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Are there any correlations between demographic characteristics, tumor location, and Ki-67 labeling index in intracranial atypical meningiomas (WHO grade II)?

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Abstract

Background/Aim: Atypical meningiomas (AMs) account for about 30% of all meningiomas and it is difficult to predict their behavior. Nevertheless, the identification of protein markers responsible for the regulation of cell proliferation can be helpful. The purpose of this study is to find possible correlations between demographical characteristics of patients with AMs, tumor anatomic location, and intratumoral immunohistochemical (IHC) expression of Ki-67 labeling index (LI). *Patients, Materials and Methods*: We carried out a retrospective review of 29 patients with intracranial AMs [*World Health Organization* (WHO) grade II] who underwent resection of AMs at "Professor Dr. Nicolae Oblu" Emergency Clinical Hospital, Iaşi, Romania, between January 1, 2014 and December 31, 2016. We searched for their demographic characteristics (age and gender) and tumor location from patients' medical files. The histological slides were reviewed in order to assess the Ki-67 LI. *Results*: Out of the 29 patients analyzed, 51.72% were females having AMs, with a mean Ki-67 LI of 8.6%, and 48.27% were males with AMs, revealing a mean Ki-67 LI of 8.5%. Considering tumor anatomic location, 82.75% were non-skull base AMs (presenting a mean Ki-67 LI of 8.9%) and 17.24% were skull base AMs (showing a mean Ki-67 LI of 8.2%). Although we did not find any statistically significant correlation between gender, age, tumor anatomic localization, and Ki-67 expression, our study revealed that the mean Ki-67 LI for AMs was 8.7% (ranging from 6% to 15%) and was close to values obtained by other authors. In terms of gender distribution, we have noticed that AMs diagnosed in male patients had a mean Ki-67 LI almost equal to that in female patients even though some studies found Ki-67/MIB-1 LIs significantly higher in male patients than in female patients. Also, we did not find any significant correlation between Ki-67 LI and tumor anatomic location as reported by other studies. *Conclusions*: Despite the fact that statistically we could not find any significant correlation regarding patients' gender and age, tumor anatomic location, and Ki-67 LI expressed by AMs, IHC detection of Ki-67 antigen remains an important tool in addition to routine histological evaluation, which can be used to predict tumor behavior of meningiomas.

Keywords: atypical meningioma, demographic characteristics, skull base, Ki-67 labeling index.

Introduction

Meningiomas are the most common primary intracranial tumors and, despite the fact that they usually are benign and slowly growing tumors, sometimes they may show a histological aggressiveness, which makes them fall under grade II and III, *World Health Organization* (WHO) Classification [1]. Out of all meningiomas, in different series, atypical meningiomas (AMs) represent 20–35% of all cases of meningiomas [2, 3], with an incidence that has increased in recent years [4, 5].

Although the behavior of meningiomas was correlated to the histopathological characteristics of the beginning of 19th century, by the renowned pathologist Rudolf Ludwig Karl Virchow (1821–1902), founder of cellular pathology [6], it is still currently difficult to predict this behavior and identifying protein markers responsible of cell proliferation can be helpful in this regard [7]. Among these, Ki-67, a non-histone protein, is an important proliferative marker, being expressed only in proliferative phase of cell cycle (G1, S, G2 and M phases). A high Ki-67 labeling index (LI) is connected to an increased risk of recurrence, which makes it an important prognostic factor in meningiomas [8–18]. Ki-67 nuclear antigen expressed by proliferating cells has become largely used, being detected on formalin-fixed paraffin-embedded tissue sections [7].

In this study, we aimed to investigate the immunohistochemical (IHC) profile of AMs by using Ki-67 LI, in order to identify the correlation between its values, the gender and age of the patient, and the anatomic location of the tumor in the intracranial space.

Patients, Materials and Methods

We carried out a retrospective review of 29 patients with intracranial AMs (*WHO* grade II) that underwent resection at "Prof. Dr. Nicolae Oblu" Emergency Clinical Hospital, Iaşi, Romania, between January 1, 2014 and December 31, 2016. We search for patients' demographic characteristics (age and gender), and tumor anatomic location from medical files. The management of the study was conducted in full compliance with the ethical principles

and informed consent has been obtained from all the patients. All tumors were totally resected and were sent to the Department of Pathology of the same Hospital.

