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Systematic Review

Immunochemotherapy in Advanced or Metastatic Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis of Prospective Randomized Trials

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Abstract

Background: To evaluate the efficacy of immunochemotherapy in advanced triple-negative breast cancer (aTNBC) or metastatic triple-negative breast cancer (mTNBC) by assessing overall survival (OS) and progression-free survival (PFS). **Methods**: Randomized controlled trials (RCTs) of immunochemotherapy in aTNBC or mTNBC were identified through a systematic literature search from different databases. The primary endpoint included OS and PFS. Grade 3/4 adverse events were included in the toxicity analysis, with 95% confidence intervals (CIs) retrieved into the meta-analysis for hazard ratios (HRs). **Results**: A total of 7 publications with 3287 patients with aTNBC or mTNBC were enrolled. In the programmed death ligand 1 (PD-L1)-positive aTNBC or mTNBC population, immunochemotherapy was associated with significantly improved PFS than chemotherapy alone ([hazard ratio] HR = 0.84; 95% CI: 0.78–0.91; $p < 0.0001$). In the intention-to-treat population, immunotherapy effectively prolonged PFS in aTNBC or mTNBC patients (HR = 0.91; 95% CI = 0.88–0.94; $p < 0.00001$), and OS benefits were limited to combined positive score (CPS) $\geq$10/20 subgroups. Although immunochemotherapy was found to have some efficacy on PD-L1-positive patients, the improvement in OS was not statistically significant in either population (HR = 0.93; 95% CI = 0.82–1.05; $p = 0.24$; HR = 0.96; 95% CI = 0.92–1.01; $p = 0.09$). Regarding adverse events, immunochemotherapy was not associated with a significantly different risk compared to placebo or chemotherapy alone (HR = 0.91; 95% CI = 0.43–1.92; $p = 0.73$). **Conclusions**: PD-L1 inhibitors prolong PFS in PD-L1-positive patients, with a greater effect observed in those with higher CPS. **Registration**: The study has been registered on https://www.crd.york.ac.uk/prospero/ (registration number: CRD420251067972; registration link: https://www.crd.york.ac.uk/PROSPERO/view/CRD420251067972).

Keywords: immunochemotherapy; programmed death ligand 1; survival; triple-negative breast cancer

1. Introduction

As of 2020, breast cancer was the most frequently diagnosed cancer worldwide, representing 30% of all cancers in women [1]. Since 2014, the incidence rate has been rising at an average annual rate of 0.5% [2]. Triple-negative breast cancer (TNBC) is defined by the lack of expression of human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), and estrogen receptor (ER), accounting for approximately 24% of all breast cancer cases. Compared to other breast cancer subtypes, TNBC is more common in younger women and is usually accompanied by a breast cancer (*BRCA*) gene mutation. It is characterized by poor differentiation, high invasiveness, early recurrence, and greater susceptibility to recurrence and metastasis [3]. The five-year survival rate is approximately 85% when diagnosed at an early stage, but drops to 12.2% if detected at an advanced stage [4]. TNBC is unresponsive to endocrine or molecular targeted therapies due to a particular molecular profile [5]. Traditional endocrine therapies (e.g., tamoxifen or aromatase inhibitors) target the ER/PR signaling pathways, whereas HER2-targeted drugs (e.g., trastuzumab) are ineffective in treating TNBC [6,7]. Most currently available targeted therapies for breast cancer focus on HER2 or hormone receptor pathways, but TNBC does not benefit from these treatments [8,9]. Chemotherapy is frequently used in clinical settings to extend patient survival, with combined treatment outperforming single-agent chemotherapy [10]. However, combination chemotherapy is associated with increased toxicity, highlighting the need for novel therapeutic options for TNBC.

Currently, immunotherapy mainly focuses on immune checkpoint inhibitors (ICIs), such as programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors. PD-1 is an immunosuppressive receptor that, when targeting its ligand PD-L1, leads to immunization against cancers [11]. Immunotherapeutic agents have been demonstrated to modulate this apoptotic process, especially when combined with chemotherapy, in patients with PD-L1 expression [12]. The effect of durvalumab on advanced breast cancer is still under investigation. However, the

US Food and Drug Administration (FDA) approved atezolizumab and pembrolizumab for PD-L1-positive, locally metastatic TNBC (mTNBC) in 2019 and 2020, respectively [13,14]. For patients with mTNBC, immunotherapy holds significant therapeutic value by prolonging survival. PD-1 inhibitors are currently recognized to have a therapeutic impact on the survival of TNBC patients. As such, we conducted a meta-analysis of immunotherapy combined with chemotherapy, comparing therapeutic effects based on overall survival (OS) and progression-free survival (PFS) in intention-to-treat (ITT) and PD-L1-positive populations, selected from randomized controlled trials (RCTs).

2. Materials and Methods

This study was previously registered with PROSPERO (CRD420251067972) and followed PRISMA guidelines [15].

2.1 Literature Review and Study Identification

The PubMed, Embase, Medline, and Cochrane Library databases were searched for relevant studies published between 1 January 2010, and 1 July 2023. In PubMed, the following search strategy was employed: ("triple-negative breast cancer" [MeSH Term]) AND ("immunotherapy" OR "PD-1 inhibitor" OR "PD-L1 inhibitor" OR "anti-PD-1" OR "anti-PDL-1" OR "atezolizumab" OR "durvalumab" OR "pembrolizumab" OR "immune checkpoint inhibitor"). In Embase, the term(s): "PD-1 inhibitor" OR "PD-L1 inhibitor" OR "anti-PD-1" OR "anti-PDL-1" OR "atezolizumab" OR "durvalumab" OR "pembrolizumab" OR "immune checkpoint inhibitors"; Year(s): 2010–2023; Title, abstract or author-specified keywords: immunotherapy; Title: "triple-negative breast cancer", were employed. In Medline, the following search method was employed: (TS = (triple-negative breast cancer)) AND (TS = (immune checkpoint inhibitors)) AND (TS = (atezolizumab)) OR (TS = (pembrolizumab)) OR (TS = (durvalumab)), Year(s): 2010–2023. The Cochrane Library employed: ("triple-negative breast cancer" in Record Title) AND ("immunotherapy" in All Text OR "PD-L1 inhibitor" in All Text OR "PD-1 inhibitor" in All Text - in Trials).

