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Nanoparticle-based delivery of immune checkpoint inhibitors: A systematic review of safety and immunotoxicity

Le Phuoc Thuc Uyen, Vo Phuoc Bao Tran

DePauw University

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) have been frequently used in cancer therapy and found to result in immune-related adverse effects due to nonspecific immune activation. Nanoparticle-based delivery systems have been proposed as a strategy to improve tumor targeting and reduce systemic toxicity; however, their safety and immunotoxicity profiles have not been comprehensively synthesized.
Method: This study adopted a systematic review design following PRISMA guidelines. The two databases of PubMed and Scopus were searched for articles published from 2015 onward concerning the application of nanoparticle-mediated delivery of PD-1, PD-L1, or CTLA-4 inhibitors in solid tumors. Inclusion criteria were applied for studies on preclinical and early-phase clinical studies reporting safety, toxicity, or immune-related outcomes. Data on nanoparticle platforms, safety parameters, and methodological quality were extracted and bias risks were assessed against the SYRCLE tool.
Results: Among the twenty-four studies meeting the inclusion criteria, the majority reported preclinical animal studies. Polymeric nanoparticles were the most commonly investigated platforms, followed by lipid-based, inorganic, albumin-based, and gene-delivery systems. Most studies reported stable body weight, preserved organ histology, and largely normal serum biochemical profiles. Cytokine analyses most commonly reported changes in IFN-γ, TNF-α, and, less frequently, IL-6, suggesting that nanoparticle-mediated ICI delivery may induce immune activation while only limited evidence of acute systemic inflammatory toxicity was observed in the included short-term studies. Risk of bias assessment revealed adequate randomization and outcome reporting but frequent uncertainty in blinding and housing procedures.
Conclusion: Nanoparticle-mediated therapies demonstrate encouraging short-term safety profiles. However, long-term immunotoxicity, nanoparticle persistence, and clinical translation remained insufficiently addressed, suggesting the need for standardized safety reporting and expanded clinical evaluation.

1. INTRODUCTION

Immune checkpoint inhibitors (ICIs) have been widely used in cancer treatment, contributing to the transformation of the therapeutic measure of the disease by enabling the durable antitumor immune responses across a range of malignancies. ICIs include various forms such as programmed cell death protein-1 (PD-1),

Corresponding author: Le Phuoc Thuc Uyen;
E-mail: uyenle_2027@depauw.edu
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programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphotocyte-associated antigen-4 (CTLA-4) inhibitors. Recent advances have also looked into nanostructures that integrate immune checkpoint blockade with photoimmunotherapy. This suggests the need to investigate controlled immune activation and favourable safety profiles in preclinical models (Chen et al., 2025).

Despite their clinical success, their immune-related adverse events (irAEs) from non-specific immune activation and how they affect various organs in human organs and their endocrine systems remain under-researched. These toxicities have raised concerns related to dose escalation and treatment length as well as patient safety and clinical management.

ICIs offer theoretical and experimental advantages, including improved tumor accumulation, controlled drug release, and reduced systemic exposure. Previous research has demonstrated how nanoparticle platforms such as liposomes, polymeric nanoparticles, albumin-based carriers, metal-organic frameworks, biomimetic nanocarriers, and virus-like particles have been carried out to deliver ICIs through surface conjugation, encapsulation, or co-delivery with chemotherapeutic, photothermal, or immunomodulatory agents (e.g. Moon et al., 2022; Pham et al., 2021; Zhang et al., 2019).

Furthermore, preclinical studies (e.g. Allen et al., 2021; Ordikhani et al., 2018; Su et al., 2021) have found that nanoparticle-mediated ICI delivery can achieve antitumor efficacy. Specifically, the studies have pointed out that NP-conjugated PD-1 or PD-L1 inhibitors accumulate in the tumor microenvironment, enhance local immune activation, and minimize systemic cytokine release in murine cancer models. Recent studies by Du et al. (2024), Li et al. (2025), and Zhang et al. (2023) have confirmed the encouraging safety profiles alongside synergistic antitumor effects after investigating the integration of ICIs into multifunctional nanoplatforms that combine immune checkpoint blockade with phototherapy, gene therapy, or immunogenic cell death induction.

It should be noted that PD-1, PD-L1, and CTLA-4 inhibitors do not directly suppress inflammatory cytokines. Instead, they modulate immune checkpoint signaling to restore antitumor T-cell activity. In the reviewed studies, cytokines such as IFN-γ and TNF-α were generally reported as indicators of immune activation, whereas IL-6 and, where assessed, IL-1β may be more informative as markers of systemic inflammatory toxicity. Therefore, cytokine profiling in this review is interpreted primarily as a safety-related immunological readout rather than as a direct therapeutic target.

Despite the reported success, the safety and toxicological implications of nanoparticle-based ICI therapies remain insufficiently synthesized in existing studies, which makes cross-study comparison difficult. Furthermore, the existing studies report evidence from short-term preclinical models, with limited evaluation of long-term immunotoxicity, nanoparticle persistence, biodegradation kinetics, and potential risks of chronic immune activation or autoimmunity. The reports from the existing studies indicate further exploration of the gaps between preclinical findings and clinical implementation.

To address these gaps, this systematic review aims to evaluate the reported safety, toxicity, and immune-related outcomes of nanoparticles-mediated immune checkpoint inhibitor therapies. It aims to evaluate the reported safety, toxicity, and immune-related outcomes of nanoparticle-mediated immune checkpoint inhibitor therapies. More specifically, it seeks to synthesize the types of nanoparticle platforms used for ICI delivery, summarize commonly assessed safety and toxicological parameters, evaluate the risk of bias in preclinical studies, and identify emerging safety concerns and knowledge gaps that must be addressed to support the clinical translation of nanoparticle-based immunotherapies.

