Journal of Coloproctology

www.jcol.org.br

Original Article

Colorectal cancer: comparative analysis of clinical and pathological characteristics in patients aged above and below 45 years of age and impact on prognosis

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ARTICLE INFO

Article history:
Received 23 January 2015
Accepted 23 April 2016
Available online 22 June 2016

Keywords:
Colorectal cancer
Age
Clinicopathological features
Survival

ABSTRACT

Introduction: Colorectal cancer, in Portugal, presents as the second most common cancer and of cancer death cause. CRC is a disease of the elderly; however, there has been an increase of incidence in younger patients and doubts have emerged about its behavior, characteristics and prognosis in this group.

Methods: In this study, we have evaluated a sample of 512 patients diagnosed with colorectal cancer submitted to surgical treatment in the period between January 1st, 2005 and January 1st, 2010, through a comparative clinical, pathological and survival analysis of patients under and over 45 years old (Groups I and II respectively).

Results: Group I patients accounted for 5.5% of the sample. There was a predominance of males and the most common site was the left colon in both age groups. In the younger group, the histological type presents with a predominance of tumors with a mucinous component and with signet ring cells ($p = 0.001$), however, there was no difference in terms of overall survival and disease-free survival.

Conclusion: In this study, colorectal cancer at younger ages shows similar characteristics to those of older patients.

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http://dx.doi.org/10.1016/j.jcol.2016.04.010

Câncer colorretal: análise comparativa das características clínicas e anatomopatológicas em doentes com idade superior e inferior a 45 anos de idade e impacto no prognóstico

Palavras-chave:
Câncer colorretal
Idade
Características clínicas e anatomopatológicas
Sobrevida

RESUMO

Introdução: O Câncer Colorectal (CCR), em Portugal, constitui o segundo câncer mais frequente em termos de incidência e de mortalidade. É uma doença do idoso, no entanto, tem-se observado um aumento da incidência em pacientes mais jovens, tendo surgido dúvidas acerca do seu comportamento, características e prognóstico neste grupo etário.
Métodos: 512 pacientes com diagnóstico de CCR operados entre Janeiro de 2005 e Janeiro de 2010 foram avaliados através da análise comparativa das características clínicas, anatomopatológicas e sobrevida em indivíduos com idade inferior e superior a 45 anos (Grupo I e II respetivamente).
Resultados: Os pacientes do Grupo I representaram 5,5% da amostra. Houve predomínio do gênero masculino e o local mais frequente foi o cólon esquerdo em ambos os grupos. No grupo mais jovem, relativamente ao tipo histológico ocorreu predomínio significativo de tumores com componente mucinoso e células em anel de sinete (p = 0,001), mas sem diferença ao nível da sobrevida global e sobrevida livre de doença.
Conclusão: Neste estudo, o CCR em idades mais jovens revelou características semelhantes às dos pacientes mais idosos.

Introduction

In recent decades, there has been an increasing prevalence of cancers in the world.[1,2] Colorectal cancer (CRC) is the most common malignancy of the gastrointestinal tract[3,4] and due to the increased incidence and mortality that occurred in recent decades, and also to the costs that are associated with diagnosis and treatment, this cancer has become a major public health problem worldwide.[5]

Worldwide, CRC is the 3rd most common cancer and the 4th leading cause of deaths by cancer; in 2008, 609,051 deaths occurred, 223,268 of them in Europe.[3]

About 95% of all CRCs arise from adenomatous polyps of the intestinal mucosa, with increasing incidence with age; however, only 10% of adenomas will result in a CRC.[6–9]

The knowledge of the natural history of the disease and the possibility of intervening at an earlier stage led to the implementation of screening programs, which currently cover the population over 50 years with no risk factors for CRC.[10,11]

There are several risk factors that are associated with the development of CRC, and some of them imply an earlier screening.[12–14] Age is one of the main risk factors for the development of CRC, with over 90% of cases occurring in individuals aged over 50 years, with a mean age of diagnosis of 65 years.[14–16] For this reason, CRC is considered a disease of the elderly.