The inclusion criteria for the literature were as follows: (1) availability of full text and raw data from publicly accessible RCTs; (2) patients diagnosed with mTNBC or advance TNBC (aTNBC); (3) immunotherapy, such as PD-1 or PD-L1 inhibitors, was employed as the primary intervention, and the observation group's interventions included chemotherapy alone or in combination with a placebo; and (4) for the analysis of OS and PFS feasibility studies, hazard ratios (HRs) and 95% confidence intervals (CIs) were utilized. The exclusion criteria were: (1) the literature's content is irrelevant to TNBC; (2) treatment in the included literature is inconsistent with immunotherapy; (3) literature without full text or raw data; and (4) non-RCT literature, and republished articles or reviews.

2.2 Assessment of Study Quality and Risk of Bias

The quality of the selected studies was assessed using the Newcastle-Ottawa scale. The results were obtained through the selection of case and control groups, comparability, and the selected articles were rated. Scores ranged from 0 to 9 points, with studies scoring 7 points or more were considered high-quality studies. Since no more than 10 articles were included, a formal bias analysis was not conducted [16].

2.3 Data Extraction

Data were collected from the included studies by two unbiased reviewers (ML and YZ). Disagreements were resolved through consensus between the reviewers. The primary data extracted included the study name, study phase, number of TNBC patients enrolled, duration of follow-up, pharmacological intervention, PD-L1 status, and adverse events graded as grade three or higher. For OS and PFS, HRs and 95% CI were calculated, with PD-L1 positivity defined as a combined positive score (CPS) of $\geq$1. In cases where reported outcomes varied, the most recent data were employed.

2.4 Statistical Analysis

For the ITT population receiving PD-1/PD-L1 inhibitors in addition to chemotherapy, as well as the PD-L1-positive population, OS and PFS were the primary endpoints. The secondary endpoint was the frequency of adverse events graded as grade three or higher. CPS was used to perform subgroup analysis.

The Cochrane Collaboration RevMan 5.4 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) was employed. Odds ratios and HRs were used for the analysis of primary endpoints. The χ^2 test with $\alpha = 0.10$ was used to examine the heterogeneity among the included studies A $p > 0.1$ and $I^2 < 50\%$ indicated no significant heterogeneity, and a fixed-effects model was utilized. If $p \leq 0.1$ and $I^2 \geq 50\%$, heterogeneity was present, and a random-effects model was used [17].

3. Results

A total of 3007 papers was obtained after searching PubMed, Embase, Medline, and The Cochrane Library. After initial data screening, 62 studies were initially selected for inclusion. After reviewing the full texts, 9 papers were excluded based on the non-RCT inclusion and exclusion criteria, 16 papers had irrelevant outcome indicators, 4 papers were post-hoc analyses or early reports, full-text data for 9 papers were single arm studies, and 17 papers were neoadjuvant chemotherapy. 7 papers were finally included [18–24]. The data collection process is depicted in Fig. 1.

All these studies were either retrospective or prospective cohort studies published from 2020 to 2022. A total of 3287 TNBC patients were included across studies, with 1932 patients in the trial group receiving immunotherapy

