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# Heterogeneity and efficacy of immunotherapy in multiple cancer: insights from a meta-analysis

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## Abstract

**Background** Immunotherapy has been recognized as a significant advancement in cancer treatment by promoting the body's immune system to identify and eliminate cancer cells more effectively. Unlike conventional therapies, immunotherapy can enhance the natural capabilities of human immune system. Chimeric Antigen Receptor T-cell (CAR-T) therapy involves genetical-modified T-cells from patients to better catch and attack cancer cells. Up to date, CAR-T therapy has shown particular promise in treating certain types of leukemia and lymphoma, highlighting the transformative potential of immunotherapy.

**Results** Literature data search using PubMed, CNKI, and Wanfang were searched to collect eligible studies up to January 2025. The primary outcomes of complete response rate (CRR), objective response rate (ORR), dead rate (DR), and other adverse reactions were evaluated. Secondary outcomes (CRR, ORR, and DR) of subgroup analysis from different cancer types, origins, and outcomes for survival rate were analyzed for our final results. A total of 649 studies were initially identified through database searching. After removing duplicates and non-clinical cancer studies, 32 eligible studies were included in this work. The pooled data included 819 patients for objective response rate (ORR), 843 patients for complete response rate (CRR), and 868 patients for dead event. In the included studies, 24 reported ORR data, revealing an objective response rate of 84.86% (695/819) with little heterogeneity (OR: 0.87, 95% CI 0.80–0.91, $P = < 0.01$, $I^2 = 61\%$); 24 studies showed a CRR of 65.30% (491/843) with significant heterogeneity (OR: 0.58, 95% CI: 0.43–0.72, $P < 0.01$, $I^2 = 84\%$); 27 studies showed a mortality rate of 23.73% (206/868) with significant heterogeneity (OR: 0.19, 95% CI: 0.11–0.32, $P < 0.01$, $I^2 = 77\%$). Subgroup analysis based on cancer type revealed that ORR was higher in multiple myeloma (86.77%, 400/461) compared with leukemia (84.92%, 259/305) and lymphoma (67.92%, 36/53). In parallel, heterogeneity observed based on case origins suggested that Chinese cases showed significantly higher ORR, CRR, and survival rates compared with American ones.

**Conclusions** This meta-analysis provides valuable insights into the potential of immunotherapy, particularly CAR-T, in cancer treatment. Findings showed the different efficacy and safety of immunotherapy in treating multiple cancers,

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with various objective response rates. Continued studies from more trials with different populations are needed to optimize their efficacy in further cancer treatment and precision medicine.

**Keywords** Hematological malignancies, Clinical outcomes, Response rate, Different population

## Introduction

Cancer is a multi-factorial disorder that poses a high risk to global health [37]. Despite significant developments in revealing cancer biology and related therapeutics, such as chemotherapy and radiation therapy, achieving long-term management from different types of cancer remains elusive [33]. Cancer immunotherapy has emerged as a transformative strategy that can enhance the human immune system to recognize and eliminate malignant cells efficiently [65]. By promoting the intrinsic immune system of humans, immunotherapy offers a promising avenue for improving patient outcomes [47]. Unlike conventional therapies which directly target and destroy cancer cells although at the cost of damaging healthy tissues, immunotherapy prefers to enhance the natural capabilities of the immune system, thus providing a more targeted and potentially less toxic treatment option for most cancer individuals [22, 48].

The development of immunotherapy has been improved by a deeper understanding of the role of immune system plays in cancer surveillance and eradication. Cancer cells have evolved adaptive strategies to "run away" from immune detection, including the expression of immune checkpoint proteins that inhibit T-cell activation. Immune checkpoint inhibitors, such as pembrolizumab (Keytruda) and nivolumab (Opdivo), have been designed to block these inhibitory signals, thus restoring the ability of the immune system to recognize and attack cancer cells [23, 44]. These inhibitors show remarkable efficacy in multiple cancers, for instance, melanoma, non-small cell lung cancer, and renal cell carcinoma, and have fundamentally altered the treatment paradigm for these diseases. Furthermore, immunotherapy can be uses as monoclonal antibodies, which laboratory-engineered and can specifically bind to antigens present on the surface of cancer cells, marking them for destruction by the immune system [21]. Monoclonal antibodies can also be conjugated with cytotoxic agents, directing these toxins precisely to cancer cells and sparing healthy tissues from collateral damage. Rituximab, trastuzumab, and bevacizumab are notable examples of monoclonal antibodies that have significantly improved the prognosis for patients with lymphomas, breast cancer, and colorectal cancer, respectively [12, 21].

Chimeric Antigen Receptor T-cell (CAR-T) therapy nowadays is one of the most personalized and innovative forms of immunotherapy [9, 50]. This technique involves the extraction and genetic modification of T-cells from patients to express chimeric antigen receptors that can be specifically designed to target cancer cells. Once CAT-T re-introduced into the patients, these engineered T-cells can target and lill cancer cells with high specificity and potency. CAR-T therapy has shown particularly promising efficacy in hematologic malignancies such as acute lymphoblastic leukemia and diffuse large B-cell lymphoma, leading to durable remissions in patients who have exhausted other treatment options [50]. However, not all patients respond to these treatments efficiently, and even worse, some can experience severe immune-related adverse effects [7, 35]. Most studies so far are focusing on the mechanisms underlying these responses and developing strategies to predict and enhance patient outcomes by CAR-T treatment. Moreover, combining immunotherapy with other strategies for cancer treatments show potentials to improve the integrative therapeutic efficacy for cancer cells elimination [2, 6, 19, 61].

These endeavors underscore the clinic potentials of immunotherapy to establish precise and lasting immune reactions against cancer. Nonetheless, an investigation and consolidation of existing studies and cases are important and valuable to gain comprehensive insights into the status of the present immunotherapy cases. Therefore, this meta-analysis aims to assess the collective outcomes of immunotherapy, particularly CAR-T, across diverse cancer types. Based on studies search and investigation, we try to reveal trends and patterns that may drive future research directions, facilitating the refinement and optimization of its application in cancer treatment.

## Materials and methods

### Literature search

The Protocol has been registered on the PROSPERO (CRD4202347646) (https://www.crd.york.ac.uk-/prospero, Supplementary Material 1). The meta-analysis was performed according to the PRISMA guideline. Trials were collected from PubMed (https://pubmed.ncbi.nlm.nih.gov/), CNKI (China National Knowledge, https://www.cnki.net/), and Wanfang database (https://www.wanfangdata.com.cn/) up to January 1, 2025. The search terms included "CAR-T", "Vector", "Tumor", and "Immunotherapy".

### Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Randomized controlled trials (RCTs), single-arm clinical trials, and retrospective studies; (2) Diagnosis of malignant tumor; (3) Intervention of CAR-T therapy based on vector modification; (4) The primary efficacy outcome of this study was defined as complete response rate (CRR), objective response rate (ORR), dead rate (DR), and secondary outcomes were the occurrence and severity of adverse events, including cytopenia, neurologic events, cytokine release syndrome: grade3.

The exclusion criteria were as follows: (1) Untreated with immunotherapy; (2) Duplicate studies and incomplete/inconsistent outcomes; (3) case reports, review, letter and other unsuitable types; (4) references with low impact (IF < 10).

### Data extraction and quality assessment

Two reviewers, QZ and XJZ, independently conducted literature searches and autonomously organized valuable clinical data. They utilized the revised version of MINORS (Methodological Index for Nonrandomized Studies, Supplementary Table 1) as their guide for assessing the quality of observational or non-randomized studies [45]. In cases of inconsistencies between the aforementioned two reviewers, a third reviewer, JM, provided resolution.

The relevant clinical data has been presented in Table 1, including baseline information such as sex, country, age, phase, and tumor type. These tables further outline primary outcomes, including ORR and CRR. For additional details, please refer to Supplementary Table 2.

### Statistical analysis

R (v4.3.0) was used to analyze the statistical data, and it was evaluated by relative risks, CRR, ORR, and multiple adverse reactions with 95% confidence intervals. Random-effects models were used to analyze the data. Publication bias was assessed by the funnel plots. Survival (v3.5.5), while Survminer (v0.4.9) were used to calculate survival analysis and these outcomes. We conducted a causal analysis of the factors by CausalNex (v0.12.1), which is a Python library that uses Bayesian networks to combine machine learning and domain expertise for causal reasoning. More details can be found in the Supplementary Material 2. To investigate the impact of CAR-T on survival rate, we collected survival data from current literature, of which a total of 16/28 was obtained with 6 eligible studies extracted by figures (https://apps.automeris.io/wpd/). Variables based on months were uniformly converted to days (days = month × 30).

### Heterogeneity analysis

To analyze heterogeneity among the studies involving case-origin data, we used the "metaprop" function from the R package "meta" (v6.5.0),a user-friendly general package providing standard methods for meta-analysis. This function is specifically designed for meta-analyses of proportions, which is suitable for our data on the efficacy and safety outcomes of immunotherapies.

We utilized the DerSimonian-Laird method for estimating between-study variance, which is particularly effective in handling the inherent variability in meta-analytic data of this type. The $I^2$ statistic and Cochran's Q test, which are integral to "metaprop", were performed to assess the degree of heterogeneity among the included studies. An $I^2$ value greater than 75% indicates significant heterogeneity.

## Results

### Study selection

A total of 649 studies were screened out in this work based on database searching. After removing the references with low impact ($N$ = 159, Impact factor < 10) and non-lentiviral cancer ($N$ = 274), 32 eligible studies were selected in total, including hematologic malignancies: myeloma (Case = 410), lymphoma (Case = 81), and leukemia (Case = 461); and solid tumors (Case = 26), (Fig. 1).

### Quality assessment

There were 11 randomized controlled trials reporting standardized oncological endpoints including progression-free survival (PFS) and overall survival (OS). 6 studies did not report inclusion criteria or reported high rates of lost-to-follow-up. 16 studies enrolled 50 or fewer patients (median 18, [range 3–35] patients) (Supplementary Table 1). Most of the single-arm studies enrolled only a small sample size of patients that may be insufficient power to detect significant treatment effects. Most non-randomized studies did not report adequate information, making it difficult to assess study quality using the Chambers checklist [5].

### Effect size estimates

The 24 studies reported the clinical data of ORR, which was found in 695/819 (84.86%) patients (OR: 0.87, 95% CI 0.80–0.91, $P$ = < 0.01, I2 = 61%, Fig. 2A) with the random-effects model and little heterogeneity. CRR was reported from 24 studies and found in 491/843 (65.30%) patients (OR: 0.58, 95% CI: 0.43–0.72, $P$ < 0.01, I2 = 84%, Fig. 2B) with the random-effects model and significant heterogeneity. Dead event was found in 27 studies with 206/868 (23.73%) patients (OR:0.19,

