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Research Article

The Effects of Type 2 Diabetes Mellitus and Hypertension on Survival in Patients with Hepatic Dysfunction and Malignant Solid Tumors

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Abstract

Objectives: The aim of this study was to evaluate the contribution of Type 2 Diabetes Mellitus (T2DM) and hypertension (HT) as comorbidity-enhancing factors on survival in patients with malignant solid tumors who have developed hepatic dysfunction.

Methods: Patients who had received treatment in the medical oncology inpatient service between January 01, 2019, and January 01, 2023, and had developed organ insufficiency.. Grading was performe dusing National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Patients requiring hospitalisation of Grade 3 or higher were included in the evaluation.

Results: 66 patients (22%) had T2DM, and 75 patients (25%) had been diagnosed with HT and were undergoing antihypertensive treatment. T2DM patients exhibited a Median Overall Survival (OS) of 7.81 months compared to 16.72 months for non-diabetic patients (p=0.002). Patients with HT had a median OS of 7.85 months compared to 17.41 months for those without HT (p=0.001), indicating significantly higher survival outcomes in those without a diagnosis of HT.

Conclusion: It has been demonstrated that T2DM and HT have vital importance in cancer patients, and the regulation of blood sugar levels and blood pressure control play a significant role in survival outcomes.

Keywords: Diabetes mellitus, Hypertension, Solid tumors, liver dysfunction

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Metabolic syndrome in patients with Type 2 Diabetes Mellitus is associated with a higher incidence of Breast, Colorectal, Endometrial, Liver, and Pancreatic cancers.[1] Despite the known associations between T2DM and various cancers, the underlying mechanisms remain elusive. The coexistence of central obesity and peripheral insulin resistance often seen in T2DM leads to hyperinsulinemia, which, in turn, triggers chronic inflammation, thereby increasing the risk of cancer development.[1]

Data indicate that comorbidities such as cardiovascular diseases and Type 2 Diabetes Mellitus (T2DM) in cancer patients contribute to increased all-cause mortality risk.[2] However, there is a lack of studies assessing the long-term mortality relationship of pre-existing T2DM and HT in newly diagnosed cancer patients. Diabetic cancer patients receive both anticancer and antidiabetic treatments at lower doses with dose adjustments. Both of these conditions adversely affect patients' survival.[3]

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Furthermore, the existing hyperinsulinemia and hyperglycemia in cancer patients may enhance cancer cell proliferation and metastasis. Additionally, acute hyperglycemia increases endothelial cell permeability due to elevated reactive oxygen species, and pre-existing hypertension also contributes to the resulting damage. It is hypothesized that this mechanism could potentially increase tumor dissemination.[4,5]

Due to all these reasons, in fact, Type 2 Diabetes Mellitus (T2DM) and hypertension (HT) contribute to the development of cancer within a chronic inflammatory context, and in cases of existing cancer, they also enhance cancer progression and proliferation. Clinicians often emphasize direct anticancer treatments in the management of cancer patients, sometimes relegating the patient's other comorbid conditions to the background. The aim of this study is not to compare T2DM and HT with other cancer treatments, but rather to demonstrate that addressing comorbid conditions can provide a beneficial contribution to survival outcomes in cancer patients. Case-based publications reporting the presence of rare tumor locations in T2DM patients are also available[6].

Methods

Patients who had been treated in the Medical Oncology Inpatient Service at Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between January 01, 2019, and January 01, 2023, and had developed organ failure, were included in the study by retrospectively scanning the hospital database. Grading was performe dusing National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Patients requiring hospitalisation of Grade 3 or higher were included in the evaluation. In the conducted analyses, parameters including complete blood count, serum Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT), Serum Bilirubin, Alkaline Phosphatase (ALP), Gamma-Glutamyl Transferase (GGT), Albumin, International Normalized Ratio (INR), Blood Urea Nitrogen (BUN), creatinine, fasting blood glucose levels (FBGL), gender, and the presence of hypertension (HT) were evaluated. In these analyses, patients with grade 3 and above toxicities requiring inpatient admission were included in the study, and survival analyses of the patients were conducted.

Ethics

The study has obtained ethical approval from the Clinical Research Ethics Committee of Health Sciences University, Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, with approval date February 15, 2023, and protocol number 2023-02/84.

Statistical Analysis

Statistical Package for the Social Sciences program was used fo ranalyses [SPSS for Windows, Version 24.0 (IBM Corp.,Armonk, NY, USA)]. Continuous variables were report edusing median (interquartilerange, IQR) and mean (standarddeviation, SD). Qualitative categorical variables were report edusing Pearson's χ^2 or Fisherexact test. Survival graphics were obtained using the Kaplan Meier survival graphics and log-rank test. A p-value of <0.05 was considered significant.

