Escolaridade									
Analfabeto / 1º ciclo	**55,1**	51,9 - 58,3	**< 0,001**	**58,4**	52,7 - 64,2	**< 0,001**	**51,2**	46,6 - 55,9	**< 0,001**
2º ciclo / 3º ciclo	**30,2**	26,6 - 33,9		**27,6**	20,9 - 34,2		**32,4**	25,8 - 39,1	
Secundário	**25,8**	22,2 - 29,3		**18,5**	13,8 - 23,2		**33,3**	28,1 - 38,6	
Ensino superior	**16,5**	13,6 - 19,4		**14,0**	9,1 - 19,0		**20,4**	13,2 - 27,7	
Trabalho									
Trabalho remunerado	**24,5**	22,3 - 26,6	**< 0,001**	**18,5**	15,1 - 21,9	**< 0,001**	**30,3**	25,4 - 35,1	**< 0,001**
Desempregado	**33,9**	28,4 - 39,4		**29,2**	20,8 - 37,6		**39,5**	32,6 - 46,3	
Outra sem atividade profissional	**54,2**	50,1 - 58,3		**57,9**	52,4 - 63,4		**49,0**	43,4 - 54,7	
Risco pobreza									
Não suporta despesa inesperada	**37,4**	33,4 - 41,4	**0,018**	**36,1**	30,7 - 41,6	**0,005**	**39,2**	32,9 - 45,5	0,237
Suporta despesa inesperada	**31,3**	29,2 - 33,4		**28,0**	25,7 - 30,3		**34,4**	29,7 - 39,1	

IC 95%: intervalo de confiança a 95%; *p*: valor-p; SM: síndrome metabólica

DISCUSSÃO

A prevalência da SM estimada no presente estudo (33,4%) situou-se entre valores obtidos em outros estudos. O estudo VALSIM[9] encontrou uma menor prevalência (27,5%), que pode estar relacionada com a participação exclusiva de utentes frequentadores dos CSP e com análises clínicas nos 12 meses anteriores, podendo existir um viés de seleção para indivíduos com maior atenção ao seu estado de saúde e com melhor acesso a cuidados. Além disso, nesse estudo foram utilizados pontos de corte superiores nas componentes do perímetro abdominal e glicemia em jejum. O estudo PORMETS[8] estimou uma maior prevalência de SM segundo a definição harmonizada (43,1%), que parece dever-se maioritariamente à inclusão de

Tabela 4 – Razão de prevalência bruta e ajustada de síndrome metabólica, estratificada por sexo, e respetivos intervalos de confiança a 95%, ponderada para a população portuguesa entre 25 e 74 anos. (2015) (Tabela 4: parte 1 de 2)

Variável	Total				Feminino				Masculino			
	RP (IC 95%)	*p*	aRP † (IC 95%)	*p*	RP (IC 95%)	*p*	aRP ‡ (IC 95%)	*p*	RP (IC 95%)	*p*	aRP ‡ (IC 95%)	*p*
Sexo												
Feminino *	ref	-	ref	-	-	-	-	-	-	-	-	-
Masculino	**1,14** (0,96 - 1,34)	0,138	**1,16** (1,01 - 1,33)	0,050	-	-	-	-	-	-	-	-
Grupo etário												
25 - 44 *	ref	-	ref	-	ref	-	ref	-	ref	-	ref	-
45 - 54	**2,26** (1,91 - 2,67)	**< 0,001**	**2,26** (1,92 - 2,67)	**< 0,001**	**3,02** (2,44 - 3,74)	**< 0,001**	**3,02** (2,44 - 3,74)	**< 0,001**	**1,89** (1,42 - 2,51)	**< 0,001**	**1,89** (1,42 - 2,51)	**< 0,001**
55 - 64	**3,72** (3,11 - 4,44)	**< 0,001**	**3,72** (3,12 - 4,43)	**< 0,001**	**5,84** (4,13 - 8,26)	**< 0,001**	**5,84** (4,13 - 8,26)	**< 0,001**	**2,67** (2,19 - 3,25)	**< 0,001**	**2,67** (2,19 - 3,25)	**< 0,001**
65 - 74	**4,13** (3,48 - 4,91)	**< 0,001**	**4,15** (3,51 - 4,91)	**< 0,001**	**6,94** (5,23 - 9,22)	**< 0,001**	**6,94** (5,23 - 9,22)	**< 0,001**	**2,71** (2,31 - 3,19)	**< 0,001**	**2,71** (2,31 - 3,19)	**< 0,001**
Região												
Norte	**0,92** (0,74 - 1,13)	0,425	**0,95** (0,75 - 1,20)	0,650	**1,00** (0,74 - 1,34)	0,984	**1,04** (0,80 - 1,36)	0,754	**0,84** (0,62 - 1,14)	0,277	**0,86** (0,64 - 1,16)	0,333
Centro *	ref	-	ref	-	ref	-	ref	-	ref	-	ref	-
Lisboa e Vale do Tejo	**0,83** (0,67 - 1,03)	0,104	**0,86** (0,68 - 1,07)	0,186	**0,83** (0,62 - 1,11)	0,224	**0,86** (0,69 - 1,09)	0,222	**0,83** (0,64 - 1,08)	0,183	**0,85** (0,64 - 1,13)	0,266
Alentejo	**0,92** (0,68 - 1,24)	0,580	**0,92** (0,68 - 1,25)	0,592	**0,88** (0,62 - 1,24)]	0,476	**0,88** (0,66 - 1,18)	0,404	**0,94** (0,64 - 1,38)	0,760	**0,95** (0,64 - 1,40)	0,779
Algarve	**0,83** (0,65 - 1,06)	0,144	**0,86** (0,67 - 1,09)	0,229	**0,76** (0,54 - 1,07)	0,122	**0,80** (0,62 - 1,04)	0,109	**0,89** (0,70 - 1,13)	0,353	**0,91** (0,70 - 1,19)	0,485
Região Autónoma da Madeira	**0,77** (0,60 - 0,98)	**0,047**	**0,84** (0,65 - 1,08)	0,187	**0,82** (0,61 - 1,10)	0,203	**0,90** (0,71 - 1,13)	0,360	**0,71** (0,55 - 0,94)	**0,021**	**0,77** (0,57 - 1,04)	0,103
Região Autónoma dos Açores	**0,86** (0,67 - 1,11)	0,266	**0,97** (0,76 - 1,24)	0,812	**0,87** (0,65 - 1,16)	0,348	**1,00** (0,79 - 1,26)	0,990	**0,85** (0,60 - 1,22)	0,389	**0,94** (0,66 - 1,34)	0,719
Tipologia área urbana												
Rural	**1,14** (1,00 - 1,29)	0,063	**1,11** (0,98 - 1,27)	0,113	**1,23** (0,98 - 1,55)	0,087	**1,21** (0,97 - 1,51)	0,105	**1,05** (0,80 - 1,38)	0,728	**1,03** (0,83 - 1,28)	0,770
Urbana *	ref	-	ref	-	ref	-	ref	-	ref	-	ref	-
Estado civil												
Solteiro *	ref	-	ref	-	ref	-	ref	-	ref	-	ref	-
Casado ou União de facto	**2,53** (2,14 - 2,99)	**<0,001**	**1,50** (1,29 - 1,75)	**<0,001**	**2,55** (1,74 - 3,73)	**<0,001**	**1,33** (0,97 - 1,82)	0,089	**2,55** (1,74 - 3,72)	**<0,001**	**1,76** (1,24 - 2,50)	**0,004**
Divorciado	**1,78** (1,37 - 2,32)	**<0,001**	**1,09** (0,84 - 1,42)	0,533	**1,70** (1,07 - 2,70)	**0,033**	**0,94** (0,58 - 1,51)	0,796	**1,89** (1,21 - 2,96)	**0,009**	**1,31** (0,89 - 1,93)	0,175
Viúvo	**3,46** (2,79 - 4,30)	**<0,001**	**1,53** (1,21 - 1,93)	**0,001**	**3,87** (2,97 - 5,04)	**< 0,001**	**1,31** (1,06 - 1,62)	**0,018**	**3,10** (1,92 - 5,00)	**< 0,001**	**1,61** (1,00 - 2,58)	0,059

Tabela 4 – Razão de prevalência bruta e ajustada de síndrome metabólica, estratificada por sexo, e respetivos intervalos de confiança a 95%, ponderada para a população portuguesa entre 25 e 74 anos. (2015) (Tabela 4: parte 2 de 2)

Variável	Total				Feminino				Masculino			
	RP (IC 95%)	*p*	aRP † (IC 95%)	*p*	RP (IC 95%)	*p*	aRP ‡ (IC 95%)	*p*	RP (IC 95%)	*p*	aRP ‡ (IC 95%)	*p*
Escolaridade												
Analfabeto / 1º ciclo	**3,34** (2,80 - 3,99)	**<0,001**	**1,76** (1,46 - 2,11)	**< 0,001**	**4,16** (2,90 - 5,96)	**< 0,001**	**1,88** (1,38 - 2,55)	**< 0,001**	**2,51** (1,75 - 3,60)	**< 0,001**	**1,53** (1,07 - 2,18)	**0,027**
2º ciclo / 3º ciclo	**1,83** (1,46 - 2,31)	**<0,001**	**1,45** (1,17 - 1,78)	**0,002**	**1,96** (1,29 - 3,00)	**0,004**	**1,39** (0,96 - 2,03)	0,092	**1,59** (1,09 - 2,31)	**0,022**	**1,37** (0,97 - 1,94)	0,084
Secundário	**1,56** (1,28 - 1,91)	**<0,001**	**1,46** (1,23 - 1,74)	**< 0,001**	**1,32** (0,86 - 2,02)	0,213	**1,32** (0,89 - 1,96)	0,174	**1,63** (1,19 - 2,24)	**0,005**	**1,51** (1,12 - 2,03)	**0,011**
Ensino superior *	ref	-	ref	-	ref	-	ref	-	ref	-	ref	-
Trabalho												
Trabalho remunerado *	ref	-	ref	-	ref	-	ref	-	ref	-	ref	-
Desempregado	**1,39** (1,14 - 1,68)	**0,002**	**1,12** (0,95 - 1,32)	0,175	**1,58** (1,08 - 2,31)	**0,024**	**1,24** (0,91 - 1,68)	0,191	**1,30** (1,01 - 1,68)	**0,048**	**1,08** (0,82 - 1,44)	0,591
Outra sem atividade profissional	**2,22** (1,93 - 2,54)	**< 0,001**	**1,06** (0,89 - 1,25)	0,512	**3,13** (2,52 - 3,90)	**< 0,001**	**1,27** (0,98 - 1,65)	0,082	**1,62** (1,35 - 1,94)	**< 0,001**	**0,85** (0,66 - 1,09)	0,211
Risco pobreza												
Não suporta despesa inesperada	**1,19** (1,04 - 1,37)	**0,016**	**1,04** (0,94 - 1,16)	0,432	**1,29** (1,10 - 1,51)	**0,003**	**1,06** (0,95 - 1,18)	0,294	**1,14** (0,92 - 1,41)	0,234	**1,03** (0,85 - 1,24)	0,792
Suporta despesa inesperada *	ref	-	ref	-	ref	-	ref	-	ref	-	ref	-

RP: razão de prevalência bruta; aRP: razão de prevalência ajustada; IC 95%: intervalo de confiança a 95%; *p*: valor-*p*

* Categoria de referência.

† Ajustada para sexo e idade; variáveis Trabalho e Risco pobreza também ajustadas para nível de escolaridade.

‡ Ajustada para idade; variáveis Trabalho e Risco pobreza também ajustadas para nível de escolaridade.

participantes com idade superior aos 74 anos e nos quais a prevalência de SM é mais alta. A nível internacional, outros estudos estimaram prevalências semelhantes em Espanha[3] (31%) e Estado Unidos da América[13] (34%).

Entre os indivíduos com SM, as componentes mais presentes foram o perímetro da cintura aumentado e HTA, semelhante ao verificado em estudos internacionais realizados pelo consórcio *Metabolic Syndrome and Arteries Research* (MARE)[7] e projeto *Monica Risk, Genetics, Archiving and Monograph* (MORGAM).[27] No presente estudo, a frequência da componente de perímetro da cintura aumentado foi mais elevada, possivelmente pela utilização de um ponto de corte mais baixo, decorrente de várias organizações considerarem existir aumento do risco de doenças cardiovasculares e diabetes tipo 2 para valores iguais ou superiores a 94 cm nos homens e iguais ou superiores a 80 cm nas mulheres.[2]

Na análise bivariável, observaram-se diferenças com significado estatístico na prevalência de SM entre as categorias das variáveis 'grupo etário', 'estado civil', 'escolaridade' e 'condição perante o trabalho', tanto na população total como em cada um dos sexos. As diferenças entre sexos verificaram-se no 'risco de pobreza' - significativo apenas para a população total e mulheres. As diferenças entre sexos verificaram-se no 'risco de pobreza' - significativo apenas para a população total e mulheres.

Após ajustamento na análise multivariável, apenas se observaram diferenças para as variáveis 'grupo etário', 'estado civil' e 'escolaridade'. Não se verificou uma diferença na prevalência de SM entre sexos. O estudo do consórcio MARE[7] observou uma diferença entre sexos muito variável nos países analisados, com uma prevalência global da SM ligeiramente superior no sexo feminino (24,6% *vs* 23,9%, $p < 0,001$). Os estudos VALSIM e PORMETS verificaram uma maior prevalência da SM nas mulheres, podendo esta diferença dever-se, novamente, ao facto do presente estudo não incluir indivíduos acima dos 74 anos. Os estudos VALSIM e PORMETS encontraram uma prevalência mais elevada nas mulheres apenas nos grupos etários acima dos 49 anos, e esta diferença acentuava-se com o aumento da idade.[9,28] Esta maior prevalência da SM nas mulheres apenas nos grupos etários acima dos 49 anos pode dever-se ao aumento acentuado da pressão arterial após a

menopausa, que inicia uma diminuição mais rápida da função endotelial nas mulheres.[27] Isto significa que a SM atinge uma maior proporção de indivíduos do sexo masculino precocemente, expondo-os prolongadamente a estes fatores de risco. Desta forma, será importante ter em consideração este grupo populacional e intervir precocemente para minimizar potenciais consequências a nível metabólico e cardiovascular.

Se tivermos em consideração a variável 'grupo etário', a prevalência da SM é progressivamente maior à medida que aumenta a idade dos indivíduos. Esta associação é transversal a todos os estudos e deve-se em grande parte à acumulação de problemas de saúde relacionados com o envelhecimento, entre eles várias das componentes da SM, como a HTA ou a hiperglicemia.

A presença de SM mostrou-se, nos homens, estar associada ao estado civil casado/unido de facto, e nas mulheres, às viúvas. Relativamente à saúde em geral, a literatura parece indicar que os indivíduos casados têm melhores resultados em saúde comparativamente aos não casados (inclui nunca casados, divorciados e viúvos).[29] No que respeita especificamente à relação entre estado civil e SM os dados são escassos e, tanto o estudo PORMETS[8] como outro estudo que utilizou uma amostra de habitantes do Porto,[30] não encontraram diferenças entre casados e não casados relativamente à prevalência de SM. Além do estado civil, poderão estar envolvidos fatores culturais, psicológicos ou da qualidade do casamento,[31] que possibilitem a interpretação desta diferença entre sexos. As questões relacionadas com a predominância da síndrome metabólica entre sexos e a sua evolução ao longo do ciclo de vida, bem como os fatores envolvidos nas diferenças encontradas entre os distintos estados civis, merecem estudos mais direcionados e aprofundados para uma melhor compreensão destas temáticas.

No presente estudo foi possível verificar que um baixo nível de escolaridade está associado a uma maior prevalência de SM. Este efeito foi mais evidente nos indivíduos analfabetos/1º ciclo, sendo mais pronunciado nas mulheres que nos homens. A relação entre educação e saúde é bem conhecida, tendo sido identificada em vários estudos internacionais sobre SM,[12–14] estando mediada por fatores o como rendimento, acesso a recursos, competências sociais e psicológicas, e literacia.[32,33]

Limitações e potenciais vieses

Dada a natureza transversal deste estudo, é possível a existência de viés de causalidade reversa, uma vez que não permite estabelecer uma relação temporal entre as associações encontradas.

A possibilidade de viés de seleção foi minimizada pelo desenho da amostra do INSEF que incluiu seleção aleatória dos participantes e estratificação por região e tipologia de área urbana, fortalecendo a sua representatividade. Apesar da taxa de participação (43,9%) ter sido acima do valor esperado e para o qual o INSEF foi planeado,[16] podem existir diferenças entre os indivíduos que aceitaram participar e aqueles que não o fizeram. Uma avaliação preliminar não encontrou diferenças significativas entre participantes e não participantes para a maioria das variáveis analisadas.[10]

Um potencial viés de informação prende-se com o facto da definição harmonizada de SM referir que o sangue colhido para análises clínicas deve ser obtido em jejum, mas a participação no INSEF ter ocorrido sem esta obrigatoriedade. Comparando a proporção de indivíduos da amostra que cumprem os critérios das diferentes componentes da SM no presente estudo e nos estudos PORMETS[8] e VALSIM,[9] é possível verificar que as maiores diferenças se verificam nas componentes não afetadas pela existência ou ausência de jejum (perímetro da cintura, tensão arterial e colesterol HDL). Na avaliação da trigliceridemia, a proporção é bastante semelhante entre os três estudos (27,7% *vs* 29,4% *vs* 30,2%), e na componente da glicemia/HbA1c existe maior proximidade entre os valores obtidos no presente estudo e no estudo PORMETS (27,7% *vs* 29,4%) que no estudo VALSIM (19,0%). De referir que no estudo VALSIM o ponto de corte para a componente glicemia foi superior (> 110 mg/dL) ao da definição harmonizada (> 100 mg/dL), o que pode justificar a menor proporção observada.

No que refere à avaliação da trigliceridemia sem jejum garantido, esta situação já se verificou noutros estudos sobre SM em que os autores referem pontos de corte alternativos entre os 200 mg/dL[34] e os 175 mg/dl,[20,35,36] ou mesmo a utilização do habitual ponto de corte de 150 mg/dL.[37] Neste estudo optou-se por substituir o ponto de corte da definição harmonizada (150 mg/dL) por um ponto de corte superior (175 mg/dL), para minimizar erros de classificação.

A glicemia não foi medida no INSEF, tendo sido analisada a HbA1c como medida indicadora da glicemia média nas últimas oito a 12 semanas. Apesar desta limitação, a evidência atual não sugere excessivos erros de classificação nesta alteração à definição de SM. Assim, neste estudo, a componente da glicemia em jejum ≥ 100 mg/dL foi substituída pela HbA1c ≥ 5,7%. Este ponto de corte deriva da definição de pré-diabetes da American Diabetes Association[38] e outros estudos[39,40] que, em termos de risco de desenvolver diabetes no futuro, consideram equivalentes a glicemia em jejum ≥ 100 mg/dL e a HbA1c ≥ 5,7%. Outros estudos mostraram uma concordância superior a 90% na classificação dos indivíduos como tendo ou não a SM segundo a definição harmonizada e utilizando a glicemia em jejum ≥ 100 mg/dL ou a HbA1c ≥ 5,7%.[41,42]

A ausência de informação sobre a toma de medicação para hipertrigliceridemia e c-HDL diminuído é também uma limitação deste estudo, podendo originar erros de classificação nestas componentes da SM.

Neste estudo não foram avaliados determinantes de saúde com relevo para a temática da síndrome metabólica como a dieta, atividade física e hábitos tabágicos. Outros parâmetros analíticos com possível relação com a SM, deviam também ter sido levados em conta, nomeadamente, o colesterol de lipoproteínas de baixa densidade e de lipoproteínas de muito baixa densidade,[43] a uricemia,[44] a creatininemia[45] e os níveis de sódio[46] e potássio.[47] A análise

destas relações constitui também uma importante área para futuros estudos.

CONCLUSÃO

A SM afeta uma grande proporção da população portuguesa, constituindo um problema de saúde pública pela sua associação a doenças cardiovasculares e diabetes tipo 2. Este estudo permitiu identificar relações da SM com o sexo, grupo etário, nível de escolaridade e estado civil dos indivíduos. Em especial, o facto da SM ser mais frequente nos indivíduos com menor escolaridade sugere que a educação, para além do impacto que tem no desenvolvimento pessoal e nas relações sociais, pode potenciar a adoção de um estilo de vida mais saudável com repercussões a nível da saúde. Por outro lado, as associações encontradas reforçam a importância de uma abordagem holística que também tenha em conta outros determinantes de saúde e parâmetros analíticos associados à síndrome metabólica e que não foram avaliados neste estudo.

CONTRIBUTO DOS AUTORES

RA: Concepção do desenho do estudo; análise e interpretação dos dados; redação do artigo.

AJS: Contribuição para a análise e interpretação dos dados; revisão crítica do artigo.

IK: Contribuição para a conceção do estudo; análise e interpretação dos dados; revisão do artigo.

BN: Contribuição para a conceção do estudo; análise e interpretação dos dados.

ACF: Interpretação dos dados; revisão crítica do artigo; aprovação da versão a publicar.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

CONFIDENCIALIDADE DOS DADOS

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

CONFLITOS DE INTERESSE

Os autores declaram não ter conflitos de interesse.

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ARTIGO ORIGINAL

Profiles on Adolescent Internet Addiction: A Taxonomy with Latent Profiling Analysis

Perfis na Dependência de Internet em Adolescentes: Análise Taxonómica de Perfis Latentes

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ABSTRACT

Introduction: Addictive use of the Internet among adolescents has been linked to a negative psychosocial development, but more detailed information about Internet addiction (IA) profiles is warranted. The aim of this study was to identify IA profiles in adolescents based on psychometric properties from the Internet Addiction test (IAT), and to assess the associations between the profiles and personal/social behaviors.

Material and Methods: A cross-sectional study was performed at public schools from a Portuguese region, using a survey that included the IAT. We performed a latent profiling analysis to identify the profiles of adolescent based on the six IAT dimensions.

Results: From the 1915 responses, students' mean age was 15 ± 1.82 years, 53% were female. IA was found in 16.5%. Four models were estimated with latent profiling analysis. Analysis of the models by fit statistics, integrated completed likelihood and Lo-Mendell-Rubin likelihood ratio test, indicated a better solution with four profiles: Profile 1 – Worrisome lack of control users, Profile 2 – Balanced users, Profile 3 – Worrisome anticipation users, Profile 4 – Problematic users.

Conclusion: This study provides a characterization of different patterns in adolescents' traits and behaviors associated with Internet addiction. Preventive approaches may be useful to reduce IA.

Keywords: Adolescent; Adolescent Behavior; Internet Addiction Disorder; Online Social Networking; Portugal

RESUMO

Introdução: A dependência da Internet em adolescentes tem sido associada a problemas no seu desenvolvimento psicossocial. Porém, a literatura carece de dados sobre diferentes perfis do uso de Internet. Este estudo pretendeu identificar perfis de dependência de Internet (DI), baseado nas características psicométricas do *Internet Addiction test* (IAT), verificando associações entre os perfis e comportamentos sociais.

Material e Métodos: Estudo transversal realizado em escolas públicas de uma região Portuguesa mediante questionário que incluiu o IAT. Realizou-se uma análise de perfis latentes (APL) para identificar perfis de adolescentes, com base nos seis domínios do IAT.

Resultados: Dos 1915 participantes, a idade média foi 15 ± 1,82 anos; 53% eram do sexo feminino. Identificou-se DI em 16,5%. A análise de modelos por qualidade de ajuste e rácio de verossimilhança de Lo-Mendell-Rubin revelou um modelo adequado com 4 perfis: 1 – Utilizadores com dificuldade de controlo; 2 – Utilizadores equilibrados; 3 – Utilizadores com problemas de antecipação; 4 – Utilizadores problemáticos.

Conclusão: Este estudo permitiu a caracterização de diferentes padrões e comportamentos de adolescentes na DI, pelo que se alerta para uma abordagem preventiva na redução da DI.

Palavras-chave: Adolescente; Comportamento do Adolescente; Perturbações de Adição à Internet; Portugal; Redes Sociais Online

INTRODUCTION

Technology is fast evolving with enhanced access to all kinds of information and resources through the Internet.[1] It has become an essential tool in our daily social, professional and academic life, among others. However, its excessive use has raised concerns about potential harmful health-related consequences,[2] especially within vulnerable groups of people, such as adolescents. It is estimated that close to 75% of European adolescents spend up to four hours a day on online activities.[3,4] Moreover, since they have not entirely developed their critical thinking skills and sense of boundaries, addiction is more likely in this age group. Kimberly Young firstly mentioned Internet addiction (IA) in 1996. Although ongoing research continues on this subject, IA classification is still controversial, with empirical studies providing inconsistent criteria to define IA.[5] Different scales have been used to assess IA, of which Young's Internet Addiction test (IAT) is one of the most used and accepted.[3] This test evaluates the degree to which Internet use affects daily routine, social life, productivity, sleeping patterns, and feelings. In Portugal, few studies have reported adolescent IA rates, ranging roughly from 16% - 19%.[3,6,7] This trend was slightly higher than the previously reported margins of Internet addiction, using the same tool.[8]

Several studies using the IAT have shown a negative impact of Internet addiction in adolescents' psychosocial development,[9,10] affecting academic performance, family relationships, and emotional development. Most of the evidence on the effects of excessive Internet use concerns health, namely obesity and lack of sleep. More recently, a focus on the influence of parental control and other

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psychosocial factors on IA has been explored, with results indicating a negative association with parental control. When students reported having any parental control over their Internet use, Internet addiction was less likely to occur.[6]

To better understand how psychologic factors may influence the risk of IA, studies were conducted to assess the widely used psychometric properties of the IAT. From these, six main dimensions that factor heavily on IA were identified – salience, excessive use, neglect of work, anticipation, lack of control, and social life neglect. Salience, excessive use, lack of control, and social life neglect are positively correlated with increased Internet use. Similarly, younger and more recent Internet users were shown to have more problems with neglecting work or social life than longer-term users.[11]

Since these issues are a growing concern in our modern world, identifying contributing factors is essential to improve prevention and intervention in IA. Hence, the aims of our study are to ascertain different patterns in the characteristics and behaviours of adolescents with Internet addiction in order to identify profiles; Identify which psychometric properties from the IAT are correlated with personal and social behaviours in our sample of adolescents.

MATERIAL AND METHODS

Study design and sample

An observational and analytical cross-sectional survey-based study was performed in the public schools of Cova da Beira region. Both elementary and secondary schools, accounting for 3788 students from grades seven through 12, were invited to participate. Approval by the Portuguese Ministry of Education and the Portuguese Data Protection Authority was obtained before the study. Written consent was obtained from all participants or, where it was applied, from their legal guardians. Participating students were asked to fill in a questionnaire under their teacher's supervision. The questionnaire had three different sections. The first one addressed sociodemographic factors, health-related questions, and lifestyle habits regarding Internet usage in and out-of-school. The second and third sections consisted of two scales that approached general well-being and Internet addiction risk. Students who did not get/return a signed consent form and those older than 17-years and 365 days were excluded from the study.

