Effects of Diabetes on Inflammatory Status and Prognosis in Cancer Patients

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Background: Cancer and diabetes mellitus (DM) are prevalent, but there still a lack of convinced evidence clearly explaining the extent of the effect of diabetes in cancer.

Data and Methods: Clinical data of 2,929 cancer patients were collected. Diabetes were diagnosed according to the Diabetes Diagnosis and Treatment Criteria. BMI was classified by the BMI standards for Chinese adults published by the Working Group on Obesity. All involved patients were classified into the non-DM group and DM group. The Kaplan–Meier curve, log-rank test and Cox regression analyses were used to perform survival analysis.

Results: Compared with non-DM patients, OS in DM patients was significant shorter in lung cancer (HR = 2.076, $P = 0.001$ in early stage; HR = 2.118, $P < 0.001$ in advanced stage), digestive tract cancer (HR = 1.768, $P = 0.020$ in early stage; HR = 2.454, $P = 0.005$ in advanced stage), leukemia (HR = 2.636, $P < 0.001$), breast cancer (HR = 2.495, $P = 0.047$ in early stage; HR = 2.929, $P = 0.019$ in advanced stage) and liver cancer (HR = 3.086, $P < 0.001$ in early stage; HR = 2.219, $P = 0.049$ in advanced stage). DM negatively influenced OS when the BMI was within the normal range in overall cancer (HR = 2.468, $P < 0.001$), lung cancer (HR = 2.297, $P < 0.001$), digestive tract cancer (HR = 2.354, $P < 0.001$), liver cancer (HR = 2.406, $P = 0.001$), leukemia (HR = 4.039, $P < 0.001$) and breast cancer (HR = 4.222, $P = 0.008$). Among those with BMI ≥ 24 kg/m², DM played a role only in lung cancer (HR = 1.597, $P = 0.037$).

Conclusions: Patients with diabetes tend to combine worse body composition and inflammation status, and that glycemic control can ameliorate the impairment of diabetes to some extent.

Keywords: cancer, diabetes, inflammation, prognosis, BMI

INTRODUCTION

Cancer is currently one of the major diseases that threaten the health of residents (1), and 8–18% cancer patients have diabetes as a comorbid medical condition (2). According to the epidemiological survey conducted by the Chinese Medical Association, the total number of people with diabetes in mainland China is 129.8 million (3). China has become the country with the highest incidence of diabetes in the world (4). Diabetes were significantly related with higher cancer occurrence and mortality in many cancer types (5). Overall cancer risk was found significantly elevated with a standardized increased ratio of 1.15 (95% CI 1.12–1.19) and 1.25 (95% CI 1.21–1.30)

in males and females, respectively (6). A systemic review of 23 studies demonstrated a 41% increased risk for long-term, all-cause mortality for diabetic patients compared with those without diabetes (7). Diabetes and associated metabolic disorders contribute directly or indirectly to cancer progression (8). Anaerobic glycolysis, known as Warburg, is classic in cancer. But Warburg does not mean glucose is unimportant. In contrast, hyperglycemia stimulates cancer proliferation (9). Most cancers predominantly express the glucose transporter 1, which has a high affinity for glucose. The increased glycolysis in cancer cells provides the materials necessary for nucleotide, amino acid, and lipid synthesis. Besides, advanced glycation end products (AGRs) due to hyperglycemia, and its receptors (RAGRs) have been reported to lead to oxidative stress and increased inflammation, which promotes cancer growth, angiogenesis, and metastases (10). Obesity, also a prevalence worldwide, is a risk factor of both diabetes and cancer (11, 12). Excessive adipose tissue generates oxidative stress by increased production of pro-inflammatory adipokines. And BMI is regarded as a typical measurement of obese. There have been numerous studies on the relationship between diabetes and cancer. However, at present, barely convinced evidence clearly explains the extent of the effect of diabetes in different cancer types, stages and body mass indices (BMI), which remains to be further investigated (13–15). In addition, as a wasting disease, the nutritional status of patients gradually deteriorates with the development of cancers (16). Therefore, this large-scale retrospective cohort study is to investigate the impact of diabetes on the prognosis of tumor patients.

DATA AND METHODS

Clinical Data Collection

Clinical data of cancer patients from November 2011 to December 2018 in the Department of Oncology, Cancer Center, First Hospital of Jilin University were collected. No specific selection criteria were established for cancer type or demographic characteristics, except for patients who declined to participate in the study. All patients were regularly followed up by telephone interviews or outpatient visits.

Main Inclusion Criteria

(1) Clear diagnosis of malignancy in pathological specimens. (2) Age ≥18 years. (3) No nutritional support treatment prior to nutritional assessment and laboratory testing.

