Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Higher glucose levels associated with worse pathologic response and survival in patients with locally advanced gastric cancer treated with neoadjuvant immunotherapy

Hongming Liu
Second Affiliated Hospital of Zhejiang University
Dong Cao
Affiliated Hospital of Shaoxing University
Jun He
Second Affiliated Hospital of Zhejiang University
Bixian Luo
Fuzhou University Affiliated Provincial Hospital
Chuanlei Tuo
Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer
Chengyu Hu
Second Affiliated Hospital of Zhejiang University
Fuping Li
Second Affiliated Hospital of Zhejiang University
Yuxin Zhong
National Cancer Center, Chinese Academy of Medical Sciences and Peking Union Medical College
Yong Liu
Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer
Weihua Gong
weihuagong@zju.edu.cn

Second Affiliated Hospital of Zhejiang University

Article

Keywords: Gastric cancer, Blood glucose, Type 2 diabetes, Neoadjuvant immunotherapy, Pathological response, Survival

Posted Date: November 17th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11356734/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Title:

Higher glucose levels associated with worse pathologic response and survival in patients with locally advanced gastric cancer treated with neoadjuvant immunotherapy

Running title: Higher glucose and gastric cancer

Hongming Liu[1#], Dong Cao[2#], Jun He[1], Bixian Luo[3], Chuanlei Tuo[4], Chengyu Hu[1], Fuping Li[1], Yuxin Zhong[*5], Yong Liu[*2], Weihua Gong[1*]

1 Department of Surgery, Second Affiliated Hospital of School of Medicine, Zhejiang University, Hangzhou, 310058, China.

2 Department of Gastrointestinal Surgery, Affiliated Hospital of Shaoxing University, Shaoxing, Zhejiang, 31200, China.

3 Department of Gastrointestinal Surgery, Fujian Provincial Hospital, Fuzhou University Affiliated Provincial Hospital, Fuzhou, Fujian, China.

4 Department of Gastric Surgery, Key Laboratory of Cancer Prevention and Therapy, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Tianjin, China.

5 Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.

# Contributed equally.

*Corresponding Author:

Dr. Weihua Gong, M.D., Department of Surgery, Second Affiliated Hospital of School of Medicine, Zhejiang University, Hangzhou, 310058, China. Jiefang Road #88, Hangzhou City, Zhejiang Province, 310009, PRC. Tel: +86 571 - 87783580. Fax: +86 571 – 87783581. E-mail: weihuagong@zju.edu.cn

Or

Yong Liu, MD, PhD, Department of Gastric Surgery, Tianjin Medical University Cancer

Institute & Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Tianjin's Clinical Research Center for Cancer, Tianjin, 300060, PR China. E-mail: libraly@126.com

Or

Yuxin Zhong Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No.17, Panjiayuan Nanli, Chaoyang District, Beijing 100021, China. E-mail: zhongyuxin@cicams.ac.cn

Word count: text - 2910; abstract - 245

Table: 3; Supplementary Table: 6

Figure: 3; Supplementary Figure: 3

Statements & Declarations

Ethical considerations

This study was approved by the Ethics Committee of the Second Affiliated Hospital, Zhejiang University School of Medicine (Approval No. C20251466).

Authors' contributions

HL and DC collected and analyzed the data, performed the literature review, and drafted the manuscript. JH, BL, CT, CH and FL assisted with data collection and interpretation of the findings. YZ contributed to the study methodology, data validation, and supervision. YL contributed to the study design, methodology, and supervision. WG conceived and supported the project, supervised the study, and critically reviewed and revised the manuscript.

Funding

This study was supported by the Key Research and Development Program of Zhejiang Province (Grant No. 2025C02054).

Acknowledgements

None

Competing interests

The authors have declared that no competing interest exists.

Availability of data and materials

Due to ethical and privacy restrictions, the data in this study can be obtained from the corresponding author upon reasonable request.

Abstract

Background

The impact of type 2 diabetes mellitus (T2DM) and glucose levels on clinical outcomes in patients with gastric cancer after neoadjuvant immunotherapy remains unclear. We assessed mean baseline glucose and T2DM status in relation to pathologic response and survival.

Methods

This retrospective cohort study included patients with gastric cancer who received NICT followed by surgery at three medical centers in China from 2021 to 2024. Random venous glucose levels within 4 weeks before ICI initiation, and T2D status, OS and PFI were collected.

Results

Among 376 patients, 86 (22.9%) had diabetes and 91 (24.2%) achieved pCR. Compared with the lowest glucose quartile, the highest quartile had a lower pCR rate (14.9% vs 28.0%) and lower adjusted odds of pCR (OR 0.33, 95% CI 0.15 to 0.74, P = 0.007). The adjusted HR for OS comparing the highest with the lowest quartile was 3.42 (95% CI 0.97 to 12.01, P = 0.055). PFI did not differ significantly across quartiles (log-rank P = 0.189). Diabetes was not associated with pCR or survival. Among 175 patients with available CPS data, CPS ≥5 was associated with higher odds of pCR and longer OS and PFI after adjustment. HbA1c was not significantly associated with treatment outcomes in the 59 patients with available data.

Conclusion

Higher mean baseline glucose was associated with poorer pathologic response and shorter survival for gastric cancer patients underwent NIT. These findings highlight the value of baseline glucose assessment and glycemic control may improve treatment outcomes.

Keywords: Gastric cancer; Blood glucose; Type 2 diabetes; Neoadjuvant immunotherapy; Pathological response; Survival;

Introduction

For locally advanced gastric cancer, surgery alone is often insufficient. Neoadjuvant therapy improves survival and is widely used[1, 2]. Immune checkpoint inhibitors have recently been introduced into the perioperative setting. KEYNOTE-585, DANTE, PANDA, and MATTERHORN showed that adding immunotherapy to chemotherapy can improve pathologic response[3-6]. However, the benefit is not uniform. Many patients do not achieve a pathologic complete response, and survival outcomes vary across trials.

Tumoral and systemic metabolism are important effector T-cell function and antitumor immune activation in the context of ICI therapy[7, 8]. Type 2 diabetes mellitus (T2DM) has shown to be associated with increased risk and poorer outcomes of several gastrointestinal malignancies[9, 10]. Moreover, a multicenter study found that T2DM treated with glucose-lowering medication was associated with shorter overall and progression-free survival after ICI treatment[11]. Another study also reported poorer survival in patients with diabetes across different advanced cancers treated with ICIs[12]. However, previous studies have largely involved advanced or metastatic cancer, evidence focused on gastric cancer treated with immunotherapy remains limited. The associations of glucose levels and T2DM with treatment outcomes remain unclear.

We therefore conducted a multicenter retrospective cohort study of patients with locally advanced gastric cancer who received neoadjuvant immunotherapy (NIT) followed by surgery. We examined the associations of mean baseline glucose and T2DM status with pathologic complete response, overall survival, and progression-free interval. We hypothesized that higher baseline glucose would be associated with poorer pathologic response and survival.

