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Systematic review of cost-effectiveness intraoperative radiation therapy compares with external beam radiation therapy in breast cancer

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Abstract

Breast cancer is the most common cancer and the leading cause of cancer deaths among women worldwide. For a large proportion of women with early localized breast cancer, the recommended treatment is breast-conserving surgery followed by postoperative radiotherapy, and whole breast external-beam radiation therapy, which requires daily therapy. The purpose of this study is to analyze the cost-effectiveness of intraoperative radiation therapy (IORT) compared with external beam radiation therapy (EBRT) for early-stage breast cancer. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines used in this study. We searched all articles from June 30, 2000, to June 30, 2022, in PubMed, Cochrane, ProQuest, and the Cumulative Index to Nursing, Allied Health Literature and non-English articles were excluded. We included cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis. This study included 1750 published studies, ten studies were entirely met the inclusion criteria. In six studies, IORT was associated with lower costs and higher effectiveness than EBRT. In conclusion, IORT can be a potential cost-saving strategy to the health systems for the adjuvant treatment of breast cancer.

Keywords: Breast cancer; Breast-conserving surgery; Intraoperative radiation therapy

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Introduction

Breast cancer is the most common cancer and the leading cause of cancer deaths and disability-adjusted life-years (DALYs) among women worldwide [1]. For a large proportion of women with early localized breast cancer [2], the recommended treatment is breast-conserving surgery (BCS) followed by postoperative radiotherapy, whole breast external-beam radiation therapy (EBRT), which requires daily therapy for 4–7 weeks [3].

EBRT after lumpectomy reduces the risk of local recurrence more than 10% at 5 years and reduces the risk of breast cancer death at 15 years for women with early invasive breast cancer

[4]. Thus, post-operative WB-EBRT is the standard of care for patients with early invasive breast cancer after breast-conserving surgery [5].

However, EBRT has some disadvantages. The long course of treatment is uncomfortable for patients and may require several travels to receive care. WB-EBRT may also be associated with short- and long-term adverse effects and can be impossible to deliver effectively in all patients [5].

New less invasive technologies such as IORT can play an essential role for patients who cannot use EBRT. The large international multicenter randomized controlled trial (RCT) of targeted intraoperative radiotherapy-alone (TARGIT-A) has confirmed the safety and effectiveness of the technique of targeted intraoperative radiotherapy (TARGIT-IORT) in women with early breast cancer [6].

TARGIT-IORT and EBRT resulted in similar local recurrence-free survival. IORT requires only 25–30 min for a single dose of radiation treatment, greatly reducing the time and travel costs required for whole breast radiation therapy [7]. IORT could potentially improve access to breast conservation by reducing costs and time required for patients to receive radiotherapy in resource-limited settings. Therefore, it is an interesting alternative for women who are candidates for breast-conserving surgery [8].

Considering the resources limitations, along with the above-mentioned innovations in the management of breast cancer, providing a light picture of the economic aspects of the technologies is increasingly important to help policymakers to efficiently allocate health system resources [9]. The purposes of this systematic review were to identify the relevant economic evaluation studies of intraoperative radiation therapy versus external beam radiation therapy, assess the quality of the included studies to support future cost effectiveness studies in this field, and summarize the cost effectiveness results on the existing therapies of early breast cancer [10].

Methods

Identification of studies

A systematic search was conducted from June 30, 2000, to June 30, 2022, in PubMed, Cochrane, ProQuest, and the Cumulative Index to Nursing, Allied Health Literature and non-English articles were excluded. The search strategy consisted of keywords and Mesh. Separate search strategies were developed for each database. List of references of eligible full text articles were further screened in order to find eligible studies. Studies were required to meet the following criteria in order to be included in the review:

- Population: people with early operable breast cancer;
- Intervention: IORT with or without post-operative WB-EBRT;
- Comparator: WB-EBRT delivered by linear accelerator after BSC;
- Outcomes: cost per life-years gained or cost per quality-adjusted life-years (QALYs)

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gained or in monetary units or incremental cost-effectiveness ratio (ICER)];