**Table 1** Primary information of study cases

| Study | Case | Vector | Age (Median) | Phase | F/M | Type Tumor |
|---|---|---|---|---|---|---|
| **Mailankody S 2022** [30] | 17 | GPRC5D CAR | 60 (38–76) | 1 | 4/13 | Myeloma |
| **Raje N 2019** [42] | 33 | anti-BCMA CAR | 60 (37–75) | 1 | 13/20 | Relapsed or Refractory Multiple Myeloma |
| **Mei H 2021** [32] | 23 | pLVX-EF1 | 59 (49–72) | 1 | 12/11 | Relapsed or refractory multiple myeloma |
| **Wang Z 2021** [56] | 15 | P4 CAR | 59 (35–70) | 1 | 7/8 | Esothelin-positive solid tumors |
| ***Blumenschein GR 2022*** [3] | 11 | MAGE-A10 | 61 (46–72) | 1 | 5/6 | Non-small cell lung cancer |
| ***Shi X 2022*** [43] | 10 | anti-CD19 scFV[a] | 54 (39–65) | 1 | 3/7 | High-risk multiple myeloma |
| ***Qu X 2022*** [41] | 31 | anti-BCMA | 61 (45–74) | 1 | 15/16 | Relapsed/refractory multiple myeloma |
| ***Wang Y 2022*** [54] | 62 | anti-BCMA scFV[b] | 58 (30–69) | 2 | 28/34 | Multiple Myeloma |
| **Zhao WH 2022** [66] | 74 | LCAR-B38M | 54.5 (27–74) | 1 | 29/45 | Relapsed or refractory multiple myeloma |
| ***Wang CM 2017*** [52] | 18 | CAR.30-CD137ζ | 33 (13–77) | 1 | 5/13 | Relapsed or Refractory Hodgkin Lymphoma |
| ***Yan ZX 2019*** [63] | 10 | anti-CD19 JWCAR029 | 47 (32–59) | 1 | 2/8 | Refractory B-Cell Non-Hodgkin's Lymphoma |
| ***Xia J 2023*** [58] | 33 | YKGPRC5D BB- 002 | 58 (39–70) | 2 | 15/18 | Relapsed/refractory multiple myeloma |
| **Yan Z 2019** [62] | 21 | anti-BCMA and anti-CD19 | NA (18–69) | 2 | NA | Relapsed/refractory multiple myeloma |
| **Bao Y 2023** [1] | 72 | BCMA CAR-T | 55 (38–75) | NA | 26/46 | Relapsed/refractory multiple myeloma |
| **Wang Q 2020** [53] | 18 | anti-BCMA | 55 (42–65) | NA | 11/7 | Relapsed/refractory multiple myeloma |
| **Xue Y 2023** [59] | 12 | scFv/CD19/4- 1BB/CD3ζ | 54 (23–69) | NA | 4/8 | Diffuse large B-cell lymphoma |
| ***Qi Y 2022*** [40] | 48 | CD19 or CD22 CAR | 31 (6–68) | NA | 18/30 | B-cell acute lymphoblastic leukemia patients with CNSL |
| ***Jin X 2022*** [17] | 10 | pCDH-MND-MCS-T2 A-Puro | 43.5 (18–73) | 1 | 6/4 | Relapsed/refractory acute myeloid leukemia |
| ***Yang J 2022*** [60] | 25 | CD19 + CAR | 20 (3–44) | 1 | 12/13 | B-cell acute lymphoblastic leukemia |
| ***Liu S 2021*** [28] | 27 | CD19 and CD22 | 21 (1.6–55) | 1 | 13/14 | Elapsed B-cell acute lymphoblastic leukemia |
| ***Lu P 2022*** [29] | 20 | CD7 CAR-T | 22 (3–47) | 1 | 6/14 | T lymphoblastic leukemia/lymphoma |
| ***Gu R 2020*** [13] | 20 | pCDH-HI19α– 4- 1BB/CD3ζ-CAR | 18 (3–52) | NA | 8/12 | Relapsed or refractory acute lymphoblastic leukemia |
| ***Pan J 2021*** [38] | 20 | CD7 CAR | 11 (2–43) | 1 | 5/15 | T-Cell Acute Lymphoblastic Leukemia |
| ***Zhang H 2021*** [64] | 4 | 4SCAR-CLL1 | 8.4 (7.3–9.6) | 1,2 | 2/2 | Relapsed/Refractory Acute Myeloid Leukemia |
| ***Frey NV 2020*** [11] | 35 | anti-CD19 | 34 (21–70) | 1 | 11/24 | Acute Lymphoblastic Leukemia |
| ***Tambaro FP 2021*** [46] | 3 | LV-CD33-CAR | 19 (18–38) | 1 | 1/2 | Relapsed/refractory acute myelogenous leukemia |
| ***Jiang H 2019*** [16] | 58 | CD19 | 28 (10–65) | NA | 27/31 | Relapsed/refractory B-cell acute lymphoblastic leukemia |
| ***Li C 2021*** [25] | 30 | PLVX-BCMA- 01 | 55 (34–65) | 1 | 13/17 | Elapsed/refractory multiple myeloma and plasma cell leukemia |
| ***Lin Y 2023*** [26] | 67 | anti-BCMA CAR | 61 (37–75) | 1 | 25/42 | relapsed and refractory multiple myeloma |
| ***Brudno JN 2024*** [4] | 21 | LSIN- 5 F11 - 28Z | 33 (18–64) | 1 | 6/15 | CD30 + lymphomas |
| ***Pan J 2023*** [39] | 81 | CD19 or CD22 CAR | NA | 2 | 30/51 | childhood refractory or relapsed B-cell acute lymphocytic leukaemia |
| ***Liang EC 2023*** [24] | 49 | CD19-scFV | 61 (55–67) | 1,2 | 16/33 | relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) |
| ***Total 32*** | **978** | | | | **378/579** | |

Age: median year (range), Sex: (Female/Male), total case 978. Sex is 301/438, NA refers to Not Available

[a] anti-CD19 scFV/4- 1BB/CD3-ζ/IL4 shRNA and anti-BCMA scFV/CD3-ζ/CD28/OX40

[b] anti-BCMA scFV/4- 1BB/CD3-ζ and anti-CD19 scFV/4- 1BB/CD3-ζ

95% CI: 0.11–0.32, $P < 0.01$, I2 = 77%, Fig. 2C) with the random-effects model and significant heterogeneity.

### Primary outcomes (CRR, ORR, DR)

Twenty-four studies reported the clinical data of ORR in multiple myeloma, lymphoma, and leukemia cancer. ORR showed higher in the multiple myeloma cancer (410/461, 88.94%) than leukemia cancer (259/305, 84.92%) and lymphoma (36/53, 67.92%) in the random-effects model with heterogeneity (OR: 0.87, 95% CI: 0.80–0.91, $P < 0.01$, $I^2 = 61\%$, $x_2^2 = 1.55$, $P = 0.46$, df = 2, Fig. 3A). 27 studies reported the clinical data of CRR for multiple myeloma,