Materials and methods

Study design and participants

This multicenter, retrospective cohort study included patients with gastric cancer who received neoadjuvant treatment (NAT) followed by gastrectomy from three medical centers between January 2021 and December 2024. Inclusion criteria were: (1) pathologically confirmed gastric adenocarcinoma; (2) receiving immunotherapy; and (3) subsequent radical gastrectomy. Patients were excluded if they had: (1) prior abdominal radiotherapy; (2) distant metastases at initial diagnosis, (3) severe comorbidities or concurrent malignancies that could affect

treatment outcomes; or (4) incomplete clinical data or were fail to follow-up. This study was approved by the Institutional Review Board of the Second Affiliated Hospital, Zhejiang University School of Medicine (Approval No. C20251466) and was conducted in accordance with relevant guidelines and the Declaration of Helsinki. The requirement for informed consent was waived by the Institutional Review Board due to the retrospective study design and no any intervention affecting patient care.

Patient and tumor characteristics

Data were collected independently from electronic medical records by two trained researchers and cross-verified to ensure accuracy. Baseline variables included age, sex, body mass index (BMI), lifestyle factors (smoking and alcohol consumption) and history of hypertension. Tumor characteristics included location, size, differentiation, Lauren type, and PD-L1 combined positive score (CPS), and mismatch repair (MMR) status. NAT regimen, neoadjuvant cycles, targeted therapy, surgical procedure, and ypT/ypN stages were also recorded. Pathologic response was assessed using the NCCN TRG system. TRG 0 was classified as pCR and TRG 1–3 as non-pCR[13].

Diabetes status and glucose levels

T2DM status upon gastric cancer diagnosis was determined based on medical history and antidiabetic medications use. Specific medications were also recorded. Four random blood glucose levels, measured within the 4 weeks leading up to ICI initiation, were documented. In cases where more than four measurements were available, the closest to the time of treatment were used. Mean baseline glucose level was calculated using at least two measurements. Available HbA1c measurements were also collected.

Follow-up

The overall survival (OS) was defined as the time from the initiation of ICI to death from any cause or the last follow-up. Progression-free interval (PFI) measured from the same starting date to tumor recurrence, progression, or death from any cause, whichever occurred first. Patients without the corresponding event were censored at their last follow-up. The data cutoff was December 1, 2024, and the median follow-up was 25 months.

Statistical analysis

Analyses were performed using R software (Version 4.6.1). Continuous variables were

summarized as means with standard deviation (SD) or medians with interquartile ranges (IQR) and compared using Mann-Whitney U or Kruskal-Wallis tests. Categorical variables were reported as n (%) and compared using chi-square or Fisher exact tests. Logistic regression assessed pCR, and Cox regression assessed OS and PFI. Kaplan-Meier curves were compared using log-rank tests. Adjusted restricted cubic splines with three knots examined the association between glucose and pCR[14]. Interactions were assessed using interaction terms and joint tests, interaction terms were used to assess for effect modification and variance inflation factors were used to assess for multicollinearity. Pearson correlation assessed the association between glucose and HbA1c. Exploratory CPS and HbA1c analyses used available measurements. All tests were two-sided, with $P < 0.05$ considered statistically significant.

Results

Patient and treatment characteristics

A total of 376 patients were finally included in the analysis (Figure 1). Patients were stratified into quartiles based on mean baseline glucose: quartile 1 (n = 93; median 4.64, IQR 4.44 to 4.81 mmol/L), quartile 2 (n = 94, median 5.13, IQR 5.00 to 5.24 mmol/L), quartile 3 (n = 95, median 5.72, IQR 5.52 to 5.90 mmol/L), and quartile 4 (n = 94; median 7.19, IQR 6.60 to 8.28 mmol/L). 286 (76.1%) were men and 86 (22.9%) had diabetes. Age, hypertension, diabetes, and glucose-lowering medication use differed across quartiles (all $P < 0.001$). The highest quartile had the greatest proportions of patients with diabetes (70.2%) and hypertension (48.9%, Table 1).

All patients received neoadjuvant chemoimmunotherapy. Chemotherapy consisted of SOX or XELOX in 89.4% patients (336/376) and FLOT or FOLFOX in 10.6% (40/376). The median number of treatment cycles was 3 (IQR 3 to 4), and only 7.7% patients (29/376) also received targeted therapy. Partial gastrectomy was performed in 204 patients (54.3%) and total gastrectomy in 172 (45.7%) (Table S1). Patients with diabetes were older than those without diabetes (median 64 vs. 61 years, $P = 0.017$) and had higher mean baseline glucose levels (median 6.96 vs. 5.19 mmol/L, $P < 0.001$). Hypertension was also more common in patients with diabetes (55.8% vs. 21.0%, $P < 0.001$), whereas tumor size was smaller (median 3.0 vs. 3.5 cm, $P = 0.019$). Among patients with diabetes, 94.2% (81/86) used glucose-lowering medication. Metformin was the most common agent, used by 75.6% patients (65/86) (Table S2).

Mean baseline glucose levels, diabetes and pathological response

Overall, 24.2% patients (91/376) achieved pCR. The rates were 28.0%, 21.3%, 32.6%, and 14.9% in Q1 to Q4, respectively. The overall TRG distribution was approaching significantly across glucose quartiles (P =0.056). Patients with and without diabetes had similar pCR rates (24.4% vs. 24.1%, P > 0.05) (Figure 2a). Compared with Q1, Q4 was associated with lower odds of pCR (OR 0.33, 95% CI 0.15 to 0.74, P =0.007). No significant associations were observed for Q2 or Q3. Diabetes status was not associated with pCR in the analysis (OR 1.02, 95% CI 0.58 to 1.78, P =0.957). Larger tumor size and total gastrectomy were also associated with lower odds of pCR in the adjusted model, whereas CPS ≥10 was associated with higher odds (Table 2). The RCS analysis showed an inverse association between mean baseline glucose modeled continuously and pCR, but neither the overall association (P = 0.151) nor nonlinearity (P = 0.374) was statistically significant (Figure 2b). In additional, interaction tests were not significant for diabetes status, neoadjuvant regimen, targeted therapy, or PD-L1 CPS (all P for interaction >0.05) (Table S4).

Mean baseline glucose levels, diabetes and survival.