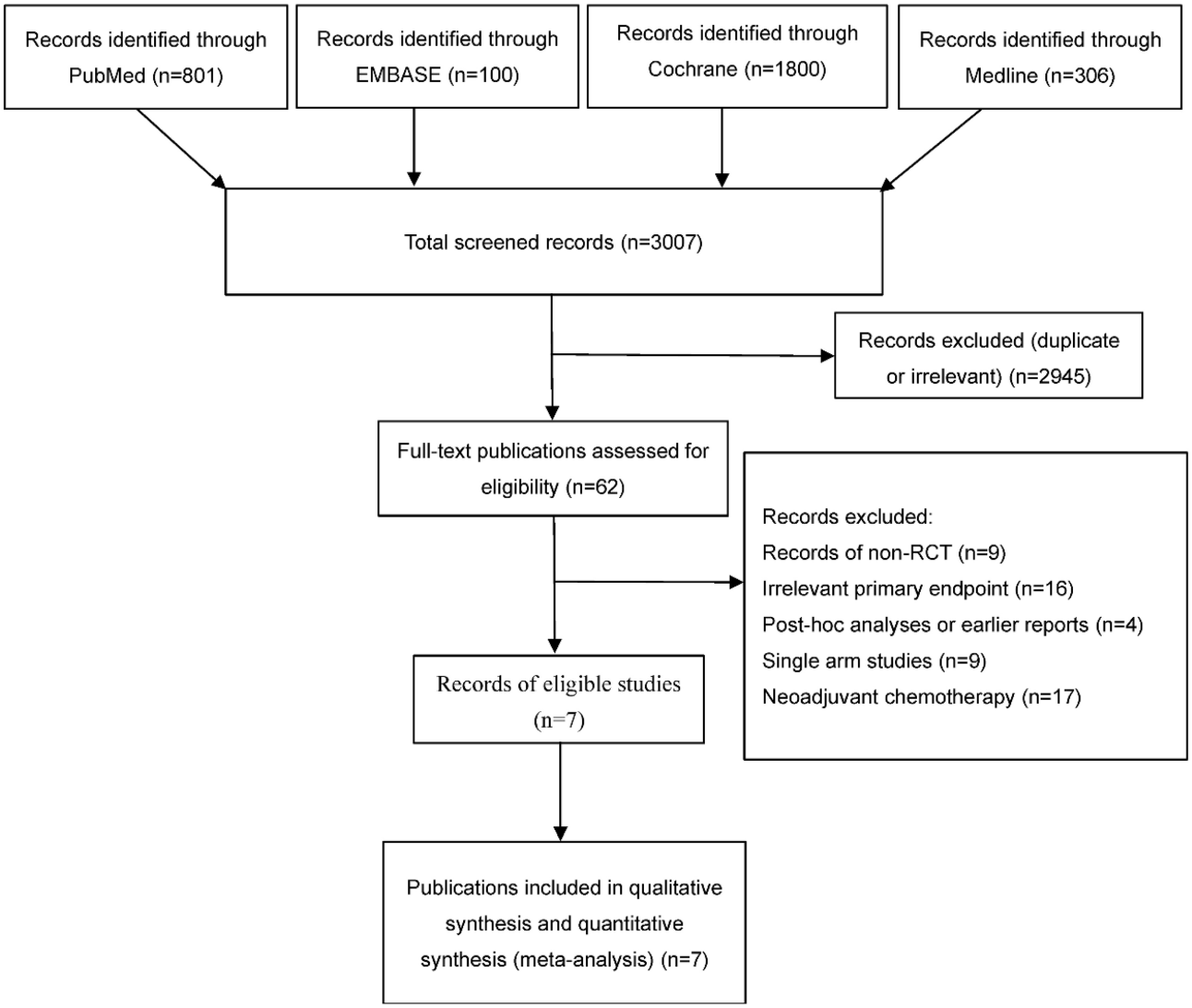

Fig. 1. Flow chart of literature screening. RCT, randomized controlled trial.

combined with chemotherapy, and 1355 patients in the control group receiving chemotherapy alone, with or without placebo. The general data of the included studies are summarized in Table 1 (Ref. [18–24]). Table 2 (Ref. [18–24]) shows the primary endpoints of the included studies. The quality of the included articles was assessed according to the Newcastle-Ottawa scale: 2 articles were classified as medium quality (4–6 points) and 5 articles were classified as high quality (7–9 points).

3.1 OS of mTNBC or aTNBC

Six trials comparing the OS of immunotherapy between chemotherapy and chemotherapy plus placebo were included. Overall, there was significant heterogeneity between the two groups regarding ITT patients ([hazard ratio] HR, 0.96; 95% CI, 0.94–0.98; $p < 0.001$) ($I^2 = 14\%$, $p = 0.29$), and the fixed-effect model was used.

For further analysis, we performed subgroup analysis of OS (Fig. 2). Subgroup analysis by chemotherapy regimen showed that a combined HR of 0.96 (95% CI: 0.92–1.01, $p = 0.09$, $I^2 = 37\%$, p for heterogeneity = 0.20) for the paclitaxel group, and 0.96 (95% CI: 0.90–1.03, $p = 0.25$, $I^2 = 51\%$, p for heterogeneity = 0.13) for the non-paclitaxel group. Subgroup analysis by sample size showed a combined HR of 0.98 (95% CI: 0.94–1.03, $p = 0.46$, $I^2 = 17\%$, p for heterogeneity = 0.30) for studies with sample size $\geq$200, and 0.93 (95% CI: 0.87–0.99, $p = 0.02$, $I^2 = 21\%$, p for heterogeneity = 0.28) for those with sample size <200. Subgroup analysis by PD-L1 inhibitors indicated that the combined HR was 0.97 (95% CI: 0.91–1.02, $p = 0.22$, $I^2 = 44\%$, p for heterogeneity = 0.17) for atezolizumab, and 0.97 (95% CI: 0.92–1.02, $p = 0.21$, $I^2 = 0\%$, p for heterogeneity = 0.47) for pembrolizumab. Overall, the pooled HR for immunotherapy versus chemotherapy was 0.96 (95% CI: 0.94–0.98, $p < 0.001$; $I^2 = 14\%$).

In the PD-L1-positive subgroup, the pooled HR for OS was 0.93 (95% CI: 0.82–1.05, $p = 0.24$), indicating no statistically significant survival advantage of immunotherapy