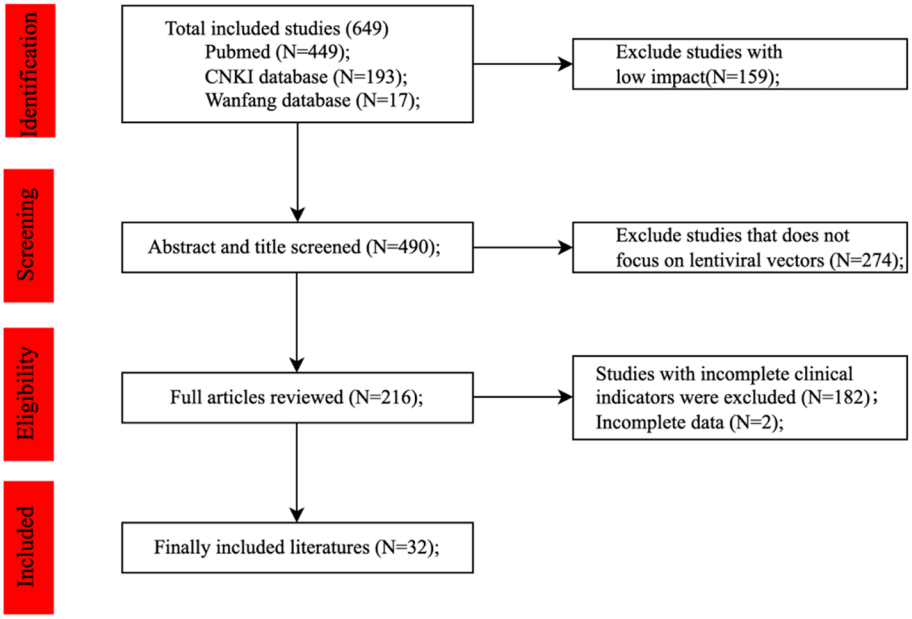



**Fig. 1** Flow diagram of the literature search and database selection

lymphoma, and leukemia cancer. CRR in leukemia was higher than it in multiple myeloma and lymphoma cancer with the random-effects model with significant heterogeneity (OR: 0.58, 95% CI: 0.42–0.73, $P < 0.01$, $I^2 = 84\%$, $x_2^2 = 9.63$, $P < 0.01$, df = 2, Fig. 3B). In parallel, CRR was lower in lymphoma cancer (11/53, 20.75%). 27 studies reported the clinical data of dead event for multiple myeloma, solid, lymphoma, and leukemia cancer. Dead rate showed significantly lower in lymphoma cancer (4/60, 6.67%) than multiple myeloma(71/372, 19.09%), leukemia (114/410, 27.80%), and solid(17/26, 65.38%) cancers (Supplementary Table 5), in the random-effects model with significant heterogeneity (OR: 0.19, 95% CI: 0.11–0.32, $P < 0.01$, $I^2 = 77\%$, $x_2^2 = 19.14$, $P < 0.01$, df = 3, Fig. 3C).

### Secondary outcomes and subgroup analysis

The secondary outcomes include Cytopenia details, specifically Neutropenia (NE), Anemia (AN), and Thrombocytopenia (TH), as well as the occurrence of Grade 3 or higher Cytokine Release Syndrome (G3) and Neurologic Events (NEU) (Table 2). Regarding cytopenia details, the occurrence of NE ranged from 33 to 100%, with an average of 94.76%. The occurrence of AN ranged from 29.70% to 100%, with an average of 74.45%. The occurrence of TH ranged from 41.90% to 100%, with an average of 65.62%. The occurrence of Grade 3 or higher Cytokine Release Syndrome (G3) ranged from 0 to 83%, with an average of 20.35%. The occurrence of Neurologic Events (NEU) ranged from 0 to 40%, with an average of 13.03%. These results highlight the heterogeneity in treatment outcomes and side effects across the studies, indicating the need for further investigation and potentially individualized approaches to immunotherapy treatment.

Substantial heterogeneity was observed within certain subgroups of the analysis, with 35 out of 71 subgroups showing heterogeneity measures above 50%. Based on subgroup analyses by different case origins (Supplementary Table 4), we found significant heterogeneity in our pooled data ($I^2 = 80\%$). The ORR and CRR in the Chinese cases showed significantly higher than it in American ones (Fig. 4A & B) (Data for American cases was collected from the United States). Moreover, a statistically significant correlation was found in the America (OR = 0.25, 95% CI 0.08–0.57, $P < 0.01$, $I^2 = 82\%$), the correlation also was significant in Chinese cases (OR = 0.69, 95% CI 0.53–0.82, $P < 0.01$, $I^2 = 84\%$, Fig. 4B). Notably, the dead event in America (55/198, 27.78%) showed over twice as much as it in Chinese cases (151/670 22.54%) with the random-effects model and significant heterogeneity (OR: 0.19, 95% CI: 0.11–0.30, $P < 0.01$, $I^2 = 77\%$, $x_2^2 = 1.21$, $P = 0.27$, df = 1, Fig. 4C).

Furthermore, the causal analysis was performed on multi-cancer data (Supplementary Material 2). The results indicated that four phenotypic variables can directly affect Cytopenia, while Grade 3 can affect dead events without obvious upstream cause. Among the four variables, country (case origins) showed a direct impact on ORR and CRR, while various factors have a direct impact on CRR. Thus, cases from different countries

