Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2024.55.008726

Negative Association between Diabetes Mellitus and the Efficacy of Cancer Immunotherapy

Raydonna Rachel Schneider[1], Ning Liu[2], Surui Liu[2], Meili Sun[1,2]*

[1]*Department of Oncology, Jinan Central Hospital, Shandong University, China*

[2]*Department of Oncology, Central Hospital Affiliated to Shandong First Medical University, China*

***Corresponding author:** Meili Sun, Department of Oncology, Jinan Central Hospital, Shandong University, Jinan, 250013, China

ARTICLE INFO

Received: March 14, 2024

Published: March 19, 2024

Citation: Raydonna Rachel Schneider, Ning Liu, Surui Liu, Meili Sun. Negative Association between Diabetes Mellitus and the Efficacy of Cancer Immunotherapy. Biomed J Sci & Tech Res 55(4)-2024. BJSTR. MS.ID.008726.

ABSTRACT

Diabetes mellitus (DM) is one of the risk factors for poor prognosis and outcomes in cancer patients. This study aimed to explore the efficacy of tumor immunotherapy for cancer patients with comorbid diabetes. A systematic electronic search on keywords including immunotherapy and tumor patients with diabetes was performed through electronic databases including PubMed, Embase and Web of Science. The primary outcome was the overall survival (OS). The secondary outcomes were the progression-free survival (PFS). Four retrospective cohort studies were included for analysis: A total of 3065 cancer patients were enrolled, including 1509 patients with comorbid diabetes. Compared to patients without diabetes, cancer patients with comorbid diabetes had a significantly lower overall survival (HR = 1.54, 95% CI: 1.27 to 1.87, P < 0.0001) and a similarly significantly shorter PFS (HR = 1.48, 95% CI: 1.24 to 1.78, P < 0.0001) after treatment with immunotherapy. This study suggested that DM might confer a shorter OS and PFS for advanced cancer patients with immunotherapy. Further prospective research is needed to confirm these findings.

Keywords: Diabetes Mellitus; Cancer Immunotherapy

Abbreviations: DM: Diabetes Mellitus; OS: Overall Survival; PFS: Progression-Free Survival; ICIs: Immune Checkpoint Inhibitors

Introduction

In recent years, immune checkpoint inhibitors (ICIs) therapy has made breakthrough progress in the field of tumor treatment, and it has demonstrated better anti-tumor therapeutic effects during clinical treatment, significantly extending the overall survival of cancer patients [1-3]. Immunotherapeutic target the T cells inhibitory receptors CTLA and PD1 and restore classically defined antitumor immune responses in tumor microenvironment [1]. However, metabolic diseases such as diabetes may negatively affect the immune system, thereby interfering with the efficacy of immune checkpoint blockade therapy [4]. In the past decades, a large number of clinical studies have evaluated the efficacy of immunotherapy in various malignancies, but few stratified analyses have been conducted specifically for patients with tumor-combined diabetes, and there is no clear clinical evidence for the efficacy of tumor immunotherapy in tumor patients with combined diabetes [5,6]. Therefore, the aim of this meta-analysis was to comprehensively analyze existing relevant studies to assess the therapeutic efficacy of tumor immunotherapy in prolonging the survival of patients with tumor-combined diabetes.

Materials and Methods

Search Strategy

We searched all the articles in PubMed, Embase and Web of Science from January 01,2009 to January 01, 2023. Based on PICOS (participants, interventions, comparisons, outcomes, and study design) guidelines, Systematic reviews and meta-analyses have become increasingly important in health care. Clinicians read them to keep up to date with their field, and they are often used as a starting point for developing clinical practice guidelines. Granting agencies may require a systematic review to ensure there is justification

for further research, and some health care journals are moving in this direction [7], using keywords ((diabetes OR diabetic) AND (immunotherapy OR immune checkpoint inhibitors OR PD-1 OR PDL1 OR CTLA4 OR atezolizumab OR nivolumab OR pembrolizumab OR ipilimumab OR durvalumab OR avelumab OR telimomab OR santolina OR tropaia) AND (cancer OR neoplasm OR tumor OR carcinoma) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial)).