In this review, safety and toxicity are interpreted in relation to reported biodistribution and organ accumulation where available, because nanoparticle targeting efficiency may influence systemic exposure and off-target effects. However, detailed data on absorption, metabolism, biodegradation, and long-term clearance were inconsistently reported across the included studies. These pharmacokinetic limitations are therefore recognized as an important gap in the current evidence base.

2. METHOD

2.1. Review Design

The study adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Haddaway et al., 2022). It aimed to synthesize existing evidence on the safety, toxicity, and immune-related outcomes of nanoparticle-mediated immune checkpoint inhibitor therapies in solid tumors.

2.2. Search Strategy

A literature search was performed in PubMed and Scopus to identify relevant studies published from January 2015 onwards, reflecting the period during which ICIs and nanoparticle-based delivery systems have been actively developed. PubMed and Scopus were selected because together they provide broad coverage for biomedical and interdisciplinary systematic reviews (Bramer et al., 2017).

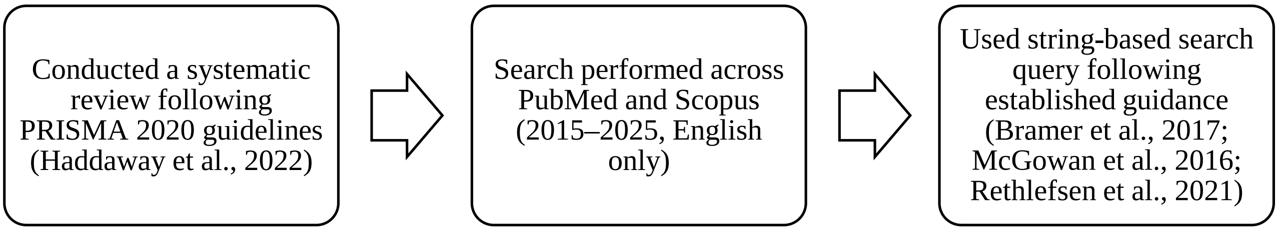

Figure 1. Search Strategy.

The search strategy combined controlled vocabulary and free-text terms related to immune checkpoint inhibitors (e.g. PD-1, PD-L1, CTLA-4), nanoparticle-based delivery systems, and safety, toxicity, or immune-related adverse effects. The strategy was developed and reported in line with guidance for systematic review searches and transparent reporting (McGowan et al., 2016; Rethlefsen et al., 2021). In addition, the reference lists of included articles were screened to identify additional eligible studies.

2.3. Study Selection

The search results were imported into Rayyan.ai for duplicate removal and screening (Ouzzani et al., 2016). Two reviewers independently screened titles and abstracts, followed by full-text assessment of potentially eligible studies. Inter-rater agreement was assessed using Cohen's kappa coefficient, indicating substantial agreement between reviewers.

2.4 Eligibility Criteria

Studies were included based on predefined eligibility criteria developed and reported in accordance with PRISMA 2020 guidelines (Page et al., 2021). In addition, they investigated immune checkpoint inhibitors targeting PD-1, PD-L1, or CTLA-4, employed nanoparticle-based delivery systems to deliver ICIs, reported safety-related outcomes, including immune-related adverse events, toxicological parameters, or immunological safety markers, and were preclinical studies (in vitro or animal models) or early-phase human studies. Besides, they had to focus on solid tumors and were original research articles published in English.

PubMed		
Step	Query	Results
1	("Immune Checkpoint Inhibitors"[MeSH Terms] OR "checkpoint inhibitors immune"[Title/Abstract] OR "immune checkpoint inhibitor"[Title/Abstract] OR "checkpoint inhibitor immune"[Title/Abstract] OR "immune checkpoint blockers"[Title/Abstract] OR "checkpoint blockers immune"[Title/Abstract] OR "immune checkpoint blockade"[Title/Abstract] OR "checkpoint blockade immune"[Title/Abstract] OR "immune checkpoint inhibition"[Title/Abstract] OR "checkpoint inhibition immune"[Title/Abstract] OR "pd l1 inhibitors"[Title/Abstract] OR "programmed death ligand 1 inhibitors"[Title/Abstract] OR "pd 1 pd l1 blockade"[Title/Abstract] OR "blockade pd 1 pd l1"[Title/Abstract] OR "pd 1 pd l1 blockade"[Title/Abstract] OR "Programmed Cell Death 1 Receptor"[MeSH Terms] OR "pd 1 inhibitors"[Title/Abstract] OR "pd 1 inhibitor"[Title/Abstract] OR "inhibitor pd 1"[Title/Abstract] OR "pd 1 inhibitor"[Title/Abstract] OR "programmed cell death protein 1 inhibitors"[Title/Abstract] OR "CTLA-4 Antigen"[MeSH Terms] OR "CTLA-4"[Title/Abstract] OR "CTLA4"[Title/Abstract] OR "CD152"[Title/Abstract] OR "cytotoxic T-lymphocyte-associated protein 4"[Title/Abstract] OR "anti-CTLA-4"[Title/Abstract] OR "CTLA-4 inhibitor"[Title/Abstract] OR "CTLA-4 blockade"[Title/Abstract] OR "ipilimumab"[Title/Abstract] OR "Ipilimumab"[MeSH Terms] OR "nivolumab"[Title/Abstract] OR "pembrolizumab"[Title/Abstract] OR "atezolizumab"[Title/Abstract] OR "tremelimumab"[Title/Abstract] OR "CTLA-4 Antigen"[MeSH Terms])	73,335

2	("nanoparticles"[Title/Abstract] OR "nanoparticles"[MeSH Terms] OR "nanocarriers"[Title/Abstract] OR "nanoformulation"[Title/Abstract] OR "nanoparticle-mediated delivery"[Title/Abstract] OR "nanoparticle delivery"[Title/Abstract] OR "nanoparticle-based"[Title/Abstract] OR "nano-immunotherapy"[Title/Abstract] OR "liposomes"[MeSH Terms] OR "liposomal"[Title/Abstract] OR "Drug Delivery Systems"[MeSH Terms] OR "Drug Carriers"[MeSH Terms])	553,680

Figure 2. PubMed Query.

