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Systematic Review

Efficacy of Sorafenib in the Management of Non-Small Cell Lung Cancer: A Systematic Review

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Abstract

Introduction

The current standard treatment approach for non-small cell lung cancer (NSCLC) is surgery. Recently, targeted therapy has emerged as a promising new treatment option. In this systematic review, the efficacy of sorafenib, when given alone or combined with erlotinib, in managing NSCLC is reviewed.

Methods

To identify English language studies published up to March 8th, 2024, the Google Scholar, CINAHL, PubMed/MEDLINE, Cochrane Library, Web of Science, and EMBASE databases were screened, and the data were assessed.

Results

The systematic search revealed 208 papers; however, only 10 were eligible to be included. The sample size was 1080 patients, of which 848 were in the sorafenib group, and 232 were in the sorafenib with erlotinib combination group. In the sorafenib group, the partial response was 2.4%, stable disease was reported in 25%, and 56 cases (6.6%) had progressive disease. In the combination group, partial response, stable disease, and progressive disease were 16.8%, 48.3%, and 19.8%, respectively. In the combination group, the median overall survival was 231 days, and the progression-free survival (PFS) was 141 days. However, in the sorafenib group, the median overall survival was 180 days, and the PFS was 82 days. Fatigue was the most common adverse event, reported in 325 (30.1%) patients. Among them, 235 cases (27.7%) were in the sorafenib group, and 90 cases (38.8%) were in the combination group.

Conclusion

Combination therapy may result in better overall survival and PFS than sorafenib alone, with slightly similar adverse events.

1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide. In the United States alone, approximately 230,000 people are annually diagnosed with lung cancer, and 135,000 people annually die as a result of it [1]. The mortality rate due to this form of cancer alone is greater than that of prostate, breast, brain, and colorectal cancer altogether [2]. Small-cell lung cancer (SCLC) represents 15% of all lung cancer cases, while non-small cell lung cancer (NSCLC) constitutes 85%, delineating the two subtypes of the disease [3]. The latter is also the most commonly studied cancer, with the greatest number of publications in 2022 [4]. According to the World Health Organization (WHO), the three main common types of NSCLC are adenocarcinoma, making up 40% of the total lung cancers; squamous cell carcinoma (25-30%) and large cell carcinoma (5-10%) [5]. Before planning management, it is essential to determine the appropriate tumor, lymph node, and metastasis (TNM) staging of the cancer, as the type of treatment usually depends on the stage and extent of metastasis [6-8]. Patients with NSCLC stage I, II, and IIIA can undergo surgery, provided that the tumor is resectable [9]. Apart from surgery, other therapies used to treat NSCLC include radiotherapy, chemotherapy, immunotherapy, and targeted molecular therapy. Targeted therapy is a relatively new treatment approach where researchers continue to unveil new information regarding novel biological targets [6]. This study is a systematic review of clinical trials investigating the efficacy of sorafenib alone or in combination with erlotinib in treating NSCLC.

2. Methods

2.1. Study design

This study was a systematic review of the clinical trials on treating NSCLC with either sorafenib alone or combined with erlotinib. The study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

2.2. Data sources and search strategy

Google Scholar, PubMed/MEDLINE, and EMBASE were searched. The (lung OR pulmonary OR bronchi OR bronchus OR chest OR pleural OR alveolus OR alveoli) AND (sorafenib OR Nexavar) keywords were used in the search.

2.3. Eligibility criteria

The study's eligibility criteria included randomized clinical trials investigating the efficacy of either sorafenib alone or sorafenib combined with erlotinib in treating NSCLC. To protect the study's validity and avoid bias, any studies published in predatory journals were excluded [10].

2.4. Study selection process

Two researchers screened the studies' titles and abstracts to identify papers based on inclusion and exclusion criteria. When the two initial researchers disagreed; a third researcher was invited to resolve the conflict.

2.5. Data item

The collected data included the first author's name, year of publication, median age of patients, gender, smoking status, type of therapy, adverse events, type of NSCLC, number of previous therapies, and the different aspects of outcome.

2.6 Data analysis and synthesis

The extracted data were collected on a Microsoft Excel (2019) workbook sheet. They were then used in a qualitative (descriptive) analysis using the Statistical Package for Social Sciences (SPSS) 26.0 software. The data were presented as frequencies, percentages, medians, and ranges.

