



## Evaluation of the Survival Rate and Clinical Outcome of Nanodrug Administration for the Treatment of Lung Cancer: A Systematic Review and Meta-analysis

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### ABSTRACT

**Background and aim:** During the last two decades, with the introduction of nanotechnology, a more promising perspective for cancer treatment appeared, and many research was conducted in nanomedicine. Based on the findings of studies, nanoparticles improve bioavailability, overcome biophysical and biochemical barriers, and reduce cytotoxicity. This study aims to evaluate the survival rate and clinical outcome of nanodrug administration for lung cancer treatment.

**Material and methods:** In this study, international databases such as PubMed, Scopus, Science Direct, ISI, Web of Knowledge, and Embase were reviewed to select articles related to the purpose of this study from January 2012 to July 2022. Effect size with 95% confidence interval (CI) with fixed effect modal and inverse-variance done. STATA.V16 software was used for data analysis.

**Results:** In the initial review, the abstracts of 183 studies were reviewed, two authors reviewed the full text of 34 studies, and finally, seven studies were selected. Overall survival rate and Progression-Free survival rate between nab-paclitaxel plus carboplatin compared solvent-based paclitaxel plus cisplatin in lung cancer patients was 88% (HR: 95% CI, 0.51 to 1.25; p=0.00) and 77% (HR: 95% CI, 0.37 to 1.17; p=0.00), respectively.

**Conclusions:** Based on the findings of the present meta-analysis, nab-paclitaxel administration can prolong the progression-free survival rate; improve the objective response rate, and increase the overall survival rate.

### 1. Introduction

According to the reports, in 2020 worldwide, one death from nine cancers is related to lung cancer, the leading cause of death and the second most common cancer.<sup>[1]</sup> Lung cancer is divided into several categories based on histological classification, such as mesenchymal tumors, metastatic tumors, epithelial tumors, lymphohistiocytic tumors, and tumors of ectopic origin.<sup>[2]</sup> The most available statistics include small-cell carcinoma (13%) and non-small-cell lung carcinoma (NSCLC) (84%).<sup>[3]</sup> Studies have shown that the 5-year survival rate in patients with lung cancer ranges from 10 to 20%, and the place of residence affects the survival rate.<sup>[4-6]</sup> Treatments like chemotherapy, radiation therapy, and surgery are used for treating lung cancer, and the choice of each treatment depends on the type of malignancy and the disease diagnosis stage.<sup>[7]</sup> Based on the available evidence, in most cases of lung cancer, the diagnosis is not early, and it is diagnosed in the stage of metastasis, which does not require surgical treatment.<sup>[8, 9]</sup> Also, studies have shown that if most

cases of NSCLC are diagnosed in the early stages, they are in an advanced stage of cancer, affecting the treatment choice.<sup>[9-11]</sup> Therefore, systemic chemotherapy is considered the main treatment for most patients with advanced lung cancer, and chemotherapy aims to improve the patient's quality of life and increase survival.<sup>[12, 13]</sup> Evidence also shows that immunotherapy can be a good treatment option and can be used alone or in combination with other treatments.<sup>[14]</sup> Studies have shown that using programmed cell death protein 1 (PD-1) in advanced NSCLC results better than chemotherapy. PD-1/programmed cell death one ligand 1 (PD-L1) has been considered in treating patients with advanced NSCLC. PD-L1 is a biomarker that predicts overall survival.<sup>[15-18]</sup> According to the cases taken and the results of the studies, choosing a suitable treatment is challenging and has many limitations. Chemotherapy drugs do not dissolve in water due to their hydrophobic nature, and their use in higher doses is impossible. Also, these drugs can affect normal cells, and their excessive toxicity makes the treatment unfavorable.<sup>[19]</sup> During

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the last two decades, a more promising perspective for cancer treatment appeared with the introduction of nanotechnology, and much research was conducted in nanomedicine. Based on the findings of studies, nanoparticles improve bioavailability, can overcome biophysical and biochemical barriers, and reduce cytotoxicity.<sup>[20, 21]</sup> In treating lung cancer, it has been reported that using therapeutic methods based on nanoparticles can reduce toxicity and increase the effectiveness of the treatment.<sup>[6, 22]</sup> The results of the studies have shown that compared to conventional treatments and nano drugs in the treatment of lung cancer, nano drugs have better results, are more efficient and less toxic, and are easier to use.<sup>[23]</sup> It should be noted that the existing studies were conducted on small sample size, and most of the subjects under study were older and older; therefore, the review of the studies and their results and the consensus of the results can provide stronger evidence in relation to the purpose of the study. Therefore, this study aims to evaluate the survival rate and clinical outcome of nanodrug administration for lung cancer treatment.