Internet addiction assessment

Internet Addiction was assessed by using a previously validated Portuguese version of Young's Internet Addiction Test,[2] which consisted of 20 questions with possible answers ranging from "1" (Never) to "5" (always), along with the "not applicable" option of "0".[2] Since each question followed a Likert-scale answer, the cut-off of > 2.5 points was established to ascertain an increased usage of Internet (as seen in Fig. 1). The maximum collective score was 100, with higher values indicating greater risk from Internet usage.[12] Average Internet users (IAT 0 - 50) and Internet-addicted users (IAT 51 - 100) were characterized accordingly. The collected data produced a highly consistent internal reliability (Cronbach α = 0.85). The IAT is composed of 20 items

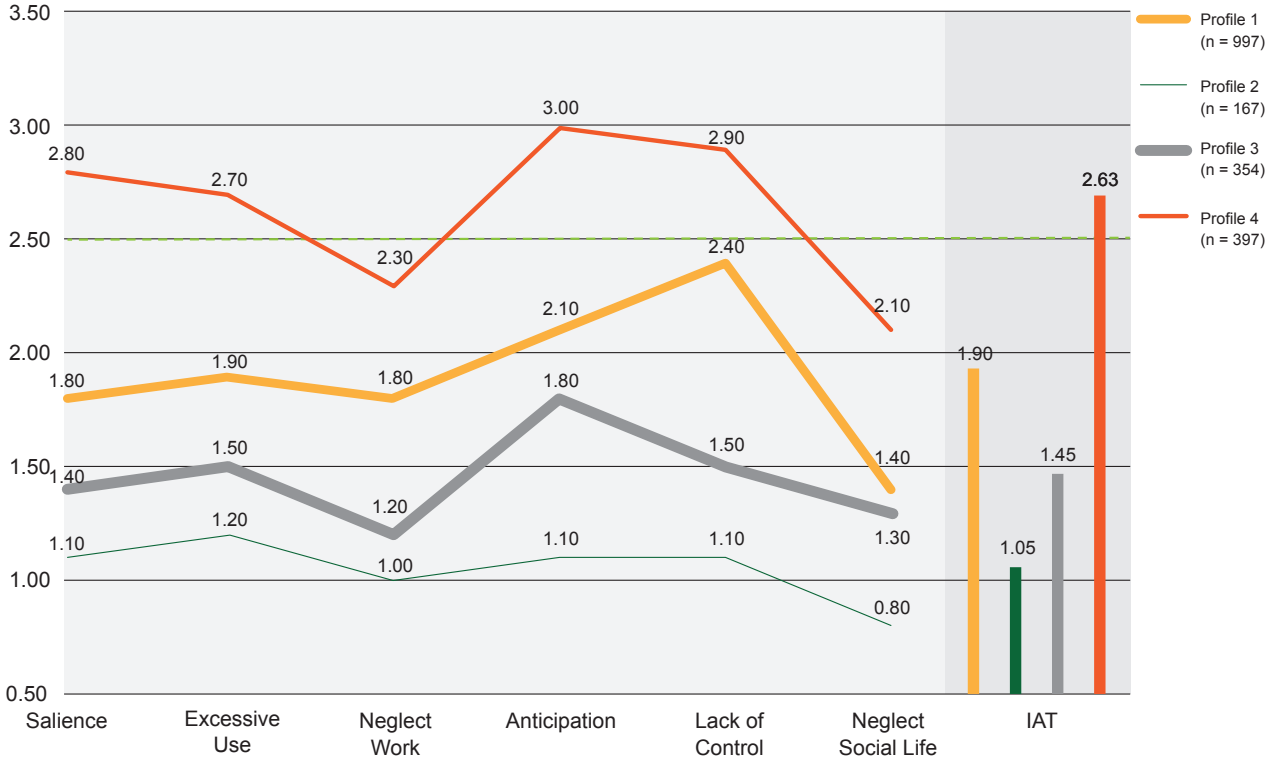


Figure 1 – Means by profile

*: green-dashed line represents the cut-off for increased Internet use

and was primarily developed as a unidimensional instrument. Meanwhile, different validations have shown a factor structure with a variable number of dimensions. Kimberly Young recommended six dimensions.[11,13,14]

- Salience (items 10, 12, 13, 15, and 19) - high scores on these items suggest that the "respondent most likely feels preoccupied with the Internet, hides the behavior from others, and may display a loss of interest in other activities and/or relationships only to prefer more solitary time online";
- Excessive Use (items 1, 2, 14, 18, and 20) - High ratings on these questions indicate that the "respondent engages in excessive online behavior and compulsive usage, and is intermittently unable to control time online that he or she hides from others";
- Neglect Work (item 6, 8, and 9) – the subjects' "performance and productivity are most likely compromised due to the amount of time spent online and the respondent may become defensive or secretive about the time spent online";
- Anticipation (items 7 and 11) - indicates that "respondent most likely thinks about being online when not at the computer and feels compelled to use the Internet when offline";
- Lack of Control (items 5, 16, and 17) - high scores on these items suggest that the "respondent has trouble managing his or her online time, frequently stays online longer than intended, and others may complain about the amount of time he or she spends online";
- Neglect Social Life (item 3 and 4) - the subject "most likely uses online relationships to cope with situational problems and/or to reduce mental tension and stress." and "uses the Internet to establish social connections that may be missing in his or her life".

General demographics

General sociodemographic data were obtained alongside specific psychosocial variables (Table 1). An adequate amount of sleeping time during weekdays was classified according to the guidelines of the American Academy of Pediatrics and presented as recommended (9 - 12 hours in children aged 8 - 12 years, and 8 - 10 hours for children aged 13 - 18 years) or less than recommended.[15] Parental behaviour was assessed by asking participants if their parents controlled overall Internet use and online time, and online-viewed content.

Latent profile analysis

We performed a latent profile analysis[16] (LPA) using the Mclust package[17] with R version 3.5.3 (R Core Team 2019) to identify profiles of teenagers with similar values in the six Internet addiction dimensions. LPA is a latent variable technique with the same objective as cluster analysis - to identify groups of observations with similar values on grouping variables[18] but with the difference that LPA is model-based and cluster analysis is not.[19] Therefore, LPA has the advantages of (1) accommodating data with a variety of forms; (2) using more rigorous criteria to decide the final model, including fit measures; (3) using the model parameter estimates of one sample to compute the posterior probabilities and assign cluster membership to observations in other samples.[19] This latter advantage allows the classification of individuals into the groups in posterior studies.

RESULTS

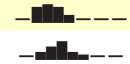
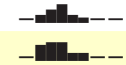
Descriptive statistics

A total of 1915 eligible responses were obtained. The participants' mean age was 15 years (SD = 1.82). The prevalence of IA was 16.5% in our sample, with a mean average IAT score of 39 (SD = 12).

All correlation coefficients between IAT dimensions and IAT score were statistically significant (Table 1). The highest correlations were obtained between IAT score and neglect social life (0.84) and salience (0.78), followed by the correlation between excessive use and lack of control (0.58), and then excessive use and salience (0.55). The lowest correlation was verified between anticipation and neglect of social life (0.21). Age was positively correlated with IAT score and all IAT dimensions, except salience and lack of control. BMI z-scores showed no significant correlation with IAT.

As shown in Table 2, there was a slight predominance of females; 24% of the students self-reported health issues and 46% reported not practicing any extracurricular sports activities. The majority stated they slept well and had no

Table 1 – Descriptive statistics and correlations. Mean, standard deviation, distribution, and correlation across IAT dimensions.

Variable	n	Mean	Median	SD	Histogram	1	2	3	4	5	6	7	8	9
1. Salience	1915	1.91	1.8	0.76		1								
2. Excessive Use	1915	1.95	1.8	0.69		0.55*	1							
3. Neglect Work	1915	1.78	1.8	0.76		0.40*	0.52*	1						
4. Anticipation	1915	2.21	1.8	0.93		0.48*	0.46*	0.36*	1					
5. Lack of Control	1915	2.28	1.7	0.91		0.46*	0.58*	0.43*	0.39*	1				
6. Neglect Social Life	1915	1.52	2	0.88		0.31*	0.26*	0.23*	0.21*	0.12*	1			
7. IAT	1915	1.71	2.3	0.67		0.78*	0.48*	0.38*	0.41*	0.34*	0.84*	1		
8. Age	1915	15	15	1.82		0.01	0.07*	0.15*	0.07*	-0.07*	0.20*	0.14*	1	
9. BMI (z-score)	1775	0	-0.02	0		0.00	-0.03	0.03	-0.02	-0.02	0.04	0.03	0.24*	1

*: Pearson correlation with $p < 0.01$; 1: Salience; 2: Excessive Use; 3: Neglect Work; 4: Anticipation; 5: Lack of Control; 6: Neglect Social Life; 7: IAT: Internet Addiction test; 8: Age; 9: BMI [z(score)]: Z-score for body mass index

Table 2 – Sample description and *t*-tests

Variable	n	%	SAL	EXU	NGW	ANT	LOC	NSL	IAT	Age (mean in years)	BMI (mean z-score)
Gender											
Female	1019	53	1.96*	1.95	1.82†	2.19	2.22†	1.74*	1.85*	15.02	-0.02
Male	891	47	1.87	1.94	1.74	2.23	2.32	1.32	1.59	14.93	0.03
With health issues											
No	1443	76	1.90	1.95	1.78	2.22	2.25	1.53	1.72	14.94	-0.04*
Yes	454	24	1.96	1.94	1.78	2.20	2.36	1.48	1.72	15.08	0.14
Sleeps well											
No	171	9	2.06*	2.15*	2.01*	2.23	2.37	1.52	1.79	15.64*	0.14†
Yes	1706	90	1.90	1.92	1.76	2.21	2.27	1.51	1.70	14.90	-0.02
Practices sports											
No	873	46	1.96†	1.96	1.80	2.25	2.33†	1.52	1.74	15.24*	0.04
Yes	1035	54	1.88	1.93	1.77	2.18	2.23	1.51	1.70	14.75	-0.03
Hard to make friends											
No	1627	85	1.89*	1.93†	1.76†	2.20	2.27	1.54*	1.71	14.91*	-0.03†
Yes	276	15	2.05	2.04	1.87	2.30	2.29	1.38	1.72	15.34	0.14
Parents control Internet											
No	961	50	1.96*	2.00*	1.86*	2.26†	2.26†	1.59*	1.77*	15.68*	0.04
Yes	943	50	1.86	1.88	1.70	2.16	2.29	1.45	1.66	14.26	-0.04

*: $p < 0.01$; †: $p < 0.05$
SAL: Salience; EXU: Excessive Use; NGW: Neglect Work; ANT: Anticipation; LOC: Lack of Control; NSL: Neglect Social Life; IAT: Internet Addiction test; BMI: body mass index

difficulty making friends. Half of the students reported no parental control over their Internet use. It was noteworthy that the variable with a stronger association with IAT was parental control. Indeed, lack of parental control was significantly associated with higher scores on all IAT dimensions, except lack of control. While health problems showed no significant association with IAT, sleeping well and sports practice were associated with lower scores on some IAT dimensions.

Model estimation and selection

Profiles of teenagers with similar values in the six Internet Addiction dimensions were identified with latent profile analysis (LPA). Four models were estimated with LPA using maximum likelihood, ranging from two to seven profiles. We used three criteria to find the optimal latent profile solution.[18] Firstly, we examined fit statistics (Table 5), namely the Akaike Information criterion (AIC) and the Bayesian Information criterion (BIC). Secondly, we considered overall uncertainty in posterior classification, assessed by entropy[20] included in the integrated completed likelihood – ICL.[21] Finally, we used the Lo-Mendell-Rubin[22] likelihood ratio test (LRT) and the bootstrap likelihood ratio test (BLRT) with $p < 0.01$. AIC, BIC, and ICL decreased until the model with four profiles. The five-profiles model showed low overall uncertainty in posterior classification, with entropy = 0.836. The Lo-Mendell-Rubin likelihood ratio test (LRT) showed that the model with four profiles (LRT = 57.33, $p < 0.0001$, see Table 5) was better than the model with three (LRT = 145.18, $p < 0.0001$) and better than the model with five profiles (LRT = 123.10, $p < 0.0001$).

Classification accuracy of the model

The probabilities of correct classification of observations are shown in the main diagonal of Table 6, ranging from 0.893 to 0.997.

We conducted a supervised classification with eigenvalue decomposition discriminant analysis – EDDA[23] to further assess the correct classification of observations. A model was fit with a randomly chosen training subsample. This model was then used to classify data in the testing subsample, with data assigned to the profile corresponding to the model with the highest posterior probability.[16]

The classification accuracy of the testing subsample was 96%, as shown in Table 7. Classification accuracy is much greater than one-fourth of the achieved by chance [24] when considering the maximum chance criterium[25] of 50.6%. The value of Press's Q = 1545.9 (N = 575, n = 552, K = 4) is greater than 6.63 (critical value from the chi-square distribution with one degree of freedom and confidence of 99%), thus confirming that results exceeded the classification accuracy expected by chance.[24]

Description of profiles

The means for each Internet addiction dimension and the global IAT and profile size are plotted by profile in Fig. 1. Profiles are described in the following sub-sections:

Profile 1 – Worrisome lack of control users - the largest group, representing 52% of the sample's teenagers (n = 997). This group scores negatively (less than 2.5, below the green, dotted bottom line) in all dimensions (Table 3), although close to the bottom line, hence its members are called worrisome lack of control users. Despite all these

Table 3 – Means and standard deviations of Profiles and ANOVA tests

Profile	SAL	EXU	NGW	ANT	LOC	NSL	IAT
P1	1.85 (0.52)	1.91 (0.48)	1.88 (0.63)	2.19 (0.75)	2.46 (0.69)	1.44 (0.71)	1.96 (0.31)
P2	1.12 (0.22)	1.2 (0.23)	1.07 (0.16)	1.19 (0.32)	1.19 (0.26)	0.84 (0.45)	1.1 (0.13)
P3	1.44 (0.34)	1.56 (0.33)	1.22 (0.27)	1.84 (0.54)	1.50 (0.40)	1.37 (0.67)	1.49 (0.19)
P4	2.83 (0.81)	2.71 (0.81)	2.33 (0.95)	3.03 (1.11)	2.97 (0.99)	2.12 (1.18)	2.66 (0.33)
F	575.888	448.338	265.143	266.323	432.916	118.867	442.392
p-value	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Standard deviations in parenthesis.
SAL: Salience; EXU: Excessive Use; NGW: Neglect Work; ANT: Anticipation; LOC: Lack of Control; NSL: Neglect Social Life; IAT: Internet Addiction test

users lacking control, they are just shy of positive values and feature the highest difference between neglect social life and the other dimensions. Neglect dimensions (both work and social life) have the smallest means in all profiles. Curiously, this profile also singles-out users with equal parental control rates or absence thereof (Table 4).

Profile 2 – Balanced users – This was the smallest group, representing 9% of the sample (n = 167). This group showed the smallest means in all six dimensions; therefore, it was named balanced users. Balanced users represent the most homogeneous group, with the smallest standard deviations for all the dimensions. Interestingly, characteristics such as female predominance and highest parental control rate, compared with other profiles, are noteworthy (Table 4).

Profile 3 – Worrisome anticipation users - includes almost one-fifth of the teenagers (18%, N = 354). This group has rather small means in most dimensions, scoring slightly higher in anticipation and excessive use. For that reason, the group was named worrisome anticipation users. Here we also highlight users with the least difficulty in making friends (Table 4).

Profile 4 – Problematic users - represents 21% of participants (N = 397). This group has the highest means of all the profiles, and most of them present values above the bottom line. Besides, it was the most heterogeneous group, with the highest standard deviation across all the dimensions. This group is the only one with positive means in the Internet addiction dimensions and a positive global IAT. In this profile, a slight predominance of the male gender, more difficulty in befriending, and lower parental control rate stood out compared with the other profiles (Table 4).

Table 4 – Profiles' description and chi-squared tests

Variable	n	%	Profile 1	Profile 2	Profile 3	Profile 4
Gender‡						
Female	1019	53%	54%	59%	52%	49%
Male	891	47%	46%	40%	47%	50%
With health issues						
No	1443	76%	75%	81%	75%	76%
Yes	454	24%	25%	18%	24%	23%
Sleeps well						
No	171	9%	10%	7%	7%	9%
Yes	1706	90%	90%	92%	93%	90%
Practices sports						
No	873	46%	45%	44%	46%	48%
Yes	1035	54%	55%	54%	54%	51%
Hard to make friends†						
No	1627	85%	85%	88%	89%	82%
Yes	276	15%	15%	11%	10%	17%
Parents control Internet*						
No	961	50%	50%	44%	46%	58%
Yes	943	50%	50%	54%	53%	41%

*: $p < 0.01$; †: $p < 0.05$; ‡: $p < 0.1$

Table 5 – Model fit for the different profile solutions

Solution	AIC	BIC	ICL	LRT	BLRT
Two profiles	23612	23834	24691	362.59	0.000
Three profiles	23275	23570	24364	145.18	0.000
Four profiles	23156	23523	24323	57.33	0.000
Five profiles	23211	23564	24487	123.10	0.000
Six profiles	23027	23539	24884	69.87	0.000
Seven profiles	22983	23567	25024	55.7	0.000

AIC: Akaike Information criterion; BIC: Bayesian Information criterion; ICL: integrated completed likelihood; LRT: Lo-Mendell-Rubin likelihood ratio test; BLRT: bootstrap likelihood ratio test; VVE model: ellipsoidal, variable volume, variable shape, equal orientation bootstrap with 5000 replications

DISCUSSION

In line with previous studies,[3,26,27] our results indicated a significant rate of adolescents that are addicted to the Internet.

As previously reported, the six IAT dimensions were positively correlated.[11,13] The highest correlation was obtained between lack of control and excessive use and between salience and excessive use. These results are corroborated by previous studies.[11,28]

Collectively, we identified four main profiles of adolescents on different aspects of Internet addiction. Regarding balanced users (Profile 2), all dimensions exhibited small means, indicating a healthy use of the Internet. We observed a slightly higher score on the excessive use criteria, perhaps reflecting the widespread use of the Internet in the youth's daily life. This group had the highest proportion of females, and highest parental control. These results are in line with previous studies. A recent study reported that 'healthy users' of the Internet and smartphones also showed a higher proportion of females and a better psychosocial profile.[29] Regarding health status, Suris *et al* have reported that average Internet users reported health problems less frequently.[12] However, this was not significantly different among IA profiles in our study.

Conversely, as seen in problematic users (Profile 4), male gender, low parental control, and difficulties befriending people have been implicated as important associated factors of Internet addiction. Recent studies[27,30,31] indicate greater propensity of males to be addicted to the Internet. Also consistent with the literature is the greater influence of parental monitoring in Internet use-related problems in their children.[31] Overall, the evidence shows that parental monitoring can prevent adolescents from becoming overinvolved on the Internet.[6,32] We reported no significant highlights concerning sleep and sports in the balanced users' profile. Nonetheless, other studies have associated better sleep,[3,12] higher levels of physical activity,[12] and satisfactory peer relationships with lower levels of IA.[33] When looking at the ability to make friends, the problematic users' profile exhibited hardship. Adolescents overinvolved on the Internet show instability in significant relationships[34] and difficulty in other leisure experiences.[35] Moreover, good peer relationships are correlated with low levels of Internet addiction,[33] implying that adolescents with unsatisfactory peer relationships rely on the Internet to relieve their loneliness.

Our study also identified two specific groups of adolescents who singled-out a specific IAT dimension that was concerning. In the case of lack of control users (Profile 1), a trend towards an increased rate of lack of control regarding Internet use was seen. Poor control regarding Internet use has been associated with users' increased sensitivity to rewards and, on the other hand, insensitivity towards punishments that derive from decision-making tasks.[36] Moreover, effective regulation, which is how we self-regulate our actions, may change one's emotional state, and may actively be involved in the development of addictive behaviors. Interestingly, a study reported that the ability to regulate affection predicted time using the Internet, whereas other psychological problems such as depression, loneliness, or social anxiety did not.[37] Male adolescents in this group were also more prone to lack of control than females, which is congruent with males being more engaged in high-risk online behaviors.[6]

Regarding anticipation as a troublesome problem (Profile 3), it is known that craving or anticipation of pleasurable relief is a subjective phenomenon, almost exclusively based on self-reports.[36] Notwithstanding, craving criteria have been linked to behavioural addictions such as IA.[36] In profile three, we noticed an increase in the score of anticipation criteria compared with other factors. Furthermore, this group was also linked to a lower degree of parental control of Internet use. As mentioned before, parental control has a protective effect on Internet addiction among adolescents[6] and alludes to two different kinds of control – psychological and behavioural. The latter, which deals with solicitation and restriction actions, was shown to be a healthier approach by parents in order to keep their children's addiction in check.[6,38] Since anticipation is largely a behavioral problem, this group's results may be associated with parental control status.

Given that IA relates to these worrisome psychological

Table 6 – Average latent profile probabilities for most likely profile membership (row) by latent profile (column)

Profile	1	2	3	4
1	0.997	0.000	0.000	0.003
2	0.000	1	0.000	0.000
3	0.107	0.000	0.893	0.000
4	0.077	0.000	0.009	0.915

Table 7 – Results of the supervised classification

	Predicted in training (n = 1340)				**Predicted in testing** (n = 575)			
Profile	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
1.	704	0	2	0	290	0	0	1
2.	0	109	3	0	0	55	0	0
3.	17	0	225	0	12	0	100	0
4.	16	0	1	263	9	0	1	107

Main diagonals contain correct classifications.
Classification error in the training set is 2.9% and 4.0% in the testing set.

traits it is important to consider what interventions are available to address these issues. Several studies have been conducted to assess how pharmacological and non-pharmacological therapies may mediate Internet addiction.[39] Results have not been consensual or generalizable given different methodologies, especially in adults. However, in adolescents and young adults, the literature has shed light on how to tackle this matter, and family-based approaches seem to offer advantages in addiction.[39] Family therapy focused on resolving conflicts, improving communication, reframing addiction symptoms, and discussing states of change showed significant reductions in Internet addiction severity.[40–42] Conversely, correctional programs seem to be largely ineffective. Cognitive-behavioral and motivational interventions may also help mediate Internet addiction since they are already used effectively in other mental health conditions.[43] Whenever modifiable risk factors for IA are identified, a few of which this study highlighted (eg.: low parental control, hardship in befriending), specific interventions should be taken into consideration when developing prevention and intervention strategies for IA.

Some limitations to our study should be noted. Firstly, this was a cross-sectional study, which means causal inferences cannot be established. Secondly, as this was a survey-based study with self-reported answers, a response bias needs to be considered. Participants using the self-report scales may misunderstand the questions or try to create a positive or negative impact by giving false or misleading responses depending on social desires. Finally, the sample was composed of students in public schools and may not represent all adolescents.

Despite limitations to this study, identifying clusters of adolescents with specific alarming symptoms toward a worsening IA can be a helpful tool for further research. Since this subject is an increasing problem among adolescents it is important to develop multidisciplinary preventative interventions for clinicians, families, schools, and students in order to enhance their awareness about the unfavourable traits of IA.

CONCLUSION

This study's results are an important step in characterizing different patterns in adolescents' characteristics and behaviors associated with Internet addiction and to raise awareness of preventive actions to decrease IA. Latent class analysis-based classification rather than total score-based classification may provide more accurate and detailed information about participants' Internet addiction profiles.

Healthcare professionals dealing with adolescents should be aware of the increasing online and social media platforms emerging nowadays and should be involved in prevention efforts to help adolescents avoid Internet addiction disorder.

AUTHORS CONTRIBUTION

MVM: Conception/design of the work. Acquisition, analysis, and interpretation of data for the work. Draft of the paper and critical review.

RGR: Acquisition, analysis, and interpretation of data for the work. Draft of the paper and critical review.

PSC, SF: Conception/design of the work. Acquisition, analysis, and interpretation of data for the work. Draft of the paper and critical review.

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

All authors report no competing interests.

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Translation and Validation of the Clinician Administered PTSD Scale (CAPS-CA-5) for Portuguese Children and Adolescents

Tradução e Validação da Clinician Administered PTSD Scale (CAPS-CA-5) em Crianças e Adolescentes Portugueses

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ABSTRACT

Introduction: The aim of this study was to translate and validate into European Portuguese the CAPS-CA-5 (Clinician Administered PTSD Scale for Children and Adolescents), a semi-structured scale for the diagnosis of post-traumatic stress disorder in children and adolescents, according to the DSM-5 criteria.

Material and Methods: This study was developed in three stages. In the first stage, the translation and back-translation of CAPS-CA-5 into European Portuguese was carried out. In the second stage, the version obtained in the previous step was subjected to a pre-test. In the third stage, the final version of CAPS-CA-5, the KIDCOPE questionnaires and the Depression, Anxiety and Stress Scale-Children were applied to 101 children who had experienced at least one potentially traumatic event. The children included in this study were between seven and 18 years old and had a follow-up period in a Child Psychiatry or Pediatrics Clinic in one of the three hospitals involved in this project of at least one month.

Results: Regarding the confirmatory factor analysis, our results show that the CAPS-CA-5 is a suitable psychometric instrument to assess the diagnosis and symptoms severity of post-traumatic stress disorder according to DSM-5. Convergent validity was comparable to its original version. Although there were negative relationships with almost all of its clusters, these were not statistically significant when applied with the positive coping strategies of the KIDCOPE. The European Portuguese version of the CAPS-CA-5 showed a good internal consistency (Cronbach's α for the total scale was 0.89).

Conclusion: The European Portuguese version of CAPS-CA-5 has similar psychometric properties to its original version

Keywords: Adolescent; Child; Interviews; Portugal; Psychometrics; Stress Disorders, Post-Traumatic; Translating

RESUMO

Introdução: O objetivo deste estudo foi traduzir e validar para português europeu a CAPS-CA-5 (*Clinician Administered PTSD Scale for Children and Adolescents*), uma escala semiestruturada para o diagnóstico de perturbação de *stress* pós-traumático em crianças e adolescentes, de acordo com os critérios do DSM-5.

Material e Métodos: Este estudo foi desenvolvido em três etapas. Na primeira, foi realizada a tradução e contra-tradução da CAPS-CA-5 para português europeu. Na segunda etapa, a versão obtida anteriormente foi submetida a um pré-teste. Na terceira etapa, a versão final da CAPS-CA-5, os questionários KIDCOPE e a Escala de Depressão, Ansiedade e Stresse - Crianças foram aplicados em 101 crianças que experienciaram pelo menos um evento potencialmente traumático. As crianças incluídas neste estudo tinham entre sete e 18 anos e tinham um período de acompanhamento em consulta de Psiquiatria Infantil ou Pediatria de pelo menos um mês, num dos três hospitais envolvidos neste projeto.

Resultados: Em relação à análise fatorial confirmatória, os nossos resultados mostram que a CAPS-CA-5 é um instrumento psicométrico adequado para avaliar o diagnóstico e a gravidade dos sintomas de perturbação de stresse pós-traumático de acordo com o DSM-5. A validade convergente foi comparável à versão original. Embora tenha havido relações negativas com quase todos os seus *clusters*, estas não foram estatisticamente significativas quando aplicadas com as estratégias de *coping* positivo do KIDCOPE. A versão em português europeu da CAPS-CA-5 apresentou boa consistência interna (α de Cronbach para a escala total foi de 0,89).

Conclusão: A versão em português europeu do CAPS-CA-5 possui propriedades psicométricas semelhantes à sua versão original.

Palavras-chave: Adolescente; Criança; Entrevistas; Perturbações de Stress Pós-Traumático; Portugal; Psicometria; Tradução

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a mental disorder that can occur at any age after exposure to a traumatic event.[1,2] However, not all individuals exposed to traumatic situations develop PTSD, and several risk and protective factors are involved before, during and/or after exposure to these events. The way children and adolescents deal with these situations, that is, their coping strategies and their capacity for resilience, are one of the points of great relevance for

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the impact of these events, as they will influence the processes of adaptation to the experiences that have occurred and will shape their course and prognosis.[1,3,4]

Symptoms of PTSD commonly develop within a month after exposure to a traumatic event; however, they may appear later, being classified as late-onset PTSD when symptoms occur six months or more after such exposure.[1,2] The DSM-5 diagnostic criteria groups the symptoms of this disorder into four clusters (cluster B - Intrusion symptoms; cluster C - Avoidance symptoms; cluster D - Cognitions and mood symptoms; cluster E - Arousal and reactivity symptoms).[1] Dissociative symptoms (depersonalization, derealization) are also considered in the diagnostic criteria as specifiers. Furthermore, in order to meet the diagnosis, the previously mentioned symptoms have to cause distress or to have a negative functional impact (cluster G).[1]

PTSD is a disorder for which there is an effective treatment, and its diagnosis can be difficult, particularly in children. Different factors may contribute to its identification, namely that many patients do not look for help or when they do, often omit their symptoms.[1,2] Additionally, PTSD is frequently associated with other comorbidities, making its presentation and consequently its diagnosis more difficult.[1,2]

These difficulties can be surpassed if the symptoms are assessed by direct questioning, which can be done by using validated scales.[2] It can help to identify not only the reminders of the trauma but also dysfunctional behaviours associated with the disorder, as well as to develop strategies that might prevent its development. Consequently, therapeutic interventions can be applied more efficiently in order to reduce the symptoms and to improve the prognosis.[2]

Even though there are internationally validated tools for assessing PTSD, such as the Clinician-Administered PTSD Scale (CAPS), to our knowledge, there are no validated instruments for its assessment in children and adolescents, according to the DSM-5 criteria, in Portugal. Although originally designed for adults, there is a version for children and adolescents, the Clinician-Administered PTSD Scale, Child/Adolescent Version (CAPS-CA) which has recently been revised according to the DSM-5 criteria - CAPS-CA-5.

The CAPS-CA-5 is a semi-structured interview used to assess PTSD in children older than seven years old.[5,6] Semi-structured scales have been described as the preferred method for assessing mental disorders and the CAPS has been frequently described as the gold standard instrument for diagnosing PTSD.[5–9] The CAPS-CA has good psychometric properties[10–13]; CAPS-CA showed good internal consistency, acceptable convergent validity with other measures of PTSD [e.g. Childhood Posttraumatic Stress Reaction Index (CPTSD-RI), or Children's Revised Impact of Events Scale (CRIES-13)] and good divergent validity with other measures like the Beck Depression Inventory (BDI) or the Revised Children's Manifest Anxiety Scale (RCMAS), and good inter-rater reliability. However, to our knowledge, there are still no studies on the CAPS-CA-5 in Portugal. In this study, we aim to fill this gap in the literature and to translate and validate the CAPS-CA-5 into European Portuguese (PT-EURO), and to evaluate its psychometric properties in a sample of Portuguese children and adolescents.