3. Results

3.1. Data analysis and synthesis

The systematic search revealed a total of 208 papers. Four non-English and 28 abstract papers were removed before further screening. This left 176 papers with titles and abstracts screened, resulting in 145 papers being excluded due to irrelevancy. Out of the 31 papers that remained, 21 were excluded due to incompatibility with inclusion criteria, leaving a total of 10 eligible papers [11-20] (Figure 1).

3.2. Characteristics of the included studies

All studies included in the study were randomized clinical trials. Nine of them were phase II clinical trials, and one was a phase III trial. The raw data and characteristics of each study are summarized in Tables 1 and 2.

3.3. Participants

A total of 1080 patients were included in this study. Patients were divided into the sorafenib group (848 patients) and the combination group of sorafenib and erlotinib (232 patients). The median age of patients in the sorafenib and combination groups was 62 and 62.5 years, respectively.

3.4. Main findings

The male gender accounted for 568 (52.6%) patients, slightly outnumbering the female gender, which represented 511 (47.3%) patients. Smoking status was positive in 417 (38.6%) patients, negative in 222 (20.6%), and not mentioned in 441 (40.8%) patients. The most common ECOG status was a score of one (58.9%), followed by a score of zero (31.9%), a score of 2 (7%), and a score of 3 (1.2%). The ECOG status was not mentioned in 11 (1%) patients. Overall, 446 (41.3%) patients had received two prior treatment therapies, 306 (28.3%) received more than two prior treatments, 213 (19.7%) received one prior therapy, and 39 (16.8%) received none. Thirty-one (2.9%) patients did not have their prior therapy mentioned. In the sorafenib group, the partial response was 2.4%, stable disease was reported in 25%, and 56 cases (6.6%) had progressive disease. In the combination group, partial response,