Inclusion and Exclusion Criteria

Inclusion criteria:

1) Subjects were diagnosed with malignant tumors without limitation of tumor type.

2) Subjects had comorbid diabetes mellitus and were receiving treatments including immune checkpoint inhibitors (e.g., PD-1 inhibitors, PD-L1 inhibitors, CTLA-4 inhibitors) and other tumor immunotherapies.

3) The included studies are publicly available randomized controlled trials (RCTs), cohort studies and clinical trials, etc., and the language is limited to English.

4) Primary data are provided in the included studies and include the main indicators in terms of efficacy, such as tumor remission rate, progression survival, and overall survival.

Exclusion Criteria:

1) Studies animal subjects.

2) Oncology patients treated with tumor immunotherapy who were also receiving other oncology treatment regimens (e.g., chemotherapy, radiotherapy, and targeted therapy).

3) Exclusion of non-original research articles, such as conference abstracts, book reviews, editorial commentaries, case reports, reviews, and meta-analyses, as well as duplicates of the published literature

4) Incomplete data or inaccessibility of the full text of the literature.

Assessment of Risk of Bias

Two researchers utilized the Cochrane manual to conduct independent assessments of the bias risk associated with each of the seventeen included articles. The evaluation of bias risk for the included studies was performed using Rev Man 5.4.1 Software. This assessment encompassed various aspects, including random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding during outcome assessment (detection bias), handling of incomplete outcome data (attrition bias), selective reporting of outcomes (reporting bias), as well as other potential sources of bias [7,8].

Data Extraction

Articles were reviewed and screened according to inclusion and exclusion criteria. Two researchers independently extracted useful data using a standardized data extraction form, which included the following information: name of the first author, country or region of study, year of publication, number of patients, number of males and females, mean age, type of tumor, type of diabetes (e.g., type 1 diabetes, type 2 diabetes), interventions, and the primary outcome of ICI-treated overall survival (OS). The secondary outcome was progression-free survival (PFS) after ICI treatment. If disagreement occurred, it was resolved by discussion with the corresponding author.

