Type 2 Diabetes Mellitus and Efficacy Outcomes from Immune Checkpoint Blockade in Patients with Cancer

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ABSTRACT

Purpose: No evidence exists as to whether type 2 diabetes mellitus (T2DM) impairs clinical outcome from immune checkpoint inhibitors (ICI) in patients with solid tumors.

Experimental Design: In a large cohort of ICI recipients treated at 21 institutions from June 2014 to June 2020, we studied whether patients on glucose-lowering medications (GLM) for T2DM had shorter overall survival (OS) and progression-free survival (PFS). We used targeted transcriptomics in a subset of patients to explore differences in the tumor microenvironment (TME) of patients with or without diabetes.

Results: A total of 1,395 patients were included. Primary tumors included non–small cell lung cancer (NSCLC; 54.7%), melanoma (24.7%), renal cell (15.0%), and other carcinomas (5.6%). After multivariable analysis, patients on GLM ($n = 226$, 16.2%) displayed an increased risk of death [HR, 1.29; 95% confidence interval (CI),1.07–1.56] and disease progression/death (HR, 1.21; 95% CI, 1.03–1.43) independent of number of GLM received. We matched 92 metformin-exposed patients with 363 controls and 78 patients on other oral GLM or insulin with 299 control patients. Exposure to metformin, but not other GLM, was associated with an increased risk of death (HR, 1.53; 95% CI, 1.16–2.03) and disease progression/death (HR, 1.34; 95% CI, 1.04–1.72). Patients with T2DM with higher pretreatment glycemia had higher neutrophil-to-lymphocyte ratio ($P = 0.04$), while exploratory tumoral transcriptomic profiling in a subset of patients ($n = 22$) revealed differential regulation of innate and adaptive immune pathways in patients with T2DM.

Conclusions: In this study, patients on GLM experienced worse outcomes from immunotherapy, independent of baseline features. Prospective studies are warranted to clarify the relative impact of metformin over a preexisting diagnosis of T2DM in influencing poorer outcomes in this population.

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Translational Relevance

In this study, we highlight how patients with advanced solid tumors and concomitant type 2 diabetes mellitus (T2DM) experience worse outcome from immune checkpoint inhibitors (ICI) independent of baseline clinicopathologic characteristics. In view of the increasing global burden of T2DM and the constantly expanding clinical indications of ICI-based therapies, the identification of metabolic host factors as determinants of immune response in patients with cancer has relevant implications for clinical practice. Prospective studies should investigate whether receipt of certain glucose-lowering medications such as metformin as opposed to quality of diabetes control might be modifiable factors to improve outcomes from immunotherapy.

Introduction

Immune checkpoint inhibitors (ICI) have led to a significant increase in the survival of patients affected by a widening variety of malignancies (1). Although reinvigoration of an immune-exhausted effector T-cell response is at the basis of the mechanism of action of ICI, several host characteristics have been increasingly recognized for their capacity to enhance or blunt ICI efficacy (2–4). Concomitant medications, patients' body mass index (BMI), and the presence of a subclinical proinflammatory response are among the accumulating traits to have emerged in the recent past as key modulators of immunotherapy efficacy (2, 5).

The complex relationship existing between metabolic syndrome, type 2 diabetes mellitus (T2DM), and cancer has been known for a long time (6). T2DM is a highly prevalent comorbidity affecting up to 15% of patients at the time of cancer diagnosis (7). In an increasingly aging and more comorbid population, cancer and T2DM share common risk factors (8) and mechanistic evidence has highlighted an increased risk of cancer among patients with a preexisting diagnosis of diabetes (9).

On the other hand, the complex metabolic changes that characterize the progression of diabetes may exert multiple immune-suppressive effects potentially impairing anticancer immunity (10). Studies on peripheral blood mononuclear cells (PBMC) have shown how hyperglycemia leads to loss of Interleukin-10 (IL-10) secretion by myeloid cells and reduced production of IFN-γ and TNF-α by T cells (11), along with lower production of IL-12 and IFN-γ in PBMC cultures after exposure to pathogens (12). Hyperglycemia can also cause neutrophil dysfunction, including defects in reactive oxygen species (ROS) production, Ig-mediated opsonization, and degranulation (13–15). The role of diabetes in promoting immune dysfunction is further supported by the finding that hyperglycemia can induce macrophage polarization toward a protumorigenic M2 phenotype (16, 17) alongside functional defects in natural killer (NK) cells' degranulation capacity (18).

In a therapeutic landscape characterized by a continuously expanding list of indications where ICIs have been proven effective (19), it is of the utmost importance to establish whether a concomitant diagnosis of T2DM carries a negative impact on ICI efficacy, to identify patients at risk of worse outcome and inform clinical practice.

In this study, we analyzed a large multicenter cohort of patients with advanced cancers treated with chemotherapy-free ICI-based regimens to evaluate whether use of glucose-lowering medications (GLM) as a surrogate for a prior history of T2DM might be associated with clinical outcome from ICIs in patients with solid tumors.

Materials and Methods

Study objectives and design

The aim of this analysis was to describe the potential impact of preexisting T2DM on clinical outcomes from ICI-based treatments in a large multicenter cohort of patients with advanced solid tumors treated outside clinical trials (20–27).

Overall, 21 institutions from Italy and the United Kingdom participated in the data collection (Supplementary Table S1) and retrospectively included patients with stage IV malignancy treated with ICIs as first- or subsequent line therapy from June 2014 to June 2020, with a data cut-off period of December 31, 2020. Patients on ICI-based combinations, such as chemo-immunotherapy and targeted therapy ICIs, were excluded.

Programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) and CTLA-4 inhibitors were administered at doses and schedules indicated in the respective summary of product characteristics.