The population under 50 years and without risk factors is excluded from the screening group and is therefore somewhat neglected, and this requires a high index of suspicion by the physician for the establishment of a diagnosis of CRC. Although occurring less frequently, CRC is also diagnosed in this age group, and there has been an increased incidence among these people, a fact that cannot be ignored.[17–19] Previous studies describe a wide variation of this frequency, with values from 1.3% to 37%, and the highest values are found in the Asian population.[19–27] This issue has aroused great interest in the medical literature, though with controversial results, and many studies have been conducted in order to evaluate possible differences in behavior and prognosis of CRC in young people compared with the general population with this cancer. Most authors argue that young age is associated with more advanced stages of the disease at diagnosis and with more aggressive histopathologic characteristics, for example, a lower degree of differentiation and mucin secretion.[19,23,24] Some authors still describe a worse prognosis in this group.[26] However, other studies contradict these findings, describing results similar to those of patients with a later diagnosis, or even with improvement in their survival.[21,22,27]

Taking into account the controversy on this subject and the lack of studies in Portugal, this project was carried out in order to make a comparative analysis of the clinical and pathological characteristics of patients with CRC diagnosed with ages over and under 45 years, and to evaluate the possible impact of the age factor in its prognosis.

Methods

The population included in this study consists of patients with a diagnosis of CRC who underwent surgery in the period from January 1, 2005, to January 1, 2010, in the Braga Hospital (BH).

In our study, the following inclusion criteria were: patients with histologically confirmed CRC who underwent surgical resection with curative intent.

Exclusion criteria were: patients with inflammatory bowel disease (IBD), namely Crohn's disease and ulcerative colitis; patients with hereditary syndromes such as familial adenomatous polyposis (FAP) and hereditary colorectal cancer not associated with polyposis (HCCNP); patients with no primary disease of the colon or rectum; patients diagnosed with CRC but who did not undergo surgery, and patients with CRC undergoing non-curative surgical treatment.

The exclusion of patients with hereditary syndromes was performed after confirmed by genetic studies in patients for whom there was a clinical suspicion.

To collect information, a prospective database of CRC was surveyed, and the following data were collected:

Clinical data and preoperative tests

Information concerning the age, gender, clinical presentation, tumor location and the presence of metastasis was evaluated. Regarding age, the patients were grouped into age under or equal to 45 years (Group I) and more than 45 years (Group II).

Pathological data

The parameters evaluated included tumor size, macroscopic appearance of the tumor, histologic type, tumor extension (pT), tálus degree of differentiation, the presence of lymph node metastases (pN), presence of venous and lymphatic invasion, and staging.

The staging was carried out according to the TNM classification of the American Joint Committee on Cancer (AJCC), Sixth Edition.[28]

Follow-up

The patients were monitored regularly.

The follow-up of patients with CRC is subdivided into three periods: 1st and 2nd year, 3rd to 5th year, and from 6th year postoperatively. Thus, in the 1st and 2nd years, the patients are evaluated in quarterly consultations; from 3rd to 5th year, the assessment becomes biannual, and after 5 years, the patient is evaluated annually. In these consultations, besides patient observation, tumor markers (CEA and CA19-9) are also accessed, and an annual chest X-ray is obtained.

Regarding colonoscopy, the procedure is performed within one year after surgical resection (or 3–6 months after surgery, if the colonoscopy was not performed pre- or transoperatively due to an obstructive lesion) with repetition 3 years after surgery; subsequently, a colonoscopy is obtained every 5 years, unless a follow-up colonoscopy reveals evidence of an advanced adenoma (villous polyp, polyp >1 cm, or high-grade dysplasia). In this case, the colonoscopy should be repeated 1 year after polypectomy.

Regarding the realization of computerized axial tomography, this procedure is performed annually in the first three years after surgery, or whenever symptoms or an increase of tumor markers warrant this procedure. In the case of rectal cancer, a pelvic NMR is also performed 6 months postoperatively, which will remain as reference NMR.

The moment of diagnosis was used as starting point for survival analysis. In the case of overall survival, this was calculated until the patient's death for any reason, and disease-free survival was considered as the time elapsed until the occurrence of a relapse. Both indicators were evaluated until August 31, 2012.

Statistical analysis

The Statistical Package for Social Sciences for Windows (SPSS version 19.0.0, SPSS Inc.) was used in the database analysis.

Statistical comparisons between groups were performed using the Pearson's chi-squared test (X^2) whenever possible, and the Fisher's exact test (values <5).

