SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 31: 193, 2026

Metformin enhances survival with immune checkpoint inhibitors in cancer patients: A meta-analysis

YU QIAO[1*], HUIYAO LI[1*], YANPING FENG[1*], SHUAI LIANG[2] and DONG HUA[1,3]

[1]Department of Oncology, The Affiliated Children's Hospital of Jiangnan University, Wuxi School of Medicine, Jiangnan University, Wuxi, Jiangsu 214000, P.R. China; [2]Department of Radiation Oncology, Weifang People's Hospital, Shandong Second Medical University, Weifang, Shandong 261000, P.R. China; [3]Department of Oncology, The Affiliated Wuxi People's Hospital of Nanjing Medical University, Wuxi Medical Center, Wuxi, Jiangsu 214000, P.R. China

Received December 15, 2025; Accepted February 23, 2026

DOI: 10.3892/ol.2026.15548

Abstract. Metformin, a primary medication for type 2 diabetes, has garnered interest due to its possible anti-tumor properties and impacts on the tumor microenvironment. This meta-analysis evaluated the impact of combining metformin with immunotherapy on overall survival (OS) and progression-free survival (PFS) in cancer patients. Relevant studies published from January 2015 to December 2024 were searched in databases such as Embase, Web of Science, PubMed and Cochrane Library. Statistical analyses were performed using STATA 18.0 software. With a total sample size of 5,014 patients, this research included 9 papers. OS and PFS were analyzed as time-to-event outcomes, and pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated. The results indicated that metformin combined with immunotherapy significantly improves OS (HR=0.78, 95% CI: 0.62-0.97, P=0.027) and PFS (HR=0.80, 95% CI: 0.69-0.93, P=0.005) in cancer patients. Subgroup analysis revealed that the Asian population benefited more (OS: HR=0.66, 95% CI: 0.47-0.91, P=0.012; PFS: HR=0.69, 95% CI: 0.58-0.82, P<0.001), whereas the non-Asian group did not demonstrate any significant connection. The results suggest that combining metformin with immunotherapy enhances outcomes, particularly in Asian populations. However, factors such as geographic location, immunotherapy protocols and metformin dosage may influence therapeutic efficacy. Future research should explore subpopulation differences and optimize combination therapy strategies.

Correspondence to: Dr Shuai Liang, Department of Radiation Oncology, Weifang People's Hospital, Shandong Second Medical University, 151 Guangwen Street, Weifang, Shandong 261000, P.R. China
E-mail: liang15194379549@126.com

Dr Dong Hua, Department of Oncology, The Affiliated Children's Hospital of Jiangnan University, Wuxi School of Medicine, Jiangnan University, 299-1 Qingyang Road, Wuxi, Jiangsu 214000, P.R. China
E-mail: wx14893@163.com

[*]Contributed equally

Key words: cancer, immunotherapy, metformin, prognosis, meta-analysis

Introduction

According to global cancer statistics for 2022, ~20 million new cancer cases were diagnosed worldwide, resulting in 9.7 million deaths. Projections suggest that the number of cancer cases will rise to 35 million by 2050, reflecting population growth and aging trends (1). These estimates highlight the serious threat posed by malignant tumors to global health, as well as their substantial social and economic impact. Therefore, improving cancer treatment is not only a medical priority but also a crucial public health objective. Cancer immunotherapy has emerged as a transformative approach that mobilizes the patient's own immune system to recognize and eliminate malignant cells (2,3). Major immunotherapeutic strategies, including immune checkpoint inhibitors (ICIs), adoptive cell transfer and cancer vaccines, have made substantial advancements in the treatment of various diseases and have provided patients with advanced cancer with the possibility of a long-term life (4,5). However, the broader application of these therapies is limited by issues such as primary or acquired resistance, limited response rates and immune-related adverse events. There is a pressing need to identify novel strategies that can enhance the efficacy and expand the applicability of cancer immunotherapy (6,7).

Metformin, a first-line biguanide agent for type 2 diabetes mellitus, is widely recognized for its favorable safety and tolerability profile. It improves glycemic control through multiple mechanisms: Reducing intestinal glucose absorption, decreasing hepatic glucose output (gluconeogenesis) and enhancing insulin sensitivity in peripheral tissues (8-10). Beyond its glucoregulatory actions, metformin has garnered significant interest in oncology over the past decade. A growing body of preclinical evidence suggests that metformin may possess direct and indirect antitumor properties and could potentially augment the efficacy of cancer immunotherapy (11-14). It may exert an anti-tumor effect via activating the adenosine monophosphate-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) pathway (12), decreasing programmed death ligand 1 (PD-L1) expression (15), suppressing mitochondrial complex I activity (16) and modulating the tumor microenvironment (TME) (17,18). Numerous clinical studies have shown its association with a lower risk and better prognosis for cancer patients (19-21). It has also been shown to work in concert with immunotherapy (22,23), establishing a theoretical basis for the concurrent use of metformin and immunotherapy (24-26).

Despite these promising preclinical and pharmacological insights, the clinical efficacy of combining metformin with immunotherapy remains controversial (27,28). Therefore, a meta-analysis was performed in the present study to synthesize the available evidence regarding the association between metformin use and survival outcomes in cancer patients receiving ICIs, with the aim of clarifying its potential role as an adjunctive therapy in immunotherapy.

Materials and methods

Search strategy and study selection. This meta-analysis was conducted in accordance with the PRISMA guidelines (29). A systematic literature search was performed using four electronic databases: PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), the Cochrane Library (https://www.cochranelibrary.com/) and Web of Science (https://www.webofscience.com/), covering publications from January 2015 to December 2024. The search strategy utilized a combination of medical subject headings and free-text terms. Key words included 'metformin', 'metoguanide', 'glucophage', 'metformin hydrochloride', 'immunotherapy', 'immune checkpoint inhibitor', 'tumor', 'cancer' and other associated terms.

The literature search and screening process employed a dual-independent reviewer approach to minimize selection bias. Any disagreements between the two reviewers (YQ and HL) at either stage were first addressed through discussion to reach a consensus. For persistent disagreements, a third reviewer (YF) was consulted to arbitrate and make the final decision.

Inclusion and exclusion criteria. The eligibility of studies was determined based on the pre-specified Population, Intervention, Comparator, Outcomes, Study design framework (30). Studies were included if they met the following criteria: i) Enrolled adult patients (≥18 years) with histologically or cytologically confirmed cancer; ii) examined the impact of metformin use, in combination with immunotherapy [e.g., anti-programmed cell death 1 (PD-1)/PD-L1, anti-cytotoxic T-lymphocyte associated protein-4 agents], on survival outcomes; iii) reported at least one of the primary outcomes of interest, such as overall survival (OS) or progression-free survival (PFS), with provision of hazard ratios (HR) and corresponding 95% confidence intervals (CI) (or sufficient data for their calculation); iv) were published in English.

Exclusion criteria: i) Duplicate publications; ii) systematic reviews, narrative reviews, editorials, commentaries and preclinical studies; iii) case reports or conference abstracts lacking full outcome data; iv) they lacked essential outcome data of interest even after attempting to contact the corresponding authors.