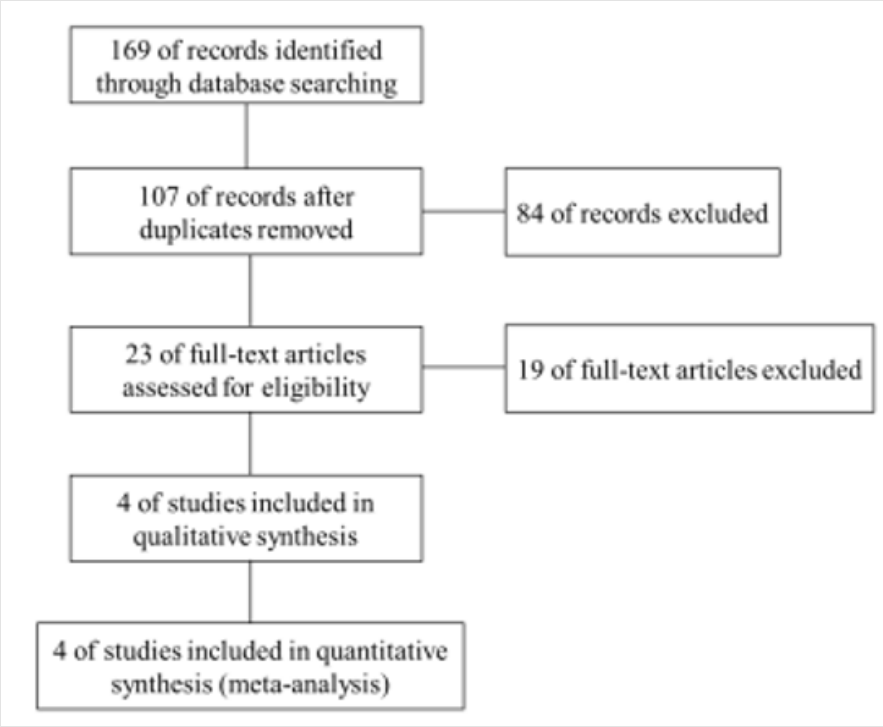
Statistical Analysis

Meta-analysis was performed using Rev Man 5.4.1 statistical software. The effect indicators of this meta-analysis included tumor remission rate, progression survival, overall survival, and quality of life assessment, etc., and the dominance ratio, risk ratio (Hazard ratio, HR), and 95% CI were used as the statistic of the effect analysis, and the forest plot was drawn. According to the recommendation of the Cochrane collaboration Network, I2 values were used to evaluate the heterogeneity among the included studies, which were divided into two grades: low and high according to the I2 value (<50% or ≥50%). $P < 0.05$ or $I2 > 50\%$ was considered significant heterogeneity. A random-effects model was used when significant heterogeneity existed, otherwise, a fixed-effects model was used. A funnel plot was used to evaluate publication bias. P values were two-tailed and statistical significance was set at 0.05 [9,10].

Results

Study Selection

The systematic search yielded 169 results: 107 publications were identified after the removal of duplicates. 84 pieces of literature were eliminated by reading the titles and abstracts of the literature, and 4 pieces of literature were finally included after reading the full text of the remaining 23 pieces of literature and carefully checking the inclusion criteria and exclusion criteria. A screening tree of the selection process is displayed in Figure 1.



Note: 169 of records were identified through database searching, 107 publications were identified after the removal of duplicates, and 4 pieces of literature were finally included according to the inclusion criteria and exclusion criteria.

Figure 1: PRISMA flow diagram of the literature search and selection.

In-Depth Study Characteristics Description

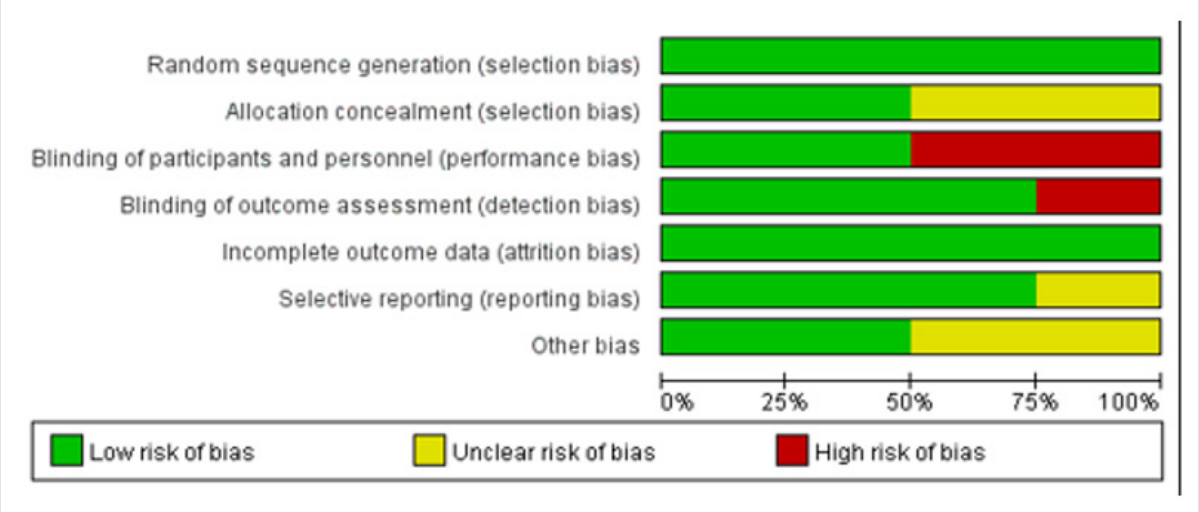
Finally, four papers were included in the Meta-analysis had a total of 3065 cancer patients of which 1509 cancer patients had diabetes mellitus and a form of cancer while 1556 patients did not have diabetes mellitus. Although the total population is large, disparity in terms of representations across the four studies is evident [11-14]. For example, study selection and contribution to this meta-analysis leads to one study contributing to the majority of participants so that 2600 cancer patients and 1395 DM patients are from a single study. As such, the other three studies contribute only 1009 cancer patients and 304 DM patients. Due to the huge disparity in participants selected for met-analysis across the four studies, generalization of the findings to the populations of patients with cancer and DM that are on immunotherapy leads to effect size that cause selection bias because when the overrepresented study is removed, the effect on the other three studies is significant such that it cannot be a representative of the population of DM and cancer patients on immunotherapy. The characteristics of the literature are shown in Table 1. The quality of the four included literature was evaluated using the Cochrane Risk of Bias Evaluation Tool, and all of them were of grade II, and the quality evaluation of the included literature is shown in Figure 2.