## 2. Material and methods

The present study is a systematic review and meta-analysis that was conducted based on PRISMA guidelines.<sup>[24]</sup> In this study, international databases such as PubMed, Scopus, Science Direct, ISI, Web of Knowledge,

and Embase were reviewed to select articles related to the purpose of this study from January 2012 to July 2022. Mesh keywords were used for searching in PubMed, and similar keywords were searched in other databases. In the current study, Table 1 shows the response to PICO; the Google Scholar search engine was also used.

MeSH terms keywords: (((((((("Lung Neoplasms"[Mesh]) OR ( "Small Cell Lung Carcinoma"[Mesh] OR "Carcinoma, Non-Small-Cell Lung"[Mesh] )) OR ( "Lung Neoplasms/chemistry"[Mesh] OR "Lung Neoplasms/classification"[Mesh] OR "Lung Neoplasms/complications"[Mesh] OR "Lung Neoplasms/diagnosis"[Mesh] OR "Lung Neoplasms/diet therapy"[Mesh] OR "Lung Neoplasms/drug effects"[Mesh] OR "Lung Neoplasms/drug therapy"[Mesh] OR "Lung Neoplasms/immunology"[Mesh] OR "Lung Neoplasms/mortality"[Mesh] OR "Lung Neoplasms/pharmacology"[Mesh] OR "Lung Neoplasms/radiotherapy"[Mesh] OR "Lung Neoplasms/statistics and numerical data"[Mesh] OR "Lung Neoplasms/surgery"[Mesh] OR "Lung Neoplasms/therapy"[Mesh] )) AND ( "Organization and Administration"[Mesh] OR "organization and administration" [Subheading] )) AND "Nanoparticles"[Mesh]) AND "Treatment Outcome"[Mesh]) AND "Survival Rate"[Mesh]) AND "Progression-Free Survival"[Mesh]) AND ( "Adverse Outcome Pathways"[Mesh] OR "Risk Management"[Mesh] ).

**Table1. PICO strategy.**

PICO Strategy	Description
P	Population: Lung cancer patients
I	Intervention: nab-paclitaxel plus carboplatin
C	Comparison: solvent-based paclitaxel plus cisplatin
O	Outcome: clinical outcome, the survival rate

### Inclusion and exclusion criteria

Randomized controlled clinical trials (RCT) and clinical trials studies, lung cancer and non-small-cell carcinoma, nanoadministration. Studies other than RCT, other cancers, conflicting data with objective, and studies without full text were excluded from the study.

### Reporting and extracting study data

It used a checklist that included the author's name, year of publication, type of study, number of patients with lung cancer, the average age of patients, stage of the disease, and type of treatment. The data of the studies were extracted and reported in Table 2; also, the data required for meta-analysis, including survival rate, adverse events, progression-free survival, and response rate, were extracted from the studies.

### Evaluating the quality of studies

In the current study, only randomized control clinical trial studies were included, and the quality of these studies was evaluated using the Cochrane Collaboration tool.<sup>[25]</sup> The scores of this tool are between 0 and 6, and the higher score showed a higher quality of study; the scoring of each item is 1 for low risk and 0 for high and unclear risk.

### Data analysis

STATA.V16 software was used for data analysis. The response rate was estimated with a risk ratio with a 95% confidence interval (CI) with a fixed effect modal and Mantel-Haenszel. Progression-free survival and overall survival rate were estimated using hazard ratio with a 95% confidence interval (CI) with fixed effect modal and Mantel-Haenszel. Effect size with 95% confidence interval (CI) with fixed effect modal and inverse-variance done. The level of heterogeneity was evaluated using the  $I^2$  index test ( $I^2 < 50\%$  = low levels,  $50 < I^2 < 75\%$  = moderate and  $I^2 > 75\%$  = high levels).