Quality evaluation. The methodological quality of the included observational studies was appraised using the Newcastle-Ottawa Scale (NOS) (31). The NOS tool assesses studies across three domains: i) The selection of the study groups, ii) the comparability of these groups, and iii) the ascertainment of the outcome. A star system is used for rating, with a maximum score of nine stars. Based on the total NOS score, studies were classified as high quality (7-9 stars), moderate quality (4-6 stars), or low quality (0-3 stars). In line with standard methodological practice, only studies rated as moderate or high quality were included in the subsequent meta-analysis to enhance the robustness of the pooled findings.

Data extraction. A standardized, pre-piloted data extraction form was used to collect relevant information from the included studies. The extracted data encompassed the following domains: First author and publication year; study design; country or region where the study was conducted; patient population characteristics, including sample size and cancer type; details of the interventions (ICI regimen and metformin usage); and primary outcomes of interest, specifically OS and PFS, with a focus on obtaining HRs and their 95% CI.

Statistical analysis. All statistical computations for the meta-analysis were performed using STATA software (version 18.0; StataCorp.). The pooled HR, along with its 95% CI, served as the primary summary measure. In accordance with the Cochrane Handbook recommendations (30), which state that heterogeneity is always expected among studies from different settings and that model selection should not be based solely on statistical tests for heterogeneity, a random-effects model was applied for all meta-analyses to provide a more conservative and generalizable estimate of the overall effect. Potential publication bias was assessed both graphically using a funnel plot and statistically using Begg's test (32). A sensitivity analysis, performed by sequentially excluding each study and recalculating the pooled estimate, was conducted to evaluate the robustness of the findings. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Basic characteristics of the included studies. A total of 1,599 papers were obtained for this investigation and 427 duplicate studies were removed. Based on a review of the article content, 931 studies irrelevant to the research topic and 218 studies lacking clinical cohorts were excluded. Additionally, 14 other studies were excluded, comprising 2 letters, 4 conference papers and 8 studies with missing data. In conclusion, this meta-analysis was comprised of 9 publications, all of which were written in English (27,28,33-39). The procedure for screening the available literature is shown in Fig. 1.

In all, there were 5,014 individuals who participated in the 9 studies, with 579 of them being metformin users. The outcome indicators of 9 articles included OS and 8 reporting on related PFS, including melanoma, lung cancer, renal cancer, lymphoma and digestive system cancer. A total of 3 articles pertained to Asian nations and there were six articles pertaining to countries that are not inside the Asian region,

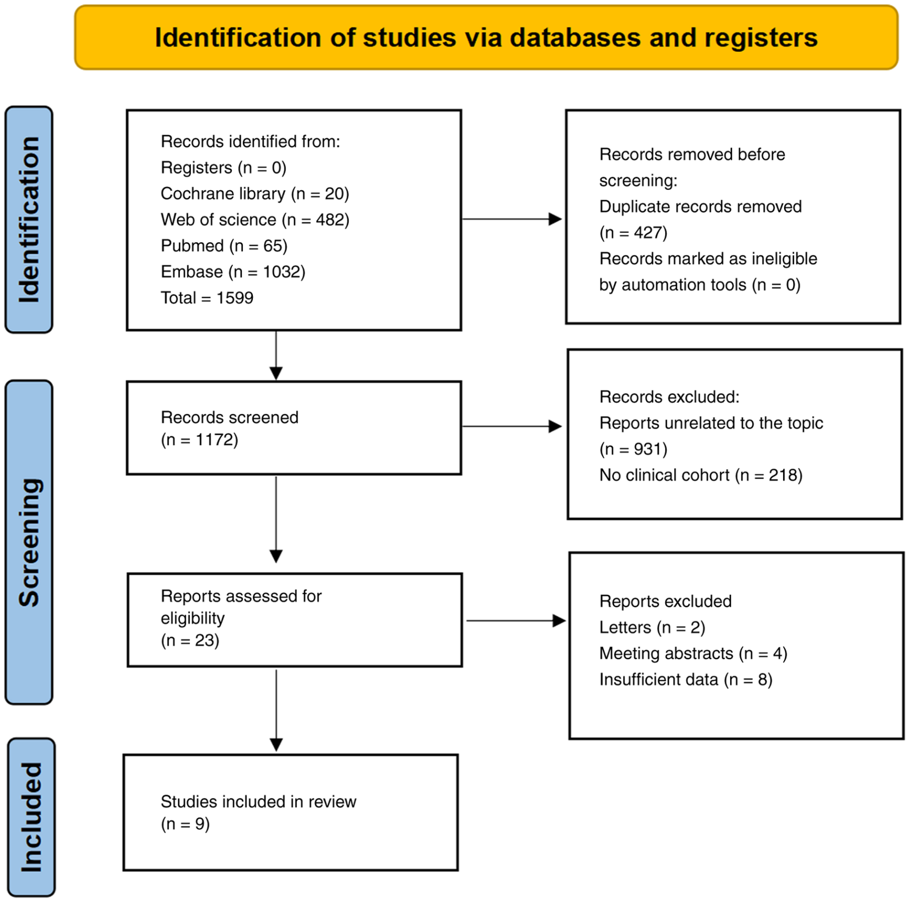

Figure 1. PRISMA flowchart for the study selection process.

such as Europe or the US. A variety of immunotherapies, such as ipilimumab, nivolumab, pembrolizumab, atezolizumab, sintilimab and camrelizumab, were used in the treatment of cancer patients. The quality scores of all articles included in the study were not less than 7 (Table I). The primary features of the included studies are shown in Table II.

PFS in patients receiving metformin with immunotherapy. A meta-analysis of 8 studies evaluating PFS was performed to assess the impact of metformin as an adjunct to ICIs in cancer patients. The pooled results indicated that concurrent administration of metformin was associated with a statistically significant improvement in PFS (HR=0.80, 95% CI: 0.69-0.93, P=0.005) (Fig. 2A). In a subgroup analysis stratified by geographical region, a significant PFS benefit was observed in Asian populations (HR=0.69, 95% CI: 0.58-0.82; P<0.001) (Fig. 2B), whereas the effect was not statistically significant in non-Asian populations (HR=0.94, 95% CI: 0.80-1.09; P=0.405) (Fig. 2C).

OS in patients receiving metformin with immunotherapy. A total of 9 studies were included in the analysis for the OS endpoint. The combined analysis revealed that the addition of metformin to immunotherapy was associated with a significant improvement in OS, yielding a pooled HR of 0.78 (95% CI: 0.62-0.97; P=0.027) (Fig. 3A). Subgroup analysis based on geographic region demonstrated a pronounced OS benefit among Asian patients (HR=0.66, 95% CI: 0.47-0.91; P=0.012) (Fig. 3B), while no significant improvement was observed in non-Asian cohorts (HR=0.91, 95% CI: 0.72-1.15, P=0.437) (Fig. 3C).

The results of this meta-analysis suggest that the concomitant use of metformin with immune checkpoint inhibitors is associated with improvements in both PFS and OS in cancer patients. However, the observed benefit exhibits regional variation, with a more pronounced effect size observed within Asian populations compared to non-Asian groups. This finding underscores the potential influence of ethnic or regional factors on treatment efficacy and highlights the need for further investigation into the underlying mechanisms driving these differences.