- Study design: Full economic evaluation studies (costeffectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA), Model-based or trial based;
- Setting, country: all countries, all settings Exclusion criteria were:
- Partial economic evaluation studies (cost-minimization analysis, cost-analysis) or non-evaluation studies
- Reviews, Commentaries (letters to the editors, editorials), protocols, Abstracts or conference presentations
- Non-English language full-text studies
- Duplicated publications

Selection of Studies

After removing duplicates, titles and abstracts of studies were screened independently by two researchers to identify all studies that potentially met the inclusion/exclusion criteria detailed above. Full text of selected studies that appeared potentially relevant were obtained. These were assessed by one researcher against the eligibility criteria and checked independently by a second researcher. Any disagreements were resolved by discussion. The agreement was reached on all included studies.

Data extraction and quality assessment of the studies

Data extraction was performed by one reviewer (JA) and checked by a second reviewer (VA). Disagreements were resolved by discussion at each stage. Data were extracted using a researcher-made extraction table. Data extracted from each study included publication year, country, perspective, willing-to-pay threshold, type of economic evaluation, modeling approach, model states, time horizon, discount rates (costs, QALY), type of costing, included costs, outcome measures, type of sensitivity analysis, industry funding, population, comparators, and results.

Included studies were then assessed using the CHEERS checklist [11]. The CHEERS tool consists of twenty four items in six sections (title and abstract, introduction, methods, results, discussion, and other) and were scored using ‘Yes’ (reported in full), ‘Partially reported’, ‘No’ (not reported), and ‘Not Applicable’. Two researchers (JA and VA) independently assessed the included studies with disagreements resolved through consensus. In order to estimate a score of reporting, we allocated a score of 1 for each item that was reported in full, 0.5 for a partial report and otherwise 0. Therefore, the maximum score for each study was 24 [12].

Then, the studies were classified based on quantitative CHEERS scores in three categories of “high quality” for scores over 75%, “moderate quality” between 50 and 75% and “low quality” below 50%.

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Data synthesis

Data were synthesized qualitatively, with tabulation of the key characteristics and results of included studies. This systematic review has been conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13].

Results

Study Selection Process

The searches identified 1155 citations (Fig. 1). After the removal of duplicates and screening of title/abstract, 12 articles were eligible for full-text assessment. Four studies were excluded because the studies were published as abstracts (16-18) or had irrelevant outcomes [14]. Finally, 8 studies were included in the systematic review.

Overview of Included Studies

The key characteristics of all included studies are reported in Table 1. All studies were published between 2013 and 2019. Four studies were conducted in the USA (2023), three studies in the UK [14] and one study [15]. All studies were used a Markov modeling approach, except the studies [16] that used reimbursement models or were trial based. Two studies were applied societal perspectives [10], two used a payer perspective [17], one study both societal and health care sector and the remaining studies reported results from the perspective of the National Health Service (NHS). All studies used quality adjusted life-years (QALYs) as the effectiveness outcome. One study applied a 5 years' time horizon [18], three studies a 10 years' time horizon, two studies a 40 years' time horizon and two studies considered a lifetime horizon. Sensitivity analysis was conducted in the majority of included studies (N=7) although the type of approaches varied [19].

Quality of Reporting Assessment

The summary results of the quality of reporting assessment for each study are presented in Table 2. Figure 2 illustrates the proportion of studies reported 'in full', 'Partially', 'not reported' and 'Not Applicable'. Quality scores ranged from 7 to 23 out of a maximum value of 24 points, with an average score of 17 (Table 2). Five studies were classified in the category of "high quality" one into the "medium quality" category and two studies [20, 21] fell into the "low" reporting quality.