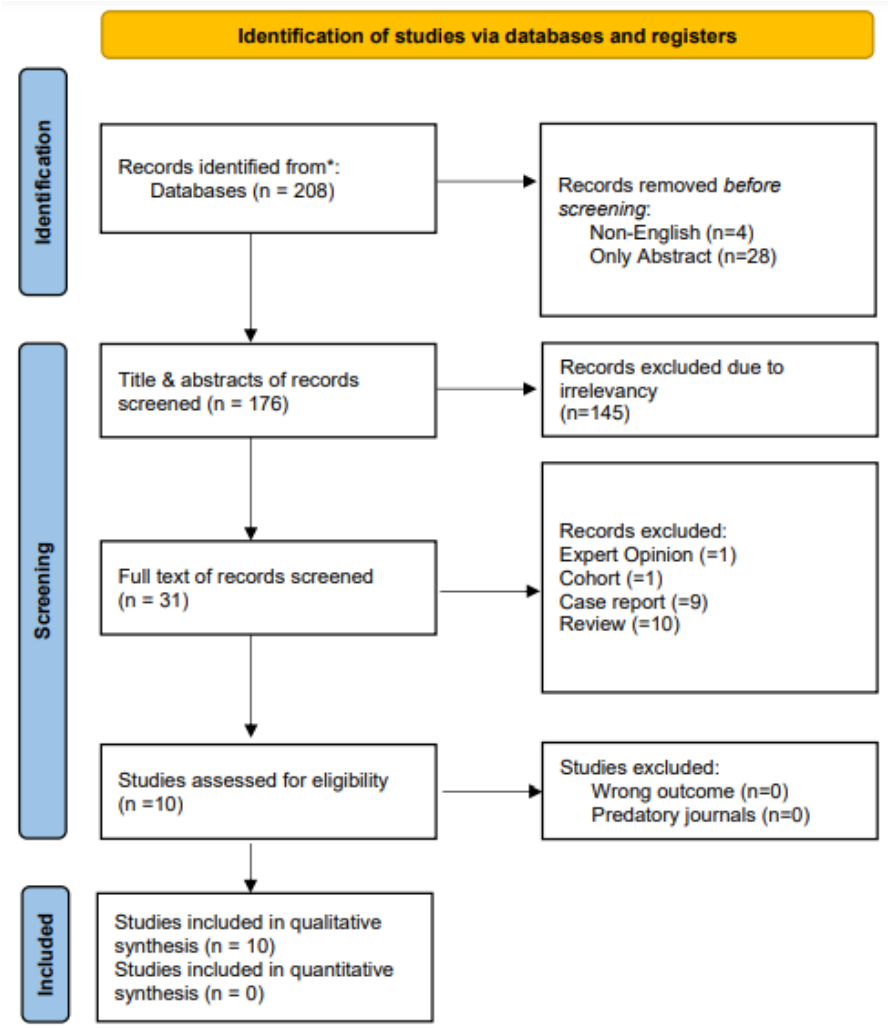

Figure 1. Study selection PRISMA flow chart.

stable disease, and progressive disease were 16.8%, 48.3%, and 19.8%, respectively (Table 3). Fatigue was the most common adverse event for the total sample size, reported in 325 (30.1%) patients. Among them, 235 cases (27.7%) were in the sorafenib group, and 90 cases (38.8%) were in the combination group. Other common adverse events included a skin rash in 26.8% of patients in the sorafenib group and 34.1% of patients in the combination group, as well as diarrhea in 26.2% of the sorafenib group and 31.5% of the combination group. Hematological and gastrointestinal adverse events were more common in the combination group, with rates of 63.8% and 89.2%, respectively, compared to 2.6% and 76.8% in the sorafenib group. In contrast, dermatological and various other adverse events were more common in the sorafenib group, with rates of 41.6% and 94.9%, respectively, compared to 36.2% and 75.9% in the combination group (Table 4). Adenocarcinoma was observed in 361 (33.4%) patients, while squamous cell carcinoma was seen in 132 (12.2%) patients, making them the most common histological subtypes of NSCLC. In the combination group, the median overall survival was 231 days and the progression-free survival (PFS) was 141 days. However, in the sorafenib group, the median overall survival was 180 days, and the PFS was 82 days (Table 3).

4. Discussion

Lung cancer is the most common type of cancer in terms of both incidence and mortality, with approximately two million diagnoses and 1.8 million deaths annually [21]. Exposure to radiation, cigarette smoke, asbestos, and metals such as chromium, nickel, and arsenic have all been associated with increasing the risk of lung cancer [22]. Smoking is considered the most significant risk factor, with studies estimating that 90% of lung cancers are attributed to it [23]. In this study, 417 (38.6%) out of the 1080 patients had a positive smoking history. As mentioned earlier, lung cancer is broadly categorized into SCLC and NSCLC, with the latter representing the majority of cases [3]. NSCLC is further subdivided into adenocarcinoma (40%), squamous cell carcinoma (25-30%), and large cell carcinoma (5-10%) [5]. The finding of this study followed a slightly similar pattern since adenocarcinoma was the most common (33.4%), followed by squamous cell carcinoma

Table 1: The raw data of each included study

Autor	Year of Publication	Type of therapy	Phase of clinical trial	No. of patients	Gender			Median Age	Smoking status			ECOG Status					Histology of lung cancer				
					M	F	N/A		Yes	No	N/A	0	1	2	3	N/A	SCC	Adeno-carcinoma	Bronchoalveolar Carcinoma	Large cell Carcinoma	N/A
Paz-Ares et al [11]	2015	Sorafenib alone	3	350	186	164	0	59	181	161	8	110	233	0	0	7	0	0	0	0	350
Blumenschein et al [12]	2009	Sorafenib alone	2	52	34	18	0	N/A	0	0	52	5	44	3	0	0	16	28	4	0	4
Dingemans et al [13]	2013	Sorafenib alone	2	57	16	41	0	58.5	0	0	57	24	30	3	0	0	1	46	4	6	0
Kelly et al [14]	2011	Sorafenib alone	2	37	18	19	0	61	26	11	0	32	5	0	0	0	3	31	0	1	2
Wakelee et al [15]	2012	Sorafenib alone	2	299	168	130	1	64	0	0	299	102	197	0	0	0	46	138	10	13	92
Spigel et al [16]	2017	Sorafenib alone	2	28	10	18	0	63	28	0	0	11	16	1	0	0	9	18	0	0	1
	2017	Sorafenib + Erlotinib	2	24	8	16	0	67	24	0	0	9	14	1	0	0	5	16	0	2	1
Dy et al [17]	2010	Sorafenib alone	2	25	10	15	0	67	0	0	25	12	10	3	0	0	5	13	1	0	6
Spigel et al [18]	2011	Sorafenib + Erlotinib	2	111	62	49	0	65	92	19	0	0	32	62	13	4	33	0	0	78	0
Lind et al [19]	2010	Sorafenib + Erlotinib	2	50	28	22	0	60	39	11	0	30	20	0	0	0	5	36	0	3	6
Lim et al [20]	2016	Sorafenib + Erlotinib	2	47	28	19	0	56	27	20	0	9	35	3	0	0	9	35	0	0	3

