

ORIGINAL ARTICLE

Clinical outcomes and cost-effectiveness of primary treatment of ovarian cancer in North-Western Romania

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Summary

Purpose: Ovarian cancer has the poorest survival rate among gynaecological malignancies. Besides the comparison of different therapeutic strategies aimed to improve outcomes, studies have also begun to focus on aspects of cost-effectiveness of these strategies. In this context, we proposed to evaluate the survival impact, costs and cost-effectiveness of two primary treatment options, primary debulking surgery (PDS) versus neoadjuvant chemotherapy (NACT), in patients with advanced ovarian cancer treated in a tertiary cancer center of the North-Western Romania.

Methods: The study included patients with stages IIIC and IV ovarian cancer treated at the "Prof. Dr. Ion Chiricuta" Institute of Oncology, Cluj-Napoca, between 2008-2011, by either PDS or NACT. Survival was the measure of the effectiveness of the two treatments. A cost-effectiveness analysis was carried out by estimating the incremental cost-effectiveness ratio (ICER) and the average cost-effectiveness ratio (ACER).

Results: There was no significant difference in overall survival between the two treatment groups. The median costs for the NACT subgroup were 3580.41 € compared to 2990.19 € for the PDS subgroup, with an incremental cost of 590.22 €. The effectiveness measured in years of survival was 3.34 years for NACT and 3.57 years for PDS. The corresponding median ICER was -2566.17 €/year of survival. ACER was higher for NACT compared to PDS (1071.98 vs. 837.59 €/year of survival).

Conclusion: Despite the higher costs, NACT did not prove to be a more effective therapeutic strategy in terms of survival of patients with stage IIIC/IV ovarian cancer. Altogether, our results state that NACT might be less cost-effective than PDS.

Key words: cost-effectiveness, ovarian cancer, primary treatment, Romania

Introduction

Ovarian cancer represents the fifth leading cause of cancer related deaths and still remains the deadliest gynecological malignancy [1]. The age-standardized incidence in Europe has been 10/100000 in 2012. Higher incidence rates have been usually reported in Northern and Eastern countries such as the U.K., Ireland, Slovakia, Latvia or Lithuania [2]. The trends in mortality rates follow almost the same pattern of geographical

distribution across Europe in 2012, according to EUCAN [3]. In Romania, the incidence of ovarian cancer was quite stable in recent years according to Globocan (6.3/100,000 in 2008 and 6.1/100,000 in 2012) [4,5] and mortality was among the five leading causes of cancer deaths [6].

The incidence of ovarian cancer increases with age, the median age at diagnosis being 60 years in sporadic cases. On the other hand, the survival

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declines with increasing age from 71% for women diagnosed between 15-44 years to 20% for those aged >75 years [2,3].

Current studies have stressed the differences in gross domestic product (GDP), the percentage of GDP invested in health and health expenditure between the Western and Eastern European countries. They managed to highlight the association of increased GDP and health expenditure in Western countries with increased incidence, better prognosis and decreased cancer mortality, explaining the variations in cancer outcomes compared to Eastern countries. In the context of a GDP difference of more than 10-fold between Western and Eastern Europe, health care costs have risen dramatically in some Western countries, with health expenditure exceeding 10-12% of their GDP [7].

A study performed in USA estimated that in 2010, medical costs of care for ovarian cancer patients were higher for both the initial phase of care and the last phase of care compared to cancers of other sites such as breast cancer, prostate cancer or malignant melanoma. They claim that these costs are also higher in younger patients of less than 65 years old versus older patients in both initial and terminal phase with 20% and 50%, respectively [8].

In most of ovarian cancer cases, one major inconvenience is diagnosis in advanced stages. Better detection methods, as well as more effective chemotherapeutic options and debulking techniques, might be responsible for the survival improvement, although yet not satisfactory. Alternatively to standard primary cytoreductive surgery followed by platinum-based chemotherapy, NACT prior to surgery has been proposed for selected patients with advanced stages, but it did not confer a significant survival increment according to the trials completed so far [9,10].