As shown in figure 2, to ensure transparency and reproducibility, the search strategy was systematically developed using a combination of controlled vocabulary (e.g., MeSH terms in PubMed) and free-text keywords. The query integrated three core concept clusters: (1) immune checkpoint inhibitors (e.g., 'PD-1', 'PD-L1', 'CTLA-4'), (2) nanoparticle-based delivery systems (e.g., 'nanoparticle', 'nanocarrier', 'liposome', 'polymeric nanoparticle'), and (3) safety- and toxicity-related outcomes (e.g., 'toxicity', 'immunotoxicity', 'adverse effects', 'cytokine'). Boolean operators (AND/OR) were applied to combine these terms in a structured manner.

The PubMed search string was iteratively refined to balance sensitivity and specificity, following established guidance for systematic review search strategies. The final query retrieved records based on titles and abstracts that were relevant to nanoparticle-mediated immune checkpoint inhibition and associated safety outcomes. These records were subsequently exported and subjected to duplicate removal and multi-stage screening, including title, abstract, and full-text review, in accordance with the predefined eligibility criteria.

Figure 2 shows the search string on PubMed with the research results of the titles and abstracts. The exclusion criteria were applied for the studies which used ICIs without nanoparticle mediation or investigated nanoparticples without immune checkpoint inhibition. Studies were excluded if they used ICIs without nanoparticle mediation, investigated nanoparticles without immune checkpoint inhibition, or reported only therapeutic efficacy outcomes (e.g., tumor shrinkage, survival, or immune response enhancement) without including any safety-related measures such as body weight, histopathology, serum biochemistry, hematology, cytokine-associated toxicity markers, or organ accumulation. Studies on non-solid tumors, review articles, editorials, conference abstracts, and non-peer-reviewed publications were also excluded. Pre-2015 or non-English articles were screened so as not be included in this paper report. In addition, non-peer-reviewed publications were also excluded (Page et al., 2021).

The research result from PubMed is displayed in figure 3.

8	#1 AND #2 AND #3 AND #4 AND #5 AND #6 NOT #7	161
9	Filter: 10 years (2015-2025), English only	160

Figure 3. The PubMed Search Result.

A similar search was conducted in Scopus (Bramer et al., 2017) and the results are presented in figure 4. The findings from the two search engines PubMed and Scopus were then inserted into PRISMA.The records retrieved from PubMed and Scopus were merged and deduplicated before screening. The use of two major bibliographic databases increased coverage of biomedical, pharmacological, and nanomedicine literature; however, the search may still not have captured all relevant studies, especially unpublished work, non-English articles, and studies indexed outside these databases. Therefore, the evidence base should be considered broad but not exhaustive.

Scopus		
Step	Query	Results
1	(TITLE-ABS-KEY (("Immune Checkpoint Inhibitors" OR "checkpoint inhibitors immune" OR "immune checkpoint inhibitor" OR "checkpoint inhibitor immune" OR "immune checkpoint blockers" OR "checkpoint blockers immune" OR "immune checkpoint blockade" OR "checkpoint blockade immune" OR "immune checkpoint inhibition" OR "checkpoint inhibition immune" OR "pd l1 inhibitors" OR "programmed death ligand 1 inhibitors" OR "pd 1 pd l1 blockade" OR "blockade pd 1 pd l1" OR "pd 1 pd l1 blockade" OR "Programmed Cell Death 1 Receptor" OR "pd 1 inhibitors" OR "pd 1 inhibitor" OR "inhibitor pd 1" OR "pd 1 inhibitor" OR "programmed cell death protein 1 inhibitors" OR "CTLA-4 Antigen" OR "CTLA-4" OR "CTLA4" OR "CD152" OR "cytotoxic T-lymphocyte-associated protein 4" OR "anti-CTLA-4" OR "CTLA-4 inhibitor" OR "CTLA-4 blockade" OR "ipilimumab" OR "Ipilimumab" OR "nivolumab" OR "pembrolizumab" OR "atezolizumab" OR "tremelimumab" OR "CTLA-4 Antigen")))	124,314
2	(TITLE-ABS-KEY (("nanoparticles" OR "nanoparticles" OR "nanocarriers" OR "nanoformulation" OR "nanoparticle-mediated delivery" OR "nanoparticle delivery" OR "nanoparticle-based" OR "nano-immunotherapy" OR "liposomes" OR "liposomal" OR "Drug Delivery Systems" OR "Drug Carriers")))	1,327,279
3	(TITLE-ABS-KEY (("toxicity" OR "Drug-Related Side Effects and Adverse Reactions" OR "Toxicity Tests" OR "adverse event" OR "irAE" OR "immunotoxicity" OR "immune-related adverse events" OR "safety" OR "cytokine release" OR "Cytokine Release Syndrome" OR "Complement Activation" OR "complement activation" OR "hypersensitivity" OR "Hypersensitivity" OR "organ accumulation" OR "biocompatibility")))	4,265,219
4	ALL ("Animal Experimentation" OR "Animals" OR "Clinical Trials as Topic" OR "Humans")	43,686,717
5	ALL ("Cells" [All Fields] OR "cell line" [All Fields] OR "In vitro" [All Fields])	3,574,959
6	(TITLE-ABS-KEY (("Neoplasms" OR "cancer")))	5,489,104
7	ALL ("Review" [Title]OR Review[Publication Type]OR Systematic Review[Publication Type]OR Meta-Analysis[Publication Type]OR Editorial[Publication Type]OR Letter[Publication Type]OR Case Reports[Publication Type]OR "News" [Publication Type] OR "Comment" [Publication Type]OR Preprint[Publication Type])	3,826,470
8	#1 AND #2 AND #3 AND #4 AND #5 AND #6 NOT #7	178
9	Filter: 10 years (2015-2025), English only	174

Figure 4. Scopus Search Result.