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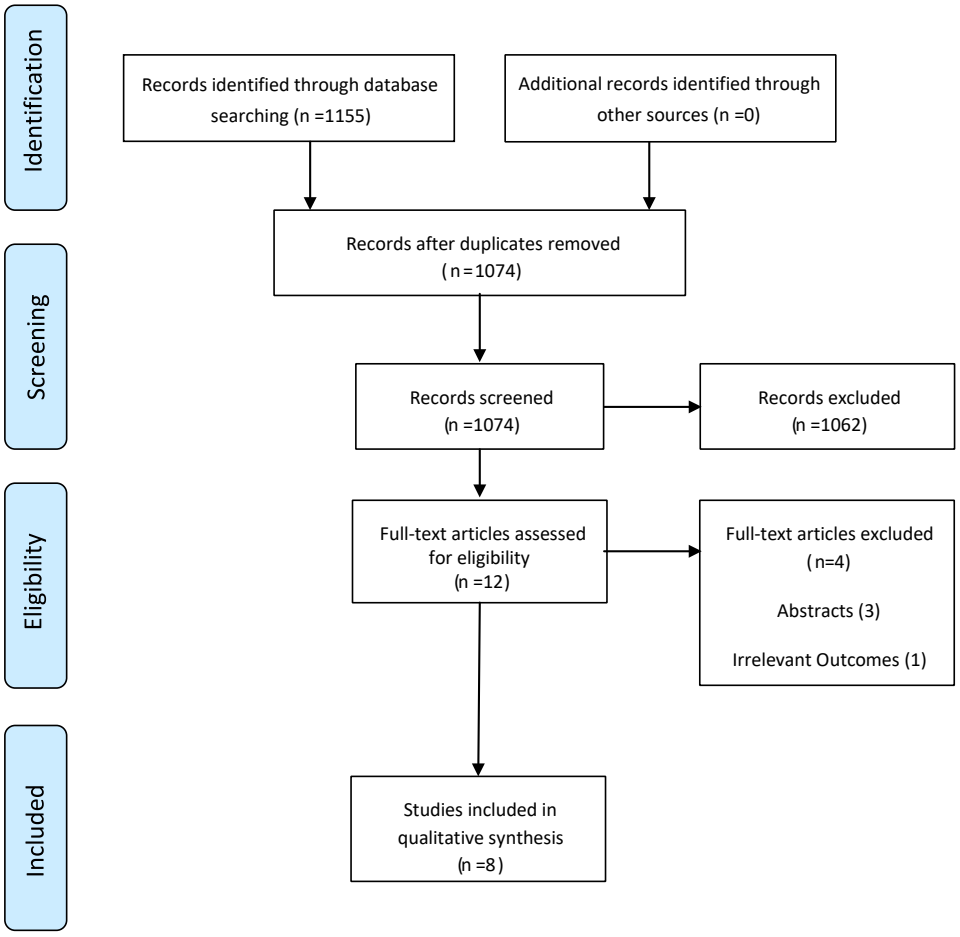

Figure 1.

PRISMA Flow diagram of literature review process

Table 1.

Key characteristics of included economic evaluations

Author, Year, Country	Type of economic evaluation	Time horizon	Type of effects	Discount rates (costs, effects)	Type of sensitivity analysis	Willing-To-Pay Threshold	Industry funding
Alvarado et al, 2013, USA (20)	CUA, Model based, Markov model	10 years	QALYs	3%, 3%	One-way, two-way, scenario analysis	US $75,000 per QALYs gained	NR
Deshmukh et al, 2017, USA (21)	CUA Model based, Markov model	lifetime	QALYs	3%, 3%	Deterministic (oneway and two-way)and probabilistic	US$50 000 and US$100 000 per QALYs gained	No
Kamenský et al, 2019, Czech (26)	CUA, Model based, Markov model	40 years	QALYs	3.5%, 3.5%	One way	1.213 million CZK	NR
Patel et al, 2017, USA (22)	CUA, Model based, Markov model	lifetime	QALYs,	3%, 3%	One-way	US $50,000 per QALYs gained	iCAD
Picot et al, 2015, UK (8)	CUA Model based, Markov model	40 years	QALYs	3.5%, 3.5%	One-way, scenario analysis and probabilistic	£20,000 and £30,000 per QALYs	No
Shah et al, 2014, USA (23)	CUA NR, analyses were based on reimbursement models	NR, assumed to be 10 years	QALYs	not reported	No	NR	NR
Vaidya et al, 2017, UK (24)	CUA, Model based, Markov model	10 years	QALYs	3.5%, 3.5%	One-way, probabilistic	0.00	Carl-Zeiss Meditec AG
Vaidya et al, 2016, UK (25)	CUA Trial based using patient-level data from the TARGIT-A trial	5 years	QALYs	3.5%, 3.5%	deterministic	£20,000–£30,000 per QALYs	Carl Zeiss