Major Exclusion Criteria

(1) Those who were unwilling to keep blood specimens. (2) Combination of other types of tumors. (3) Combination of other metabolic or immunological diseases. (4) Those who had incomplete records of necessary indexes. Clinical-pathological variables including age, sex, BMI, tumor types, TNM stages (AJCC 7th edition), alcohol consumption, smoking status. Scales including Karnofsky Performance Status (KPS), the Patient-Generated Subjective Global Assessment (PG-SGA) and the Nutritional Risk Screening-2002 score (NRS-2002),

and quality of life (QoL-C30). Laboratory examinations including total protein(TP), albumin, prealbumin (PAB), transferrin (TFN), C-reaction protein(CRP), neutrophil to lymphocyte ratio (NLR) and platelets to lymphocyte ratio (PLR). Anthropometric indices including hand-grip strength (HGS) and visceral fat area (VFA) by bioelectrical impedance analysis.

TABLE 1 | Patient characteristics stratified by diabetes.

Characteristics	Groups			
	Non-DM (n%)	DM (n%)	Total	P-value
Age (year)				
<65	2,038 (80.5)	287 (72.5)	2,325 (79.4)	<0.001
≥65	495 (19.5)	109 (27.5)	604 (20.6)	
Sex				
Male	1,102 (43.5)	169 (42.7)	1,271 (43.4)	0.757
Female	1,431 (56.5)	227 (57.3)	1,658 (56.6)	
Smoking				
No	1,519 (60.0)	249 (62.9)	1,768 (60.4)	0.271
Yes	1,014 (40.0)	147 (37.1)	1,161 (39.6)	
Alcohol consumption				
No	2,050 (80.9)	327 (82.6)	2,377 (81.2)	0.437
Yes	483 (19.1)	69 (17.4)	552 (18.8)	
Tumor types				
Lung	773 (30.5)	125 (31.6)	898 (30.7)	0.001
Digestive tract	507 (20.0)	91(23.0)	598 (20.4)	
Liver	136 (5.4)	41 (10.4)	177 (6.0)	
Leukemia	284 (11.2)	31 (7.8)	315 (10.8)	
Breast	625 (24.7)	76 (19.2)	701(23.9)	
Others	208 (8.2)	32 (8.1)	240(8.2)	
TNM stages				
I	448 (18.6)	51 (13.3)	499 (17.9)	<0.001
II	569 (23.7)	86 (22.5)	655 (23.5)	
III	594 (24.7)	131 (34.2)	725 (26.0)	
IV	475 (19.8)	85 (22.2)	560 (20.1)	
Leukemia	318 (13.2)	30 (7.8)	348 (12.5)	
PG-SGA				
0–1	1,035 (40.9)	133 (33.6)	1,168 (39.9)	0.002
2–3	437 (17.3)	62 (15.7)	499 (17.1)	
4–8	744 (29.4)	130 (32.8)	874 (29.9)	
≥9	314 (12.4)	71 (17.9)	385 (13.2)	
NRS-2002				
<3	2,077 (90.7)	328 (92.7)	24,05 (90.9)	0.224
≥3	214 (9.3)	26 (7.3)	240 (9.1)	
QoL-C30				
<60	795 (31.5)	140 (35.4)	935 (32.0)	0.117
≥60	1,730 (68.5)	255 (64.6)	1,985 (68.0)	
VFA (cm²)				
<90	1,352 (53.4)	188 (47.5)	1,540 (52.6)	0.029
≥90	1,181 (46.6)	208 (52.5)	1,389 (47.4)	

DM, diabetes mellitus; PG-SGA, the Patient-Generated Subjective Global Assessment; NRS-2002, the Nutritional Risk Screening-2002 score; QoL-C30, quality of life; VFA, visceral fat area.

TABLE 2 | Basic clinical information for all involved patients stratified by DM.