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Table 2: The treatment and outcome of each included study

Author	No of patients	No. of previous treatment					Type of therapy	Outcome				Median Survival in days	
		0	1	2	>2	N/A		Partial Response	Stable Disease	Progressive Disease	Not mentioned	Overall survival	Progression-free survival
Paz-Arez et al [11]	350	0	0	188	158	4	Sorafenib alone	N/A	N/A	N/A	N/A	296	82
Blumenschein et al [12]	52	0	35	15	0	2	Sorafenib alone	0	30	18	4	201	81
Dingemans et al [13]	57	34	14	3	6	0	Sorafenib alone	5	25	27	0	159	69
Kelly et al [14]	37	0	17	4	16	0	Sorafenib alone	2	20	N/A	15	N/A	100
Wakelee et al [15]	299	0	0	173	126	0	Sorafenib alone	9	117	0	173	69	219
Spigel et al [16]	28	0	28	0	0	0	Sorafenib alone	1	14	11	2	357	57
	24	0	24	0	0	0	Sorafenib + Erlotinib	2	10	9	3	93	267
Dy et al [17]	25	0	0	0	0	25	Sorafenib alone	3	6	0	16	84	264
Spigel et al [18]	111	0	73	38	0	0	Sorafenib + Erlotinib	9	51	29	22	135	101
Lind et al [19]	50	50	0	0	0	0	Sorafenib + Erlotinib	14	23	8	5	327	N/A
Lim et al [20]	47	0	22	25	0	0	Sorafenib + Erlotinib	14	28	0	5	348	141

(12.2%), and large cell carcinoma (9.5%). In a study conducted by Ruano-Ravina et al., 25.6% of the 13,950 participants were female. The study also found that, on average, women were younger, while male patients reported higher rates of smoking [24]. In contrast to the previous study, the current study showed no gender predominance, with 52.6% of patients being male and 47.3% being female.

By the time NSCLC is diagnosed, the disease has usually reached an advanced state. According to a study conducted by Xing et al., the most common initial symptom of NSCLC was a chronic cough, which was present in 65% of the patients. Other symptoms included hemoptysis (33%), chest pain (17.9%), dyspnea (17%), and lymphadenopathy (9.8%), occurring less frequently [25]. Seghal et al. conducted a study on patients with advanced stages of NSCLC receiving pembrolizumab. They found that patients with an ECOG score of 2 or higher not only had significantly decreased disease control rates but also experienced shortened median overall survival and median progression-free survival (PFS). These results emphasize the significance of the initial ECOG status on the efficacy of treatments [26,27]. In this study, the most common ECOG status was a score of one (58.9%), followed by a score of zero (31.9%).

