Screening Criteria for Colorectal Cancer for Patients with Type II Diabetes Mellitus

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Abstract

Colorectal cancer and diabetes mellitus represent a major public health issue, first, by the number of new cases which are at an alarming rate. Secondly, by the negative effect over the quality of life, socio-economic status and lifespan, representing high morbidity and mortality causes. Diabetes Mellitus is the disease of the century with a global prevalence (standardised-age) which doubled since 1980, rising from 4.7% to 8.5% in adult population. In 2012, the estimated number of fatalities caused by diabetes mellitus and other related complications were at 3.7 million, out of which 43% were patients under the age of 70. Neoplasia represents the second cause of death, after cardiovascular disease. Colorectal cancer (CRC) ranks the 3rd regarding the global neoplasia incidence (10.2%) and the second regarding the mortality (9.5% of all cancer deaths). Colorectal cancer screening refers to the periodic evaluation of asymptomatic patients at risk of developing this neoplasia. Colorectal cancer has a number of peculiarities that make it ideal for screening. Since the end of the 19th century, the suspicion has been raised that diabetes mellitus has been involved, through directly etiological mechanisms, in carcinogenesis (breast, endometrium, colorectal, pancreas, liver, non-Hodgkin lymphoma). At the moment, there is already a consensus in the literature on the role of diabetes as an independent risk factor for colorectal cancer. However, despite the existence of numerous experimental evidence, epidemiological studies and meta-analyses, there is currently no adaptation of colorectal cancer screening for these patients. Material and method: Prospective case-control study conducted over a 2-year period including a number of 442 patients presented at „Dr. I Cantacuzino” Clinical Hospital, asymptomatic, who underwent lower digestive endoscopies in order to assess and define using anamnestic, clinical and paraclinical criteria, the profile of the patient with type II diabetes mellitus that should be given an endoscopic examination because diagnosing precursor lesions or even CRC is likely probable. Results: In the analyzed group, statistically significant correlations (p<0.05) were recorded between positive colonoscopy results (defined as precursor lesions – polyps- or tumors) and certain clinical characteristics (age, sex, BMI, duration of diabetes, type of antidiabetic treatment) and also paraclinical (reactive C protein and glycated hemoglobin). Conclusions: Criteria of patients with type II diabetes who have the maximum probability of developing colorectal cancer have been outlined. Thus this patient is more likely male, with a BMI > 25, aged over 60 years, with an unbalanced diabetes mellitus counted by HbA1c > 7 mg/dL, with over 5 years of diabetes evolution, in treatment with insulin most likely or combined insulin with oral antidiabetics and with an inflammatory biological profile expressed by PCR> 2 mg/dL threshold values.