Assessment of publication bias and sensitivity analysis. Potential publication bias was evaluated using a funnel plot inspection and Begg's rank correlation test. The Begg's test result was not statistically significant (P>0.05), and the funnel plot showed approximate symmetry. These findings suggest that publication bias is unlikely to have substantially influenced the overall results of this meta-analysis (Fig. 4). A sensitivity analysis was performed to assess the robustness and stability of the pooled results. This was conducted using the leave-one-out method, which involves iteratively removing each individual study and recalculating the summary effect size for the remaining studies. The results demonstrated that no single study exerted a disproportionate influence on the overall effect estimate. This confirms that the meta-analytic

Table I. Newcastle-Ottawa scale scores for quality assessment of included studies.

	Selection				Comparability		Outcome				
Author/s, year	Representa-tiveness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome absent at baseline	Control for age and sex	Adjust for potential confounders	Assessment of outcome	Sufficiently long follow-up duration	Adequacy of follow-up of cohorts	Total	(Refs.)
Chiang *et al*, 2023	1	1	1	1	1	1	1	1	1	9	(27)
Afzal *et al*, 2018	0	1	1	1	1	1	1	1	0	7	(28)
Afzal *et al*, 2019	0	1	1	1	1	1	1	1	0	7	(33)
Wang *et al*, 2020	1	1	1	1	1	1	1	1	0	8	(34)
Gaucher *et al*, 2021	1	1	1	1	1	1	1	1	0	8	(35)
Cortellini *et al*, 2021	1	1	1	1	1	1	1	1	0	8	(36)
Yang *et al*, 2023	1	1	1	1	1	1	1	1	0	8	(37)
Fiala *et al*, 2023	1	1	1	1	1	1	1	1	1	9	(38)
Wang *et al*, 2024	1	1	1	1	1	1	1	1	1	9	(39)

findings are robust and not unduly dependent on any particular study included in the analysis (Fig. 5).

Discussion

The present meta-analysis, encompassing 9 studies and 5,014 cancer patients, investigated the association between concomitant metformin use and survival outcomes in patients receiving ICIs. The pooled results demonstrate that metformin use is significantly associated with improved PFS (HR=0.80, 95% CI: 0.69-0.93, P=0.005) and OS (HR=0.78, 95% CI: 0.62-0.97; P=0.027) in this patient population. However, subgroup analyses revealed a striking geographical disparity: The survival benefit was statistically significant and pronounced in Asian populations (OS: HR=0.66, 95% CI: 0.47-0.91, P=0.012; PFS: HR=0.69, 95% CI: 0.58-0.82, P<0.001) but was not observed in non-Asian cohorts. These findings suggest a complex interaction between metformin and immunotherapy, potentially modulated by regional factors.

Previous meta-analyses, including the study by Wen *et al* (40), evaluated metformin across various anticancer treatment modalities. In contrast, the present analysis focused specifically on ICI-based therapies, thereby offering a more immunotherapy-oriented perspective. In addition, compared with the meta-analysis conducted by Shen *et al* (41), which reported no significant survival benefit and suggested a potential unfavorable effect of metformin on overall survival, the present study incorporated additional clinical studies published up to 2024 and applied stricter inclusion criteria by excluding conference abstracts, letters, studies lacking complete survival data and those with lower methodological quality, which may enhance data completeness and analytical reliability. By contrast, the pooled analysis performed in the present study demonstrated a statistically significant improvement in both OS and PFS with metformin use in combination with ICIs. The present subgroup analysis further provides meta-analytic evidence suggesting a potentially greater survival benefit among Asian patients. This regional trend was not clearly delineated in prior studies and may offer new insights into population-based stratification strategies in precision immunotherapy. Furthermore, this observation raises the possibility that differences in metabolic phenotype, genetic background or treatment patterns may interact with metformin-mediated immunomodulation.

The observed OS benefit aligns with the premise derived from preclinical studies that metformin can potentiate anti-tumor immunity (42-44). Metformin can inhibit the proliferation and metabolism of tumor cells by activating the AMPK signaling pathway and inhibiting mTOR signaling (45). It can also reduce the expression of PD-L1 and block PD-1/PD-L1 signaling, thereby enhancing the anti-tumor activity of T cells (46). Metformin may also enhance immune-cell activity and regulate the TME. A theoretical foundation for its combination with immunotherapy is provided by the aforementioned findings. Turpin *et al* (16) published an article in 2024 examining the utilization of patient-derived explant culture (PDEC) to investigate the tumor immune microenvironment (TIME), employing this model to assess the impact of anti-tumor agents, including the combination of venetoclax and metformin, on immune-cell functionality. The study's findings indicated that the PDEC

Table II. The main characteristics of studies included in this meta-analysis.

Author/s, year	Country	Cancer type	Study design	ICIs	Total sample size	Males, n (%)	Metformin vs. no metformin	Outcome measures	(Refs.)
Chiang *et al*, 2023	China	Lung, gastrointestinal, hepatobiliary, gynecological	Cohort	NA	878	NA	86/599	OS, PFS	(27)
Afzal *et al*, 2018	US	Melanoma	Cohort	Ipilimumab, Nivolumab, Pembrolizumab	55	34 (61.8)	33/22	OS, PFS, DCR	(28)
Afzal *et al*, 2019	US	NSCLC	Cohort	Nivolumab, Pembrolizumab, Atezolizumab	50	28 (56.0)	21/29	OS, PFS, ORR	(33)
Wang *et al*, 2020	Multiple countries	Melanoma	Cohort	Nivolumab, Pembrolizumab	330	209 (63.0)	34/296	OS, PFS	(34)
Gaucher *et al*, 2021	France	Lung, melanoma, renal and urothelial, head and neck, Hodgkin lymphoma	Cohort	Ipilimumab, Nivolumab, Pembrolizumab	372	244 (65.6)	17/355	OS	(35)
Cortellini *et al*, 2021	Multiple countries	NSCLC	Cohort	Pembrolizumab	1,545	1,028 (66.5)	125/1420	OS, PFS, ORR	(36)
Yang *et al*, 2023	Korea	NSCLC	Cohort	Pembrolizumab, Nivolumab, Atezolizumab	466	347 (74.5)	89/377	OS, PFS	(37)
Fiala *et al*, 2023	Multiple countries	Metastatic urothelial cancer	Cohort	Pembrolizumab	802	491 (61.2)	98/704	OS, PFS	(38)
Wang *et al*, 2024	China	Lung, esophageal, gastrointestinal, hepatobiliary and pancreatic	Cohort	Sintilimab, Camrelizumab, Tirelizumab, Pembrolizumab	516	393 (76.2)	76/440	OS, PFS	(39)

Quality score: The Newcastle-Ottawa scale was used for assessment. OS, overall survival; PFS, progression-free survival; DCR, disease control rate; ORR, overall response rate; NSCLC, non-small cell lung cancer; ICI, immune checkpoint inhibitor; NA, not available.