A management plan can be designed based on the state and staging of the cancer. Immunotherapy, chemotherapy, radiotherapy, molecular targeting therapy, and surgery can all be considered according to the specificity of the case. Curative surgical excision is generally reserved for patients with lower TNM staging, such as stage I and II. However, the patient's general health needs to be stable enough to withstand the stress of surgery [9]. Although it initially dominated the clinical treatments for lung cancer, the usage of chemotherapy has gradually decreased over the years. Targeted molecular therapies have surpassed chemotherapy in treating NSCLC since the identification of implicated genes [28]. Radiotherapy, on the other hand, is indicated in different stages of NSCLC for local control of the disease. The efficacy of radiotherapy is determined in cases of unresectable tumors, especially stage III tumors, which represent about 30% of NSCLC cases [29]. Targeted therapy is a recent and crucial approach for managing NSCLC. This approach is based on the understanding that multiple oncogenic mutations must occur for lung cancers to develop. With the identification of these genes, novel targeted therapies can be developed to address them directly [28]. Using diagnostic assays, the specific molecular mutation that has led to the development of the tumor can be identified and hence, targeted [30]. Apart from treating NSCLC, targeted therapies have also demonstrated positive outcomes in addressing other types of cancer. Pembrolizumab and durvalumab have shown effectiveness in treating mesothelioma [31,32]. Gefitinib, erlotinib, dacomitinib, and osimertinib are other targeted therapies used in NSCLC that are approved by the United States Food and Drug Administration (FDA). These drugs have been found to significantly prolong the median overall survival and PFS of patients. Gefitinib prolonged PFS by up to 10.8 months, erlotinib by almost 14 months, and dacomitinib by up to 14.7 months [28]. Another agent extensively researched in clinical

Table 3: The baseline characteristics of the study

Variables	Frequency/ Percentage
Number of patients	
Total patients	1080 (100%)
Sorafenib	848 (78.5%)
Sorafenib + Erlotinib	232 (21.5%)
Median age (years)	
Sorafenib Group	62
Sorafenib + Erlotinib	62.5
Sex	
Male	568 (52.6%)
Female	511 (47.3%)
Not mentioned	1 (0.1%)
Phase of clinical trial	
Phase II	9 (90%)
Phase III	1 (10%)
ECOG Status	
Score 0	344 (31.9%)
Score 1	636 (58.9%)
Score 2	76 (7%)
Score 3	13 (1.2%)
Not mentioned	11 (1%)
Smoking Status	
Smoker	417 (38.6%)
Non-Smoker	222 (20.6%)
Not mentioned	441 (40.8%)
Histology of non-small cell lung cancer	
Squamous cell carcinoma	132 (12.2%)
Adenocarcinoma	361 (33.4%)
Bronchoalveolar	19 (1.8%)
Large cell Carcinoma	103 (9.5%)
Not mentioned	465 (43.1%)
Number of previous treatments	
No previous treatment	84 (7.8%)
1 previous treatment	213 (19.7%)
2 previous treatments	446 (41.3%)
More than 2 previous treatments	306 (28.3%)
Not mentioned	31 (2.9%)
Response in sorafenib group	
Partial Response	20 (2.4%)
Stable Disease	212 (25%)
Progressive Disease	56 (6.6%)
Not Mentioned	560 (66%)
Response in combination group	
Partial Response	39 (16.8%)
Stable Disease	112 (48.3%)
Progressive Disease	46 (19.8%)
Not Mentioned	35 (15%)
Median survival in sorafenib group	
Overall Survival	180 Days
Progression Free Survival	82 Days
Median survival in combination group	
Overall Survival	231 Days
Progression Free Survival	141 Days

Table 4: The difference in adverse events between the different therapy groups.

Adverse events	Each per total sample size	Each per sorafenib (848)	Each per sorafenib + erlotinib (232)
Hematological			
Anemia	98 (9.0%)	8 (0.9%)	90 (38.8%)
Leukocytopenia	22 (2.0%)	4 (0.5%)	18 (7.7%)
Neutropenia	14 (1.3%)	5 (0.6%)	9 (3.9%)
Thrombocytopenia	36 (3.3%)	5 (0.6%)	31 (13.4%)
Gastrointestinal			
Nausea	152 (14.1%)	128 (15.1%)	24 (10.3%)
Vomiting	76 (7.0%)	64 (7.5%)	12 (5.2%)
Diarrhea	295 (27.3%)	222 (26.2%)	73 (31.5%)
Constipation	66 (6.1%)	58 (6.8%)	8 (3.4%)
Anorexia	270 (25.0%)	180 (21.2%)	90 (38.8%)
Dermatological			
Skin Rash	306 (28.3%)	227 (26.8%)	79 (34.1%)
Dry Skin	35 (3.2%)	35 (4.1%)	0 (0.0%)
Alopecia	96 (8.9%)	91 (10.7%)	5 (2.1%)
Others			
Fever/Chills	52 (4.8%)	45 (5.3%)	7 (3.0%)
Fatigue	325 (30.1%)	235 (27.7%)	90 (38.8%)
Hypertension	140 (12.9%)	117 (13.8%)	23 (10.0%)
Cough	97 (9.0%)	84 (10.0%)	13 (5.6%)
Dyspnea	127 (11.8%)	112 (13.2%)	15 (6.5%)
Headache	55 (5.1%)	44 (5.2%)	11 (4.7%)
Pain	166 (15.4%)	149 (17.6%)	17 (7.3%)
Weight Loss	18 (1.6%)	18 (2.1%)	0 (0%)