Overall survival and disease-free survival curves were calculated using the Kaplan–Meier method, and the comparison between the two groups was performed using the log-rank test.

p-values <0.05 were considered statistically significant.

This study was submitted to, and approved by, the Braga Hospital Ethics Committee.

Results

In the period between January 1, 2005, and January 1, 2010, 672 patients with CRC were diagnosed in BH; 512 patients met the criteria previously described.

Group I accounted for 5.5% ($n = 28$) of the sample and Group II for 94.5% ($n = 484$). In both groups a predominance of males was noted: 67.86% ($n = 19$) for Group I and 61.98% ($n = 300$) for Group II, with no statistically significant difference ($p = 0.533$). Most patients in both groups had symptoms at the moment of diagnosis (92.86%, $n = 26$ and 81.2%, $n = 393$, respectively). The most common site was the left colon, with a total of 48.44% of cases ($n = 248$) followed by the rectum with 28.13% ($n = 144$) and the right colon with 23.44% ($n = 120$). Comparing the site by age group, we found similar results.

At diagnosis, we found that 32.19% ($n = 9$) and 20.04% ($n = 97$), respectively, had metastases. As to the variables studied, no significant differences were observed between groups (Table 1).

A slightly higher frequency was observed in patients with CRCs $\leq$45 mm, occurring in 57.62% ($n = 295$) of cases. In the analysis by age group, it was found that CRCs $\leq$45 mm accounted for 50% ($n = 14$) of Group I and 58.06% ($n = 281$) of Group II. The polypoid type predominated both in Group I and Group II, representing 60.71% ($n = 17$) and 50.41% ($n = 244$) of cases, respectively, followed by the ulcerative type. The infiltrative type stood as the third most frequent type in Group II (8.40%) and as the fourth type in Group I (3.57%); in the latter group, the third place was taken by the exophytic type (10.71%). The villous type was the rarest of all, being represented only in Group II ($n = 2$). Regarding histological type, the most common type was adenocarcinoma in 93.36% ($n = 478$) of cases, followed by the mucinous type in 10.55% ($n = 54$) of cases and by signet ring cell/mucinous area type in 0.78% ($n = 4$). Mucinous type and signet ring cell/mucinous area type were statistically more frequent in Group I, with 14.29% ($n = 4$) and 7.14% ($n = 2$) respectively, *versus* 10.33% ($n = 50$) and 0.41% ($n = 2$) in Group II ($p = 0.001$). "Well-differentiated" was the predominant degree of tumor differentiation in the sample, occurring

Table 1 – Distribution of variables related to clinical and preoperative test data, according to the age group, in the sample under study.

	Group I % (n)	Group II % (n)	p[a]
Age	5.5% (28)	94.5% (484)	
Gender			
Male	67.86% (19)	61.98% (300)	0.533
Female	32.14% (9)	38.02% (184)	
Clinical presentation			
Symptomatic	92.86% (26)	81.2% (393)	0.137
Asymptomatic	7.14% (2)	18.8% (91)	
Location			
Right colon	28.57%(8)	23.14%(112)	
Left colon	46.43%(13)	48.55%(235)	0.794
Rectum	25%(7)	28.31%(137)	
Metastases			
Absent	67.86%(19)	79.96(387)	0.124
Present	32.19% (9)	20.04% (97)	

[a] Calculated by Fisher's exact test.

in 43.95% ($n = 225$) of cases. The smaller the differentiation, the lower the frequency. However, in Group I, the most frequent category was that of "moderately differentiated" tumor, occurring in 42.86% ($n = 12$) of cases. It was also found in this group that well-differentiated grade was less frequent; poorly differentiated grade was more often seen, with 32.14% ($n = 9$) and 18% ($n = 5$), respectively, compared to Group II, with 44.63% ($n = 216$) and 9.09% ($n = 44$), respectively.

In this group, we also found a lower frequency of well differentiated grade tumors and a higher frequency of poorly differentiated grade tumors, with 32.14% ($n = 9$) and 18% ($n = 5$), respectively, compared to group II, with 44.63% ($n = 216$) and 9.09% ($n = 44$), respectively.