OS differed across glucose quartiles (log-rank P = 0.005), with the poorest survival observed in Q4. There was no significant difference in PFI (log-rank P = 0.189) (Figures 3a and 3b). Patients with diabetes had shorter OS than those without diabetes (log-rank P = 0.037), whereas the difference in PFI was not significant (log-rank P = 0.406) (Figures 3c and 3d). In the univariable analysis, Q4 was associated with a higher mortality hazard than Q1 (HR 4.01, 95% CI 1.53 to 10.54, P = 0.005). This association was attenuated after adjustment but still approaching statistical significance (HR 3.42, 95% CI 0.97 to 12.01, P = 0.055). Diabetes was not associated with OS after adjustment (HR 0.91, 95% CI 0.24 to 3.48, P = 0.896) (Table 3). Patients who achieved pCR had longer OS (adjusted HR 0.11, 95% CI 0.03 to 0.48, P = 0.003) and PFI (adjusted HR 0.15, 95% CI 0.05 to 0.42, P <0.001) (Tables 3 and S3). Overall interaction tests involving glucose quartiles and diabetes status, chemotherapy regimen, targeted therapy, or CPS were not significant for OS, or PFI (all P for interaction >0.05) (Table S4).

PD-L1 CPS and treatment outcomes

PD-L1 CPS data were available for 175 patients, including 131 without diabetes and 44 with diabetes. The pCR rate was 30.0% in patients with CPS ≥5 and 12.6% in those with CPS <5

(Supplementary Figure 1a). CPS ≥5 was associated with higher odds of pCR after adjustment (OR 2.36, 95% CI 1.04 to 5.38, P = 0.040). In patients without diabetes, the adjusted OR was 3.65 (95% CI 1.09 to 12.26, P = 0.036). In patients with diabetes, no association with pCR was observed (OR 1.07, 95% CI 0.24 to 4.66, P = 0.932) (Table S5).

Patients with CPS ≥5 had longer OS and PFI in both the overall population and the subgroup without diabetes (all log-rank P <0.001, Supplementary Figure 1). These associations remained significant after adjustment for OS (HR 0.21, 95% CI 0.08 to 0.57, P = 0.002) and PFI (HR 0.26, 95% CI 0.11 to 0.61, P = 0.002) (Table S5). In patients with diabetes, Kaplan-Meier comparisons were not significant for OS (log-rank P = 0.262) or PFI (log-rank P = 0.196). After adjustment, CPS ≥5 was associated with longer OS (HR 0.19, 95% CI 0.04 to 0.99, P = 0.049) and PFI (HR 0.19, 95% CI 0.04 to 0.94, P = 0.041) (Table S5).

HbA1c and treatment outcomes

HbA1c data of 59 patients were accessible. The proportion with data was 36.0% (31/86) among patients with diabetes and 9.7% (28/290) among those without diabetes. HbA1c correlated positively with mean baseline glucose in this subset (r = 0.50, P <0.001). The correlations were not significant in patients with diabetes (r = 0.27, P = 0.147) or without diabetes (r = 0.07, P = 0.723) (Supplementary Figure 2). HbA1c was not significantly associated with pCR (OR 0.82, 95% CI 0.39 to 1.61, P = 0.569), OS (HR 1.56, 95% CI 0.74 to 2.99, P = 0.223), or PFI (HR 1.54, 95% CI 0.72 to 2.97, P = 0.247) after adjustment. Survival did not differ significantly between groups defined by the median HbA1c level in any of the three populations (all log-rank P > 0.05; Supplementary Figure 3). Adjusted analyses in the diabetes subgroup also showed no significance between HbA1c and prognosis (Table S6).

Discussion

In this multicenter cohort of patients with locally advanced gastric cancer receiving NICT, the highest quartile of mean baseline glucose was associated with lower odds of pCR after adjustment. OS was also poorer in this quartile.

Overall, our data suggest that hyperglycemia is an unfavorable factor for worse response to immunotherapy and long-term survival in gastric cancer. Similar findings have been reported in other cancers. Arici et al. found that higher fasting glucose was linked to poorer pathologic response in breast cancer patients receiving neoadjuvant chemotherapy[15]. Higher glucose

was also associated with shorter OS in NSCLC treated with ICIs and gastric cancer after curative surgery[16, 17]. Blood glucose level is therefore a metabolic indicator worthy of attention to guide prognosis.

Nevertheless, another study reported opposite results. Fasting blood glucose was positively correlated with the pCR probability that plateaued above 7.0 mmol/L, with the most favorable range at 5.6-7.0 mmol/L (P for nonlinearity 0.038)[18]. Our spline curve also showed some curvature, but neither the overall association nor nonlinearity was statistically significant. It must be pointed out that these RCS data should be interpreted as exploratory and hypothesis-generating, rather than as intervention targets for clinical practice. Differences in glucose assessment and patient selection may contribute to the contrasting findings. Li et al. used pretreatment fasting glucose and excluded patients who had recently received insulin or GLP-1 receptor agonists. We assessed mean random glucose using multiple pretreatment measurements. These differences limit direct comparisons. The favorable blood glucose range of immunotherapy requires further optimization and preclinical validation.

Poor ICI efficacy related to hyperglycemia may be directly associated with metabolic effects on immune cell activation. Nojima et al. reported reduced glycolysis and a lower basal metabolic rate in circulating $CD8^+$ T cells from patients with T2DM, accompanied by reduced cytokine production[19]. Diabetic mice with colon cancer showed lower CCL7/CXCL9 expression, dendritic cell and $CD8^+$ T cell infiltration, and anti-PD-1 efficacy[20]. High glucose also remodels the immunosuppressive microenvironment. In pancreatic cancer, it downregulates PTRH1 through EGFR/RAS signalling, increasing PD-L1 and suppressing $CD8^+$ T cell cytotoxicity[21]. In colorectal cancer, it stabilizes VISTA through ERK2-mediated phosphorylation and USP22-mediated deubiquitination, and targeting this pathway sensitizes diabetic mice to PD-1 blockade[22]. Furthermore, CCL3/CCR1 signalling recruits peripheral monocytes to liver metastases, increasing immunosuppressive myeloid cell accumulation[23]. These impairments may limit immune recovery after PD-1/PD-L1 blockade and explain poor treatment response and tumor progression.

Previous studies have often reported diabetes status linked to poorer survival in cancer patients. Among patients receiving ICIs, Cortellini et al. found shorter OS and progression-free survival in those taking glucose-lowering medication for T2DM[11]. Yekedüz et al.' study also

supported poorer survival in advanced cancer patients receiving ICIs combined with diabetes[12]. Nevertheless, our cohort did not replicate this finding. Patients with diabetes in this study had shorter OS in the univariable analysis and Kaplan-Meier curves, but this relationship was not significant after adjustment.

In additional, our results showed no association between diabetes and pathological response. Similarly, Showalter et al. reported a lower pCR rate in patients with diabetes than in those without diabetes after neoadjuvant chemoradiotherapy for gastroesophageal cancer, although the difference was not statistically significant (P = 0.31). Pathological downstaging also did not differ significantly between groups[24]. Hassinger et al. also found no independent association between diabetes and pCR in breast cancer patients receiving neoadjuvant chemotherapy[25]. Our data show that high HbA1c levels were not found to have a significant impact on treatment outcomes or prognosis.