Table 1: Characteristics of the included literature.

Ref.	Publication time	Country/ region	No. of patients		Gender (male vs. female)		Mean age(yr)	Cancer type	Comobidities	Treatment	Follow-up (months)	Outcome
			DM-	DM+	DM-	DM+						
Yekedüz E [11]	2022	Turkey	102	35	62/40	29/6	65	Melanoma Renal cell carcinoma NSCLC SCLC	Hypertension Cardiovascular disease Hyperlipidemia Obesity COPD	Nivolumab Pembrolizumab Ipilimumab Atazolizumab	25.6	①②

Hisanaga K [12]	2021	Japan	57	22	45/12	17/5	66	Lung cancer	N/A	Nivolumab Pembroli-zumab	30	①②
Jacobi O [13]	2018	Israel	192	57	116/76	39/18	69	NSCLC	N/A	N/A	12.8	①②
Cortellini A [14]	2021	Italy	1205	1395	N/A	N/A	68	NSCLC Melano-ma Renal cell carcino-ma	N/A	N/A	N/A	①②

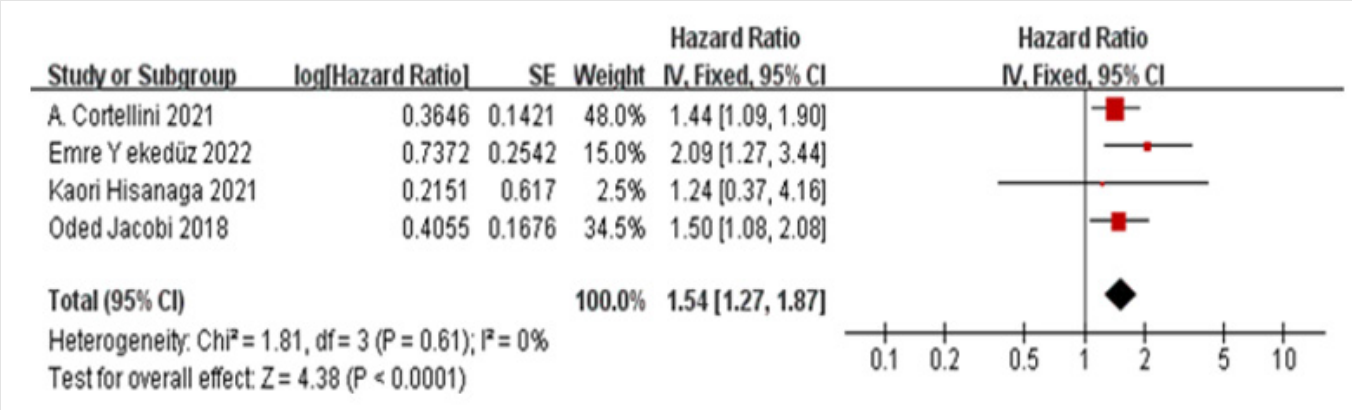
Note: ① =Over Survival; ② =Progression survival. N/A= Not Mentioned.



Note: Cochrane Risk of Bias Evaluation Tool was used to evaluate the quality of the four included literature and all of them were of grade II.
Figure 2: Assessment of Risk of Bias.

Effects of DM on OS of Patients Treated with Immunotherapy

Four studies reported the overall survival of patients, and a total of 3065 cancer patients were included, including 1509 patients with comorbid diabetes. The results of heterogeneity test showed that there was no heterogeneity among the studies (I2=0%, P=0.61), and the HR and 95% CI of OS of each study were combined using a fixed-effects model. Meta-analysis showed that cancer patients with DM had a significant shortening of overall survival (HR=1.54, 95% CI: 1.27-1.87, P<0.0001), as shown in Figure 3.