A series of cost-effectiveness analyses have been carried out in recent years, aiming to compare different therapeutic strategies for ovarian cancer. Comparisons are mostly performed with the standard of care. Cost-effectiveness is commonly expressed through the ICER, and besides costs, it should quantify both the impact on survival and the quality of life, which are referred to as cost per quality-adjusted life year (QALY). Altogether, in the USA a cost of less than US \$50,000 per QALY might be the cut-off value for an intervention to be considered cost-effective compared to an alternative intervention [11]. So far, very few studies have compared two primary treatment alternatives of advanced ovarian cancer (PDS versus NACT) in terms of cost-effectiveness.

In this context, with some data coming particularly from Western countries, this study aimed

to evaluate the survival impact, costs, and cost-effectiveness of two primary treatment strategies among advanced ovarian cancer patients treated in a tertiary cancer center serving the population of North-Western Romania.

Methods

Study population

A total of 874 patients diagnosed between January 1, 2008, and December 31, 2011, with invasive ovarian cancer were identified in the North-Western Regional Cancer Registry database. The North-Western Region of Romania includes 6 counties: Bihor, Bistrita-Nasaud, Cluj, Maramures, Satu-Mare and Salaj. Of the total of 874 cases, 530 were consulted, diagnosed and/or received treatment in "Prof.Dr. Ion Chiricuta" Institute of Oncology in Cluj-Napoca (IOCN). Demographics (age, date of diagnosis, date of death, the number of population at risk) and data regarding primary tumor site, tumor morphology, stage and treatment were provided by the Epidemiology Department of IOCN and North-Western Regional Cancer Registry. We took into consideration all cases reported as ovarian cancers with International Statistical Classification of Diseases, 10th Revision [ICD100], code C56, and we excluded cases with unknown stage, missing tumor histology, germ cell, sex cord tumors, as well as borderline tumors.

The mainstay of treatment for ovarian cancer is primary cytoreductive surgery aimed to diagnose, stage and completely remove all tumor volume, followed by platinum-based adjuvant chemotherapy. The standard protocol for first-line postoperative chemotherapy consists of Paclitaxel 175mg/m² and Carboplatin AUC 6 every 3 weeks for 6 cycles [12]. Hence, in order to perform a cost analysis and to compare the outcomes of patients treated with PDS versus the ones receiving NACT, we considered only cases with stages IIIC and IV ovarian cancer (237 patients), treated at IOCN, who received both surgery and chemotherapy (186 patients). Patients who received surgery first followed by adjuvant chemotherapy were placed in the PDS group, whereas patients with chemotherapy preceding surgery were included in the NACT group. The number of chemotherapy cycles was recorded for each subject.

Survival analysis

The survival time reflects overall survival of patients and was defined as the time between diagnosis and death or last follow-up (July 15, 2015). Kaplan-Meier method and Log-rank test were used to investigate any significant difference in survival between patients who received surgery first followed by adjuvant chemotherapy and patients with chemotherapy preceding surgery.

Cost analysis

In order to analyze the costs related to each primary treatment strategy, we took into consideration direct medical costs associated with surgery and the afferent hospitalization. The equivalent value reimbursed by The

National Health Insurance House of Romania (CNAS) to each hospital per case (price per case solved- TCR), depends on the complexity of the surgery procedures reflected by a relative value (VR), the number of hospitalization days, including Intensive Care Unit (ICU) days. We used data from the Administrative Department of IOCN to categorize cases operated at the IOCN according to the surgical procedures performed, complications and comorbidities. The VR for ovarian cancer surgery without complications was 1.6949, whereas in the presence of complications and comorbidities the VR jumped to 3.0243. Eventually, the final cost associated with the surgical act was obtained by multiplying the average price allocated by the CNAS for each case with the equivalent relative value. Regarding chemotherapy, an average price per cycle was estimated for years 2008-2011 with the support of IOCN Pharmacy. Due to the large variation of the prices achieved at auctions in The National Oncology Program PN3, we considered the prices settled in accordance with C2 list, in line with Government Resolution no.720/2008 [13]. The expenses afferent to the hospitalization for chemotherapy administration are separately reimbursed by the CNAS and were added to the costs of chemotherapeutic agents. Eventually, a final cost for the primary treatment including surgery, chemotherapy cycles and the corresponding hospitalizations was estimated for each patient. Due to inaccurate data concerning the rate of chemotherapy-related toxicities, we could not provide detailed estimates of the costs of hospitalizations for the management of toxicities.