trials for advanced stages of NSCLC is sorafenib [33]. Sorafenib functions as a multi-targeted receptor tyrosine kinase inhibitor. The drug primarily exerts anti-angiogenic effects on the tumor by inhibiting vascular endothelial growth factors II and III, as well as platelet-derived growth factors [33]. Dy et al. conducted a phase II clinical trial on stage IIIB-IV NSCLC patients to evaluate the effectiveness of sorafenib as a first-line therapy. The study found that 12% of the patients had a partial response to the treatment, while 24% experienced stable disease and the median PFS was 2.8 months [17]. In the sorafenib group of the current study, 20 (2.4%) of the patients showed a partial response, 212 (25%) had stable disease, and 56 (6.6%) had progressive disease. Additionally, the PFS was 82 days, while the median overall survival was 180 days. It is worth pointing out that sorafenib is not always given as a first-line treatment. In this study, only 84 (7.8%) patients received sorafenib as a first-line therapy. Out of the remaining patients, 446 (41.3%) patients had a history of two prior treatment therapies, 213 (19.7%) had a history of one prior therapy, and 306 (28.3%) patients had a history of more than two previous treatments. Sorafenib has also been evaluated with other therapies such as chemotherapeutic agents and other targeted therapies. Spigel et al. found that in patients with wild-type EGFR mutations, combining sorafenib with erlotinib resulted in a better response compared to using erlotinib with a placebo. The PFS and overall survival were 3.88 months and 8 months, respectively, for the sorafenib/erlotinib group, while in the erlotinib/placebo group, the median PFS and overall survival were 1.77 months and 4.5 months, respectively [16]. The median overall survival for the sorafenib/erlotinib group in the current study was 231 days, and PFS was 141 days. Additionally, among patients in this group, 39 (16.8%) had a partial response, 112 (48.3%) had stable disease, and 46 (19.8%) had progressive disease.

Even though it may show clinical benefits, the adverse events and toxicities due to sorafenib cannot be overlooked. Both the vascular endothelial growth factor receptors and Ras that are

targeted by sorafenib are very essential for the homeostasis of many organs; therefore, sorafenib, although clinically beneficial, yields non-negligible toxicities [34,35]. Common adverse events include rashes, fatigue, dyspnea, and gastrointestinal symptoms such as diarrhea, anorexia, and nausea [34]. In this study, 306 patients (28.3%) experienced a rash following therapy. The incidence of skin rash was higher in the combination group, with 34.1% of patients affected, compared to 26.8% in the sorafenib group. Additionally, diarrhea (27.3%) and anorexia (25%) were the most common gastrointestinal symptoms. In the sorafenib group, 26.2% of patients reported diarrhea, and 21.2% reported anorexia, while in the combination group, these numbers were 31.5% and 38.8% respectively. Fatigue was the most frequently reported adverse event, with 30.1% of patients experiencing it. In the sorafenib group, 27.7% reported fatigue, while in the combination group, 38.8% reported fatigue. The study findings may be limited due to the lack of categorization of results based on the number of therapies received, ECOG score, and tumor stage, as well as unequal sample sizes between the two groups and missing data. These factors could significantly impact the outcomes of this study.

5. Conclusion

Combination therapy may result in greater overall survival and PFS with slightly similar adverse events when compared to sorafenib alone in patients with NSCLC. Proving these findings through meta-analysis studies is deemed necessary.

Declarations

Conflicts of interest: The author(s) have no conflicts of interest to disclose.

Ethical approval: Not applicable, as systematic reviews do not require ethical approval.

Patient consent (participation and publication)**:** Not applicable.

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Use of AI: AI was not used in the drafting of the manuscript, the production of graphical elements, or the collection and analysis of data.

Data availability statement: Note applicable.

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