MATERIAL AND METHODS

Participants

The study included 101 children and adolescents between the ages of seven and 18, who had experienced at least one traumatic event and had a follow-up period in a Child Psychiatry or Paediatrics Clinic in one of the three hospitals involved in this project (Centro Hospitalar de Lisboa Ocidental, Hospital Fernando da Fonseca, Hospital Beatriz Ângelo) of at least one month. Certain exclusion criteria were considered: difficulties in fluency in the Portuguese language, cognitive impairment or having a psychotic disorder.

In the sample, 51.5% of the participants were female, and 48.5% were male. Regarding age, the mean value was 13.6 years, with a standard deviation of 2.93 years, ranging from a minimum of seven to a maximum of 18 years old. Grouping ages, 35.6% were children (seven to 12 years old), and 64.4% were adolescents (13 to 18 years old).

Measures

CAPS-CA-5

The CAPS-CA-5 is a 30-item interview to assess DSM-5 criteria of PTSD in children and adolescents between the ages of seven and 18.[5] It is a modified version of the CAPS (for adults) that includes age-appropriate items and image response options.[5,14] The CAPS-CA-5 was designed to be administered by clinicians and clinical researchers who have a working knowledge of PTSD, but it can also be administered by appropriately trained paraprofessionals.[5,14] The interview takes 30 to 75 minutes, depending on the child's age and trauma history.[5]

Similarly to the CAPS-5, the CAPS-CA-5 assesses the 20 symptoms of PTSD grouped in clusters defined in DSM-5.[5,14,15] These items are rated on a 5-point severity scale ranging from 0 (absent) to 4 (extreme/ incapacitating).[5,14,15] In addition, the CAPS-CA-5 consists of questions regarding the onset and duration of the disturbance (Cluster F) and dissociative symptoms of depersonalization and derealization.[5,14,15] With these latter two items, a dissociative subtype of PTSD can be determined. According to the basic CAPS-5 symptom scoring rule (SEV2 rule), a symptom or impairment is considered present if its severity is rated with 2 or higher.[5,14,15] Using the DSM-5 algorithm in combination with the SEV2 rule, it is possible to establish whether or not participants meet the PTSD diagnosis.[5,14,15] In addition, by adding the 20 symptom severity scores (clusters B–E), a total PTSD symptom severity score is computed ranging between 0 and 80 with higher scores indicating higher PTSD symptom severity.[5,14,15]

Other versions of the CAPS-CA have shown good internal consistency, as verified in the study by Saltzman *et al*[13] with a sample of children aged between seven and 14 years old (Cronbach's a for the total score was 0.82), but also in the study by Diehle *et al*[11] with a sample of children aged

between eight and 18 years old (Cronbach's a for the total score was 0.83). The coefficient of the various diagnostic symptom clusters appears to range between 0.52 and 0.9, with a trend towards better coefficients in older children.[11–13] Regarding convergent validity, Carrion *et al*[10] demonstrated for children in the age range of seven to 14 years old that the CAPS-CA has acceptable convergent validity by correlating significantly with the Reaction Index (r = 0.51). In child populations older than 14, Erwin *et al*[12] and Harrington[16] found that the CAPS-CA correlated significantly with the PTSD checklist (r = 0.64) and with the Child PTSD Inventory (0.74). In the Dutch version,[11] the CAPS-CA showed moderate to strong correlations with the Children's Revised Impact of Events Scale (CRIES-13) (Pearson correlation coefficient for total score was 0.67). Regarding divergent validity, Harrington´s validation study[16] also states a good divergent validity in CAPS-CA, checking lower correlations with measures of depression (Beck Depression Inventory II, BDI), anxiety (Revised Children's Manifest Anxiety Scale, RCMAS), and behavior and emotional problems (Youth Self Report, YSR) than with self-report measures of PTSD (Child PTSD Symptom Scale, CPSS, and Children's PTSD Inventory). In the Dutch version, Diehle *et al*[11] found that correlations with the RCADS and SDQ subscales were moderate to strong (with some exceptions). As for the inter-rater reliability, it has shown excellent intraclass correlation coefficient (ICC) values, both in the original version (ICC = 0.97) and in other versions, such as the Dutch version (ICC = 0.99).[10,11]

KIDCOPE questionnaires

The KIDCOPE questionnaires evaluate coping strategies in children (7 - 12 years old) and adolescents (13 - 18 years old), with a version for each age group.[17] They are self-reported questionnaires, with 15 items in the children's version and 10 items in the adolescent version, and take 10 minutes or less to complete.[17] Coping strategies can be analysed alone or under a two-factor model (Positive/Confrontative Coping and Negative/Avoidant Coping).[17] Due to the abbreviated format of the instruments, the scope of a considerable age group, and their previous use in different populations and cultural contexts, its use is advised for several clinical and scientific applications.

Most of the studies conducted to date on the psychometric performance of KIDCOPE have been carried out in adolescents.[17] In the original instrument,[17] the results attested the temporal stability (test-retest) and the concurrent validity of the KIDCOPE questionnaires. Because only one to two items evaluate each coping strategy, the instrument's internal consistency was not analysed, and the authors hypothesized that this value was reduced.[17] The psychometric studies on the PT-EURO versions of the KIDCOPE questionnaires are currently under development, and definitive results on their psychometric performance are not yet available.[17]

Depression, Anxiety and Stress Scale - Children (EADS-C)

The Depression, Anxiety and Stress Scale for Children (EADS-C) is the PT-EURO version of the Lovibond and Lovibond's Depression Anxiety Stress Scale[18] adapted by Pais Ribeiro, Honrado and Leal[19] for children and adolescents between eight and 15 years old. It consists of 21 items, divided into three dimensions with seven items each: Depression, Anxiety and Stress.[20] The answer is given on a Likert-type scale, in which the individual evaluates the extent to which they experienced each symptom during the previous week, on a scale of four points of severity or frequency, corresponding to values from 0 to 3.[20]

The values of internal consistency, assessed using Cronbach's a, were respectively: for the Depression Scale 0.85 (0.93 in the 14-item version) in the adult version, and 0.78 in the children and adolescents version (with the item dimension correlations, corrected for overlap, ranging between 0.37 and 0.65, most of them above 0.40); for the Anxiety Scale 0.74 for the Anxiety Scale (0.83 in the 14-item version) for adults, and 0.75 in the version for children and adolescents (with item dimension correlations, corrected for overlap, varying between 0.38 and 0.58 the majority above 0.40); for the stress scale 0.81 (0.88 in the 14-item version) for adults and 0.74 in the children and adolescents version (with item dimension correlations, corrected for overlap, ranging between 0.36 and 0.56 the majority above 0.40).[20]

Procedures of data collection and analysis

This study is part of a research project on the impact of traumatic events in childhood and adolescence in Portugal. Throughout the study, the ethical and deontological principles recommended for research in the area of Health Sciences were complied with, as described in the Declaration of Helsinki, World Health Organization and European Community. First, the author's permission to use the instruments was obtained. Approvals were also obtained by the Ethics Committees of the hospital entities involved in the study (Centro Hospitalar de Lisboa Ocidental, Hospital Fernando da Fonseca, Hospital Beatriz Ângelo).

Permission to adapt the scale to the Portuguese language was requested to the authors of the original version of the CAPS-CA-5. There were three possible versions for adults - "Make current (past month) diagnosis of PTSD", "Make lifetime diagnosis of PTSD", "Assess symptoms PTSD over the past week", but for children/adolescents there was only the version "Make current (past month) diagnosis of PTSD". Thus, the possibility of adjusting a version that encompassed both the latter and the "Make lifetime diagnosis of PTSD" version was requested and approved by the authors of the original version.

After the previous step, the original version was translated into PT-EURO by two native Portuguese physicians, from the field of Psychiatry and Child and Adolescent Psychiatry. The translations were carried out separately and, later, a single final version was prepared by consensus, after discussion with a Review Committee. The members of

this Committee were Child and Adolescent Psychiatry physicians, Clinical Psychologists, a Child Health Nurse and a Social Worker, affiliated to Centro Hospitalar de Lisboa Ocidental.

Then, the resulting version was translated back into English by two physicians from the Adult Psychiatry Unit of Centro Hospitalar de Lisboa Ocidental, fluent in Portuguese and English, who did not have access to the original scale. The translations were carried out separately and were subsequently discussed. The discrepancies found were analysed and discussed with the Review Committee in order to obtain a final version of the back-translated scale. During this process, when further clarifications were needed, the authors of the original scale were contacted.

Subsequently, a pre-test was carried out with seven children/adolescents; no changes were needed. At the end of the study, the final version of the CAPS-CA-5 in PT-EURO was found and sent to the authors of the original scale at the National Centre for PTSD, who gave positive feedback.

The participants' selection took place between September 2018 and June 2020. From March to June 2020, according to the contingency plan in Portugal for infection by SARS-CoV-2, the interviews were conducted by video consultation, following the same principles that will be presented below.

The selection was made by the physicians of the departments involved, who selected, from their list of patients, those who met the inclusion criteria. Considering that this evaluation involved the reliving of experiences that are often difficult and/or frightening, and not always innocuous, an assessment of the potential need/benefit of conducting a follow-up consultation in Child and Adolescent Psychology or Psychiatry was carried out, in order to prevent a negative impact on the course of each case.

On the participation day, the principal investigator provided detailed information about the study. Confidentiality was guaranteed by assigning a code number to the research protocol, depending on the institution in which it was collected, so that the subjects could not be identified. Those patients who agreed to participate signed an informed consent form, along with their parents/legal guardians. The interviews were conducted by a single researcher, trained in the application of the CAPS.

After the application, some minor linguistic changes were made, in order to improve the clarity of the questions, especially for younger children **-** the words/expressions "adverse events", "circulate" and "things looked cloudy" were replaced, respectively, by "difficult events", "tick", "things looked messed up")**.** The data analysis was performed with SPSS version 23. All 101 children/adolescents included in the study completed the CAPS-CA-5. Of the 101 children/adolescents, 89 completed the KIDCOPE questionnaire. Regarding the EADS-C, 86 answered the questions on Depression, 83 on Stress and 83 on Anxiety. For correlation analysis, the missing items at the subscale level were considered as absent.

The analysis of internal consistency allows the study of the properties of the measurement scales and of their questions.[21,22] For the investigation of internal consistency of the CAPS-CA-5, we calculated Cronbach's a for the total scale and the three subscales, using the severity score for each item. Due to the fact that previous studies[11–13] found higher Cronbach's a in older children than in younger, we performed a separate analysis in the age ranges 7 - 12 and 13 - 18.

The Harman's single factor test is a method for bias assessment when the same measurement instrument is used to measure different constructs.[23] The total variance extracted by one factor is 33.9%, which is less than the recommended threshold of 50%, so we can conclude that common method bias is not present in this study.

Confirmatory factor analysis allows us to study the validation of the dimensions of the scales, based on their items. The measurement model allows verifying whether the items are significant and consistent to measure the constructs, which allows drawing conclusions on the validity of each construct. A reflective model is used (the causal relationship goes from the construct to the indicators). The estimation method uses the covariance matrix and consists of the maximum likelihood method. Thus, we proceeded to identify the groups of symptoms of PTSD that provided the best diagnostic algorithm of the disorder. The data analysis was performed with SPSS version 23 and AMOS version 23.[24]

To carry out the convergent validity analysis, we studied the relationship between the CAPS-CA-5 scale (and its dimensions) with the EADS-C scale (and respective dimensions) and the negative coping strategies of the KIDCOPE. To carry out the analysis of the divergent validity, the relationship between the CAPS-CA-5 scale (and its dimensions) with the positive coping strategies of KIDCOPE was studied. The association analysis was performed using Pearson's coefficient.

We performed a separate analysis for the age groups 7 - 12 and 13 - 18 since previous studies have demonstrated that the CAPS-CA-5 showed higher correlations with related measures in older children than in younger children.[10–12]

RESULTS

Construct validity

The model tested for confirmatory factor analysis is represented in Fig. 1. In an initial analysis, it appears that all variables' saturation (items) measured in the respective subscales were statistically significant ($p < 0.001$ or $p < 0.05$ for item E1), (Fig. 1, Table 1).

For each subscale, the mean of the saturation factor, the internal consistency and the composite reliability, as well as the proportion of the extracted variance were calculated (Table 2).

There was a convergent validity of all clusters since the factorial saturations were high with mean values above the required minimum of 0.500 for clusters B, C and D and close to the reference value for cluster E. Factorial saturations were also significant (t values > 1.96; $p < 0.001$ or $p < 0.05$ for item E1) as we have already pointed out.

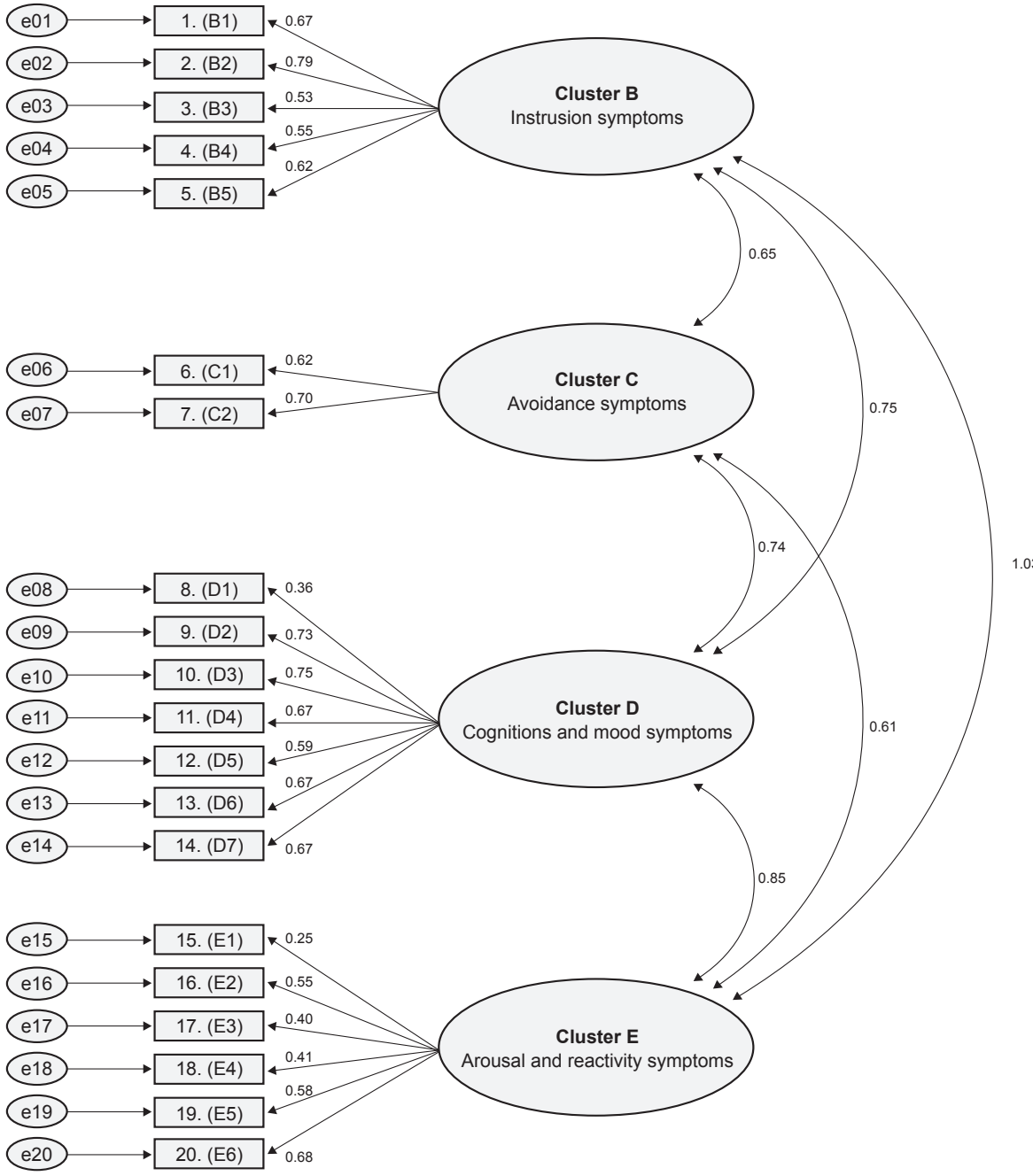

Figure 1 – Standardized estimates of the CAPS-CA-5 clusters

The reliability of the construct was verified because the values of internal consistency were higher than the minimum acceptable of 0.60 (25 – 27), varying between the minimum of 0.602 and the maximum of 0.831. In turn, the values of composite reliability were always higher than the required minimum of 0.70, with the minimum observed value being 0.729; only the extracted variance was less than the desired value of 0.50. Therefore, the convergent validity validates the clusters of the CAPS-CA-5 scale, namely in the variables that determine the total severity of the CAPS-CA-5 symptoms (items 1 - 20). The convergent validity of the measurement scale was further confirmed by the existence of positive and statistically significant saturations ($t > 1.96$; $p < 0.001$) among all the clusters of this construct.

The measures indicated an adequate global adjustment of the proposed model to the collected data, if we consider the chi-square/df = 1.479, IFI = 0.880, CFI = 0.875 and RMSEA = 0.087, an inadequate adjustment only if we take NFI = 0.703 into account, although the latter value was affected by the large sample size (28 – 30).

Regarding the construct under study, the measure model allows us to conclude that the items: i) were significant;

Table 1 – Saturations of the CAPS-CA-5 clusters, resulting from SEM and convergent validity

Clusters	Variable	Saturation				
		Not standardized	Standardized	Standard error	*t*-Test	*p*
Cluster B (Intrusion symptoms)	B1	0.854	0.674	0.119	7.191	**< 0.001
	B2	0.912	0.699	0.121	7.540	**< 0.001
	B3	0.716	0.534	0.133	5.404	**< 0.001
	B4	0.607	0.548	0.109	5.575	**< 0.001
	B5	0.831	0.624	0.127	6.525	**< 0.001
Cluster C (Avoidance symptoms)	C1	0.738	0.620	0.132	5.612	**< 0.001
	C2	0.928	0.699	0.150	6.170	**< 0.001
Cluster D (Cognitions and mood symptoms)	D1	0.327	0.361	0.093	3.502	**< 0.001
	D2	1.035	0.730	0.128	8.060	**< 0.001
	D3	1.107	0.752	0.132	8.393	**< 0.001
	D4	0.979	0.672	0.136	7.212	**< 0.001
	D5	0.824	0.587	0.135	6.080	**< 0.001
	D6	0.918	0.671	0.127	7.200	**< 0.001
	D7	0.946	0.670	0.131	7.193	**< 0.001
Cluster E (Arousal and reactivity symptoms)	E1	0.306	0.250	0.126	2.435	* 0.015
	E2	0.614	0.548	0.109	5.656	**< 0.001
	E3	0.528	0.405	0.131	4.039	**< 0.001
	E4	0.525	0.413	0.127	4.130	**< 0.001
	E5	0.750	0.578	0.125	6.019	**< 0.001
	E6	0.960	0.684	0.131	7.350	**< 0.001

*: $p < 0.05$; **: $p < 0.001$

Table 2 – Validation criteria of the CAPS-CA-5 clusters

Cluster	Items	Mean of the factorial saturations	Internal consistency	Composite reliability	Proportion of the extracted variance
Cluster B	5	0.616	0.750	0.967	0.384
Cluster C	2	0.660	0.602	0.729	0.437
Cluster D	7	0.634	0.831	0.990	0.418
Cluster E	6	0.480	0.646	0.938	0.250

ii) were consistent; iii) had convergent validity. In addition, the model presented an adequate quality of adjustment according to practically all indexes. Therefore, we can conclude that the clusters studied can be used to measure the CAPS-CA-5.

Convergent validity

There were positive and statistically significant associations between the CAPS-CA-5 and almost all of its clusters with the dimensions of the EADS-C scale, with the exception of the relationships between cluster C. "Avoidance" and the dimensions "Depression" and "Stress", and "cluster G: Distress or impairment" and "Anxiety" (Table 3). Thus, it was concluded that the convergent validity of the CAPS-CA-5 scale with the EADS-C scale was verified.

When the analysis was carried out separately for each age group, there were some differences compared with the global sample, with a greater tendency (although not consistent) for the 13-18-year-old group (except for "Depression" dimension).

There were statistically significant and positive associations between the CAPS-CA-5 and almost all of its clusters with the number of negative coping strategies on the KIDCOPE, with the exception of their relationship with the symptom dissociation cluster (Table 4). Thus, we can conclude that the convergent validity of the CAPS-CA-5 was verified.

When the analysis was performed separately for each age group, there were some differences compared with the global sample, with a greater tendency (although not consistent) for the 13-18-year-old group (except for "Depression" dimension).

Therefore, globally, we can conclude that the convergent validity of the CAPS-CA-5 with the other scales under study was verified.

Divergent validity

There were negative relationships between the CAPS-CA-5 and almost all of its clusters with the number of positive coping strategies on the KIDCOPE, however, these

Table 3 – Correlation coefficients to study the relationship between the CAPS-CA-5 scale and the EADS-C scale and the Number of KIDCOPE coping strategies

		Depression	Stress	Anxiety	Number of negative coping strategies	Number of positive coping strategies
		Total (n = 86) 7 - 12 (n = 26) 13 - 18 (n = 60)	**Total (n = 83)** 7 - 12 (n = 25) 13 - 18 (n = 58)	**Total (n = 83)** 7 - 12 (n = 23) 13 - 18 (n = 60)	**Total (n = 85)** 7 - 12 (n = 25) 13 - 18 (n = 60)	**Total (n = 80)** 7 - 12 (n = 24) 13 - 18 (n = 56)
Cluster B (Intrusion symptoms)		0.320**	0.271*	0.292**	0.379**	-0.023
		0.561**	0.215	0.345	0.446*	0.073
		0.200	0.301*	0.268*	0.363**	-0.051
Cluster C (Avoidance symptoms)	Total	0.150	0.115	0.296**	0.339**	-0.038
	7 - 12	-0.036	-0.218	0.131	-0.208	0.277
	13 - 18	0.219	0.312*	0.342**	0.497**	-0.037
Cluster D (Cognitions and mood symptoms)	Total	0.483***	0.299**	0.299**	0.498***	-0.272*
	7 - 12	0.716**	0.336	0.282	0.452*	-0.033
	13 - 18	0.421**	0.358**	0.297*	0.522**	-0.232
Cluster E (Arousal and reactivity symptoms)	Total	0.379***	0.397***	0.329**	0.305**	-0.093
	7 - 12	0.640**	0.388	0.297	0.273	0.066
	13 - 18	0.229	0.403**	0.341**	0.326*	-0.171
Total of symptoms severity of CAPS-CA-5 (items 1 - 20)	Total	0.461***	0.363**	0.370**	0.476***	-0.164
	7 - 12	0.679**	0.309	0.338	0.383	0.076
	13 - 18	0.361**	0.426**	0.372**	0.506**	-0.176
Cluster G (Distress or impairment)	Total	0.291**	0.259*	0.169	0.380**	-0.090
	7 - 12	0.448*	0.411*	0.425*	0.453*	0.128
	13 - 18	0.206	0.209	0.049	0.362**	-0.088
Dissociative symptoms	Total	0.233*	0.360**	0.323**	0.105	0.016
	7 - 12	0.202	0.068	0.084	-0.062	0.000
	13 - 18	0.259*	0.542**	0.449**	0.165	0.016

***: $p < 0.001$; **: $p < 0.01$; *: $p < 0.05$

relationships were only statistically significant for "cluster D: Cognitions and mood symptoms" (Table 3). Thus, we cannot conclude that there was a divergent validity of the CAPS-CA-5 with the number of positive coping strategies of the KIDCOPE.

When the analysis was carried out separately for each of the age groups, there were some differences compared to the global sample.

Internal consistency

The CAPS-CA-5, Table 4, presents Cronbach's a and item-total correlations for the three subscales and the total scale of the CAPS-CA-5 for the whole sample clustered by age group. The value of Cronbach's a was higher than 0.60 for all clusters, so we can consider the data acceptable as one-dimensional; for cluster D and for the total scale, it was greater than 0.8 which indicates an adequate internal consistency. The item-total correlations were always positive and greater than 0.3 in most situations. There was a tendency for the internal consistency of the scales to show higher values for the age group between 13 - 18 years compared to the age group 7 - 12 years.

Regarding the KIDCOPE questionnaires, because only one to two items evaluate each coping strategy, the internal consistency of the instrument was not analysed, and the authors hypothesized that this value (i.e. Cronbach's alpha, for example) would be reduced.[17]

Regarding the EADS-C, the value of Cronbach's a is higher than the value of 0.70 for all dimensions, so we can consider the acceptable data as one-dimensional. For the "Depression" dimension, the value was greater than 0.8, which indicates a proper internal consistency (Table 5). The item-total correlations were always positive and with minimum values greater than 0.3 in most situations (Table 5). There was a tendency for the internal consistency of the scales to show higher values for the age group between 7 - 12 years compared to the age group 13 - 18 years (Table 5).

DISCUSSION

Our study suggests that the psychometric properties of the PT-EURO version of the CAPS-CA-5 are comparable to those of the English version of the CAPS-CA.[12,13,31]

Regarding the analysis of internal consistency, Cronbach's a for the total scale was 0.89; since 'total scale' is used in this and other studies[11] we can consider the data acceptable as one-dimensional. In general, considering

Table 4 – Item total correlations and Cronbach's a for the CAPS-CA total and subscales for the total sample and per age group

	n Items	Sample	Cronbach's α	Correlation item-total
Cluster B (Intrusion symptoms)	5	Total	0.750	0.442 - 0.630
		7 - 12	0.773	0.384 - 0.685
		13 - 18	0.736	0.396 - 0.598
Cluster C (Avoidance symptoms)	2	Total	0.602	0.433 - 0.433
		7 - 12	0.419	0.267 - 0.267
		13 - 18	0.651	0.488 - 0.488
Cluster D (Cognitions and mood symptoms)	7	Total	0.831	0.332 - 0.689
		7 - 12	0.693	-0.173 - 0.697
		13 - 18	0.849	0.444 - 0.681
Cluster E (Arousal and reactivity symptoms)	6	Total	0.646	0.233 - 0.502
		7 - 12	0.691	0.266 - 0.689
		13 - 18	0.623	0.202 - 0.481
Total scale	20	Total	0.893	0.211 - 0.683
		7 - 12	0.865	-0.244 - 0.665
		13 - 18	0.898	0.165 - 0.667
Cluster G (Distress or impairment)	3	Total	0.655	0.367 - 0.562
		7 - 12	0.658	0.393 - 0.527
		13 - 18	0.628	0.334 - 0.562
Dissociative symptoms	2	Total	0.606	0.436 - 0.436
		7 - 12	0.338	0.218 - 0.218
		13 - 18	0.744	0.595 - 0.595

studies with mixed samples of children and adolescents,[11,31] the value of the coefficient is comparable to the values found. After analysis, considering the differentiation of the two age groups in the CAPS-CA, it appears that the coefficient was slightly higher than that found by Saltzman *et al*[13] for younger children and also slightly higher than that found by Erwin *et al*[12] for older children. In our study, there were no significant differences regarding internal consistency for the two age groups.

As reported in other studies, the cluster with the lowest coefficient is cluster C,[11,12,31] and the two age groups differ mainly in this cluster.[11] The cluster C coefficient was lower for younger children, mainly at the expense of the item C2, possibility because these children are less able to avoid activities or places that remind them of the traumatic event than older children.[11] It may also be related to the stage of development, greater difficulty in understanding these issues and their associated meaning, the coping strategies acquired (or in development) and less autonomy in the decision to change daily life activities that allow the eviction of certain activities or places. More research on younger children is important to better understand these items and for the development of cluster C diagnostic criteria.

On the other hand, in contrast with other studies, that reported that the cluster with a higher value of Cronbach's a is cluster B,[11–13] in our study it was cluster D.

Regarding the confirmatory factor analysis, an assay was performed to identify the constellations of PTSD symptoms in groups of homogeneous symptoms, in order to provide the best diagnostic algorithm to assist the development of specific treatment interventions. Our results indicated that CAPS-CA-5 is a suitable psychometric instrument to assess the diagnosis and severity of symptoms in Portuguese children and adolescents. Although there are still no other studies in which the confirmatory analysis of the CAPS-CA-5 is analysed, we found that, as reported in the literature for the adult version of the CAPS,[32,33] the four symptom clusters model for PTSD fits the data.