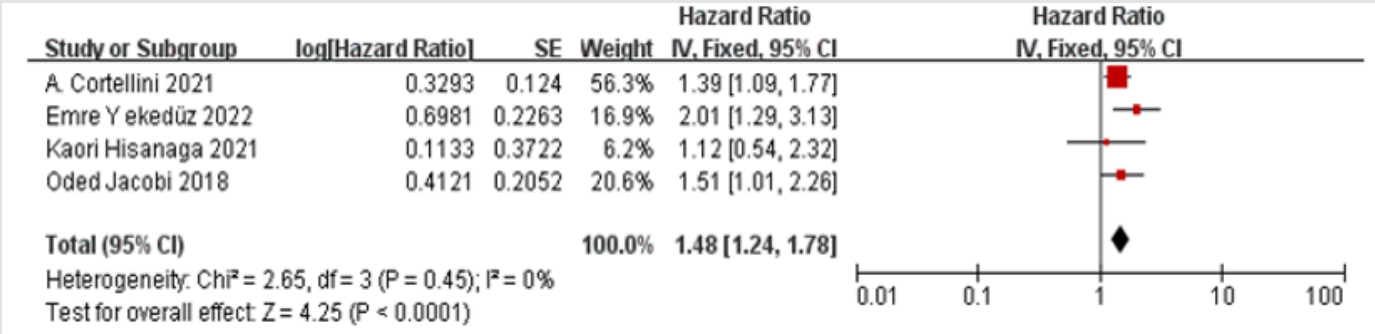


Note: The heterogeneity test showed that there was no heterogeneity among the studies (I2=0%, P=0.61). Meta-analysis showed that cancer patients with DM had a significant shortening of OS (HR=1.54, 95% CI: 1.27-1.87, P<0.0001).

Figure 3: Forest plot of hazard ratios for overall survival of cancer patients with Diabetes versus non-Diabetes around immune checkpoint inhibitor treatment.

Effects of DM on PFS of Patients Treated with Immunotherapy

Four studies reported the progression-free survival of patients and included a total of 3065 cancer patients, including 1509 patients with comorbid diabetes. The results of heterogeneity test showed that there was no heterogeneity among the studies (I2 = 0%, P=0.45), and the HR and 95% CI of PFS of each study were combined using a fixed-effects model. Meta-analysis showed that the PFS was significantly shorter in cancer patients with DM (HR = 1.48, 95% CI: 1.24-1.78, P<0.0001), as shown in Figure 4. Sensitivity analysis was done to eliminate the doubt that over representation of participants in the meta-analysis by one study could cause selection bias from the effect size. The findings show that removal of the overrepresented study and analysis of the other three shows minimal effect on the results because the y = 488.06 in the sensitivity test when the large population is included but this reduced to y = 314.08 when it is removed, which means that all the four studies show a common trend in terms of the positive effect size.



Note: The heterogeneity test showed that there was no heterogeneity among the studies (I2 = 0%, P=0.45). Meta-analysis showed that the PFS was significantly shorter in cancer patients with DM (HR = 1.48, 95% CI: 1.24-1.78, P<0.0001).

Figure 4: Forest plot of hazard ratios for progression-free survival of cancer patients with Diabetes versus non-Diabetes around immune checkpoint inhibitor treatment.

Discussion

Immune checkpoint blockade therapy is a revolutionary cancer treatment that attacks and inhibits tumor growth by activating the patient›s own immune system [15,16]. This therapy has shown extremely significant potential to effectively inhibit tumor growth and progression, while prolonging the overall survival of patients [17,18]. Although the exact cellular mechanisms that predict patient responses to immune checkpoint blockade therapy have not yet to be well defined, patients with increased T cell infiltration into the tumor microenvironment and heightened activation of intratumorally cytotoxic T lymphocytes might benefit form immune checkpoint blockade therapy [19, 20]. Numerous studies have shown that diabetic patients are often accompanied by abnormalities of the

immune system, including alterations in the number and function of immune cells and the development of autoimmune diseases [21,22]. To date, many preclinical and clinical studies have been conducted on the effects of hyperglycemia on the immune system [23]. These studies concluded that hyperglycemia induces T-cell dysfunction, increases M2 macrophages in the tumor microenvironment, and decreases natural killer cell-mediated tumor death [24]. Researchers demonstrated that hyperglycemia significantly reduces in vivo immune function of memory CD8+ T cells, which results in diminished immune cell killing of tumor cells and consequently tumor proliferation [22,25].