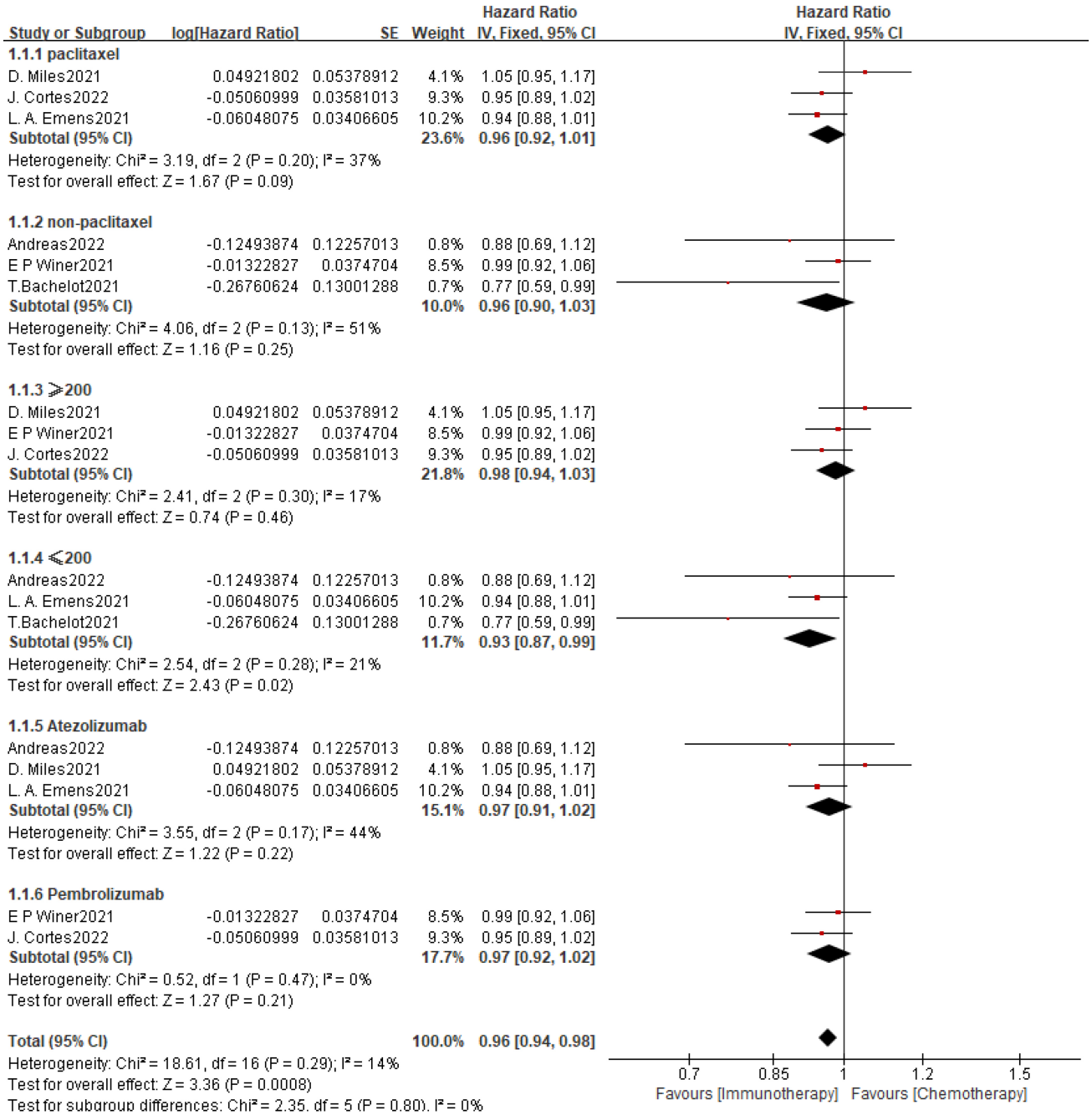

Fig. 2. Summary and subgroup analysis of effects of PD-L1 inhibitors in combination with chemotherapy on OS in the ITT population of mTNBC patients. Subgroup analyses were performed according to chemotherapy regimen (paclitaxel vs. non-paclitaxel), sample size (≥200 vs. <200), and type of PD-L1 inhibitor (atezolizumab vs. pembrolizumab). The pooled HR in the ITT population favored immunotherapy with statistical significance (HR = 0.96, 95% CI: 0.94–0.98, $p < 0.001$; $I^2 = 14\%$). No significant heterogeneity was observed across subgroups. PD-L1, programmed death ligand 1; OS, overall survival; ITT, intention-to-treat; mTNBC, metastatic triple-negative breast cancer; CI, confidence interval; HR, hazard ratio.

Table 1. Characteristics of the included studies.

Trial	Trial alias	Phase	Study arm (n)	Control arm (n)	Median follow-up (month)	PD-L1-positive (n)	Grade ≥3 AEs (n)
Ref. [18]	IMpassion130	III	Atezolizumab plus Nab-Paclitaxel (451)	Nab-Paclitaxel plus placebo (451)	13.0/12.5	185.0/184.0	230.0/190.0
Ref. [19]	IMpassion131	III	Atezolizumab plus paclitaxel (432)	Placebo plus paclitaxel (217)	9.0/8.6	191.0/101.0	49.0/11.0
Ref. [20]	SAFIR02-BREAST IMMUNO	II	Durvalumab plus chemotherapy (131)	Maintenance chemotherapy (68)	19.7	18.0/14.0	/
Ref. [21]	KEYNOTE-119	III	Pembrolizumab plus chemotherapy (312)	Chemotherapy (310)	31.4/31.5	352.0	60.0/199.0
Ref. [22]	IMpassion130	III	Atezolizumab plus Nab-Paclitaxel (451)	Nab-Paclitaxel plus placebo (451)	21.0/18.7	185.0/184.0	239.0/186.0
Ref. [23]	KEYNOTE-355	III	Pembrolizumab plus chemotherapy (566)	Placebo plus chemotherapy (281)	25.9/26.3	645.0/314.0	383.0/181.0
Ref. [24]	ALICE	IIb	Atezolizumab plus chemotherapy (40)	Placebo plus chemotherapy (28)	32.2	36.0/23.0	25.0/12.0

AEs, adverse events; PD-L1, programmed cell death ligand 1. "/" means not reported

Table 2. Primary endpoints of the included studies.

Trial \ I + C/C (m)	ITT OS	ITT PFS	PD-L1-positive OS	PD-L1-positive PFS	CPS ≥1 OS/PFS	CPS ≥10 OS/PFS	CPS ≥20 OS/PFS
Ref. [18]	21.0/18.7	7.2/5.5	25.0/18.0	7.5/5.3	/	/	/
Ref. [19]	19.2/22.8	5.9/5.6	22.1/28.3	7.2/6.4	/	/	/
Ref. [20]	21.2/14.0	/	27.3/12.1	/	/	/	/
Ref. [21]	9.9/10.8	/	/	/	OS 10.7/10.2	OS 12.7/11.6	OS 14.9/12.5
Ref. [22]	21.0/18.7	/	25.4/17.9	/	/	/	/
Ref. [23]	17.2/15.5	7.5/5.6	/	/	OS 17.6/16.0 PFS 7.6/5.6	OS 23.0/16.1 PFS 9.7/5.6	/
Ref. [24]	Not mentioned	4.3/3.5	/	4.7/1.8	/	/	/

CPS, combined positive score; I+C/C, immunochemotherapy + chemotherapy/chemotherapy; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival. "/" means not reported.

Table 3. Sensitivity analysis of immunochemotherapy efficacy stratified by PD-L1 expression thresholds.

PD-L1 Threshold	PFS HR (95% CI)	*p*	OS HR (95% CI)	*p*
CPS ≥1	0.89 (0.82–0.97)	<0.01	0.94 (0.86–1.02)	0.14
CPS ≥10	0.72 (0.64–0.82)	<0.01	0.85 (0.74–0.98)	0.03
CPS ≥20	0.78 (0.60–1.02)	0.07	0.88 (0.68–1.15)	0.35

CI, confidence interval; HR, hazard ratio.

over chemotherapy. However, there was significant heterogeneity among the included studies (I^2 = 70%, p $_{\text{heterogeneity}}$ = 0.02), and a random-effect model was applied.