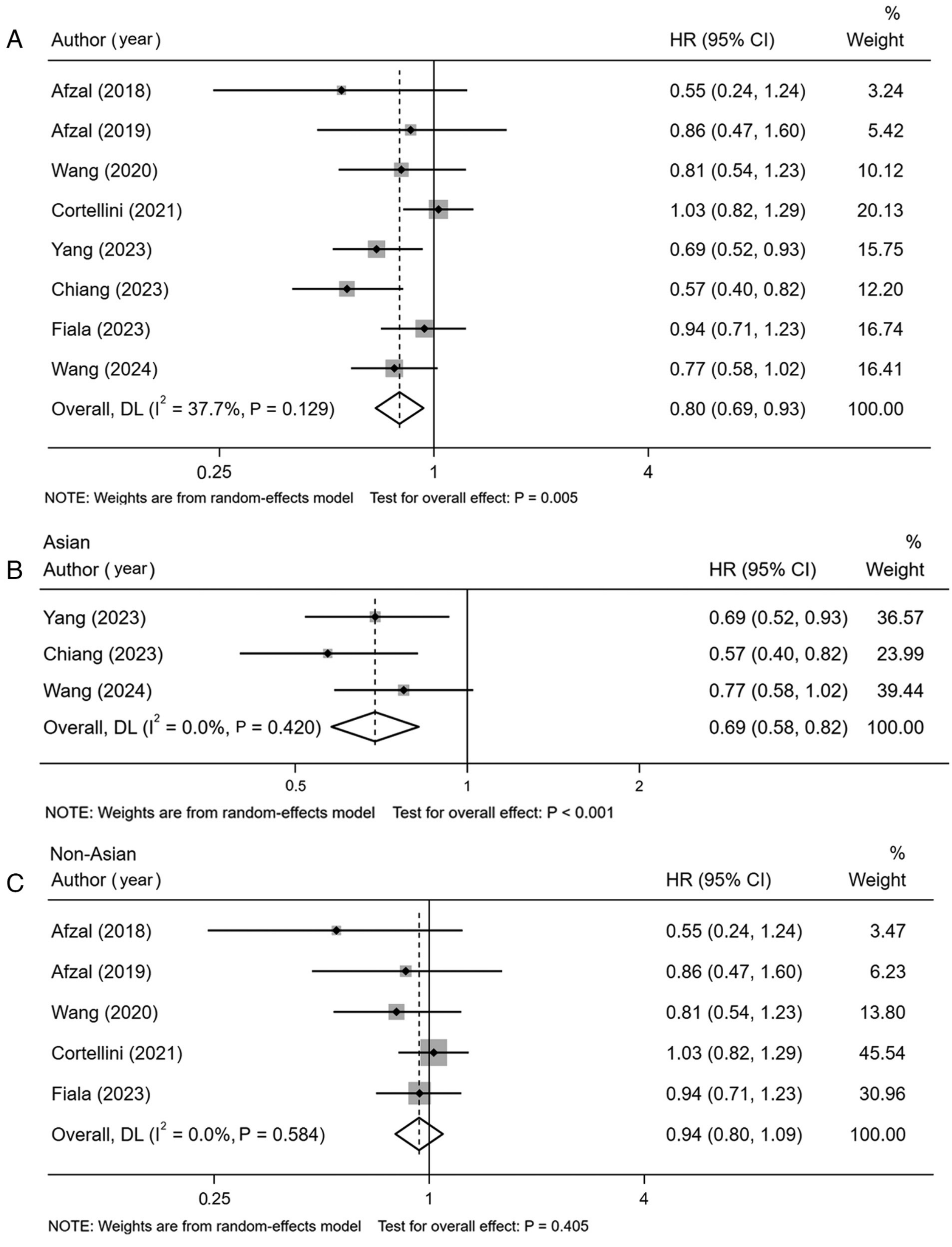

Figure 2. Effect of metformin on progression-free survival in cancer patients receiving immune checkpoint inhibitors. (A) Overall analysis. (B) Subgroup analysis for Asians. (C) Subgroup analysis for non-Asians. HR, hazard ratio. DL, DerSimonian and Laird method.

model demonstrated that metformin activated dendritic cells within the TIME by inhibiting mitochondrial respiratory chain complex, thereby augmenting the anti-tumor immune response of CD4+ T cells, and underscored the significance of the PDEC model in investigating the TIME and the mechanisms of drug action. Tan *et al* (47) assessed the anti-tumor efficacy of combining PD-1 inhibitors with mTOR inhibitors rapamycin or metformin in triple-negative breast cancer (TNBC). According to their data, metformin and rapamycin may both significantly lower PD-L1 expression and inhibit mTOR pathway activity in TNBC. The combination of PD-1 inhibitors with these agents markedly decreased tumor growth and metastasis, increased CD8+ T-cell infiltration and tumor-cell apoptosis, and amplified the anti-tumor efficacy of PD-1 inhibitors. Wabitsch *et al* (26) revealed that non-alcoholic steatohepatitis (NASH) reduces the efficacy of ICI therapy for liver cancer by impairing the metabolism and migration capabilities of CD8+ T cells. In NASH mice, metformin therapy may enhance CD8+ T-cell metabolic