These discrepant findings suggest that acute and chronic hyperglycemia may have opposite effects on immunity as ICI initiation. In our cohort, HbA1c had a weak correlation with mean baseline glucose in patients with diabetes but no correlation in those without diabetes. Several factors may contribute to this. In patients with active cancer, cancer-related anemia or treatment-induced decreased red blood cell may make HbA1c less reliable[26-28]. This could be interpreted by stress hyperglycemia during acute or critical illness or infection or cardiovascular events[29-31]. Random glucose can also alter due to food, glucocorticoid use, and glucose-lowering treatment[32]. Previous disease duration, glycemic control, and treatment regimens may also affect such relationship[33]. Furthermore, HbA1c was available in only 59 patients of our study so that selective testing and limited statistical power may have masked its true association with treatment outcomes.

It should be noted that we did not find a correlation between the use of metformin or other medications and treatment response or survival. Previous studies regarding metformin usage in patients receiving ICIs have reported inconsistent results. Some suggested metformin usage was correlated with longer overall survival, whereas others have found no association or reported shorter survival[11, 34, 35]. Our analysis of metformin was limited by statistical power. The lack of dose information also precluded assessment of dose-response relationships and may have limited comparisons with other studies. Due to preclinical evidence that metformin may

enhance antitumor immunity through mechanisms beyond glucose lowering, further studies are warranted[36, 37].

Components of metabolic syndrome have different associations with ICI outcomes. In addition to diabetes history, assessment before immunotherapy should include baseline blood glucose levels, which may provide complementary information. This assessment may guide metabolic management, with potential benefits for cardiovascular and overall health. These benefits may be particularly relevant to patients who achieve long-term survival with ICIs[38]. Current studies support that better glycemic control could improve ICI efficacy and cancer-related outcomes. Prospective interventional studies are needed to test this hypothesis and establish appropriate glucose targets.

Among patients with available CPS data, CPS ≥5 was associated with a higher pCR rate and longer OS and PFI. This finding is broadly consistent with the DANTE trial, which reported a more pronounced improvement in histopathological complete regression at CPS ≥10[4]. Despite similar CPS distributions by diabetes status, treatment outcomes and prognosis among patients with CPS ≥5 were poorer in those with diabetes. We hypothesize that diabetes may not affect CPS levels but could influence treatment response at a given CPS level[11]. These findings require further validation in larger cohorts.

This study has several limitations. Random glucose measurements were obtained without standardized sampling times or fasting conditions, limiting comparability and the generalizability of our findings. Incomplete HbA1c data and the absence of long-term glucose monitoring. Comorbidities were identified from medical histories that provided limited detail regarding other metabolic abnormalities. We also lacked detailed glucose-lowering drug doses in patients with type 2 diabetes. In additional, we lacked data on race, socioeconomic status and the neutrophil-to-lymphocyte ratio which are important confounding factors influencing metabolic phenotypes and immunotherapy. Retrospective data collection from three hospitals may have introduced selection bias. Prospective studies should incorporate standardized metabolic assessments, longitudinal glucose monitoring and more complete confounder data to validate these findings.

Conclusion

Higher mean baseline glucose was associated with poorer pathologic response and shorter overall survival in patients with locally advanced gastric cancer receiving NICT, but diabetes and HbA1c was not associated with pCR or survival after adjustment. These findings support baseline glucose assessment and suggest that better glycemic control may improve treatment outcomes. Prospective studies are needed to validate these associations, particularly for survival, and determine whether glycemic management improves response and survival.

Reference

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229–63.

[2] Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet. 2019;393:1948–57.

[3] Shitara K, Rha SY, Wyrwicz LS, Oshima T, Karaseva N, Osipov M, et al. Neoadjuvant and adjuvant pembrolizumab plus chemotherapy in locally advanced gastric or gastro-oesophageal cancer (KEYNOTE-585): an interim analysis of the multicentre, double-blind, randomised phase 3 study. Lancet Oncol. 2024;25:212–24.

[4] Lorenzen S, Götze TO, Thuss-Patience P, Biebl M, Homann N, Schenk M, et al. Perioperative Atezolizumab Plus Fluorouracil, Leucovorin, Oxaliplatin, and Docetaxel for Resectable Esophagogastric Cancer: Interim Results From the Randomized, Multicenter, Phase II/III DANTE/IKF-s633 Trial. J Clin Oncol. 2024;42:410–20.

[5] Verschoor YL, van de Haar J, van den Berg JG, van Sandick JW, Kodach LL, van Dieren JM, et al. Neoadjuvant atezolizumab plus chemotherapy in gastric and gastroesophageal junction adenocarcinoma: the phase 2 PANDA trial. Nat Med. 2024;30:519–30.

[6] Janjigian YY, Al-Batran SE, Wainberg ZA, Muro K, Molena D, Van Cutsem E, et al. Perioperative Durvalumab in Gastric and Gastroesophageal Junction Cancer. N Engl J Med. 2025;393:217–30.

[7] Coleman MF, Cozzo AJ, Pfeil AJ, Etigunta SK, Hursting SD. Cell Intrinsic and Systemic Metabolism in Tumor Immunity and Immunotherapy. Cancers. 2020;12.

[8] Chang CH, Qiu J, O'Sullivan D, Buck MD, Noguchi T, Curtis JD, et al. Metabolic Competition in the Tumor Microenvironment Is a Driver of Cancer Progression. Cell. 2015;162:1229–41.

[9] Ling S, Brown K, Miksza JK, Howells L, Morrison A, Issa E, et al. Association of Type 2 Diabetes With Cancer: A Meta-analysis With Bias Analysis for Unmeasured Confounding in 151 Cohorts Comprising 32 Million People. Diabetes Care. 2020;43:2313–22.

[10] De la Torre K, Song M, Abe SK, Rahman MS, Islam MR, Saito E, et al. Diabetes and gastric cancer incidence and mortality in the Asia Cohort Consortium: A pooled analysis of more than a half million participants. J Diabetes. 2024;16:e13561.

[11] Cortellini A, D'Alessio A, Cleary S, Buti S, Bersanelli M, Bordi P, et al. Type 2 Diabetes Mellitus and Efficacy Outcomes from Immune Checkpoint Blockade in Patients with Cancer. Clin Cancer Res. 2023;29:2714–24.

[12] Yekedüz E, Köksoy EB, Yazgan SC, Karataş G, Şenler F, Utkan G, et al. Chronic hyperglycemia based on diabetes is independently associated with decreased survival in

patients with advanced cancer treated with immune checkpoint inhibitors. Anticancer Drugs. 2022;33:1145–9.

[13] Sinnamon AJ, Savoldy M, Mehta R, Dineen SP, Peña LR, Lauwers GY, et al. Tumor Regression Grade and Overall Survival following Gastrectomy with Preoperative Therapy for Gastric Cancer. Ann Surg Oncol. 2023;30:3580–9.