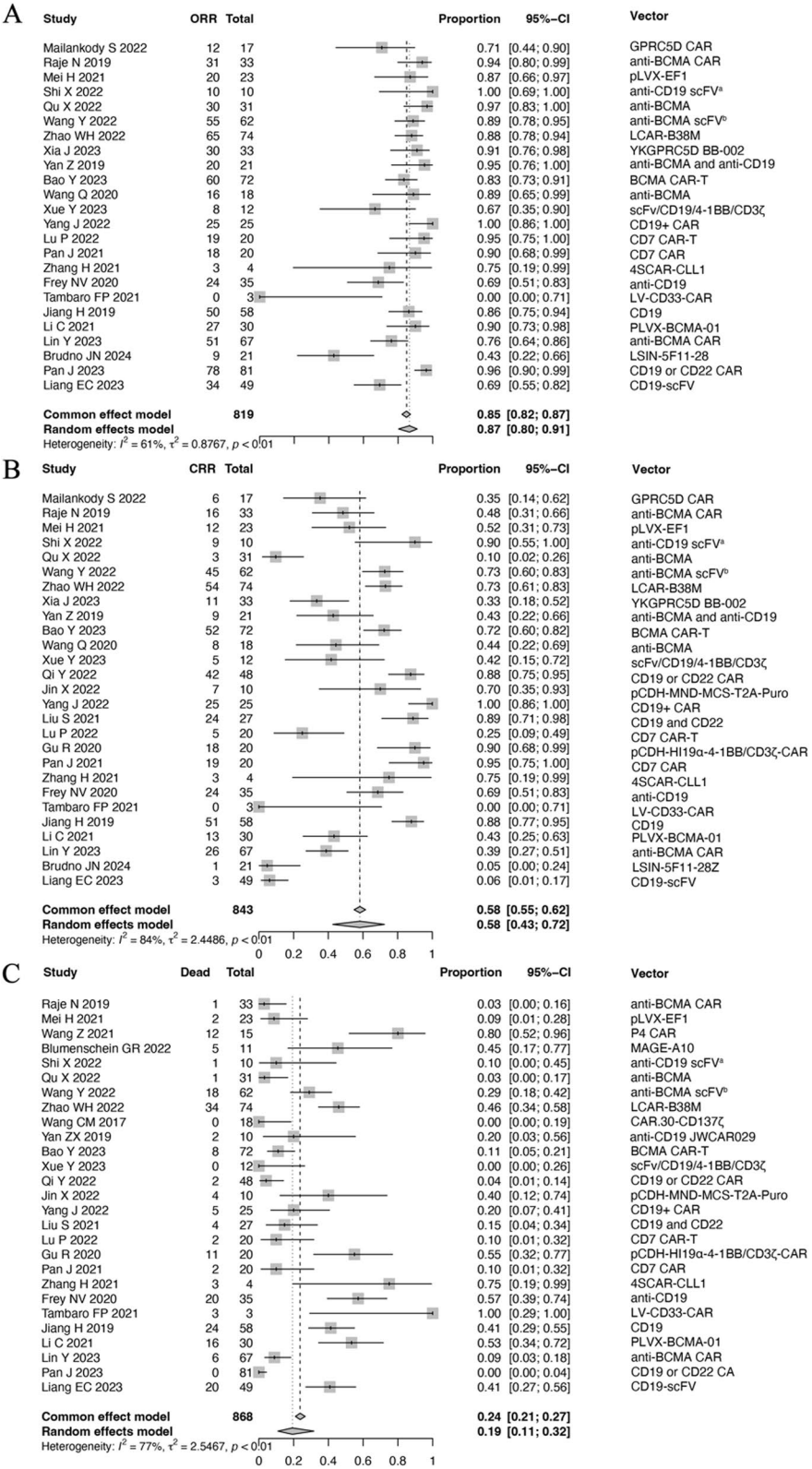
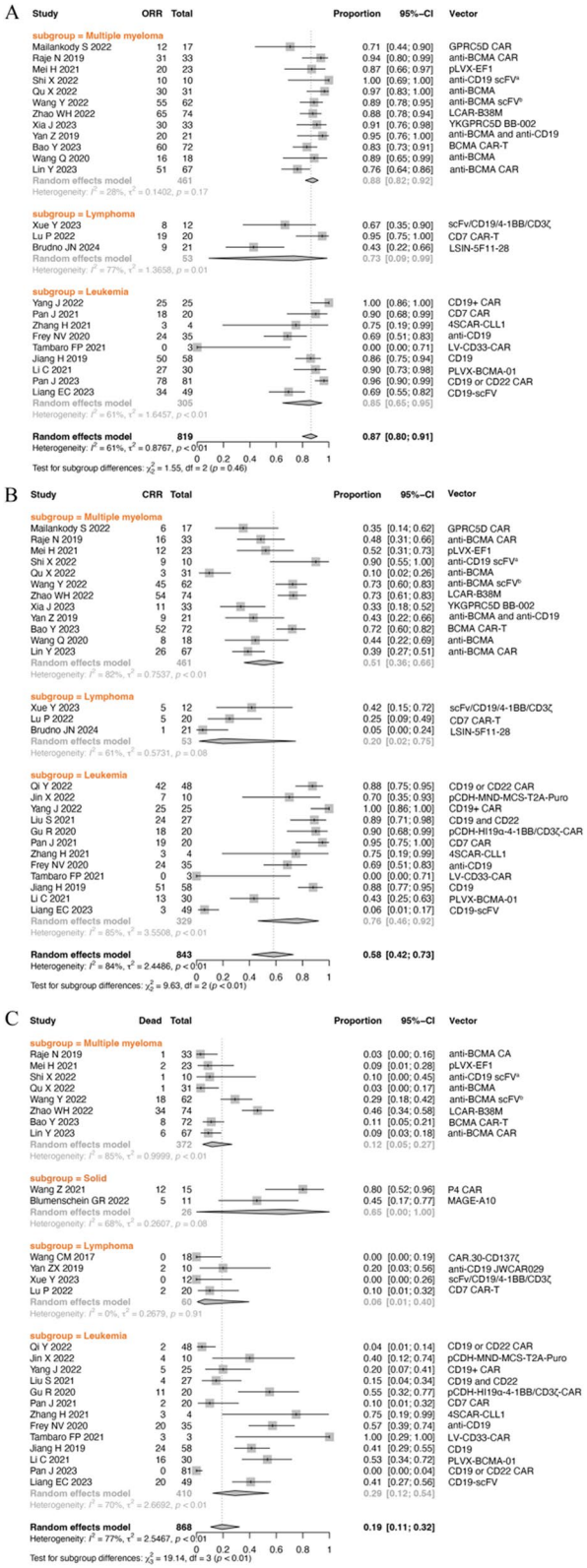



**Fig. 2** Primary outcomes of immunotherapy, which includes ORR, CRR, Dead number. **a** objective response rate (ORR). **b** Complete response rate (CRR). **c** Dead event present. [a]: anti-CD19 scFV/4- 1BB/CD3-ζ/IL4 shRNA and anti-BCMA scFV/CD3-ζ/CD28/OX40. [b]: anti-BCMA scFV/4- 1BB/CD3-ζ and anti-CD19 scFV/4- 1BB/CD3-ζ




◀ **Fig. 3** Secondary outcomes of immunotherapy for various cancer. **a** Objective response rate (ORR). **b** Complete response rate (CRR). **c** Dead event present. [a]: anti-CD19 scFV/4- 1BB/CD3-ζ/IL4 shRNA and anti-BCMA scFV/CD3-ζ/CD28/OX40. [b]: anti-BCMA scFV/4- 1BB/CD3-ζ and anti-CD19 scFV/4- 1BB/CD3-ζ

could affect MR directly and consequently drive dead events.

### Survival

The survival rate of different types of tumors was significantly different ($P < 0.01$, Fig. 5A). The survival rate in solid tumors showed the lowest, while it in lymphoma showed the highest. Although the survival rate in American cases was significantly higher than those from China ($P = 0.048$, Fig. 5B), the explanatory power of this survival rate was limited due to the sampling bias. In Supplementary Table 5, it can be seen that the overall dead rate in America is 35.37% (29/82), which was significantly higher ($P < 0.05$) than that in China, which was 25.64% (151/589).

## Discussion

The present study (PRISMA checklist shows in Supplementary Material 3) aims to evaluate the efficacy and safety of immunotherapy across various cancer types, analyzing a total of 649 studies with a focus on hematologic malignancies and solid tumors. The selection process, which filtered out studies based on impact factor and relevance, resulted in the inclusion of 32 eligible studies, including cases of myeloma, lymphoma, leukemia, and solid tumors. This comprehensive analysis provides valuable insights into the differential outcomes and challenges associated with immunotherapy, particularly CAR-T. Tumors are highly diverse in their genetic makeup, antigen presentation, and immune microenvironments, thereby certain subtypes of cancer may exhibit exceptional responses to immune treatments, while others may perform resistance or limited benefits. The ORR across the selected studies was found to be significantly promising (84.86%), which confirmed CAR-T showed substantial efficacy in the treatment of various cancer types [19, 49]. Notably, the ORR stands out as a reliable metric, notably within the subgroups of tumor types such as multiple myeloma and leukemia, where a substantial number of studies have been included. The significance of the results, combined with the dramatically low heterogeneity observed, enhances the credibility of these findings, positioning them as robust clinical evidence. Moreover, the CRR was observed to be 58.24% and it indicates that a substantial portion of patients exhibits a