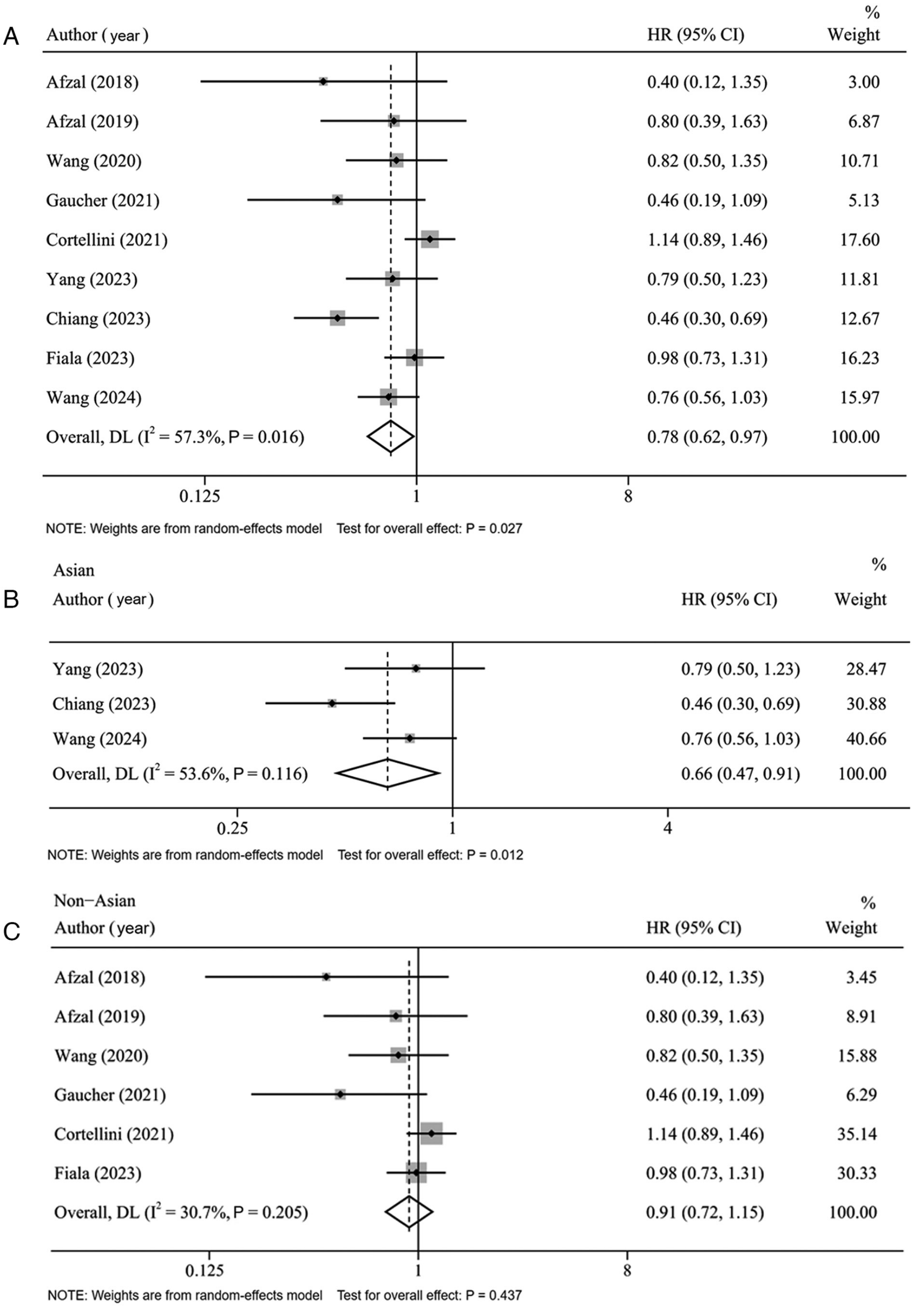

Figure 3. Effect of metformin on overall survival in cancer patients receiving immune checkpoint inhibitors. (A) Overall analysis. (B) Subgroup analysis for Asians. (C) Subgroup analysis for non-Asians. HR, hazard ratio; DL, DerSimonian and Laird method.

activity, regaining the effectiveness of ICI treatment. These fundamental study results provide a strong theoretical foundation for metformin's possible use in cancer immunotherapy. Building on this mechanistic understanding, a recent study on TNBC has demonstrated that low-dose metformin activates the AMPK-acetyl-CoA carboxylase-fatty acid β-oxidation signaling axis, thereby inducing Src kinase activation and enhancing anti-tumor immunity, whereas high-dose metformin suppresses this pathway and may even exert tumor-promoting effects (48). However, critical details regarding metformin dosage, treatment duration, timing of metformin initiation relative to ICI therapy (before, concurrent with or after ICI), and steady-state blood concentration in patients were unavailable in the included studies, limiting further exploration of optimal therapeutic parameters. Future prospective studies designing combination therapies should emphasize dose optimization and clearly report the timing of metformin initiation relative to ICI to maximize efficacy while minimizing toxicity.

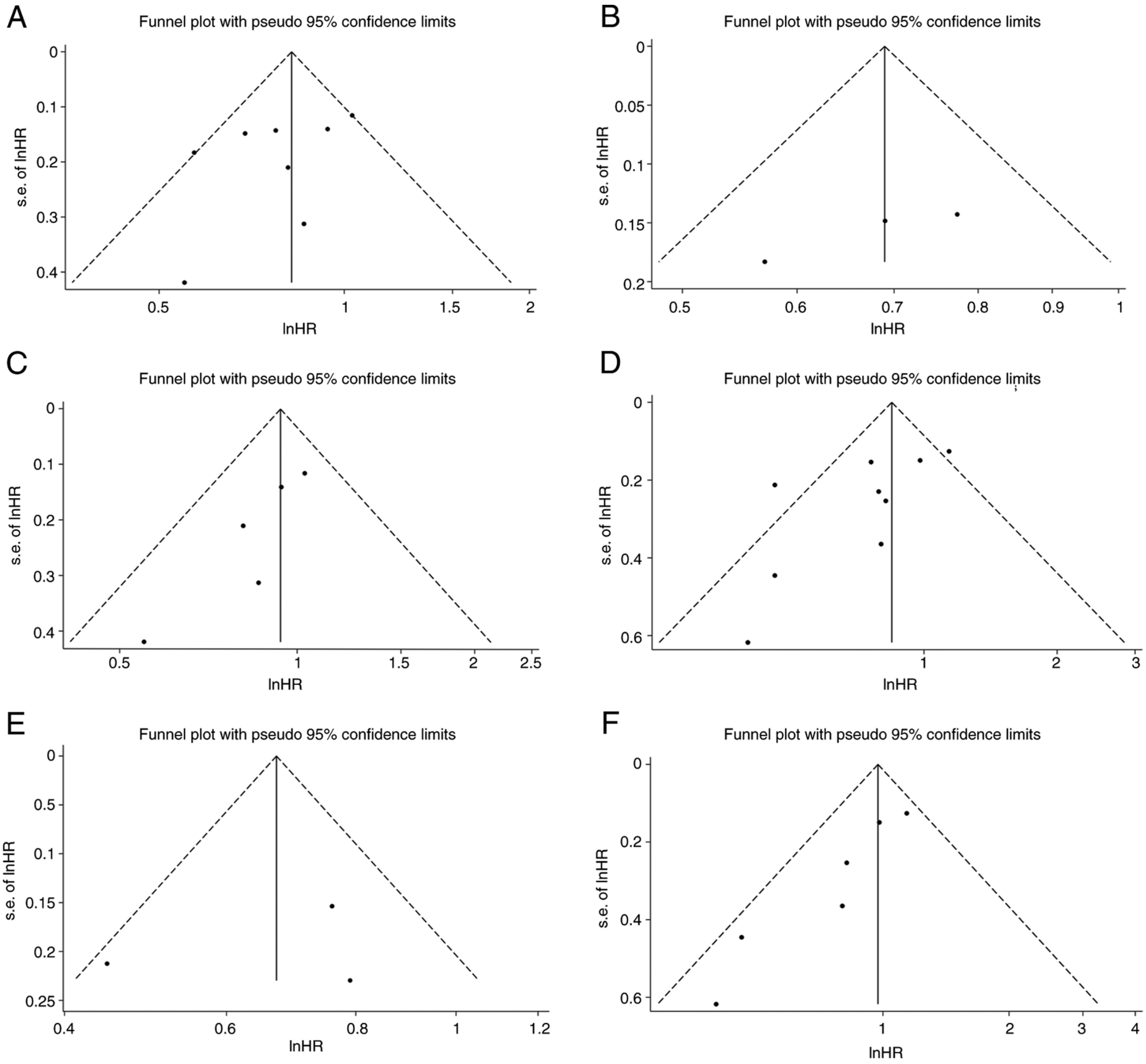

Figure 4. Funnel plots: Progression-free survival (A) Overall analysis. (B) Subgroup analysis for Asians. (C) Subgroup analysis for non-Asians. Overall survival (D) Overall analysis. (E) Subgroup analysis for Asians. (F) Subgroup analysis for non-Asians. lnHR, natural logarithm of the hazard ratio; s.e., standard error.

Additionally, studies indicate that diabetes can alter the immune landscape within the TME of solid tumors, potentially fostering an immunosuppressive state (49). The immunomodulatory benefits of metformin, particularly its potential to enhance antitumor immunity, may be closely linked to the improvement of diabetic metabolic conditions. This interplay warrants further investigation through well-controlled animal studies employing both diabetic and non-diabetic models to dissect the specific contributions of metabolic normalization vs. direct drug effects. Beyond metabolic factors, substantial evidence suggests that heterogeneity in the TME may lead to differential efficacy. For instance, brain tumors and uveal melanomas, characterized by minimal tumor-infiltrating immune cells and a macrophage-dominated milieu, often exhibit resistance to ICIs (50-52). In contrast, malignancies such as lung adenocarcinoma, head and neck squamous cell carcinoma and cutaneous melanoma, which typically display richer immune cell infiltration, tend to respond more favorably to immunotherapy (53-55). Future multi-center studies with large-sample cohorts for individual cancer types are warranted to explore the impact of metformin on immunotherapy outcomes across different tumor sites.