In most studies regarding the convergent validity of the CAPS-CA, the authors have compared it with other instruments of evaluation of PTSD or acute stress disorder[10–12,31,34]; however, in Portugal, at the beginning of this study, there were no other tools that could be used for this purpose. In our study, considering the convergent validity of the CAPS-CA-5, we concluded that, overall, there was convergent validity between the CAPS-CA-5 and EADS-C and negative coping strategies (assessed by the KIDCOPE). When the analysis was performed separately for each age group, there were some differences in comparison to the global sample, with a greater tendency (although not consistent) for the 13 - 18-year-old group. However, it should be noted that the correlation values found were lower than expected. We expected a greater agreement between the CAPS-CA-5 and EADS-C, since the exposure to traumatic events correlates with higher levels of anxiety and depression in the short, medium and long term and because depressive and anxiety disorders are the most common comorbidities associated with PTSD.[1,35,36] Furthermore, this

may also be related with the large overlap between the symptoms of PTSD and depressive and anxiety disorders, which may be confounding factors for the diagnosis of these disorders. On the other hand, the use of inappropriate coping strategies (that is, the inability to solve or improve the problem) and anxiety and anguish when experiencing the traumatic event are associated with a higher risk of developing PTSD.[37,38] For this reason, we expected higher levels of correlation between the CAPS-CA-5 and the negative coping strategies assessed by the KIDCOPE. The fact that the version of the CAPS-CA-5 applied was associated with the 'worst month' of the child's/adolescent's life and not to the 'last month', could lead the children/adolescents to incorrectly remember about the coping strategies used for the selected event, and could explain these findings.

Regarding divergent validity, research on this point is still very scarce. In our research, we did not find results regarding the divergent validity of the English version of the CAPS-CA. However, Diehle et *al,*[11] in their CAPS-CA validation study for the population of Dutch children and adolescents, found a convergent correlation between the CAPS-CA and ADIS-C/P (Anxiety Disorders Interview Schedule*,* a structured clinical interview that can be used to assess anxiety and mood disorders in children and adolescents), but also a divergent correlation with the RCADS (Revised Children's Anxiety and Depression Scale), a questionnaire that inquires about symptoms of anxiety and depression. In our study, there were negative relationships between the CAPS-CA-5 scale and practically all of its clusters with the number of positive coping strategies on the KIDCOPE scale. However, these relationships were only statistically significant for "cluster D: Negative changes in cognitions and in the mood". These results once again show the difficulty of framing the symptoms of mood changes and making the differential diagnosis with PTSD, which may often also occur as a comorbidity.

We also underline that the work developed will allow us to analyse other aspects resulting from the application of CAPS-CA-5, namely the types of trauma experienced, potential individual epidemiological and clinical risk factors, and the temporal association between exposure and the development of symptoms, which will be presented in a separate paper.

Strengths and limitations

This study has some limitations. Given the extensive workload in the child and adolescent psychiatry departments, and the impossibility of recording the interviews for later comparison (for confidentiality reasons), it was not possible to have other collaborators conducting the interviews, which made it impossible to assess inter reliability-interviewing. However, it must be emphasised that the validation and availability of this instrument will raise the possibility that other technicians will apply it in the future, which will make it possible to evaluate this data over time. In the course of our study, it was not possible to perform test-retest reliability, which will be an important point to analyse in the future. At the time of data collection, there were no other validated psychometric measures for the diagnosis, or the assessment of, the severity of PTSD in childhood and adolescence, according to the DSM-5 criteria, limiting the examination of the scale's validity with other measures. In addition, the fact that CAPS-CA-5 and KIDCOPE are applied in relation to any point in the life of the child/adolescent, may also lead to the responses having biases related with some memory failures or confusion about the selected event. On the other hand, it will be important to bear in mind that there were children/adolescents who participated in the study already during the pandemic phase. However, the data obtained for the validation of the scale is about the "worst event of your life"; as none of these participants reported an event after the beginning of the pandemic, it was considered that there was no bias in obtaining data referring to the objective of this study. Another limitation is the absence of an analysis of its sensitivity to distinguish between clinical and non-clinical population.

Overall, this study provides robust support for the use of the CAPS-CA-5 and ensures the intercultural validity of a diagnostic instrument that is used worldwide, often referred to as the gold standard for the diagnosis of PTSD. As far as we know, it is the first study in Portugal to demonstrate psychometric data from the CAPS-CA-5 version. It comprises a reference interview, not only to determine the diagnosis, but also the severity of the symptoms of PTSD in children and adolescents, according to the DSM-5 clusters.

CONCLUSION

This is the first study to examine the feasibility of a Portuguese version of CAPS-CA-5 (Clinician-Administered PTSD Scale for DSM-5 Child/Adolescent Version and it indicates high internal consistency and adequate levels of validity. It ensures the intercultural validity of a diagnostic instrument for worldwide use, often referred to as the gold standard for the diagnosis of PTSD. This will enable a more accurate identification of children and adolescents at high risk for development of PTSD, and to implement appropriate and earlier treatment interventions, thus improving the prognosis.

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AUTHORS CONTRIBUTION

IB: Substantial contributions to the conception and design of the work; acquisition, analysis, and interpretation of data; draft of the work; approval of the final version;

leadership of the research team.

AV, GC, CMS: Substantial contributions to the conception and design of the work; draft of the work; approval of the final version.

GR: Substantial contributions to the conception and design of the work; approval of the final version.

RPC, JM, LSM, DSS: Substantial contributions to the conception and design of the work; critical review; approval of the final version.

PAP: Substantial contributions to the conception and design of the work; analysis, and interpretation of data; critical review; approval of the final version.

IP, PSC: Substantial contributions to the conception and design of the work; analysis, and interpretation of data; critical review; approval of the final version; supervision of all steps of project development, from conception, design, analysis of results and final review.

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

All the authors declared that no competing interests exist.

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Consequências Fisiopatológicas e Abordagem Anestésica em Doentes Consumidores de Cigarros Eletrónicos e Produtos de Tabaco Aquecido: Revisão Narrativa

The Health Effects and Anesthetic Management for Patients Using E-Cigarettes and Heat-Not-Burn Tobacco Products: A Narrative Review

ARTIGO DE REVISÃO

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RESUMO

Introdução: A implementação de medidas políticas para a cessação tabágica levou à diminuição do consumo de tabaco. Contudo, em contrapartida, tem-se verificado um aumento do consumo de sistemas eletrónicos de administração de nicotina e sistemas eletrónicos sem nicotina, também conhecidos como cigarros eletrónicos, e produtos de tabaco aquecido. O objetivo deste trabalho é rever as implicações fisiopatológicas da utilização destes dispositivos e as suas implicações no peri-operatório.

Material e Métodos: A pesquisa na literatura foi efetuada pelos autores, identificando artigos de língua inglesa nas plataformas de pesquisa PubMed e MEDLINE, entre os anos 2007 e 2021, e usando os termos 'vaping', 'electronic nicotine delivery systems', 'heated tobacco products', 'IQOS' e 'anesthesia'. Foram obtidas 654 publicações, tendo sido selecionadas as mais pertinentes.

Resultados: Existe atualmente pouca informação relativamente às implicações peri-operatórias da utilização dos cigarros eletrónicos e dos produtos de tabaco aquecido. Estes sistemas libertam várias substâncias potencialmente nocivas, incluindo nicotina, com implicações negativas para a saúde dos consumidores. Interferem com o sistema cardiovascular, respiratório e imunológico e apresentam várias interações farmacológicas, com influência na abordagem anestésica. Verifica-se ainda um risco acrescido de lesões causadas por explosão do dispositivo e desenvolvimento de neoplasias. São sugeridas medidas para otimizar a abordagem destes doentes.

Conclusão: O conhecimento sobre os potenciais efeitos deletérios da utilização destes dispositivos, assim como as suas implicações peri-operatórias, é fundamental e permite adotar medidas que minimizem riscos e melhorem a evolução destes doentes.

Palavras-chave: Anestesia; Sistemas Eletrónicos de Dispensa de Nicotina; Uso de Cigarro Eletrónico/efeitos adversos

ABSTRACT

Introduction: The implementation of policies aimed at promoting smoking cessation led to a decrease in the use of tobacco. There has been an increase in the use of systems such as electronic nicotine delivery systems and electronic non-nicotine delivery systems - also known as electronic cigarettes, and heat-not-burn tobacco products. The aim of this review is to describe the pathophysiological implications of these devices and their perioperative impact.

Material and Methods: A literature search was carried out by the authors to identify studies published in English on PubMed and MEDLINE between 2007 and 2021, and using the terms 'vaping', 'electronic nicotine delivery systems', 'heated tobacco products', 'IQOS' and 'anesthesia'. A total of 654 articles were found, and the most relevant ones were selected.

Results: There is currently insufficient information available regarding the perioperative implications of electronic cigarettes and heat-not-burn tobacco products. These devices release potentially harmful substances - such as nicotine – that have a negative impact on the health of consumers. These substances affect the cardiovascular, respiratory and immune systems, and can interact with multiple drugs, which can affect the anesthetic management. The users of these devices are also at a higher risk of explosion injuries and cancer. A number of interventions that may improve the perioperative management of these patients are suggested.

Conclusion: Awareness of the potential harmful effects of these devices, and their perioperative implications, is essential, as it enables the implementation of interventions to minimize the risks and improve patient outcomes.

Keywords: Anesthesia; Electronic Nicotine Delivery Systems; Vaping/adverse effects

INTRODUÇÃO

Nos últimos anos, com a implementação de medidas políticas e campanhas de cessação tabágica, tem-se verificado um decréscimo sustentado no consumo de tabaco.[1] Nesse sentido, têm surgido no mercado várias alternativas, com o intuito de ajudar no processo de cessação tabágica. Entre estas incluem-se os sistemas eletrónicos de administração de nicotina e sistemas eletrónicos sem nicotina (SEAN/SESN), também designadas de cigarros eletrónicos, e os produtos de tabaco aquecido (PTA).

O objetivo deste trabalho é rever as consequências fisiopatológicas do consumo de cigarros eletrónicos, assim como as implicações na abordagem anestésica e evolução peri-operatória dos doentes consumidores deste tipo de produtos.

MATERIAL E MÉTODOS

Os autores efetuaram uma revisão narrativa identificando artigos de língua inglesa, publicados nas plataformas de pesquisa PubMed e MEDLINE, entre os anos 2007 e 2021. Foram pesquisados os termos 'vaping', 'electronic

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nicotine delivery systems', 'heated tobacco products', 'IQOS' e 'anesthesia'. Os autores encontraram 654 publicações, das quais foram selecionadas as mais pertinentes.

RESULTADOS

Constituição dos cigarros eletrónicos e produtos de tabaco aquecido

Os cigarros eletrónicos foram criados em 2003 na China e comercializados nos Estados Unidos em 2007.[2,3] Foram introduzidos inicialmente no mercado como uma ferramenta segura para ajudar na cessação tabágica. Contudo, um estudo recente realizado pelo Centro de Controlo e Prevenção de Doenças (CDC) revelou que a utilização de cigarros eletrónicos, não só não diminuiu o tabagismo, como demonstrou que os doentes acabavam por utilizar os dois métodos.[4,5]

Apesar de serem produtos recentemente comercializados, o seu consumo tem tido um crescimento exponencial, sobretudo nos mais jovem, e muitas vezes não fumadores.[6,7] Nesta população, o consumo de cigarros eletrónicos já ultrapassou o consumo de cigarros tradicionais, sendo neste momento a principal forma de consumo de nicotina.[7]

Os termos 'cigarros eletrónicos' ou '*e-cigarette*', referem-se a um sistema de aerossolização, que consiste num cartucho descartável que contém uma solução a ser vaporizada, com uma bateria de lítio que fornece energia a uma fonte de aquecimento, e uma câmara de vaporização com uma peça que se adapta à boca do consumidor e através do qual o vapor é inalado. Estes elementos são envolvidos por um tubo com *designs* variados que funcionam como estratégia de *marketing*.[2,3,8]

A solução contém nicotina e um solvente, podendo ainda apresentar um ou mais de 7000 sabores.[2,9] Estes sabores tornam estes dispositivos atrativos para jovens, especialmente entre não-fumadores.[10] Os ingredientes primários destes dispositivos incluem, nicotina (0 – 24 mg), propilenoglicol e glicerina, estes últimos utilizados como solventes. Estão presentes muitos outros constituintes nomeadamente acetona, formaldeído, acetaldeído e tolueno.[11,12]

Os PTA também foram introduzidos no mercado com o intuito de reduzir o risco associado ao consumo de cigarros tradicionais. Foram lançados em 1998, mas não tiveram sucesso.[13] Em 2014, a multinacional Philip Morris Internacional lançou, em grande escala, o dispositivo conhecido por iQOS® - (*I Quit Ordinary Smoking*). Atualmente, é o único sistema de PTA comercializado em Portugal.[14-17] O IQOS® consiste num sistema de aquecimento de tabaco com três componentes: *heatsticks* (unidade de tabaco aquecido), um suporte e um carregador.[18] Enquanto que os cigarros eletrónicos aquecem uma solução que contém nicotina, os PTA aquecem diretamente o tabaco, em aproximadamente seis minutos, a uma temperatura que oscila entre 330ºC a 350ºC (*versus* 600ºC com o tabaco convencional), sem causar a sua combustão.[14,15,18] Libertam vapor de nicotina, compostos orgânicos voláteis, hidrocarbonetos aromáticos policíclicos, monóxido de carbono, alcatrão, acetaldeído, acrilamida, nitrosaminas, metabolito da acroleína, entre outras substâncias potencialmente nocivas.[15,19] Os PTA, em comparação com os cigarros eletrónicos, geram uma maior quantidade de produtos químicos, que é contudo menor do que os cigarros tradicionais.[15,20] Apesar da quantidade de substâncias nocivas libertadas ser inferior ao cigarro tradicional,[14,15] várias sociedades científicas consideram ter um efeito prejudicial à saúde.[16,21]

Implicações cardiovasculares

Os efeitos cardiovasculares decorrentes da utilização dos cigarros eletrónicos e PTA devem-se sobretudo à presença da nicotina.[6] Esta estimula o sistema nervoso autónomo, conduzindo a um aumento da frequência cardíaca e da pressão arterial sistémica, aumento da contractilidade miocárdica, aumento do consumo miocárdico de oxigénio, aumento das resistências vasculares periféricas, e em adultos saudáveis, ao aumento da rigidez da aorta.[11,22] Estes efeitos simpaticomiméticos não são observados aquando da utilização de cigarros eletrónicos sem nicotina.[23,24] A nicotina, por sua vez, leva à libertação de catecolaminas, conduzindo a instabilidade hemodinâmica sob anestesia geral,[1,11] e produz ainda a disfunção endotelial, aumento de lípidos e resistência a insulina.[11] Esta atua sinergicamente com a angiotensina II promovendo o *remodeling* (alterações estruturais e funcionais) cardiovascular.[6] Em alguns estudos foi demonstrado que a utilização dos cigarros eletrónicos se associava a um aumento do stresse oxidativo,[25] diminuição da biodisponibilidade e produção de óxido nítrico pelas células endoteliais.[6,22]

A intoxicação por nicotina pode ainda conduzir a náuseas, vómitos, tonturas, diaforese, taquicardia, convulsões e morte.[11] Assim, no período pré-operatório, será importante questionar especificamente sobre o consumo de nicotina e quantidade de nicotina consumida.

Apesar dos efeitos da nicotina já terem sido extensamente estudados, as implicações dos produtos de degradação térmica gerados pelos cigarros eletrónicos, foram menos estudados. A evidência recente revela múltiplos efeitos adversos: a inalação aguda dos compostos aerossolizados de cigarros eletrónicos sem nicotina mostrou, em jovens não fumadores, aumentar os marcadores de stresse oxidativo e índices de inflamação com lesão endotelial[25]; já a inalação prolongada de acroleína, produto da degradação térmica do glicerol, parece promover o processo aterosclerótico.[11]

A exposição aos aerossóis gerados pelos cigarros eletrónicos pode resultar em alterações do desenvolvimento cardíaco fetal, devendo ser evitada a sua utilização sobretudo em crianças, grávidas e mulheres em idade reprodutiva.[3,11]

Estudos em animais e humanos revelaram que a utilização de PTA tem efeitos cardiovasculares negativos como o aumento da tensão arterial e da incidência de arritmias ventriculares, com o *remodeling* do ventrículo esquerdo e o aumento da incidência de doença cardíaca isquémica e disfunção do endotélio vascular.[20,26-28] Estudos em animais

revelaram uma maior incidência de fibrose cardíaca, toxicidade dos cardiomiócitos e redução da função cardíaca, efeitos que se associaram à nicotina.[20,29] Assim, o anestesiologista deve estar atento a possíveis complicações cardiovasculares no período peri-operatório.

Implicações respiratórias

A evidência atual demonstra que a exposição aos cigarros eletrónicos pode induzir alterações estruturais pulmonares e conduzir a um comprometimento significativo da função pulmonar.[6] Alguns estudos mostram um aumento das resistências das vias aéreas, indicando obstrução das mesmas, aumento dos índices de stresse oxidativo e ICAM-1, sugerindo lesão tecidular e inflamação.[6] O uso repetido destes dispositivos também parece aumentar a proteólise pulmonar, o que pode induzir um aumento de risco de desenvolvimento de doença pulmonar crónica.[6] Estes efeitos devem ser investigados no período pré-operatório.

O propilenoglicol e a glicerina formam aldeídos quando são aquecidos. Estes, uma vez inalados, são conhecidos por causar tosse e alterações nas provas de função respiratória, mimetizando doença pulmonar obstrutiva crónica, que se traduz numa diminuição da razão entre volume expiratório forçado no primeiro segundo (FEV1) e a capacidade vital forçada (CVF) (FEV1/CVF),[6] o que pode condicionar dificuldades na ventilação e oxigenação durante o período intra-operatório. Além disso, o propilenoglicol aerossolizado produz matéria particulada ultrafina (com partículas < 2,5 µm de diâmetro) que os utilizadores dos cigarros eletrónicos inalam em doses iguais ou superiores ao que os fumadores de cigarros tradicionais são expostos. Esta matéria particulada ultrafina é conhecida por diminuir a função pulmonar e precipitar crises asmáticas em indivíduos suscetíveis.[30]

A inalação do vapor contendo diacetil foi também associado a bronquiolite obliterativa, popularmente conhecida como '*popcorn lung*'.[30] Esta é uma doença rara, sendo uma forma de doença pulmonar crónica sem tratamento conhecido, caracterizada por inflamação e fibrose dos bronquíolos distais e terminais, resultando em obstrução da via aérea.[30-32]

A manifestação mais evidente de lesão pulmonar resultante da utilização dos cigarros eletrónicos foi identificada em 2019-2020 como *e-cigarette or vaping use-associated lung injury* (EVALI), denominação dada pelo Centers from Disease Control and Prevention (CDC).[4] A fisiopatologia da EVALI é desconhecida. Os achados histopatológicos parecem revelar uma forma de lesão pulmonar aguda, incluindo pneumonite fibrinosa aguda, lesão alveolar difusa ou pneumonia organizativa, habitualmente bronquiolocêntrica e associada a bronquiolite.[31] Muitos dos doentes com EVALI apresentam concomitantemente história de asma, patologia cardíaca ou obesidade, o que os pode tornar mais suscetíveis a lesão pulmonar.[6,33] A EVALI apresenta-se habitualmente com tosse, dispneia e sintomas constitucionais como febre. Os achados radiográficos e histopatológicos são consistentes com um padrão de lesão pulmonar aguda. Por ser inespecífico, o seu diagnóstico é de exclusão. O tratamento é de suporte e a mortalidade associada é baixa.[4,7,34,35]

Relativamente aos PTA, os estudos incidem predominantemente nos dispositivos IQOS®, tendo sido associados a toxicidade e inflamação pulmonar em animais e humanos.[36] Estes estudos não mostraram diferenças entre fumadores de cigarros convencionais e IQOS®.[36] Verifica-se também uma redução aguda da função pulmonar e um aumento da resistência das vias aéreas com a utilização destes dispositivos.[37]

Implicações imunológicas

Os cigarros eletrónicos afetam o sistema imunitário inato e adquirido.[6] Verifica-se um aumento dos níveis plasmáticos de IgE e produção de citocinas pro-inflamatórias, como IL-6, IL-8, pelos macrófagos, neutrófilos e células dendríticas, com aumento do *stress* oxidativo, ativação de uma resposta inflamatória e diminuição da atividade fagocítica.[6,12,38] Como consequência ocorre uma desregulação da função antimicrobiana, com aumento da suscetibilidade para infeções bacterianas, virais e fúngicas e promoção da formação de biofilme.[6,38,39] Os fumadores de cigarros eletrónicos parecem apresentar um elevado nível de supressão de genes na mucosa nasal, em comparação com os fumadores de tabaco convencional (75 *vs* 18 genes), com consequente supressão do sistema imunitário e maior suscetibilidade a infeções.[38] Vários autores consideram que a resposta inflamatória é dose dependente.[38,39] Alguns cigarros eletrónicos contêm mais nicotina que os tradicionais, associando-se a pior *outcome*. A nicotina apresenta propriedades antiproliferativas e diminuição da síntese de colagénio, o que predispõe a um atraso no processo de cicatrização.[11] Estudos realizados em ratos demonstraram que a taxa de necrose cutânea foi maior no grupo exposto ao vapor do cigarro ou fumo de cigarros convencionais em comparação com o grupo de não fumadores. No entanto, não se sabe se esse aumento foi devido à exposição à nicotina ou a outros constituintes do vapor.[40] São assim necessários mais estudos para avaliar a segurança e os efeitos dos cigarros eletrónicos no sistema imunitário.

O consumo de PTA aumenta a exposição a radicais livres, ativação de resposta inflamatória e aumento do *stress* oxidativo nas vias aéreas.[14]

Interações farmacológicas

A exposição a elevadas concentrações de composto volátil que inclui o tolueno, produzido pelos cigarros eletrónicos, induz sedação, imobilidade e inconsciência. Em baixas concentrações, prejudica a função neurológica e o desempenho comportamental.[11] É importante saber que podem ocorrer interações com fármacos anestésicos nomeadamente, com os agentes voláteis, opióides e bloqueadores neuromusculares.

Agentes voláteis

Pelo efeito depressor do sistema nervoso central do

tolueno, verifica-se uma diminuição da concentração alveolar mínima (MAC) dos halogenados, em doentes consumidores de cigarros eletrónicos.[11] Por outro lado, a nicotina induz a enzima CYP2E1 responsável pela metabolização destes fármacos.[11] Apesar de não existirem dados claros sobre a interação dos cigarros eletrónicos com os agentes voláteis, há evidências de que o aumento da sua metabolização produz níveis elevados de metabolitos que podem ser potencialmente tóxicos.[41,42]

Relaxantes musculares

O consumo crónico de nicotina pode interferir com o número e a sensibilidade dos recetores nicotínicos na membrana pós-sináptica, diminuindo a potência dos relaxantes musculares aminoesteroídes.[41,42] Estudos verificaram que a dose necessária de vecurónio e rocurónio nos fumadores era de 25%, isto é, superior aos não fumadores.[41] No entanto outros estudos mostraram resultados inconsistentes. Atualmente, não há evidências claras da necessidade de aumentar a dose dos relaxantes musculares nos doentes fumadores.[42]

Opióides

O uso de nicotina está associado a um maior risco de dor crónica e aumento da necessidade de opióides no pós-operatório.[11] Este mecanismo não está totalmente esclarecido, mas deve-se provavelmente, a alterações no limiar de dor ou tolerância dos recetores.[11,41]

Os vários constituintes dos cigarros eletrónicos apresentam propriedades farmacológicas que podem interferir com numerosos efeitos dos agentes anestésicos. No entanto, os mecanismos de interação não estão totalmente esclarecidos.[41]

Lesões associadas

O uso de cigarros eletrónicos aumenta o risco de ocorrência de lesões associadas a explosão do dispositivo e de desenvolvimento de neoplasias.[17,30]

Explosão dos dispositivos

As baterias de lítio podem sobreaquecer e causar um curto-circuito com consequente explosão, resultando em queimadura térmica. Entre 2016 e 2018 foram reportados 93 casos de lesões por explosão de baterias de lítio dos cigarros eletrónicos, a maioria em indivíduos do sexo masculino com uma média de idades de 31 anos.[30] As áreas mais frequentemente envolvidas são as mãos, face, coxas e genitais (por transporte no bolso), sugerindo que a explosão pode ocorrer tanto durante a sua utilização, como durante o período de carregamento.[30] A fuligem e outros detritos resultantes da explosão penetram na ferida podendo causar queimadura química. A irrigação abundante da ferida permite eliminar os detritos e minimizar o risco de infeção.[30]

Cancro

Existe evidência de que o uso de cigarros eletrónicos está associado a um aumento do risco de desenvolvimento de neoplasias.[11,30] Células em culturas expostas ao vapor do cigarro eletrónico apresentam um aumento de

Tabela 1 – Evidência científica e sugestões na abordagem anestésica de consumidores de cigarros eletrónicos e produtos de tabaco aquecido

Evidência
Os doentes que utilizam cigarros eletrónicos e/ou PTA muitas vezes não se assumem como fumadores.
Existem cigarros eletrónicos sem nicotina.
A nicotina tem efeitos deletérios principalmente a nível do sistema cardiovascular.
Alguns solventes e sabores têm efeitos deletérios ao nível do sistema respiratório.
O consumo de cigarros eletrónicos mostrou ter um efeito deletério ao nível da microcirculação o que pode prejudicar a cicatrização.
O uso de cigarros eletrónicos apresenta um risco menor no peri-operatório do que o consumo de cigarros tradicionais.
Possibilidade de lesão pulmonar.
Pode existir hiperatividade das vias aéreas.
Aumenta o risco de dor crónica.
Sugestões
Questionar diretamente o doente acerca da utilização de cigarros eletrónicos e regularidade de consumo.
Questionar acerca da utilização e dependência de nicotina e quantidade de nicotina utilizada nos cigarros eletrónicos.
Deve ser incentivada a abstinência antes e depois da cirurgia.[30-31, 44] Os doentes são aconselhados a suspender o consumo destes produtos pelo maior período de tempo possível (como por exemplo não fumar na manhã da cirurgia) porque dados indicam que existe beneficio mesmo com curtos períodos de abstinência.[45]
Doentes consumidores de tabaco tradicional, que fizeram alteração no peri-operatório, para cigarros eletrónicos devem ser incentivados a continuarem a abster-se da utilização dos primeiros.
Avaliação pré-operatória com especial destaque para avaliação cardiovascular e pulmonar.
Promover técnicas de reabilitação respiratória para diminuir complicações pulmonar no pós-operatório.
Promoção de analgesia multimodal pelo risco aumentado de dor crónica.

alterações no DNA, o que pode mimetizar um precursor para o desenvolvimento de tumores e conduzir a alterações necessárias para a ocorrência de metástases no cancro do pulmão.[30] A nicotina, por si só, não é cancerígena, mas os seus metabolitos são. Estudos realizados em ratos demonstraram que os produtos aromatizantes apresentam propriedades carcinogéneas e o vapor, constituído por metais pesados como o cobre, níquel e cádmio, promove o crescimento de tumores.[30] No entanto, quando comparados com os cigarros convencionais, a quantidade de compostos cancerígenos presentes nos cigarros eletrónicos foi menor. Uma vez que as neoplasias ocorrem predominantemente na população idosa, e devido ao uso recente dos cigarros eletrónicos, não existem estudos que avaliem o risco a longo prazo.[30] Em modelos animais têm sido reportados casos de adenocarcinoma do pulmão e hiperplasia urotelial após exposição prolongada aos cigarros electrónicos.[6] Foram ainda relatados dois casos de neoplasia da cavidade oral, em homens sem antecedentes pessoais relevantes nem história prévia de consumo de tabaco, e que foram consumidores de cigarros eletrónicos durante 13 anos.[15]

Sugestões de medidas a adotar no período peri-operatório

A utilização crescente de cigarros eletrónicos e PTA, associada à falta de informação sobre estes dispositivos, torna este tema de extrema importância entre a comunidade científica, e em especial entre os anestesiologistas.

Como foi referido, a utilização de cigarros eletrónicos e PTA, particularmente importante entre jovens, é um fator de risco para patologia respiratória e cardiovascular.

Existe atualmente pouca informação relativamente às implicações peri-operatórias da utilização destes dispositivos. Baseados nesta revisão narrativa, os autores sugerem algumas medidas de abordagem peri-operatória dos doentes consumidores de cigarros eletrónicos e de PTA, de forma a diminuir potenciais complicações e melhorar *outcomes* (Tabela 1).

CONCLUSÃO

Os cigarros eletrónicos e PTA estão a ganhar popularidade. A comunidade médica em geral, e os Anestesiologistas em particular, devem estar atentos aos potenciais efeitos deletérios decorrentes da sua utilização e implicações no ato anestésico.

CONTRIBUTO DOS AUTORES

DP, ASB: Conceção, organização, redação do trabalho, revisão crítica e aprovação da versão final.

AGA: Conceção do trabalho, revisão crítica e aprovação da versão final.