**Table 2** Primary and secondary outcomes

| Study | ORR | CRR | DR | CY | Cytopenia details | | | G3 | NEU |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | NE | AN | TH | | |
| **Mailankody S 2022** [30] | 71.00 | 35.00 | NA | 100 | 100 | 88.00 | 88.00 | 6.00 | 6.00 |
| **Raje N 2019** [42] | 85.00 | 45.00 | 3.03 | 85.00 | 85.00 | 45.00 | 45.00 | 6.00 | 42.00 |
| **Mei H 2021** [32] | 87.00 | 53.00 | 8.07 | 96.00 | 96.00 | 43.00 | 61.00 | 22.00 | NA |
| **Wang Z 2021** [56] | NA | NA | 80.00 | NA | NA | NA | NA | 0.00 | 0.00 |
| **Blumenschein GR 2022** [3] | NA | NA | 45.45 | 82.00 | 82.00 | 82.00 | 45.00 | 9.00 | NA |
| **Shi X 2022** [43] | 100 | 90.00 | 10.00 | 100 | 90.00 | 100 | 100.00 | 0.00 | 0.00 |
| **Qu X 2022** [41] | 96.40 | 10.70 | 3.23 | 100 | 100.00 | 83.90 | 90.30 | 9.70 | 3.20 |
| **Wang Y 2022** [54] | 87.80 | 73.00 | 29.03 | 98.00 | 98.00 | 94 | 79.00 | 10.00 | 11.00 |
| **Zhao WH 2022** [66] | 87.80 | 73.00 | 45.95 | 41.90 | NA | 29.70 | 41.90 | 9.50 | 1.40 |
| **Wang CM 2017** [52] | NA | NA | 0.00 | 100 | Nearly all patients had these | | | 11.11 | 5.60 |
| **Yan ZX 2019** [63] | NA | NA | 20.00 | 100 | 100 | 30.00 | NA | 0.00 | 10.00 |
| **Xia J 2023** [58] | 91.00 | 33.00 | NA | 100 | 100 | 53.00 | 45.00 | 0.00 | 9.00 |
| **Yan Z 2019** [62] | 95.00 | 43.00 | NA | 62.00 | NA | 62.00 | 62.00 | 5.00 | 10.00 |
| **Bao Y 2023** [1] | 82.70 | 72.40 | ≥ 11.11 | 100 | 100 | 98.60 | 84.70 | 18.00 | 12.50 |
| **Wang Q 2020** [53] | 88.90 | 44.40 | NA | 100 | 100 | 100 | 94.40 | 16.70 | 5.60 |
| **Xue Y 2023** [59] | 66.00 | 41.00 | 0.00 | NA | NA | NA | NA | 0.00 | 0.00 |
| **Qi Y 2022** [40] | NA | 87.50 | 4.17 | 87.50 | 87.50 | 66.70 | 60.40 | 18.80 | 22.90 |
| **Jin X 2022** [17] | NA | 70.00 | 40.00 | 100 | 100 | 100 | 100.00 | 60.00 | 0.00 |
| **Yang J 2022** [60] | 100 | 100.00 | 20.00 | 76.00 | 64 | 76.00 | 76.00 | 24.00 | 28.00 |
| **Liu S 2021** [28] | NA | 89.50 | 14.81 | NA | NA | NA | NA | 30.00 | 11.00 |
| **Lu P 2022** [29] | 95.00 | 25.00 | 10.00 | 100 | 100 | 100 | 95.00 | 5.00 | 0.00 |
| **Gu R 2020** [13] | NA | 90.00 | 55.00 | 100 | 100 | 100 | 95.00 | 45.00 | 30.00 |
| **Pan J 2021** [38] | 90.00 | 95.00 | 10.00 | 100 | 100 | 100 | 100.00 | 10.00 | 15.00 |
| **Zhang H 2021** [64] | 75.00 | 75.00 | 75.00 | 100 | 75.00 | 100 | NA | 0.00 | 25.00 |
| **Frey NV 2020** [11] | 69.00 | 69.00 | 57.14 | NA | NA | NA | NA | 72.00 | 40.00 |
| **Tambaro FP 2021** [46] | 0.00 | 0.00 | 100 | 33.30 | 33.30 | NA | NA | 33.00 | 33.00 |
| **Jiang H 2019** [16] | 87.60 | 87.60 | 41.38 | NA | NA | NA | NA | 38.0 | 16.00 |
| **Li C 2021** [25] | 90.00 | 43.3 | 53.33 | 100 | 100 | 100 | 100.00 | 17.00 | 3.30 |
| **Lin Y 2023** [26] | 75.80 | 38.70 | 8.96 | 88.70 | 88.70 | 56.50 | 56.50 | 6.50 | 1.60 |
| **Brudno JN 2024** [4] | 43.00 | 4.80 | NA | 100 | 100 | 48.00 | 48.00 | 4.80 | 24 |
| **Pan J 2023** [39] | 96.00 | NA | 0.00 | 100 | 100 | 89.00 | 89.00 | 19.00 | 5 |
| **Liang EC 2023** [24] | 70.00 | 6.00 | 40.82 | NA | NA | NA | NA | 83.00 | 33 |
| **Total Average**[a] | 84.86 | 58.24 | 23.73 | –– | 94.76 | 74.45 | 65.62 | 20.35 | 13.03 |

*ORR* Objective response rate, *CRR* complete response rate, *DR* dead rate, *CY* cytopenia, *NE* neutropenia, *AN* anemia, *TH* thrombocytopenia, *G3* Grade 3 or higher cytokine release syndrome occurred, *NEU* neurologic events occurred. All columns are percentage

[a] weighted average of representative data

complete response to immunotherapy. It's important to note that there was significant heterogeneity among the studies, which suggested that CRR performs differently depending on the specific cancer type and treatment protocol [49]. The analysis of mortality rates revealed an overall rate of 23.73% and highlighted that a proportion of patients in these studies did not survive despite the treatment. However, similar to CRR, there was substantial heterogeneity in this outcome, which underscores the need for further investigation into factors influencing patient survival.