The most intriguing finding of the present analysis is the significant disparity in treatment effect between Asian and non-Asian populations. The reasons for this heterogeneity are likely multifactorial and may involve differences in tumor biology, genetic predisposition, pharmacogenomics and clinical practice patterns. The lack of a statistically significant benefit in non-Asian cohorts underscores the potential influence of divergent genetic backgrounds, lifestyles or clinical management approaches. Future research should integrate multi-omics data, including genomics and metabolomics, to elucidate the underlying mechanisms, and conduct multicenter trials to validate and refine population-specific therapeutic strategies. The study by Bouchi *et al* (56) highlighted that the pathophysiology of diabetes, levels of obesity and insulin resistance among patients vary across Eastern and Western populations, along with disparities in pharmacological choices and treatment methodologies. Lin *et al* (57) utilized genome-wide association analysis, cross-ancestry meta-analysis and Mendelian randomization analysis to explore the genetic structure of metabolites in Han Chinese and European populations and their correlation with diseases. They revealed

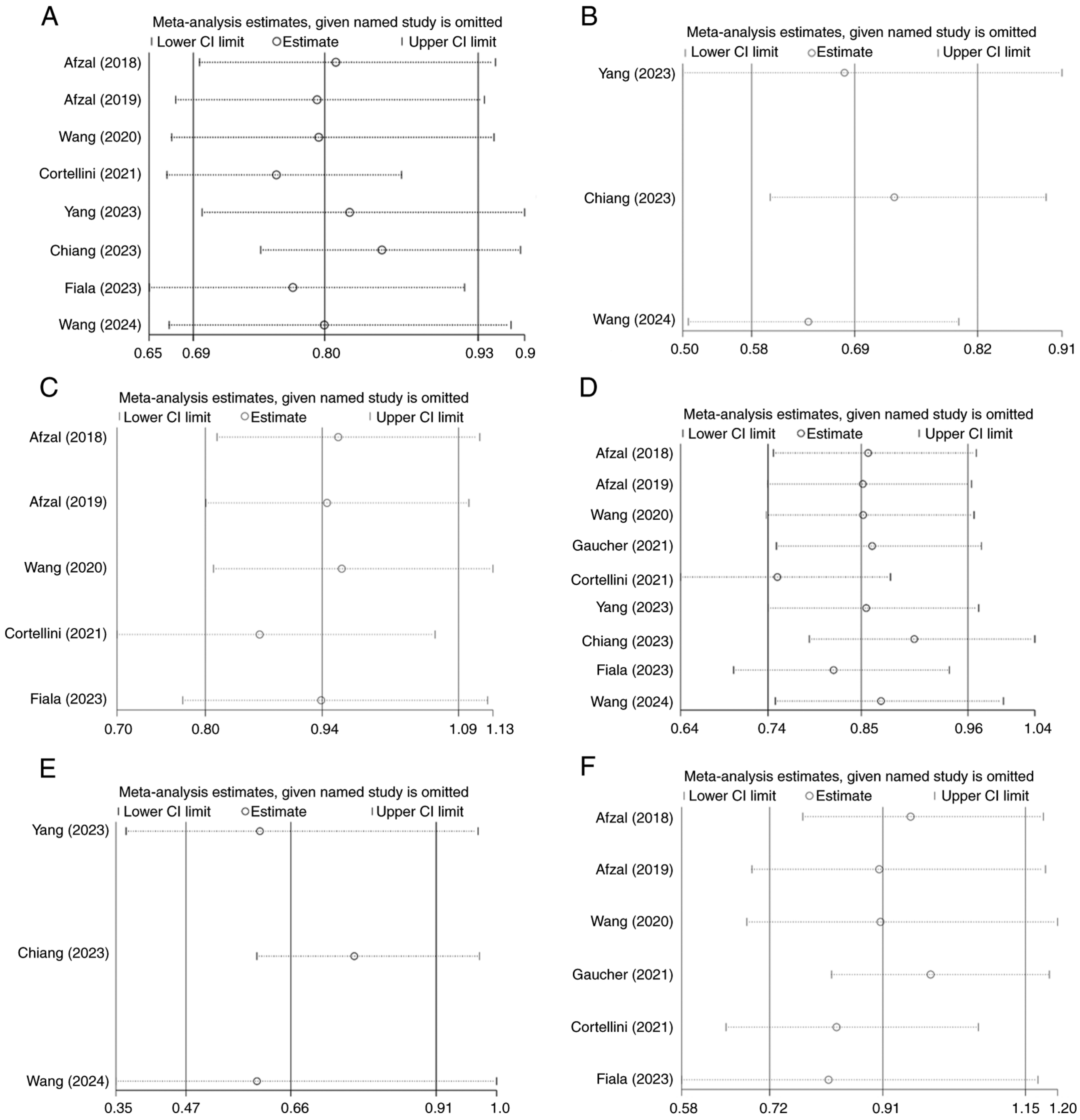

Figure 5. Sensitivity analysis: Progression-free survival (A) Overall analysis. (B) Subgroup analysis for Asians. (C) Subgroup analysis for non-Asians. Overall survival (D) Overall analysis. (E) Subgroup analysis for Asians. (F) Subgroup analysis for non-Asians. CI, confidence interval.

the genetic differences in metabolites between these ethnic groups and their impact on complex diseases, underscoring the importance of ethnic diversity in genetic research. These recent advances in metabolic research also provide unique insights into the present subgroup analysis results. The metabolic genetics, pharmacological sensitivities, immunological responses and other characteristics of individuals from different locations may be very different from one another. The efficiency of immunotherapy in combination with metformin metabolic processes may be impacted by changes in dietary and lifestyle practices. Subsequent research should account for additional personalized variables and investigate its mechanism of action in more depth.

The present meta-analysis has several limitations. Selection bias may exist, since all of the included studies are retrospective cohort studies. The lack of individual patient data prevented more detailed analyses, such as examining the impact of gene expression or metabolic state on the outcomes. In conclusion, it may be suggested that metformin may enhance the anti-tumor efficacy of immunotherapy by collaborating with it, offering a theoretical foundation for future combination treatment strategies that emphasize immune modulation.

In conclusion, this meta-analysis provides evidence that metformin use is associated with enhanced survival outcomes in cancer patients treated with immune checkpoint inhibitors, with a particularly significant effect observed in Asian populations.

These results underscore the potential of metformin as an inexpensive, widely available and generally well-tolerated agent to augment cancer immunotherapy. However, the geographical heterogeneity in treatment response cautions against its broad, indiscriminate use and emphasizes the necessity for predictive biomarkers. Future efforts should be directed toward prospective, randomized controlled trials specifically designed to validate the efficacy of metformin and ICI combination therapy. These trials should prioritize biomarker-driven patient selection, potentially focusing on individuals whose tumors exhibit specific metabolic vulnerabilities or who belong to ethnic subgroups most likely to benefit.

Acknowledgements

Not applicable.