Results

A total of 300 patients, consisting of 160 (53.3%) males and 140 (46.7%) females, were included in the study by retrospectively scanning the database. The median age was 57.0 (range 55.01-57.2) years. The diagnoses of the included patients are presented in Table 1. Among the patients, a total of 66 (22%) had previously been diagnosed with diabetes and were using some form of antidiabetic treatment during follow-up. In the conducted survival analyses, it was observed that diabetic (T2DM) patients had a superior median Overall Survival (OS) of 7.81 months compared to 16.72 months (p=0.002) for non-diabetic patients after hepatic dysfunction (Fig. 1). Among these 66 T2DM patients, 42 (63.63%) were assessed to have hepatosteatosis through imaging methods, and a total of 154 (51.3%) patients had developed hepatosteatosis. There were 128 patients (42.1%) with grade 1 steatosis, 21 patients (7%) with grade 2 steatosis, and 5 patients (1.7%) with grade 3 steatosis. A total of 49 patients (16.3%) had no liver metastasis, while 251 patients (83.7%) had liver metastasis. In the analysis,

Table 1. The primary diagnosis of patients with hepatic dysfunction

Diagnosis	N	Diagnosis	N
Colorectal Cancers	57 (%19.0)	Primary unknown cancer	23 (%7.7)
Breast cancer	53 (%17.7)	Bile duct cancers	14 (%4.7)
Pancreatic cancer	50 (%16.7)	Ovarian cancers	10 (%3.3)
Gastric cancer	40 (%13.3)	Others	30 (%10)
Lung cancer	23 (%7.7)		

there were 75 patients (25%) diagnosed with hypertension (HT) who were receiving antihypertensive treatment. In the survival analysis following liver metastasis, it was observed that patients with HT had a median OS of 7.85 months compared to 17.41 months for those without HT, with significantly higher survival outcomes in patients without a diagnosis of HT (Fig. 1). Out of the 66 diabetic patients, 10 patients (15.2%) did not have a detected liver metastasis. Demographic characteristics such as age, gender, and survival analyses are presented in Table 2. Among males, colorectal cancer (CRC) was present in 43 patients (26.9%), gastric cancer in 29 patients (18.1%), pancreatic cancer in 26 patients (16.1%), and lung cancer in 19 patients (11.9%). Among females, breast cancer was present in 53 patients (37.9%), pancreatic cancer in 24 patients (17.1%), CRC in 14 patients (10%), gastric cancer in 11 patients (7.9%), and lung cancer in 4 patients (2.9%). The relationship between liver metastasis and T2DM is provided in Table 3.

Table 2. Laboratory and demographic characteristics*

	Median OS (95% CI)	p
Age, median		
≤50	25.62 (19.14-32.10)	< 0.001
>50	9.13 (5.96- 12.30)	
Gender		
Male	8.04 (5.67-10.42)	<0.001
Female	20.92 (15.34-26.51)	
Glucose		
<126	15.83 (11.11-20.55)	0.140
≥126	13.20 (5.00-21.41)	
ALT		
<40	11.00 (7.10-14.90)	0.680
≥40	16.52 (11.80-21.24)	
Albumine		
< 3	11.30 (5.49-17.11)	0.490
≥ 3	15.37 (10.21-20.54)	
INR		
< 1.5	13.53 (8.36-18.70)	0.680
≥ 1.5	16.72 (11.63-21.80)	
Hb		
< 11	11.17 (6.04-16.29)	0.213
≥ 11	17.41 (11.79-23.03)	
T2DM		
Yes	7.81 (3.21-12.42)	0.002
No	16.72(12.34-21.10)	
HT		
Yes	7.85 (4.64-11.06)	0.001
No	17.41 (13.23-21.58)	

*Kaplan Meier Survival Analyses.

Table 3. Relationship between Liver metastasis and Diabetes.

	Liver Metastasis	
	Yes	No
T2DM		
Yes	56 (%84.8)	10 (%15.2)
No	195 (%83.3)	39 (%16.7)

*Pearson's χ^2.