Keywords: diabetes, colorectal cancer, screening.
de la 4,7% la 8,5% (2014) la populația adultă. Numărul deceselor datorate diabetului zaharat și complicațiilor acestuia era estimat în 2012 la 3,7 milioane, iar 43% dintre acestea la pacienți sub 70 de ani. A doua cauză de mortalitate, după bolile cardiovasculare este reprezentată de neoplasii. Cancerul colo-rectal (CCR) se încadrează pe locul al 3 lea în ceea ce privește incidența globală în rândul neoplasiilor (10.2%) și pe locul al doilea în ceea ce privește mortalitatea (9,5% din totalul deceselor prin cancer). Screeni-нгура cancerului colo-rectal se referă la evaluarea periodică a pacienților asimptomatici cu risc de a dezvolta această neoplazie. Cancerul colo-rectal are o serie de particularități care îl fac ideal pentru screening. Încă de la sfârșitul secolului al XIX lea s-a ridicat suspiciunea că diabetul zaharat tip II ar fi implicat, prin mecanisme direct etiologice, în carcinogeneza (săn, endometru, colo-rectal, pancreas, ficat, limfom non-Hodgkin). În momentul de față, există deja un consens în literatura de specialitate privitor la rolul diabetului zaharat tip II ca factor de risc independent în cancerul colo-rectal. Însă, în pofida existenței a numeroase de-vezi experimentale, studii epidemiologice și metaanalize, nu exista la momentul actual o adaptare a screeningului pentru cancerul colo-rectal la acești pacienți. Material și metodă: Studiu prospectiv de tip caz control desfășurat pe o perioadă de 2 ani ce include un număr de 442 de subiecți prezenți la Spitalul Clinic „Dr. I Cantacuzino”, asimpto-matici la care s-au efectuat endoscopii digestive inferioare cu scopul de a evalua în ce măsură poate fi definit prin criterii anamnestice, clinice și paraclinice profilul paciențului cu DZ tip II care ar trebui îndrumat către un examen colonoscopic întrucât diagnosticul unor leziuni precursoare sau chiar a CCR este probabil. Rezultate: În cadrul lotu-lui analizat s-au pus în evidență corelații semnificative statistic (p<0,05) între rezultatele pozitive ale colonoscopiei (definite ca leziuni precursoare-polipi sau formaționi tumorale) și anumite caracteristici clinice (vârstă, sex, IMC, durata evoluției diabetului zaharat, tipul de tratament antidiabetic) cât și paraclinice (valorile proteinei C reacti-ve și ale hemoglobinei glicate). Concluzii: S-a realizat conturarea unor criterii asociate paciențului cu DZ tip II care are o probabilitate maximă de a dezvolta cancer colo-rectal. Astfel acest pacient este mai probabil de sex masculin, cu un IMC > 25, în vârstă de peste 60 de ani, cu un diabet zaharat dezechilibrat contorizat prin valori ale HbA1c > 7 mg/dl în evoluție a peste 5 ani, în tratament cu insulină cel mai probabil sau combinat insulină cu ADO și cu un profil biologic inflamator exprimat prin valori prag ale PCR > 2 mg/dL. Cuvinte cheie: diabet zaharat, cancer colo-rectal, screening.
In terms of overall cancer mortality, colorectal neoplasia ranks 2nd after bronchopulmonary cancer, with 880,792 deaths representing 9.2% of all cancer deaths (Figure 3). 52% of these deaths occur in less developed countries, reflecting a much lower survival rate in these countries. There is less geographical variability in mortality rates (6 times for men and 4 times for women), with the highest estimated mortality rate for both sexes in Central and Eastern Europe (20.3 in 100,000 men and 11.7 for 100,000 women), while the lowest mortality rate is recorded in West Africa (3.5 and 3 respectively) (Figure 3).

In Romania, in 2018 the incidence of colorectal cancer was placed second both for males and female sexes (14.4% and 11.9% respectively). Regarding the mortality rates, CRC ranks second after bronchopulmonary cancer with a mortality rate of 12.4% (Figure 4).
Colorectal cancer screening refers to the periodic evaluation of asymptomatic patients at risk of developing this neoplasia. Colorectal cancer has a number of peculiarities that make it ideal for screening: it is a common condition with fatal development if it is not diagnosed and treated in the early stages; it develops from well-defined precursor lesions, colorectal adenomas, whose excision prevents the development of cancer; it progresses slowly from the early surgically curable stages to the advanced and metastatic stages; the screening tests used are cost-effective and widely accessible. A 2017 study of the U.S. population shows that colorectal cancer mortality rates declined progressively from 2004 to 2013 by about 2.7% per year. Improvement due to detection and excision of colonic polyps, CRC diagnosed at an early stage, more effective adjuvant treatment and intervention on modifiable risk factors (diet, lifestyle, physical exercise and smoking). A microsimulation model (MISCAN-Colon) suggests that screening may be attributed to approximately 53% of the reduction rate observed in colorectal cancer mortality. A study of temporal trends in colorectal cancer related to incidence and screening rates in the U.S. reported that approximately 250,000 to 500,000 cases could have been prevented between 1987-2010, along with their early detection. This decrease was attributed to the recognition of risk factors and thus the limitation of exposure to them as well as effective prevention screening.

DIABETES MELLITUS – INDEPENDENT RISK FACTOR FOR COLORECTAL CANCER

A relationship between diabetes mellitus and the risk of colorectal cancer is biologically plausible. Type II diabetes is characterized by high levels of insulin in the early stages. Hyperinsulinemia or insulin-resistance related factors, such as hyperglycemia or hypertriglycerideremia, were associated with colorectal carcinogenesis. Insulin may stimulate cell proliferation through a minor pathway involving direct activation of insulin receptors or insulin-like growth factor (IGF-I) receptors and a major pathway that works by inhibiting IGF regulating proteins (in particular IGFBP-1 and IGFBP-2), which may result in increased free IGF-I and the bioavailability. An important role of insulin and IGF-I in colorectal carcinogenesis is reinforced by in vitro studies, animal models and epidemiological studies. In addition, studies have reported that chronic insulin therapy has been associated with a statistically significant increase in the risk of colorectal cancer for patients with type II diabetes.