In addition, hyperglycemia may also affect the tumor microenvironment and inhibit the infiltration and activity of immune cells [26]. The impairment of recruitment of CD8+T cells was correlated with attenuated expression of cell adhesion molecules in mice with diabetes [27]. In this study, we conducted a systematic evaluation and meta-analysis to assess the impact of hyperglycemia on the outcome of ICIs in patients with advanced cancer. Meta-analysis showed that cancer patients with diabetes mellitus had a significantly lower overall survival and progression-free period after immunotherapy compared to patients without diabetes mellitus. These results suggest that diabetes has a negative effect on tumor patients placed on immunotherapy. Leshem Y et al found that DM was an independent risk factor for shorter PFS and OS in patients with non-small cell lung cancer treated with pembrolizumab [28]. Tortellini et al found that patient with type 2 diabetes mellitus and solid tumor displayed an reduced overall survival benefits from immune checkpoint inhibitors [29]. Exposure to metformin, but not other glucose-lowering medications, was associated with an increased risk of death and disease progression. Literature review also showed that diabetes mellitus has a significant impact on patients with hepatocellular carcinoma receiving immune checkpoint blockade therapy [30]. The mechanism of action of immune checkpoint blocking drugs relies on the normal functioning of the immune system; however, diabetes-induced impairment of immune function may reduce the efficacy of the drugs, and the effectiveness of this therapeutic strategy may be limited.

Comorbidities and complications often negatively impact the therapeutic efficacy of immune checkpoint blockade therapy [31]. Some studies have shown that diabetic patients also face a higher risk of autoimmune diabetes and immune-related adverse effects such as immune inflammatory response and immune-related thyroid disease when receiving immune checkpoint blockade therapy, and these immune disorders may lead to decreased responsiveness to immune checkpoint blockade therapies and diminish the effectiveness of the anti-tumor immune response [32-35]. Also, these side effects may further exacerbate a patient›s pre-existing diabetic condition, leading to a variety of cytokines releasing, some of which may affect insulin secretion and use. Therefore, insulin therapy in diabetic patients may need to be adjusted accordingly when immune checkpoint blockade therapy is administered. In view of the above implications, clinicians need to pay more attention to the management and monitoring of diabetes in diabetic patients receiving immune checkpoint blockade therapy. This includes closely monitoring blood glucose levels and making timely adjustments to insulin regimens to ensure good control of diabetes; regularly assessing immune-related side effects for early detection and management; and weighing efficacy against risk by integrating the patient›s diabetic status into the treatment regimen. Cofounding factors in the study such as comorbidities could influence patient outcomes because their effect on treatment outcomes has not been documented.

For example, some of the patients have other comorbidities such as obesity, cardiovascular disease, hypertension, or dyslipidemia, which are affect the choice of treatment of diabetes and decrease the quality of life in a patient by increasing the risk of multiorgan failure and even death. However, because these comorbidities are not variables in the current study their effect on the participants cannot be isolated from the outcomes because the occurrence of some of them such as cardiovascular disease, hypertension, and dyslipidemia alongside diabetes and cancers diminishes the chances of survival depending on the stage of each disease the patient has and prognosis. In addition, the four studies do not mention the stage of the cancer (stage of disease), and this is a vital component in the study because advanced stages of the disease are associated with poor prognosis and low survival rates while early stages of the disease coupled with comorbidities are also associated with poor prognosis and low survival rates. As such, understanding the effect of the comorbidities and stage of the disease on the cancer treatment by immunotherapy among cancer patients with diabetes would influence the results if such components of the patient's condition were considered as variable. Hence the cofounders in the study including the presence of comorbidities and stage of the disease are variables that influence disease prognosis and outcome in terms of survival, but their effects have not been assessed despite their presence being mentioned.

Conclusion

Overall, DM was significantly associated with poor survival in cancer patients receiving immunotherapy. However, the effect of the stage of the cancer, presence of comorbidities needs to be assessed by comparing data of the outcomes from non-DM patients with cancer on immunotherapy to DM patients. Further study is needed to confirm these findings.