Representative surgical specimens were fixed in 10% neutral buffered formalin, embedded in paraffin and then 4 µm sections were stained with Hematoxylin and Eosin (HE). Then, representative 4-µm sections were processed according to a two-step, non-Avidin–Biotin method (EnVision+, Dako Corporation). The slides were reviewed by two pathologists (G.F.D and A.S) in order to assess the presence of IHC staining. Ki-67 LI was defined as the percentage of positive cells (having brown nuclear staining) counted among 100 tumor cells in the fields with the largest number of positive cells. Data were analyzed by using Statistical Package for the Social Sciences (SPSS) 13 for Windows.

Results

In our study, the occurrence of AMs was slightly more common in female than in male patients (F:M ratio 1.07:1) (Figure 1). Most of AMs (8/15 cases) diagnosed in female patients showed a Ki-67 LI lower than 7% (Figures 2–4). Most of AMs diagnosed in male patients (8/14 cases) expressed predominantly a value of Ki-67 LI ranging from 8% to 10% (Figures 3, 5, and 6). The mean Ki-67 LI showed small variation in relation with gender (8.6% for female patients *vs.* 8.5% for male patients) (Table 1), being 8.7% of the total number of cases taken into consideration (Table 2).

As for the age distribution, 19/29 (65.31%) patients were over 60. Most patients (34.48%, *n*=10) were over 70 years, followed by those aged from 40 to 59 years (31.03%) and those from 60 to 69 years (31.03%) (Figure 7). The mean age at surgery was 62.8 years (range 20–77 years). Regarding the age of the patients with AMs, the older group (>60 years) expressed a Ki-67 LI higher than 8%, while in the younger age (40–59) groups AMs showed a Ki-67 LI lower than 7%. Furthermore, in patients over 70 years, 50% (*n*=5) had Ki-67 LI <7%, followed by three patients with Ki-67 LI ranging from 8% to 10% and two patients with Ki-67 LI higher than 10% (Figure 8). With respect to the anatomic location of intracranial AMs, most of these (82.75%, *n*=24) were non-skull base, followed by five cases located at the skull base (Figure 9). Regarding the correlation between tumor location and Ki-67 LI, we found that non-skull base AMs showed a higher mean Ki-67 LI than skull base AMs (8.9% *vs.* 8.2%). Ki-67 LI varied from non-skull base meningiomas from 6% to 15%, and skull base meningiomas from 7% to 10%. Furthermore, AMs with Ki-67 LI from 8% to 10% were all located in the non-skull base. Females had a variation of Ki-67 LI from 6% to 15% and men from 7% to 13%, with a mean Ki-67 LI of 8.6% in females and 8.5% in males (Figure 10; Table 1). Statistically, there was no significant correlation regarding gender, age, anatomic location and Ki-67 expression in AMs presented in this paper.

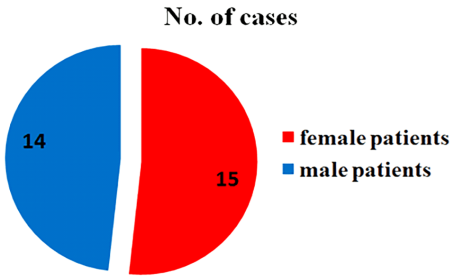

Figure 1 – ***Gender distribution among AMs patients (n=29). AMs: Atypical meningiomas.***

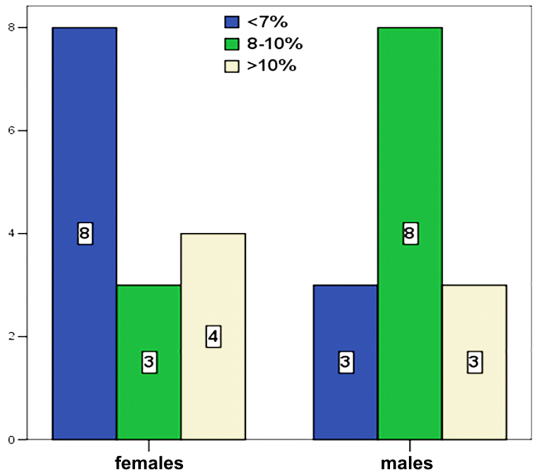

Figure 2 – ***Ki-67 LI distribution according to patients' gender (n=29). LI: Labeling index.***