PROTEÇÃO DE PESSOAS E ANIMAIS

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

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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Natural Tolerance Development to Peach in a Child with Lipid Transfer Protein Allergy

Aquisição Natural de Tolerância ao Pêssego numa Criança Alérgica a Proteínas de Transferência de Lípidos

CASO CLÍNICO

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ABSTRACT

Non-specific lipid transfer proteins (LTPs), present in multiple plant foods and pollens, are the predominant allergen in peach allergy in the Mediterranean region and may induce life-threatening allergic reactions. Although reasonably studied in adults, LTP allergy has been rarely described in children, and to the best of the author's knowledge, natural tolerance development during childhood to this allergen has not been reported to date. The authors reported the case of a 21 month-old boy who presented urticaria and facial edema 15 minutes after eating a peach. Sensitization to peach LTP was confirmed by skin prick tests and specific IgE. At the age of 32 months, skin prick tests and specific IgE to peach LTP were negative, so a food challenge was performed. The child tolerated one medium-sized peach. Peach and peach-related fruits were reintroduced in the child's diet. The authors discuss the relevance of regular allergy workup and dietary recommendations in children with LTP allergy.

Keywords: Carrier Proteins/immunology; Child; Food Hypersensitivity; Fruit Proteins/immunology; Immune Tolerance; Prunus Persica

RESUMO

As proteínas de transferência de lípidos [*lipid transfer proteins* (LTP)] são proteínas presentes em alimentos vegetais e pólenes, e constituem os principais alergénios na alergia a pêssego na região mediterrânica, podendo induzir anafilaxia. A alergia a estas proteínas tem sido predominantemente reportada em adultos e casos de aquisição natural de tolerância não foram descritos. Os autores descrevem o caso de uma criança de 21 meses que apresentou urticaria e angioedema da face 15 minutos após a ingestão de um pêssego. A sensibilização a LTP foi confirmada por testes cutâneos por picada e IgE específica positivos para a LTP do pêssego. Onze meses depois, estes testes para a LTP do pêssego foram negativos, tendo sido realizada prova de provocação em que a criança tolerou um pêssego médio. A reintrodução na dieta de pêssego e frutos relacionados foi bem tolerada. Os autores discutem a necessidade da reavaliação regular e orientação da dieta de evicção nas crianças com alergia a LTPs.

Palavras-chave: Criança; Hipersensibilidade Alimentar; Proteínas da Fruta/imunologia; Proteínas de Transporte/imunologia; Prunus Persica; Tolerância Imunológica

INTRODUCTION

Non-specific lipid transfer proteins (LTPs) are ubiquitous plant allergens, described as the main cause of primary food allergy in adults from Southern Europe.[1,2] LTPs are the major allergens in *Rosaceae* fruits (e.g. peach, apple, cherry), but they can be present in other plant-derived foods as well as in pollens.[1-4]

In LTP-allergic patients, the wide range of reaction-eliciting foods may be explained by their molecular similarity, resulting in cross-reactivity between LTPs present in botanically related and unrelated foods.[1,3,5]

Since LTPs are stable to heat, gastric digestion, and food preservation methods, they may induce symptoms with ingestion of fresh and/or processed food, and clinical manifestations may range from mild symptoms to anaphylaxis.[1,2,4]

Allergy to LTPs has been reasonably described in adults but rarely in children. Moreover, the development of natural tolerance in an LTP allergic child has not been previously reported.

CASE REPORT

The authors report the case of a 21 month-old boy who presented with facial and abdominal urticaria, as well as with edema of the lips and eyelids 15 minutes after eating an unpeeled peach. No other foods were ingested at that time. He was treated with oral corticosteroids and antihistamines in the emergency department and discharged symptom-free two hours later. Peach was previously tolerated but the child stopped eating peach, apricot and nectarine after this reaction. Peeled apple, pomegranate, peanut and walnut ingestion was continued, without symptoms. Skin prick tests (SPTs) to *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Lepidoglyphus destructor*, cat, dog, birch, olive, grass pollen mix, *Parietaria*, *Alternaria* (Roxall-Aristegui®, Bilbao, Spain) were negative (positive if wheal diameter ≥ 3.0 mm; histamine 10 mg/mL, 3.0 mm; negative control, 0 mm). As seen in Table 1, SPTs with food extracts were positive to peach LTP, peach, walnut, almond and cherry, and negative to apple and peanut. Specific IgE (sIgE) to rPru p 3 (peach LTP; ≥ 0.35 UK_A/L, positive) was 0.62 UK_A/L and 0.43 UK_A/L for rJug r 3 (walnut LTP; ≥ 0.35 UK_A/L, positive), as seen in Table 1. At this point, parents were advised to maintain peach, apricot and nectarine avoidance. Despite positive SPTs, tree nut ingestion was continued since it did not induce any symptoms.[6] Emergency medication, a written action plan and LTP allergy

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Table 1 – Summary of workup

Tests	Age, months	7	21	32	55
SPTs, mean wheal diameter measure in millimetres †, ‡	Cow's milk	3.0	4.5	3.0	NP
	α-lactoalbumin	7.0	5.0	7.0	NP
	β-lactoglobulin	5.0	3.0	5.0	NP
	Casein	3.5	7.5	3.5	NP
	Peach LTP	NP	6.5	0.0	NP
	Peach	NP	4.0	0.0	NP
	Walnut	NP	5.0	0.0	NP
	Hazelnut	NP	7.5	0.0	NP
	Almond	NP	4.0	0.0	NP
	Cherry	NP	3.0	0.0	NP
	Histamine 10 mg/mL	6.0	3.0	4.0	NP
	Negative control	0.0	0.0	0.0	NP
Specific IgE, kU_A/L §	Total IgE, KU/L	39.60	123.00	NP	46.10
	Cow's milk	14.40	27.10	NP	7.05
	nBos d 4 (α-lactoalbumin)	10.90	6.10	NP	1.54
	nBos d 5 (β-lactoglobulin)	2.68	2.66	NP	0.30
	nBos d 8 (casein)	7.15	23.80	NP	6.72
	rPru p 3 (peach LTP)	NP	0.52	0.04	NP
	rJug r 3 (walnut LTP)	NP	0.43	0.03	NP

†: Skin Prick tests (SPTs) were considered positive if wheal diameter ≥ 3.0 mm (Roxall-Aristegui, Bilbao, Spain); ‡: SPTs were negative to apple and peanut at 21 and 32 months-old; §: ImmunoCap, Thermo-Fisher.
NP: not performed.

information were provided to the parents. No accidental ingestions were reported.

As relevant medical history, the child presented at the age of seven months perioral urticaria and lip swelling five minutes after eating milk-containing baby food. At 18 months old, during a visit to his uncle's house, he presented generalized urticaria and conjunctivitis after eating a ham sandwich (the ham was stored in contact with cheese). There were no more accidental exposures. SPT and sIgE to milk and components performed at 7, 21, 32 and 55 months are all described in Table 1. At 12 months, an oral food challenge (OFC) with milk was suggested but the parents refused. Considering the probability of milk allergy resolution in childhood, SPT and sIgE to milk and peach LTP were repeated at 32 months.[7] After this reaction, sIgE nBos d 8 (casein) increased from 7.15 UK_A/L to 23.80 UK_A/L and the authors decided to postpone the OFC with milk. At the 55 months reassessment, no accidental reactions were reported and sIgE to nBos d 4, nBos d 5 and nBos d 8 decreased, but the parents did not consent to an OFC with milk.

While monitoring milk allergy at 32 months old, evaluation of peach LTP sensitization was contemplated, and previously positives SPTs to peach LTP, peach, walnut, almond and cherry, as well as the sIgE to rPru p 3 and rJug r 3, turned negative. Skin prick-to-prick tests (SPPTs) to peach peel and pulp were negative (histamine 10 mg/mL, 4 mm; negative control, 0 mm). Considering the negative SPT and SPTT to peach, and the negative SPT and sIgE to peach LTP, an OFC with unpeeled peach was performed after parental written informed consent at four years old, after being postponed twice for viral infections and later because of the COVID-19 pandemic. OFC started with lip challenge, followed by four doses of peach administered 30 minutes apart, with semi-logarithmic increases, reaching a cumulative dose of 154.23 g (a full medium peach).[8] The period of observation after the last dose was two hours, and no symptoms occurred during this period. Peach, apricot and nectarine were reintroduced in the child's diet at home and no reactions were reported upon re-exposure.

DISCUSSION

Natural tolerance is well described in children with milk and egg allergies, with most patients outgrowing milk and/or egg allergy throughout childhood. Other prevalent food allergies, such as peanut and fish allergy, have a less favourable prognosis.[9] Allergy to LTPs in children is a scarcely reported but emerging subject.

The authors reported the first case of natural tolerance to peach in a LTP allergic child. The diagnosis was suspected based on the clinical symptoms elicited by peach ingestion and supported by the positive SPT to peach LTP, peach, almond and walnut extracts, and positive sIgE to rPru p 3 and rJug r 3.[10] Tolerance to peach was confirmed by a negative oral food challenge (performed after negative SPTs to peach LTP, peach, almond and walnut extracts, negative sIgE to rPru p 3 and rJug r 3, and negative SPPT to peach)

and successful reintroduction of peach and peach-related fruits in the child's diet.

Some methodological limitations need to be mentioned, as the lack of an OFC to confirm the diagnosis of LTP allergy. This diagnosis was based on a suggestive history, and positive SPT and sIgE, supporting an LTP sensitization pattern. The child's age, risk of severe reaction upon re-exposure, and parental concerns were all taken into account in the decision of not performing an OFC with peach.

To the authors' knowledge, this is the first report of natural tolerance development in an LTP allergic child. The present case reinforces the importance of regularly testing sensitized young children as routinely done in egg and milk allergies; this is a particularly relevant since management of LTP allergy involves challenging preventive strategies, given the widespread diffusion of the protein and its variable degree of cross-reactivity.

Dietary avoidance of important nutritious foods, such as fruits and vegetables, may affect the child's health, growth, and not only the child's quality of life but also their parents' and caretakers'. For these reasons, dietary avoidance measures should be based on clinical reactivity and not merely on sensitization.[6]

As such, the child was advised to avoid only the food, which triggered symptoms (peach and similar fruits) and to preserve the regular ingestion of other LTP-containing foods that elicited no symptoms upon ingestion, including those with positive SPT (almond and walnut). The partial homology between LTP from different foods, the fact that sensitization does not indicate allergy, allows LTP-allergic subjects to ingest all tolerated foods until evident symptoms arise.[6] This approach may avert unnecessary and deleterious restrictive diets and potentially contribute to natural tolerance development as a physiological form of immunotherapy.[6,11]

AUTHORS CONTRIBUTION

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

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

The authors declare having followed the institutional protocols regarding publication data.

PATIENT'S CONSENT

Obtained.

COMPETING INTERESTS

The authors have no competing interests to declare concerning this work.

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Tongue Hyperpigmentation Associated with Temozolomide as a Single Agent: Case Report

Hiperpigmentação da Língua Associada a Temozolomida em Monoterapia: Caso Clínico

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ABSTRACT

Hyperpigmentation of the tongue has been associated with chemotherapy, specifically cytotoxic drugs, but the exact pathophysiological mechanism is still not well understood. We describe a 37-year-old black woman that presented with tongue hyperpigmentation one week after the initiation of chemotherapy with temozolomide as a single agent. No cases of tongue hyperpigmentation associated with temozolomide as a single agent have been reported before. The diagnosis of drug associated pigmentary changes is based on the confirmation the onset of the clinical observations shortly after the initiation of the chemotherapy agent. The tongue hyperpigmentation is usually self-limited. This case constitutes a challenge for healthcare professionals and patients and emphasizes the importance of documenting these cases in order to guide healthcare professionals in managing the expectations of the patients and the potential adverse effects associated with certain drugs.

Keywords: Hyperpigmentation/chemically induced; Temozolomide/adverse effects; Tongue Diseases/chemically induced

RESUMO

A hiperpigmentação da língua tem sido associada a quimioterapia, especificamente a fármacos citotóxicos, mas o mecanismo fisiopatológico exato não é conhecido. Apresentamos o caso clínico de uma mulher de raça negra, de 37 anos que apresentou hiperpigmentação da língua uma semana após o início da quimioterapia com temozolomida em monoterapia. Nenhum caso de hiperpigmentação da língua associada à temozolomida em monoterapia foi antes relatado. O diagnóstico de alterações pigmentares associadas ao medicamento é baseado na correlação temporal do início dos achados clínicos com o início do agente quimioterápico. A hiperpigmentação da língua geralmente é autolimitada. Este caso constitui um desafio para os profissionais de saúde e para os doentes e enfatiza a importância de documentar estes casos, a fim de orientar os profissionais de saúde na gestão das expectativas dos doentes e dos potenciais efeitos adversos associados a determinados fármacos.

Palavras-chave: Doenças da Língua/induzida quimicamente; Hiperpigmentação/induzida quimicamente; Temozolomida/efeitos adversos

INTRODUCTION

Drug-induced pigmentation accounts for up to 20% of all cases of acquired pigmentation.[1] Hyperpigmentation of the tongue has been associated with chemotherapy, specifically cytotoxic drugs, but the exact pathophysiological mechanism is still not well understood.[1] Temozolomide appears in the literature associated with tongue hyperpigmentation in combination therapy.[2] No cases of tongue hyperpigmentation associated with temozolomide as a single agent have been reported before. We describe a woman of African ancestry who was receiving chemotherapy with temozolomide as a single agent and developed tongue hyperpigmentation.

CASE REPORT

A 37-year-old black woman was diagnosed with Isocitrate dehydrogenase (IDH) wild-type glioblastoma in the left parietal lobe, in another hospital center, in August 2020. She was treated initially with left parietal craniotomy with excision of lesion. The surgery was followed by focal radiation therapy (RT) and a course of concomitant daily temozolomide at 75 mg/m^2 in September 2020, at our hospital. The patient was previously treated with levetiracetam and during chemotherapy, she was treated with ondansetron according to the protocol. One week after the initiation of chemotherapy with daily temozolomide as a single agent, the patient presented multiple black macules on the dorsal surface of the tongue, without any associated symptoms (Fig. 1). She never had similar lesions in the past, nor change in the color of the palms, fingernails or other parts of the body. At the same time, the radiotherapy and concomitant chemotherapy with temozolomide (Stupp protocol) was interrupted, following the histological revision of the tumor at our hospital to a diagnosis of embryonal tumor (World Health Organization - WHO, Grade IV). The patient started neuro-axis RT with boost to the residual lesion plus Vincristine weekly, according to the Packer protocol. Two months after stopping temozolomide chemotherapy, there was an improvement in patient's tongue hyperpigmentation with almost complete resolution (Fig. 2).

DISCUSSION

Temozolomide is an alkylating agent that performs the alkylation of adenine/guanine residues, leading to DNA damage, thus inhibiting DNA and cellular replication.

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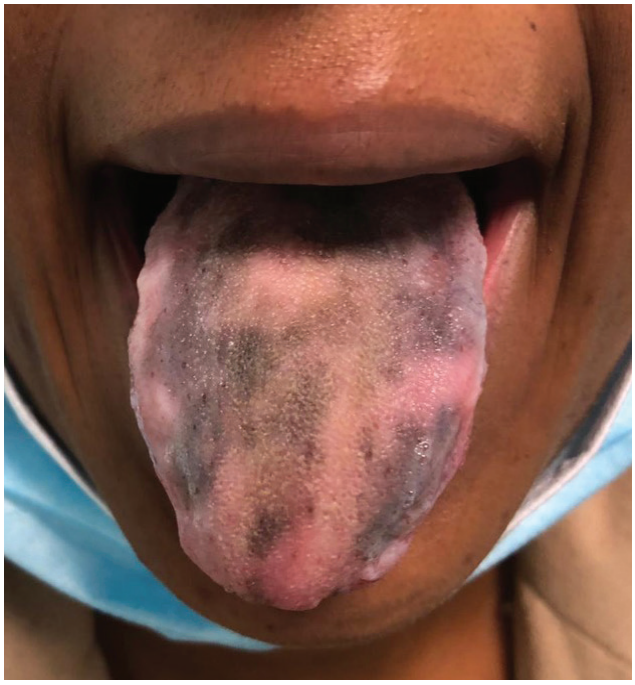

Figure 1 – Frontal view of the tongue with multiple macular areas of hyperpigmentation, one week after chemotherapy with temozolomide as single agent

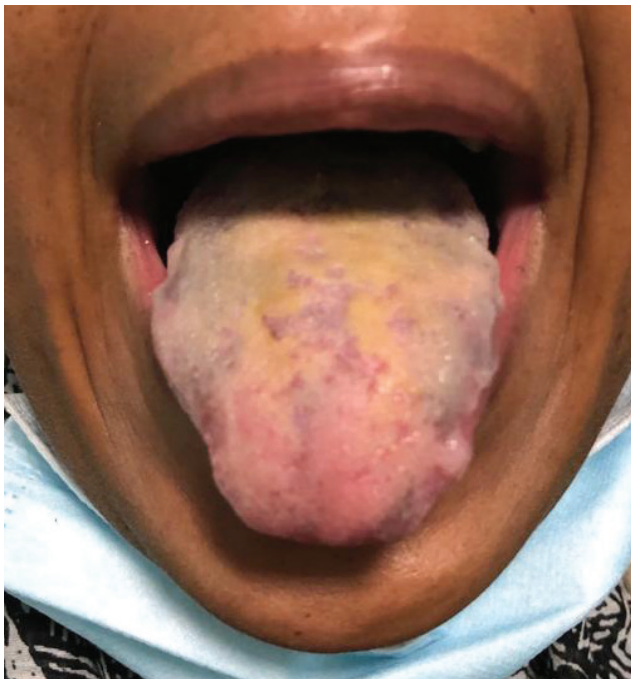

Figure 2 – Frontal view of the tongue, two months after stopping chemotherapy with temozolomide as single agent

It is indicated in the treatment of glioblastoma multiforme, anaplastic astrocytoma, Ewing's sarcoma, neuroendocrine tumors, pituitary tumours and other tumors.[3]

Antineoplastic therapy, as a single agent or combination drug, can be associated with several side effects including dermatological, neurological, gastrointestinal and others.[2] Hyperpigmentation of the tongue has been associated with various chemotherapy agents, specifically cytotoxic drugs, that commonly induce pigmentation and may affect the hair, nails, and mucous membranes in local or diffuse patterns.[1,2,4,5] Although the exact pathophysiological mechanism is still not well understood, four mechanisms of drug-induced pigmentation are suggested. The first mechanism may be associated with stimulation of the excessive production of melanin and deposition on the lingual mucous membrane; the second mechanism involves accumulation of the drug, saturating dermal macrophages, which are unable to eliminate these foreign bodies; the third mechanism involves synthesis of new pigment, such as lipofuscin, under the direct influence of the insulting drug. The fourth mechanism involves deposition of iron: drug-induced dermal vascular damage may induce leakage of red blood cells into the dermis, and subsequent lysis of these red blood cells throughout the dermis can result in pigmentation.[1] Hyperpigmentation of the tongue following a treatment with chemotherapy has been reported with several single agents such as doxorubicin, cyclophosphamide, capecitabine and Adriamycin.[4,6-9] A report of tongue hyperpigmentation and brown longitudinal streaking with blue lunular pigmentation of the fingernails and toenails has been described following use of combination chemotherapy involving cisplatin, ifosfamide, temozolomide, and vincristine.[2] Drug-induced pigmentation often occurs slowly and worsens over the course of months to years upon initiation of the offending agent.[2] The tongue hyperpigmentation, previously described, is usually self-limited and disappears a few weeks after treatment is completed.[4] There are not reported cases of tongue hyperpigmentation associated with levetiracetam and ondansetron.

This case constitutes a challenge for healthcare professionals and the patient, as it is not an expected or described side effect in temozolomide monotherapy, which emphasizes the importance of documenting these cases in order to guide healthcare professionals in managing the expectations of the patients and also the potential adverse effects associated with certain drugs.

AUTHORS CONTRIBUTION

LG: Draft of the manuscript, literature research, corresponding author.

JM, DS: Contributed to the draft of the manuscript, critical review, approval of the final version.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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Alopecia Porphyrinica in a Patient with Chronic Hepatitis C

Alopécia Porfirínica em Doente com Hepatite C Crónica

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Keywords: Alopecia; Porphyria Cutanea Tarda; Hepatitis C, Chronic
Palavras-chave: Alopecia; Hepatite C Crónica; Porfiria Cutânea Tardia

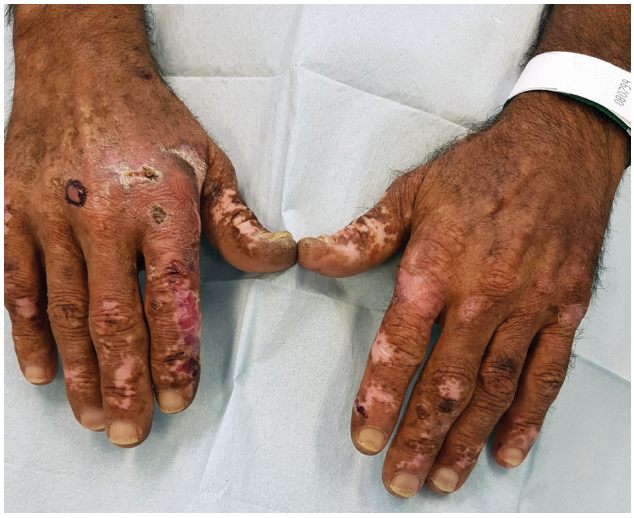

Figure 1 – Serohemorrhagic bullae, erosions and whitish stellate scars on the hands

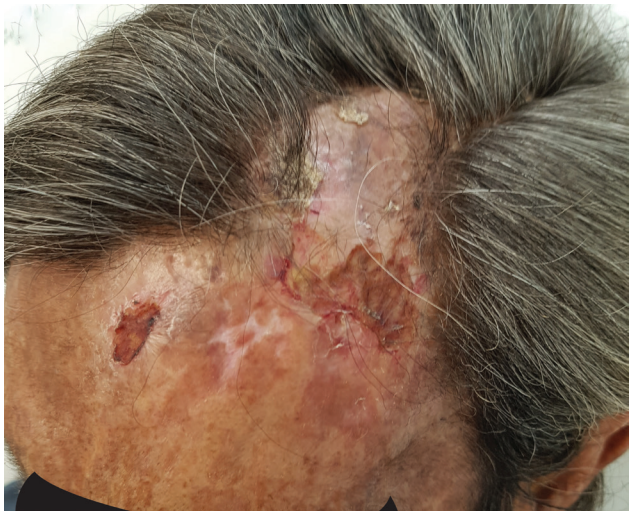

Figure 2 – Cicatricial alopecia, as shown by the white-reddish sclerotic plaque with loss of hair, crusts and depressed scars on the left forehead

A 52-year-old homeless man, having a medical history of chronic hepatitis C virus (HCV) infection and drug abuse, presented with a 10-year history of hair loss and recurrent bullae on the hands and scalp. Physical examination revealed tense serohemorrhagic bullae, erosions and whitish stellate scars (Fig. 1). He also had focal cicatricial alopecia (Fig. 2). Severe facial dermatoheliosis (i.e. a specific dermatological term to describe specific skin changes induced by chronic UV exposure) and hypertrichosis were seen. The histopathology examination of a fresh bullae showed dermal papillae protruding into a subepidermal bulla in a festooned pattern (i.e. a histopathological hallmark presentation of porphyria cutanea *tarda*. Its presence, albeit not necessary, is strongly suggestive of the diagnosis). High levels of uroporphyrin (1843 µg/24 hours) and serum ferritin (1103 ng/mL) were present. A diagnosis of porphyria cutanea tarda (PCT) was made. HCV infection was treated with direct-acting antivirals. Topical corticosteroids and regular phlebotomies were offered for PCT, but the patient was lost to follow-up.

PCT is a photosensitive disorder strongly associated with HCV infection.[1] Scleroderma-like changes are uncommonly found (2% - 18%),[2] but they may present as scarring alopecia, either isolated or as a feature of florid presentations.

AUTHORS CONTRIBUTION

SB, BD: Case description and discussion.
AR: Critical review of the work.

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.

INFORMED CONSENT

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Portuguese Consensus Recommendations for Next-Generation Sequencing of Lung Cancer, Rare Tumors, and Cancers of Unknown Primary Origin in Clinical Practice

Recomendações Portuguesas para a Utilização de Sequenciação de Nova Geração na Prática Clínica em Tumores do Pulmão, Raros e de Origem Primária Desconhecida

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ABSTRACT

Next-generation sequencing (NGS) has been implemented in clinical oncology for diagnosis, prognosis, and therapeutic guidance. Among the various NGS applications in molecular oncology, we focused on the following topics: laboratory standards for targeted gene panels (somatic mutations) and therapeutic guidance based on NGS of lung cancer and rare cancers, namely sarcomas and cancers of unknown primary. Multiple quality control checkpoints should be addressed in the pre-analytical phase for good quality and interpretation of the NGS results. It includes tumor size and cellularity, tissue processing and decalcification, tumor fraction, tumor viability, fixatives, and staining. Communication between clinicians and laboratory support is also essential. In lung cancer, all patients with non-squamous non-small cell lung cancer should be tested with a NGS panel, and it should include not only genes with approved targeted therapies (*ALK*, *BRAF*, *EGFR*, *MET*, *NTRK*, *RET*, and *ROS1*) but also genes with potentially actionable genomic alterations (*HER2* and *KRAS*). Since there is a lack of extensive knowledge regarding the use of NGS in rare tumors, performing comprehensive genomic profiling panels to better manage the disease is recommended. Moreover, other patients with other incurable solid tumors may benefit from being included in biomarker-driven clinical trials. Multidisciplinary tumor boards with the participation of experts with the ability to integrate genomic profiling data are essential to tailor the best strategy for each patient. Considering that there are no national guidelines, this article aims to guide laboratory and clinical practice for the use of NGS in the context of lung cancer, rare tumors, and cancer of unknown primary in Portugal.

Keywords: High-Throughput Nucleotide Sequencing; Lung Neoplasms/genetics; Neoplasms, Unknown Primary/genetics; Sarcoma/genetics

RESUMO

Na área da oncologia clínica, a sequenciação de nova geração (NGS) foi implementada com o objetivo de contribuir para o diagnóstico, prognóstico e orientação terapêutica. A utilização de NGS em oncologia molecular é vasta, focalizando-se estas recomendações nas: normas laboratoriais para painéis genéticos direcionados (mutações somáticas) e na orientação terapêutica baseada em NGS de cancro do pulmão e cancros raros, nomeadamente sarcomas e cancros de origem desconhecida. Para que sejam obtidos resultados de NGS com a qualidade que permita a sua correta interpretação, devem ser abordados múltiplos controlos de qualidade na fase pré-analítica que disponibilizem informação sobre o tamanho e celularidade do tumor, processamento e descalcificação de tecidos, fração tumoral, viabilidade do tumor, fixadores e coloração utilizados. A comunicação entre os diferentes intervenientes no processo, em particular entre os clínicos e o laboratório também contribui, de forma inequívoca, para a interpretação dos resultados de NGS. Todos os doentes com cancro do pulmão de não pequenas células não escamoso devem ser testados com um painel de NGS, que deve incluir não só genes com terapias dirigidas aprovadas (*ALK*, *BRAF*, *EGFR*, *MET*, *NTRK*, *RET* e *ROS1*), mas também genes com alterações genómicas identificadas como potenciais alvos terapêuticos (*HER2* e *KRAS*). Dada a escassez de evidência científica sobre a utilização de NGS em tumores raros, recomenda-se a realização de painéis genómicos abrangentes que poderão

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contribuir para uma melhor gestão da doença. Adicionalmente, outros doentes, com outros tumores sólidos incuráveis, podem beneficiar da inclusão em ensaios clínicos orientados por biomarcadores. A realização de reuniões multidisciplinares com a participação de diferentes especialistas capazes de integrar dados dos perfis genómicos são fundamentais para a escolha da melhor estratégia para cada doente. Considerando que não existem recomendações nacionais, este artigo visa orientar a prática laboratorial e clínica para a utilização de NGS em tumores do pulmão, raros e cancros de origem primária desconhecida em Portugal.
Palavras-chave: Neoplasias Primárias Desconhecidas/genética; Neoplasias do Pulmão/genética; Sarcoma/genética; Sequenciação de Nucleotídeos em Larga Escala

INTRODUCTION

Molecular mechanisms that can impact tumor initiation, growth, progression, and metastasis[1] have become clinically valuable with the advance of targeted therapies and diagnostic tools, contributing to precision medicine.[2]

When assessed by hematoxylin-eosin staining, the pathologist assesses the morphology of the tumor tissue and the pattern of expression in order to provide an overview of tissue characteristics.[3] Although some biomarkers can be assessed by immunohistochemistry (IHC) with a predictive result (e.g., ER, PR, HER2), the detailed molecular characterization is not entirely clarified this way, and developments in sequencing techniques allow for a more detailed understanding of the tumor molecular mechanisms.[3]

Next-generation sequencing (NGS) is a technology that decodes genetic information easier, faster, and at a lower cost compared to than Sanger sequencing. The term NGS includes a group of technologies, also called *massively parallel sequencing*, that share the ability to simultaneously analyze multiple genomic regions through data capture from millions of sequencing reactions.[4-7] This technique is linked with bioinformatic tools which are essential for analyzing the vast amount of generated data.[8] These data can be used to support patient management.[3]

NGS is a widely accepted molecular biology technique that can analyze DNA and RNA, contributing to an accurate diagnosis and the detection of actionable mutations that sensitize the tumor to specific therapies.[2,9] Its applicability ranges from clinical research, usually with broader approaches like whole-genome, whole-exome, and transcriptome, to more focused clinical applications by targeted gene panels evaluation.[2] The NGS workflow comprises three main processes: library preparation, sequencing, and bioinformatics data analysis.[10]

Among the various NGS applications in molecular oncology, we will focus on laboratory standards for targeted gene panels (somatic mutations) and their use in the diagnosis, therapeutic guidance, and prognosis of lung carcinomas and rare tumors such as sarcomas and cancers of unknown primary.