Multiple studies have already shown that type II diabetes is an independent risk factor for colorectal cancer, an association observed regardless of gender, common risk factors (obesity, diet, physical exercise) or tumor localization.

With regard to antidiabetic therapy, there are numerous studies that have concluded that metformin monotherapy has the lowest risk of developing colorectal cancer, some even show that the use of metformin is an independent protective factor against the development of CCR, and the protective capacity of metformin has been reduced in those with long-term therapy, the risk of CCR progressively decreasing with increased cumulative dose or increased intensity of metformin use. Adding metformin to insulin treatment reduced progression to cancer. Compared to metformin, insulin therapy increases the risk of colorectal cancer.

An important aspect is the evolution, prognosis and mortality of diabetic patients that develop colorectal cancer. Large-scale studies have shown that in these patients, type II diabetes is definitely a negative factor.

SCREENING

MATERIAL AND METHOD

Prospective case-control study was conducted between 01.2017-12.2018, including a number of 442 subjects presented at the „Dr. I Cantacuzino” Clinical Hospital. Colonoscopies were performed in the gastroenterology department - laboratory of digestive endoscopy, after signing in advance an informed consent, elaborated in full accordance with the current ethical norms of practice. Patients were divided in 2 groups: 1 group of patients with type II diabetes (N=194) and one group of patients without type II diabetes (N=248). The patient’s selection was made in the order of clinical admission and in order to meet the criteria for inclusion. These criteria are as follows:

Criteria for inclusion:
1. Type II diabetes for group 1;
2. Asymptomatic patients in terms of digestive disorders (except abdominal meteorism and tendency to constipation) or general symptomatology specific to neoplastic diseases;
Exclusion criteria:
1. Family or personal history of neoplasia, familial polyposis, genetic syndromes or inflammatory bowel disease;
2. Patients with type I diabetes;
3. Reduced patient compliance or incomplete information;
4. Refusal of endoscopic examination or incomplete colonoscopy
5. Moderate or severe anemic syndrome (hemoglobin threshold value - 10 g/dL)

The information used to carry out this study was obtained from clinical observation sheets, previous discharge notes, laboratory data, colonoscopy protocols and histopathological analysis charts. We analysed general information about patients (sex, age, environment of provenance, behavior - tobacco consumption, alcohol, drugs, family and personal history, reasons for presenting to the hospital, symptomatology, BMI, and for patients with type II diabetes - onset of disease, type of treatment), results of laboratory tests (reported at the reference values of the laboratory of the „Dr. I. Cantacuzino” Clinical Hospital), results of endoscopy examinations and histopathological results. As far as diet and daily physical exercise we have concerns and consider it difficult to quantify these variables objectively, completely and accurately, so we decided to remove these variables from the study. The data obtained has been entered and processed with Microsoft Office Excel 2017 program. The categorical data (ordinal and nominal) were converted into numeric, and the Stata 11 program was used for statistical analysis.

The distribution of the group model meets the condition of normality, which was tested using the Skewness and Kurtosis test, the values obtained by 0, confirming the normality test hypothesis. The degree of binding between variables was tested using the Pearson correlation coefficient, chi square test. As a significant statistical value, we took into account a probability of error below 0.05 (p).

**RESULTS**

The distribution of patients according to sex at the level of the two groups is similar, with a leading role for males in both groups (group 1 - 53.61%, group 2 - 59.27%). As far as the provenance is concerned, patients are roughly evenly distributed, with the predominance of urban patients in the group with type II diabetes (54.12%) compared to the group 2, where a predominance of those in rural areas (54.04%) is noted (Table 1).

In terms of patient behavior, the number of smokers is evenly distributed in the 2 groups (23.71% vs. 23.38%), while the number of chronic alcohol consumers is higher in the non-diabetic patient group (9.27% vs. 11.69%) (Table 1).

It can be seen from the patient distribution based on age groups, that most patients fall into the 60-69 age group (47.94% vs. 34.67%) and 70–79 years (20.62% vs. 28.62%), which is also probably due to current indications of performing colonoscopy (Table 1).