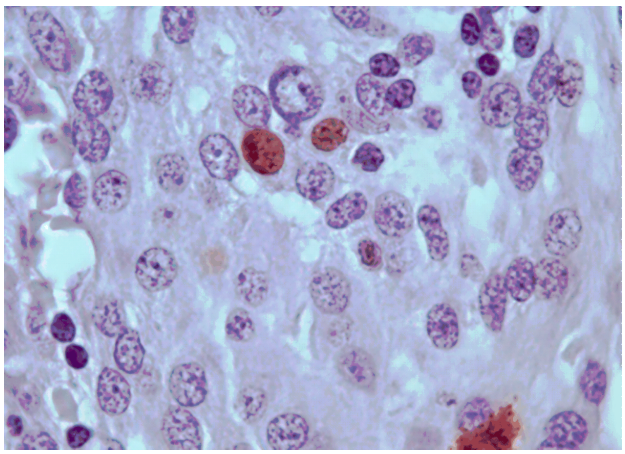

Figure 3 – ***F, 61-year-old, with a skull base AM: low expression of Ki-67 LI (6% nuclear staining) (immuno-histochemical staining using MIB-1 clone, ×100). F: Female; AM: Atypical meningioma; LI: Labeling index.***

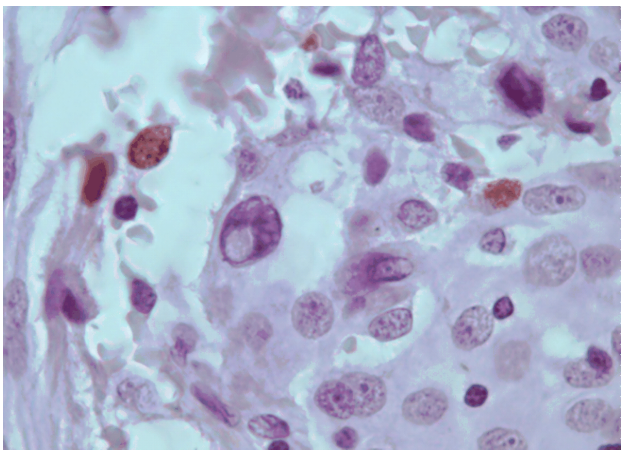

Figure 4 – ***F, 56-year-old, with a non-skull base AM: low expression of Ki-67 LI (7% nuclear staining) (immuno-histochemical staining using MIB-1 clone, ×100). F: Female; AM: Atypical meningioma; LI: Labeling index.***

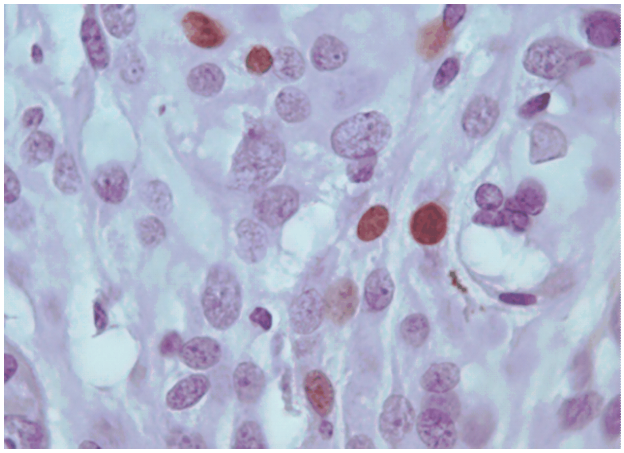

Figure 5 – *M, 62-year-old, with a non-skull base AM: high expression of Ki-67 LI (12% nuclear staining) (immunohistochemical staining using MIB-1 clone, ×100). M: Male; AM: Atypical meningioma; LI: Labeling index.*