Clinical outcomes of interest included progression-free survival (PFS), defined as the time from treatment initiation to disease progression or death (whichever occurred first) and overall survival (OS), defined as the time from treatment initiation to patients' death or loss to follow-up. Periodic tumor reassessment was performed at the discretion of treating clinicians with frequency ranging from 12 to 16 weeks. Investigators were asked to provide disease progression information according to RECIST (V. 1.1) criteria (28). For PFS as well as for OS, patients without events were considered as censored at the time of the last follow-up.

To reproducibly assess the effect of T2DM on ICI outcomes, we used the receipt of any GLMs at the moment of ICI initiation as a surrogate of a diagnosis of T2DM and define the population of interest. GLMs started at any time prior to and taken until immunotherapy initiation were grouped in accordance to the international guidelines and recommendations (29) as metformin, other oral diabetes medications (including sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase inhibitors, DPP-4 inhibitors, SGLT2 inhibitors, and cycloset) and insulin therapy.

We first assessed the impact of diabetes on OS and PFS with univariable and multivariable analyses. In addition, considering the differential distribution of baseline patients' characteristics between patients with and without diabetes, we also performed a propensity score matching (PSM) between the two groups and explored OS and PFS across the matched populations.

Subsequently, we conducted two additional PSM subanalyses among patients with non–small cell lung cancer (NSCLC) and melanoma, to explore the association between the receipt of baseline GLMs and OS/PFS in the two matched cohorts.

Baseline exposure to each class of antidiabetic medication was also verified for their association with OS and PFS following ICI therapy. We then stratified patients with diabetes according to the receipt of one class versus multiple classes of GLMs at the time of ICI commencement, a methodology that allowed us to infer potential association between oncologic outcomes and surrogates of diabetes severity and duration.

In an attempt to verify the independence between the diagnosis of diabetes and type of antidiabetic treatment received, we performed two separate PSM procedures between metformin-exposed patients (after the exclusion of patients on any non-metformin antidiabetic drug), patients on other oral antidiabetic drugs/insulin therapy only (after the exclusion of patients on metformin) and those without diabetes.

To investigate whether chronic hyperglycemia is associated with systemic inflammation in patients with cancer, we computed the

median baseline glycemia (MBG) from up to three random blood sugar test samples performed within 3 months prior to ICI initiation. We described the association between MBG and the pretreatment neutrophil-to-lymphocyte ratio computed from routine full blood counts test taken within 30 days prior to ICI therapy initiation.

In an ancillary translational analysis and to complement our clinical findings, we intended to establish whether the tumor microenvironment (TME) of patients with preexisting diabetes was associated with significantly different features in the intratumoral immune infiltrate. After total RNA extraction of macrodissected unstained sections containing >20% of tumor tissue, targeted transcriptome profiling was performed on a subset of primary tumor samples of patients with diabetes and nondiabetic controls extracted from the Imperial College London (London, England) cohort, using the NanoString PanCancer Immune Profiling panel on an nCounter Analysis System (NanoString Technologies). Methodology of targeted transcriptomic analysis follow established protocols (30) with details reported in Supplementary Methods.

The procedures followed were in accordance with the precepts of good clinical practice and the Declaration of Helsinki. Written informed consent was obtained from alive patients at the moment of data collection, although it was waived by competent authorities due to anonymized nature of patient data and retrospective design of the study for deceased patients. The study was approved by the respective local ethical committees on human experimentation of each institution, after previous approval by the coordinating center (University of L'Aquila, L'Aquila, Italy, internal review board protocol no. 32865, approved on July 24, 2018).

Statistical analysis

Baseline patients' characteristics were reported with descriptive statistics as appropriate. The χ^2 and test was used to compare categorical variables. PFS/OS were evaluated and compared using the Kaplan–Meier method and the log-rank test. Duration of follow-up was calculated according to the reverse Kaplan–Meier method. Cox proportional hazards regression was used for the univariable and multivariable analysis of the risk of disease progression/death and death, and to compute the HR with 95% CIs.

Fixed multivariable models were used including all the variables already known to significantly impact clinical outcomes in the cohort including primary tumor types [NSCLC, melanoma, renal cell carcinoma (RCC), and others], age (continuous), biological sex (male vs. female), Eastern Cooperative Oncology Group-Performance Status (ECOG-PS; 0–1 vs. ≥ 2), burden of disease (number of metastatic sites ≤ 2 vs. > 2), treatment line (first vs. second vs. further lines), BMI – continuous, corticosteroids at immunotherapy initiation (dose ≥10 mg prednisone daily or equivalent —yes vs. no), and systemic antibiotics at immunotherapy initiation (yes vs. no; both taken within 30 days prior to ICIs initiation; refs. 20–26, 31).

Acknowledging that data source consisted of 21 different institutions, which could represent a source of bias, a center-specific conditional interpretation by using frailty models was applied to correct all the 95% CIs from multivariable Cox regressions.

To respectively compare the outcome of patients on metformin only and those on other oral antidiabetic drugs/insulin therapy only with those without diabetes, separated PSM procedures with nearest method, 1:4 ratio and a caliper of 0.2 were performed, including all the above mentioned clinical characteristics (32). The balancing ability of the PSM were estimated through the standardized mean differences (SMD) of the matched characteristics. Considering differences in sample size and prevalence of patients with diabetes between different primary tumor groups, a 1:1 ratio, 0.1 caliper and 1:3 ratio, 0.1 caliper were used for the PSM in the NSCLC and melanoma cohorts, respectively (33).

The Kruskal–Wallis test was used to compare MBG between patients with diabetes and nondiabetes. Linear regression and logistic regression with ORs and 95% CIs were used to the associations between the MBG and the neutrophil-to-lymphocyte ratio (NLR).