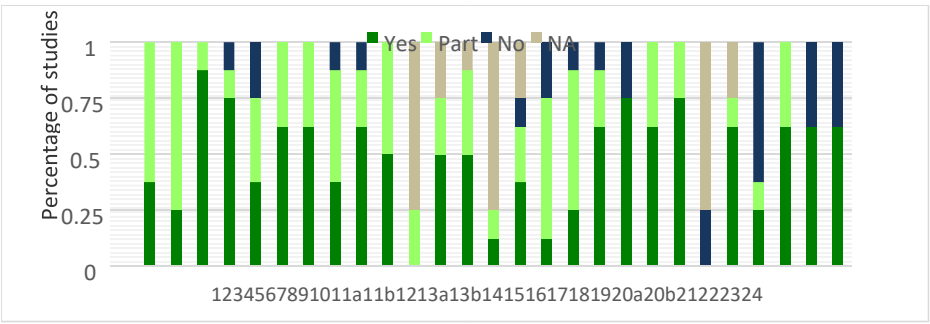

Figure 2.

Quality of reporting of included studies per items of the CHEERS checklist.

CHEERS Consolidated Health Economic Evaluation Reporting Standards, NA not applicable, No not reported, Part partially reported, Yes reported

Results of Cost-Effectiveness Analysis

The results of the eight full economic evaluation studies included in this systematic review are summarized in Table 3. In four studies, which took place in the United States and the United Kingdom, IORT was the dominant option.

In all four studies, this technology was associated with lower costs and higher effectiveness than conventional radiotherapy. These studies were conducted from different perspectives and time horizons. Other studies assessed the cost-utility of TARGIT-IORT during lumpectomy compared with EBRT (15 fractions) in the prepathology stratum of the TARGIT-A trial [22]. The analysis took the UK NHS and personal social services (PSS) perspective and a time horizon of 5 years. The study found that IORT was less costly than EBRT (mean incremental cost –£685) and resulted in slightly more QALYs than EBRT (mean QALYs gained 0.034).

The difference in costs between the two groups was statistically significant but the difference in QALYs was not. IORT had a positive incremental net monetary benefit that was borderline statistically significantly different from zero and had a probability of > 90% of being cost-effective. The study concluded that using IORT routinely instead of EBRT in eligible patients may be a potential budget saving to the NHS (around £8–9.1 million each year). Other performed a cost-utility analysis using decision-analytic modeling for the UK setting and National Health Service (NHS healthcare payer's perspective) for a time horizon of 10 years. They found that in the base case analysis, TARGIT-IORT was the dominant strategy over EBRT, yielding higher QALY gain at a lower cost than EBRT [23].

The results were robust to one-way and probabilistic sensitivity analyses. Moreover, based on probabilistic analysis, TARGIT-IORT had a 98% chance of being cost-effective at zero WTP. Other reported a full economic evaluation study based on the US health-care system by developing a Markov decision model to assess the cost-effectiveness of IORT(INTRABEAM) compared with WB-EBRT, based on the trial results of the TARGITA [24]. The analysis was performed over a 10-year time horizon and from a societal perspective.

The study concluded that single-dose IORT was the dominant, more cost-effective strategy that provides greater QALYs at a decreased cost compared with 6-week WB-EBRT. The model was most sensitive to health state utilities and local and distant recurrence rates. IORT was always preferred, and in most cases, the dominant strategy across all sensitivity analyses. In all of the probability and rate sensitivity analyses, the ICER for WB-EBRT was significantly greater than the society's willingness-to-pay of $75,000/QALY.