For further analysis, we did subgroup analysis of OS (Fig. 3). A total of three subgroups were included to compare the OS of mTNBC patients with CPS ≥1, CPS ≥10, or CPS ≥20 receiving chemotherapy versus chemotherapy alone with pembrolizumab. Subgroup analysis by chemotherapy protocols showed that the combined HR was 0.94 (95% CI = 0.88–1.00, p = 0.03, I^2 = 0%, p for heterogeneity= 1.00) for CPS ≥1, 0.88 (95% CI = 0.81–0.97, p = 0.006, I^2 = 0%, p for heterogeneity = 0.75) for CPS ≥10, and 0.84 (95% CI = 0.74–0.94, p = 0.002, I^2 = 0%, p for heterogeneity = 0.43) for CPS ≥20. The sensitivity analysis results for evaluating the impact of different PD-L1 thresholds (CPS ≥1, ≥10, and ≥20) on survival outcomes are listed in Table 3. Moreover, funnel plots for the primary outcomes (ITT OS and PD-L1-positive OS) used to assess potential publication bias are exhibited in **Supplementary Figs. 1,2**.

3.2 PFS of mTNBC or aTNBC

Four studies compared PFS with and without immunotherapy in the mTNBC treatment. Patients with mTNBC receiving chemotherapy combined with PD-1 inhibitors had longer PFS (HR, 0.91; 95% CI, 0.88–0.94; $p <$ 0.00001) (I^2 = 0%, p = 0.58000) (Table 4 or Fig. 4).

There were only three studies that analyzed PFS with or without applying PD-1/PD-L1 inhibitors to chemotherapy in the PD-L1-positive mTNBC population. The outcomes demonstrated significantly increased PFS when PD-1 inhibitors were combined with chemotherapy (HR, 0.84; 95% CI, 0.78–0.91; $p <$ 0.00001) (I^2 = 0%, p = 0.72000) (Table 4 and Fig. 5).

3.3 Adverse Events

PD-L1 inhibitors mainly included durvalumab, atezolizumab, and pembrolizumab. A total of five studies were included (Table 5), demonstrating that grade 3–4 adverse reactions to atezolizumab primarily involved neutropenia, peripheral neuropathy, decreased neutrophil count, fatigue, and occasional hyper- or hypothyroidism. The paclitaxel plus placebo group had fewer side effects than the atezolizumab plus paclitaxel group (HR, 1.38; 95% CI, 1.18–1.62; $p <$ 0.01; I^2 = 0%, p = 0.78). The most prevalent adverse effects reported in the two studies on pembrolizumab were neutropenia, reduced neutrophil count and anemia, and leukopenia. The findings showed no significant variations in grade 3–4 adverse effects among pembrolizumab plus chemotherapy and chemotherapy adjuvant placebo (HR, 0.37; 95% CI, 0.04–3.67; p = 0.39; I^2 = 99%, $p <$ 0.00001). Adverse events stratified by drug type and severity are listed in Table 6.

4. Discussion

This meta-analysis systematically evaluated the efficacy and safety of ICIs combined with chemotherapy in aTNBC or mTNBC. TNBC is a highly invasive and genetically unstable cancer characterized by negative expression of both hormone receptors and HER2, which is prone to germline *BRCA1* mutations [25]. Since the antitumor activity of ICIs was demonstrated by the KEYNOTE-012 in 2015 [26], the efficacy of ICIs combined with chemotherapy in aTNBC has been increasingly explored. However, RCTs articles and comprehensive analyses on this topic remain limited.

This meta-analysis included seven RCTs, comprising a total of 3219 patients with aTNBC or mTNBC. We demonstrated that combining ICIs, such as atezolizumab, pembrolizumab, and durvalumab, with chemotherapy significantly improved PFS in both the ITT and PD-L1-positive populations. Importantly, the analysis highlighted that pembrolizumab combined with chemotherapy delivered a significantly greater PFS benefit, particularly in patients with higher CPS scores (CPS ≥10 points). Despite the observed PFS benefit, our analysis revealed no significant improvement in OS across the PD-L1-positive or ITT populations.

Previous studies, such as IMpassion130, demonstrated clinical benefits of atezolizumab combined with nab-paclitaxel in PD-L1-positive patients [23,27]. The concurrent studies validated it through SP263, 22C3, or CPS analyses [28]. In 2019, Adams *et al.* [29] evaluated the efficacy of atezolizumab combined with nab-paclitaxel in 33 women with stage IV or locally recurrent TNBC who had received prior chemotherapy, finding a median PFS and OS of 5.5 and 14.7 months, respectively. PD-L1-positive patients had OS and PFS of 21.9 and 6.9 months, respectively, compared to 11.4 and 5.1 months in PD-L1–negative patients. The combination of atezolizumab and ipatasertib with capecitabine extended PFS to 8.2 months in mTNBC patients naive to platinum-based chemotherapy and ICIs, which was twice as long as the 3.9 months observed with chemotherapy alone [30].