## 3. Results

The search was conducted based on the mentioned keywords, and 183 studies were found in the introduced databases; After entering the studies into the EndNote.x8 software, duplicate studies were removed, and finally, the abstract of 176 studies was reviewed, and the studies that met the inclusion criteria were left out for the full-text review; at this stage, 142 studies were removed. The full text of 34 studies was carefully reviewed, and studies that had incomplete data, very low quality, or did not include the inclusion criteria and matched the exclusion criteria were excluded from the study (27 articles); finally, seven articles were selected, and their data were extracted for meta-analysis (Fig. 1).

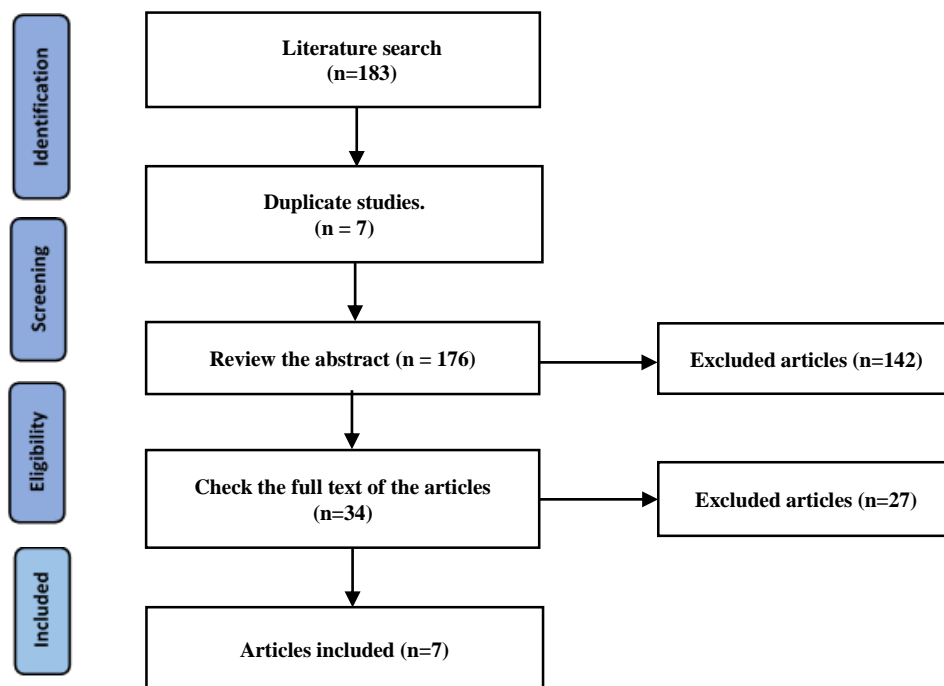


Fig. 1. PRISMA flowcharts.

**Characteristics**

Seven RCT studies have been included in the present article. The number of patients in the group treated with nab-paclitaxel plus carboplatin and solvent-based paclitaxel plus cisplatin group was 2179 and 2016, respectively; A total of 4239 patients were examined; A summary of the data of the selected studies is reported in Table 2.

**Bias assessment**

According to the Collaboration's tool, all studies were at low risk of bias, which indicates the high quality of the studies; three studies scored 6 out of 6, and three studies scored 5 out of 6; Except for the study of Lange et al., 2015,<sup>[29]</sup> which was of moderate quality and scored 4 out of 6. (Table 3).

Table 1. Summary of demographic and clinical data of studies selected.