Cost-effectiveness analysis

Taking into account the costs and the effectiveness of each treatment strategy (PDS versus NACT), we aimed to perform a cost-effectiveness analysis by the estimation of ICER [14]. We considered survival time as the measure of the effectiveness of the treatments compared. In our case, ICER was defined as the ratio of the difference in costs to the difference in effectiveness between these two competing treatment strategies. Given that, generally, costs distribution has a certain amount of skewness, in order to estimate the ICER value, we used the mean and median of costs and effectiveness. The formula used for ICER was the following [11]:

$$ICER_{median} = \frac{\text{median}(C_{NACT}) - \text{median}(C_{PDS})}{\text{median}(E_{NACT}) - \text{median}(E_{PDS})};$$

$$ICER_{mean} = \frac{\text{mean}(C_{NACT}) - \text{mean}(C_{PDS})}{\text{mean}(E_{NACT}) - \text{mean}(E_{PDS})}$$

The interpretation of ICER value was done according to the cost-effectiveness plane. We also estimated average cost-effectiveness ratio (ACER) in order to quantify the amount of cost per year of survival for each treatment. The formula used for ACER was the following [15]:

$$ACER_{NACT} = \frac{\text{median}(C_{NACT})}{\text{median}(E_{NACT})};$$

$$ACER_{PDS} = \frac{\text{mean}(C_{PDS})}{\text{mean}(E_{PDS})}$$

Statistics

Statistical analysis was performed using advanced environment for statistical computing R (v.3.2.4, Vienna, Austria) and STATISTICA (StatSoft, USA, version 6). Descriptive statistics were used to summarize the clinical characteristics. Chi square was used to check if there was a relationship between two categorical variables, and Mann-Whitney U test was used to compare differences between two independent groups when appropriate. Survival analysis was estimated according to Kaplan-Meier method and comparison of differences was done with Log-rank test. A significance level of 0.05 was used for all two-sided statistical tests, and a test result was considered significant when p was lower than 0.05.

Results

Of the 237 patients with stage IIIC and IV ovarian cancer 78% (186) had been treated with both surgery and chemotherapy. Out of this subpopulation, 67.2% (125) of patients were part of the PDS group and 32.8% (61) of patients received primary chemotherapy followed by cytoreductive surgery, as part of the NACT group. The average number of chemotherapy cycles was 5.8 in the PDS group and 8.01 in the NACT group, with a median of 5.4 cycles administered before surgery.

The mean patient age was 56 years (range 25-77) and the majority of them (57%) were younger than 60 years, whilst about 10% were over 70 years. The distribution of patients according to the administered treatment for each age group is displayed in Table 1. For each age group, the proportion of patients treated with PDS was around 70%, except for patients older than 70. A slight difference was observed in this subgroup of age, 54.5% of patients being treated with PDS, whilst 45.5% received NACT. However, when chi-square test was performed, no significant differences regarding the frequency of each treatment within each age group have been found (p=0.756).

Table 1. The frequency distribution by age and treatment type

Variables	Type of treatment	
	PDS n (%)	NACT n (%)
Age categories (years)		
≤39	9 (69.2)	4 (30.8)
40-49	22 (71.0)	9 (29.0)
50-59	43 (69.4)	19 (30.6)
60-69	39 (67.2)	19 (32.8)
≥70	12 (54.5)	10 (45.5)
Total	125 (67.2)	61 (32.8)

PDS: primary debulking surgery, NACT: neoadjuvant chemotherapy

Furthermore, Table 2 presents the type of treatment depending on the time of diagnosis. Regardless of the period of diagnosis, there was no statistical significant difference between the two treatment groups ($p=0.25$), although a trend toward an increase of NACT administration might be observed in the more recent years (38.1% in 2010-2011 vs. 28.1% in 2008-2009).

By the end of the follow-up period, 121 (65.05% of patients) deaths had been recorded, while only 65 (34.94%) patients were still alive, 37.5% in the PDS group compared to 29.5% in the NACT group (Table 3). Overall, the median survival time was 42.8 months (95% CI: 33.26-52.33).

When analyzing overall survival according to the treatment (PDS vs. NACT), the median survival time was superior for the patients in the PDS group compared to the patients in the NACT group (Figure 1), but the difference did not reach statistical significance (42.86 vs. 40.1 months, $p=0.33$), according to Log-rank test (Table 4).