All *P* values were two-sided and CIs set at the 95% level, with significance predefined to be at < 0.05. Analyses were performed using the R-studio software [R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing] and the MedCalc Statistical Software version 20 (MedCalc Software Ltd, 2021; https://www.medcalc.org).

Data availability statements

The datasets used during this study are available from the corresponding author upon formal reasonable request and after approval of the study steering committee.

Results

Patients' characteristics

Overall, 1,395 consecutive patients with advanced solid tumors treated with nivolumab (766, 54.9%), pembrolizumab (499, 35.8%), atezolizumab (71, 5.1%), ipilimumab (35, 2.5%), and other ICIs (24, 1.7%) were included in the analysis. As reported in **Table 1**, median age was 68 years (range: 21–91), male/female ratio was 888/507 and primary tumors were: NSCLC (54.7%), melanoma (24.7%), RCC (15.0%), and others (5.6%). In total, 226 patients (16.2%) were on GLMs, of which 147 (65.0%) on metformin, 125 (55.3%) on other oral diabetes medication, and 76 (33.6%) patients on insulin therapy. Details of diabetes medications are summarized in Supplementary Table S2. Of note, 41 patients had preexisting autoimmune disorders (8 cases of thyroid dysfunction, 10 skin disorders, 4 inflammatory bowel disease, 2 vasculitis, 2 neurologic disorders, and 15 others). There were no cases of preexisting type 1 diabetes.

Patients with diabetes were older (median age 71 vs. 68 years; $P < 0.0001$), more likely males (73.9% vs. 61.7%; $P = 0.0005$), with higher BMI (median 25.6 vs. 24.9; $P = 0.0075$). Patients with diabetes more frequently presented with a low-burden disease (≤ 2 metastatic sites 41.2% vs. 49.3%; $P = 0.0253$).

At the median follow-up of 32.5 months (95% CI, 31.1–34.0) the median OS and PFS for the overall population were 17.7 months (95% CI, 15.5–19.5; 832 events) and 8.2 months (95% CI, 7.3–9.2; 1,057 events).

Preexisting T2DM is associated with worse outcome from ICIs

In the overall population, patients receiving GLMs displayed an increased risk of death (HR, 1.23; 95% CI,1.03–1.47; **Fig. 1A**) but not of disease progression/death (HR, 1.14; 95% CI, 0.97–1.33; **Fig. 1B**) in comparison with the control group. Considering the differential distribution of baseline features between the two groups, multivariable analyses were performed for both the clinical endpoints. After adjustment for all the available confounders (**Table 2**), receipt of GLMs resulted to be independently associated with an increased risk of death (HR, 1.29; 95% CI,1.07–1.56) and disease progression/death (HR, 1.21; 95% CI, 1.03–1.43).

After the PSM procedure, 225 patients on GLMs were matched with 808 patients from the control group, with an optimal balancing ability (Supplementary Table S3). Within the matched cohorts, the receipt of GLMs was associated with an increased risk of death (HR, 1.25; 95%

Table 1. Baseline patients' characteristics for the overall population and according to the receipt of diabetes medications.

	Total ($N = 1,395$) n° (%)	No GLM ($n = 1,169$) n (%)	GLM ($n = 226$) n (%)	P
Age (years)	—	—	—	$P < 0.0001$
Median	68	68	71	—
Range	21–91	21–91	22–88	—
Sex	—	—	—	$P = 0.0005$
Male	888 (63.7)	721 (61.7)	167 (73.9)	—
Female	507 (36.3)	448 (38.3)	59 (26.1)	—
ECOG-PS	—	—	—	$P = 0.7963$
0–1	1,205 (86.4)	1011 (86.5)	194 (85.8)	—
≥2	190 (13.6)	158 (13.5)	32 (14.2)	—
Primary tumor	—	—	—	$P = 0.0730$
NSCLC	763 (54.7)	625 (53.5)	138 (61.1)	
Melanoma	345 (24.7)	296 (25.3)	49 (21.7)	—
RCC	209 (15.0)	185 (15.8)	24 (10.6)	—
Others	78 (5.6)	63 (5.4)	15 (6.6)	—
No. of metastatic sites	—	—	—	$P = 0.0253$
≤2	726 (52.0)	593 (50.7)	133 (58.8)	—
>2	669 (48.0)	576 (49.3)	93 (41.2)	—
Treatment line of immunotherapy				$P = 0.0522$
First	519 (37.2)	422 (36.1)	97 (42.9)	—
Nonfirst	876 (62.8)	747 (63.9)	129 (57.1)	—
BMI (kg/m^2)	—	—	—	$P = 0.0075$
Median (range)	25.1 (13.6–50.8)	24.9 (13.6–50.8)	25.6 (16.4–43.2)	—
Underweight (≤18.5)	59 (4.2)	54 (4.6)	5 (2.2)	—
Normal weight (18.5–25)	628 (45.0)	538 (46.0)	90 (39.8)	$P = 0.0711$
Overweight (25-30)	508 (36.4)	415 (35.5)	93 (41.2)	—
Obese (≥ 30)	200 (14.3)	162 (13.9)	38 (16.8)	—
Baseline steroids				$P = 0.3135$
No	1,043 (74.8)	868 (74.3)	175 (77.4)	—
Yes	352 (25.1)	301 (25.7)	51 (22.6)	—
Baseline systemic antibiotics	—	—	—	$P = 0.0502$
No	1,043 (74.8)	1,076 (92.0)	199 (88.1)	—
Yes	352 (25.1)	93 (8.0)	27 (11.9)	—
Metformin	—	—	—	—
No	1,248 (89.5)	—	147 (65.0)	—
Yes	147 (10.5)	—	—	—
Other oral diabetes medications	—	—	—	—
No	1,270 (91.0)	—	125 (55.3)	—
Yes	125 (9.0)	—	—	—
Insulin therapy		—	—	—
No	1,319 (94.6)	—	76 (33.6)	—
Yes	76 (5.4)	—	—	—

CI,1.04–1.50; **Fig. 1C**) and a tendence toward and increased risk of disease progression/death (HR, 1.17; 95% CI, 0.99–1.38; **Fig. 1D**).