No	Study. Years	Study Design	Number of Patients		Disease Stage	Mean of Age (Years)	
			Intervention	Control		Intervention	Control
1	Gu et al., 2022 <sup>[26]</sup>	RCT	224	224	IIIB/IV	58	57
2	Shi et al., 2021 <sup>[27]</sup>	RCT	300	148	IIIB/IV	60	60
3	Hirsh et al., 2016 <sup>[28]</sup>	RCT	26	27	IIIB/IV	70	71
4	Lange et al., 2015 <sup>[29]</sup>	RCT	513	524	IIIB/IV	64	68
5	Socinski et al., 2013 <sup>[30]</sup>	RCT	521	531	III/IV	57	57
6	Satouchi et al., 2013 <sup>[31]</sup>	RCT	74	75	IIIB/IV	65	64
7	Socinsk et al., 2012 <sup>[32]</sup>	RCT	521	531	IIIB/IV	58	59

**Table 3. Risk of bias assessment (Collaboration’s tool).**

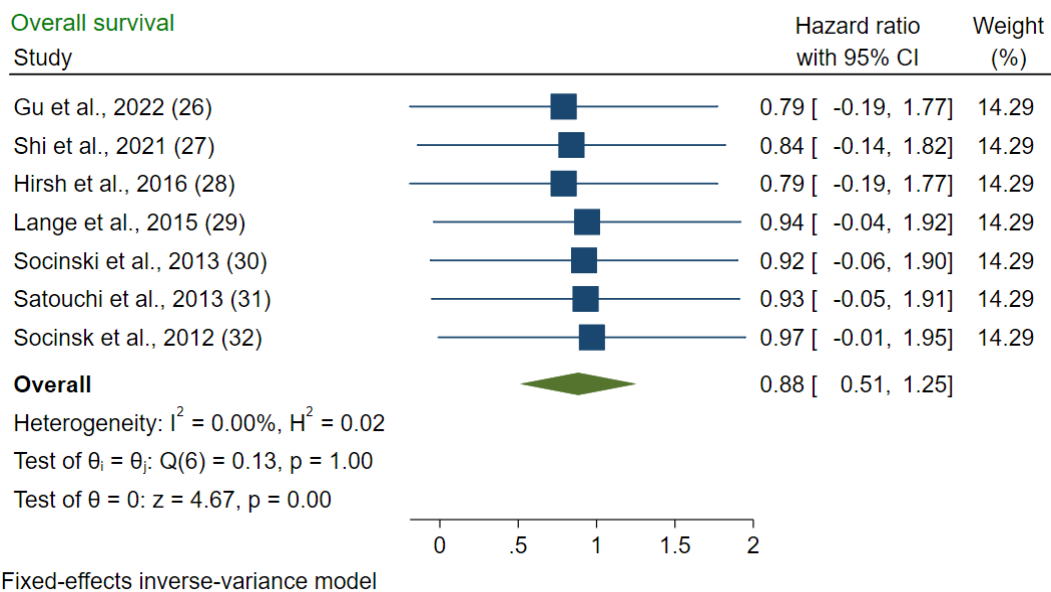
Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Total Score
Gu et al., 2022 <sup>[26]</sup>	+	+	+	+	+	+	6
Shi et al., 2021 <sup>[27]</sup>	+	?	+	+	+	+	5
Hirsh et al., 2016 <sup>[28]</sup>	+	+	+	+	+	+	6
Lange et al., 2015 <sup>[29]</sup>	+	?	?	+	+	+	4
Socinski et al., 2013 <sup>[30]</sup>	+	+	+	+	+	+	6
Satouchi et al., 2013 <sup>[31]</sup>	+	?	+	+	+	+	5
Socinsk et al., 2012 <sup>[32]</sup>	+	?	+	+	+	+	5

(Low (+), unclear (?), high (-)).

**Overall survival rate**

Overall survival rate between nab-paclitaxel plus carboplatin compared solvent-based paclitaxel plus cisplatin in lung cancer patients was 88% (HR: 95% CI, 0.51 to 1.25; p=0.00) (I<sup>2</sup><0%; P=1.00; low heterogeneity). According to Fig. 2, a statistically significant difference was observed in terms of Overall

survival between the two groups (p=0.00); in the intervention group, the Overall survival rate was higher than the control group. These findings show that the overall survival rate was higher in lung cancer patients treated with nab-paclitaxel plus carboplatin.