Parameters	Lung Cancer (N = 898)			Digestive tract Cancer (N = 598)			Liver Cancer (N = 177)			Leukemia (N = 315)			Breast Cancer (N = 701)			Others (N = 240)		
	Non-DM	DM	P	Non-DM	DM	P	Non-DM	DM	P	Non-DM	DM	P	Non-DM	DM	P	Non-DM	DM	P
NRS2002	0.64	0.89	0.027	0.85	0.64	0.106	0.67	0.62	0.813	0.29	0.38	0.603	0.21	0.42	0.034	0.74	0.59	0.564
KPS	89.43	88.88	0.554	86.49	87.69	0.425	88.82	86.83	0.347	89.79	86.77	0.251	91.95	92.24	0.780	89.09	88.75	0.874
TP (g/L)	67.78	67.99	0.724	64.02	66.09	0.032	65.38	64.90	0.716	64.17	59.36	<0.001	69.12	70.36	0.069	68.11	69.56	0.282
Albumin (g/L)	39.26	38.62	0.151	37.15	37.41	0.664	36.90	35.20	0.084	37.81	35.42	0.014	41.73	41.76	0.961	39.50	38.60	0.370
PAB (g/L)	0.21	0.21	0.257	0.19	0.19	0.794	0.18	0.17	0.971	0.22	0.21	0.765	0.23	0.24	0.562	0.21	0.19	0.082
TFN (g/L)	4.18	2.20	0.669	2.41	2.48	0.696	2.33	2.29	0.801	10.21	3.33	0.728	2.72	2.47	0.412	2.37	2.32	0.786
CRP (mg/L)	15.12	22.39	0.072	24.37	20.46	0.431	12.18	18.23	0.375	26.70	22.52	0.614	5.80	9.57	0.340	26.43	16.22	0.494
Height (cm)	1.65	1.65	0.211	1.67	1.65	0.068	1.66	1.65	0.349	166.60	167.65	0.505	158.83	157.68	0.073	1.61	1.61	0.696
Weight (kg)	63.91	65.33	0.204	61.82	63.60	0.181	63.52	61.29	0.239	64.87	67.72	0.214	62.87	62.49	0.749	60.83	62.19	0.480
BMI (kg/m^2)	23.15	23.92	0.016	22.15	23.24	0.007	22.89	22.36	0.328	23.30	24.07	0.258	24.90	25.10	0.641	23.43	23.84	0.513
HGS (kg)	26.34	25.11	0.197	25.94	23.89	0.068	27.04	22.85	0.031	25.61	26.69	0.580	20.38	18.29	0.004	21.15	20.40	0.616
VFA (cm^2)	90.49	99.31	0.009	79.57	91.94	0.003	85.69	85.83	0.981	78.07	95.98	0.004	100.26	106.25	0.148	91.79	89.74	0.758
NLR	3.23	5.88	0.003	4.38	6.80	0.089	4.15	4.55	0.686	2.89	2.82	0.934	2.22	5.98	<0.001	3.87	3.01	0.059
PLR	171.55	174.12	0.839	180.08	216.81	0.050	147.52	185.18	0.074	174.68	184.85	0.795	146.04	168.90	0.022	188.54	173.66	0.611

DM, diabetes mellitus; NRS-2002, the nutritional risk screening-2002 score; KPS, karnofsky performance status; TP, total protein; PAB, prealbumin; TFN, transferrin; CRP, C-reaction protein; BMI, body mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelets to lymphocyte ratio; HGS, hand-grip strength; VFA, visceral fat area.

TABLE 3 | Basic clinical information of E-DM vs. non-DM patients.

Parameters	Lung Cancer (N = 898)			Digestive tract Cancer (N = 598)			Liver Cancer (N = 177)			Leukemia (N = 315)			Breast Cancer (N = 701)			Others (N = 240)		
	Non-DM	E-DM	P	Non-DM	E-DM	P	Non-DM	E-DM	P	Non-DM	E-DM	P	Non-DM	E-DM	P	Non-DM	E-DM	P
NRS2002	0.64	1.07	0.004	0.85	0.71	0.513	0.67	0.92	0.478	0.29	0.80	0.069	0.21	0.64	0.001	0.75	0.57	0.540
KPS	89.41	88.85	0.636	86.63	86.88	0.901	88.82	85.00	0.254	89.79	87.14	0.341	91.97	91.72	0.877	89.01	88.70	0.899
TP (g/L)	67.78	66.99	0.345	64.16	66.18	0.072	65.38	64.29	0.607	64.17	56.00	<0.001	69.13	69.65	0.625	68.02	69.03	0.521
Albumin (g/L)	39.26	38.29	0.114	37.23	37.59	0.652	36.90	34.89	0.191	37.81	33.76	0.004	41.74	41.02	0.348	39.47	38.64	0.475
PAB (g/L)	0.21	0.21	0.529	0.19	0.18	0.465	0.18	0.15	0.270	0.22	0.18	0.127	0.23	0.22	0.251	0.21	0.18	0.092
TFN (g/L)	4.19	2.08	0.748	2.42	2.39	0.910	2.33	2.20	0.577	2.49	2.40	0.891	2.72	2.58	0.738	2.37	2.27	0.649
CRP (mg/L)	15.16	17.41	0.618	23.40	23.26	0.983	12.18	9.08	0.774	10.21	5.63	0.321	5.80	12.00	0.246	26.66	17.36	0.579
Height (cm)	1.66	1.64	0.098	1.67	1.66	0.453	1.66	1.63	0.097	1.67	1.69	0.250	1.59	1.57	0.140	1.61	1.61	0.949
Weight (kg)	63.81	62.69	0.457	61.79	63.39	0.362	63.52	60.01	0.240	64.87	64.48	0.907	62.87	60.42	0.185	60.77	61.03	0.907
BMI(kg/m^2)	23.12	23.14	0.963	22.16	22.97	0.128	22.89	22.66	0.785	23.30	22.49	0.406	24.91	24.38	0.435	23.37	23.48	0.881
HGS (kg)	26.32	24.27	0.119	26.00	24.12	0.203	27.04	18.02	0.003	25.61	24.21	0.622	20.38	17.33	0.008	21.21	19.64	0.363
VFA (cm^2)	90.22	94.22	0.384	79.45	84.93	0.319	85.69	83.10	0.788	78.07	79.29	0.891	100.28	99.47	0.901	91.25	88.44	0.710
NLR	3.23	4.31	0.014	4.34	9.06	0.017	4.15	4.50	0.822	2.89	2.73	0.892	2.22	3.40	<0.001	3.88	2.85	0.047
PLR	171.69	182.99	0.529	179.75	234.08	0.032	147.52	210.40	0.051	174.68	194.66	0.727	146.10	183.39	0.011	188.47	178.58	0.775