Multiple myeloma patients showed the highest ORR (88.94%), followed by leukemia (84.92%).On the other hand, mortality rates were significantly lower in lymphoma (6.67%) compared with multiple myeloma (19.09%), leukemia (27.80%), and solid tumors (65.38%). These differences emphasize the importance of tailoring treatment approaches to specific cancer types. In the previous study, subgroup analyses showed variations in treatment response among different cancer types [14]. Melanoma and lung cancer patients appeared to derive substantial benefits from immunotherapy immunotherapy, exhibiting higher ORRs

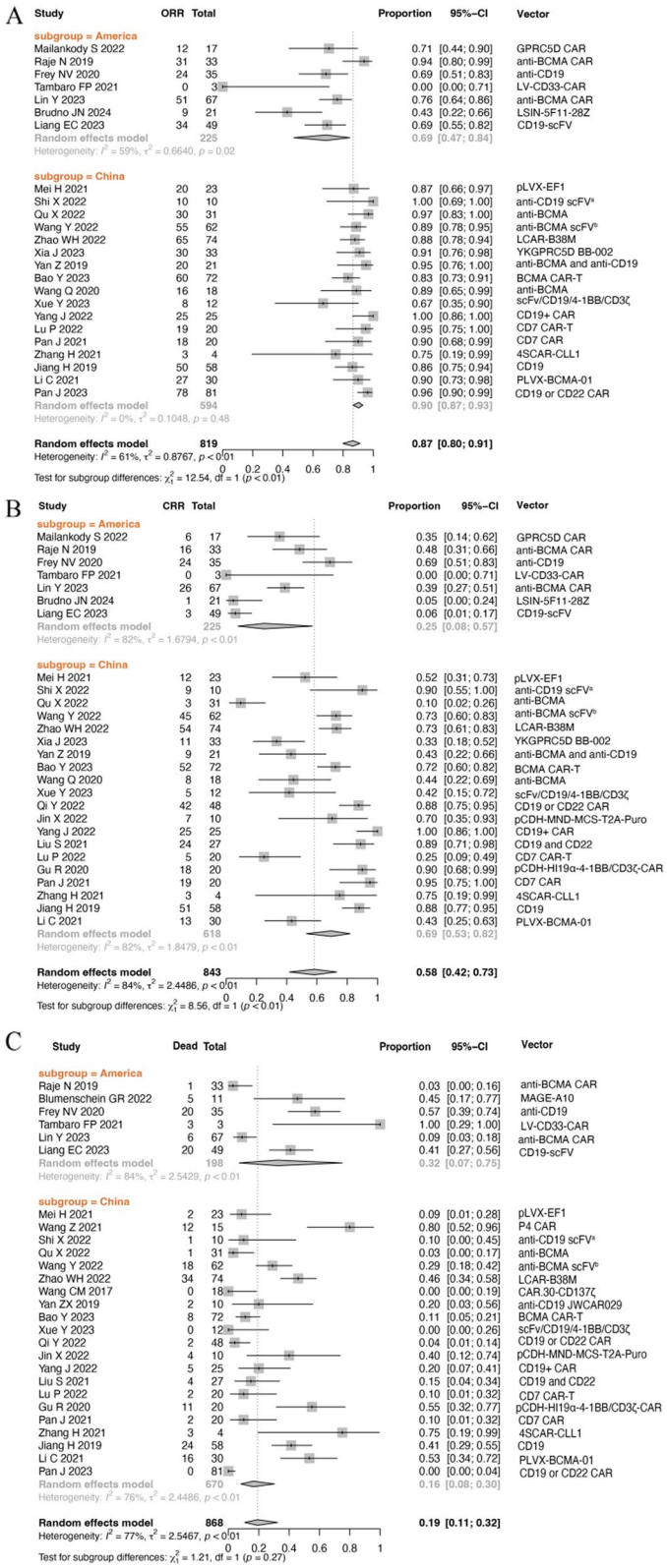



**Fig. 4** Secondary outcomes of immunotherapy for cancer (American vs China). **a** Objective response rate (ORR). **b** Complete response rate (CRR). **c** Dead event present. [a]: anti-CD19 scFV/4- 1BB/CD3-ζ/IL4 shRNA and anti-BCMA scFV/CD3-ζ/CD28/OX40. [b]: anti-BCMA scFV/4- 1BB/CD3-ζ and anti-CD19 scFV/4- 1BB/CD3-ζ