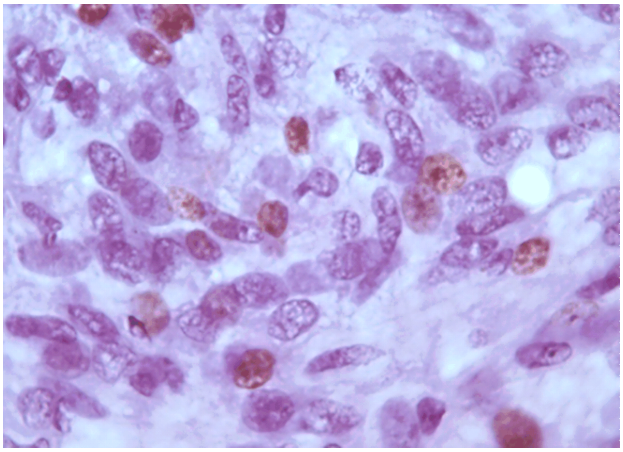

Figure 6 – *M, 59-year-old, with a non-skull base AM: high expression of Ki-67 LI (13% nuclear staining) (immunohistochemical staining using MIB-1 clone, ×100). M: Male; AM: Atypical meningioma; LI: Labeling index.*

Table 1 – *Ki-67 LI values according to patients' gender and tumor anatomic location (n=29)*

		Ki-67 LI <7%	Ki-67 LI 8–10%	Ki-67 LI >10%	Mean Ki-67 LI [%]	Ki-67 LI range [%]
Patients' gender	*Female*	8	3	4	8.6	6–15
	Male	3	8	3	8.5	7–13
Tumor anatomic location	*Non-skull base*	8	11	5	8.9	6–15
	Skull base	3	0	2	8.2	7–10

LI: Labeling index.

Table 2 – *Comparison of our results with other studies of Ki-67 LI in AMs*

Authors	Year of publication	Country	No. of meningioma cases	No. of AMs from all cases	Mean Ki-67 LI [%] in AMs
Current study	2019	Romania	29	29	8.7
Al-Nuaimy *et al.* [19]	2012	Iraq	50	5	5.4
Rao *et al.* [20]	2009	India	123	10	13.7
Uzüm & Ataoğlu [21]	2008	Turkey	246	46	8.61
Karabağli & Sav [22]	2006	Turkey	87	31	6.53
Roser *et al.* [18]	2004	Germany	600	45	9.95
Amatya *et al.* [23]	2001	Japan	146	27	8.1
Hsu *et al.* [24]	1998	USA	57	24	3.2

LI: Labeling index; AMs: Atypical meningiomas.

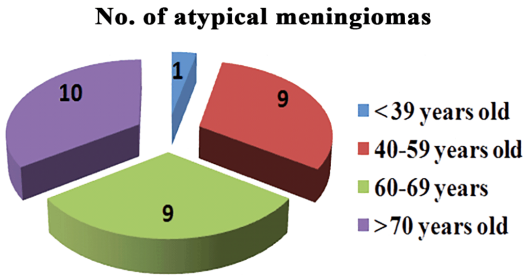

Figure 7 – *Number of treated patients divided in age groups (n=29).*

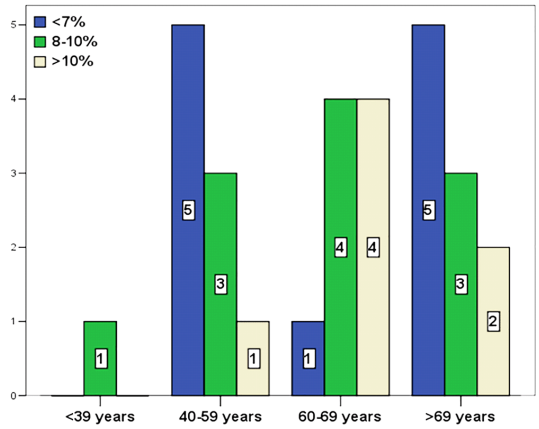

Figure 8 – *Ki-67 LI distribution according to patients' age (n=29). LI: Labeling index.*

Discussions

Until now, almost all of the studies from the previous literature have shown a positive correlation between Ki-67 proliferating marker and tumor grade of meningiomas [13, 25]. For grade I meningiomas, the estimated mean Ki-67 LI is 3% (range 1–16%) and for grade III meningiomas it is 17% (range 7–32%), and an index higher than 4% is a reasonable threshold value to indicate the risk of recurrence [25].

As for the AMs, the average value is an intermediary one (8%), ranging between 2% and 20% [7, 15, 18]. Concerning neurofibromatosis-2-associated meningiomas, studies showed that Ki-67 LI was higher than in sporadic meningiomas, demonstrating a more aggressive behavior of these meningiomas [18, 26].