Declaration of Interests

The authors have declared that no competing interest exists.

References

1. Kubli S, Berger T, Araujo D, Lillian L Siu, Tak W Mak, et al. (2021) Beyond immune checkpoint blockade: emerging immunological strategies. Nat Rev Drug Discov 20(12): 899-919.
2. Korman AJ, Garrett Thomson SC, Lonberg N (2022) The foundations of immune checkpoint blockade and the ipilimumab approval decennial. Nat Rev Drug Discov 21(7): 509-528.
3. Huang AC, Zappasodi R (2022) A decade of checkpoint blockade immunotherapy in melanoma: understanding the molecular basis for immune sensitivity and resistance. Nat Immunol 23(5): 660-670.
4. Monami M, Naletto L, Nreu B, Ilaria Dicembrini, Giorgio Sesti, et al. (2020) Immune checkpoints inhibitors and hyperglycemia: A Meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 162: 108115.
5. Rojas A, Schneider I, Lindner C, Ileana Gonzalez, Miguel A Morales, et al. (2023) Association between diabetes and cancer. Current mechanistic insights into the association and future challenges. Mol Cell Biochem 478(8): 1743-1758.
6. Biadgo B, Abebe M (2016) Type 2 Diabetes Mellitus and Its Association with the Risk of Pancreatic Carcinogenesis: A Review. Korean J Gastroenterol 67(4): 168-177.
7. Moher D, Liberati A, Tetzlaff J, et al. (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.Open Med 3(3): e123-130.
8. Higgins J, Altman D, Gøtzsche P, Peter Jüni, David Moher, et al. (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343: d5928.
9. Higgins J, Thompson S, Deeks J, Douglas G Altman, et al. (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414): 557-560.
10. Ioannidis J (2008) Interpretation of tests of heterogeneity and bias in meta-analysis. J Eval Clin Pract 14(5): 951-957.
11. Yekedüz E, Köksoy E, Yazgan S, Göktürk Karataş, Filiz Çay Şenler, et al. (2022) Chronic hyperglycemia based on diabetes is independently associated with decreased survival in patients with advanced cancer treated with immune checkpoint inhibitors. Anticancer Drugs 33(10): 1145-1149.
12. Hisanaga K, Uchino H, Kakisu N, Masahiko Miyagi, Fukumi Yoshikawa, et al. (2021) Pre-Existing Diabetes Limits Survival Rate After Immune Checkpoint Inhibitor Treatment for Advanced Lung Cancer: A Retrospective Study in Japan. Diabetes Metab Syndr Obes 14: 773-781.
13. Jacobi O, Landman Y, Reinhorn D, Oded Icht, Michal Sternschuss, et al. (2021) The Relationship of Diabetes Mellitus to Efficacy of Immune Checkpoint Inhibitors in Patients with Advanced Non-Small Cell Lung Cancer. Oncology 99(9): 555-561.
14. Cortellini A, Mallardo D, Cleary S, M Bersanelli, D Santini, et al. (2021) 966P Diabetes therapy burden as proxy of impairment of immune checkpoint inhibitors efficacy. Annals of Oncology 32(Suppl 5): S834.
15. Bagchi S, Yuan R, Engleman E (2021) Immune Checkpoint Inhibitors for the Treatment of Cancer: Clinical Impact and Mechanisms of Response and Resistance. Annu Rev Pathol 16: 223-249.
16. Lahiri A, Maji A, Potdar P, Navneet Singh, Purvish Parikh, et al. (2023) Lung cancer immunotherapy: progress, pitfalls, and promises. Mol Cancer 22(1): 40.
17. Zhou F, Qiao M, Zhou C (2021) The cutting-edge progress of immune-checkpoint blockade in lung cancer. Cell Mol Immunol 18(2): 279-293.
18. Srinivas S, Bajpai J (2021) Immunotherapy in Special and Rare Situations: A Brief Review. J Immunother Precis Oncol 4(4): 180-184.
19. Sharma P, Allison J (2015) The future of immune checkpoint therapy. Science. 348(6230): 56-61.