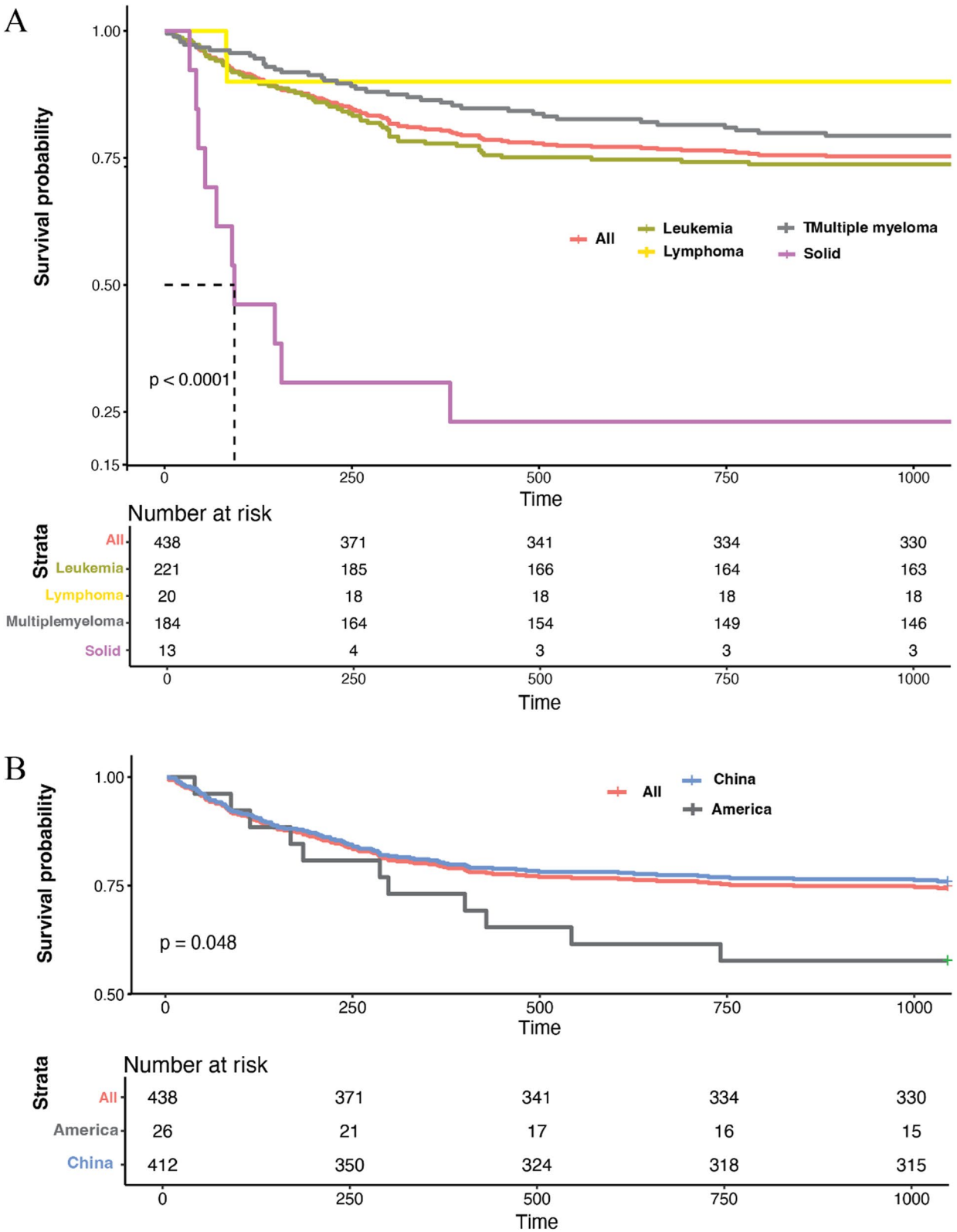



**Fig. 5** The survival rate analysis based on different subgroup analysis. **a** Multiple cancer type subgroup. **b** Different population subgroup

and prolonged PFS [10, 18]. Meanwhile, the response in other malignancies, including pancreatic and ovarian cancer, was more modest [31, 51]. The difference may be attributed to the diversity of tumor microenvironments, mutation burdens, and the availability of target antigens [8, 15]. In parallel, it is vital to recognize that treatment outcomes can vary significantly across different populations due to genetic, demographic, and environmental factors [20]. In this analysis, we delve into the implications of immunotherapy in two group cases from different countries. Besides, age can be a crucial factor that influences the effectiveness of immunotherapies [57]. The gradual deterioration of the immune system with age may limit the immune response to immunotherapy treatments in older populations [55]. In-depth genetic profiling and the identification of predictive biomarkers are essential steps toward tailoring immunotherapy to individual patients or specific populations [27]. Furthermore, the genetic diversity within tumors themselves, known as intra-tumor heterogeneity, poses challenges to immunotherapy application [36]. Our analysis found that the CRR, ORR, and survival rate in Chinese cases showed higher than them in Americans. Therefore, immunotherapy holds substantial promise across diverse patient populations. However, the effectiveness of this approach can vary significantly depending on cancer type, patient age, genetic factors, and other variables. Future research should focus on the identification of biomarkers, the development of combination therapies, and the promotion of inclusivity in clinical trials to advance the field of immunotherapy, thus improving outcomes for all cancer patients, irrespective of their demographic characteristics.

Although the promising outcomes were observed in this meta-analysis, there are several limitations. Heterogeneity in clinical trial designs, patient populations, and treatment protocols cannot be avoided, which may have introduced bias into our findings and weakened the evidence strength. In parallel, publication bias cannot be ruled out, as negative or inconclusive results are less likely to be published. The continued evolution of immunotherapy holds great potential in the ever-expanding landscape of cancer treatment. To further enhance the effectiveness of immunotherapy, combinations of immunotherapy with checkpoint inhibitors, monoclonal antibodies, or other immunomodulatory agents would be valuable in overcoming resistance mechanisms and broadening the spectrum of responsive cancers. It is acknowledged that the current comparison may not fully encompass the spectrum of available data. This study only included the references with high impact (Impact factor > = 10) for obtaining possible reliable findings. During the data collection phase, harmonized data inclusion and exclusion criteria were selected. Data from Clinical Trials (https://clinical-trials.cyntegrity.com/) show that China's growth rate (477.23%) in clinical studies has been much faster than that of the USA (46.72%) between 2010 and 2021. The clinical data in China compared to the USA may lead to this bias. Miller et al. reported in The Lancet Oncology that Black and white patients treated with immune checkpoint inhibitors showed the same two-year overall survival rate of 36.5%, but the reasons why Black patients experienced fewer immune-related side effects remain unclear [34]. Future studies should include more clinical trials for offering a more comprehensive analysis of the varied therapeutic modalities in subsequent sections.

This meta-analysis investigated the outcomes and efficacy of immunotherapy across diverse cancer types and shows potential to benefit clinical practice by expanding treatment options, enabling tailored therapies, facilitating combination treatments, improving response prediction, and advancing the field of cancer immunotherapy.

## Conclusions

The findings of this study underscore the complexity of immunotherapy outcomes and the critical need for more rigorous and comprehensive research. Future studies should focus on larger, well-designed RCTs with standardized endpoints to provide more definitive evidence of efficacy and safety. Additionally, exploring the underlying causes of heterogeneity in treatment responses and adverse events will be crucial in optimizing immunotherapy protocols. While immunotherapy offers promising benefits for cancer treatment, its application is challenging, including significant adverse events and variability in outcomes. Addressing these issues through robust research and personalized treatment strategies will be essential in advancing the field and improving patient care. This meta-analysis conclusively demonstrates the variable effectiveness of CAR-T therapy, as one of the novel immunotherapies, across different cancer types, and firmly establishes the necessity for adaptive treatment modalities that are sensitive to individual patient profiles. The compelling evidence from this study advocates for a strategic shift towards more precision-focused research to tailor therapies that maximize benefits and minimize risks for patients.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12575-025-00274-5.

Supplementary Material 1: Supplementary Table 1. MINORS score of the included articles.

Supplementary Material 2: Supplementary Table 2. Additional details of the included articles.

Supplementary Material 3: Supplementary Table 3. PRISMA checklist.

Supplementary Material 4: Supplementary Table 4. Subgroup data and summary.

Supplementary Material 5: Supplementary Table 5. All forest and funnel figure table index.

Supplementary Material 6: Supplementary Material 1. PROSPERO.

Supplementary Material 7: Supplementary Material 2. Supplementary Methods and Figures.

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**Authors' contributions**
XX, JYL, and PYF: Conceptualization, Data curation, Writing–original draft. WDW and BL: Formal Analysis, Methodology, Visualization, Software. QZ and XJZ: Data curation, Formal Analysis, Methodology, Visualization, Software, Writing–review & editing. WDW and BL: Data curation, Methodology, Visualization, Writing–review & editing.

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**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
This article does not cover animal or human testing.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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