2.5. Data Extraction

Data were then extracted using a standardized form capturing study characteristics (year, model, tumor type), nanoparticle platform and ICI loading strategy, administration route, dosing, and reported safety outcomes (Haddaway, et al., 2022). We also summarized the distribution of study types, tumor models, and ICI formats to describe the scope of the included evidence rather than to claim epidemiological representativeness. Of the 24 included studies, 23 were preclinical and 1 was clinical. The most frequently studied tumor models included melanoma, hepatocellular carcinoma, breast cancer, and colorectal cancer.

More importantly, data must show safety and toxicity outcomes assessed, immune-related adverse effects, and key safety-related findings. Based on these extraction criteria ensurance, the findings were extracted with study types including *in vivo* & *in vitro* (n = 23) and clinical (n = 1). The findings also show cancer types: HCC (n = 4), Melanoma (n = 5), TNMC (n = 1), colorectal (n = 4), colon cancer (n = 1), lung cancer (n = 2), ovarian cancer (n = 1), gastric carcinoma (n = 1), breast cancer (n = 3), PDAC (n = 2). In addition, the results indicate: ICI types: aPD-L1 (n = 4), aPD-1 (n = 4), PD-L1 siRNA (n = 3), PD-L1 aptamer (n = 2), PD-L1 peptides (n = 4), PD-L1 CRISPR k/o (n = 1), PD-L1 (n = 1), others (n = 4).

3. RESULTS

3.1 Study selection

The database search yielded a total of 49 papers after duplicate removal. Following title and abstract screening, 24 were selected for full-text review. These studies satisfied the inclusion criteria and were included in the final synthesis as in figure 5 (PRISMA Flow Chart).

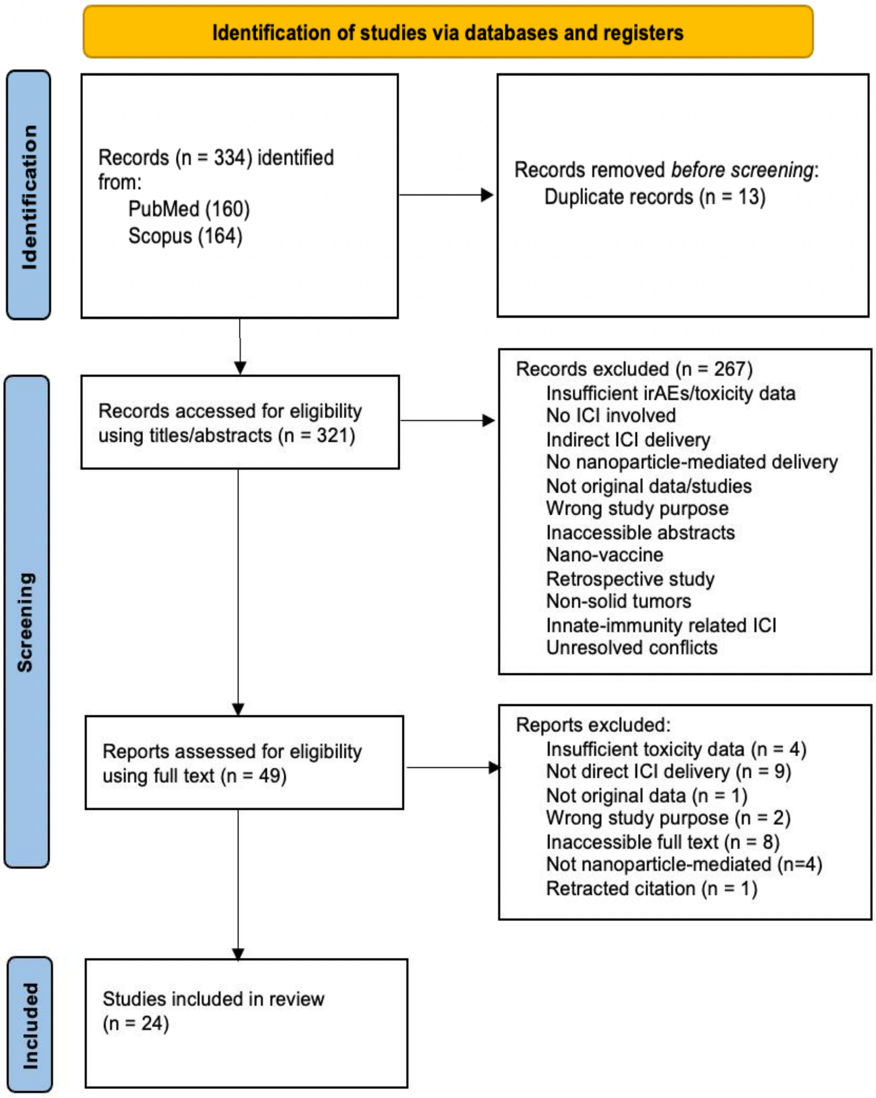

Figure 5. Prisma Flow Chart: Identification of Studies via Databases and Registers.