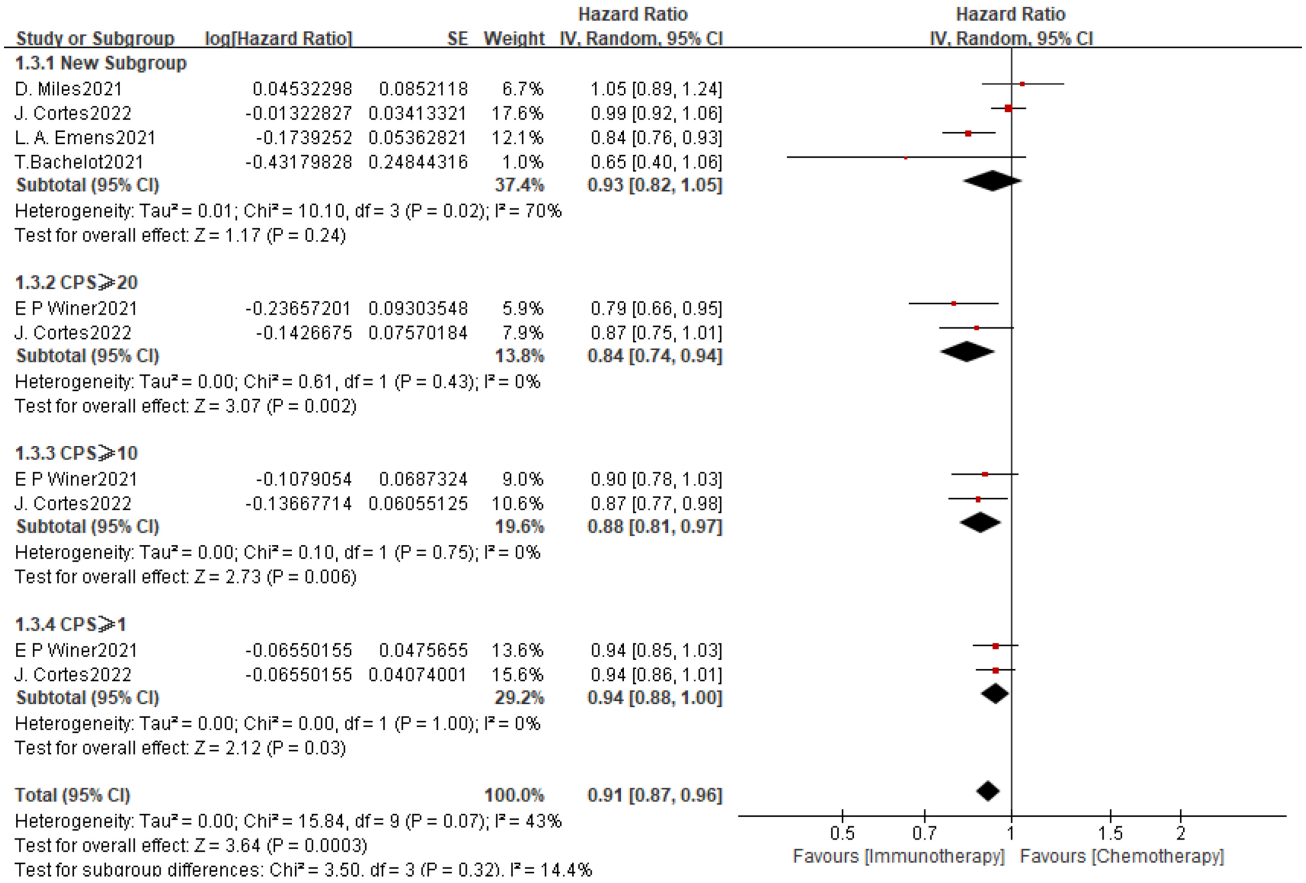

Fig. 3. Summary and subgroup analysis of effects of PD-L1-inhibitors in combination with chemotherapy on OS in the PD-L1-positive population of mTNBC patients. This figure presents OS outcomes in PD-L1-positive subgroups, including an overall pooled analysis of 4 studies (HR = 0.93, 95% CI: 0.82–1.05, $p = 0.24$; $I^2 = 70\%$, $p = 0.02$), and stratified analyses by PD-L1 CPS (CPS $\geq$1, $\geq$10, and $\geq$20). Statistically significant survival benefits were observed in patients with higher CPS (CPS $\geq$10: HR = 0.88; CPS $\geq$20: HR = 0.84). No heterogeneity was detected in CPS-based subgroups ($I^2 = 0\%$). CPS, combined positive score.

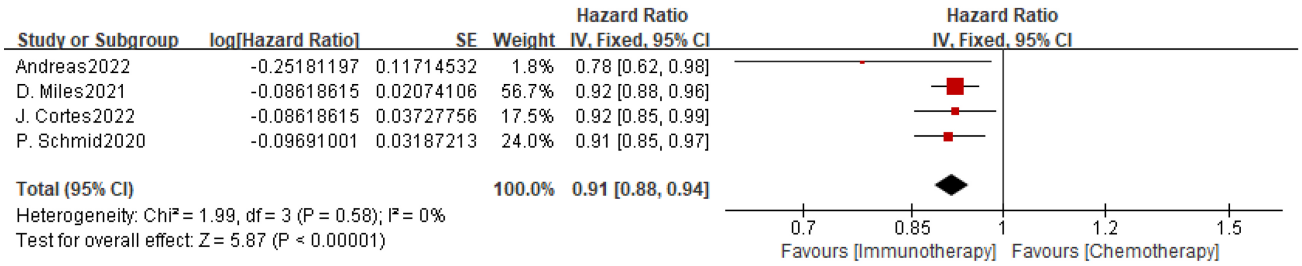

Fig. 4. Effect of PD-L1 inhibitors combined with chemotherapy on PFS in the ITT population of patients with mTNBC.

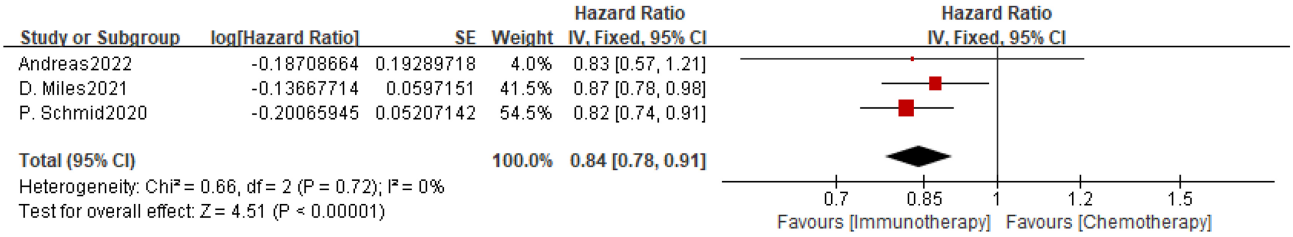

Fig. 5. Effect of PD-L1 inhibitors in combination with chemotherapy on PFS in PD-L1-positive patients with mTNBC.