In addition, the scenario analysis showed that IORT was the dominant strategy compared with a 3-week accelerated WB-EBRT schedule of 16 fractions in terms of both QALYs and life expectancy. In this study, a probabilistic sensitivity analysis (PSA) was not conducted. Other

used a Markov model to assess the cost-effectiveness of IORT versus a 6-week WB-EBRT in treating early-stage (stage I–IIA/IIB) breast cancer over the life of the patients for the USA setting from the healthcare payer and found that IORT was the dominant (less costly with greater QALYs) versus EBRT and at a willingness to pay of $50,000 for each additional QALY [25], the net monetary benefit demonstrated that IORT was the most cost-effective option. The model used in their study was sensitive to the probabilities of recurrent cancer and death for both IORT and EBRT. The study concluded that IORT was the more cost-effective option (lower cost with improved QALYs) for use in patients with early-stage ER+ breast cancer [26].

In three studies the dominant option was conventional radiotherapy [27, 3, 28]. In these studies, IORT also was associated with fewer costs, but its effectiveness was lower than that of conventional radiotherapy. Other carried out an economic evaluation based on TARGIT-A and the Electron Intraoperative Radiotherapy (ELIOT) trial and a societal perspective, including both direct and indirect costs, for a time horizon of 10 years in the USA [27]. They found that EBRT was a more cost-effective treatment compared to IORT.

In the study, the costs per QALY for WB-EBRT compared with INTRABEAM IORT ranged from $89,234 to $108,735 depending on the difference in whole-breast irradiation rates. The study concluded that IORT is a potential cost-saving in the management of early-stage breast cancer But, WBI represents a cost-effective option and remains the standard of care [28]. The results of the sensitivity analysis were consistent with the results of the baseline scenario. Then, in the basic scenario, IORT was less expensive but less effective than EBRT. The ICER of the IORT versus EBRT was below the threshold of 1.213 million CZK and therefore, in this study IORT was found not to be cost-effective for patients with early breast cancer. Picot et al. in their study [29] assessed the cost-effectiveness of IORT compared with WB-EBRT for early breast cancer from the NHS perspective and a lifetime (40-year) horizon in the UK.

The study found IORT to be less costly but also less effective than WB-EBRT. The base-case ICER to replace WB-EBRT with intraoperative radiation therapy was £1596 saved per QALY lost. Therefore, IORT was not costeffective at a willingness-to-pay (WTP) threshold of £20,000 per QALY. The PSA indicated that WB-EBRT at the £20,000 and £30,000 WTP thresholds and IORT at thresholds of around £5000 per QALY or less has a greater probability than each other of being cost-effective [30].

In the study of Deshmukh et al. (21), which was conducted with two social and health care perspectives, 3-week radiotherapy was the dominant option as compared to 6week radiotherapy IORT. In this study, 6-week radiotherapy was a dominated option and IORT was less costly and less effective than 3-week radiotherapy. In the last four studies, IORT was not cost-effective on the basis of the willingness to pay thresholds, but these studies pointed to the potential for the cost-effectiveness of IORT (8, 21, 23, 26). In these studies, the money saved per QALY lost due to the replacement of IORT with conventional radiotherapy was used. Similar results were obtained in the study of Kamensky et al. and Picot et al., which used the same Markov models (8, 26). Finally, there was also heterogeneity in terms of the thresholds of

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willingness to pay, the structure of models and their assumptions among the included studies, even in studies conducted in the United States or the United Kingdom [31].

Drivers of Cost-Effectiveness

One-way sensitivity analyses were reported in 7 out of 8 included studies. Yet, numerous studies did not perform one-way sensitivity analyses on all model parameters or only conducted one-way sensitivity or scenario analyses on a few input parameters. Among the eight included studies, the model was most sensitive to probabilities of recurrent cancer and death for both IORT and EBRT [32], health state utilities and local and distant recurrence rates [33], the probability of metastasis after treatment, and treatment cost of HF-WBI and IORT, and the probability of any other recurrence assumed for WB-EBRT and INTRABEAM, the beta coefficient for the time to local recurrence (INTRABEAM) and the probability of death from breast cancer (INTRABEAM) [34]. In the remaining studies, model outputs were robust to one-way and probabilistic sensitivity analyses.