20. Daud A, Loo K, Pauli M, Robert Sanchez-Rodriguez, Priscila Munoz Sandoval, et al. (2016) Tumor immune profiling predicts response to anti-PD-1 therapy in human melanoma. J Clin Invest 126(9): 3447-3452.
21. Abdihamid O, Omar A, Rugambwa T (2021) Defining the correlation between immune-checkpoint inhibitors-related adverse events and clinical outcomes: a narrative review. Ecancermedicalscience 15: 1314.
22. Dyck L, Lynch L (2023) Diverse effects of obesity on antitumor immunity and immunotherapy. Trends Mol Med 29(2): 112-123.
23. Berbudi A, Rahmadika N, Tjahjadi A, Rovina Ruslami (2020) Type 2 Diabetes and its Impact on the Immune System. Curr Diabetes Rev 16(5): 442-449.
24. Daryabor G, Atashzar M, Kabelitz D, Seppo Meri, Kurosh Kalantar, et al. (2020) The Effects of Type 2 Diabetes Mellitus on Organ Metabolism and the Immune System. Front Immunol 11: 1582.
25. Kavazović I, Krapić M, Beumer-Chuwonpad A, Bojan Polić, Tamara Turk Wensveen, et al. (2022) Hyperglycemia and Not Hyperinsulinemia Mediates Diabetes-Induced Memory CD8 T-Cell Dysfunction. Diabetes 71(4): 706-721.
26. Rojas A, Lindner C, Schneider I, Ileana Gonzàlez, Hernan Araya, et al. (2021) Diabetes mellitus contribution to the remodeling of the tumor microenvironment in gastric cancer. World J Gastrointest Oncol 13(12): 1997-2012.
27. Kumar M, Roe K, Nerurkar P, Beverly Orillo, Karen S Thompson, et al. (2014) Reduced immune cell infiltration and increased pro-inflammatory mediators in the brain of Type 2 diabetic mouse model infected with West Nile virus. J Neuroinflammation 11: 80.
28. Leshem Y, Dolev Y, Siegelmann-Danieli N, Sarah Sharman Moser, Lior Apter, et al. (2023) Association between diabetes mellitus and reduced efficacy of pembrolizumab in non-small cell lung cancer. Cancer 129(18): 2789-2797.
29. Cortellini A, D'Alessio A, Cleary S, Sebastiano Buti, Melissa Bersanelli, et al. (2023) Type 2 Diabetes Mellitus and Efficacy Outcomes from Immune Checkpoint Blockade in Patients with Cancer. Clin Cancer Res 29(14): 2714-2724.
30. Rimassa L, Personeni N, Czauderna C, Friedrich Foerster, Peter Galle, et al. (2021) Systemic treatment of HCC in special populations. J Hepatol 74(4): 931-943.
31. Von Itzstein M, Gonugunta A, Mayo H, John D Minna, David E Gerber, et al. (2020) Immunotherapy Use in Patients with Lung Cancer and Comorbidities. Cancer J 26(6): 525-536.
32. Minlikeeva A, Freudenheim J, Cannioto R, J Brian Szender, Kevin H Eng, et al. (2017) History of hypertension, heart disease, and diabetes and ovarian cancer patient survival: evidence from the ovarian cancer association consortium. Cancer Causes Control 28(5): 469-486.
33. De Filette J, Pen J, Decoster L, Thomas Vissers, Bert Bravenboer, et al. (2019) Immune checkpoint inhibitors and type 1 diabetes mellitus: a case report and systematic review. Eur J Endocrinol 181(3): 363-374.
34. Zhang Z, Sharma R, Hamad L, Grazyna Riebandt, Kristopher Attwood, et al. (2023) Incidence of diabetes mellitus in patients treated with immune checkpoint inhibitors (ICI) therapy - A comprehensive cancer center experience. Diabetes Res Clin Pract 202: 110776.
35. Atkinson M, Lansdown A (2022) Endocrine immune-related adverse events: Adrenal, parathyroid, diabetes insipidus, and lipoatrophy. Best Pract Res Clin Endocrinol Metab 36(3): 101635.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2024.55.008726

Meili Sun. Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php