Table 4. Summary and subgroup analysis of the association between ICIs and survival of mTNBC.

Factor	Number of studies	Number of patients	HR (95% CI)	Overall effect *p*-value	Heterogeneity	
					I^2 (%)	*p*
ITT OS						
Overall	6	3287	0.96 (0.94, 0.98)	<0.01000	14%	0.29000
Chemotherapy						
Paclitaxel	3	2400	0.97 (0.91, 1.02)	0.26000	37%	0.20000
Non-paclitaxel	3	887	0.91 (0.78, 1.05)	0.21000	51%	0.13000
Sample size						
≥200	3	2120	0.98 (0.94, 1.04)	0.54000	17%	0.30000
<200	3	1167	0.91 (0.82, 1.00)	0.05000	21%	0.28000
ICIs						
Atezolizumab	3	1612	0.97 (0.89, 1.06)	0.53000	44%	0.17000
Pembrolizumab	2	1469	0.97 (0.92, 1.02)	0.21000	0%	0.47000
PD-L1+ OS						
Overall	4	1540	0.93 (0.82, 1.05)	0.24000	70%	0.02000
CPS						
CPS ≥1	2	1041	0.94 (0.88, 1.00)	0.03000	0%	1.00000
CPS ≥10	2	517	0.88 (0.81, 0.97)	<0.01000	0%	0.75000
CPS ≥20	2	313	0.84 (0.74, 0.94)	<0.01000	0%	0.43000
ITT PFS						
Overall	4	2459	0.91 (0.88, 0.94)	<0.00001	0%	0.58000
PD-L1+ PFS						
Overall	3	729	0.84 (0.78, 0.91)	<0.00001	0%	0.72000
AEs						
Overall	6	3287	0.91 (0.43, 1.92)	0.73000	96%	<0.01000
ICIs						
Atezolizumab	4	1612	1.38 (1.18, 1.62)	<0.01000	0%	0.78000
Pembrolizumab	2	1469	0.37 (0.04, 3.67)	0.39000	99%	<0.00001

PD-L1+, protein programmed cell death ligand 1positive expression.

Voorwerk *et al*. [31] demonstrated that atezolizumab in combination with platinum agents also exhibited promising antitumor activity in patients with TNBC. Among the six individuals, four were TNBC patients who had increased expression of cluster of differentiation 8 positive T cells ($CD8^+$ T) cells and immune checkpoint markers. Furthermore, Røssevold *et al*. [24] conducted a pioneering study using atezolizumab combined with pegylated liposomal doxorubicin (PLD) for mTNBC treatment. The results indicated that this combination prolonged OS and PFS in mTNBC patients, with lower cardiac toxicity compared to anthracycline-based drugs [32]. In contradiction to the above findings, the IMpassion131 study reported that atezolizumab in combination with paclitaxel did not significantly benefit OS or PFS [19], which may be attributed to paclitaxel's sensitizing effects and the concomitant use of dexamethasone [33].

In addition to atezolizumab, pembrolizumab for mTNBC treatment has been gradually studied in recent years. In 2021, Winer *et al*. [21] conducted a study that categorized tumor status into CPS ≥1 and CPS <1 groups according to PD-L1 expression. The results indicated that pembrolizumab combined with eribulin increased the objective remission rate in PD-L1-positive patients in comparison to the PD-L1-negative patients, demonstrating potent antitumor activity of this chemo-immunotherapy combination [34]. The combination of pembrolizumab with doxorubicin yielded a median PFS of 7.5 months, an OS of 3.3 months, and a positive overall remission rate of 78% in patients regardless of prior anthracycline use, demonstrating a strong immune cell response [35]. A study of pembrolizumab monotherapy in mTNBC patients with prior paclitaxel or anthracycline chemotherapy revealed the final median PFS of 2 months and a median OS of 9 months [36]. Several studies have indicated that higher CPS are associated with more aggressive tumors and higher sensitivity to pembrolizumab [18,37,38]. High numbers of M1 macrophages, $CD8^+$ T cells, and follicular helper T cells were found in tumor cells with high PD-L1 expression, while tumor cells with low PD-L1 expression exhibited a high proportion of $CD4^+$ T cells, which may explain the relative benefit in OS and PFS in PD-L1-positive patients [39]. Patients with $CD8^+$ T infiltrating lymphocytes in both epithelial and mesenchymal tumors compartments, where PD-L1 expression was active in the epithelial cells of fully inflamed tumors and in the stromal cells of the stroma-

Table 5. Adverse events.