DM, diabetes mellitus; E-DM, euglycemia diabetes mellitus; NRS-2002, the nutritional risk screening-2002 score; KPS, karnofsky performance status; TP, total protein; PAB, prealbumin; TFN, transferrin; CRP, C-reaction protein; BMI, body mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelets to lymphocyte ratio; HGS, hand-grip strength; VFA: visceral fat area.

Diabetes Diagnosis Criteria

According to the Diabetes Diagnosis and Treatment Criteria established by the American Diabetes Association (ADA), (1) Fasting blood glucose $\geq$7.0 mmol/L (overnight blood glucose without food for at least 8–10 h); (2) Oral glucose tolerance test (OGTT) two-hour blood glucose $\geq$11.1 mmol/L; (3) Hemoglobin A1c (HbA1c) $\geq$6.5%; (4) Random blood glucose $\geq$11.1 mmol/L, along with symptoms related to diabetes such as polydipsia, polyphagia, polyuria and emaciation. Meeting any one of the above four conditions can be diagnosed with diabetes mellitus.

Classification of BMI

The BMI ranges were reclassified into normal (18.5 kg/m²-23.9 kg/m²), overweight (24.0 kg/m²-27.9 kg/m²) and obese ($\geq$28 kg/m²) according to the BMI standards for Chinese adults published by the Working Group on Obesity (WGO).

Operation Rules of Anthropometric Indices

HGS was examined in all subjects using a Jamar hydraulic grip dynamometer (Sammons Preston Rolyan, Illinois, USA). Patients were comfortably seated in an upright position with the shoulders tucked in, neutral rotation, 90° elbow flexion, and the forearms and wrists in a neutral position. The patient gripped the dynamometer with maximum strength. The test is performed three times in a row, with a 1-min rest at the end of each set, and the maximum grip strength is recorded.

VFA is assessed by the Inbody S10 (Biospace Co.®), a multi-frequency bioelectrical impedance body composition analyzer. For analysis on patients in the supine position, electrode pads are attached to the ipsilateral upper and lower extremities and all procedures are performed according to the manufacturer's recommendations.

Statistical Analysis

Data were analyzed by SPSS for Windows version 26.0 (IBM SPSS Statistics, IBM Corp., Armonk, NY) and R version 4.0 (R Foundation for Statistical Computing, Vienna, Austria). All involved patients were classified into the non-DM group and DM group according to the ADA diagnosis criteria. The Kolmogorov–Smirnov test was used to confirm normal distributions of continuous data. Independent t-tests were used for normally distributed data. Counting data were examined by using the chi-square test. The Kaplan–Meier curve, log-rank test, and Cox regression analyses were used to perform survival analysis in specific cancer types, stages and BMI and in all participants. $P < 0.05$ was taken to indicate statistical significance.

RESULTS

Among the 2,929 cancer patients recruited, 43.4% were men and 56.6% were women, with a mean age of 55 years. The mean follow-up period was 36.24 months and 791 patients died. According to the ADA criteria for the management of DM, 2,533 patients were included in the non-DM group and 396 patients were included in the DM group. The demographic, clinical and pathological characteristics of patients in the non-DM and DM groups were shown in **Table 1**. DM was significantly associated with age, PG-SGA, VFA, tumor types and stages ($\underline{P} < 0.05$).

