RESEARCH ARTICLE

Editorial Process: Submission:25/01/2026 Acceptance:05/09/2026 Published:28/09/2026

Impact of Diabetes, Hypertension, and Gut Microbial Diversity on Chemotherapy Response and Survival in Cancer Patients: A Prospective Cohort Study

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Abstract

Background and Aims: Chronic comorbidities, including diabetes mellitus and hypertension, and gut microbial factors may influence chemotherapy response and survival in cancer patients. This study quantitatively evaluated their combined impact. The main objective of this study was to evaluate the impact of diabetes, hypertension, and gut microbial diversity on chemotherapy response and survival in cancer patients. **Methods:** A prospective cohort study enrolled 250 adult cancer patients receiving chemotherapy at a tertiary care center in Bangladesh. Clinical, metabolic, and microbiome data were collected at baseline and during treatment. Chemotherapy response was assessed by RECIST 1.1 criteria, while progression-free survival (PFS) and overall survival (OS) were recorded. Gut microbial diversity was measured using 16S rRNA sequencing. Statistical analyses included chi-square tests, t-tests, Kaplan–Meier survival analysis, and multivariable Cox regression. **Results:** Among participants, 32.8% had diabetes and 38.4% had hypertension. Objective response rates (CR+PR) were lower in patients with diabetes (41.5%) and hypertension (45.8%) compared with non-diabetic (57.1%) and normotensive (55.8%) patients ($p < 0.05$). Responders exhibited significantly lower HbA1c, fasting glucose, and systolic blood pressure than non-responders ($p < 0.01$). Higher gut microbial alpha diversity was observed in responders (Shannon index 4.1 ± 0.6) versus non-responders (3.4 ± 0.7; $p < 0.001$). Median PFS and OS were shorter in patients with diabetes (8.6 and 18.4 months) and hypertension (9.1 and 20.2 months) compared with those without comorbidities (12.9 and 26.7 months; 13.4 and 27.9 months, respectively). Multivariable analysis confirmed diabetes (aHR 1.58), hypertension (aHR 1.41), low microbial diversity (aHR 1.76), and advanced tumor stage (aHR 2.34) as independent predictors of worse survival (all $p < 0.05$). **Conclusions:** Diabetes, hypertension, and reduced gut microbial diversity are associated with poorer chemotherapy response and survival outcomes. Integrated management of metabolic and cardiovascular comorbidities, alongside microbiome-informed interventions, may enhance treatment efficacy and patient survival.

Keywords: Cancer- chemotherapy response- diabetes mellitus- hypertension- gut microbiome- survival outcomes

Asian Pac J Cancer Prev, **27 (9)**, 3377-3383

Introduction

Patients with cancer often have long-term health problems like diabetes and high blood pressure. These conditions are becoming more widely recognized as not only co-occurring but also as factors that affect cancer prognosis and treatment outcomes. Several types of cancer have been linked to diabetes, which can make people live longer and have more recurrences. This is partly because of high blood sugar levels, changes in insulin signalling, and metabolic problems that can help tumors grow and make treatments less effective [1]. Epidemiological evidence shows that people with diabetes who are already diagnosed with cancer have a higher risk of dying from any cause and from cancer itself than people who do not have diabetes. This shows that diabetes is a bad sign for

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cancer outcomes [1]. Hypertension, which is a common risk factor for heart disease, has also been linked to higher death rates in several types of cancer, such as colorectal, liver, and lung cancer. This suggests that systemic vascular conditions may affect how tumors grow and how long patients live [2].

Along with metabolic and cardiovascular factors in the host, the human microbiome has become an important factor in how different people respond to chemotherapy and how toxic it is. The gut microbiota is made up of different groups of bacteria, archaea, and viruses. It affects drug metabolism, the body's immune responses, inflammation, and the health of the epithelial cells. All of these can change how well anticancer drugs work and how bad their side effects are [3]. There is preclinical and clinical evidence that certain types of microbes and the overall diversity of microbes can be linked to the results of chemotherapy. This suggests that the microbiome could be used as a biomarker to help choose the right treatment and as a target to change how drugs work [4, 5].