AEs (ICI + C/C) (%) / Trial	Common adverse events		Immune-mediated adverse events	
	Grade <3	Grade 3, 4, or 5	Grade <3	Grade 3, 4, or 5
IMpassion130	Alopecia (57.2%/57.4%) Fatigue (47.0%/45.1%) Nausea (46.7%/38.4%)	Neutropenia (8.0%/8.0%) Peripheral neuropathy (6.0%/3.0%) Decreased neutrophil count (5.0%/4.0%), fatigue (4.0%/3.0%)	Rash (35.9%/26.0%) Hypothyroidism (18.3%/4.4%) Hyperthyroidism (4.8%/1.2%), pneumonitis (3.9%/0.2%)	Hepatitis (1.5%/0.2%) Rash (1.1%/0.5%) Colitis (0.4%/0.2%)
IMpassion131	Alopecia, anaemia, peripheral neuropathy, diarrhoea, fatigue, nausea (25.0%/18.0%)	Diarrhea, vomiting, decreased appetite, hypothyroidism, hyperthyroidism (53.0%/46.0%)	Rash (30.0%/33.0%), hypothyroidism (6.0%/14.0%), hepatitis (0.9%/2.0%)	Diabetes mellitus (0.9%/0.9%) Colitis (0.9%/0.2%), rash (0.9%/0.9%)
SAFIR02-BREAST IMMUNO	Not mentioned	Not mentioned	Not mentioned	Not mentioned
KEYNOTE-119	Fatigue (11.0%/13.0%) Nausea (10.0%/21.0%) Hypothyroidism (7.0%/0)	Increased aspartate aminotransferase (3.0%/1.0%) Asthenia (1.0%/<1.0%), anaemia (1.0%/3.0%)	Hypothyroidism (7.0%/1.0%) Hyperthyroidism (4.0%/0) Pneumonitis (1.0%/0)	Pneumonitis (1.0%/0) Severe skin reaction (1.0%/<1.0%), myositis (1.0%/0)
KEYNOTE-355	Anemia (49.1%/45.9%), neutropenia (41.1%/38.1%) Nausea (39.3%/41.3%)	Neutropenia (29.7%/29.9%), neutrophil count decrease (17.4%/20.3%), anemia (16.5%/14.6%)	Hypothyroidism (15.8%/3.2%), hyperthyroidism (4.3%/1.1%), pneumonitis (2.5%/0)	Severe skin reactions (1.8%/0), pneumonitis (1.1%/0)
ALICE	Rash (65.0%/39.0%) Nausea (57.0%/54.0%) Palmar-plantar erythrodysaesthesia syndrome (52.0%/11.0%)	Decreased lymphocyte count (15.0%/18.0%) Rash (18.0%/0) Palmar-plantar erythrodysesthesia syndrome (8.0%/4.0%)	Hypothyroidism (12.0%/7.0%) Pneumonitis (10.0%/4.0%) Rash (8.0%/4.0%)	Pneumonitis (5.0%/0) Rash (5.0%/0) Pancreatitis (2.0%/0) Pyrexia (2.0%/0)

ICI, immune checkpoint inhibitors.

restricted tumors, demonstrated the best prognosis [40]. Pembrolizumab was approved by the FDA in 2022 as postoperative adjuvant therapy for high-risk TNBC [41]. Compared to atezolizumab, pembrolizumab has demonstrated superior clinical outcomes [42,43].

In 2018, Santa-Maria *et al.* [44] carried out a pilot study using durvalumab and demonstrated a high benefit for TNBC. To further explore the efficacy of durvalumab, Al Sayed *et al.* [45] combined it with paclitaxel, resulting in increased $CD8^+$ T-cell infiltration, enhanced immune check-

Table 6. Adverse events stratified by drug type and severity.

Drug type	AEs	No. of patients (%)	HR (95% CI)	*p*
Atezolizumab	All-grade	70.20%	1.25 (1.10–1.42)	<0.01
Atezolizumab	Grade 3/4	28.50%	1.38 (1.18–1.62)	<0.01
Pembrolizumab	All-grade	64.80%	0.95 (0.78–1.15)	0.60
Pembrolizumab	Grade 3/4	22.10%	0.37 (0.04–3.67)	0.39

point expression and reduced T-cell exhaustion, as well as fewer adverse effects on mTNBC patients. In 2021, Ghebeh *et al*. [46] conducted a 2-year follow-up after combining every-5-week paclitaxel with every-2-week durvalumab, giving PFS and OS of 5 months and 20.7 months, respectively. They attributed the results to increased peripheral blood eosinophil counts [47]. This study further confirmed the efficacy of durvalumab on treating aTNBC.

Considering the high heterogeneity (I^2 = 96%) observed in the pooled analysis of adverse events, and recognizing the distinct toxicity profiles among different ICIs, we further stratified the analysis by drug type and by severity of adverse events (grade 3/4 versus all grades). When analyzed separately, atezolizumab combined with chemotherapy demonstrated a higher incidence of grade 3/4 adverse events (HR, 1.38; 95% CI, 1.18–1.62; $p < 0.01$; $I^2 = 0\%$, $p = 0.78$), while pembrolizumab combined with chemotherapy showed no statistically significant increase in grade 3/4 adverse events compared to chemotherapy alone (HR, 0.37; 95% CI, 0.04–3.67; $p = 0.39$; $I^2 = 99\%$, $p < 0.00001$). When evaluating all-grade adverse events, atezolizumab was associated with a higher frequency of immune-related events, particularly rash, hypothyroidism, and pneumonitis, whereas pembrolizumab was more frequently linked to hypothyroidism and fatigue, without a significant increase in severe toxicities. These findings suggest drug-specific toxicity profiles that warrant individualized monitoring and management strategies in clinical practice.

Limitations

However, this meta-analysis has some limitations. First, the included studies employed different chemotherapy regimens, and comprehensive studies evaluating various combinations of ICIs and chemotherapy in mTNBC remain limited, introducing potential bias. Additionally, the number of studies involving durvalumab and PLD is limited, which may cause bias. Second, although pembrolizumab has shown OS benefits in patients with CPS $\geq$10, the extension in survival was less than one year, and the higher incidence rate of immune-related adverse events than chemotherapy alone may compromise the quality of life. Third, most studies only reported OS and PFS outcomes in CPS-defined subgroups treated with pembrolizumab. Although some trials have indicated OS improvement, it remains controversial whether immunotherapy significantly prolongs OS in both the ITT and PD-L1-positive populations, due to the heterogeneity and variability among studies.

5. Conclusions

Immunotherapy using PD-L1 inhibitors prolong PFS in the PD-L1-positive population, with a more pronounced effect observed at higher CPS levels. Understanding and utilizing CPS thresholds allow clinicians to personalize treatment strategies, ensuring that patients most likely to benefit from immunotherapy are appropriately identified. It also helps prevent unnecessary exposure to potential side effects in patients less likely to respond. Incorporating CPS assessment into clinical decision-making potentially enhances the precision of TNBC management.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Author Contributions

HC, XL and ML designed the research study. The table was conducted by HC, while the graphic figures were created by LS; the data from studies were compiled by XL. YZ and LS acquired, analyzed, and interpreted the data. HC and ML contributed to preparing the draft and editorial revisions. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG37642.

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