[14] Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Stat Med. 2010;29:1037–57.

[15] Arici S, Geredeli C, Secmeler S, Cekin R, Sakin A, Cihan S. The effects of diabetes and fasting plasma glucose on treatment of breast cancer with neoadjuvant chemotherapy. Curr Probl Cancer. 2020;44:100485.

[16] Osataphan S, Awidi M, Jan YJ, Gunturu K, Sundararaman S, Viray H, et al. Association between higher glucose levels and reduced survival in patients with non-small cell lung cancer treated with immune checkpoint inhibitors. Lung Cancer. 2024;198:108023.

[17] Lv L, Chen C, Chen H, Huang J, Tam W, Han Y, et al. Preoperative hyperglycemia as an independent predictor of reduced long-term survival after gastric cancer surgery. Eur J Med Res. 2025;31:54.

[18] Li F, Guo H, Wu J, Wu H, Wang Z, Li X, et al. Metabolic syndrome as an independent predictor of response and survival in locally advanced gastric cancer treated with neoadjuvant immunochemotherapy. Frontiers in oncology. 2026;16:1842129.

[19] Nojima I, Eikawa S, Tomonobu N, Hada Y, Kajitani N, Teshigawara S, et al. Dysfunction of CD8 + PD-1 + T cells in type 2 diabetes caused by the impairment of metabolism-immune axis. Sci Rep. 2020;10:14928.

[20] Ito M, Iwama S, Sugiyama D, Yasuda Y, Okuji T, Kobayashi T, et al. Anti-tumor effects of anti-programmed cell death-1 antibody treatment are attenuated in streptozotocin-induced diabetic mice. Sci Rep. 2023;13:5939.

[21] Gao C, Chen J, Bai J, Zhang H, Tao Y, Wu S, et al. High glucose-upregulated PD-L1 expression through RAS signaling-driven downregulation of PTRH1 leads to suppression of T cell cytotoxic function in tumor environment. J Transl Med. 2023;21:461.

[22] Liu X, Liu Q, Guo D, Zhao Z, Wang J, Xiang Y, et al. Hyperglycemia drives lmmune evasion in colorectal cancer through VISTA stabilization. Cell Commun Signal. 2026;24:88.

[23] Peng H, Pan Y, Sun Y, Wang X, Fan X, Wang Y, et al. Hyperglycemia induces an immunosuppressive microenvironment in colorectal cancer liver metastases by recruiting peripheral blood monocytes through the CCL3-CCR1 axis. J Immunother Cancer. 2025;13.

[24] Showalter SL, Rosato EL, Anne PR, Scott W, Mitchell E, Berger AC. Does diabetes mellitus influence pathologic complete response and tumor downstaging after neoadjuvant chemoradiation for esophageal and gastroesophageal cancer? A two-institution report. J Surg Oncol. 2010;101:43–6.

[25] Hassinger TE, Berger AC, Christopher A, Knisely AT, Mehaffey JH, Brenin DR, et al.

Diabetes Mellitus and Metformin Are Not Associated With Breast Cancer Pathologic Complete Response. J Surg Res. 2020;247:52–8.

[26] Cohen RM, Franco RS, Khera PK, Smith EP, Lindsell CJ, Ciraolo PJ, et al. Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA1c. Blood. 2008;112:4284–91.

[27] Xu H, Xu L, Page JH, Cannavale K, Sattayapiwat O, Rodriguez R, et al. Incidence of anemia in patients diagnosed with solid tumors receiving chemotherapy, 2010-2013. Clin Epidemiol. 2016;8:61–71.

[28] Hart L, Ogbonnaya A, Boykin K, Deyoung K, Bailey R, Heritage T, et al. Burden of chemotherapy-induced myelosuppression among patients with extensive-stage small cell lung cancer: A retrospective study from community oncology practices. Cancer medicine. 2023;12:10020–30.

[29] Roberts GW, Quinn SJ, Valentine N, Alhawassi T, O'Dea H, Stranks SN, et al. Relative Hyperglycemia, a Marker of Critical Illness: Introducing the Stress Hyperglycemia Ratio. J Clin Endocrinol Metab. 2015;100:4490–7.

[30] Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med. 2009;37:3001–9.

[31] Yang J, Zheng Y, Li C, Gao J, Meng X, Zhang K, et al. The Impact of the Stress Hyperglycemia Ratio on Short-term and Long-term Poor Prognosis in Patients With Acute Coronary Syndrome: Insight From a Large Cohort Study in Asia. Diabetes Care. 2022;45:947–56.

[32] Korytkowski MT, Muniyappa R, Antinori-Lent K, Donihi AC, Drincic AT, Hirsch IB, et al. Management of Hyperglycemia in Hospitalized Adult Patients in Non-Critical Care Settings: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2022;107:2101–28.

[33] Rathmann W, Bongaerts B, Kostev K. Association of characteristics of people with type 2 diabetes mellitus with discordant values of fasting glucose and HbA1c. J Diabetes. 2018;10:934–41.

[34] Chiang CH, Chen YJ, Chiang CH, Chen CY, Chang YC, Wang SS, et al. Effect of metformin on outcomes of patients treated with immune checkpoint inhibitors: a retrospective cohort study. Cancer Immunol Immunother. 2023;72:1951–6.

[35] Afzal MZ, Dragnev K, Sarwar T, Shirai K. Clinical outcomes in non-small-cell lung cancer patients receiving concurrent metformin and immune checkpoint inhibitors. Lung Cancer Manag. 2019;8:Lmt11.

[36] Eikawa S, Nishida M, Mizukami S, Yamazaki C, Nakayama E, Udono H. Immune-mediated antitumor effect by type 2 diabetes drug, metformin. Proc Natl Acad Sci U S A. 2015;112:1809–14.

[37] Scharping NE, Menk AV, Whetstone RD, Zeng X, Delgoffe GM. Efficacy of PD-1 Blockade Is Potentiated by Metformin-Induced Reduction of Tumor Hypoxia. Cancer Immunol Res. 2017;5:9–16.

[38] Wu L, Tsang V, Clifton-Bligh R, Carlino MS, Tse T, Huang Y, et al. Hyperglycemia in patients treated with immune checkpoint inhibitors: key clinical challenges and multidisciplinary consensus recommendations. J Immunother Cancer. 2025;13.

Figure legend:

Figure 1. Study flow diagram.

Figure 2. Glucose level, diabetes status, and pathological response.

Figure 3. Glucose level, diabetes status, and survival.

Table 1. Patient characteristics stratified by quartile of mean baseline glucose levels.