Among 763 patients with NSCLC, 138 (18.1%) were on baseline GLMs. After PSM, 135 of them were matched with 135 patients from the control group with a good balancing ability (Supplementary Table S4). Within the matched NSCLC cohorts, the receipt of baseline GLMs was associated with an increased risk of death (HR, 1.49; 95% CI, 1.11–2.01; Supplementary Fig. S1A), alongside a nonsignificant effect on the risk of disease progression/death (HR, 1.17; 95% CI, 0.89–1.33; Supplementary Fig. S1B).

Among 345 patients with melanoma, 49 (16.5%) were on baseline GLMs. These were propensity score matched with 128 patients from the control group with a good balancing ability (Supplementary Table S5).

The median OS of patients receiving GLM was 22.9 months (95% CI, 12.0–NR; 25 events) while the OS of the control group was not reached (52 events) with a tendence toward an increased risk of death (HR, 1.39; 95% CI, 0.86–2.23; Supplementary Fig. S1C). Similarly, the median PFS of patients exposed to GLMs was 11.4 months (95% CI, 4.9–23.4; 37 events) while that of the control group was 13.8 months (95% CI, 8.7–26.0; 77 events; HR, 1.35; 95% CI,0.91–2.01; Supplementary Fig. S1D).

Increasing GLM burden does not impact clinical outcome from immunotherapy

Among 226 patients on treatment for diabetes, 102 (45.1%) were receiving GLM monotherapy, whereas 124 (54.9%) were receiving a combination treatment. We sought to determine whether diabetes medication burden was associated with a progressive detrimental impact on clinical outcomes. However, we found that only patients on monotherapy experienced an increased risk of death in comparison with the control group (HR, 1.29; 95% CI,1.01–1.65), while no significant effect was associated with being on multiple diabetes medications (Supplementary Fig. S2A). Similarly, neither

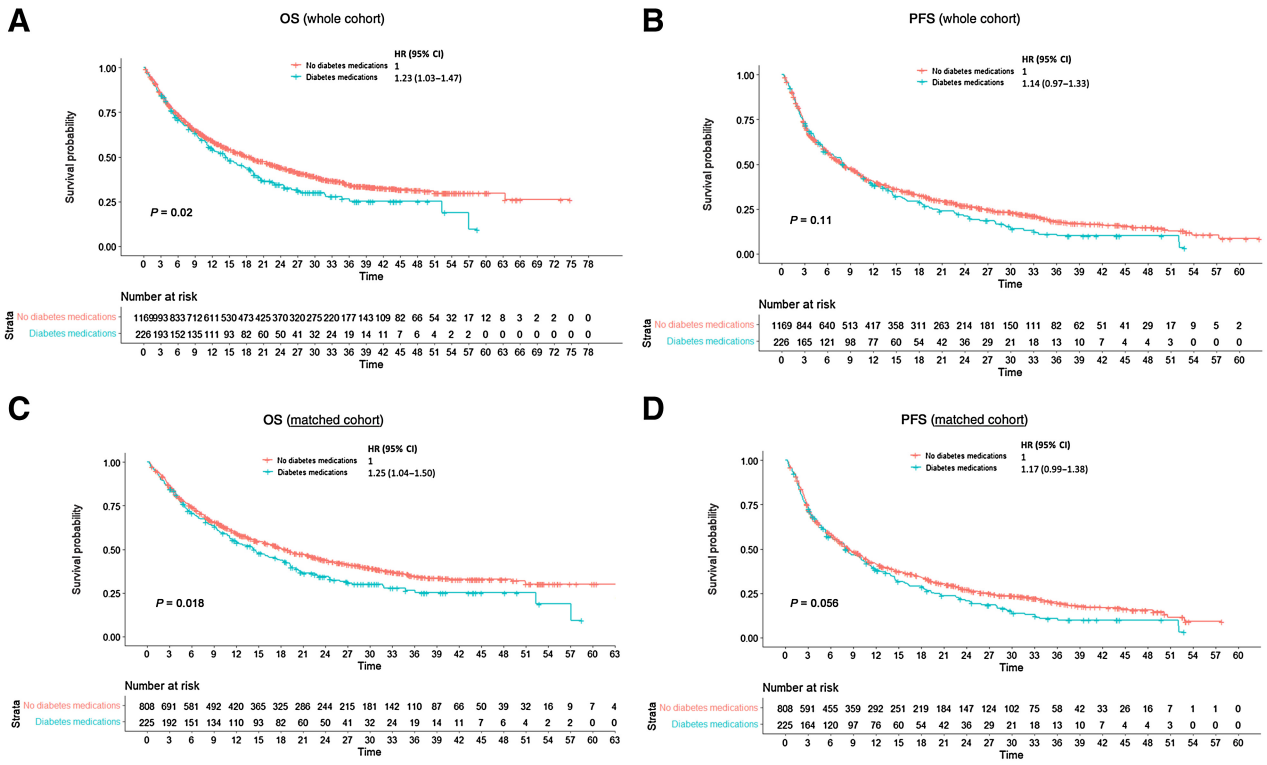

Figure 1.

