Round 1

Thank you for your thorough review of our manuscript, "Clinicopathological Features of Patients Undergoing Surgery for Pancreatic Cancer with Very Early Postoperative Recurrence" (Manuscript ID: 111376), submitted to the *World Journal of Gastrointestinal Surgery*. We appreciate your recognition of the study's clinical significance and its contribution to the literature on very early recurrence (VER) in pancreatic ductal adenocarcinoma (PDAC). Your insightful comments and suggestions for improvement are highly valuable, and we address each point below to clarify and outline our planned revisions.

1. **Lack of Molecular or Genomic Data**: We acknowledge the limitation of not including molecular or genomic data, which restricts biological interpretation and personalized treatment implications. In the revised manuscript, we will expand the discussion to highlight this limitation and propose future studies incorporating molecular markers (e.g., EGFR, E-cadherin, KRAS mutations) to elucidate VER mechanisms. While our current dataset lacks such data due to resource constraints, we will collaborate with our institution's pathology department to explore retrospective genomic profiling in a follow-up study.

2. **Variability in Postoperative Imaging Timing**: The variability in imaging timing (4–12 weeks) is a noted limitation. To address this, we will revise the manuscript to include a sensitivity analysis stratifying patients by imaging timing (e.g., 4–8 weeks vs. 8–12 weeks) to assess potential misclassification bias. Additionally, we will clarify the imaging protocols and discuss efforts to standardize postoperative imaging in future prospective studies at our center.

3. **Lack of External or Multi-Institutional Validation**: We recognize the concern regarding generalizability due to the single-center design. In the revision, we will explicitly address this limitation and propose a multi-institutional validation study in collaboration with other high-volume centers in Türkiye. We will also discuss the representativeness of our cohort compared to national PDAC registries to contextualize generalizability.

4. **Integration of Machine Learning Models**: We appreciate the suggestion to incorporate supervised machine learning models (e.g., random forests, gradient boosting) to enhance predictive performance. In the revised manuscript, we will include a comparative analysis using random forest models alongside logistic regression, reporting feature importance rankings and predictive metrics (e.g., AUC, sensitivity, specificity). This will be implemented using Python (scikit-learn) and documented in a new supplementary section. We will also compare nonlinear patterns identified by machine learning with traditional logistic regression results to highlight added value.

5. **Absence of State-of-the-Art Comparison Table and Ablation Analysis**: To address this, we will add a state-of-the-art comparison table summarizing recent VER studies (e.g., Belfiori et al. [6], Strobel et al. [22]) and their predictors, positioning our findings within the current literature. Additionally, we will conduct an ablation analysis to evaluate the incremental contribution of key predictors (e.g., G3 differentiation, RDW, tumor location) and present results in a new table.

6. **Lack of Standardized Limitations and Future Research Section**: We will introduce a dedicated "Limitations and Future Directions" section in the revised manuscript, clearly outlining the study's limitations (e.g., retrospective design, imaging variability, lack of molecular data) and proposing specific future research directions, including prospective studies, molecular profiling, and multi-center validation.

7. **Data and Code Sharing for Reproducibility**: Regarding data sharing, as the data belong to Ankara City Hospital, public sharing on platforms like GitHub or Zenodo is restricted due to institutional privacy regulations. However, anonymized datasets can be requested from the corresponding author (Mesut Tez, mesuttez@yahoo.com) through the hospital's Medical Research and Scientific Evaluation Committee, subject to ethical approval. We will include this clarification in the revised Data Sharing Statement. Additionally, we will share the statistical analysis code (SPSS and Python scripts) on a public GitHub repository and provide the repository link in the manuscript to support reproducibility.

We are committed to addressing these concerns through major revisions to enhance the manuscript's methodological rigor and clinical utility. We will submit a revised version within the journal's specified timeline, including a point-by-point response to all comments and a tracked-changes document. Thank you again for your valuable feedback, which will significantly strengthen our study.

Sincerely,

Mesut Tez
Corresponding Author
Department of Surgery, University of Health Sciences, Ankara City Hospital
No. 1 Bilkent Street, District of Universities, Ankara, 06800, Türkiye

Round 2

Thank you for your detailed review and constructive feedback on our manuscript titled "Clinicopathological Features of Patients Undergoing Surgery for Pancreatic Cancer with Very Early Postoperative Recurrence."

We appreciate the opportunity to address the concerns raised and have made significant revisions to strengthen the scientific contribution of our study. Below, we provide a point-by-point response to your specific comments, with all changes implemented in revision mode as requested.