In Group I, there were more patients with the presence (53.57%) *versus* absence (42.86%) of nodal metastases; On the other hand, the opposite occurred in Group II, with 40.29% and 56.61%, respectively. The venous invasion occurred more often in Group I, 50% of cases, as opposed to Group II, 41.32%. In both age groups, the presence of lymphatic invasion prevailed, 57.14% and 52.45% respectively. As for staging, the stages II, III and IV were the most frequent in the sample, with 28.57% ($n = 8$) 35.71% ($n = 10$) and 28.57% ($n = 8$) patients, respectively, in Group I and 36.98% ($n = 179$), 35.71% ($n = 10$) and 30.99% ($n = 150$), respectively, in Group II. Comparing the two age groups, a higher frequency of stages III and IV was noted in Group I. For the several variables studied, significant differences between groups were not observed, except for histological type (Table 2).

The follow-up time ranged from 2 to 7 years. Overall survival was 63%, with a median survival of approximately 63 ± 2 months (Fig. 1).

Group I showed a 5-year overall survival of 61% and a median survival of approximately 58 ± 6 months. In Group II, 5-year overall survival was 63% and the median survival was approximately 63 ± 2 months (Fig. 2). There was no statistically significant difference between groups with respect to survival ($p = 0.738$).

Table 2 – Distribution of variables related to pathological data, according to the age group, in the sample under study.

	Group I % (n)	Group II % (n)	p[a]
Measurement			
≤45 mm	50% (14)	58.06% (281)	0.963
>45 mm	32.14 (9)	36.57% (177)	
Macroscopic aspect			
Polypoid	60.71% (17)	50.41% (244)	
Ulcerative	14.29% (4)	23.97% (116)	0.588
Infiltrative	3.57% (1)	8.68% (42)	
Exophytic	10.71% (3)	8.06% (39)	
Villous	0.0% (0)	0.41% (2)	
Histological type			
Adenocarcinoma	78.57(22)	88.26 (432)	
Mucinous	14.29 (4)	10.33 (50)	0.001
Signet ring cells	7.14 (2)	0.41 (2)	
Differentiation			
Well differentiated	32.14% (9)	44.63% (216)	
Moderately differentiated	42.86% (12)	41.53% (201)	0.337
Poorly differentiated	18% (5)	9.09% (44)	
Undifferentiated	0.0 (0)	0.83% (4)	
Ganglionic metastases			
Absent	42.86% (12)	56.61% (274)	0.153
Present	53.57% (15)	40.29% (195)	
Venous invasion			
Absent	46.43%(13)	53.72% (260)	0.394
Present	50.0%(14)	41.32% (200)	
Lymphatic invasion			
Absent	39.29% (11)	41.32% (200)	0.699
Present	57.14% (16)	51.45% (249)	
Stage			
I	7.14% (2)	15.5% (75)	
II	28.57% (8)	36.98% (179)	0.224
III	35.71% (10)	30.99% (150)	
IV	28.57% (8)	14.05% (68)	

[a] Calculated by Fisher's exact test.

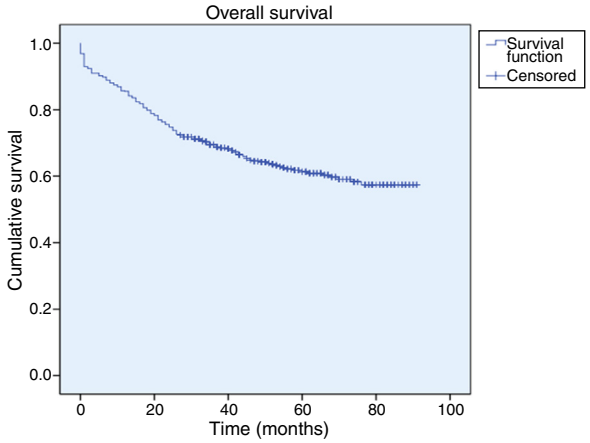

Fig. 1 – Cumulative overall survival in the study sample.