Kaplan–Meier survival estimates according to the receipt of any diabetes medication. **A,** OS whole cohort; patients on any diabetes medication: 14.5 months (95% CI, 11.1–18.3; 148 events), patients not receiving diabetes medications: 18.9 months (95% CI, 15.9–21.5; 684 events). **B,** PFS whole cohort; patients on any diabetes medication: 8.0 months (95% CI, 6.2–10.4; 185 events), patients not receiving diabetes medications: 8.2 months (95% CI,7.1–9.4; 872 events). **C,** OS PSM cohort; patients on any diabetes medication: 14.4 months (95% CI,11.2–18.7; 148 events), patients not receiving diabetes medications: 18.7 months (95% CI, 16.1–22.1; 466 events). **D,** PFS PSM cohort; patients on any diabetes medication: 8.0 months (95% CI, 6.2–10.6; 185 events), patients not receiving diabetes medications: 8.4 months (95% CI, 7.5–10.1; 593 events).

monotherapy, nor combination therapy were associated with worse PFS (Supplementary Fig. S2B).

Differential effect of metformin and other antidiabetes medications on clinical outcomes

Overall, 147 patients were on metformin and 134 were on other oral antidiabetic drugs/insulin therapy. On univariable analysis, receipt of metformin therapy was associated with an increased risk of death (HR, 1.35; 95% CI,1.09–1.66; Supplementary Fig. S3A) and disease progression/death (HR, 1.23; 95% CI,1.02–1.49; Supplementary Fig. S3B). On the contrary, being on other oral antidiabetic drugs/insulin therapy was not associated with both the OS and PFS (Supplementary Fig. S4).

Stratifying patients into those who were on baseline metformin either alone or in combination and those who were on diabetes medications other than metformin only, we reported similar trends for OS (log-rank $P = 0.018$) and PFS (log-rank $P = 0.086$) but without significant differences between exposure to metformin and other diabetes medications only (Supplementary Fig. S5).

After the exclusion of 54 patients (23.9%) on metformin, other oral hypoglycemic and insulin therapy combinations, and one patient (0.4%) on metformin and insulin therapy combination, 92 patients (40.7%) on metformin monotherapy and 79 (34.9%) on other antidiabetic medications (of which 21% –26.6% on other oral hypoglycemic medications, 11% –13.9% on insulin monotherapy, and 47%–59.5% on combinations of both) were included in the respective PSM analysis.

Compared with patients who were not taking diabetes medications, those on metformin only were older (median age 71 vs. 68 years; $P = 0.0035$) and more frequently males (66.3% vs. 61.7%; $P = 0.0384$; Supplementary Table S6). After the PSM procedure, 92 patients on metformin only were matched with 363 patients from the control group, with an optimal balancing ability (Supplementary Table S7). Within the matched cohorts, being on metformin only was associated with an increased risk of death (HR, 1.53; 95% CI, 1.16–2.03; **Fig. 2A**) and disease progression/death (HR, 1.34; 95% CI, 1.04–1.72; **Fig. 2B**).

Compared with the control group, patients on other oral antidiabetic drugs/insulin therapy only were older (median age 72 vs. 68 years; $P < 0.0001$), with a higher BMI (median 25.9 vs. 24.9; $P = 0.0108$) and a higher burden of metastatic sites (63.3% vs. 50.7%; $P = 0.0306$); they also were more likely males (78.5% vs. 61.7%; $P = 0.0028$) and with a higher proportion of NSCLC (72.2% vs. 53.5%; $P = 0.0143$; Supplementary Table S8).

After the PSM procedure, 78 patients on other oral antidiabetic drugs/insulin therapy only were matched with 299 patients from the control group, with an optimal balancing ability (Supplementary Table S9). Within the matched cohorts, being on other oral antidiabetic drugs/insulin therapy only was not associated with either the risk of death (HR, 1.03; 95% CI, 0.75–1.41; **Fig. 2C**), nor that of disease progression/death (HR, 0.99; 95% CI, 0.75–1.31; **Fig. 2D**).

Table 2. Fixed multivariable analyses for the risk of death and disease progression/death within the whole cohort.

	Multivariate analysis	
	Risk of death	Risk of disease progression/death
Variables	HR (95% CI)	HR (95%CI)
GLM		
No	1	1
Yes	1.29 (1.07–1.56)	1.21 (1.03–1.43)
BMI		
Continuous	0.97 (0.96–0.99)	0.98 (0.97–0.99)
Age		
Continuous	0.99 (0.99–1.00)	0.99 (0.99–1.00)
Primary tumor		
NSCLC	1	1
Melanoma	0.72 (0.56–0.93)	0.87 (0.68–1.10)
Kidney	0.55 (0.43–0.71)	0.74 (0.59–0.92)
Others	0.89 (0.64–1.23)	1.09 (0.82–1.44)
Sex		
Female	1	1
Male	1.14 (0.98–1.32)	1.13 (0.99–1.29)
Treatment line		
First	1	1
Nonfirst	1.24 (1.05–1.46)	1.24 (1.07–1.44)
No. of metastatic sites		
≤2	1	1
>2	1.57 (1.36–1.83)	1.41 (1.24–1.62)
ECOG PS		
0–1	1	1
≥2	2.32 (1.91–2.80)	1.92 (1.61–2.30)
Baseline corticosteroids		
No	1	1
Yes	1.64 (1.39–1.93)	1.51 (1.30–1.75)
Baseline antibiotics		
No	1	1
Yes	1.44 (1.15–1.81)	1.35 (1.09–1.68)

Note: A center-specific conditional interpretation by using frailty models was applied to correct all the 95% CIs.

Diabetes and poor glycemic control are associated with unopposed systemic inflammation and distinctive immune-suppressive features within the TME

Overall, MBG data were available for 133 patients (Supplementary Table S10).