The database search yielded 49 records after duplicate removal. Following title and abstract screening, 24 studies were selected for full-text review and met the inclusion criteria (Figure 5). Among these included studies, the majority were preclinical animal studies, with only one early-phase clinical study identified. Most studies were published after 2020, reflecting the rapid expansion of nanoparticle-based immunotherapy research in recent years. The most commonly investigated tumor models included melanoma, breast cancer, hepatocellular carcinoma, colorectal cancer, and pancreatic cancer.

The synthesis of the reviewed papers indicates that they comprised preclinical animal models with a small number of early-phase clinical investigations. In addition, most of them were published after 2020 reflecting the rapid expansion of nanoparticle-based immunotherapy research. Common tumor models included melanoma, breast cancer, hepatocellular carcinoma, colorectal cancer, and pancreatic cancer.

3.2. Nanoparticle platforms and ICI loading strategies

Chart 1 presents the findings related to the nanoparticle platforms identified from the papers.

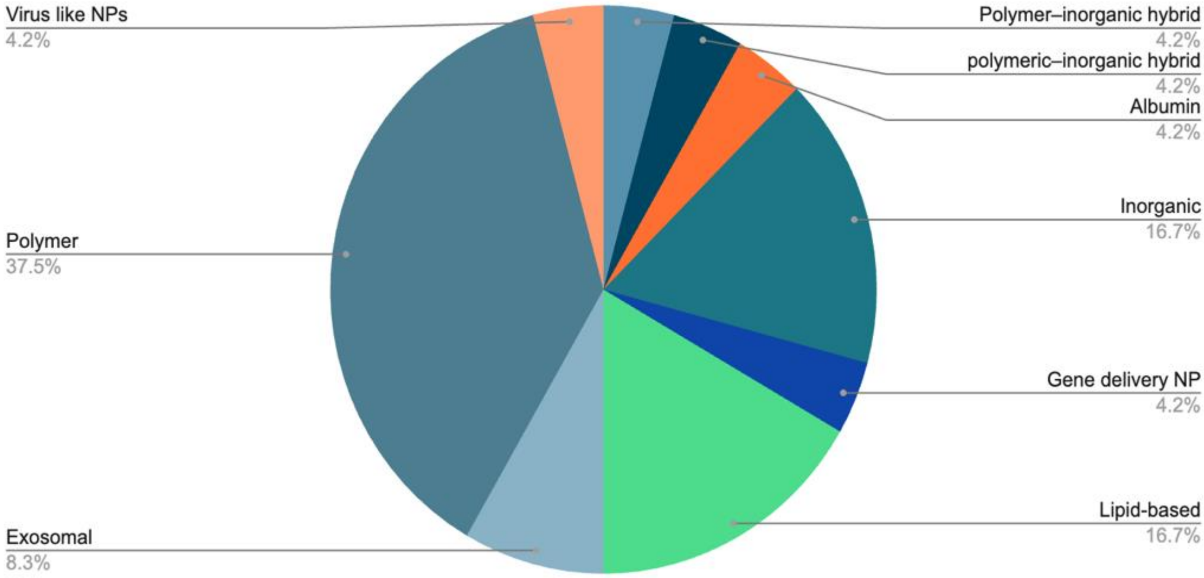

Chart 1. Types of Nanoparticle Platforms.

Chart 1 indicates that polymeric nanoparticles were the most frequently investigated platform in the reviewed paper, at 37.5%. This figure reflects the versatility of polymeric systems which are particularly suitable for ICI delivery. The second most commonly investigated were lipid-based and inorganic ones, each accounting for 16.7%. For example, PD-1-conjugated nanoliposomes co-loading chemotherapeutic agents have been researched for combined chemo-immunotherapy for short-term safety profiles in preclinical liver cancer model (Gu et al., 2022). The exosomal category made up a substantial percentage of the reviewed platform, accounting for 8.3%. Other nanoparticle platforms including virus-like nanoparticles, polymer-inorgnanic hybrid, polymeric-inorganic hybrid, albumin, and gene delivery NP represented a less frequently investigated, each constituting 4.2%. Overall, the statistics in chart 1 suggest a predominance of polymeric and lipid-based nanocarriers in the reviewed papers, consistent with their demonstrated versatility and applicability in nanoparticle-mediated immune checkpoint inhibitor delivery (Moon et al., 2022).

Some ICI loading types are reviewed from the published papers. According to Zhang et al. (2019), GOP@aPD1 nanoparticles combine photothermal therapy with immune checkpoint blockade. Laser-induced vaporization of the nanoparticle core facilitates localized anti-PD1 release, while photothermal effects promote tumor antigen release and immune activation, resulting in enhanced antitumor efficacy. A total of 11 studies (45.8%) in this category were included in the reviewed paper. In the included studies, ICIs were associated with nanoparticle surfaces through different mechanisms depending on platform design, including covalent conjugation, linker-mediated attachment, physical adsorption, or ligand functionalization (Pham et al., 2021).

Albumin-based nanoparticle platform used for ICI delivery was also present in nine out of 24 studies reviewed (37.5%). For example, Pham et al. (2021) illustrated paclitaxel-loaded human serum albumin nanoparticles (PTX@HSA) which were functionalized with PD-L1-targeting ligands (PD-L1-PLL), resulting in a dual-function nanoplatform that combines chemotherapeutic delivery with immune checkpoint blockade. This surface modification strategy enables targeted interaction with PD-L1-expressing tumor cells while simultaneously facilitating localized drug release. Pham et al. (2021) developed PD-L1/PTX@HSA nanoparticles by conjugating PD-L1-targeting poly-L-lysine to paclitaxel-loaded human serum albumin nanoparticles. This strategy integrates chemotherapy and immune checkpoint targeting within a single nanocarrier, potentially enhancing tumor-selective delivery and antitumor efficacy.