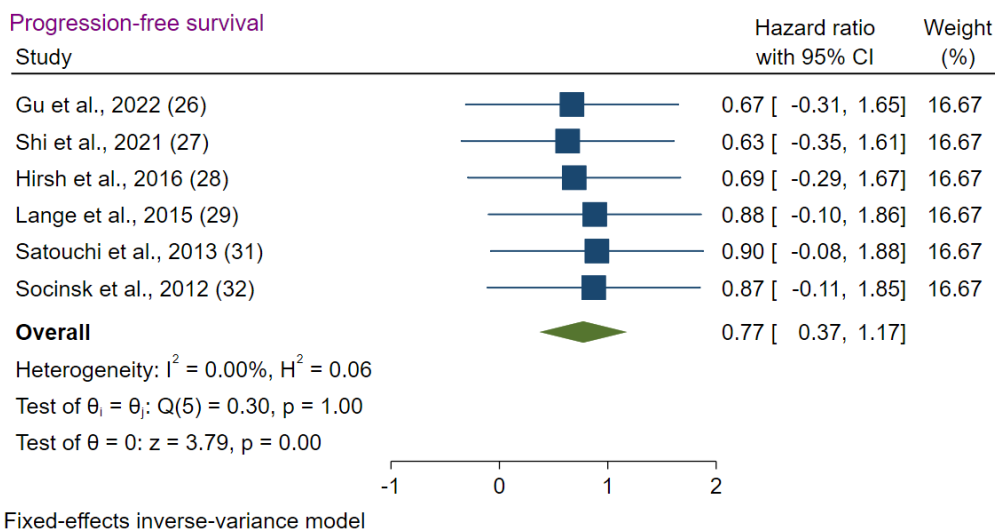


**Fig. 2. The Forest plot showed the Overall survival rate between nab-paclitaxel plus carboplatin compared to solvent-based paclitaxel plus cisplatin.**

**Progression-free survival rate**

Progression-Free survival rate between nab-paclitaxel plus carboplatin compared solvent-based paclitaxel plus cisplatin in lung cancer patients was 77% (HR: 95% CI, 0.37 to 1.17; p=0.00) ( $I^2 < 0\%$ ;  $P = 1.00$ ; low heterogeneity). According to Fig. 3, a statistically significant difference was observed in the

Progression-Free survival rate between the two groups ( $p = 0.00$ ); in the intervention group, the Progression-Free survival rate was higher than the control group. These findings show that nab-paclitaxel plus carboplatin administration prolongs the Progression-Free survival in lung cancer patients.

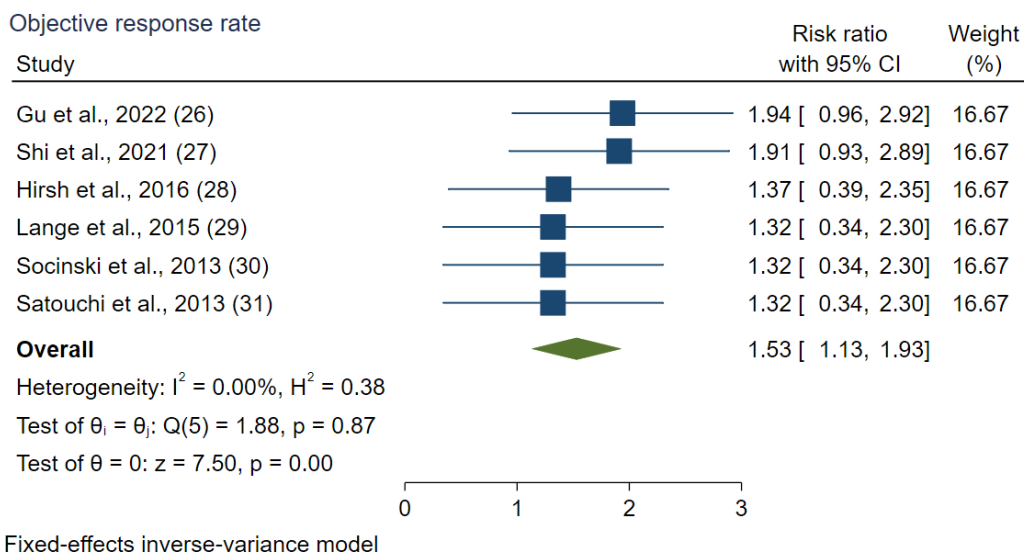


**Fig. 3. The Forest plot showed a Progression-Free survival rate between nab-paclitaxel plus carboplatin compared to solvent-based paclitaxel plus cisplatin.**