The median MBG value for the overall cohort was 5.7 mmol/L (range 4.1–19.9) and significantly different among diabetic ($n = 19$; median 8.0 mmol/L; range: 5.6–19.9) and nondiabetic patients ($n = 114$; median 5.6 mmol/L; range: 5.6: 4.1–8.7; $P < 0.0001$). Median NLR for the 133 patients evaluable for MBG was 3.8 (range 0.1–36.5). Increasing levels of MBG were significantly associated with increasing NLR values [F (1, 131) = 4.09; $P = 0.04$] with an R^2 of 0.030 (Supplementary Fig. S6). To discriminate the effect of concomitant corticosteroid therapy in influencing the relationship between MBG and NLR, we performed a multivariable logistic regression using the median NLR value as cutoff. This model confirmed that baseline corticosteroid therapy was not associated with pretreatment NLR (OR, 1.87; 95% CI, 0.51–6.87), whereas increasing MBG was confirmed to be significantly associated with a high NLR (OR, 1.58; 95% CI, 1.17–2.14).

In view of the negative association between T2DM and outcome from immunotherapy we performed an exploratory targeted transcriptomic profiling experiment in a small subset of 22 primary tumor samples selected from the Imperial College London cohort, including 11 controls and 11 diabetic patients. Clinical features of included patients are summarized in Supplementary Table S11. Using a bulk transcriptomic approach of macrodissected tumor tissue, we found that samples from patients with diabetes were characterized by distinctive characteristics suggestive of more profound immune suppression compared with nondiabetic controls (Supplementary Fig. S7). In particular, directed gene-set enrichment analysis (GSEA) suggested significant downregulation of a number of gene signatures involved in adaptive and innate immune responses in diabetic samples (Supplementary Fig. S3). Analysis of candidate genes highlighted the decreased expression of single transcripts belonging to the inflammatory response (CXCL9, CXCL11, and BIRC5) and to the modulation of T-cell function (LAG3; Supplementary Fig. S8A and S8B) in diabetic samples (34, 35).

Discussion

The wide therapeutic index of ICI has broadened the reach of systemic therapy in solid tumors, making it possible to safely treat elderly and multiply comorbid patients who may not qualify for cytotoxic or targeted therapies (36, 37). Polypharmacy and comorbidities can, however, affect efficacy of ICI (25). Despite being a highly prevalent comorbidity in patients with cancer (38–40), and some preliminary descriptive findings in patients with lung cancer (41), there is no convincing evidence to suggest whether a coexisting diagnosis of diabetes leads to worse outcomes from immunotherapy.

In our large observational study of approximately 1,400 ICI recipients, we were able to demonstrate that a concomitant diagnosis of T2DM at ICI initiation was independently associated with inferior outcomes from immunotherapy—a finding that relies on the use of multivariable models and PSM analyses.

While hyperglycemia and T2DM are hallmarks of the metabolic syndrome, together with dyslipidemia, increased waist circumference, and arterial hypertension (42), our study is the first to suggest an opposite effect of T2DM compared with obesity in shaping ICI-mediated immune reconstitution. Obesity has been paradoxically associated with improved outcomes from ICIs (2), with preclinical and clinical evidence suggesting the presence of an obesity-related T-cell dysfunction that can be rapidly reversed upon checkpoint blockade (20, 43).

Although we reported an association between GLM exposure and increasing BMI, our understanding of the relationship between obesity and response to ICIs has significantly evolved, calling into question a number of concurrent host factors (20). Distribution of adiposity and body composition are more complex factors in dictating outcomes from immunotherapy, all imperfectly recapitulated by simple BMI computation. Obesity, dyslipidemia (2, 44), chronic hyperglycemia, and the development of peripheral insulin resistance could be interpreted as a progressive, time-dependent derangement of the host metabolic response, where high body weight and accumulation of subcutaneous fat precedes an increase in visceral adiposity, accumulation of intramuscular adipose tissue and secretion of adipocytokines, ultimately leading to progressive weight loss (45) in the context of active malignancy. Higher subcutaneous fat distribution is in fact associated with better outcomes from immunotherapy, whereas the opposite is true for intermuscular fat and sarcopenic-obesity, traits that are increasingly associated with unopposed systemic inflammation and worse outcomes from ICIs (46–50).

In our study, patients with diabetes experienced worse outcome independent of common clinicopathologic features of their oncologic