Relationship Between DM and Clinical Parameters

Compared with non-DM patients, NRS-2002 was higher in DM patients with lung cancer (0.89 vs 0.64, $P = 0.027$) and breast cancer (0.42 vs 0.21, $P = 0.034$). BMI (23.92kg/m² vs 23.15kg/m², $P = 0.016$), VFA (99.31 vs 90.49cm², $P = 0.009$), and NLR (5.88 vs 3.23, $P = 0.003$) were higher in patients with lung cancer combined with diabetes than in patients without diabetes. Digestive tract cancer patients with DM had higher BMI (23.24 vs 22.15kg/m², $P = 0.007$), PLR (216.81 vs 180.08, $P = 0.050$) and VFA (91.94 vs 79.57cm², $P = 0.003$) than non-DM patients. Liver cancer patients with DM had lower HGS compared with non-DM patients (22.85 vs 27.04kg, $P = 0.031$). TP (64.17 vs 59.36g/L, $P < 0.001$) and albumin (37.81 vs 35.42 g/L, $P = 0.014$) were higher, while VFA was lower (78.07 vs 95.98 cm², $P = 0.004$) in patients with leukemia combined without diabetes than in patients with diabetes. In addition, HGS was lower (18.29 vs 20.38kg, $P = 0.004$) while NLR (5.98 vs 2.22, $P < 0.001$) and PLR (168.90 vs 146.04, $P = 0.022$) were higher in patients with breast cancer combined with diabetes than in patients without diabetes (**Table 2**).

Relationship Between Glycemic Control and Clinical Indicators in DM Patients

Compared with non-DM patients, NRS-2002 was higher in E-DM patients with lung cancer (1.07 vs 0.64, $P = 0.004$) and breast cancer (0.64 vs 0.21, $P = 0.001$). DM patients with euglycemia

TABLE 4 | Hazard risk for all cancers mortality in patients with diabetes stratified by stages.

Specific tumor types	HR	95% CI	*P*-values
Overall cancer			
Early	2.599	2.024–3.336	<0.001
Advanced	2.427	1.887–3.121	<0.001
Lung cancer			
Early	2.076	1.332–3.236	0.001
Advanced	2.118	1.437–3.121	<0.001
Digestive tract cancer			
Early	1.768	1.093–2.863	0.020
Advanced	2.454	1.316–4.576	0.005
Liver cancer			
Early	3.086	1.668–5.708	<0.001
Advanced	2.219	1.004–4.906	0.049
Leukemia	2.636	1.628–4.269	<0.001
Breast Cancer			
Early	2.495	1.011–6.155	0.047
Advanced	2.929	1.193–7.189	0.019
Others			
Early	4.320	2.103–8.871	<0.001
Advanced	3.691	0.830–16.411	0.086

(E-DM) had higher NLR than non-DM patients in lung cancer (4.31 vs 3.23, $P = 0.014$), gastrointestinal tumors (9.06 vs 4.34, $P = 0.017$), and breast cancer (3.40 vs 2.22, $P = 0.014$) (**Table 3**). Although the differences were not always statistically significant, E-DM patients had lower TFN, lower albumin and lower HGS than non-DM patients. It indicated that good glycemic control can make up the adverse effects of diabetes to some extent.

Prognostic Impact of DM in Different Cancer Types Stratified by Stages

Table 4 and **Figure 1** showed the relationship between DM and OS in specific cancer types stratified by stages. Compared with non-DM patients, OS in DM patients was significant shorter in overall cancer, lung cancer, gastrointestinal tract tumors, leukemia, advanced stage breast cancer and early stage liver cancer. The HR was 2.599 (95% CI: 2.024–3.336, $P < 0.001$) in early stage overall cancer, 2.427 (95% CI: 1.887–3.121, $P < 0.001$) in advanced overall cancer, 2.076 (95% CI: 1.332–3.236, $P = 0.001$) in early stage lung cancer, 2.118 (95% CI: 1.437–3.121, $P < 0.001$) in advanced lung cancer, 1.768 (95% CI: 1.093–2.863, $P = 0.020$), in early stage digestive tract cancer, 2.454 (95% CI: 1.316–4.576, $P = 0.005$) in advanced digestive tract cancer, 3.086 (95% CI: 1.668-5.708, $P < 0.001$) in early stage liver cancer, 2.219 (95% CI: 1.004-4.906, $P = 0.049$) in advanced liver cancer, 2.636 (95% CI: 1.628–4.269, $P < 0.001$) in leukemia, 2.495 (95% CI:

TABLE 5 | Hazard risk for all cancers mortality in patients with diabetes stratified by BMI (kg/m^2).