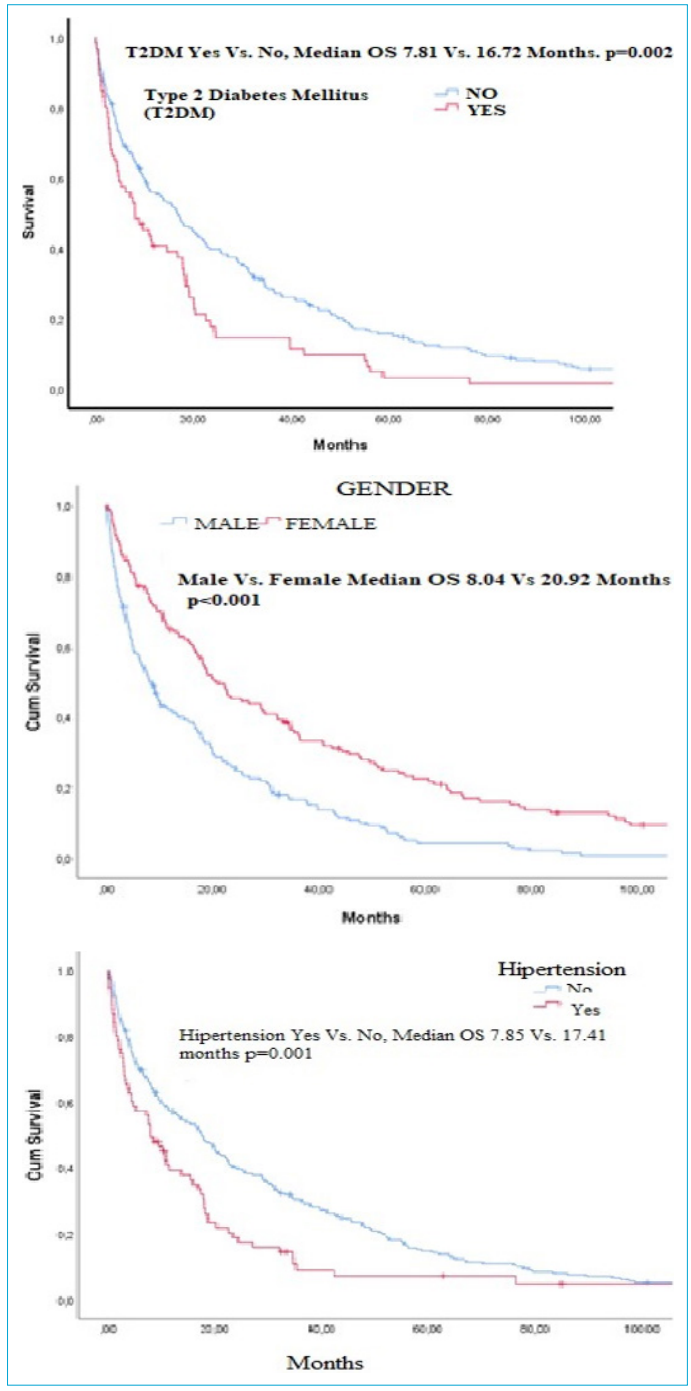

Figure 1. Mortality Analyses.

Discussion

Next-generation oncological treatments have gained momentum with targeted agents and patient-specific therapeutic modalities in cancer. Throughout this process, the newly defined next-generation treatments entail significant costs for national budgets and reimbursement institutions. Despite the cost increase, the success rates with these next-generation treatments are not yet at the desired level. Additionally, the survival benefits achieved in metastatic patients are limited to a few months. However, by regulating certain comorbid conditions that have an impact on the overall status of patients, survival outcomes can be nearly equivalent to those achieved with next-generation treatments. Furthermore, it is important due to its cost-effectiveness. Richardson et al. found that for various cancer types, the risk of all-cause mortality is 1.41 times higher in patients with pre-existing Type 2 Diabetes Mellitus (T2DM) at the time of diagnosis compared to those without T2DM. [3] Additionally, the prevalence of hypertension is higher in cancer survivors compared to the general population [7] A1. In a study conducted by Piccirillo JF and et al. encompassing approximately 17,000 patients, it was determined that hypertension was the most common coexisting condition with cancer [8] A2. The co-occurrence of cancer and hypertension at an approximate rate of 40% leads to the conclusion of elevated cardiovascular diseases and complications in cancer patients compared to the normal population[9-10] A3-A4. This study also identified that cancer patients with hypertension had their overall survival significantly reduced, in alignment with the literature, with 7.85 months versus 17.41 months, marking a fifty-percent decrease.

As a result, numerous studies have gained momentum in different cancer patients.[7,8] The aim of this study is to demonstrate the impact of T2DM and hypertension (HT) on survival during liver dysfunction in patients with malignant solid tumors.

Another study conducted on CRC patients demonstrated that both in cases of hepatic dysfunction and T2DM, patients received insufficient antidiabetic treatment.[9,10] Similarly, Poll Franse et al. indicated in their study that due to increased infection risk and lower treatment response rates in T2DM patients, along with a higher occurrence of diabetic neuropathy, nephropathy, and cardiovascular diseases, dose adjustments were made in their treatments, and they were treated with lower doses.[11] Consequently, T2DM, insulin resistance, and hyperinsulinemia, which are associated with chronic inflammation, not only lead to shorter survival durations but also further decrease treatment response rates due to the inability to receive optimal treatment doses.

Interestingly, following retrospective reports indicating improved survival rates for diabetic patients using the antidiabetic drug metformin in various cancer types, it has garnered significant interest as a potential anticancer therapy. [12] However, in this study, the analyses conducted did not demonstrate a contribution of metformin to survival outcomes.

This study has certain limitations. Due to its retrospective nature and the heterogeneity of both primary tumors and patient characteristics, more homogeneous subgroup analyses and larger patient populations, including case-control studies covering the used antidiabetic agents, are needed. However, despite all these aspects, the scarcity of publications in the literature necessitates further research. Therefore, this study has been planned with the aim of addressing this gap.

Conclusion

In conclusion, T2DM and HT were found to be associated with approximately twofold worse survival outcomes in cancer patients with organ dysfunction. It was demonstrated that achieving low-cost, effective, and improved survival outcomes can be attained through blood sugar and blood pressure regulation.

Disclosures

Ethics Committee Approval: The study has obtained ethical approval from the Clinical Research Ethics Committee of Health Sciences University, Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, with approval date February 15, 2023, and protocol number 2023-02/84.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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