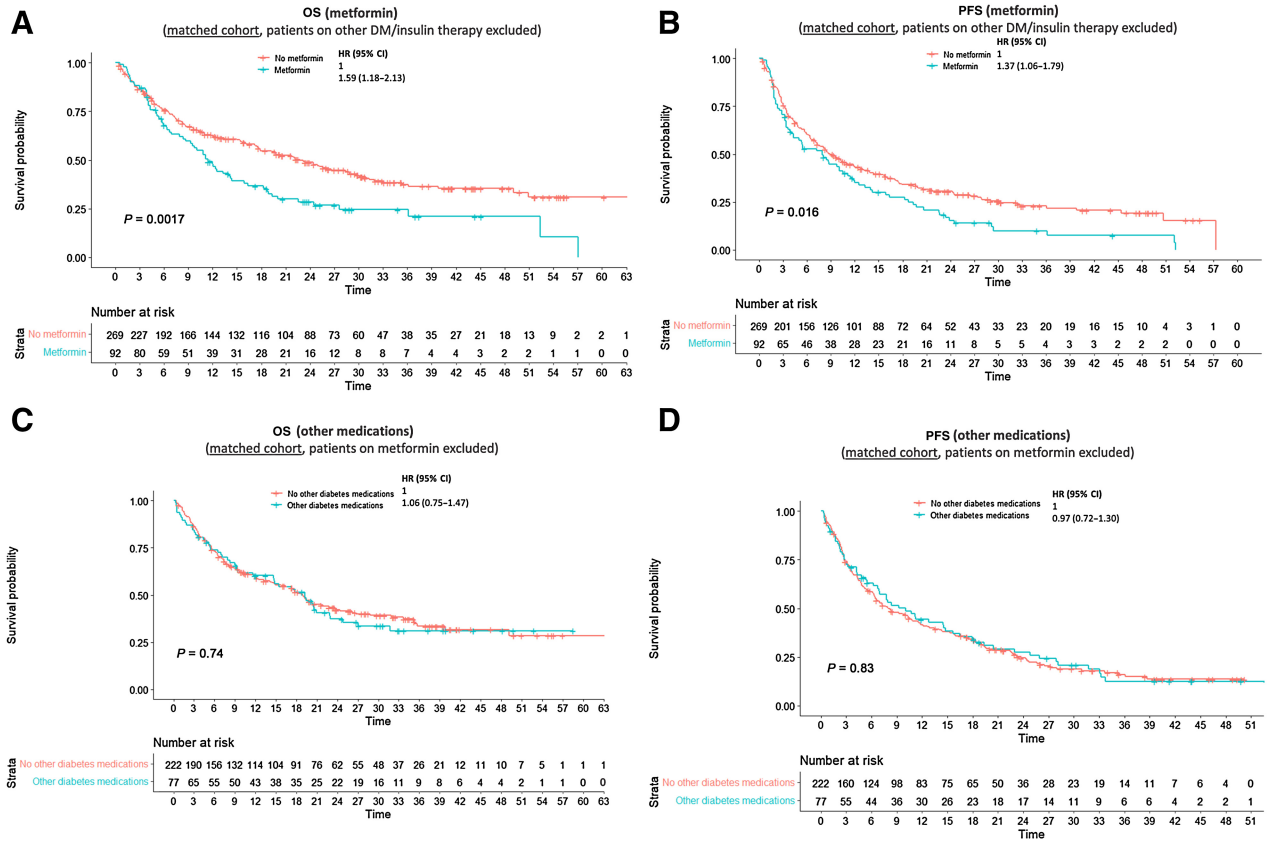

Figure 2.

Kaplan–Meier survival estimates according to the receipt of metformin only after the exclusion of patients on other diabetes medications and insulin therapy. **A,** OS PSM cohort; patients on metformin only: 11.4 months (95% CI, 9.3–15.9; 66 events), patients not receiving metformin: 20.4 months (95% CI, 17.5 – 26.3; 363 events). **B,** PFS PSM cohort; patients on metformin only: 7.9 months (95% CI, 4.3–11.4; 79 events), patients not receiving metformin: 8.9 months (95% CI, 7.3–10.9; 260 events). Kaplan–Meier survival estimates according to the receipt of other DM/insulin therapy only after the exclusion of patients on metformin. **C,** OS PSM cohort; patients on other DM/insulin therapy only: 19.3 months (95% CI, 14.7–24.8; 48 events), patients not receiving DM/insulin therapy: 18.1 months (95% CI, 14.8–21.9; 174 events). **D,** PFS PSM cohort; patients on other DM/insulin therapy only: 10.1 months (95% CI, 6.9–16.5; 61 events), patients not receiving DM/insulin therapy: 8.2 months (95% CI, 6.6 – 11.6; 222 events).

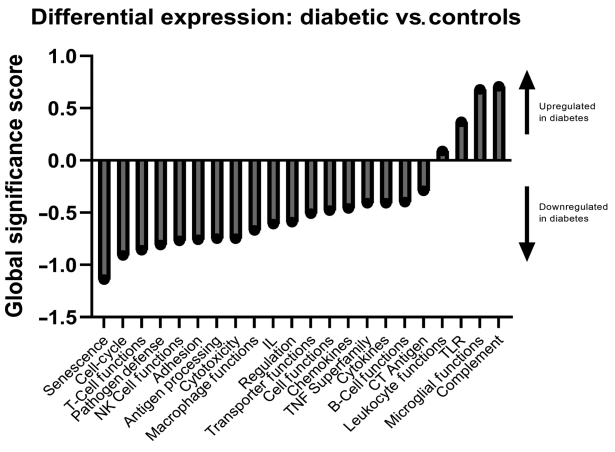

Figure 3.

Gene-set analysis showing the differential regulation of 22 gene expression signatures on the basis of diabetic status. Targeted transcriptomic analysis using NanoString PanCancer immune profiling was performed to compare patients with diabetes ($n = 11$) with nondiabetic controls ($n = 11$). Methodologic information for the GSEA and its interpretation is provided as Supplementary Methods.

disease, including tumor site of origin and disease burden, giving credence to the hypothesis that diabetes may exert a preconditioning effect against ICI efficacy (10). Despite the limited sample size and different prevalence of diabetes across different primary tumors, results of the survival analysis performed among the NSCLC and melanoma matched cohorts seem to support this, confirming a detrimental effect of preexisting T2DM on OS for patients with NSCLC and a similar trend for patients with melanoma.

T2DM leads to an exquisitely immune-suppressive state. Patients with diabetes are less reactive to pathogens (12), with chronic hyperglycemia leading to dysfunctional innate immune responses (13–15) and functional repercussions on all major immune cell subsets, including macrophages, dendritic cells, T cells, and NK cells (51). Hyperglycemia has also been associated with the increase of circulating $CD8^+$ $PD\text{-}1^+$ T cells in patients with T2DM, which show reduced glycolysis and impaired cytokine secretion (52).