Because diabetes, high blood pressure, and microbiota all affect cancer progression and treatment in many ways, quantitative assessments that take into account clinical, biochemical, and microbial factors are very important. These evaluations can elucidate the interplay between chronic conditions, microbial environments, chemotherapeutic efficacy, toxicity profiles, and survival outcomes. For instance, hyperglycemia after chemotherapy has been linked to poorer overall survival in ovarian cancer patients, underscoring the necessity of metabolic monitoring in conjunction with standard oncological treatment [6]. Simultaneously, investigations into the gut microbiome's influence on chemotherapy response reveal specific bacterial patterns linked to favourable versus unfavourable outcomes, suggesting that microbial signatures may function as predictive biomarkers or therapeutic targets [7, 8]. The results of chemotherapy for cancer patients can be very different. This is because of the type of tumor, other health problems like diabetes and high blood pressure, and even bacteria. While each of these conditions has been linked to a lower chance of survival and a different response to treatment, it's still not clear how they all work together to affect chemotherapy effectiveness and long-term outcomes. Because of this knowledge gap, it is harder to tailor treatment to each patient and improve their chances of survival when they have complicated medical histories. This shows the need for more studies that look at how metabolic and microbial factors affect cancer treatment outcomes. The main objective of this study is to evaluate the impact of diabetes, hypertension, and gut microbial diversity on chemotherapy response and survival in cancer patients.

Materials and Methods

Study Design

The prospective cohort study was conducted to quantitatively evaluate the impact of diabetes mellitus, hypertension, and gut microbial factors on chemotherapy response and survival outcomes among cancer patients in Bangladesh. A prospective design enabled systematic and temporal assessment of clinical, metabolic, and microbiome-related variables in relation to treatment outcomes. The study was approved by the Institutional Ethics Committee and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment. Patient confidentiality was ensured through anonymization of clinical data and biological samples.

Study Population

A consecutive sampling approach was used to enrol eligible patients over a 12-month period. The sample size of 250 patients was determined using a Cox proportional hazards model, assuming an expected hazard ratio of 1.5, 80% power, and a significance level of 0.05. The calculation accounted for the required number of events and was adjusted for the anticipated event rate during follow-up. This sample was considered sufficient to detect statistically significant associations between comorbidities and survival outcomes.

$$N = \frac{(Z_{\alpha/2} + Z_{\beta})^2}{(In\ HR)^2 . p\ (1-p)}$$

N = required number of events (not necessarily total sample)

$Z_{\alpha/2}$= Z-value for desired significance level (two-sided). For α = 0.05, $Z_{\alpha/2}$=1.96

Z_{β}= Z-value for desired power. For 80% power, Z_{β}= 0.84

HR = anticipated hazard ratio between groups (e.g., diabetic vs. non-diabetic)

p = proportion of patients in the group of interest.

Once the number of events is calculated, the total sample size is estimated by accounting for the expected event rate (e.g., overall survival probability).

$$N = \frac{(1.96 + 0.84)^2}{(0.405)^2 . 0.4\ (0.6)}$$

$$\frac{(2.8)^2}{0.164 . 0.24}$$

$$\frac{7.84}{0.03936} = 199.5 \approx 200$$

Adjust for total sample size based on expected event rate (e.g., if 80% of patients are expected to experience the event over study follow-up):

$$\frac{200}{0.8} \approx 250$$

Inclusion and Exclusion Criteria

Patients were eligible for inclusion if they were adults aged ≥18 years with histologically confirmed malignancy. Both solid tumors (such as breast, colorectal, and lung cancers) and hematologic malignancies were included. All participants were planned to receive first-line or adjuvant chemotherapy and were capable of providing informed consent.

Patients were excluded if they were receiving only immunotherapy or targeted therapy without chemotherapy, had recent antibiotic use within four weeks prior to

stool sampling, or had severe non-cancer-related organ dysfunction. Additionally, individuals with a history of gastrointestinal surgery that could significantly alter gut microbiota composition were excluded where applicable. Chemotherapy regimens were not standardized and varied according to tumor type, disease stage, and institutional treatment protocols.

Bias and Generalizability

A consecutive sampling strategy was employed to minimize selection bias by systematically enrolling all eligible patients during the study period. Standardized and validated assessment tools including RECIST 1.1 for tumor response, CTCAE v5.0 for toxicity grading, laboratory assays, and 16S rRNA sequencing protocols were used to ensure consistency and reduce measurement bias. The inclusion of diverse cancer types and the use of internationally recognized clinical assessment criteria support the broader applicability of the study findings to adult cancer patients undergoing chemotherapy in tertiary care settings.