With regard to body mass index (BMI) values, it can be seen that at the level of both groups, most patients fall within the range of 25-29.9, but with differences in their median values: at the level of group 1 the median is 31.25 with a minimum value of 24.5 and the maximum value of 38, while at the group 2 level, the median is 27.7, with a minimum value of 23 and a maximum value of 32.4 (Figure 5).

If we discuss the values of laboratory analyses, it should be noted that all the constants of the base panel (hemoleucogram, CRP, INR, TGO, TGP, urea, creatinine) have been analyzed, but we consider it useful to mention the following constants: hemoglobin (Hb), C-reactive protein (CRP) and in the case of diabetic patients glycated hemoglobin (HbA1c).

In terms of hemoglobin levels, patients with moderate or severe anemic syndrome were excluded from the study, with the minimum value for inclusion in the study set at 10 g/dL. The average value in group

| Sex              | Group 1 (type II diabetes +) n=194 | Group 2 (DZ type II -) n=248 |
|------------------|-------------------------------------|-------------------------------|
| Male             | 104 (53.61%)                        | 147 (59.27%)                  |
| Female           | 90 (46.39%)                         | 101 (40.73%)                  |

| Environment of provenance | Group 1 (type II diabetes +) n=194 | Group 2 (DZ type II -) n=248 |
|---------------------------|-------------------------------------|-------------------------------|
| Urban                     | 105 (54.12%)                        | 114 (45.96%)                  |
| Rural                     | 89 (45.88%)                         | 134 (54.04%)                  |

| Smoking | Group 1 (type II diabetes +) n=194 | Group 2 (DZ type II -) n=248 |
|---------|-------------------------------------|-------------------------------|
| Smoking | 46 (23.71%)                         | 58 (23.38%)                   |

| Alcohol | Group 1 (type II diabetes +) n=194 | Group 2 (DZ type II -) n=248 |
|---------|-------------------------------------|-------------------------------|
| Alcohol | 18 (9.27%)                          | 29 (11.69%)                   |

| Age (years) | Group 1 (type II diabetes +) n=194 | Group 2 (DZ type II -) n=248 |
|-------------|-------------------------------------|-------------------------------|
| 30-39       | 1 (0.52%)                           | 3 (1.20%)                     |
| 40-49       | 11 (5.67%)                          | 19 (7.66%)                    |
| 50-59       | 34 (17.53%)                         | 46 (18.54%)                   |
| 60-69       | 93 (47.94%)                         | 86 (34.67%)                   |
| 70-79       | 40 (20.62%)                         | 71 (28.62%)                   |
| 80-89       | 15 (7.73%)                          | 23 (9.27%)                    |
Figure 5. Distribution of patients by BMI value; Group 1 (n=194), Group 2 (n=248).

Figure 6. Distribution of the patients according to the value of hemoglobin; Group 1 (n=194), Group 2 (n=248).

Figure 7. Distribution of patients by CRP value (mg/dL); Group 1 (n=194), Group 2 (n=248).
Screening Criteria for Colorectal Cancer for Patients with Type II Diabetes Mellitus

Glycated hemoglobin (HbA1c) values were ranged between 6.8 and 10.1% with a median of 8.45%. As can be seen in Figure 8, most results (170 patients) were between 7 and 9% (Figure 8).

A subgroup division was developed according to the time elapsed since the diagnosis of diabetes mellitus (type II DM) and the time of colonoscopy. It can be seen, that most patients are in the subgroup 5-9.9 years (71 patients), followed by the subgroup 10-14.9 years (54 patients) (Figure 9).

In terms of the distribution of diabetic patients depending on treatment, it was found that most patients were in treatment with oral antidiabetics (ADOs) – 88 patients (45.36%), followed by patients receiving insulin treatment– 51 patients (26.29%) (Figure 10).

All patients included in the two groups were asymptomatic in terms of digestive sphere disorders (only pa-
patients accusing abdominal meteorism and constipation were included) or in terms of general manifestations specific to neoplastic diseases. They performed lower digestive endoscopy after having previously signed the informed consent developed in accordance with the ethical rules of good practice. The results of the lower digestive endoscopy for the 2 groups were summarized in the table below (Table 2).