Lack of detailed peripheral immune cell characterization limits our ability to establish mechanistic links between T2DM and outcome. However, our study highlights a linear relationship between MBG and the patients' NLR, a solid and reproducible measure of systemic inflammation (53), postulating a link between T2DM and impaired ICI efficacy through defective modulation of innate immune pathways (54, 55).

To provide further insight as to the mechanisms linked to inferior outcome from immunotherapy in ICI recipients, we performed an exploratory analysis of a small cohort of patients with and without diabetes with available pretreatment archival tissue. While limited by small sample size and exploratory intent, targeted transcriptomic analyses highlight downregulation of gene expression programs involved in the innate and adaptive immune response in the TME of patients with diabetes (56), in line with previous evidence showing worse T-cell exhaustion in diabetic patients with melanoma treated with ipilimumab (57).

The transcriptomic data presented in this study are hypothesis generating and cannot be viewed as exhaustive of all plausible explanations justifying inferior survival of patients with T2DM. Compositional changes in the gut microbiota can additionally be mentioned among potential underlying mechanisms to our findings, given that complex interplay existing between T2DM, metabolic dysfunction, and perturbation of gut homeostasis (58). A significant increase in the bacteroidetes/firmicutes ratio (59) and reduction in the presence of commensal bacterial species specifically associated with improved ICI efficacy, such as Akkermansia muciniphila (60–62), have been reported among patients with diabetes.

The increasingly appreciated role of concomitant medications as an alternative or perhaps complimentary cause of altered responsiveness to ICI raises the question of whether individual GLM classes may be important in influencing prognosis.

While the number of GLMs was not associated with prognosis, stratification of outcome by GLM class suggested that the detrimental effect on clinical outcomes we observed was restricted to metformin recipients.

While we cannot conclude whether the negative prognostic effect for metformin exposure is causative rather than associative, it is important to highlight that a consistent body of evidence supports metformin as preferred initial therapy for T2DM, along with a substantial patient–provider resistance to start diabetes combination treatments at metformin failure and poor adherence to insulin in Western countries (63–67). When these considerations are taken into account, it might be assumed that metformin exposure may capture patients with long-standing and potentially suboptimally controlled diabetes. In fact, metformin was mainly given as monotherapy in our cohort, whereas other GLMs were mostly coadministered with insulin: a finding that makes it impossible to fully disentangle the effect of improved T2DM control associated with insulin therapy as opposed to a true mechanistic detrimental effect from metformin alone.

On the other hand, tumor-modulating role of metformin has been described for a long time in patients with cancer (68, 69), although evidence in support of an immune-modulating effect of metformin in the context of immunotherapy of cancer is scantly and mostly limited to the preclinical setting (70–72)

Metformin may have immune-suppressive properties, through targeted inhibitory effect on leukocyte function including AMPK-induced mTORC1 inhibition and the reduction of mitochondrial ROS production (73, 74). In addition, multiple studies confirmed that metformin can lead to gut dysbiosis and gut microbial perturbation in healthy volunteers (75), which in turn are associated with gastrointestinal adverse effects following metformin intake (76). A recent deep-learning multi-omics phenotyping study of 789 patients with newly diagnosed T2DM (77) reported an association between metformin and dysregulation of CXCL8 and CD177, which are involved in both the innate and adaptive anticancer immune response (78, 79), alongside with a distinctive shift in gut metagenomics data.

Taken together, our data suggest a statistically significant and clinically meaningful difference in survival for patients receiving GLMs for diabetes prior to ICI, with a greater effect observed for those exposed to metformin. Although hypothesis generating, these data require validation in prospective clinical studies before solid clinical recommendations are made, so that the relative contribution of metformin over adequacy and quality of T2DM control can be evaluated for their putative mechanistic linkage with outcome from immunotherapy.

In addition, further research efforts should provide a more comprehensive evaluation of diabetes severity, including prevalence of micro and macrovascular complications, dietary habits, treatment adherence, and baseline HbA1c levels (80, 81) factors that cannot be reconstructed from our data due to the retrospective nature of our study.

Primary analyses in the whole study population were adjusted for primary tumor type, resulting in an optimal balancing ability. However, we acknowledge that the inclusion of different tumors is a significant source of heterogeneity. The separate PSM performed among the NSCLC and melanoma cohorts suggest similar detrimental effects for preexisting T2DM across different malignancies, even though the reduced sample size and a lower proportion of patients with diabetes within the melanoma group limited the analysis, which did not reach the statistical significance threshold.

In addition, despite the concordant trend of a reduced PFS for diabetic patients at the matched analysis, the lack of a statistically significant increase in the risk of disease progression/death (HR, 1.17; 95% CI, 0.99–1.38; $P = 0.056$) needs to be mentioned and might be related to the relatively small number of events across groups. Small sample size of the cohort included in the MBG and targeted transcriptomic analyses should also be considered in interpreting the results, which – although provocative – do not allow us to infer conclusive considerations about differential role of systemic inflammation and expression of immune-related genes in the TME of patients with diabetes.

Despite these limitations and the preliminary nature of our findings, our study is the first to our knowledge to report a clear detrimental effect of diabetes on clinical outcomes from ICIs in patients with solid tumors. In view of the constantly expanding clinical indications of ICI-based therapies across different cancer types (19) and the increasing global burden of metabolic syndrome, obesity, and T2DM (82, 83), our findings are of clinical importance and need to be carefully considered in the provision of cancer immunotherapy.

Further prospective research efforts are needed to fully elucidate the underlying mechanisms in support of our findings, to assess the putative detrimental role of metformin therapy and other GLM, and to investigate whether patients with cancer requiring an ICI-based treatment should be prioritized for optimization of T2DM therapy.

Authors' Disclosures

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Authors' Contributions

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Note

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