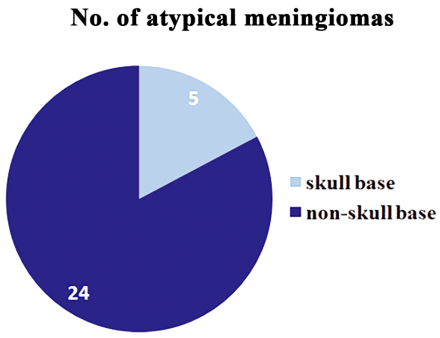

Figure 9 – ***Anatomic location of intracranial AMs (n=29). AMs: Atypical meningiomas.***

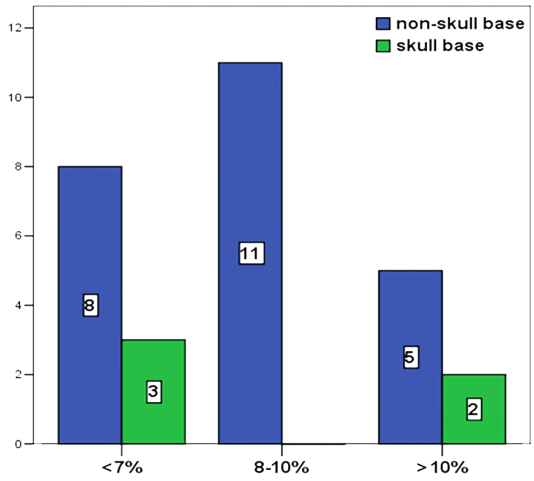

Figure 10 – ***Ki-67 LI distribution according to the anatomic location of AMs (n=29). LI: Labeling index; AMs: Atypical meningiomas.***

However, Ki-67 LI for grade I–III meningiomas varied considerably from a study to another, while tumor heterogeneity with regional differences in cell proliferation is well known, thus tumor sampling becomes an important source of error [25, 27, 28]. In this context, it is crucial to choose the representative sample of meningioma tissue in order to make a correct calculation [25].

Also, between grade I and grades II/III meningiomas, all studies demonstrated a statistically significant difference in Ki-67/MIB-1 LIs, difference that was not always valid for grade II and III meningiomas [25]. In our study, the mean Ki-67 LI was 8.7% (ranging from 6% to 15%), being close to values obtained by Uzüm & Ataoğlu [21] and Amatya *et al.* [23] (Table 2). A low Ki-67 LI does not always show a low-grade meningioma, even more so the grade II/III meningiomas may show a low proliferative activity [25]. Taking these into account, the significance of Ki-67 proliferation marker in the regular diagnosis of meningiomas should be evaluated together with other histological parameters [4–19 mitoses/10 high-power fields (HPFs)], brain invasion, or three or more of the following features: (*i*) increased cellularity; (*ii*) uninterrupted pattern less or sheet-like growth; (*iii*) small cells with a high nuclear/cytoplasmic ratio; (*iv*) prominent nucleoli; (*v*) foci of "spontaneous" necrosis; (*vi*) tumor histological subtype (simple AM, clear cell meningioma, or chordoid meningioma); (*vii*) age and gender of the patient; (*viii*) his/her hormonal status; (*ix*) tumor anatomic location [25].

In a retrospective study made on 38 spheno-orbital meningiomas, Belinsky *et al.* [29] showed that the use of a combination of *WHO* grade and Ki-67 LI can predict spheno-orbital meningiomas behavior and has important clinical implications for the identification of patients at higher risk of recurrence and can guide the individualized treatment and surveillance strategies. Moreover, authors found statistically significant correlations between Ki-67 and disease clinical progression, considering the following findings at presentation: decreased vision, proptosis, epiphora, optic neuropathy and diplopia [29].