Characteristic	Quartiles of mean baseline glucose				*P* value
	One (n = 93)	Two (n = 94)	Three (n = 95)	Four (n = 94)	
Metabolic parameters					
Average glucose, median (IQR), mmol/L	4.64 (4.44–4.81)	5.13 (5.00–5.24)	5.72 (5.52–5.90)	7.19 (6.60–8.28)	<0.001
HbA1c, median (IQR), %[a]	5.8 (5.5–6.0)	5.7 (5.4–5.8)	5.8 (5.5–6.3)	6.4 (6.0–6.9)	0.003
Patient characteristics					
Age, median (IQR), years	57 (52–64)	61 (56–68)	64 (58–68)	64 (59–69)	<0.001
Female sex, n (%)	31 (33.3%)	19 (20.2%)	21 (22.1%)	19 (20.2%)	0.106
BMI, median (IQR), kg/m²	22.5 (19.9–25.1)	22.6 (20.8–24.7)	22.6 (20.4–24.1)	23.0 (20.9–25.0)	0.581
History of drinking, n (%)	36 (38.7%)	39 (41.5%)	43 (45.3%)	35 (37.2%)	0.690
History of smoking, n (%)	33 (35.5%)	38 (40.4%)	44 (46.3%)	38 (40.4%)	0.513
Comorbidities					
Hypertension, n (%)	13 (14.0%)	23 (24.5%)	27 (28.4%)	46 (48.9%)	<0.001
Diabetes mellitus, n (%)	6 (6.5%)	1 (1.1%)	13 (13.7%)	66 (70.2%)	<0.001
Glucose-lowering medications					
Any glucose-lowering medication, n (%)	5 (5.4%)	1 (1.1%)	12 (12.6%)	63 (67.0%)	<0.001
Insulin, n (%)	0 (0.0%)	0 (0.0%)	3 (3.2%)	18 (19.1%)	<0.001
Metformin, n (%)	5 (5.4%)	1 (1.1%)	9 (9.5%)	50 (53.2%)	<0.001
Sulfonylurea, n (%)	1 (1.1%)	1 (1.1%)	1 (1.1%)	7 (7.4%)	0.015
SGLT2 inhibitor, n (%)	2 (2.2%)	0 (0.0%)	1 (1.1%)	8 (8.5%)	0.003
DPP-4 inhibitor, n (%)	2 (2.2%)	0 (0.0%)	6 (6.3%)	24 (25.5%)	<0.001
Tumor characteristics					
Tumor location, n (%)					0.699
Esophagogastric junction	7 (7.5%)	7 (7.4%)	9 (9.5%)	14 (14.9%)	

Characteristic	Quartiles of mean baseline glucose				*P* value
	One (n = 93)	Two (n = 94)	Three (n = 95)	Four (n = 94)	
Upper	17 (18.3%)	19 (20.2%)	11 (11.6%)	14 (14.9%)	
Middle	32 (34.4%)	28 (29.8%)	27 (28.4%)	24 (25.5%)	
Lower	30 (32.3%)	33 (35.1%)	40 (42.1%)	33 (35.1%)	
Overlapping	7 (7.5%)	7 (7.4%)	8 (8.4%)	9 (9.6%)	
Tumor size, median (IQR), cm	4.0 (3.0–6.0)	3.5 (3.0–5.0)	3.5 (2.9–4.8)	3.2 (2.5–5.0)	0.188
Differentiation, n (%)					0.655
Moderate	24 (25.8%)	27 (28.7%)	27 (28.4%)	32 (34.0%)	
Poor	69 (74.2%)	67 (71.3%)	68 (71.6%)	62 (66.0%)	
Lauren type, n (%)					0.509
Intestinal	44 (47.3%)	32 (34.0%)	45 (47.4%)	42 (44.7%)	
Diffuse	29 (31.2%)	35 (37.2%)	27 (28.4%)	29 (30.9%)	
Mixed	14 (15.1%)	21 (22.3%)	20 (21.1%)	19 (20.2%)	
Unknown	6 (6.5%)	6 (6.4%)	3 (3.2%)	4 (4.3%)	
PD-L1 combined positive score, n (%)					0.330
<1	12 (12.9%)	13 (13.8%)	6 (6.3%)	16 (17.0%)	
1–4	10 (10.8%)	11 (11.7%)	11 (11.6%)	16 (17.0%)	
5–9	11 (11.8%)	11 (11.7%)	6 (6.3%)	5 (5.3%)	
≥10	10 (10.8%)	8 (8.5%)	14 (14.7%)	15 (16.0%)	
Not reported	50 (53.8%)	51 (54.3%)	58 (61.1%)	42 (44.7%)	
MMR status, n (%)					0.636
pMMR	91 (97.8%)	89 (94.7%)	90 (94.7%)	89 (94.7%)	
dMMR	2 (2.2%)	5 (5.3%)	5 (5.3%)	5 (5.3%)	
Treatment characteristics					
Neoadjuvant therapy regimen, n (%)					0.424

Characteristic	Quartiles of mean baseline glucose				*P* value
	One (n = 93)	Two (n = 94)	Three (n = 95)	Four (n = 94)	
SOX/XELOX	86 (92.5%)	81 (86.2%)	83 (87.4%)	86 (91.5%)	
FLOT/FOLFOX	7 (7.5%)	13 (13.8%)	12 (12.6%)	8 (8.5%)	
Targeted therapy, n (%)	9 (9.7%)	7 (7.4%)	7 (7.4%)	6 (6.4%)	0.858
Number of neoadjuvant cycles, median (IQR)	3 (3–4)	3 (3–4)	3 (3–4)	3 (3–4)	0.478
Surgical procedure, n (%)					0.732
Partial gastrectomy	46 (49.5%)	51 (54.3%)	54 (56.8%)	53 (56.4%)	
Total gastrectomy	47 (50.5%)	43 (45.7%)	41 (43.2%)	41 (43.6%)	

Average glucose ranges (mmol/L) were 3.68–4.89, 4.90–5.37, 5.38–6.21, and 6.23–16.52 mmol/L for Q1–Q4, respectively. P values are from Kruskal–Wallis, χ^2, or Fisher exact tests. HbA1c was available for 59 of 376 patients. IQR, interquartile range; BMI, body mass index; SGLT2, sodium–glucose cotransporter 2; DPP-4, dipeptidyl peptidase 4; PD-L1, programmed death ligand 1; MMR, mismatch repair.

Table 2. Associations of patient characteristics with pathological response.