A representative gene delivery strategy was reported by Sun et al. (2024), who developed siRNA-CaP@PD1-NVs. The platform integrates calcium phosphate-mediated siRNA delivery with PD1-functionalized nanovesicles, thereby combining gene therapy and immune checkpoint modulation within a single nanoparticle system. In this system, small interfering RNA (siRNA) is encapsulated within a calcium phosphate core, providing protection against enzymatic degradation and enabling controlled intracellular release. The nanoparticle surface is further functionalized to target the PD-1 pathway, facilitating selective interaction with immune cells.

3.3. Safety and Toxicological Outcomes

Some themes related to safety and toxicological outcomes emerged from the reviewed papers including body weight monitoring, hematological and serum biochemical parameters, histopathological examination of major organs, cytokine profiling, and assessment of immune cell activation. Table 1 presents the finding for this topic.

As shown in table 1, the 24 studies included in the systematic review indicate that the nanoparticle-mediated ICI therapies reveal short-term evaluations and that most studies reported preserved organ architecture and absence of severe immune-related adverse events. Body weight (22, 91%) was the most frequently assessed parameter in the total of the 24 studies Most studies (21) reported stable body weight throughout the treatment period and only one reported a mild increase. These findings suggest the absence of overt systemic toxicity. For example, Zhu et al. (2024) reported minimal systemic toxicity and preserved organ histology, which indicates the safety advantages of localized immunotherapeutic delivery strategies.

Among the 21 studies on histopathology (H&E staining), 17 (81%) showed no organ damage. This finding indicates preserved tissue architecture across major organs such as the liver, spleen, kidneys, lungs, and heart during the treatment period. Two (9.5%) reported clear toxicity and the remaining showed mild alterations.

Table 1. Safety and Toxicological Parameters across the Reviewed Studies

Parameter	Studies Evaluated (n=24)	Key Findings
Body Weight (BW)	22 (91%)	Most studies reported stable body weight; one reported a mild increase.
Histopathology (H&E staining)	21 (87.5%)	17 (81%) showed no organ damage; 2 (9.5%) reported clear toxicity; remaining showed mild alterations.
Serum Biochemistry	15 (62.5%)	~73% normal liver/kidney profiles; 2 elevated ALT/AST; isolated cases of reduced AST/ALT or bilirubin/BUN.
Cytokine Profile	18 (75%)	Commonly reported IL-6 (4.2%), TNF-α (54.2%), IFN-γ (66.7%) upregulation.
Organ Accumulation	9 (37.5%)	Predominant liver and spleen localization; partial tumor accumulation.
Hematology profile	5 (20.8%)	No hemolysis or red blood cell abnormalities observed.

Serum biochemistry was investigated in 15 studies (62.5%). Approximately 73% of these studies reported normal biochemical profiles, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and blood urea nitrogen (BUN) levels. Nonetheless, isolated cases of elevated ALT/AST were reported in two studies. Besides, sporadic reductions in AST/ALT or bilirubin/BUN were observed in a small number of cases. Table 1 also shows that 18 (75%) focused on cytokine profile with the most commonly reported was IFN-γ (66.7%) upregulation followed by TNF-α (54.2%) and the least was IL-6 (4.2%). The finding suggests that the cytokine pattern is consistent with localized immune activation associated with immune checkpoint blockade. The finding also indicates the relatively low incidence of IL-6 elevation. In the included studies, IL-6 elevation was reported less frequently than changes in IFN-γ or TNF-α. However, this pattern should be interpreted cautiously because cytokine panels were not assessed consistently across studies.

Some studies (9, 37.5%) investigated organ accumulation with the result showing predominant liver and spleen localization. Partial accumulation within tumor tissues was also reported, supporting the tumor-targeting potential of these nanocarriers. The lowest number belongs to hematology profile with five studies (20.8%), reporting no hemolysis or red blood cell abnormalities observed.

Overall, the 24 reviewed studies reveal that the majority of the nanoparticle-mediated ICI therapies demonstrate a short-term safety profile, there were inconsistencies in safety endpoint selections and limited cross-study comparison.

3.4. Risk of Bias Assessment

The review also considers the risk of bias assessment using Systematic Review Centre for Laboratory animal Experimentation (SYRCLE)'s tools. It was found that some studies had unclear or high risk of bias in such domains as randomization, blinding, and allocation concealment as shown in chart 2.

Chart 2 reveals that average overall methodological quality in the included animal studies. More specifically, sequence generation and selective outcome reporting were assessed as low risk of bias in 100% studies, which indicates appropriate randomization and reporting practices. Besides, allocation concealment and random outcome assessment were rated as low risk in the about 80-85% of the studies. The remaining studies were classified as having unclear risk due to insufficient reporting.

However, as shown in chart 2, other domains including random housing, blinding of caregivers, and blinding of outcome assessors were rated as having unclear risk of bias in nearly 100% studies. Furthermore, incomplete outcome data reveals a low risk profile at about 95%. Other sources of bias were considered as low risk in approximately 75% of studies.

In general, the key domains related to randomization and reporting were well addressed in the reviewed studies but uncertainty in blinding and housing procedures need more consideration in interpreting safety outcomes.