Endoscopic findings of tumors and neoplastic precursor lesions (polyps) have been defined as positive results at colonoscopy. Thus, 52 patients with polyps (26.80%) and 29 patients (14.95%) with tumors in different localizations were found at the level of group 1. The most common localization was in the sigmoid colon (7 patients) followed by the ascending colon (6 patients). It can be observed that in group 1, no tumors have been located at the rectal level. In terms of group 2, there were identified 41 patients with polyps (16.53%) and 14 patients with tumors (5.63%), of whom the most common localizations were at the ascending colon (4 patients) and transverse colon (4 patients) (Table 2).

Consistent with the literature, at the level of this study we also observed a slightly higher frequency of the male sex in relation to the positive results of colonoscopy (Figure 11, Figure 12).

As far as age group distribution is concerned, it is noted that patients in the age groups 60-69 and 70-79 years predominate at the level of both groups. At the level of group 1, in the 60-69 age category were the most patients (46 patients of whom at 19 were endoscopically detected tumors), while 20 patients with positive results were classified in the 70-79 age category, 9 of whom had colon tumors (Figure 13). As for group 2, there is a reversal in the ranking of the 2 categories of age, the first place being occupied by the category

![Figure 10. Distribution of patients by treatment (n=194).](image)

### Table 2. Lower digestive endoscopy results

| Colonoscopy results | Group 1 (n=194) | Group 2 (n=248) |
|---------------------|----------------|-----------------|
| Normal              | 117 (39.69%)   | 176 (70.97%)    |
| Melanosis coli      | 2 (1.03%)      | 0               |
| Diverticulosis      | 31 (15.98%)    | 17 (6.85%)      |
| Diverticulosis and polyps | 3 (1.54%) | 0               |
| Polyp               | 52 (26.80%)    | 41 (16.53%)     |
| Cec tumor           | 4 (2.06%)      | 0               |
| Ascending colon tumor | 6 (3.09%) | 4 (1.61%)       |
| Transverse colon tumor | 4 (2.06%) | 4 (1.61%)       |
| Descending colon tumor | 6 (2.58%) | 3 (1.21%)       |
| Sigmoid tumor       | 7 (3.61%)      | 1 (0.40%)       |
| Rectosigmoid tumor  | 3 (1.54%)      | 1 (0.40%)       |
| Rectum tumor        | 0              | 1 (0.40%)       |
70-79 years with a number of 19 patients with positive results, 4 of which were tumors, while in the 60-69 age category, 15 patients were found of which only 3 patients had colon tumors. It can also be observed, that at the level of group 2, the categories with the most endoscopic results consisting in tumor (6), was the category 80-89 years (Figure 14).

Analyzing the 2 groups, we found that in terms of body mass index (BMI), the distribution of patients with positive colonoscopy results was similar, with a maximum in the 25-29.99 group. In this group of patients, a total of 132 patients were registered, including 46 patients with positive results (34.85%); at 15 of the-
significant correlated ones, namely C-reactive protein (CRP) and in the case of group 1 the glycated hemoglobin (HbA1c).

It was found that in group 1, most patients with positive results (35 patients) at colonoscopy were classified in the PCR range of 2-2.99 mg/dL. Of these, 12 patients were detected with colon tumors. However, it can be observed that after the value of 3 mg/dL, the probability of the positive result being of the tumor is much higher: of the total of 23 patients included in the group with values > 3 mg/dL, 18 patients were those with positive results, 16 of whom were those with colon tumors (Figure 19).

In relation to group 2, most patients were classified in the range 0-0.99 mg/dL, but for no patient in this category were detected tumors. It is found, that the probability of the positive result being of colon tumor is much higher over 1 mg/dL (out of the total of 30 patients included in the group, 16 had positive results, and of these 14 were colon tumors) (Figure 20).

In terms of the treatment of diabetic patients, it was found that the most patients with positive results were those with insulin treatment: 32 patients out of a total of 51 patients included in the group (62.74%), patients in combined insulin treatment with oral antidiabetics: 24 patients with positive results from a total of 37 patients included in the study group (64.86%) (Figure 18).