Discussion

In this study, we reviewed eight full economic evaluation IORT in comparison with conventional radiotherapy in adjunct management of early breast cancer. The quality of the studies based on the average reporting quality score of the 8 articles reviewed by the Cheers checklist was moderate (17/24). The cost-effectiveness results of the IORT showed that this technology is located in two areas in the cost-effectiveness plane (more effective, less costly, and less effective and less costly).

However, in all studies, IORT reduced costs in comparison with conventional and even hypofractionation WB-EBRT, but this reduction was trivial in the Picot study. On the other hand, in three studies, QALYs were improved with IORT compared to the WBI. In other studies, QALYs were reduced for IORT compared to the WBI. In terms of cost-effectiveness results, we can say that the current evidence is scattered, and the number of studies conducted is low.

In general, by reviewing eight economic assessments, there can be no definitive answer to the cost-effectiveness of IORT, but this evidence suggests that IORT can be a cost-effective alternative to early breast cancer treatment by reducing therapeutic costs.

So that the cost of IORT in all studies was lower than the cost of EBRT, and this technology provided some cost savings compared to that. Similar findings are also reported in other studies [35]. Including other social costs and travel costs will further add to the cost-effectiveness of the IORT (11). Also, the results of these studies showed that the QALYs differences between IORT and EBRT are low.

In the review study, the results should be interpreted with caution for several reasons. There is heterogeneity in terms of perspectives, time horizons, model assumptions, and the settings of studies. Most studies were conducted in the United States and Canada. Various cost-

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effectiveness thresholds have been used in different studies. Sources of financing for most studies (5.7 study) were the industry or not mentioned. cost-effectiveness analysis [3].

Sources of effectiveness data for economic models for the majority of included studies are based on efficacy data from TARGIT or Elliot trials that may cause a risk of bias. It seems that, as mentioned in the findings, the effectiveness outcomes in the included studies are influenced by these parameters and can affect the results of the studies [36].

This study has several strengths. First, the present study is one of the first systematic reviews of cost-effectiveness evidence of IORT compared with conventional radiotherapy in early breast cancer. Second, in this study, the quality of the reporting of the studied studies was evaluated, and the strengths and weaknesses of these studies were shown. Identifying the weaknesses of present literature can help to improve future cost-effectiveness analysis studies of these technologies. Third, the present study used the principles of the PRISMA statement for conducting research and reporting.

This study has some limitations. Posters or reports that only had only abstracts and without full text were removed because there was not enough information available to assess reporting quality. Also, studies with non-English full text were not included in the review. Another limitation was that given the fact that these studies were conducted in different countries, it was difficult to compare their ICER results because the thresholds for their willingness to pay were different. Finally, it's worth noting that poor reporting does not necessarily mean poor quality of a study. In our review, we did not assess the methodological quality of studies. In this context, the use of assessment tools such as the Philips checklist [37] can be useful. Finally, we identified cost-effectiveness drivers based on reported findings of sensitivity analysis in the included studies, and we did not conduct additional analysis for the determination of the mentioned drivers.

There is a need for future economic evaluation studies in the field. In future studies, the best practice guidelines for conducting and reporting economic evaluations should be used to ensure that all elements and assumptions in these studies are adequately and transparently reported.

Future economic modeling studies should also take into account all the costs and outcomes associated with technology, and from the societal perspective and the right time horizons. In addition, In order to address the uncertainty surrounding the model assumptions, there should be used comprehensive, relevant types of sensitivity analyses to address all principal types of uncertainty including methodological, structural, parameter, and patient population-related uncertainty [38]. parameter uncertainty by using diverse kinds of sensitivity analyses. The results of this study show that IORT can be a potential cost-saving strategy to the health systems for the adjuvant treatment of early breast cancer if the technology is carried out routinely in eligible patients. However, these results should be interpreted with caution because of the heterogeneity of studies and possible publication bias.

Conclusion

We identified eight cost-effectiveness analyses of IORT versus EBRT for early breast cancer published to March 2019. This review shows the need for better reporting and more attention to the model assumptions and structural uncertainty, as well as the more commonly recognized

Conflict of Interests

The authors declare that they have no competing interests.

Ethics Statement

Non

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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