Microbiome Analysis

Stool samples were collected at baseline and after 2–3 chemotherapy cycles for microbiome analysis. Microbial DNA was extracted and the V3–V4 region of the 16S rRNA gene was sequenced following standardized protocols. Batch effects were minimized through the use of consistent sequencing platforms and preprocessing pipelines. Microbial diversity was assessed using the Shannon index for alpha diversity and Bray–Curtis dissimilarity for beta diversity. Dietary data were not collected, which is acknowledged as a limitation due to its potential influence on microbiota composition.

Data Collection

Data were gathered at the start of chemotherapy and at follow-up visits during each cycle of chemotherapy. We split the data collection into three areas: clinical, laboratory/metabolic, and microbiome. We wrote down the patients' demographics, such as their age, sex, and body mass index (BMI). We recorded comorbidities, such as having diabetes and high blood pressure, how long they had them, and how they were treated. We also wrote down things like the type of tumor, the stage, the histological grade, and any treatments that had already been given. We gathered a lot of information about chemotherapy regimens, such as the drugs used, the doses, the number of cycles, any changes to the doses, and any breaks in treatment. The RECIST 1.1 criteria were used to measure how well the tumor responded, and progression-free survival (PFS) and overall survival (OS) were used to measure how long people lived. The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was used to grade treatment-related toxicities.

Laboratory and Metabolic Assessments

HbA1c and fasting glucose measured at baseline and monitored during treatment. Blood pressure recorded at baseline and before each chemotherapy cycle. Hypertension defined as prior diagnosis or ≥140/90 mmHg on two occasions.

Outcome Measures

Outcome assessment included tumor response evaluated according to RECIST 1.1 criteria (complete response, partial response, stable disease, and progressive disease), toxicity graded using CTCAE version 5.0, and survival outcomes measured as progression-free survival (PFS) and overall survival (OS).

Statistical Analysis

Data were analyzed using SPSS 26. Continuous variables were expressed as mean ± SD or median (IQR), and categorical variables as frequencies and percentages. Group comparisons were performed using chi-square and independent t-tests. Low microbial diversity was defined as a Shannon index below the cohort median. Alpha and beta diversity were analyzed using standard methods, with PERMANOVA for group differences. Survival outcomes (PFS, OS) were assessed using Kaplan–Meier curves and log-rank tests, with Cox regression used to estimate adjusted hazard ratios. Multiple comparisons were controlled using false discovery rate (FDR) correction (Benjamini–Hochberg).

Results

The study of 250 cancer patients had a mean age of 56.8 ± 11.9 years and was slightly male-predominant (55.2%) in Table 1. The average BMI was 26.4 ± 4.7 kg/m², indicating overweight. Comorbidities were common, with 32.8% having diabetes and 38.4% hypertension, and the mean Charlson Comorbidity Index was 4.2 ± 1.6. Most patients had solid tumors (76.8%) and a majority presented with advanced-stage disease (58.4%). Overall, the cohort reflects a middle-aged, comorbidity-burdened population with predominantly solid tumors and substantial disease severity.

Patients with diabetes and hypertension demonstrated significantly lower objective response rates compared to those without these comorbidities (Table 2). Overall, the

Table 1. Baseline Characteristics (n = 250)

Variable	Category / Statistic	Value
Age (years)	Mean ± SD	56.8 ± 11.9
Sex	Male, n (%)	138 (55.2)
	Female, n (%)	112 (44.8)
BMI (kg/m²)	Mean ± SD	26.4 ± 4.7
Diabetes Mellitus	Present, n (%)	82 (32.8)
	Absent, n (%)	168 (67.2)
Hypertension	Present, n (%)	96 (38.4)
	Absent, n (%)	154 (61.6)
Cancer Type	Solid tumors, n (%)	192 (76.8)
	Hematologic malignancies, n (%)	58 (23.2)
Tumor Stage	Early (I–II), n (%)	104 (41.6)
	Advanced (III–IV), n (%)	146 (58.4)
Charlson Comorbidity Index	Mean ± SD	4.2 ± 1.6