The aim of this article is to provide recommendations for the use of NGS in Portuguese clinical practice since there are currently no national guidelines.

Practical recommendations for NGS from an expert group

NGS is a relatively new field in solid tumors, and therefore few guidelines are currently available,[11,12] including the latest 2020 ESMO guidelines.[13] The genes to be tested depend on the testing purpose and will also rely on the availability of targeted treatments and reimbursement schemes that are different in each country.[13] The elected method should be an assay detecting clinically actionable genomic alterations, defined by the clinical diagnosis and/or availability of targeted drug therapies. Genomic alterations

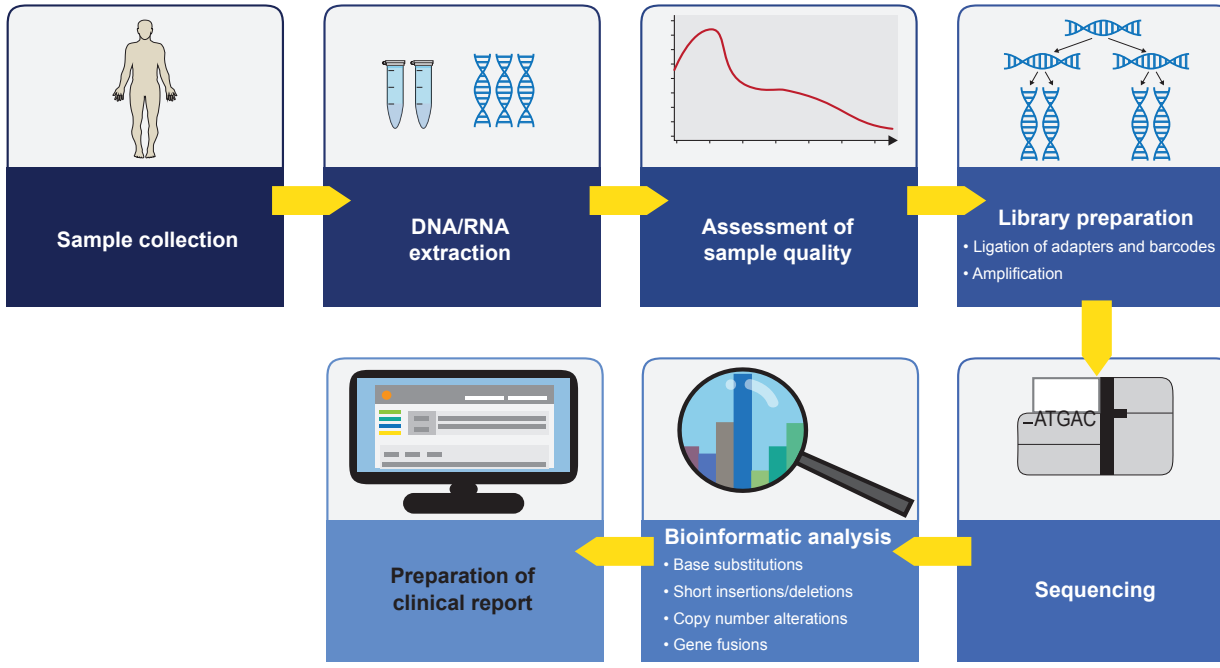

Figure 1 – Next-generation sequencing workflow

associated with acquired resistance to target-based agents are also being included in genomic panels.[11]

Although NGS is a powerful technique to assess clinically relevant genetic alterations in tumors, some issues need to be addressed in the NGS workflow (Fig. 1), namely in its implementation, laboratory standards, and data interpretation.

NGS

What pre-analytical conditions should be met to perform NGS?

Recommendation: The multiple quality control checkpoints in the pre-analytical phase should include tumor size and cellularity, tissue processing and decalcification, tumor fraction, tumor viability, and fixatives and staining. In a patient with multiple specimens available from different timepoints, the most recent one should be used for NGS. Morphologic control is one of the leading quality control checkpoints that could significantly impact the reliability and interpretation of NGS results. Testing procedures needed to be validated locally and that include defining minimum DNA input and minimum tumor cell content. Multidisciplinary communication is essential for the optimization of specimen acquisition and processing.

The success of molecular diagnostics in oncology depends on various factors. One of the most important is the proper selection of tumor samples, the quantity, the quality of the tumor specimen, and tumor cellularity.[14,15] Every stage from collecting the specimen to its analysis can influence NGS results, treatment decisions, and clinical outcomes. One of the main challenges in the molecular oncology of solid tumors is the quality of nucleic acids, as the process of formalin fixation of specimens could compromise DNA and RNA integrity through chemical cross-linking of protein and nucleic acids.[16,17] Nevertheless, with the improvement of methods of processing formalin-fixed paraffin-embedded (FFPE) material, that is no longer a limitation for the use of NGS as routine testing in these samples.[11,18] Moreover, nucleic acid yield could be low due to limited tissue obtained through fine-needle aspiration and core-needle biopsy.[15]

Therefore, there is a need to standardize pre-analytical conditions to ensure the accuracy and reliability of the results, which increases the credibility and the use of NGS in clinical practice.

The pre-analytical factors associated with the success of NGS are the cold ischemia time, tissue fixation, processing and storage, sample size and cellularity, tumor cell fraction, tumor viability, use of decalcification, and other factors such as the presence of blood and mucin.[15]

Type of procedure: Tumor samples can be obtained by surgical resection, endobronchial biopsy excisions, fine-needle aspiration, and core-needle biopsy.[15] The first is associated with a larger tumor section and higher DNA yield.[15,19]

Tumor site: After adjusting for tumor size and, in the absence of decalcification, the various solid tumors, sampled by the different procedures showed similar NGS success rates.[19]

Tissue processing and storage: Direct preservation of tissue specimens ideally follows a controlled and defined process, such as formalin (buffered formalin at 10%) fixation beginning immediately after removal.[20,21] The volume of buffered formalin should be adequate since the fixation time is dependent on the specimen volume (minimum six hours/maximum 72 hours).[21,22] The preferred tissue conservation methods to preserve the molecular profiles of cells and cytology samples are FFPE tumor tissue and cryopreservation (-80ºC to -190ºC).[23,24]

Tumor size and cellularity: One of the most important pre-analytical requirements for a reliable NGS assay is the specimen's quantity and quality. The obtained material should be sufficient for a correct and accurate morphologic diagnosis and control and posterior biomarker analysis through NGS.[14,24] The size of the tumor area and the number of viable tumor cells will determine the DNA yield.[15,19] The morphological diagnosis and cellularity estimation in tissue and cytological material are vital to the correct execution of NGS.[11] The sample should include as many tumor cells as possible, but NGS works with very low tumor cell content. Each laboratory should define its threshold. If a sample is below the defined threshold and there is a negative result, then there is a risk of being a false negative and that should be clearly stated in the report.

A molecular pathologist, using macrodissection, should guide the nucleic-acid extraction area, marking tumor tissue and normal tissue, thus increasing the yield of the sequencing technique. It requires specific staff training and institutions should have dedicated pathologists to perform this task.[14,15]

Tumor fraction: Another important point to consider is the proportion of tumor cells in the specimen, the so-called tumor fraction or tumor purity.[14] Diverse NGS assays could have different tumor fraction requirements due to different NGS platforms' distinctive technical sensitivities. Ideally, a NGS assay should be able to detect a mutation with a variant allele frequency (VAF) as low as 5%. Given the heterozygous nature of somatic mutations in most tumors and the possibility of genetic intratumor heterogeneity, the selected specimen area should have a tumor cell fraction of at least 20%.[15,25-29] In small specimens, such as core needle biopsies and cytology samples, NGS could be less successful than in larger samples such as the ones obtained from resection and excisions. Other types of samples may be acceptable as long as they are validated locally in the laboratory.

Tumor viability: The viability of the tumor tissue is essential for the success of NGS. Necrosis can occur among the different tumor types and should be carefully analyzed and interpreted.[15]

Decalcification of bone specimens: Before decalcification, it is necessary to perform an adequate tissue fixation.[15] Only bony samples that undergo formic-acid- or EDTA-based decalcification procedures are adequate for both

morphologic analysis and NGS.[30] A solution consisting of formic acid (88% formic acid diluted 1:10 in distilled water) with constant stirring can be used for tissue decalcification after formalin fixation. For checking the decalcification process, x-ray analysis may be performed daily until decalcification is demonstrated by radiographic evidence. For neutralization of the decalcified block, a solution of 0.3% ammonium hydroxide in 80% ethyl alcohol can be used.[19]

How to implement NGS in a diagnostic laboratory?

Recommendation: Quality control should be implemented for all pre-analytic, analytic, and interpretation procedures. If that is not possible, an external molecular biology laboratory is the best option.

It is essential to test and validate the method before the implementation of any NGS-based diagnostic test. Besides all the pre-analytical conditions included in the previous section that should be under periodical quality control assessment, the assay's adequacy to cover clinically relevant variants to a sufficient depth for variant calling, as well as optimization of the bioinformatics pipeline to detect relevant mutations, are essential.[11,31] This typically includes an assessment of sensitivity, specificity, and reproducibility, in addition to other performance characteristics as required by the relevant laboratory-certifying authority. The performance characteristics of NGS assays can be readily determined for the most common somatic alterations. However, the reliability of detection for uncommon somatic alterations or specific categories of mutations, such as large insertion-deletions (indels) or certain chromosomal alterations may be more challenging to establish. Hence, laboratories should have procedures to verify any unexpected results, namely those that are discordant with other results, equivocal, or of compromised confidence. These include obtaining alternative samples, testing with an orthogonal methodology with a different selectivity of the primary NGS method, or testing in another laboratory. If the local molecular biology laboratory does not have sufficient capacity, an external NGS laboratory with quality control is the best option.

Which information should be given to the molecular biology laboratory?

Recommendation: Information to be given to the molecular biology laboratory should include:

1. Patient identification, with at least two identifiers.
2. Diagnosis or potential diagnosis, with staging information, if available.
3. Test results from other previously performed molecular tests, if available.
4. Specimen information, type of specimen, tumor cell content.
5. The objective of the test:
   a. Differential diagnosis?
   b. Need to distinguish between two primary tumors or between one primary tumor and one metastasis?
   c. Therapy decision at diagnosis?
   d. Therapy decision after resistance acquisition to previous targeted therapy?
   (describing previous therapies and their sequence)
   e. More comprehensive biomarker testing for possible inclusion in a clinical trial or off-label therapy?

For optimizing the NGS analysis and consequently obtaining better results for patients, communication between the clinic, pathology laboratory and molecular biology laboratory is key.

Which information should be included in the NGS report sent to the clinician?

Recommendation: The report should be standardized and include all the essential information for the correct interpretation of the results. An example of an appropriate report for clinicians is included in the Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/17680/Appendix_01.pdf).

There are international diagnostic standards such as ISO 15189 and guidelines that should be followed to report the results.[11,12,31-34] The length of the report should not exceed one page, be easily read, and contain the following essential information: patient identification, sample type, tissue/tumor type, tissue sample identification, the restatement of the clinical question, percentage of tumor sample content used for NGS, depth coverage, NGS method used, sensitivity of the method, reference sequences for tested genes, results using the Human Genome Variation Society mutation nomenclature, how/where additional information can be obtained, biological and clinical interpretation of the results and conclusion.[11] Information on the variant allele frequencies (VAFs) may also be provided. Results and conclusions according to the clinical question should be highlighted. Moreover, the results section should be divided into clinical, clinical trials, and research domains.[11] Clinical domain: variants with a current approved therapeutic indication or used for diagnosis, prognosis, or therapeutic monitoring; clinical trials domain: variants that can predict response to new drugs and allow the enrollment in a clinical trial; research domain: variants of uncertain clinical significance, with an unknown biological role in oncogenesis.[11]

Decisions based on the NGS results should consider all other pathology and clinical data and eventually be discussed in a multidisciplinary or molecular tumor board (MTB) context.

Lung cancer

Lung cancers are classified into two main histological types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC has a higher prevalence accounting for 85% of bronchogenic carcinomas.[29,35] Among NSCLC, adenocarcinoma and squamous cell carcinoma

are the most common histologic types.[35]

In which histological type of lung cancers should NGS be performed?

Recommendation: Due to the expanding number of actionable genomic alterations, all non-squamous NSCLC should be tested with a NGS panel. Exceptions may be considered in the multidisciplinary meeting.

NGS allows the identification of genomic alterations down to single-base-pair resolution with a high level of precision and accuracy.[35] This leads to therapeutic progress and the development of new drugs.[36] Approximately 69% of patients with NSCLC could have a potentially actionable molecular target.[37]

In adenocarcinoma, the most commonly mutated oncogenes are *KRAS*, *EGFR, PIK3CA*, *MET,* and *BRAF*; the mutated tumor suppressors are *TP53*, *STK11*, *KEAP*, *NF1*, *RB1,* and *CDKN2A*.[38] Gene fusion and rearrangement of *ALK*, *ROS1*, *NTRK1*, *NRG1*, *FGFR4*, *ERBB4,* and *RET* are also important modifications in lung adenocarcinoma, with *ALK*, *ROS1*, *NTRK* and *RET* already having approved targeted therapies.[38-43] Squamous-cell carcinoma is characterized by fewer mutations in genes coding for receptor tyrosine kinase and a higher frequency of mutations in tumor suppressor genes such as *TP53*, *PTEN*, *NOTCH1,* and *RB1*.[44] FGFR-gene family rearrangements have been reported in squamous-cell cancer and can be targetable.[45] While the known adenocarcinoma targetable alterations are well characterized, personalized medicine in the treatment of squamous cell carcinoma is lagging far behind adenocarcinoma and NGS could be a powerful technique to identify genetic alterations and allow easy integration in clinical practice.[46]

At what disease stage should NGS be performed?

Recommendation: All patients with advanced disease must be tested. Patients with limited disease, candidates for adjuvant targeted therapies e.g., *EGFR*, should be considered for testing. Moreover, patients with limited disease are at high risk of progression; thus, we recommend that earlier testing, at diagnosis, may be considered. At the time of progression, in the setting of targeted therapy, a new NGS test is recommended.

The recommended treatment for patients with stage I-II NSCLC is surgery complemented by adjuvant chemotherapy for some patients.[47] For patients with locally advanced (stage IIIA-B) unresectable tumors, stereotactic body radiotherapy with concurrent chemotherapy delivery is recommended.[47] More recently, durvalumab (anti-PD-L1 antibody) has been approved as maintenance therapy in this setting.[48,49] In these earlier stages of the disease, there is currently no role for targeted therapy outside clinical trials. However, this is expected to change shortly, with the ADAURA trial results showing a disease-free survival (DFS) advantage for using osimertinib in stages IB-IIIA EGFR mutation-positive NSCLC.[50] Despite these treatment advances, patients diagnosed at this stage are at high risk of relapse and survival remains low.[51]

At the time of progression, genomic-guided treatments are becoming increasingly relevant. Although tissue re-biopsy to repeat molecular testing is not always feasible, blood liquid biopsy is likely to become a validated routine alternative.

Which are the genes that should be included in the NGS panel?

Recommendation: The initial testing NGS panel should include genes with clinical relevance:

- genes with approved targeted therapies: *ALK, BRAF, EGFR, MET, NTRK, RET and ROS1*
- other oncodrivers: *HER2 and KRAS.*

Recently published ESMO guidelines for NGS recommend performing tumor multigene NGS to assess level I genomic alterations.[13] Level I genomic alterations include *EGFR*, *M*ET, and *BRAF* mutations and *ALK*, *ROS1*, *NTRK,* and *RET* fusions.[13] Additionally, larger panels can be used considering the total cost burden strategy, assuming an accurate ranking of alterations is reported. For clinical research centers, performing multigene sequencing panels in molecular screening programs is highly recommended. It will increase access to innovative drugs and speed up clinical research.[13]

EGFR somatic mutations have been reported in 20% of Caucasians with NSCLC, and therapies with tyrosine kinase inhibitor (TKI) targeting EGFR were pioneers in the era of targeted therapy.[52,53] In Portuguese patients with metastatic NSCLC, 14% harbor *EGFR* somatic mutations.[54] Among the first-generation EGFR-TKI are gefitinib and erlotinib which have been used as first-line therapy in patients harboring *EGFR* mutations (exon 21 L858R and exon 19 deletions).[55,56] Second generation EGFR-TKI such as afatinib and dacomitinib inhibit the four members of the ERBB family.[57,58] Resistance to first- and second-generation EGFR-TKI is common amongst patients and is mediated by the T790M resistance mutation in half of them.[53] Third-generation irreversible EGFR-TKI targeted therapy, such as osimertinib, is selective for EGFR-TKI sensitizing and T790M resistance mutations.[59-61] Treatment with osimertinib as second-line therapy requires the detection of the *EGFR T790M* mutation in a liquid biopsy or in a tissue re-biopsy. If a liquid biopsy is chosen as the initial test, and if negative, a tissue re-biopsy should be performed due to sensitivity limitations, if feasible.[62] The search for mechanisms of resistance to EGFR-TKI therapy should not be limited to *T790M EGFR* mutations, as other genes are involved as well, including *HER2, BRAF* (V600E), *KRAS* (G12D/C, A146T), and *PIK3CA* mutations, SPTBN1-ALK fusions and MET amplifications.[53] Moreover, as resistance to osimertinib also occurs, other mutations in the *EGFR* gene, such as C797S, should also be searched for. Therefore, NGS testing in this context should be performed.[42]

ALK rearrangements occur in 5% of lung adenocarcinomas, namely in non-smoker younger adults.[53] Crizotinib was the first ALK inhibitor with identified resistance emerging from two major secondary mutations, L1196M and C1156Y.[53,63] Alectinib is a second-generation ALK inhibitor with high selectivity for *ALK* rearrangements that overcomes these two mutations.[64] Brigatinib, ceritinib, and lorlatinib are also specific inhibitors that can overcome resistance through other secondary mutations.[42] Thus, in case of resistance, and although it is not included in the international guidelines[62], tissue re-biopsy or liquid biopsy for NGS analysis can be a potential tool for the choice of a subsequent ALK inhibitor.[42,53,65-67]

ROS1 rearrangements are less common than *ALK* rearrangements and share approximately 70% of homology.[53] Crizotinib has also shown activity in *ROS1* rearrangements and is approved for this indication.[42,68] Entrectinib is a ROS1 inhibitor with the ability to penetrate and remain in the central nervous system. It is approved for the treatment of advanced NSCLC in *ROS1* positive patients. Data from entrectinib and crizotinib approvals plus the ongoing trials with other inhibitors, highlight the need to test for *ROS1* fusion in NSCLC to broaden the therapeutic options in these patients.[69]

NGS is a validated technique for sequencing *ALK* and *ROS1* rearrangements, with an advantage over immunohistochemistry and fluorescence *in situ* hybridization (FISH) for detecting potential actionable molecular alterations.[70]

Among the 1% - 2% of advanced NSCLCs with *BRAF V600E* mutation, 85% are adenocarcinomas.[71] The combination of dabrafenib with trametinib, a *MEK* inhibitor, demonstrated good results in previously untreated patients.[72]

In *NTRK* fusion-positive NSCLC tumors, larotrectinib and entrectinib have shown effective results and are approved for the treatment of these patients.[73] *NTRK* gene fusions are present in 0.2% - 3.3% of NSCLC tumors and the approval was based on basket trials that included different solid malignancies.[74-76]

RET rearrangements are commonly found in younger patients below 60 years old, non-smokers, or former light smokers.[77] So far, multikinase inhibitors (like cabozantinib, lenvatinib, and vandetanib) have been used *off label* for *RET*-positive NSCLC. Nevertheless, both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have already approved more selectively targeted and potentially effective TKIs, like pralsetinib and selpercatinib.[78,79]

Mutations and amplification of *MET* are commonly found in elderly patients and non-smokers, and therapies such as crizotinib, capmatinib, and tepotinib have shown effectiveness in treating these patients.[80-82] Thus, *MET* should be included in earlier NGS panel tests.[83]

Besides these seven genes implemented in clinical practice, other target driver oncogenes have been studied in NSCLC, such as *KRAS* mutations and *HER2* mutations.[42,53,83-85]

KRAS is the most commonly mutated oncogene in NSCLC (in approximately 30% of the patients), and although it is not considered in the ESMO recommendations, it should be included in all NGS genomic panels since it is a prognostic biomarker.[62,86] Moreover, *KRAS* mutations when associated with *TP53* and *STK11* co-mutations may be vulnerable to immunotherapy approaches.[84,87,88] Aside from that, sotorasib and adagrasib, two novel *KRAS* G12C small molecule inhibitors, showed overall early promising results with antitumor activity and a manageable safety profile in heavily pre-treated patients with NSCLC.[89,90]

HER2 mutation in NSCLC is an oncologic driver mutation that is a promising target for treating patients with advanced disease that progressed on or after platinum-based therapy. Trastuzumab deruxtecan has promising results in this context.[85]

Repotrectinib is a novel next-generation ROS1-TKI inhibitor with promising results, namely high activity in the central nervous system, in ROS1 positive and recalcitrant crizotinib-resistant G2032R mutation NSCLC.[91]

A summary of the approved therapies and under clinical investigation is summarized in Table 1.

Should an NGS-based liquid biopsy be performed in lung cancer?

Recommendation: Liquid biopsy for NGS evaluation of actionable mutations can be performed, if validated, at diagnosis or in cases of resistance/progression under targeted therapy when a tissue biopsy cannot be performed. Moreover, liquid biopsies can complement tissue biopsies, providing an in-depth idea of tumor heterogeneity.

Tissue biopsies remain irreplaceable as the basis for histopathological diagnosis. Liquid biopsies (circulating cell-free tumor DNA) are routinely used to detect resistance mutations upon progression on TKIs, such as *EGFR* T790M mutation after first-line therapy with EGFR inhibitor, to address intra-tumor heterogeneity and also in the detection of new mutations.[110] In the context of diagnosis, liquid biopsy is recommended in the following specific situations[36,111]:

- tissue biopsy is not safe, contraindicated, or declined by the patient;
- the quantity and quality of tumor tissue is not enough for a correct molecular diagnosis;
- delay is expected to occur in the availability of tumor tissue.

In case of resistance to first or second-line EGFR-TKI, NGS using circulating cell-free DNA has shown high sensitivity, identifying multiple resistance alterations.[112,113]

Recently, the FDA approved a pan-cancer cell-free DNA (cfDNA) based comprehensive genomic profiling assay for cancers of solid origin.[114] cfDNA is isolated from plasma derived from anti-coagulated peripheral blood of cancer patients collected in specific tubes.[114] Apart from the *in vitro* diagnosis of a high number of target genes and although these biomarkers are currently not validated in lung cancer, these tests also allow the assessment of TMB (tumor mutational burden), MSI (microsatellite instability), and tumor

Table 1 – Targeted therapies for genomic alterations in advanced NSCLC

Genomic alteration	Targeted therapy
Approved	
***EGFR*-activating mutations**	Gefitinib[92]
	Erlotinib[93]
	Afatinib[94]
	Dacomitinib[95]
	Osimertinib[96]
***ALK* translocation and rearrangements**	Crizotinib[97]
	Alectinib[98]
	Ceritinib[99]
	Brigatinib[100]
	Lorlatinib[101]
***ROS1* translocation and rearrangements**	Crizotinib[97]
	Entrectinib[102]
***BRAF V600E* mutation**	Dabrafenib with trametinib[103,104]
***NTRK* fusions**	Larotrectinib[105]
	Entrectinib[102]
***MET* mutation and amplification**	Capmatinib[106]
	Tepotinib[82]
***RET* translocation and rearrangements**	Pralsetinib[107]
	Selpercatinib[108]
In clinical trials	
***HER2* mutation**	Trastuzumab deruxtecan[85]
***KRAS* mutation**	Sotorasib[89]
	Adagrasib[109]
***ROS1* translocation and mutation**	Repotrectinib[91]

fraction values.

Also, in case of resistance to an ALK inhibitor, tissue re-biopsy or liquid biopsy for NGS analysis enables the evaluation of the resistance mutation profile to first-line therapy. However, this is currently not really necessary for the choice of the second-line ALK inhibitor.[42,53,65-67]

Although some reports show some discrepancies between tissue- and liquid- biopsies, this could be due to the intrinsic differences of the sample, assays, bioinformatics tools, and tumor heterogeneity.[8] Each liquid biopsy test must be validated. There are already commercially approved NGS-based liquid biopsy tests based on a clinically validated comprehensive cell-free DNA analysis that identifies recommended biomarkers at the rate as high as standard-of-care tissue genotyping, with high tissue concordance.[115,116]

Rare tumors

Rare Cancers Europe defines rare cancers as occurring in fewer than six out of 100 000 people each year.[117] This type of tumor includes, among others, sarcomas and cancers of unknown primary and are more difficult to prevent, diagnose and treat than other types of cancer.[118] Tissue samples from 5945 patients with refractory and underexplored cancer types were analyzed in the clinical trial National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH). The results showed that actionable genomic alterations were present in 11.9% of samples and resistance mutations were present in 71.3% of the specimens. The authors conclude that NGS is feasible and can help sort patients to investigational therapy in genetically complex tumors.[119]

Sarcomas

Sarcomas are rare mesenchymal malignancies that include at least 100 different subtypes.[120,121] Diagnosis is based on morphological, immunohistochemical, and molecular characterization, although a differential diagnosis is often difficult.[121] In the most recent years, a significant number of translocations have been described, helping in the diagnosis and characterization of sarcomas. Nevertheless, in clinical practice, targeted therapies are still poorly implemented, except for some subtypes such as gastrointestinal stromal tumor (GIST) and the use of pazopanib in soft tissue sarcomas.[122-124]

How can NGS be used in sarcomas?

Recommendation: NGS is a valuable tool in the management of sarcomas. Comprehensive genomic profiling NGS panels are already available, but they are expensive. More data is essential and therefore patients should be included in biomarker-driven clinical trials when available. These patients should be managed in centers with a considerable number of patients/year and multidisciplinary teams.

A NGS panel containing probes for 87 fusion genes and seven genes with frequent copy number alteration was designed and applied on 113 DNA samples extracted from FFPE samples of soft-tissue and bone sarcomas. FISH or RT-PCR had already analyzed these samples and the results showed that NGS is a feasible and cost-effective approach allowing to test a wide range of genomic aberrations at the same time, which can be very useful for the differential diagnosis of sarcomas.[121]

Current therapy includes cytotoxic chemotherapy drugs and tyrosine kinase inhibitors such as pazopanib for most patients with metastatic sarcomas.[125] Other approved targeted therapies for actionable mutations are imatinib, sunitinib, and regorafenib for GIST and imatinib for dermatofibrosarcoma protuberans.[122,126]

A recent study involving 133 tumor samples from patients diagnosed with different types of sarcomas analyzed over 400 cancer-related genes and found that most mutations are in genes related with the cell cycle, including *TP53*, *CDKN2A/B* and *RB1,* with 75 mutations occurring in targetable genes. Tumor mutational burden and microsatellite instability were generally low.[125] Another study using comprehensive genomic profiling also showed that among different types of sarcoma such as leiomyosarcoma, dedifferentiated liposarcoma, osteosarcoma, well-differentiated liposarcoma, carcinosarcoma and rhabdomyosarcoma, 93% of patients had at least one genomic alteration with a mean of six mutations per patient.[122]

Besides actionable mutations, chromosomal translocations and fusion genes were common among different types of sarcomas, such as rhabdomyosarcoma, Ewing's sarcoma, synovial sarcoma, and liposarcoma.[127] The resulting chimeras have altered functions and potential oncogenic activity.[128] This could increase the possibility of using a targeted therapy even in combination with conventional chemotherapy.[127] Immunotherapy, even in combination with other therapies, could be another option for sarcomas with high MSI and/or high TMB.[129] *NTRK* fusions are rare genomic alterations that can be present in several sarcoma subtypes and have been identified as an agnostic biomarker for the treatment response with entrectinib and larotrectinib.[130,131]

Taken together, these results highlight the importance of incorporating comprehensive panels in the diagnosis and management of sarcoma, thus allowing a more precise differential diagnosis, treatment and the inclusion of patients in basket clinical trials.