Funding

This work was supported by the 2024 'Wild Goose Array Talents' Discipline Leader Fund of Wuxi People's Hospital (grant no. 2024-YZ-XKDTR-HD-2024), 2025 'Wild Goose Array Talents' Discipline Leader Fund of Wuxi People's Hospital (grant no. YZ-XKDTR-HD-2025), 2020 'Taihu Lake Talent Program' Leading Experts (2020-2024) (grant no. 2020-THRC-LJ-HD) and Oncology-Wuxi Municipal Innovation Team (14th Five-Year Plan) (grant no. CXTD-1).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YQ, HL and YF contributed to study conceptualization, data curation, formal analysis, investigation, methodology, writing of the original draft, and review and editing of the manuscript. SL and DH were involved in study conceptualization, supervision, validation, and review and editing of the manuscript. SL and DH confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
2. Mellman I, Coukos G and Dranoff G: Cancer immunotherapy comes of age. Nature 480: 480-489, 2011.
3. Wang DR, Wu XL and Sun YL: Therapeutic targets and biomarkers of tumor immunotherapy: Response versus non-response. Signal Transduct Target Ther 7: 331, 2022.
4. Yang L, Ning Q and Tang SS: Recent advances and next breakthrough in immunotherapy for cancer treatment. J Immunol Res 2022: 8052212, 2022.
5. Kong X, Zhang J, Chen S, Wang X, Xi Q, Shen H and Zhang R: Immune checkpoint inhibitors: Breakthroughs in cancer treatment. Cancer Biol Med 21: 451-472, 2024.
6. Weiss SA and Sznol M: Resistance mechanisms to checkpoint inhibitors. Curr Opin Immunol 69: 47-55, 2021.
7. Dobosz P, Stępień M, Golke A and Dzieciątkowski T: Challenges of the immunotherapy: Perspectives and limitations of the immune checkpoint inhibitor treatment. Int J Mol Sci 23: 2847, 2022.
8. Hunter RW, Hughey CC, Lantier L, Sundelin EI, Peggie M, Zeqiraj E, Sicheri F, Jessen N, Wasserman DH and Sakamoto K: Metformin reduces liver glucose production by inhibition of fructose-1-6-bisphosphatase. Nat Med 24: 1395-1406, 2018.
9. Horakova O, Kroupova P, Bardova K, Buresova J, Janovska P, Kopecky J and Rossmeisl M: Metformin acutely lowers blood glucose levels by inhibition of intestinal glucose transport. Sci Rep 9: 6156, 2019.
10. Zhou ZY, Ren LW, Zhan P, Yang HY, Chai DD and Yu ZW: Metformin exerts glucose-lowering action in high-fat fed mice via attenuating endotoxemia and enhancing insulin signaling. Acta Pharmacol Sin 37: 1063-1075, 2016.
11. Hua Y, Zheng Y, Yao Y, Jia R, Ge S and Zhuang A: Metformin and cancer hallmarks: Shedding new lights on therapeutic repurposing. J Transl Med 21: 403, 2023.
12. Foretz M, Guigas B and Viollet B: Metformin: Update on mechanisms of action and repurposing potential. Nat Rev Endocrinol 19: 460-476, 2023.
13. O'Connor L, Bailey-Whyte M, Bhattacharya M, Butera G, Hardell KNL, Seidenberg AB, Castle PE and Loomans-Kropp HA: Association of metformin use and cancer incidence: A systematic review and meta-analysis. J Natl Cancer Inst 116: 518-529, 2024.
14. Mu W, Jiang Y, Liang G, Feng Y and Qu F: Metformin: A promising antidiabetic medication for cancer treatment. Curr Drug Targets 24: 41-54, 2023.
15. Lu Y, Xin D, Guan L, Xu M, Yang Y, Chen Y, Yang Y, Wang-Gillam A, Wang L, Zong S and Wang F: Metformin downregulates PD-L1 expression in esophageal squamous cell catrcinoma by inhibiting IL-6 signaling pathway. Front Oncol 11: 762523, 2021.
16. Turpin R, Liu R, Munne PM, Peura A, Rannikko JH, Philips G, Boeckx B, Salmelin N, Hurskainen E, Suleymanova I, *et al*: Respiratory complex I regulates dendritic cell maturation in explant model of human tumor immune microenvironment. J Immunother Cancer 12: e008053, 2024.
17. Nishida M, Yamashita N, Ogawa T, Koseki K, Warabi E, Ohue T, Komatsu M, Matsushita H, Kakimi K, Kawakami E, *et al*: Mitochondrial reactive oxygen species trigger metformin-dependent antitumor immunity via activation of Nrf2/mTORC1/p62 axis in tumor-infiltrating CD8T lymphocytes. J Immunother Cancer 9: e002954, 2021.
18. Hanahan D, Michielin O and Pittet MJ: Convergent inducers and effectors of T cell paralysis in the tumour microenvironment. Nat Rev Cancer 25: 41-58, 2025.
19. Yao K, Zheng H and Li T: Association between metformin use and the risk, prognosis of gynecologic cancer. Front Oncol 12: 942380, 2022.
20. Brancher S, Støer NC, Weiderpass E, Damhuis RAM, Johannesen TB, Botteri E and Strand TE: Metformin use and lung cancer survival: A population-based study in Norway. Br J Cancer 124: 1018-1025, 2021.
21. Almeida-Nunes DL, Silvestre R, Dinis-Oliveira RJ and Ricardo S: Enhancing immunotherapy in ovarian cancer: The emerging role of metformin and statins. Int J Mol Sci 25: 323, 2023.
22. Zhu L, Yang K, Ren Z, Yin D and Zhou Y: Metformin as anticancer agent and adjuvant in cancer combination therapy: Current progress and future prospect. Transl Oncol 44: 101945, 2024.
23. Munoz LE, Huang L, Bommireddy R, Sharma R, Monterroza L, Guin RN, Samaranayake SG, Pack CD, Ramachandiran S, Reddy SJC, *et al*: Metformin reduces PD-L1 on tumor cells and enhances the anti-tumor immune response generated by vaccine immunotherapy. J Immunother Cancer 9: e002614, 2021.