According to Log-rank test, there was a significant difference in survival time between stage III and IV disease, the distribution of survival time being significantly different among the two groups ($p=0.016$). The survival time favored patients with stage III disease compared to those in stage IV (Figure 2).

Table 2. Distribution of patients by period of diagnosis

Variables	Type of treatment	
	PDS n (%)	NACT n (%)
Period of diagnosis (years)		
2008-2009	69 (71.9)	27 (28.1)
2010-2011	56 (61.8)	34 (38.2)
Total	125 (67.2)	61 (32.8)

Table 3. Distribution of patients by type of treatment

Type of treatment	No. of patients	No. of deaths	No. of patients alive, n (%)
PDS	125	78	47 (37.6)
NACT	61	43	18 (29.5)
Total	186	121	65 (34.9)

Table 4. Survival time statistics by the type of primary treatment

Type of treatment	Estimated mean survival time (months)	95% CI	Estimated median survival time (months)	95% CI
PDS	50.85	44.80-56.90	42.86	30.64-55.09
NACT	44.36	37.59-51.13	40.10	24.24-55.95
Overall	49.37	44.58-54.17	42.80	33.26-52.33

Moving forward to a cost analysis, there was a significant difference between the costs of each primary treatment strategy (Mann-Whitney U test, $p<0.001$). We noticed that the cost values were significantly higher for the NACT subgroup

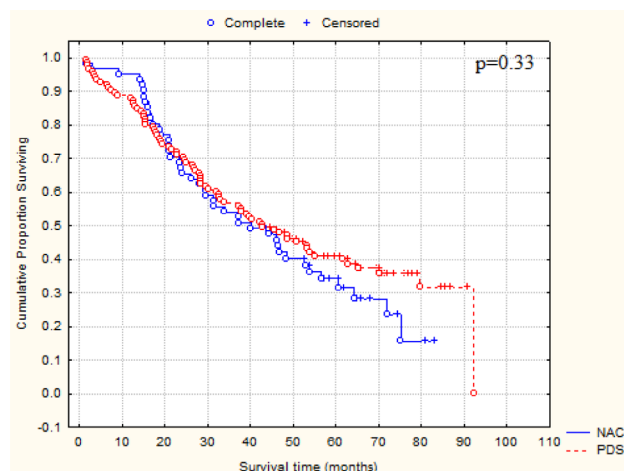


Figure 1. Survival time distribution between compared groups.

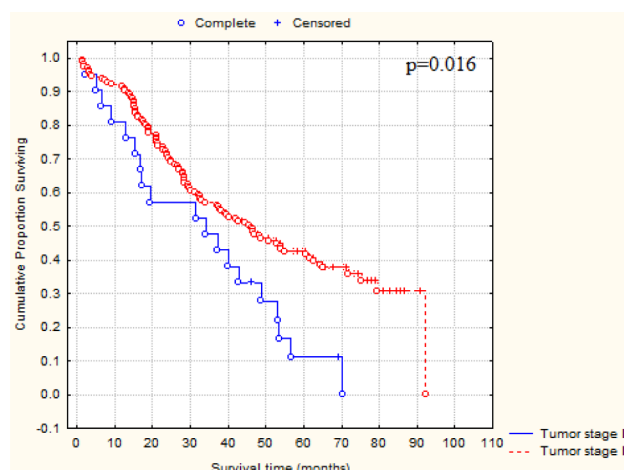


Figure 2. Survival time distribution between tumor stages.

Table 5. Cost-analysis statistics

<i>Cost analysis based on means</i>						
<i>Type of treatment</i>	<i>Mean costs (€)</i>	<i>Incremental cost</i>	<i>Mean survival time (years)</i>	<i>Effectiveness</i>	<i>ICER_{mean}</i>	<i>ACER</i>
PDS	2831.50	668.69	4.24	-0.54	-1238.31	667.81
NACT	3500.20		3.70			946
<i>Cost analysis based on medians</i>						
<i>Type of treatment</i>	<i>Mean costs (€)</i>	<i>Incremental cost</i>	<i>Mean survival time (years)</i>	<i>Effectiveness</i>	<i>ICER_{mean}</i>	<i>ACER</i>
PDS	2990.19	590.22	3.57	-0.23	-2566.17	837.59
NACT	3580.41		3.34			1071.98

For abbreviations see text

compared to PDS subgroup as follows: 3580.41 € (25th-75th percentile: 2740.38-4003.75) vs. 2990.19 € (25th-75th percentile: 2616.19-3078.23). The incremental cost was 590.22 €. The effectiveness, expressed in years of survival, was 3.34 years for the NACT group and 3.57 years for the PDS group, respectively.