Characteristic	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Average glucose quartile				
Q1	Ref		Ref	
Q2	0.70 (0.36–1.36)	0.290	0.63 (0.30–1.31)	0.211
Q3	1.25 (0.67–2.33)	0.486	0.98 (0.49–1.96)	0.952
Q4	0.45 (0.22–0.93)	0.032	0.33 (0.15–0.74)	0.007
Patient characteristics				
Age, per year	1.01 (0.98–1.03)	0.680		
Female versus male	1.19 (0.69–2.04)	0.532		
BMI, per kg/m²	1.05 (0.97–1.14)	0.251		
Drinking history, yes versus no	0.94 (0.58–1.52)	0.801		
Smoking history, yes versus no	0.88 (0.55–1.43)	0.619		
Hypertension, yes versus no	1.04 (0.62–1.75)	0.869		
Diabetes mellitus, yes versus no	1.02 (0.58–1.78)	0.957		
Glucose-lowering medications				
Insulin, yes versus no	0.72 (0.24–2.21)	0.572		
Metformin, yes versus no	1.03 (0.55–1.91)	0.932		
Sulfonylurea, yes versus no	0.34 (0.04–2.73)	0.310		
SGLT2 inhibitor, yes versus no	1.18 (0.31–4.55)	0.809		
DPP-4 inhibitor, yes versus no	1.25 (0.56–2.81)	0.589		
Tumor characteristics				
Tumor location				
Esophagogastric junction	Ref			
Upper	1.08 (0.40–2.89)	0.879		
Lower	1.68 (0.71–3.97)	0.240		

Characteristic	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Middle	0.80 (0.32–2.00)	0.628		
Overlapping	0.87 (0.27–2.85)	0.818		
Tumor size, per cm	0.66 (0.56–0.78)	<0.001	0.71 (0.58–0.85)	<0.001
Poor versus moderate differentiation	0.50 (0.31–0.82)	0.007	0.92 (0.48–1.77)	0.795
Lauren type				
Intestinal	Ref		Ref	
Diffuse	0.49 (0.27–0.89)	0.019	0.74 (0.35–1.55)	0.422
Mixed	0.63 (0.32–1.21)	0.167	0.94 (0.43–2.05)	0.868
Unknown	2.22 (0.85–5.81)	0.104	2.29 (0.77–6.84)	0.137
PD-L1 combined positive score				
<1	Ref		Ref	
1–4	1.43 (0.42–4.89)	0.564	1.07 (0.29–3.95)	0.924
5–9	1.50 (0.40–5.66)	0.550	1.15 (0.29–4.67)	0.841
≥10	5.70 (1.91–17.04)	0.002	4.06 (1.24–13.27)	0.020
Not reported	3.16 (1.19–8.41)	0.021	2.78 (0.99–7.82)	0.053
MMR status				
dMMR versus pMMR	0.66 (0.19–2.35)	0.521		
Neoadjuvant treatment				
FLOT/FOLFOX versus SOX/XELOX	0.64 (0.27–1.49)	0.299		
Targeted therapy, yes versus no	1.00 (0.41–2.41)	0.993		
Number of NAT cycles, per cycle	0.92 (0.78–1.08)	0.322		
Surgery procedure				
Total versus partial gastrectomy	0.36 (0.21–0.60)	<0.001	0.49 (0.27–0.87)	0.015

OR, odds ratio; CI, confidence interval; BMI, body mass index; CPS, combined positive score; EGJ, esophagogastric junction; MMR, mismatch repair; NAT, neoadjuvant therapy; SGLT2, sodium–glucose cotransporter 2; DPP-4, dipeptidyl peptidase 4.

Table 3. Associations of patient characteristics with overall survival.

Characteristic	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Average glucose quartile				
Q1	Ref		Ref	
Q2	2.66 (0.95–7.48)	0.063	2.68 (0.92–7.81)	0.071
Q3	1.62 (0.56–4.67)	0.375	1.43 (0.48–4.24)	0.515
Q4	4.01 (1.53–10.54)	0.005	3.42 (0.97–12.01)	0.055
Patient characteristics				
Age, per year	1.00 (0.97–1.03)	0.853		
Female versus male	1.98 (1.14–3.47)	0.016	2.52 (1.38–4.61)	0.003
BMI, per kg/m²	0.96 (0.88–1.06)	0.453		
Drinking history, yes versus no	0.84 (0.48–1.49)	0.556		
Smoking history, yes versus no	1.03 (0.60–1.79)	0.906		
Hypertension, yes versus no	0.85 (0.47–1.55)	0.593		
Diabetes mellitus, yes versus no	1.80 (1.03–3.16)	0.040	0.91 (0.24–3.48)	0.896
Glucose-lowering drug classes				
Insulin, yes versus no	1.80 (0.77–4.22)	0.174		
Metformin, yes versus no	1.85 (1.01–3.36)	0.045	0.91 (0.28–2.90)	0.867
Sulfonylurea, yes versus no	1.08 (0.26–4.46)	0.910		
SGLT2 inhibitor, yes versus no	1.61 (0.50–5.17)	0.427		
DPP-4 inhibitor, yes versus no	1.36 (0.54–3.42)	0.516		
Pretreatment tumor characteristics				
Tumor location				
Esophagogastric junction	Ref			
Upper	0.58 (0.22–1.57)	0.286		
Middle	0.53 (0.23–1.24)	0.141		

Characteristic	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Lower	0.65 (0.30–1.43)	0.281		
Overlapping	0.61 (0.19–1.98)	0.411		
Tumor size, per cm	1.06 (0.93–1.21)	0.398		
Poor versus moderate differentiation	2.05 (1.07–3.92)	0.030	1.53 (0.60–3.91)	0.378
Lauren type				
Intestinal	Ref		Ref	
Diffuse	2.06 (1.09–3.89)	0.025	1.31 (0.54–3.15)	0.552
Mixed	2.63 (1.27–5.46)	0.009	1.99 (0.78–5.09)	0.150
Unknown	0.74 (0.10–5.56)	0.769	1.01 (0.12–8.45)	0.996
PD-L1 combined positive score				
<1	Ref		Ref	
1–4	6.36 (2.42–16.72)	<0.001	7.30 (2.65–20.14)	<0.001
5–9	0.25 (0.03–2.05)	0.195	0.33 (0.04–2.88)	0.318
≥10	0.59 (0.17–2.09)	0.413	1.43 (0.38–5.32)	0.594
Not reported	0.81 (0.33–1.97)	0.646	1.47 (0.58–3.72)	0.412
MMR status				
dMMR versus pMMR	1.67 (0.60–4.64)	0.323		
Neoadjuvant treatment				
FLOT/FOLFOX versus SOX/XELOX	1.63 (0.70–3.84)	0.259		
Targeted therapy, yes versus no	0.45 (0.11–1.86)	0.270		
Number of NAT cycles, per cycle	1.06 (0.90–1.25)	0.468		
Surgery procedure				
Total versus partial gastrectomy	1.01 (0.59–1.75)	0.965		
Pathological response				
pCR versus non-pCR	0.09 (0.02–0.37)	<0.001	0.11 (0.03–0.48)	0.003

HR, hazard ratio; CI, confidence interval; BMI, body mass index; CPS, combined positive score; EGJ, esophagogastric junction; MMR, mismatch repair; NAT, neoadjuvant therapy; SGLT2, sodium–glucose cotransporter 2; DPP-4, dipeptidyl peptidase 4.