24. Cha JH, Yang WH, Xia W, Wei Y, Chan LC, Lim SO, Li CW, Kim T, Chang SS, Lee HH, *et al*: Metformin promotes antitumor immunity via endoplasmic-reticulum-associated degradation of PD-L1. Mol Cell 71: 606-620.e7, 2018.
25. Eikawa S, Nishida M, Mizukami S, Yamazaki C, Nakayama E and Udono H: Immune-mediated antitumor effect by type 2 diabetes drug, metformin. Proc Natl Acad Sci USA 112: 1809-1814, 2015.
26. Wabitsch S, McCallen JD, Kamenyeva O, Ruf B, McVey JC, Kabat J, Walz JS, Rotman Y, Bauer KC, Craig AJ, *et al*: Metformin treatment rescues CD8+ T-cell response to immune checkpoint inhibitor therapy in mice with NAFLD. J Hepatol 77: 748-760, 2022.
27. Chiang CH, Chen YJ, Chiang CH, Chen CY, Chang YC, Wang SS, See XY, Horng CS, Peng CY, Hsia YP, *et al*: Effect of metformin on outcomes of patients treated with immune checkpoint inhibitors: A retrospective cohort study. Cancer Immunol Immunother 72: 1951-1956, 2023.
28. Afzal MZ, Mercado RR and Shirai K: Efficacy of metformin in combination with immune checkpoint inhibitors (anti-PD-1/anti-CTLA-4) in metastatic malignant melanoma. J Immunother Cancer 6: 64, 2018.
29. Page MJ, Bossuyt PM, Boutron I, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, *et al*: The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Int J Surg 88: 105906, 2021.
30. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ and Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions. 2nd edition. John Wiley & Sons, Chichester, 2019.
31. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M and Tugwell P: The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute; 2014.
32. Begg CB and Mazumdar M: Operating characteristics of a rank correlation test for publication bias. Biometrics 50: 1088-1101, 1994.
33. Afzal MZ, Dragnev K, Sarwar T and Shirai K: Clinical outcomes in non-small-cell lung cancer patients receiving concurrent metformin and immune checkpoint inhibitors. Lung Cancer Manag 8: LMT11, 2019.
34. Wang DY, McQuade JL, Rai RR, Park JJ, Zhao S, Ye F, Beckermann KE, Rubinstein SM, Johnpulle R, Long GV, *et al*: The impact of nonsteroidal anti-inflammatory drugs, beta blockers, and metformin on the efficacy of anti-PD-1 therapy in advanced melanoma. Oncologist 25: e602-e605, 2020.
35. Gaucher L, Adda L, Séjourné A, Joachim C, Guillaume C, Poulet C, Liabeuf S, Gras-Champel V, Masmoudi K, Houessinon A, *et al*: Associations between dysbiosis-inducing drugs, overall survival and tumor response in patients treated with immune checkpoint inhibitors. Ther Adv Med Oncol 13: 17588359211000591, 2021.
36. Cortellini A, Di Maio M, Nigro O, Leonetti A, Cortinovis DL, Aerts JG, Guaitoli G, Barbieri F, Giusti R, Ferrara MG, *et al*: Differential influence of antibiotic therapy and other medications on oncological outcomes of patients with non-small cell lung cancer treated with first-line pembrolizumab versus cytotoxic chemotherapy. J Immunother Cancer 9: e002421, 2021.
37. Yang J, Kim SH, Jung EH, Kim SA, Suh KJ, Lee JY, Kim JW, Kim JW, Lee JO, Kim YJ, *et al*: The effect of metformin or dipeptidyl peptidase 4 inhibitors on clinical outcomes in metastatic non-small cell lung cancer treated with immune checkpoint inhibitors. Thorac Cancer 14: 52-60, 2023.
38. Fiala O, Buti S, Takeshita H, Okada Y, Massari F, Palacios GA, Dionese M, Scagliarini S, Büttner T, Fornarini G, *et al*: Use of concomitant proton pump inhibitors, statins or metformin in patients treated with pembrolizumab for metastatic urothelial carcinoma: Data from the ARON-2 retrospective study. Cancer Immunol Immunother 72: 3665-3682, 2023.
39. Wang J, Lin J, Guo H, Wu W, Yang J, Mao J, Fan W, Qiao H, Wang Y, Yan X and Guo H: Prognostic impact of metformin in solid cancer patients receiving immune checkpoint inhibitors: Novel evidences from a multicenter retrospective study. Front Pharmacol 15: 1419498, 2024.
40. Wen J, Yi Z, Chen Y, Huang J, Mao X, Zhang L, Zeng Y, Cheng Q, Ye W, Liu Z, *et al*: Efficacy of metformin therapy in patients with cancer: A meta-analysis of 22 randomised controlled trials. BMC Med 20: 402, 2022.
41. Shen J, Ye X, Hou H and Wang Y: Clinical evidence for the prognostic impact of metformin in cancer patients treated with immune checkpoint inhibitors. Int Immunopharmacol 134: 112243, 2024.
42. Xue J, Li L, Li N, Li F, Qin X, Li T and Liu M: Metformin suppresses cancer cell growth in endometrial carcinoma by inhibiting PD-L1. Eur J Pharmacol 859: 172541, 2019.
43. Wang Z, Lu C, Zhang K, Lin C, Wu F, Tang X, Wu D, Dou Y, Han R, Wang Y, *et al*: Metformin combining PD-1 inhibitor enhanced anti-tumor efficacy in STK11 mutant lung cancer through AXIN-1-dependent inhibition of STING ubiquitination. Front Mol Biosci 9: 780200, 2022.
44. Jiang H, Suo H, Gao L, Liu Y, Chen B, Lu S, Jin F and Cao Y: Metformin plays an antitumor role by downregulating inhibitory cells and immune checkpoint molecules while activating protective immune responses in breast cancer. Int Immunopharmacol 118: 110038, 2023.
45. Kim K, Yang WH, Jung YS and Cha JH: A new aspect of an old friend: The beneficial effect of metformin on anti-tumor immunity. BMB Rep 53: 512-520, 2020.
46. Panaampon J, Zhou Y and Saengboonmee C: Metformin as a booster of cancer immunotherapy. Int Immunopharmacol 121: 110528, 2023.
47. Tan X, Li Y, Hou Z, Zhang M, Li L and Wei J: Combination therapy with PD-1 inhibition plus rapamycin and metformin enhances anti-tumor efficacy in triple negative breast cancer. Exp Cell Res 429: 113647, 2023.
48. Park JH, Jung KH, Jia D, Yang S, Attri KS, Ahn S, Murthy D, Samanta T, Dutta D, Ghidey M, *et al*: Biguanides antithetically regulate tumor properties by the dose-dependent mitochondrial reprogramming-driven c-Src pathway. Cell Rep Med 6: 101941, 2025.
49. Garstka MA, Kedzierski L and Maj T: Diabetes can impact cellular immunity in solid tumors. Trends Immunol 46: 295-309, 2025.
50. Salmon H, Remark R, Gnjatic S and Merad M: Host tissue determinants of tumour immunity. Nat Rev Cancer 19: 215-227, 2019.
51. Giraldo NA, Becht E, Vano Y, Petitprez F, Lacroix L, Validire P, Sanchez-Salas R, Ingels A, Oudard S, Moatti A, *et al*: Tumor-infiltrating and peripheral blood T-cell immunophenotypes predict early relapse in localized clear cell renal cell carcinoma. Clin Cancer Res 23: 4416-4428, 2017.
52. Ganss R: Tumour vessel remodelling: New opportunities in cancer treatment. Vasc Biol 2: R35-R43, 2020.
53. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, *et al*: Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375: 1823-1833, 2016.
54. Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G Jr, Psyrri A, Basté N, Neupane P, Bratland Å, *et al*: Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): A randomised, open-label, phase 3 study. Lancet 394: 1915-1928, 2019.
55. Larkin J, Chiarion-Sileni V, Cowey CL, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, *et al*: Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 373: 23-34, 2015.
56. Bouchi R, Kondo T, Ohta Y, Goto A, Tanaka D, Satoh H, Yabe D, Nishimura R, Harada N, Kamiya H, *et al*: A consensus statement from the Japan Diabetes Society: A proposed algorithm for pharmacotherapy in people with type 2 diabetes. J Diabetes Investig 14: 151-164, 2023.
57. Lin C, Xia M, Dai Y, Huang Q, Sun Z, Zhang G, Luo R, Peng Q, Li J, Wang X, *et al*: Cross-ancestry analyses of Chinese and European populations reveal insights into the genetic architecture and disease implication of metabolites. Cell Genom 5: 100810, 2025.