Cancers of unknown primary

Cancers of unknown primary (CUP) account for approximately 3% - 5% of all tumors. CUPs can be divided into two main subgroups, with very different prognosis.[132] Approximately 85% of the diagnosed CUPs are included in the category of neoplasms with poor prognosis and short overall survival.[132,133] These are a group of heterogeneous metastatic tumors in which it is not possible to identify the site of origin and are the main focus of this subchapter. The treatment of these tumors is mainly based on chemotherapy regimens guided by histopathological features and likely site of origin. However, the results are not encouraging.[133]

How can NGS be used in cancers of unknown primary?

Recommendation: This type of tumor should be treated in centers with many patients/year. Since the only available therapy for CUPs with a poor prognosis is chemotherapy, the inclusion of these patients in Clinical Trials should be encouraged. Comprehensive NGS panels should be performed earlier in CUP, aimed at helping diagnose and direct therapy. Nevertheless, NGS testing must not delay the beginning of the approved therapy. The best strategy for each patient should be discussed on an individual basis and in multidisciplinary meetings.

NGS could represent a new option for these patients, providing insights into tumor biology, identifying potentially targetable genomic alterations aiming at personalizing the treatment of CUPs.[134] Comprehensive genomic profiling by NGS in CUP[133,135,136] has shown that although it was not possible to find a CUP-specific molecular signature,[136] almost all CUP samples have at least one clinically relevant genomic alteration that could influence personalized therapy.[135]

A recently published systematic review also showed that 85% of CUPs harbored at least one genomic alteration and 47.3% presented a potentially targetable alteration for approved/off-label/clinical trial available drugs.[134] The key mutated genes were *TP53, RAS, CDKN2A, MYC, ARID1A, PIK3CA, or BRAF*, which are not tissue-specific.[137-139]

One of the comprehensive CUP analyses also evaluated response to immune checkpoint blockade therapy. Mutations in 592 genes and 52 gene fusions in 389 cases of CUP were analyzed. TMB and MSI were calculated from the NGS results and showed that 11.8% of CUPs have high TMB and 1.8% MSI.[139] Thus, the multiplex testing approach calculated that 28% of CUPs harbored one or more predictive biomarkers (high-MSI, PD-L1, and/or high-TMB) to immune checkpoint blockade.[139]

Treatment decisions based on genomic alterations identified in CUP are only reported in case-studies since clinical trials are still ongoing.[140] A recently published non-randomized phase II clinical trial, conducted in Japan and involving 97 previously untreated patients with an unfavorable subset of CUP, showed that the gene expression profile and genomic alterations identified by NGS contributed to the

site-specific treatment of patients.[141]

The CUPISCO study is a phase II clinical trial for a CUP population that, through NGS techniques, will compare the efficacy and safety of targeted therapy or cancer immunotherapy versus platinum-based chemotherapy. The tested drugs include alectinib, vismodegib, ipatasertib, olaparib, erlotinib, bevacizumab, vemurafenib, cobimetinib, trastuzumab, pertuzumab, atezolizumab, carboplatin, paclitaxel and gemcitabine.[142]

One of the problems of tissue-agnostic therapy is the extrapolation of therapeutic actionability since the clinical activity of the mutations could differ between cancer tissues.[134,140] So far, putative primary sites have always been considered in CUP therapy.[134]

Nevertheless, the Cancer Genome Atlas demonstrated recently that the tissue of origin of a tumor might be less critical to prognosis and response to therapy than the identification of targetable mutations and optimal predictive biomarkers.[143,144]

FINAL CONSIDERATIONS

In which additional tumor types should NGS be applied as a diagnostic and therapy management tool or as a guide to clinical trials?

In these Portuguese consensus recommendations, lung cancer, sarcomas, and CUPs were included as the main types of solid tumors in which NGS must be performed for accurate tumor characterization and therapeutic decision. Nevertheless, there are other types of solid tumors, namely metastatic breast, and colorectal cancer, that may benefit from NGS use. According to the latest ESMO recommendations, NGS should be routinely used in patients with prostate cancer, ovarian cancers, and cholangiocarcinoma.[13] Patients with breast, colorectal, pancreatic and hepatocellular cancer should be included in clinical research for molecular screening programs proposing access to clinical trials with innovative agents.[13]

Comprehensive analysis of different types of cancers such as lung, colorectal, breast, ovarian, and sarcoma demonstrated that high-throughput techniques could identify an actionable mutation in a high percentage of cases, with clinical benefit in 25% of the patients.[145] Of the patients broadly tested by NGS, 37% have at least one clinically relevant mutation that could be targeted, cost-effectively, with either an off-label therapy or included in a clinical trial.[146] In the context of immuno-oncology, NGS is also an emerging technology through the identification of tumors with high MSI and TMB that will determine whether the patient is likely to respond to immunotherapy.[147,148]

The contribution of NGS to the deep understanding of genomic alterations that could occur in various tumor types has been studied in clinical trials, namely basket trials.[149] Basket trials include patients that harbor the same genomic alteration regardless of the histology.[131] These trials are of particular interest for patients with hard-to-treat tumors, which are commonly advanced tumors after multiple lines of therapy and rare malignancies.[150] Different basket trials have been designed and developed to detect genomic alterations that have a clinical benefit to patients with intractable cancers.[149,150] The results of different basket trials have demonstrated that molecular-targeted cancer therapy could benefit unmanageable cancers; nevertheless, there is a need to improve the selection of the molecular alterations.[151-174] In Portugal, there are two ongoing biomarker-driven clinical trials in solid tumors with FGF/FGFR aberrations[175] and *NTRK* Fusion-Positive Tumors.[176] The TAPISTRY trial, a phase II global multicentric study that evaluates the safety and efficacy of targeted therapies or immunotherapy in patients with an unresectable, locally advanced or metastatic solid tumor that harbor actionable genomic alteration or high TMB validated by NGS, is currently recruiting in Portugal.[177]

Finally, evaluation of patient outcomes showed that NGS testing could positively impact progression-free survival with manageable healthcare costs[178] and improved clinical outcomes in 33% of metastatic cancer patients with "hard to treat" disease.[153]

Thus, the benefit of NGS testing may impact the management of cancer patients, regardless of tumor type. Apart from the previously mentioned indications (non-squamous NSCLC, sarcoma, and CUP), NGS can be proposed for patients with metastatic disease, pending the discussion between the patient and the attending clinician of the expected benefits and the economic evaluation by the healthcare payer.[8]

CONCLUSION

NGS is a powerful technique that can identify predictive biomarkers for a targeted therapy that otherwise might not be considered. With this information, along with the expertise of multidisciplinary molecular tumor boards, clinicians will develop an optimal treatment plan for their patients. At this time, non-squamous NSCLC, sarcomas, and CUP are the main tumor types in which NGS should be used. However, in metastatic patients, NGS can be considered for all types of tumors where the standard of care has been exhausted and targeted therapy is still possible, especially if clinical trial participation is considered. NGS should also be considered if a new drug is available or there is a high clinical suspicion of the presence of a rare mutation. Furthermore, NGS data should be integrated with medical records and hospital information systems, allowing the creation of data repositories for clinical investigation. These approaches will allow for more patients to be treated with different therapeutic options.

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Clostridioides difficile Treatment Protocol and Healthcare Burden

Protocolo de Tratamento e Encargos em Saúde da Infeção por Clostridioides difficile

Keywords: Clostridium Infections; Fidaxomicin; Health Care Costs; Portugal
Palavras-chave: Controle de Gastos em Saúde; Fidaxomicina; Infecções por Clostridium; Portugal

In a previous edition of Acta Médica Portuguesa two original articles focused on an important topic – *Clostridioides difficile* infection (CDI).[1,2]

The epidemiology of *Clostridioides* infection in Portugal reveals that most patients were aged over 70 years-old and most episodes (56%) occurred in hospitalized patients. This infection is associated very frequently with recent antibiotic exposure. There is a recurrence rate between 12%[1] and 14%.[2]

However, neither of the articles focused on the treatment protocol used.

Vancomycin and metronidazole have been considered the main treatment of *Clostridioides* infection. However, in the latest update of the American guidelines on management of clostridioides difficile infection in adults., fidaxomicin has been stated as the preferred treatment in initial infection.[3] On the other hand, National Institute of Health and Care Excellence (NICE) guidelines recommend use of fidaxomicin as a second-line treatment and/or if there is a relapse within 12 weeks.[4] Fidaxomicin is a narrow spectrum macrocyclic antibiotic approved for the treatment of CDI, but is a more expensive drug, which could restrict its access in clinical practice.

A standard treatment course of fidaxomicin is estimated to cost on average between €3866.95 and €4128.92 euros, while a standard course of oral vancomycin costs on average between €61.47 and €328.06 euros.[5] However, cost-effectiveness studies have found fidaxomicin to be cost effective in most scenarios, regardless of the severity of the infection.[6]

We would like to add to this reflection that prolonged length of stay in internal medicine wards, which sometimes occurs due to social issues, may increase the risk of nosocomial infection and the use of large spectrum antibiotics, and could consequently increase the risk of *Clostridioides* infection.

Besides the evidence, from our experience, the preferred treatment in Portugal is still vancomycin. Even in relapsing infection, use of fidaxomicin has not been allowed, and prolonged pulsed regimens of oral vancomycin have been advocated by local antibiotic stewardship commissions, leading to longer length of hospital stay.

We wonder if the overall costs of occupying a hospital bed on prolonged treatment with oral vancomycin would not be higher than the costs of using fidaxomicin for 10 days.

According to a national cost-effectiveness study of this drug, the bulk of the costs stems from the hospital stay. Although the cost of treatment is higher with fidaxomicin compared with vancomycin (€2736 *vs* €71), the overall cost in the following year including length of stay, complications and outpatient appointments is similar between the two drugs. Additionally, the number of recurrences is lower with fidaxomicin.[7] So, as suggested by Gouveia *et al* in a study using a Markov model to compare one group under vancomycin treatment and another under fidaxomicin, the ratio of the increased costs over the health gain is favorable to the use of fidaxomicin.[8]

So, apart from focusing only on medication costs, we would like to raise awareness to the overall costs of *Clostridioides* infection. We understand that, although vancomycin is an interesting option in case of initial infection, in relapsing infection, and depending on the overall costs associated with prolonged length of stay, fidaxomicin should be a more accessible treatment. Developing national recommendations and standardization of clinical practice would be useful to guide physicians and infection control committees.

AUTHORS CONTRIBUTION

ICC, MA: Draft and approval of the final version of the manuscript.

TF: Conception and approval of the final version of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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DATA CONFIDENTIALITY

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COMPETING INTERESTS

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Analysis of an Observational Study: The Patient Perspective Regarding Ambulatory Surgery

Análise de um Estudo Observacional: A Perspetiva do Doente Sobre a Cirurgia em Regime de Ambulatório

Keywords: Ambulatory Surgical Procedures; Patient Satisfaction
Palavras-chave: Procedimentos Cirúrgicos Ambulatórios; Satisfação do Doente

Dear Editor,

We enjoyed reading this article concerning ambulatory, or outpatient, surgery.[1] There are known discrepancies between clinicians' and patients' aims and objectives regarding outpatient surgery.[2] We recognise the importance of analysing patients' perspectives, as medicine is patient oriented and patient satisfaction and understanding goes on to impact practice. From personal encounters with patients and senior doctors, we have begun to appreciate the importance of providing adequate information to patients regarding their concerns and expectations.

We found the prospective study's use of primary data from a local hospital to be commendable. We also found that valuable information was gathered about patient knowledge regarding outpatient surgeries that could be used to inform public health initiatives in the future. However, we did find some areas that could be compounded on in future investigations.

We believe it would be useful to include some graphical representations of data analysis. At certain points in the paper, different data analysis methods were mentioned, and *p*-values given. However, there were no graphs or visual tools used to supplement them. We believe adding them would lend more legitimacy to the results gathered.

In terms of the data collection, there are some areas that could be expanded upon. While a range of patients were questioned in terms of gender, age and education level, all patients came from the same hospital, which indicates that all the patients were from the same geographical area. This introduces the possibility of a confounding factor that impacts their perceptions about outpatient surgery, for example local public health education programs.

Furthermore, we noticed that there were many non-respondents in the questionnaire. For example, 48.6% did not respond when asked what they fear most concerning ambulatory surgery. This may lead to misinterpretation of the data in certain respects. For instance, the study investigated the association between knowledge about ambulatory surgery and general level of education and found it to be not statistically significant (*p* value of 0.099). However, those that did not understand the procedure may have not responded to the question rather than answering negatively, thus diluting the results.

As future clinicians, we recognise the importance of studies that focus on patients' perspectives as we try to lean towards patient-oriented care. This study has identified a deficit in patient understanding regarding ambulatory surgery in their local population, and it is our opinion that further research should be conducted to fully investigate this issue.

AUTHORS CONTRIBUTION

AMP, APP: Substantial contributions to the conception and design of the work. Drafting and critical review of the paper.

VP: Substantial contributions to the conception and design of the work. Drafting and critical review of the paper, approval of the final version of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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DATA CONFIDENTIALITY

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COMPETING INTERESTS

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Is COPD a Cause of Premature Death?

A DPOC é Causa de Morte Prematura?

Keywords: Mortality, Premature; Pulmonary Disease, Chronic Obstructive/mortality
Palavras-chave: Doença Pulmonar Obstrutiva Crónica/mortalidade; Mortalidade Prematura

Patients Chronic obstructive pulmonary disease (COPD) is currently the third most important cause of death worldwide.[1] Although absolute COPD deaths and crude mortality rates are rising in many countries, age-standardized mortality rates have been declining in many parts of the world. This has led some authors to argue that, in the future, patients will die with COPD but not from COPD.[2] In the present study we aimed to understand the circumstance of death in COPD patients and if COPD can be considered a cause of premature death.

A total of 303 stable COPD patients over 40 years of age, diagnosed according to the GOLD criteria, were recruited consecutively at the ambulatory pulmonology clinic of Guimarães Hospital, between March 2016 and May 2017. The exclusion criteria were refusal to participate or inability to understand simple questionnaires, such as the COPD assessment test or the Medical Research Council Dyspnoea Questionnaire. The patients were followed for 46 to 60 months, and some preliminary results are discussed in the present paper. A statistical analysis was performed with SPSS Statistics for Windows software, version 22.0. Armonk, NY: IBM Corporation. The level of significance was set at $p < 0.05$.

Five years after the start of recruitment, patients who had died were identified, and their ages and clinical notes, by the time of death, were recorded and analysed. The study was approved by the Ethics Committee of Guimarães Hospital.

The demographic, clinical and functional characteristics

Characteristics	n = 303
Male gender	241 (79.5)
Mean age (years)	67.5 ± 10.2
Age ≥ 65 years	186 (61.4)
Mean smoking amount (pack/years)	49.3 ± 32.4
mMRC grade ≥ 2	185 (61.1)
Frequent ECOPD (≥ 2/last year)	115 (38.0)
Post-brochodilator FEV_1%	53.2% ± 19.7
GOLD stage	
I	30 (9.9)
II	127 (41.9)
III	106 (35.05)
IV	40 (13.2)
GOLD 2017 classification	
A	70 (23.1)
B	120 (39.6)
C	7 (2.3)
D	106 (35.0)

Data shown as mean ± S/D or n (%)
mMRC: Medical Research Council Dyspnoea Questionnaire; ECOPD: COPD exacerbations; GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease

of the 303 COPD patients, by the time of their recruitment, have been previously published,[3,4] and some are presented in Table 1.

In the meantime, 61 patients (20.13%) died. Their median and mean age of death was, respectively, 77.00 and 77.02 (± 8.78) years, being 77.00 and 77.45 (± 8.51) years for male patients and 76.50 and 74.13 (± 10.6) years for female patients. The mean FEV_1% of the patients who died and those still alive was 43.36 and 54.40, respectively (P = 0.032), at the time of recruitment. However, we found no statistically significant association between death and the GOLD classification nor with a history of frequent exacerbations.

Thirty-two patients presented COPD exacerbation with acute-on-chronic respiratory failure by the time of death. Pneumonia, heart failure, advanced stage lung cancer and kidney failure were the other most important causes of death. In 27 patients, two or more different disorders contributed and were present at the time of death.

COPD exacerbation with acute-on-chronic respiratory failure was the most important cause contributing to death, suggesting that most of these patients have died, in fact, because of COPD. Taking into account the current average life expectancy of the Portuguese population[5] – 81.06 years, 78.07 for men and 83.67 for women – COPD was associated with a shorter life expectancy, particularly in female patients.

COMPETING INTERESTS

The authors have no competing interests to declare related to this study.

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A Case Report of Acute Hepatitis of Unknown Origin

Caso Clínico de Hepatite Aguda de Origem Desconhecida

Keywords: Biomarkers; Child; Disease Outbreaks; Hepatitis
Palavras-chave: Biomarcadores; Criança; Hepatite; Surtos de Doenças

Dear Editor,

Since the first international alert on the 5th April 2022 and the ongoing news, probable cases of hepatitis of unknown origin have been reported in children worldwide. The etiology and pathogenic mechanisms of the disease remain under investigation, and so far the evidence suggests adenovirus or SARS-CoV-2 as being the most likely infectious causes, although toxins, drugs or environmental exposures have been considered as well. Further hypotheses point out a novel pathogen or variant of adenovirus or SARS-CoV-2.[1]

In Portugal, according to the most recent data from the European Centre for Disease Prevention and Control (ECDC), published on the 1st July there are only 19 suspected cases.[2]

We report, to the best of our knowledge, the very first suspected case of non-viral A-E hepatitis in Portugal.

The patient was a previously healthy 22-month-old female child, with a history of SARS-CoV-2 infection in January 2022. During April 2022, she presented with prolonged fever (maximum 40.2ºC) that was managed with antipyretics, not exceeding therapeutic daily doses, with complete resolution after day-10. She also presented with anorexia and malaise, and on days four and five with non-bloody diarrhea. On day nine she had limited vomiting.

During the acute illness there were no signs of jaundice, choluria or acholic stools. A good general appearance was kept throughout the disease course.

With no relevant previous results, follow-up bloodwork

at day-11 showed elevation of serum aspartate and alanine aminotransferase (1163 U/L and 814 U/L respectively), lactate dehydrogenase (1003 U/L), alkaline phosphatase (358 U/L) and gamma-glutamyl transpeptidase (239 U/L), and hence a diagnosis of acute hepatitis was made. Abnormal results had nearly normalized by day-23 of symptom onset. Liver function tests, as well as bilirubin levels, remained normal throughout the rest of the disease course.

Microbiologic evaluation excluded hepatitis A-E virus. The serology for SARS-CoV-2 was IgG positive and IgM negative, suggesting a non-recent infection. A subspecies C adenovirus was isolated in the respiratory tract. No toxicology tests were performed. No relevant epidemiological link was found, including recent trips, or known contact with similar cases.

This case strengthens the role of adenovirus as a possible etiologic agent, identifying a similar enteric subtype when compared with both respiratory and fecal samples from children in the United Kingdom.[3] It also emphasizes a possible consequence of adenovirus infection in children previously infected by SARS-CoV-2, supporting previous knowledge on the subject.[4]

The nonspecific clinical spectrum should be emphasized, suggesting that this entity can present even in the absence of more specific clinical signs of hepatitis. On another note, it is important to raise awareness that not all potential cases progress to acute liver failure or hospital admission, and that there are milder courses of disease as reported here.

We recommend a systematic approach to all cases of acute hepatitis, highlighting the need for a thorough clinical and epidemiological characterization and reporting.

AUTHORS CONTRIBUTION

All authors contributed equally to this manuscript.

PROTECTION OF HUMANS AND ANIMALS

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DATA CONFIDENTIALITY

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

INFORMED CONSENT OF THE PATIENT

Obtained.

COMPETING INTERESTS

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Commentary to the Paper "Prevalence of the Most Frequent Neuropsychiatric Diagnoses in Hospitalized SARS-CoV-2 Patients Evaluated by Liaison Psychiatry: Cross-Sectional Study"

Comentário ao Artigo "Prevalence of the Most Frequent Neuropsychiatric Diagnoses in Hospitalized SARS-CoV-2 Patients Evaluated by Liaison Psychiatry: Cross-Sectional Study"

Keywords: COVID-19; Delirium; Mental Health Services; Psychiatry; Referral and Consultation
Palavras-chave: COVID-19; Delírio; Encaminhamento e Consulta; Psiquiatria; Serviços de Saúde Mental

Dear Editor,

We have read with great interest the article by Fernandes *et al*[1] recently published in Acta Médica Portuguesa reporting the prevalence of neuropsychiatric diagnoses in hospitalized COVID-19 patients evaluated by a consultant liaison (CL) psychiatry unit. They found delirium to be the most prevalent neuropsychiatric condition in this population, which is in line with what has been described, although lower prevalence rates were reported by other studies.[2] There are several articles reporting a high prevalence of delirium in COVID-19 patients but there is a lack of studies directly comparing the incidence and prevalence of delirium between COVID-19 and non-COVID-19 hospitalized patients. Therefore, it is still unclear if SARS-CoV-2 infection is specifically associated with delirium leading to a higher risk for this syndrome when compared with other similar diseases.

We recently analyzed the referral pattern to our CL psychiatric unit (March 2020 to March 2021) and delirium was the most prevalent condition (23.8%). Followed by depressive (18.9%) and anxious (16.9%) syndromes. However, the prevalence of delirium was not significantly different when comparing COVID-19 and non-COVID-19 patients. Jäckel *et al* in 2020 and 2021[3] evaluated the prevalence of delirium in intensive care units (ICU), and they also found that delirium was not more frequent in COVID-19 patients. In their first study, the prevalence of delirium did not differ between patients with viral acute respiratory distress syndrome due to influenza or SARS-CoV-2,[3] being actually lower in in COVID-19 patients.[3] These findings should be carefully interpreted when compared to our results, since delirium is more prevalent in ICU regardless of the primary health condition.[4] Nevertheless, the overall prevalence of delirium in hospitalized patients in a 2016 metanalysis study was approximately 23%,[4] which is similar to the reported rates in another metanalysis of delirium prevalence in COVID-19 patients.[2]

Moreover, previous authors attempted to determine if there were specific characteristics of delirium associated with COVID-19 infection, namely, if there was a specific subtype or different response profiles to pharmacological interventions.[5] However, clear evidence of distinct characteristics was not found.

Despite the apparent specificity of the neurological tropism of the virus,[2] taking all this evidence together, we must admit the possibility that SARS-CoV-2 infection may not be a specific risk factor for delirium. Its high prevalence may be related with the prevalence of other risk factors for delirium, which may be also shared by hospitalized COVID-19 patients. More studies comparing delirium in hospitalized COVID-19 and non-COVID-19 patients should be conducted.

AUTHORS CONTRIBUTION

GA, RS: First author. Data collection, conception of the work, draft of the paper.

LG, CG: Critical review of the manuscript.

FN: Draft and critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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DATA CONFIDENTIALITY

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COMPETING INTERESTS

GA, RS, LG, CG: Declared no competing interests exist.

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Comment on: Diffuse Large B-Cell Lymphoma with Axillary Cutaneous Invasion in a HIV Positive Patient

Comentário a: Linfoma Difuso de Grandes Células B com Invasão Cutânea Axilar num Doente com Infeção VIH

Keywords: HIV Infections; Lymphoma, Large B-Cell, Diffuse
Palavras-chave: Infecções por HIV; Linfoma Difuso de Grandes Células B

Dear Editor,

We read with great interest the article published by Dias *et al*.[1] The authors report the case of a 34-year-old man with untreated HIV-1 infection that was admitted to the hospital with obstructive jaundice and progressive swelling of the left axillary region.[1] An imaging study by computed tomography scan revealed an expansive 3.2 cm pancreatic mass and multiple hypodense liver lesions. Hepatic and pancreatic biopsy confirmed the presence of stage IV diffuse large B-cell lymphoma.

Additionally, on dermatological examination, the presence of multiple erythematous papules and nodules of variable size, upon an area of nontender swelling, in the left axillary region was also evident, which the authors identified as cutaneous invasion by diffuse large B-cell lymphoma.

The cutaneous manifestations of systemic lymphomas can be varied and are often non-specific. Their diagnosis relies on correlation with histopathological examination and immunohistochemical staining of an appropriate skin biopsy.[2] This procedure would be a necessary step to establish a definitive diagnosis of skin infiltration by diffuse large B-cell lymphoma.

Notably, a broad spectrum of infectious, inflammatory, and neoplastic skin conditions may develop in the setting of HIV infection,[3] particularly in severely immunosuppressed patients, who often have mixed infections or combined infectious–neoplastic or inflammatory–neoplastic lesions.[3] The reported patient had a $CD4^+$ T-cell count of 133 cells/mm^3 (11.8%), which is classified as WHO clinical stage 4 HIV infection (the severely symptomatic stage) and can encompass all the AIDS-defining illnesses.[3] In this setting, the differential diagnosis of multiple erythematous papules and nodules is broad and includes entities such as Kaposi sarcoma, cutaneous tuberculosis and non-tuberculous mycobacterial skin infections, fungal infections (for example, chromoblastomycosis, coccidioidomycosis or histoplasmosis) and cutaneous leishmaniasis.[4]

With this comment, we wish to draw attention to the importance of clinical-histopathological correlation for an accurate diagnosis of cutaneous manifestations of systemic diseases.

AUTHORS CONTRIBUTION

JB: Draft of the paper.
MC: Critical review, approval of the final version.

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Swift Reversal of Hypercortisolism-Related Dermatological Features Following Treatment in a Patient with Cushing's Disease

Reversão Rápida das Manifestações Cutâneas Associadas ao Hipercortisolismo após Tratamento da Doença de Cushing

Keywords: Alopecia/etiology; Cushing Syndrome/complications; Skin Diseases/etiology; Skin Manifestations/drug therapy
Palavras-chave: Alopecia/etiologia; Doenças da Pele/etiologia; Manifestações Cutâneas/tratamento farmacológico; Síndrome de Cushing/complicações

Cushing's syndrome (CS) is a rare disorder caused by exposure to high levels of glucocorticoids. Dermatological manifestations are common and often discriminatory of this condition.[1] We report the case of a female with an adrenocorticotropic hormone (ACTH)-dependent CS who had prominent dermatological features at presentation, which remarkably improved after treatment of the hypercortisolism.

A 74-year-old female presented with prominent and troublesome hair loss and easy bruising of the skin for nine months. She also complained about proximal muscular weakness and had recently been diagnosed with hypertension and diabetes. She denied exposure to exogenous corticosteroids. On clinical examination, she had severe frontovertical alopecia, with the scalp crown practically devoid of hair, suggestive of type III female pattern alopecia (Ludwig classification) (Fig. 1A). She also had reduced skin-fold thickness and exuberant ecchymosis in her upper limbs (Fig. 1B). Facial plethora, hirsutism, purple striae and skin hyperpigmentation were absent. Her laboratory work-up confirmed endogenous hypercortisolism, with an elevated 24h-urinary free cortisol at 2300 µg/24h (reference range: 124 - 581; urinary volume of 2 liters) and an unsuppressed cortisol level of 35.4 µg/dL (normal < 1.8 µg/dL) following a 1 mg-overnight dexamethasone suppression test. ACTH was elevated at 377 pg/mL (reference range: 7.2 - 63.3) and her serum potassium level was normal at 4.3 mmol/L (reference range: 3.5 - 5.1). The diagnosis of an ACTH-dependent CS was established and a magnetic resonance imaging (MRI) test revealed a large 3 cm-pituitary macroadenoma invading the right cavernous sinus, the sphenoidal sinus and the skull base with significant clival destruction, but with no optic chiasm compression.

The patient started on metyrapone achieving eucortisolemia within a month, after which she underwent bilateral adrenalectomy, as curative pituitary surgery had been deemed unfeasible at our multidisciplinary team meeting. Within three months, her CS-related dermatologic manifestations improved remarkably (Figs. 1C and D).

Skin manifestations in CS patients are frequent and reflect the hypercatabolic effects of cortisol excess on collagenous subcutaneous fibers.[2,3] Excessive levels of cortisol also reduce the synthesis of proteins, such as hyaluronan and proteoglycans. These proteins are important skin components, but also elements of the hair follicles and are essential for a normal hair follicle cycling and growth.[4] High levels of ACTH can also lead to overproduction of adrenal androgens, which in turn may further contribute to the CS-related alopecia. Thus, hypercortisolism may impact the fine-tuned mechanisms of hair follicles resulting in hair growth disruption and hair loss.[4]

Figure 1 – Female patient with ACTH-dependent Cushing's syndrome (A) with alopecia (B) and skin ecchymosis, (C, D) which improved remarkably within three months after the treatment of hypercortisolism

Patients with CS may first present to dermatologists with a wide and heterogeneous spectrum of dermatological features, which should be recognized and lead to a prompt referral to an endocrinologist. A timely diagnosis and treatment of CS is essential, not only to prevent the metabolic and cardiovascular complications, but also to improve the patient's quality of life. As illustrated here, CS-related dermatologic manifestations may significantly and rapidly improve after prompt therapy targeting the cortisol overproduction.