In our study, we did not find any significant correlation between patients' gender and Ki-67 LI of their AMs (p=0.172) as it was shown by other studies [7, 30–32]. In our study, the occurrence of AMs was slightly more common in female than in male patients (F:M ratio 1.07:1), in agreement with other studies [33]. We have noticed that AMs diagnosed in male patients had a mean Ki-67 LI of 8.5%, being almost equal to the mean Ki-67 LI in female patients (8.6%). Some other reports have found Ki-67/MIB-1 LIs significantly higher in male patients than in female patients [34, 35], while other studies have not reached the same conclusions [18, 36]. We also noticed that 78.57% (n=11) of males had Ki-67 >8%, compared to females, who summed up 46.66% (n=7) at the same value of Ki-67. Furthermore, in males prevailed Ki-67 from 8% to 10% at a rate of 57.14% (n=8), and in the group of fames it was as low as 20% (n=3), in agreement cu other studies [34, 35]. The prevalence of Ki-67 >8% in men may mean higher aggressiveness of AMs in male population compared to female population, various authors reporting that male gender could be a factor of negative prognosis [37–39], even a risk factor for a shorter survival [38].

No significant relation was found between the Ki-67 LI and patients' age. Similar findings were reported in literature [18, 19, 30–32, 40]. However, it is worth mentioning that our study found out that patients being in their 7th decade of life and diagnosed with AMs had a Ki-67 LI higher than 8%. Similarly, Yamamoto *et al.* [41] reported on a series of 70 consecutive intracranial meningiomas that elderly patients exhibited a high Ki-67 proliferation index, when compared with younger meningioma patients. Unfortunately, AMs accounted for merely 6.3% [41] and this is the reason why studies on large groups of patients are needed to assess age as a factor of prognosis for grade II meningiomas.

Also, we did not find any significant correlation between Ki-67 LI and tumor anatomic location as reported by other studies [7, 18, 31]. In our research, we have noticed a higher prevalence of non-skull base meningiomas. Other studies proved that non-skull base meningiomas have an increased risk to be of grade II or III [42–44], and this difference can be explained by a distinct embryological origin of skull base and non-skull base dura, which may lead towards a propensity for developing of different histological subtypes meningiomas [45–47]. Various authors showed that skull base meningiomas may have a more aggressive biology, due to a higher MIB-1 LI [48] or significantly higher cluster of differentiation 34 (CD34) levels compared to the non-skull base meningiomas group [49].

As for the correlation between the value of Ki-67 and the location of meningiomas within the intracranial space, Liang *et al.* [50] analyzed the immunohistochemistry with

Ki-67 in 368 samples out of a total of 1239 of atypical and anaplastic meningiomas. He noticed that the percentage of patients with Ki-67 LI ≥5% in convexity meningiomas was higher than in non-convexity location (52.8% *vs.* 38.5%, p=0.006), concluding that convexity meningiomas are a significant risk factor for the AM [50]. Although we did not find a significant statistical correlation the value of Ki-67 and the anatomic location of the tumor in agreement with previous studies [32], we noticed that 72.72% (n=8) of the meningiomas with Ki-67 <7%, 100% of the meningiomas with Ki-67 between 8–10% (n=11) and 71.42% (n=5) of the meningiomas with Ki-67 >10% were with non-skull base location. Therefore, 66.66% (n=16) of the non-skull meningioma had Ki-67 >8%. Furthermore, the mean Ki-67 LI was higher in non-skull base meningiomas compared to skull base meningiomas (8.9 *vs.* 8.2) (Table 1).

In a study, Ciocan *et al.* demonstrated on 65 patients with anterior skull base meningiomas, out of which 15.38% were AMs, that in these the mean Ki-67 LI was 4.1% [51], much higher than our mean Ki-67 LI calculated for the meningiomas in the entire skull base, not only in the anterior fossa.

Although regional differences regarding meningioma proliferative activity have not been found between meningiomas occurring in intracranial or orbital locations, there are some studies reporting lower Ki-67 LIs in spinal AMs [18, 35, 52, 53]. Even though our study has been carried only on cases of intracranial meningiomas, this difference is worth mentioning, since it opens new lines of research.

Conclusions

The use of Ki-67 LI in the anatomopathological history of meningiomas is a supplement in determining the histological grade, not a substitute. Despite the fact that statistically we could not find any significant correlation regarding patients' gender and age, tumor anatomic location, and Ki-67 LI expressed by AMs, IHC detection of Ki-67 antigen remains an important tool in addition to routine histological evaluation, which can be used to predict tumor behavior of meningiomas. Together with the histopathological characteristics of meningioma malignancy, Ki-67 LI can be used as a potential indicator of recurrence.

Conflict of interests

The authors declare that they have no conflict of interests.

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