Analyzing the duration of the evolution of diabetes from the time of diagnosis to colonoscopy, we found that most results were in the 5-9.9 year category. But from a total of 71 cases included in the group, 28 were positive (39.44%), while in the 10-14.9 year category, out of a total of 54 patients, 25 patients with positive results (46.30%) were detected of which 9 with tumors, and in the 15-19.9 year category out of a total of 30 patients included in the group, 19 were enrolled with positive colonoscopy results (63.33%) (Figure 17).

Several variables were checked for laboratory analyses, but we will mention only the statistically

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**Figure 16.** Distribution of patients in group 2 with positive results based on BMI (n=55).

**Figure 17.** Distribution of patients in group 2 with positive results based on the time from type II DM diagnose (n=81).

**Figure 18.** Distribution of patients in group 1 with positive results depending on treatment (n=81).

**Figure 19.** Distribution of group 1 with positive results depending on PCR value (mg/dL) (n=81).
Screening Criteria for Colorectal Cancer for Patients with Type II Diabetes Mellitus

With a progressive risk increasing with age, the threshold value being considered, in this study, the category over 60 years) and between the results of colonoscopy and the increase in the body mass index. BMI values comparable in the two groups suggests that obesity (consistent with the literature) would be an important independent contributor to the risk of colorectal cancer (Table 3).

With regard to treatment with oral antidiabetics and diet, a negative correlation with the positive result of colonoscopy was revealed, while insulin and combined treatment insulin with oral antidiabetics, achieved a statistically significant positive correlation. In other words, patients with insulin in monotherapy or in combination with OAD have a higher risk of developing colon tumors or precursor lesions (polyps), while diet or treatment with ADO alone appear to have a protective role (Table 3).

There is also, a positive correlation between the duration of diabetes's progression and the positive results of colonoscopy, a risk that increases progressively beyond the 5-year duration of diabetes evolution (Table 3).

Taking into account the laboratory result analysis, it is found that there is a positive correlation between the positive results of colonoscopy and the values of the reactive C protein and those of glycated hemoglobin. PCR values are positively correlated with positive colonoscopy results in both groups, with significantly higher values in group 1, which suggest a pro-inflammatory status of these patients and may contribute to the detection of patients at risk of developing a neoplastic lesion. From the statistical and descriptive analysis, the threshold value of 2 mg/dL has been established as being correlated with the risk of a positive result at colonoscopy. That is why I consider it appropriate to propose the average value of CRP in patients with type II DM of 2 mg/dL as a threshold value that makes the difference between patients who should benefit from endoscopic screening from those to whom it could be postponed (Table 3).

Also, with regard to hemoglobin values, it is found that there is a negative correlation, predictably, establishing the association between lower hemoglobin values with the increase in positive results on the endoscopic examination (Table 3).

From the in-depth statistical processing of the data from the current study, gathered in a coherent construct, a phenotypic profile of the patient with type II DM can be developed, which has a maximum probability of developing colorectal cancer. Thus, this patient

**CONCLUSIONS AND DISCUSSIONS**

After a review of the literature as well as a thorough and concise descriptive analysis, presented above, it was possible to outline specific directions for the orientation of the statistical study. Thus, the following statistically significant correlations (p<0.005) were made in order to be able to outline the profile of the patient with type II diabetes mellitus, a definite candidate for screening for colorectal cancer.

It should be noted from the outset that at the level of this study, the descriptive analysis of the data revealed from the beginning a slight predominance of the male sex in patients with positive results in colonoscopy (a fact also found by the statistically significant correlation only at the level of group 2), but in terms of smoking, alcohol and the environment, a statistically significant correlation could not be established (Table 3).

A statistically significant positive correlation at the level of group 1 was observed between the patient’s age and the occurrence of positive results at colonoscopy.
is more likely male, with a BMI > 25, aged 60, with an unbalanced diabetes mellitus counted by HbA1c > 7% value, in evolution over 5 years, with insulin treatment most likely or combined insulin with ADO and with an inflammatory biological profile expressed by threshold values of PCR> 2 mg/dL.

There is a current national and international problem, given the ever-increasing number of diabetic patients and the significant increase in colorectal neoplasms as well as the improvement of prognosis and survival through screening programs, the importance of knowing that type II diabetes mellitus is an independent risk factor for the development of colorectal neoplasms, but in particular the establishment of appropriate screening criteria for them to improve the quality of life of these patients and the socio-economic impact is a necessary prerequisite for the content of the phenomenon at the Global level.

**Compliance with ethics requirements:** The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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