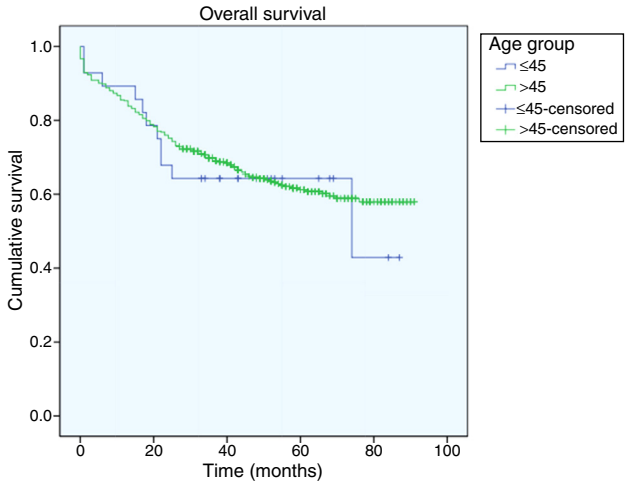

Fig. 2 – Cumulative overall survival by age group in the sample under study. Calculated by Log-Rank test. $p = 0.738$.

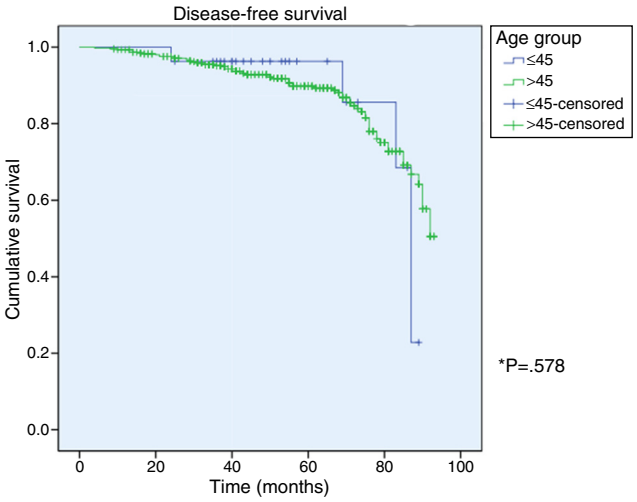

Fig. 4 – Disease-free survival by age group in the sample under study. *Calculated by Log-Rank test.

Survival curves were estimated by the TNM staging system; it was found that the more advanced the stage at diagnosis, the lower the 5-year overall survival, with 91% in stage I, 70% in stage II, 56% in stage III and 33% in stage IV. Five-year survival on stage I was 100% in Group I and 91% in Group II; on stage II, 88% and 69%, respectively; on stage III, 70% and 55%, respectively; and on stage IV, 13% and 36%, respectively. Comparing the two age groups, we found a better survival in Group I for those cases in which the diagnosis was established in stages I, II and III, and a worse survival in stage IV. However, these differences were not statistically significant, despite the trend observed for stage IV (stage I: $p = 0.659$, stage II: $p = 0.252$; stage III: $p = 0.504$; stage IV: $p = 0.061$). In the study sample, the 5-year disease-free survival was approximately 86%, with a mean of 83 ± 1 month (Fig. 3). In Group I there was a 5-year disease-free survival of 81%, with a mean of 82 ± 3 months, a slightly lower result *versus* Group II, in which this parameter was 86% with a mean of 83 ± 1 months, but without statistically significant difference ($p = 0.578$) (Fig. 4).

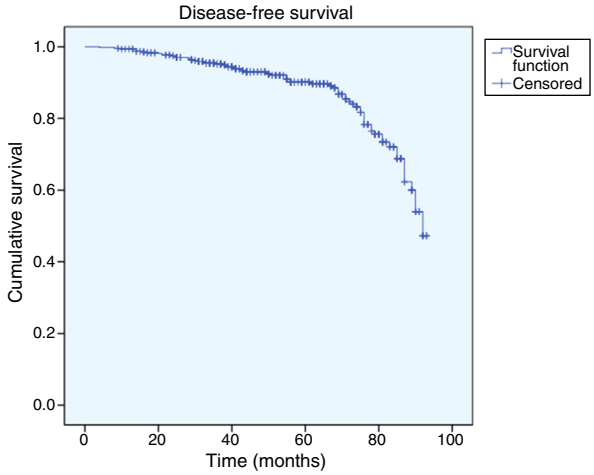

Fig. 3 – Disease-free survival in the sample under study.

Discussion

CRC is a disease of the elderly, occurring more frequently in the sixth and seventh decades of life, although it was observed increased incidence in younger individuals in recent decades.[17–19] In the literature, the impact of "age" in the prognosis of patients with CRC is an object of controversy and has been the subject of much interest and research. Taken into account that there are no data on the Portuguese reality, this study sought to better understand this issue in patients treated at the Braga Hospital, through an analysis of clinical and pathological characteristics of CRC in patients divided into two age groups, and the assessment of the impact of this factor on survival.