In order to economically manipulate these findings in a cost-effectiveness analysis of the primary treatment of ovarian cancer, we corroborated the costs with the effectiveness of treatment measured in survival time (Table 5). Therefore, we calculated the mean and median ICER and we obtained a value of -1238.21 €/year of survival and -2566.17 €/year of survival, respectively. Considering individually each treatment strategy, ACER was higher for NACT compared to PDS (1071.98 and 837.59 €/year of survival, respectively).

Discussion

The 5-year relative survival for women diagnosed with ovarian cancer between 2000-2007 was 38%, according to EURO CARE5 [16]. Data from a recent CONCORD2 study have shown a modest increase in 5-year survival in most of the European countries of less than 2-4% between 1995-1999 and 2005-2009. For several countries, such as Bulgaria, Denmark, France, Latvia or Portugal, the 5-year survival has increased by 5-10% or with more than 10% in Estonia. However, the discrepancies in survival across European countries were more striking in Northern countries (36% in Denmark, 31% in Ireland/UK vs. 44% in Sweden) than in Eastern countries [17]. In Romania, the North-Western Regional Cancer Registry has reported approximately 15% of cancer deaths due to gynecological cancers and for ovarian cancer an average age-adjusted incidence rate of 8.31 per 100,000 in

the period 2008-2011 [6], higher than Globocan estimates from 2008 (6.3 per 100,000) and 2012 (6.10 per 100,000) [4,5]. Hence, the implementation of population-based national/regional cancer registries even in less developed countries, leads to more accurate reporting from areas previously uncovered.

In our study, we aimed to highlight the outcomes of patients with stage IIIC and IV ovarian cancer treated in a tertiary cancer center that serves the population of the North-Western region of Romania. Two primary therapeutic approaches suitable for this group of patients were evaluated, the current standard primary debulking surgery, followed by postoperative chemotherapy versus NACT followed by surgery. Most of the patients (67.2%) underwent cytoreductive surgery as initial treatment whereas 32.8% had NACT followed by surgery. No significant relationship was observed between the age of the patients or the period of diagnosis and the choice of one of the therapeutic strategies. Overall, the median survival time was of 42.8 months and a survival benefit of almost 3 months was observed for primary debulking surgery, although not statistically significant. However, the 5-year survival rate ranged between 30-40% for both treatment groups. For patients receiving secondary surgery for recurrent disease (9.67%), a survival benefit of approximately 5 months was reached, yet not statistically significant.

Continuous concerns are intended to streamline actual therapies while also focusing on the costs-effectiveness of different strategies for primary treatment, for treatment of recurrences and/or end-of-life care. One important topic refers to centralization of care for patients with ovarian cancer. Recent research has shown that high-volume centers with specialized gynecologic oncologists provide the best outcomes and survival for advanced-

stage ovarian cancer because of the higher rates of successful optimal cytoreductive surgery, compliance to chemotherapy and proper application of guidelines [8]. A study performed in the USA by Bristow et al. was the first to assume that referral to high-volume centers would be associated with definite efficiency (5,12 QALYs) at higher costs per patient (50,652\$) compared to less specialized centers (39,957 overall costs for 2.78 QALYs). The difference of 2.78 QALYs at an incremental cost of 10.695\$ was considered cost-efficient and encouraged the centralization of care [18]. Similarly, a Dutch study compared general hospitals with semi-specialized hospitals and tertiary cancer centers in terms of cost-effectiveness of treatment. The authors concluded that the treatment provided by semi-specialized gynecologists in semi-specialized centers was the most cost-effective strategy, whereas treatment in tertiary centers involved substantially higher costs and might be considered cost-effective if optimal debulking would be achieved in more than 70% of cases. General hospitals do not represent a feasible option for ovarian cancer treatment due to more modest results and restraints from therapy in advanced stages [19].