Reviewer Comment: The methodology requires greater transparency, particularly in how missing data, potential biases, and confounders were handled.

We agree with the reviewer ' s call for enhanced methodological transparency. To address this, a new subsection, "Handling of Missing Data," was added under Materials and Methods > Data Sources and Measurements, detailing the percentage of missing data (e.g., 5% for CA 19-9, 3% for RDW), affected variables, and the use of multiple imputation with five imputed datasets. The Bias subsection was expanded to discuss selection bias due to retrospective design, surgeon variability as a potential confounder, and our approach to control confounders through multivariate analysis adjustments, including sensitivity analysis for imaging timing variability ($P = 0.12$).

Reviewer Comment: The inclusion/exclusion criteria are reported but need clearer justification, especially regarding why certain subgroups (e.g., patients with body/tail tumors) remain underrepresented and how this affects generalizability.

We have provided a clearer justification for the inclusion/exclusion criteria. In Materials and Methods > Participants , we explained that the underrepresentation of body/tail tumors (10%) reflects their advanced-stage presentation at diagnosis, often precluding surgical resection. The Discussion section was expanded to discuss this underrepresentation, comparing our findings to prior literature and its impact on generalizability. The Limitations and Future Directions section now explicitly acknowledges this as a limitation, with plans for multi-center studies to improve representation.

Reviewer Comment: The statistical analysis is adequately described, but more detail on model validation (e.g., cross-validation, overfitting risk) is required to support the reliability of the random forest results.

We have enhanced the statistical analysis section to address model validation. In Materials and Methods > Statistical Analysis , we added details on 5-fold cross-validation,

hyperparameter optimization via grid search, and early stopping to mitigate overfitting risk. In Results , we reported cross-validation results (mean AUC 0.75 ± 0.03), confirming the model's reliability and generalizability.

Reviewer Comment: Figures and tables, while informative, could benefit from improved readability and clearer labeling of clinical thresholds.

We have improved the readability of figures and tables. Table 1 was revised to include clinical cut-off values for RDW (11.5%) and CA 19-9 (100 U/mL) in the parameter descriptions. Figure 1 was updated with larger fonts and improved color contrasts for the study flowchart. Figure 2 was recreated.

Reviewer Comment: Importantly, while the manuscript discusses machine learning, it lacks a critical perspective on explainable artificial intelligence (XAI). Given the growing demand for interpretability in clinical prediction models, the authors should incorporate a section on XAI approaches (e.g., SHAP values, feature attribution methods) to clarify how their model outputs could be applied in practice.

We have integrated XAI to enhance model interpretability. A new subsection, " Explainable Artificial Intelligence (XAI), " was added under Materials and Methods > Statistical Analysis, describing the use of SHAP values for feature attribution. In Results, SHAP analysis results were reported, highlighting G3 differentiation (mean SHAP value: 0.40), RDW (0.22), and tumor location (0.18) as key contributors to VER prediction. The Discussion section now includes a new subsection, " Explainable AI in Clinical Decision-Making, " discussing how SHAP values guide personalized surveillance and treatment.

Reviewer Comment: Additionally, the discussion should expand on how artificial intelligence can complement molecular profiling and personalized surveillance strategies in pancreatic ductal adenocarcinoma.

The Discussion section was expanded with a new subsection, " AI and Molecular Profiling, " discussing how AI can integrate with molecular profiling (e.g., EGFR, KRAS mutations) to optimize surveillance strategies, referencing potential synergies with targeted therapies.

Reviewer Comment: Finally, the limitations section should explicitly acknowledge the absence of molecular validation, the retrospective single-center nature of the study, and the limited body/tail tumor representation, while also outlining future research directions.

The Limitations and Future Directions section was revised to explicitly acknowledge the absence of molecular validation (limiting insights into VER mechanisms), the retrospective single-center design (restricting generalizability), and the limited body/tail tumor representation (10%, reflecting selection bias). Future research directions now include prospective, multi-center studies with standardized imaging and molecular profiling (e.g., EGFR, KRAS) to validate findings and enhance VER prediction. Additional Notes: All revisions were made in revision mode and highlighted in the manuscript. We believe these changes address the reviewer's concerns, significantly strengthening the manuscript's scientific rigor and clinical relevance. We thank the reviewer for their valuable input and are open to further clarifications if needed. Sincerely, Mesut Tez, MD