It was found that 5.5% of patients were aged 45 years or younger (Group I), which is consistent with the values found in the literature. Male gender was the most frequent in this study, both in the total sample and in age groups, which is in line with the general distribution of gender in those cases of CRC described by GLOBOCAN 2008,[3] and in some studies based on young populations,[21,23] with no statistical difference regarding this parameter. Other studies based on young people describe an equal distribution between genders.[19,24,26]

In both groups, the presence of symptoms prevailed at diagnosis, indicating that the correct valuation and assessment of symptoms through additional tests to an accurate establishment of the diagnosis is essential for the diagnosis of CRC, regardless of age. These results are in agreement with those found by other studies.[27]

The sites most commonly affected by CRC are sigmoid colon and rectum,[19,21,27] which is in line with our results, in which left colon predominance was noted in both groups.

Tumors with size ≤45 mm occurred in greater numbers and the macroscopic appearance more often seen was the polypoid type in both groups; these parameters are no subject of difference between age groups.

In patients with CRC, adenocarcinoma is the most common histological type,[29] as we found in this study. With respect to

mucinous and signet ring cell/mucinous area types, a statistically significant difference was noted; these latter types were more often seen in Group I ($p = 0.001$), as already mentioned by other authors.[19,24,26] Despite the description of these histological types in association with a worse prognosis,[30] this was not the case in this study, and the overall survival was similar in both groups.

Several studies have reported lower differentiation grades in younger patients, which would characterize CRC in this group as a more aggressive tumor;[19,24] however, other studies contradicting these findings were published.[21,27] In our study, the degree found more frequently was the moderately differentiated; in Group I, a well-differentiated grade was found less frequently, and poorly differentiated grade was the most prevalent, although without statistical difference between groups. This finding shows that CRC in younger patients does not show more aggressiveness.

The presence of venous and lymphatic invasion was similar in both groups. The venous invasion occurred in about half the cases, and lymphatic invasion occurred in greater proportion, contributing to a more advanced stage in the sample, which agrees with results from other studies.[21,27]

Several authors describe the presence of a more advanced disease at diagnosis in younger patients.[24,26] In this sample, advanced stages were more frequent, reflecting the insidious and usually silent (or with few symptoms) nature of this disease, which results in delayed diagnoses. Despite the slight predominance of stages III and IV in Group I, there was no statistical difference; and the results were equivalent to those of Group II. Most CRCs were seen in stage T3, nodal metastases were present in about 41% of the sample, and metastases at diagnosis were uncommon, but for none of these variables a statistical difference was observed, confirming that the stage is similar in both age groups. Some studies have confirmed the results of this study with respect to the stage.[19,21,27,29]

Some authors report a lower survival rate[26] in younger patients; however, most of the recently published studies have found opposite results.[19,21,22,24,27] In this study, there were no significant differences in overall survival and disease-free survival. In group I, in patients aged 45 years or less the overall survival was 61% and the disease-free survival was 81% – values similar to those found in Group II. These findings demonstrate that a diagnosis in younger patients is not associated with a worse prognosis.

Survival depends largely on the stage at diagnosis: the more advanced the stage, the worse the survival, with values of 91%, 70%, 56% and 33% for stages I, II, III and IV, respectively, which agrees with the values found in the literature.

Conclusion

In this study, it was found that several clinical and pathological parameters evaluated were very similar in both age groups analyzed, and an increased incidence of tumors with mucinous and signet ring components were found in Group I; however, these findings did not impact on the level of survival.

It is essential that health professionals are aware of this diagnosis, even in patients at younger ages; It should also be emphasized the importance of health promotion campaigns to change habits and lifestyles, and to disease prevention with screening programs, in order to achieve a reduction in the incidence and mortality associated with this disease.

We believe that this study is only a preliminary assessment of the impact of the age factor on the survival of patients with CRC. Taking into account that this is a study of patients from only one hospital, it would be important to extend it to other centers as well as to increase the follow-up period, to better know the Portuguese reality.

Conflicts of interest

The authors declare no conflicts of interest.

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