Specific tumor types	HR	95% CI	*P*-values
Overall Cancer			
$18.5 \leq BMI < 23.9$	2.468	2.004 to 3.041	<0.001
$BMI \geq 24$	1.898	1.410 to 2.556	<0.001
Lung Cancer			
$18.5 \leq BMI < 23.9$	2.297	1.635 to 3.229	<0.001
$BMI \geq 24$	1.597	1.029 to 2.479	0.037
Digestive tract Cancer			
$18.5 \leq BMI < 23.9$	2.354	1.508 to 3.675	<0.001
$BMI \geq 24$	1.220	0.588 to 2.534	0.594
Liver Cancer			
$18.5 \leq BMI < 23.9$	2.406	1.414 to 4.092	0.001
$BMI \geq 24$	2.203	0.718 to 6.762	0.168
Leukemia			
$18.5 \leq BMI < 23.9$	4.039	2.291 to 7.120	<0.001
$BMI \geq 24$	1.496	0.580 to 3.858	0.405
Breast Cancer			
$18.5 \leq BMI < 23.9$	4.222	1.466 to 12.164	0.008
$BMI \geq 24$	1.526	0.447 to 5.210	0.500
Others			
$18.5 \leq BMI < 23.9$	2.002	0.760 to 5.271	0.160
$BMI \geq 24$	6.747	2.769 to 16.441	<0.001

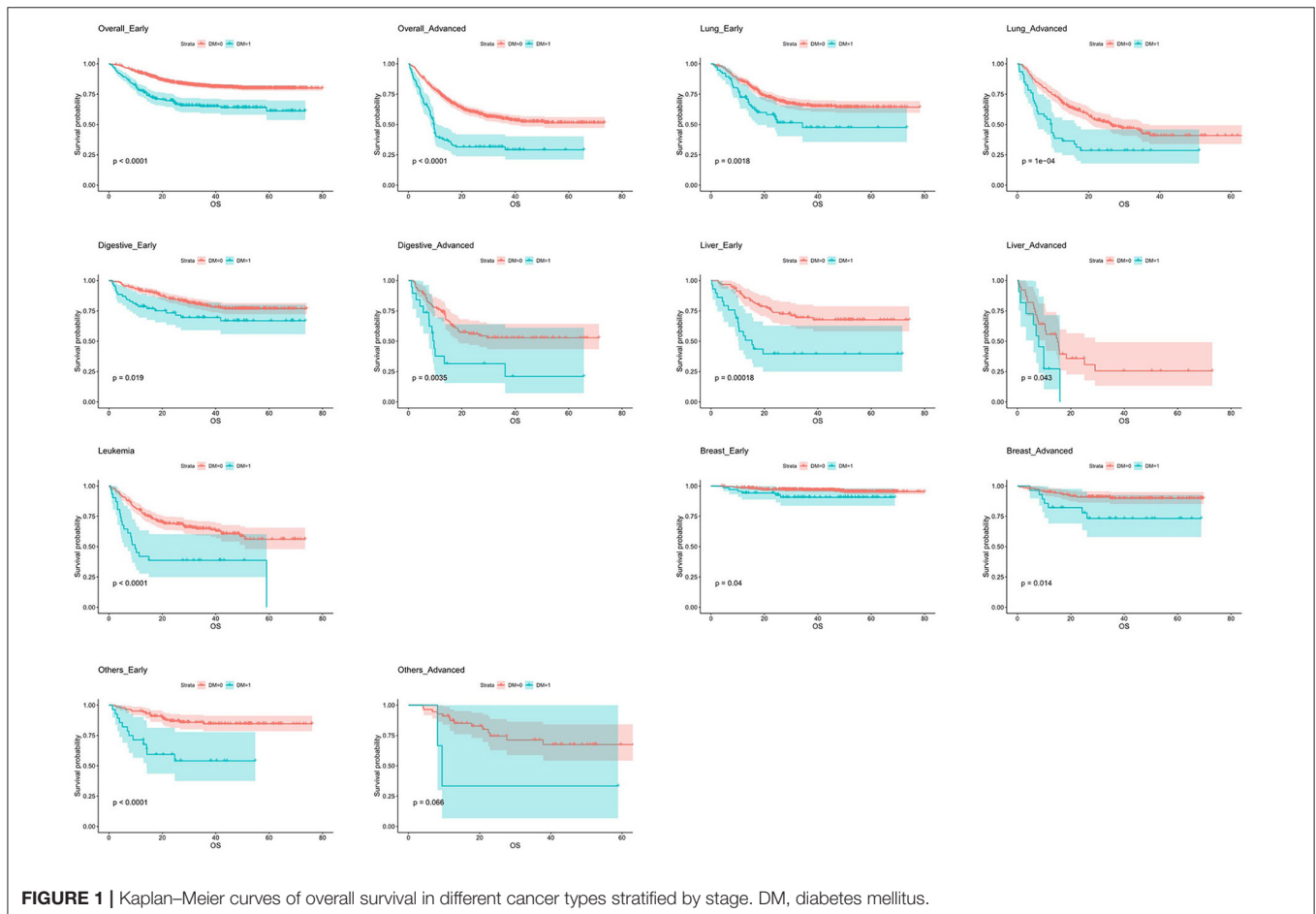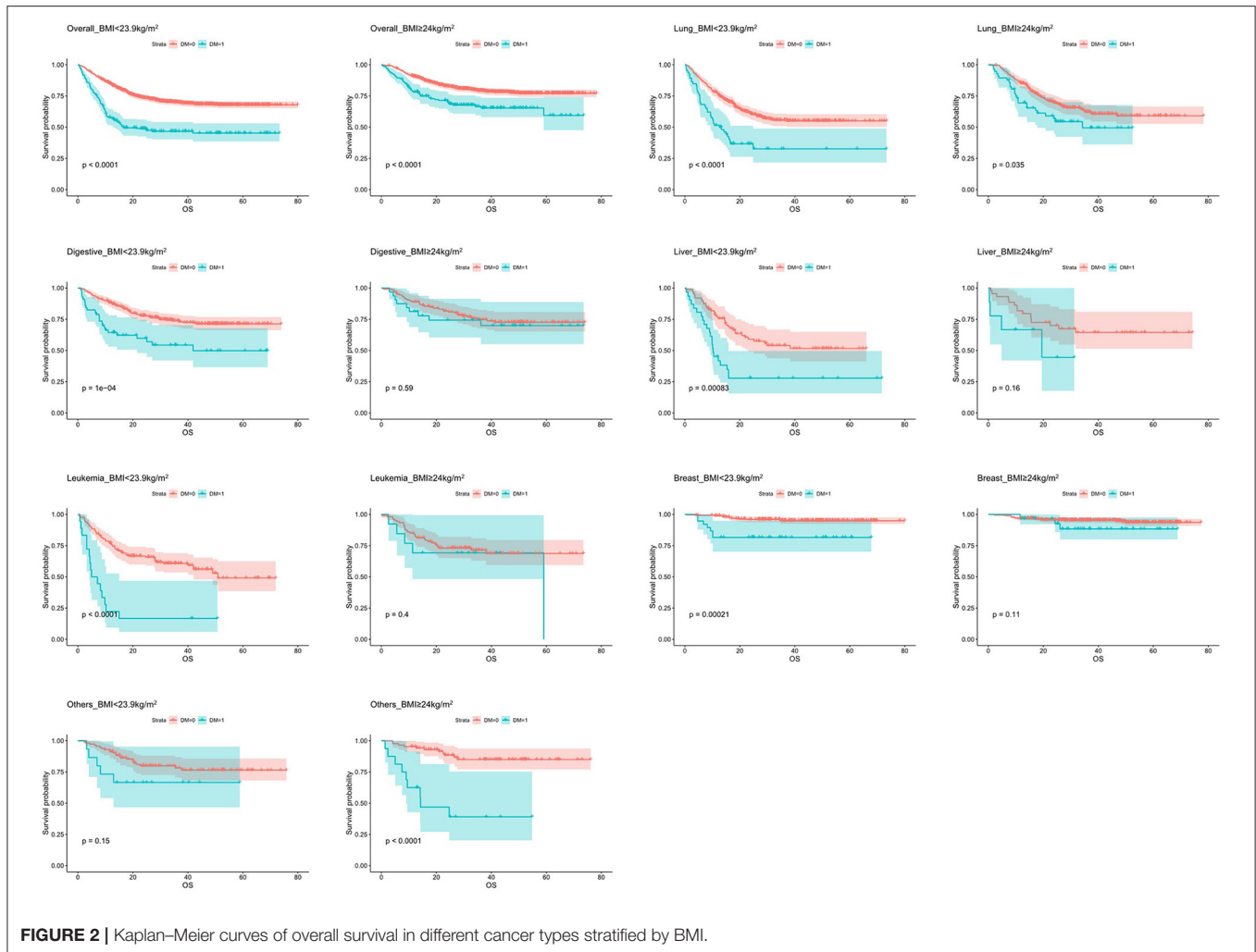**FIGURE 1 |** Kaplan–Meier curves of overall survival in different cancer types stratified by stage. DM, diabetes mellitus.