AUTHORS CONTRIBUTION

MIA: Conception of the manuscript.

PMG, PM: Critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

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

DATA CONFIDENTIALITY

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

INFORMED CONSENT OF THE PATIENT

Obtained.

COMPETING INTERESTS

All authors declared no competing interests.

FUNDING SOURCES

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Ethics in Authorship: Considerations and Concerns

Reflexão sobre Ética em Autoria Científica

Keywords: Authorship; Ethics; Retraction of Publication as Topic; Scientific Misconduct

Palavras-chave: Autoria; Ética; Má Conduta Científica; Retratação de Publicação como Assunto

Dear Editor,

The exponential proliferation of scientific publications in recent decades was accompanied by emerging issues related to ethics in research and publication. In the last five years, Retraction Watch identified 485 retracted papers involving concerns related to authorship,[1] with the more frequent issues being disputes concerning right of authorship, fake authorship, forged authorship, bought authorship, ghost authorship and honorary authorship.[2]

Local ideological concepts of authorship criteria in many clinical and research departments are outdated and do not comply with current international recommendations. Many authors fail to adhere to ethical principles or may not be aware of the definitions of authorship and its criteria. The same issues apply to conference presentations[3] which in Portugal may be decisive for medical career progression.

Ethical transgressions related to authorship discredit scientific publications and jeopardize the reputation of authors. We are aware of several widespread misconceptions and unethical historical practices in clinical departments: 1) bestowing authorship to an individual who performed diagnostic tests (e.g. radiology, histology) in the setting of everyday clinical care of patients; 2) the widespread practice of including the head of the department as the senior author in conference papers but also in research publications; 3) bestowing authorship to physicians responsible for the clinical care of patients included in research, despite not participating in the study conception, interpretation of data and draft of the manuscript; 4) extensive reciprocal authorship sharing among residents when submitting conference papers.

There are several guidelines in different fields of research which define the criteria for authorship. The most widely used in the scientific medical literature originate from the International Committee of Medical Journal Editors and comprise all of the following: 1) substantial contribution to the study conception and design, or data acquisition, or analysis and interpretation; 2) drafting or revising the article; 3) approval of the final version; 4) agreement to be accountable for all aspects of the work.[4] Strategies which may help to avoid authorship misconduct include definition of authorship prior to study initiation, use of the Acknowledgments section for collaborators who do not fulfil authorship criteria, review of journal authorship guidelines before submitting the manuscript, and increasing awareness of the types of authorship misconduct in the biomedical community.[5]

The topic of ethics and good practices in publication represents a touchstone for science production and communication. It should be included not only in undergraduate but especially in postgraduate medical curricula, in order to honour science and the academia.

AUTHORS CONTRIBUTION

IP: Conception and design of the work; literature research; first draft of the manuscript.

JP: Literature research; approval of the final version.

FN: Conception and design of the work; approval of the final version.

COMPETING INTERESTS

IP: Received payment or honoraria for manuscript writing from Roche (InfoCancro) and received support for congress fees and/or travel grants from Roche and from Gilead.

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Errata ao artigo "Reconciliação Terapêutica na Admissão de um Serviço de Medicina Interna: Estudo-Piloto", Publicado em Ahead of Print em Acta Med Port 2022.

Correction to the article "Medication Reconciliation During Admission to an Internal Medicine Department: A Pilot Study", Published as Ahead of Print on Acta Med Port 2022.

Na página 9, Figura 2 onde se lê: (assinalado a vermelho):

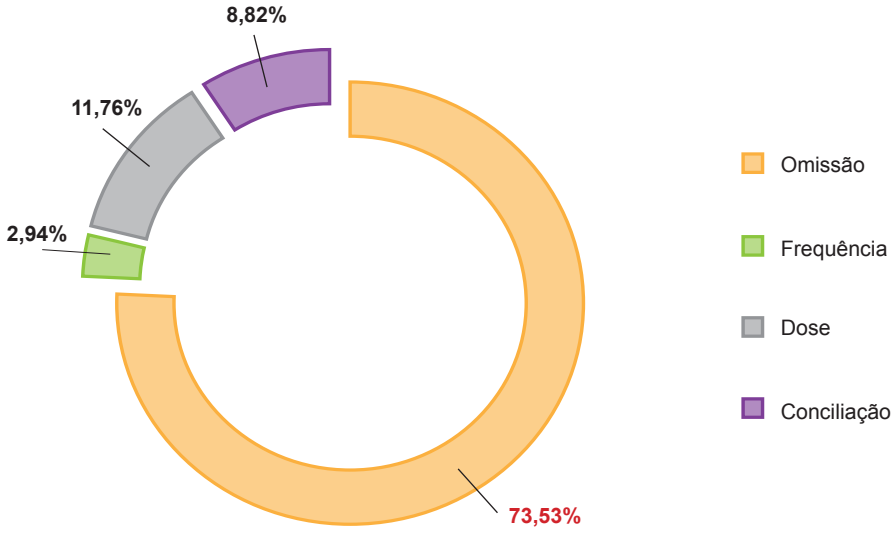

Figura 2 – Categorização das Discrepâncias Não Intencionais

Deverá ler-se: (assinalado a azul)

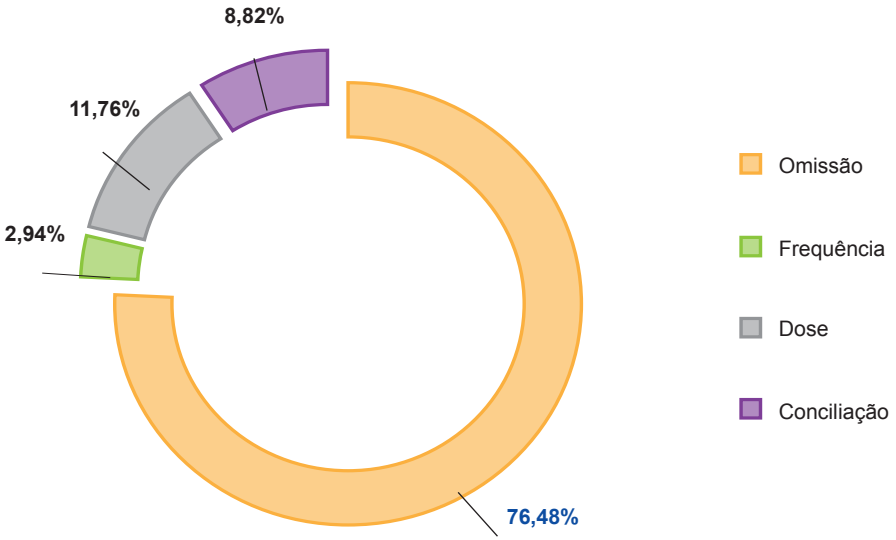

Figura 2 – Categorização das Discrepâncias Não Intencionais

Artigo publicado com erros:
https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/16892

ERRATA

On page 9, figure 2, where it reads: (in red)

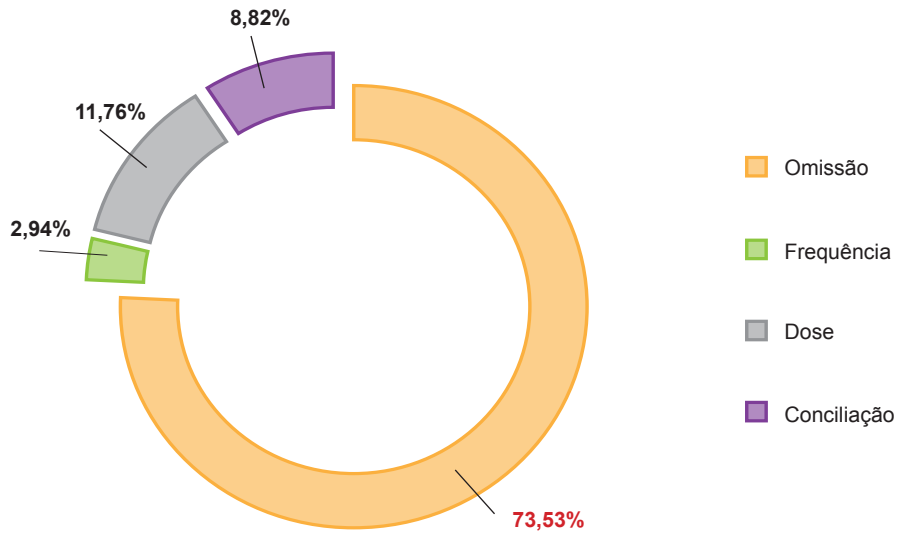

Figura 2 – Categorização das Discrepâncias Não Intencionais

It should read: (in blue)

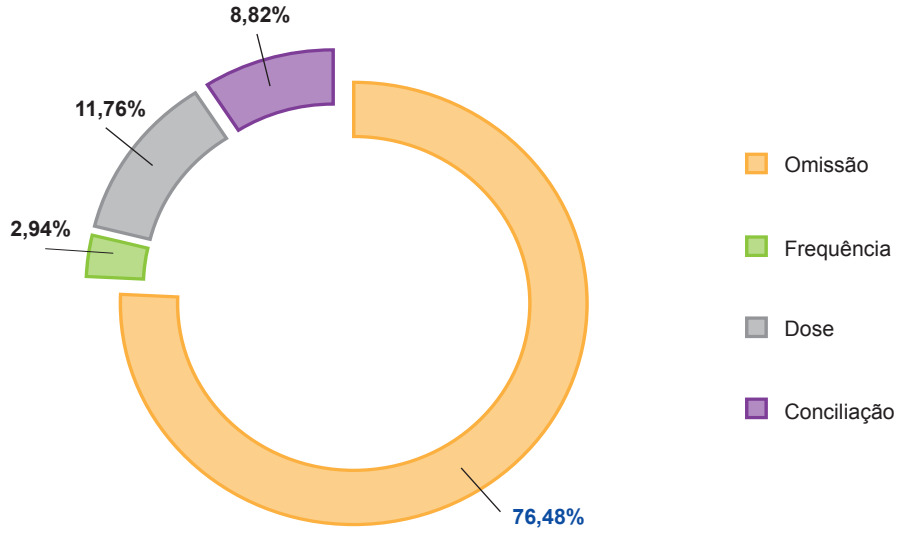

Figura 2 – Categorização das Discrepâncias Não Intencionais

Article published with errors:
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https://doi.org/10.20344/amp.18348

Correction to the article "Profiles on Adolescent Internet Addiction: A Taxonomy with Latent Profiling Analysis", Published on Acta Med Port 2022 Sep;35(9):644-651.

Errata ao artigo "Perfis na Dependência de Internet em Adolescentes: Análise Taxonómica de Perfis Latentes", Publicado em Acta Med Port 2022 Sep;35(9):644-651.

On page 646, Section 'RESULTS',
On paragraph 'Model estimation and selection',
Line 3, where it reads (in red):
Firstly, we examined fit statistics (Table 5), namely the Akaike Information criterion (AIC) (...)
It should read (in blue):
Firstly, we examined fit statistics (Table 3), namely the Akaike Information criterion (AIC) (...)

Line 9, where it reads (in red):
(...) (LRT = 57.33, $p < 0.0001$, see Table 5) (...)
It should read (in blue):
(...) (LRT = 57.33, $p < 0.0001$, see Table 3) (...)

On paragraph 'Classification accuracy of the model',
Line 1, where it reads (in red):
The probabilities of correct classification of observations are shown in the main diagonal of Table 6, (...)
It should read (in blue):
The probabilities of correct classification of observations are shown in the main diagonal of Table 4, (...)

Line 7, where it reads (in red):
The classification accuracy of the testing subsample was 96%, as shown in Table 7.
It should read (in blue):
The classification accuracy of the testing subsample was 96%, as shown in Table 5.

On page 647,
Chapter Description of profiles, 2nd paragraph, **line 4, where it reads (in red):**
This group scores negatively (less than 2.5, below the green, dotted bottom line) in all dimensions (Table 3), (...)
It should read (in blue):
This group scores negatively (less than 2.5, below the green, dotted bottom line) in all dimensions (Table 6), (...)

On page 648,
Line 6, where it reads (in red):
(...) equal parental control rates or absence thereof (Table 4).
It should read (in blue):
(...)equal parental control rates or absence thereof (Table 7).

2nd paragraph, **line 9, where it reads (in red):**
(...) compared with other profiles, are noteworthy (Table 4).
It should read (in blue):
(...) compared with other profiles, are noteworthy (Table 7).

3rd paragraph, **line 7, where it reads (in red):**
Here we also highlight users with the least difficulty in making friends (Table 4).
It should read (in blue):
Here we also highlight users with the least difficulty in making friends (Table 7).

4th paragraph, **line 10, where it reads (in red):**
(...) and lower parental control rate stood out compared with the other profiles (Table 4).
It should read (in blue):
(...) and lower parental control rate stood out compared with the other profiles (Table 7).

As a result of these corrections, the **Tables 3 to 7** are reordered as follows (original order in **red**, correct order in **blue**):

Table 3 – Means and standard deviations of Profiles and ANOVA tests

Profile	SAL	EXU	NGW	ANT	LOC	NSL	IAT
P1	1.85 (0.52)	1.91 (0.48)	1.88 (0.63)	2.19 (0.75)	2.46 (0.69)	1.44 (0.71)	1.96 (0.31)
P2	1.12 (0.22)	1.2 (0.23)	1.07 (0.16)	1.19 (0.32)	1.19 (0.26)	0.84 (0.45)	1.1 (0.13)
P3	1.44 (0.34)	1.56 (0.33)	1.22 (0.27)	1.84 (0.54)	1.50 (0.40)	1.37 (0.67)	1.49 (0.19)
P4	2.83 (0.81)	2.71 (0.81)	2.33 (0.95)	3.03 (1.11)	2.97 (0.99)	2.12 (1.18)	2.66 (0.33)
F	575.888	448.338	265.143	266.323	432.916	118.867	442.392
p-value	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Standard deviations in parenthesis.
SAL: Salience; EXU: Excessive Use; NGW: Neglect Work; ANT: Anticipation; LOC: Lack of Control; NSL: Neglect Social Life; IAT: Internet Addiction test

Table 3 – Model fit for the different profile solutions

Solution	AIC	BIC	ICL	LRT	BLRT
Two profiles	23612	23834	24691	362.59	0.000
Three profiles	23275	23570	24364	145.18	0.000
Four profiles	23156	23523	24323	57.33	0.000
Five profiles	23211	23564	24487	123.10	0.000
Six profiles	23027	23539	24884	69.87	0.000
Seven profiles	22983	23567	25024	55.7	0.000

AIC: Akaike Information criterion; BIC: Bayesian Information criterion; ICL: integrated completed likelihood; LRT: Lo-Mendell-Rubin likelihood ratio test; BLRT: bootstrap likelihood ratio test; VVE model: ellipsoidal, variable volume, variable shape, equal orientation bootstrap with 5000 replications

Table 4 – Profiles' description and chi-squared tests

Variable	n	%	Profile 1	Profile 2	Profile 3	Profile 4
Gender‡						
Female	1019	53%	54%	59%	52%	49%
Male	891	47%	46%	40%	47%	50%
With health issues						
No	1443	76%	75%	81%	75%	76%
Yes	454	24%	25%	18%	24%	23%
Sleeps well						
No	171	9%	10%	7%	7%	9%
Yes	1706	90%	90%	92%	93%	90%
Practices sports						
No	873	46%	45%	44%	46%	48%
Yes	1035	54%	55%	54%	54%	51%
Hard to make friends†						
No	1627	85%	85%	88%	89%	82%
Yes	276	15%	15%	11%	10%	17%
Parents control Internet*						
No	961	50%	50%	44%	46%	58%
Yes	943	50%	50%	54%	53%	41%

*: $p < 0.01$; †: $p < 0.05$; ‡: $p < 0.1$

Table 4 – Average latent profile probabilities for most likely profile membership (row) by latent profile (column)

Profile	1	2	3	4
1	0.997	0.000	0.000	0.003
2	0.000	1	0.000	0.000
3	0.107	0.000	0.893	0.000
4	0.077	0.000	0.009	0.915

Table 5 – Model fit for the different profile solutions

Solution	AIC	BIC	ICL	LRT	BLRT
Two profiles	23612	23834	24691	362.59	0.000
Three profiles	23275	23570	24364	145.18	0.000
Four profiles	23156	23523	24323	57.33	0.000
Five profiles	23211	23564	24487	123.10	0.000
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Seven profiles	22983	23567	25024	55.7	0.000

AIC: Akaike Information criterion; BIC: Bayesian Information criterion; ICL: integrated completed likelihood; LRT: Lo-Mendell-Rubin likelihood ratio test; BLRT: bootstrap likelihood ratio test; VVE model: ellipsoidal, variable volume, variable shape, equal orientation bootstrap with 5000 replications

Table 5 – Results of the supervised classification

	Predicted in training (n = 1340)					**Predicted in testing** (n = 575)			
Profile	**1**	**2**	**3**	**4**		**1**	**2**	**3**	**4**
1.	704	0	2	0		290	0	0	1
2.	0	109	3	0		0	55	0	0
3.	17	0	225	0		12	0	100	0
4.	16	0	1	263		9	0	1	107

Main diagonals contain correct classifications.
Classification error in the training set is 2.9% and 4.0% in the testing set.

Table 6 – Average latent profile probabilities for most likely profile membership (row) by latent profile (column)

Profile	1	2	3	4
1	0.997	0.000	0.000	0.003
2	0.000	1	0.000	0.000
3	0.107	0.000	0.893	0.000
4	0.077	0.000	0.009	0.915

Table 6 – Means and standard deviations of Profiles and ANOVA tests

Profile	SAL	EXU	NGW	ANT	LOC	NSL	IAT
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P3	1.44 (0.34)	1.56 (0.33)	1.22 (0.27)	1.84 (0.54)	1.50 (0.40)	1.37 (0.67)	1.49 (0.19)
P4	2.83 (0.81)	2.71 (0.81)	2.33 (0.95)	3.03 (1.11)	2.97 (0.99)	2.12 (1.18)	2.66 (0.33)
F	575.888	448.338	265.143	266.323	432.916	118.867	442.392
p-value	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Standard deviations in parenthesis.
SAL: Salience; EXU: Excessive Use; NGW: Neglect Work; ANT: Anticipation; LOC: Lack of Control; NSL: Neglect Social Life; IAT: Internet Addiction test

Table 7 – Results of the supervised classification

	Predicted in training (n = 1340)				**Predicted in testing** (n = 575)			
Profile	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
1.	704	0	2	0	290	0	0	1
2.	0	109	3	0	0	55	0	0
3.	17	0	225	0	12	0	100	0
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Classification error in the training set is 2.9% and 4.0% in the testing set.

Table 7 – Profiles' description and chi-squared tests

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Male	891	47%	46%	40%	47%	50%
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No	1443	76%	75%	81%	75%	76%
Yes	454	24%	25%	18%	24%	23%
Sleeps well						
No	171	9%	10%	7%	7%	9%
Yes	1706	90%	90%	92%	93%	90%
Practices sports						
No	873	46%	45%	44%	46%	48%
Yes	1035	54%	55%	54%	54%	51%
Hard to make friends†						
No	1627	85%	85%	88%	89%	82%
Yes	276	15%	15%	11%	10%	17%
Parents control Internet*						
No	961	50%	50%	44%	46%	58%
Yes	943	50%	50%	54%	53%	41%

*: $p < 0.01$; †: $p < 0.05$; ‡: $p < 0.1$

Article published with errors:
https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/17047

Na página 646, Secção 'RESULTS',
No parágrafo 'Model estimation and selection',
Linha 3, onde se lê (assinalado a vermelho):
Firstly, we examined fit statistics (Table 5), namely the Akaike Information criterion (AIC) (...)
Deve ler-se (assinalado a azul):
Firstly, we examined fit statistics (Table 3), namely the Akaike Information criterion (AIC) (...)

Linha 9, onde se lê (assinalado a vermelho):
(...) (LRT = 57.33, $p < 0.0001$, see Table 5) (...)
Deve ler-se (assinalado a azul):
(...) (LRT = 57.33, $p < 0.0001$, see Table 3) (...)

No parágrafo 'Classification accuracy of the model',
Linha 1, onde se lê (assinalado a vermelho):
The probabilities of correct classification of observations are shown in the main diagonal of Table 6, (...)
Deve ler-se (assinalado a azul):
The probabilities of correct classification of observations are shown in the main diagonal of Table 4, (...)

Linha 7, onde se lê (assinalado a vermelho):
The classification accuracy of the testing subsample was 96%, as shown in Table 7.
Deve ler-se (assinalado a azul):
The classification accuracy of the testing subsample was 96%, as shown in Table 5.

Na página 647,
No capítulo Description of profiles, 2º parágrafo, **linha 4, onde se lê (assinalado a vermelho):**
This group scores negatively (less than 2.5, below the green, dotted bottom line) in all dimensions (Table 3), (...)
Deve ler-se (assinalado a azul):
This group scores negatively (less than 2.5, below the green, dotted bottom line) in all dimensions (Table 6), (...)

Na página 648,
Linha 6, onde se lê (assinalado a vermelho):
(...) equal parental control rates or absence thereof (Table 4).
Deve ler-se (assinalado a azul):
(...)equal parental control rates or absence thereof (Table 7).

2º parágrafo, **linha 9, onde se lê (assinalado a vermelho):**
(...) compared with other profiles, are noteworthy (Table 4).
Deve ler-se (assinalado a azul):
(...) compared with other profiles, are noteworthy (Table 7).

3º parágrafo, **linha 7, onde se lê (assinalado a vermelho):**
Here we also highlight users with the least difficulty in making friends (Table 4).
Deve ler-se (assinalado a azul):
Here we also highlight users with the least difficulty in making friends (Table 7).

4º parágrafo, **linha 10, onde se lê (assinalado a vermelho):**
(...) and lower parental control rate stood out compared with the other profiles (Table 4).
Deve ler-se (assinalado a azul):
(...) and lower parental control rate stood out compared with the other profiles (Table 7).

Resultado destas correções, as **Tabelas 3 a 7** são reordenadas da seguinte forma (ordem original assinalada a **vermelho**, ordem correcta a **azul**):

Table 3 – Means and standard deviations of Profiles and ANOVA tests

Profile	SAL	EXU	NGW	ANT	LOC	NSL	IAT
P1	1.85 (0.52)	1.91 (0.48)	1.88 (0.63)	2.19 (0.75)	2.46 (0.69)	1.44 (0.71)	1.96 (0.31)
P2	1.12 (0.22)	1.2 (0.23)	1.07 (0.16)	1.19 (0.32)	1.19 (0.26)	0.84 (0.45)	1.1 (0.13)
P3	1.44 (0.34)	1.56 (0.33)	1.22 (0.27)	1.84 (0.54)	1.50 (0.40)	1.37 (0.67)	1.49 (0.19)
P4	2.83 (0.81)	2.71 (0.81)	2.33 (0.95)	3.03 (1.11)	2.97 (0.99)	2.12 (1.18)	2.66 (0.33)
F	575.888	448.338	265.143	266.323	432.916	118.867	442.392
p-value	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Standard deviations in parenthesis.
SAL: Salience; EXU: Excessive Use; NGW: Neglect Work; ANT: Anticipation; LOC: Lack of Control; NSL: Neglect Social Life; IAT: Internet Addiction test

Table 3 – Model fit for the different profile solutions

Solution	AIC	BIC	ICL	LRT	BLRT
Two profiles	23612	23834	24691	362.59	0.000
Three profiles	23275	23570	24364	145.18	0.000
Four profiles	23156	23523	24323	57.33	0.000
Five profiles	23211	23564	24487	123.10	0.000
Six profiles	23027	23539	24884	69.87	0.000
Seven profiles	22983	23567	25024	55.7	0.000

AIC: Akaike Information criterion; BIC: Bayesian Information criterion; ICL: integrated completed likelihood; LRT: Lo-Mendell-Rubin likelihood ratio test; BLRT: bootstrap likelihood ratio test; VVE model: ellipsoidal, variable volume, variable shape, equal orientation bootstrap with 5000 replications

Table 4 – Profiles' description and chi-squared tests

Variable	n	%	Profile 1	Profile 2	Profile 3	Profile 4
Gender‡						
Female	1019	53%	54%	59%	52%	49%
Male	891	47%	46%	40%	47%	50%
With health issues						
No	1443	76%	75%	81%	75%	76%
Yes	454	24%	25%	18%	24%	23%
Sleeps well						
No	171	9%	10%	7%	7%	9%
Yes	1706	90%	90%	92%	93%	90%
Practices sports						
No	873	46%	45%	44%	46%	48%
Yes	1035	54%	55%	54%	54%	51%
Hard to make friends†						
No	1627	85%	85%	88%	89%	82%
Yes	276	15%	15%	11%	10%	17%
Parents control Internet*						
No	961	50%	50%	44%	46%	58%
Yes	943	50%	50%	54%	53%	41%

*: $p < 0.01$; †: $p < 0.05$; ‡: $p < 0.1$

Table 4 – Average latent profile probabilities for most likely profile membership (row) by latent profile (column)

Profile	1	2	3	4
1	0.997	0.000	0.000	0.003
2	0.000	1	0.000	0.000
3	0.107	0.000	0.893	0.000
4	0.077	0.000	0.009	0.915

Table 5 – Model fit for the different profile solutions

Solution	AIC	BIC	ICL	LRT	BLRT
Two profiles	23612	23834	24691	362.59	0.000
Three profiles	23275	23570	24364	145.18	0.000
Four profiles	23156	23523	24323	57.33	0.000
Five profiles	23211	23564	24487	123.10	0.000
Six profiles	23027	23539	24884	69.87	0.000
Seven profiles	22983	23567	25024	55.7	0.000

AIC: Akaike Information criterion; BIC: Bayesian Information criterion; ICL: integrated completed likelihood; LRT: Lo-Mendell-Rubin likelihood ratio test; BLRT: bootstrap likelihood ratio test; VVE model: ellipsoidal, variable volume, variable shape, equal orientation bootstrap with 5000 replications

Table 5 – Results of the supervised classification

	Predicted in training (n = 1340)					**Predicted in testing** (n = 575)			
Profile	**1**	**2**	**3**	**4**		**1**	**2**	**3**	**4**
1.	704	0	2	0		290	0	0	1
2.	0	109	3	0		0	55	0	0
3.	17	0	225	0		12	0	100	0
4.	16	0	1	263		9	0	1	107

Main diagonals contain correct classifications.
Classification error in the training set is 2.9% and 4.0% in the testing set.

Table 6 – Average latent profile probabilities for most likely profile membership (row) by latent profile (column)

Profile	1	2	3	4
1	0.997	0.000	0.000	0.003
2	0.000	1	0.000	0.000
3	0.107	0.000	0.893	0.000
4	0.077	0.000	0.009	0.915

Table 6 – Means and standard deviations of Profiles and ANOVA tests

Profile	SAL	EXU	NGW	ANT	LOC	NSL	IAT
P1	1.85 (0.52)	1.91 (0.48)	1.88 (0.63)	2.19 (0.75)	2.46 (0.69)	1.44 (0.71)	1.96 (0.31)
P2	1.12 (0.22)	1.2 (0.23)	1.07 (0.16)	1.19 (0.32)	1.19 (0.26)	0.84 (0.45)	1.1 (0.13)
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F	575.888	448.338	265.143	266.323	432.916	118.867	442.392
p-value	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Standard deviations in parenthesis.
SAL: Salience; EXU: Excessive Use; NGW: Neglect Work; ANT: Anticipation; LOC: Lack of Control; NSL: Neglect Social Life; IAT: Internet Addiction test

Table 7 – Results of the supervised classification

	Predicted in training (n = 1340)				**Predicted in testing** (n = 575)			
Profile	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
1.	704	0	2	0	290	0	0	1
2.	0	109	3	0	0	55	0	0
3.	17	0	225	0	12	0	100	0
4.	16	0	1	263	9	0	1	107

Main diagonals contain correct classifications.
Classification error in the training set is 2.9% and 4.0% in the testing set.

Table 7 – Profiles' description and chi-squared tests

Variable	**n**	**%**	**Profile 1**	**Profile 2**	**Profile 3**	**Profile 4**
Gender‡						
Female	1019	53%	54%	59%	52%	49%
Male	891	47%	46%	40%	47%	50%
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No	1443	76%	75%	81%	75%	76%
Yes	454	24%	25%	18%	24%	23%
Sleeps well						
No	171	9%	10%	7%	7%	9%
Yes	1706	90%	90%	92%	93%	90%
Practices sports						
No	873	46%	45%	44%	46%	48%
Yes	1035	54%	55%	54%	54%	51%
Hard to make friends†						
No	1627	85%	85%	88%	89%	82%
Yes	276	15%	15%	11%	10%	17%
Parents control Internet*						
No	961	50%	50%	44%	46%	58%
Yes	943	50%	50%	54%	53%	41%

*: $p < 0.01$; †: $p < 0.05$; ‡: $p < 0.1$

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