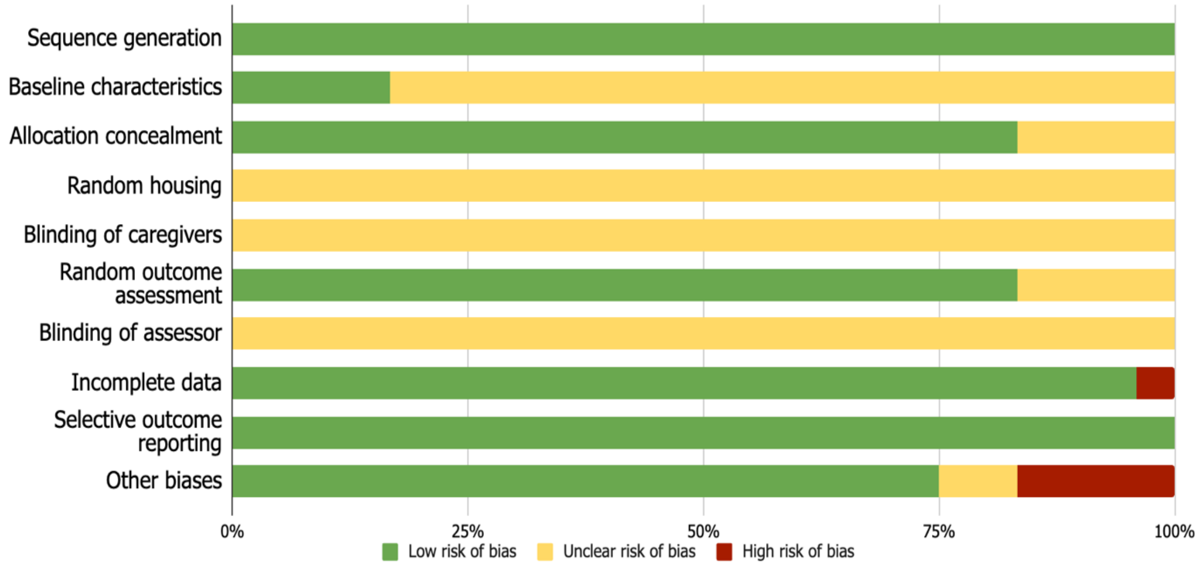

Chart 2. Risk of Bias Assessment.

4. DISCUSSION

This systematic review synthesized 24 studies investigating the safety and toxicity profiles of nanoparticle-mediated ICI therapies. Overall, the findings suggest that nanoparticle-based delivery systems can enhance the safefy profile of ICIs by promoting localized immune activation while reducing systemic exposure (Su et al., 2021).

4.1. Overall safety profile of nanoparticle-mediated ICI therapy

The majority of the reviewed studies reported stable body weight, preserved organ histology, and largely normal serum biochemical parameters after nanoparticle-mediated ICI treatment (e.g. Allen et al., 2021; Lai et al., 2023; Lo et al., 2024; Moon et al., 2022; Sun et al., 2024; Wang et al., 2024; Yen et al., 2025). This finding suggests that the therapy can reduce off-target immune activation by improving tumor-localized delivery and limiting systemic exposure. Besides, most studies reported no detectable organ damage or only mild alterations in livers, spleens, kidneys, lungs or hearts (see Su et al., 2021; Zhang et al., 2023 for example).

Other studies explored more complex platforms, for examples, biomimetic nanocarriers, virus-like nanoparticles, metal-organic frameworks, and hybrid polymer-inorganic systems less frequently and reported promising safety profiles preclinically (Liang et al., 2024; Ordikhani et al., 2018; Sergent et al., 2024; Zhang et al., 2023). Furthermore, gene delivery-based nanoparticle systems such as siRNA-loaded nanovesicles targeting immune checkpoint pathways promoted precise immune modulation with minimal acute toxicity despite their long-term safey insufficiently reported (e.g. Du et al., 2024; Liu et al., 2023; Yang et al., 2021).

4.2. Influence of nanoparticle platform on safety outcomes

One theme that emerged from the review was the predominance of polymeric nanoparticle indicating their structural versatility, tunable degradation kinetics, and favourable safety profiles as in the studies Allen et al., (2021), Pham et al., (2021), Su et al. (2021) and Zhang et al. (2023). More complex platforms such as biomimetic nanocarriers, virus-like nanoparticles, metal-organic frameworks and hybrid polymer-inorganic systems were less frequently studied but reported more promising safety outcomes in preclinical settings as in the studies by Liang et al. (2024) Ordikhani et al. (2018), and Sergent et al. (2024). Gene delivery-based nanoparticle systems such as siRNA-loaded nanovesicles targeting immune checkpoints enabled precise immune modulation with minimal acute toxicity but their long-term safety was not sufficiently reported (e.g. Liu et al., 2023; Du et al., 2024, Yang et al., 2021).

4.3. Immune activation and cytokine responses

Among the reviewed studies, the findings also indicate cytokine profiling revealing controlled immune activation from frequent upregulation of IFN-γ and TNF-α which are consistent with effective immune checkpoint blockade while systemic inflammatory markers such as IL-6 were less commonly elevated as reported in the studies by Moon et al. (2022), Sun et al. (2024), Xiao et al. (2023), Yin et al. (2025), and Zhang et al. (2019). The findings suggest that nanoparticle-mediated delivery may enhance antitumor immunity. However, there was limited cross-study comparability. Besides, few studies explored chronic immune activation, autoimmunity markers, or delayed toxicity.

4.4. Organ accumulation and biodistribution considerations.

Some of the studies (e.g. Allen et al., 2021; Sun et al., 2024; Zhang et al., 2019; Yin et al., 2025) reported predominant accumulation of nanoparticles in livers and spleens due to uptake by the reticuloendothelial system but did not translate into overt hepatosplenic toxicity in short-term studies. Other studies found partial tumor accumulation, indicating nanoparticle-enabled tumor targeting (e.g. Moon et al., 2022; Pham et al., 2021; Wang et al., 2024; Zhao et al., 2025).