FIGURE 2 | Kaplan–Meier curves of overall survival in different cancer types stratified by BMI.

1.011–6.155, $P = 0.047$) in early stage breast cancer, 2.929 (95% CI: 1.193–7.189, $P = 0.019$) in advanced breast cancer, and 4.320 (95% CI:2.103–8.871, $P < 0.001$) in patients with early stage other tumors (**Figure 1**).

Prognostic Impact of DM in Different Cancer Types Stratified by BMI

Patients was classified by BMI into normal ($18.5 \leq$ BMI < 23.9 kg/m^2) and obese (BMI ≥ 24.0 kg/m^2) categories according to WGO. **Table 5** and **Figure 2** showed the relationship between DM and OS in specific cancer types stratified by BMI. The combination of diabetes had negative impact on OS when the BMI was within the normal range in lung cancer (HR = 2.297, 95% CI: 1.635–3.229, $P < 0.001$), digestive tract cancer (HR = 2.354, 95% CI: 1.508–3.675, $P < 0.001$), liver cancer (HR = 2.406, 95% CI: 1.414–4.092, $P = 0.001$), leukemia (HR = 4.039, 95% CI: 2.291–7.120, $P < 0.001$) and breast cancer (HR = 4.222, 95% CI: 1.466–12.164, $P = 0.008$). In contrast, among those with BMI $\geq$ 24 kg/m^2, DM played a role only in lung cancer (HR = 1.597, 95% CI: 1.029–2.479, $P = 0.037$) and other tumors (HR = 6.747, 95% CI: 2.769–16.441, $P < 0.001$). Furthermore, it was observed that,

the HR of DM patients with BMI in normal range (HR = 2.468, 95% CI: 2.004–3.041, $P < 0.001$) was significantly higher than those whose BMI $\geq$ 24 kg/m^2 (HR = 1.898, 95% CI: 1.410–2.556, $P < 0.001$) in overall tumors.

DISCUSSION

In previous studies, significant differences in inflammatory status, nutritional status, and quality of life between diabetic and non-diabetic patients have been demonstrated (17, 18). But there was no large-scale data on the differences between diabetic and non-diabetic patients and whether effective glycemic control can make up the adverse effects of diabetes in cancer patients. In the present study, we found that body composition and inflammatory parameters in cancer patients with diabetes differed from those without diabetes, suggesting that diabetes exacerbated the systemic inflammatory response of the body (19). For diabetic patients with good glycemic control, there still existed relatively more active inflammatory status compared to patients without diabetes, especially NLR. But quite a few indicators, such as albumin, PAB and CRP were not statistically

different, suggesting that good glycemic control can reduce the adverse effects of diabetes to some extent.

DM has a negative impact on tumor patients in different stages. For most types of tumors, the prognosis of patients with DM is poor [20]. Diabetes has a greater impact on patient prognosis in early stage liver cancer patients due to the combination of systemic metabolic changes and the development of systemic inflammation in patients with liver cancer at early stages [21]. However, DM behaved as a stronger risk factor in advanced patients compared with those in early stage in colon cancer, lung cancer and breast cancer, which may due to the longer survival period of advanced cancer that allows the risk of DM to unfold. Therefore, the management of blood glucose in cancer patients with relatively longer survivals becomes increasingly important [22]. It is worth mentioning that the adverse effects of diabetes were observed in leukemia, which may further illustrate the role of abnormal metabolism in malignant hematologic diseases and provide a theoretical basis for subsequent studies on the mechanisms of hematologic metabolism.

The BMI stratification was also discussed, and the risk of diabetes was more pronounced in patients with normal BMI. Patients with normal BMI and diabetes tend to have a longer disease duration and are less tolerant of treatment, while patients with higher BMI even without diabetes continuously exist a similar systemic inflammatory response as diabetic patients [23], which may account for the differences in diabetes risk across populations with different BMIs.

There is a limitation for choosing blood glucose as a marker of glycemic control mainly for the shortcomings of possibly inaccurate assessment of long term blood glucose control. The reasons are listed following. First, the glycated hemoglobin A1C (HbA1c), a reliable measurement of glycemic control, was not chose in this study as a marker of glycemic control mainly due to the inconvenience. In real clinical settings, HbA1c was mainly tested when DM was newly diagnosed or a DM patient with unsatisfied blood glucose levels. Second, although the cutoff value of HbA1c for DM is clearly defined, the reasonable threshold of HbA1c for predicting the prognosis was not a consensus [24], which may bring bias if HbA1c was chose as a glycemic control marker. Third, measurements of DM which also have an

impact on cancer development should be taken into analysis as confounders. Several diabetes medications are reported related with cancer prognosis, typically metformin. To be accurate, the mechanisms are still unclear and the results of metformin in cancer prognosis are not always positive [25, 26]. Given the limited patients using metformin (only 1.2%) in this study, the stratified sub-analysis was not committed. This topic should be further investigated.

In summary, we found that patients with diabetes tend to combine worse body composition and inflammatory indicators, and that glycemic control can ameliorate the impairment of diabetes to some extent. The above results suggest the negative influence of hyperglycemia in systemic inflammation metabolism. Besides, the risk posed by diabetes is not the same in patients with different tumor types and stages. Thus, the management of diabetes should be emphasized, especially for patients in early stages, which may bring a more durable disease-free state. Finally, we analyzed patients with different BMI to further analyze the relationship between body composition and diseases, and we believe that more studies should be done in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

XL, KZ, and WJ conducted and drafted the manuscript. WZ and YL collected and analyzed the data. ML, JC, and WL designed the manuscript. ML, JC, WL, XL, KZ, and WJ revised the manuscript. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

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