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Age and red cell distribution width in pancreatic cystic neoplasms: A simple tool for preoperative malignancy risk stratification

Age and RDW in PCNs

Abstract

The study conducted by Martli *et al.*, on the preoperative risk stratification of malignant potential in pancreatic cystic neoplasms (PCNs), identifies age and red cell distribution width (RDW) as independent predictors. This study offers a simple and cost-effective clinical tool for preoperative assessments. The significance lies in its integration of routine laboratory parameters with clinical features, effectively addressing the limitations associated with the accessibility and operator dependency of imaging and invasive diagnostic methods. However, factors such as the retrospective design, single-center setting, small sample size, and selection bias because of the inclusion of only surgical cases limit the generalizability of the findings. Future studies should emphasize multi-center prospective validation to further clarify the biological role of RDW in the malignant transformation of PCNs and to explore integrated models that combine RDW with imaging characteristics and molecular biomarkers, ultimately enhancing precision in individualized clinical decision-making.

Key Words: Pncreatic cystic neoplasms; Red cell distribution width; Age; Preoperative assessment; Malignancy risk stratification

Ren SQ, Han YH, Cai C. Age and red cell distribution width in pancreatic cystic neoplasms: A simple tool for preoperative malignancy risk stratification. *World J Gastrointest Surg* 2025; In press

Core Tip: This article underscores the significance of age and red cell distribution width (RDW) as independent predictors for preoperative malignant risk stratification in pancreatic cystic neoplasms (PCNs). A model that integrates these factors demonstrated high accuracy (area under the curve [AUC] = 0.858), with age \geq 60 years and RDW \geq 15.5% indicating increased risk. This accessible, non-invasive tool may help to identify high-risk patients for intervention, though future multicenter validation is required. The biological role of RDW in the progression of PCN also warrants further study.

TO THE EDITOR

With advancements in medical imaging technology and heightened public awareness of self-healthcare, the rate of detection of pancreatic cystic neoplasms (PCNs) has been steadily increasing[1]. Although most PCNs are benign or exhibit low malignant potential, a significant proportion display high-grade dysplasia or confirmed malignant characteristics. Thus, accurate preoperative differential diagnosis is essential for formulating appropriate treatment strategies[2]. Currently, clinical practice predominantly relies on imaging modalities (*e.g.*, computed tomography, magnetic resonance imaging) and invasive techniques such as endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) for assessment of risk. These methods are often operator-dependent and associated with potential complications and demonstrate considerable variability in terms of accessibility, cost-effectiveness, and diagnostic accuracy[1,3]. Consequently, there is an urgent clinical need to develop simple, non-invasive, and broadly applicable tools for predicting malignant risk.

Currently, one of the few serum biomarkers recommended by guidelines is carbohydrate antigen 19-9 (CA 19-9) that assists in the evaluation of malignant risk in pancreatic cysts. However, it has limited sensitivity and specificity, particularly in

early-stage malignant lesions or non-mucinous cysts. This limits its value as a standalone diagnostic tool[4,5]. Thus, identification of more discriminative biological or clinical indicators has become important.

Recently, Martli *et al.*[6] published a retrospective study in the *World Journal of Gastrointestinal Surgery* that provides new insights into this field. The study proposed using two routine clinical indicators -- age and red cell distribution width (RDW). These were used as independent predictors for the evaluation of the malignant risk of PCNs preoperatively. This approach exhibited strong discriminatory ability, providing clinicians a simple and practical auxiliary tool for the initial screening of high-risk patients. In addition, novel perspectives and methodologies for risk stratification of PCNs are also introduced.