4.5. Methodological quality and risk of bias implications

The SYRCLE risk-of-bias assessment reveal methodological quality regarding sequence generation and selective outcome reporting across most reviewed studies. However, blinding of caregivers and outcome assessors as well as random housing were considered to be insufficient reporting (Ordikhani et al., 2018; Pham et al., 2021; Liang et al., 2024). These limitations may lead to an overestimation of safety outcomes and suggest the need for improved methodological transparency in preclinical nanomedicine research.

5. CONCLUSION

The systematic review of the 24 papers indicates that nanoparticle-based delivery systems can enhance the safety profile of ICIs due to promoting localized immune activation. The findings provide evidence of short-term safety of nanoparticle mediated ICI therapy but suggests some knowledge gaps that must be addressed to ensure effective and safe clinical application.

The review of the studies reveal several important gaps. First, the majority of evidence is derived from short-term murine models; thus, long-term immunotoxicity, chronic immune activation, and nanoparticle biodegradation need further investigation. Second, cross-study comparison of dosing regimens, and safety endpoints was limited in the reviewed studies, suggesting a knowledge gap. Since the methodological limitations across the preclinical studies exist, reported safety outcomes should be interpreted with caution.

The systematic review contributes valuable insights into the focus on safety and toxicity of nanoparticle-mediated ICI therapy, an area that has received comparatively less attention than therapeutic efficacy. The standardized screening and formal risk of bias assessment further enhances the methodological rigor of the paper. However, the review relies on preclinical studies, which limits generalizability to clinical settings, and publication bias toward positive safety outcomes cannot be overlooked.

In conclusion, nanoparticle-mediated delivery of ICIs demonstrate encouraging short-term safety and biocompatibility in preclinical and early-phase studies. Future studies should delve into the topics of harmonized safety reporting, and expanded clinical evaluation to ensure the safe implementation of these advanced immunotherapeutic strategies.

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Phân phối chất ức chế điểm kiểm soát miễn dịch dựa trên hạt Nano: Tổng quan hệ thống về độ an toàn và độc tính miễn dịch

Lê Phước Thục Uyên, Võ Phước Bảo Trân

Trường Đại học DePauw

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Tác giả liên hệ:
Lê Phước Thục Uyên
Địa chỉ e-mail:
uyenle_2027@depauw.edu

TÓM TẮT

Bối cảnh: Các chất ức chế điểm kiểm soát miễn dịch (ICIs) ngày càng được sử dụng rộng rãi trong điều trị ung thư, nhưng đã được ghi nhận là gây ra các tác dụng bất lợi liên quan đến miễn dịch do sự hoạt hóa miễn dịch không đặc hiệu. Các hệ thống phân phối dựa trên hạt nano đã được đề xuất như một chiến lược nhằm cải thiện khả năng hướng đích khối u và giảm độc tính toàn thân; tuy nhiên, hồ sơ an toàn và độc tính miễn dịch của chúng vẫn chưa được tổng hợp một cách toàn diện.
Phương pháp: Nghiên cứu này thực hiện tổng quan hệ thống theo hướng dẫn PRISMA. Hai cơ sở dữ liệu PubMed và Scopus được tìm kiếm đối với các bài báo được công bố từ năm 2015 trở đi liên quan đến việc ứng dụng hệ thống phân phối qua trung gian hạt nano của các chất ức chế PD-1, PD-L1 hoặc CTLA-4 trong các khối u đặc. Tiêu chí lựa chọn được áp dụng cho các nghiên cứu tiền lâm sàng và các thử nghiệm lâm sàng giai đoạn sớm có báo cáo về độ an toàn, độc tính hoặc các kết quả liên quan đến miễn dịch. Dữ liệu về các nền tảng hạt nano, các thông số an toàn và chất lượng phương pháp luận được trích xuất, đồng thời nguy cơ sai lệch được đánh giá bằng công cụ SYRCLE.
Kết quả: Trong số 24 nghiên cứu đáp ứng tiêu chí lựa chọn, phần lớn là các nghiên cứu tiền lâm sàng trên động vật. Hạt nano polymer là nền tảng được nghiên cứu phổ biến nhất, tiếp theo là các hệ thống dựa trên lipid, vô cơ, albumin và hệ thống vận chuyển gen. Hầu hết các nghiên cứu ghi nhận cân nặng cơ thể ổn định, mô học cơ quan được bảo tồn và các chỉ số sinh hóa huyết thanh nhìn chung ở mức bình thường. Phân tích cytokine thường ghi nhận sự thay đổi của IFN-γ, TNF-α và ít thường xuyên hơn là IL-6, cho thấy việc phân phối ICI qua trung gian hạt nano có thể gây hoạt hóa miễn dịch, trong khi chỉ có bằng chứng hạn chế về độc tính viêm toàn thân cấp tính trong các nghiên cứu ngắn hạn được đưa vào. Đánh giá nguy cơ sai lệch cho thấy có sự ngẫu nhiên hóa và báo cáo kết quả tương đối đầy đủ, nhưng thường thiếu rõ ràng về quy trình làm mù và điều kiện nuôi giữ.
Kết luận: Các liệu pháp qua trung gian hạt nano cho thấy hồ sơ an toàn ngắn hạn đầy hứa hẹn. Tuy nhiên, độc tính miễn dịch dài hạn, sự tồn lưu của hạt nano và khả năng chuyển giao sang lâm sàng vẫn chưa được giải quyết đầy đủ, cho thấy cần có các tiêu chuẩn báo cáo an toàn thống nhất và mở rộng đánh giá lâm sàng.