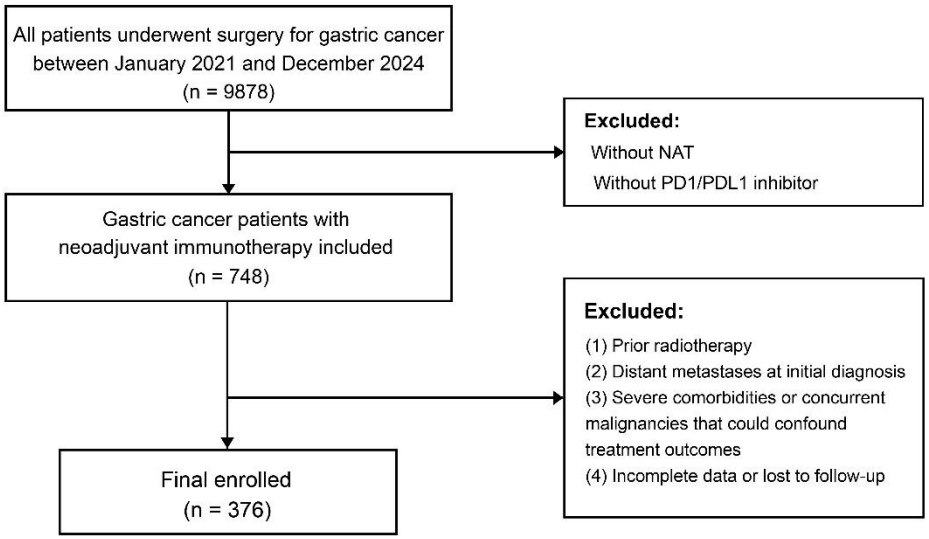


Figure 1. Study flow diagram.

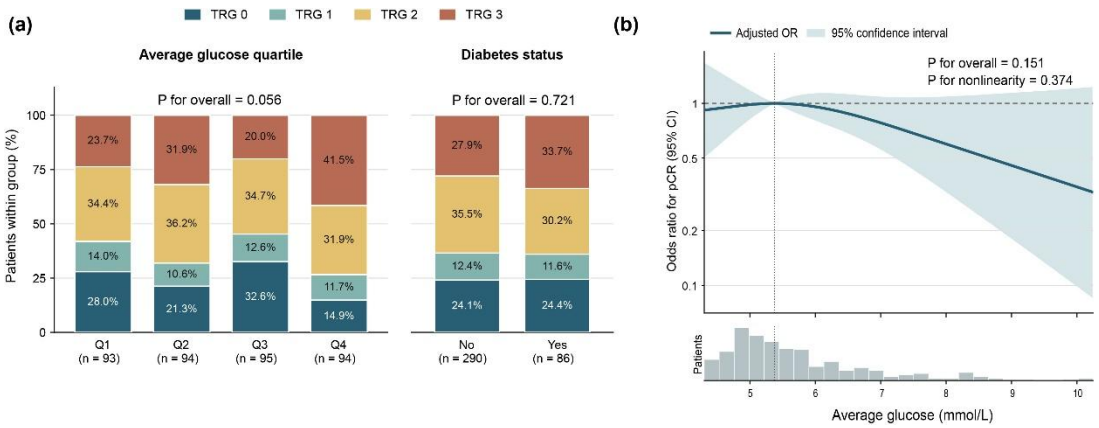


Figure 2. Glucose level, diabetes status, and pathological response. (a) Distribution of tumor regression grades by quartiles of mean glucose and diabetes status. (b) Adjusted RCS curve of mean glucose and pathological response.

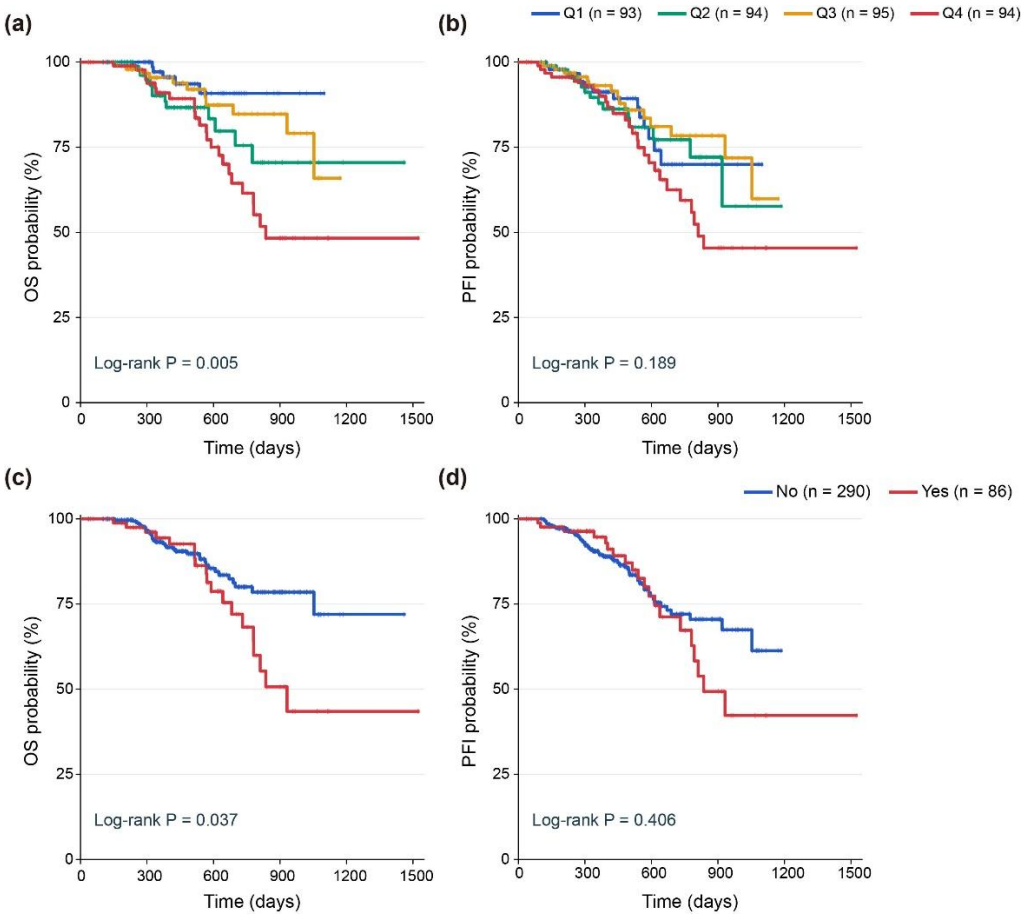


Figure 3. Glucose level, diabetes status, and survival. Kaplan–Meier estimates of overall survival (OS) and progression-free interval (PFI) by mean blood glucose quartile (a and b) and diabetes status (c and d).