The role of aggressive surgery for ovarian cancer has been also analyzed from the economic perspective. Besides the survival advantage of 1.32 years granted by more complex surgery (characterized by the number and complexity of surgical procedures), the afferent costs were clearly higher compared to less aggressive surgery. However, these differences in costs were considered economically affordable when considering the clinical benefit [20]. Since primary cytoreductive surgery of advanced ovarian cancer might be really provocative, NACT represents an option increasingly used, especially for bulky disease and poor performance status (PS), aiming to facilitate the forthcoming optimal surgery. Apart from some retrospective studies [21], no improvement in survival was conferred by NACT in the so far concluded phase III randomized trials, except for less complications and postoperative mortality [6,7]. So far, very few studies have addressed the issue of cost-effectiveness of primary treatment strategies in advanced ovarian cancer. A recent study performed in the USA concluded that PDS is more cost-effective than NACT for stage IIIC ovarian cancer (ICER=\$19.259/QALY gained). This was not the case for stage IV disease due to a much higher ICER of \$130.083/QALY gained, which exceeds the willingness to pay threshold of \$50.000 accepted in the USA [22]. On the other hand, a survival benefit associated with less morbidity and more cost-effectiveness might favor NACT mostly for high-risk patients (age 75+,

stages IIIC/IV, poor performance status), according to a recent retrospective study [23]. Therefore, the survival and cost-benefits are controversial within studies even for elderly women [24].

This is the first study in our country that aimed to approach the issue of cost-effectiveness of different primary therapeutic strategies for ovarian cancer treatment. In this study, the expenditure related to primary treatment in the NACT group was significantly higher than in the PDS group. This might be partially explained by a higher number of chemotherapy cycles administered in the NACT group, even though the costs related strictly to surgery were lower in this subgroup compared to the PDS group. Patients with advanced-stage disease having debulking surgery as initial treatment often require more aggressive surgical procedures and therefore might experience longer hospitalizations due to higher rates of postoperative complications and more ICU days. Despite the higher costs, NACT did not prove to be a more effective therapeutic strategy in terms of survival of patients with stage IIIC/IV ovarian cancer (NACT:3.34 years vs. PDS:3.57 years, median survival time). According to these quantified parameters, we calculated the incremental cost-effectiveness ratio (ICER) and ascertained a median ICER of -2566.17€ per life year saved. The negative values obtained for the mean and median ICER are due to the difference in effectiveness between the two treatment strategies. In the studied sample we noticed a negative effectiveness explained by the lower survival time in the NACT group compared to PDS, while the incremental cost was positive. Furthermore, we extended our economic analysis by estimation of ACER for each treatment strategy. A difference of costs per year of survival was revealed, with higher ACER for the group treated with NACT. Altogether, we might conclude that NACT is less cost-effective than PDS for women with stage IIIC/IV ovarian cancer.

A certain limitation met within the study was the inability to include quality of life estimates due to the retrospective design of our study. This would have led to a more comprehensive measurement of cost-effectiveness expressed through costs per QALY. Moreover, the results of this cost-effectiveness analysis are eloquent for the studied sample and in the absence of a confidence interval for ICER and a sensitivity analysis it cannot be extrapolated for the entire population with stage IIIC/IV ovarian cancer. Some other encountered limitations referred to the lack of quantification of expenses related to chemotherapy toxicities, physician costs, outpatient costs or potential home health costs and possible biases due to retrospective data analysis (selection/ misclassification biases).

A consistent increase in the economic burden of ovarian cancer treatment might be the addition of biologic agents to standard chemotherapy. Bevacizumab has shown a progression-free survival benefit of 3.8 months when administered concurrently with chemotherapy and followed by maintenance, according to GOG 218 trial [25]. The hypothetical cost-effectiveness analysis of this strategy showed a total cost of 78.3 million \$ and an ICER of 401.088\$ per progression-free life-year saved when compared with chemotherapy alone [21]. The substantially high cost of Bevacizumab makes this strategy not cost-effective.

The estimated costs of cancer care in the USA are expected to grow throughout 2010 to 2020 with 27% from the projected 124.57 billion \$ in 2010 to 157.77 billion \$ in 2020. Taking into consideration the future perspective of declining incidence and increasing survival associated with cancer, this increment might be even more consistent [26] and larger studies are warranted for the consolidation of an effective therapeutic strategy.

Conflict of interests

The authors declare no conflict of interests.

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