**Objective response rate**

Objective response rate between nab-paclitaxel plus carboplatin compared solvent-based paclitaxel plus cisplatin in lung cancer patients was 1.53 (RR: 95% CI, 1.13 to 1.93; p=0.00) ( $I^2 < 0\%$ ;  $P = 0.87$ ; low heterogeneity). According to Fig. 4, a statistically significant difference was observed in

terms of Objective response rate between the two groups ( $p = 0.00$ ); these findings show that in lung cancer patients, nab-paclitaxel plus carboplatin administration improved the objective response rate.



**Fig. 4. The Forest plot showed an Objective response rate.**

**4. Discussion**

According to worldwide statistical reports, lung cancer deaths account for 18% of all deaths.<sup>[11]</sup> Several factors can increase the risk of lung cancer, including air pollution, smoking, occupation, chronic lung disease, and low

education level.<sup>[33]</sup> During the recurrence of the disease, treatment options are limited, and the patient with lung cancer cannot receive adequate treatment; nab-paclitaxel is effective and safe in treating elderly patients once a week, based on the available evidence.<sup>[34]</sup> Based on the available reports and

evidence, lung cancer treatment is very challenging, and many studies are needed in this field. The most important treatment is systemic chemotherapy, which can improve the quality of life and increase the survival rate. However, chemotherapy drugs have poor solubility in water, and their toxicity is high.<sup>[35]</sup> Today, nab-paclitaxel is approved for lung cancer treatment and is used in the clinic. Based on the findings of studies, higher doses of nab-paclitaxel are without increasing toxicity.<sup>[36]</sup> The selected studies were of high quality, and only one study was of moderate to high quality; Heterogeneity between studies was very small, and it can be said that heterogeneity was not observed. All selected studies were RCTs in which clinical outcomes and survival rates were examined. The present meta-analysis showed that the progression-free survival rate was longer in patients who received nab-paclitaxel than in the control group; also, the survival rate was higher in the group receiving nab-paclitaxel. Nab-paclitaxel also improved the objective response rate. The reason for examining the three variables, Overall survival rate, Progression-Free survival rate, and Objective response rate, was in accordance with the 2020 guidelines for approving cancer drugs in clinical trials.<sup>[37]</sup> Nanomedicine can improve pharmacokinetics, reduce toxicity, and be used in treating all types of cancers to transfer therapeutic molecules.<sup>[38]</sup> Among the advantages proposed for nanomedicine, we can mention the following: 1. Solubility in water and improved pharmacokinetics;<sup>[39]</sup> 2. Presentation in high doses;<sup>[40]</sup> 3. Minimizing damage to non-cancerous cells.<sup>[41]</sup> The present study showed that nanomedicine could effectively treat lung cancer patients. As a result, nanodrug delivery is considered an effective method in drug administration; more experiments are needed to confirm the present evidence. Maintaining the quality of life of patients with lung cancer is very important; Based on the findings of the present study and the results of previous studies, nab-paclitaxel does not interfere with the daily life needs of patients with less neurotoxicity; it also increases the survival rate of patients.<sup>[42]</sup> The present study had some limitations. First, the number of RCT studies related to the purpose of the study in 10 years was very small, so more studies need to be conducted to provide stronger evidence. In the studies of the nanodrug delivery method, it was nano-albumin-binding paclitaxel; richer types of drugs need to be investigated.

## 5. Conclusion

Based on the findings of the present meta-analysis, the administration of nab-paclitaxel can prolong the progression-free survival rate, improve the objective response rate and increase the overall survival rate. This treatment method is somewhat safe and effective in treating lung cancer patients.

## Conflict of Interest

The authors declared that there is no conflict of interest.

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