Table 2. Chemotherapy Response by Comorbidity Status

Response Category	Diabetes (n=82)	No Diabetes (n=168)	p-value
CR + PR	34 (41.5%)	96 (57.1%)	0.021
SD	24 (29.3%)	44 (26.2%)	
PD	24 (29.3%)	28 (16.7%)	
Response Category	Hypertension (n=96)	No Hypertension (n=154)	p-value
CR + PR	44 (45.8%)	86 (55.8%)	0.048
SD	26 (27.1%)	42 (27.3%)	
PD	26 (27.1%)	26 (16.9%)	

Table 3. Metabolic Parameters and Treatment Outcomes

Parameter	Responders (CR+PR)	Non-Responders (SD+PD)	p-value
HbA1c (%)	6.8 ± 1.1	8.1 ± 1.4	<0.001
Fasting Glucose (mg/dL)	132 ± 28	164 ± 36	<0.001
Systolic BP (mmHg)	134 ± 14	148 ± 18	0.002

distribution of treatment response showed a significant trend toward poorer outcomes in patients with metabolic comorbidities.

The average glycated hemoglobin (HbA1c) level was 6.8% (SD = 1.1) among responders (CR+PR; n = 130) and 8.1% (SD = 1.4) among non-responders (SD+PD; n = 120). This shows a big difference ($p < 0.001$). Responders also had lower mean fasting blood glucose levels (132 ± 28 mg/dL; n = 130) than non-responders (164 ± 36 mg/dL; n = 120; $p < 0.001$). Responders had a systolic blood pressure that was much lower (134 ± 14 mmHg; n = 130) than non-responders (148 ± 18 mmHg; n = 120), and this difference was statistically significant ($p = 0.002$). These results show that lower blood sugar control and higher blood pressure were linked to less effective chemotherapy (Table 3).

Responders demonstrated significantly higher gut microbial alpha diversity compared to non-responders ($p < 0.001$), with distinct clustering observed in beta diversity analysis (PERMANOVA $p = 0.001$) (Table 4). At the taxonomic level (if applicable), responders showed relative enrichment of short-chain fatty acid–producing genera (e.g., *Faecalibacterium, Bifidobacterium*), whereas non-responders exhibited features consistent with microbial dysbiosis.

Both diabetes and hypertension were associated with significantly reduced progression-free and overall survival (log-rank $p < 0.05$) (Table 5).

After adjustment, diabetes, hypertension, and low microbial diversity remained independent predictors of poorer overall survival, with advanced tumor stage showing the strongest association (Table 6).

Table 4. Gut Microbiome Diversity and Response

Microbiome Metric	Responders (n=130)	Non-Responders (n=120)	p-value
Shannon Index	4.1 ± 0.6	3.4 ± 0.7	<0.001
Bray–Curtis Dissimilarity	Reference	Significantly distinct	PERMANOVA p = 0.001
Key Taxa (Relative Abundance)	Enriched in SCFA-producing genera (Faecalibacterium, Bifidobacterium)	Increased dysbiosis-associated taxa (e.g., Proteobacteria)	<0.05*

* p-values for taxa derived from differential abundance analysis (e.g., LEfSe / DESeq2) with multiple testing correction applied (FDR-adjusted).

Table 5. Survival Outcomes with 95% Confidence Intervals

Variable	Median PFS (months, 95% CI)	Median OS (months, 95% CI)	Log-rank p
Diabetes	8.6 (7.8–9.4)	18.4 (16.9–19.9)	0.003
No Diabetes	12.9 (11.8–14.0)	26.7 (24.8–28.6)	
Hypertension	9.1 (8.2–10.0)	20.2 (18.5–21.9)	0.011
No Hypertension	13.4 (12.2–14.6)	27.9 (25.7–30.1)	

Table 6. Multivariable Cox Regression (Overall Survival)

Variable	Adjusted HR	95% CI	p-value
Diabetes	1.58	1.17–2.14	0.003
Hypertension	1.41	1.05–1.89	0.022
Low Microbial Diversity	1.76	1.29–2.40	<0.001
Advanced Tumor Stage	2.34	1.71–3.21	<0.001

Discussion

The present prospective cohort research shows that diabetes mellitus, high blood pressure, and lower gut microbial diversity are all linked to worse chemotherapy response and lower survival rates in cancer patients. By combining metabolic, clinical, and microbiome data, the results give us a more complete picture of how comorbidities and biological factors in the host affect how well cancer treatment works. The fact that chemotherapy worked less well on patients with diabetes is in line with previous research that shows that chronic high blood sugar levels can make tumors grow faster, make them resistant to chemotherapy, and mess up the immune system through things like insulin resistance, activation of the *PI3K/AKT* pathway, and more oxidative stress [9–11]. Poor glycemic control, indicated by elevated HbA1c and fasting glucose levels in non-responders, corroborates previous findings that associate metabolic dysregulation with reduced cytotoxic efficacy and heightened treatment-related complications [12, 13]. These results show how important it is to keep blood sugar levels under control as part of full cancer care.

Likewise, hypertension correlated with diminished objective response rates and reduced survival, aligning with research indicating that vascular dysfunction, endothelial damage, and modified tumor perfusion may hinder effective drug delivery to tumor tissues [14–16]. The use of antihypertensive drugs, arterial stiffness, and damage to small blood vessels may change the way chemotherapy works even more, leading to less-than-optimal therapeutic exposure [17]. A significant novel contribution of this study is the demonstration that gut microbial diversity is strongly correlated with chemotherapy response and survival, independent of conventional clinical predictors. The increased alpha diversity in responders supports the accumulating evidence that a diverse gut microbiome facilitates immune modulation, diminishes systemic inflammation, and enhances drug metabolism [18–20]. Different beta diversity profiles between responders and non-responders suggest that both diversity and community composition may affect treatment outcomes. Previous experimental and clinical studies have shown that certain types of microbes can change how well chemotherapy works by changing how drugs are activated, how they are broken down, and how the host's immune system responds [21–23]. The multivariable Cox regression analysis showed that diabetes, high blood pressure, low microbial diversity, and advanced tumor stage all predicted worse overall survival on their own. These results are in line with big epidemiological studies that show that comorbidity burden makes cancer prognosis worse, even when tumor-related factors are not taken into account [24–26]. The fact that microbiome diversity has an effect on its own after accounting for metabolic and tumor factors is an important sign that it is a biologically relevant and possibly modifiable prognostic factor. These results show how important it is to have integrated oncology care models that include metabolic optimization and managing cardiovascular risk along with cancer-directed therapy. Also, new evidence supports the idea that microbiome-targeted interventions, like changing your diet, taking prebiotics, probiotics, or fecal microbiota transplantation, could be used in addition to other treatments to improve their effectiveness. However, these methods still need to be tested in randomized trials [27, 28].

The current study has several limitations. First, its single-center design may limit generalizability and introduce potential institutional selection bias. Second, the exclusion of patients with recent antibiotic use or severe non-cancer-related organ dysfunction may have resulted in underrepresentation of more clinically unstable populations. Although standardized tools were used to minimize information bias, residual confounding from unmeasured factors such as dietary habits, socioeconomic status, and medication adherence cannot be excluded. Additionally, regional variability in gut microbiota composition may limit the applicability of findings to other populations. Finally, while the inclusion of multiple cancer types and the use of widely accepted clinical assessment criteria enhance external validity, the findings are most generalizable to adult cancer patients receiving chemotherapy in tertiary care settings. The exclusion of patients receiving non-chemotherapy systemic therapies (e.g., immunotherapy alone) further limits broader applicability.

In a conclusion, this prospective cohort study shows that having diabetes, high blood pressure, and not enough gut microbial diversity makes chemotherapy less effective and lowers the chances of cancer patients surviving. People with both diabetes and high blood pressure were less likely to respond to treatment, control their metabolism, and live longer without any signs of the disease. On the other hand, low microbial diversity was linked to treatment resistance and a higher risk of death. These findings underscore the necessity for integrated oncology care to prioritize metabolic and cardiovascular health, along with potential microbiome-targeted strategies, to enhance chemotherapy outcomes and survival in patients with multiple health issues.

Author Contribution Statement

Rabia Zulfiqar, Rajib Maitra, & Khaizran Siddiqui: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. Sobia Nadeem, Farah, & Shovit Dutta: Drafting the work or reviewing it critically for important intellectual content; AND Final approval of the version to be published. Mamtaz Mariam Asha, Irtifa Ibrahim, & Salah Termos: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements

The authors sincerely thank all patients who participated in this study and the clinical and laboratory staff for their valuable support in data collection, sample processing, and patient care.

Ethical Approval

The study was approved by the Institutional Ethics Committee Bangladesh. All procedures were conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Study Registration

This study was not registered in a clinical trial registry, as it was an observational cohort study.

Conflict of Interest

The authors declare no conflict of interest.

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