SUMMARY OF THE STUDY

The retrospective cohort study conducted by Martli *et al.*[6] included 70 patients with PCNs who underwent surgical treatment at Ankara Bilkent City Hospital between February 2019 and March 2023. Based on postoperative pathological findings, the patients were classified into Group A (benign or low-grade dysplasia, $n = 40$) and Group B (malignant or high-grade dysplasia, $n = 30$). Univariate and multivariate logistic regression analyses identified age and RDW as independent predictors of malignant PCNs, with area under the receiver operating characteristic curve (AUC) values of 0.798 and 0.801, respectively. The combined AUC values were 0.858, indicating strong discriminatory power. Moreover, the study established cut-off values of age ≥ 60 years and RDW $\geq 15.5\%$ for predicting malignant risk, which increased the risk of malignancy by 15.3-fold and 22.6-fold, respectively. These results suggest that age and RDW are simple, non-invasive preoperative assessment tools to assist in identifying high-risk patients who may need further advanced examinations, such as EUS, or surgical intervention. This could potentially inform clinical decision-making upon future validation. However, the single-center design and modest sample size

suggest that larger-scale, multicenter investigations are warranted to validate these findings.

STRENGTHS AND LIMITATIONS OF THE STUDY

The main strength of this study is that the proposed predictors -- age and RDW -- are routine clinical parameters that are widely available and highly reproducible. To potentially aid in the identification of high-risk patients with PCNs, these two variables could be considered for future integration into standard preoperative assessment protocols; thus, optimizing the indication for EUS and FNA[3]. The model is structurally straightforward and demonstrates strong clinical applicability, showing promise for enhancing the efficiency of preoperative risk stratification while minimizing unnecessary invasive procedures.

In contrast to some previous studies that concentrated on inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR)[7], this research emphasizes the independent significance of RDW in predicting the malignant potential of PCNs, further broadening the understanding of systemic inflammatory biomarkers in the assessment of these conditions. Additionally, compared to risk stratification strategies that are primarily based on imaging characteristics[8], this study provides a non-invasive, cost-effective, and easily implementable auxiliary tool that can serve as a valuable enhancement to imaging evaluations, collectively improving the comprehensiveness of differential diagnosis. It is particularly noteworthy that this study represents the first systematic assessment and validation of RDW's role in predicting malignant risk in PCNs. A simple yet effective predictive model has been developed by combining it with patients' age, exhibiting a certain degree of innovation and clinical translational potential.

However, this study has several limitations that warrant further investigation. First, the study's single-center retrospective design and small sample size ($n = 70$), limited to patients who underwent surgeries, may introduce selection bias and reduce the generalizability and external validity of the findings. Second, although RDW is closely

related to systemic inflammation and immune-nutritional status, it remains unclear whether it specifically reflects local tumor microenvironment (TME) alterations related to PCNs or merely serves as a surrogate marker of systemic inflammation or nutritional status. The underlying biological mechanisms warrant further exploration. In addition, as a non-specific risk factor, age was defined using a threshold of ≥ 60 years. Whether this cut-off value is universally applicable across populations with different geographic, ethnic, and risk factor profiles requires validation through multicenter, large-sample studies.

RESEARCH IMPLICATIONS AND FUTURE DIRECTIONS

This study highlights the independent predictive value of age and RDW in the malignant risk stratification of PCNs, offering insights for clinical decision-making. However, further validation in broader populations is needed, along with exploration of the underlying biological mechanisms. Future research should prioritize:

First, multicenter, prospective cohort studies to assess the age-RDW model's generalizability and stability across diverse populations and healthcare settings. These studies should include larger sample sizes that encompass patients from diverse geographic regions, ethnicities, and stages of the disease. Moreover, these studies should integrate imaging features (such as the degree of main pancreatic duct dilation and mural nodules) and other laboratory indicators (*e.g.*, CA 19-9, NLR) to enhance the predictive models, such as clinical prediction nomograms, for identification of high-risk patients.

Second, the potential biological mechanisms by which RDW influences the malignant transformation of PCNs should be investigated. Elevated RDW, as a nonspecific marker of systemic inflammation and oxidative stress, may relate to immune nutritional status and contribute to the malignant progression of PCNs. Studies[9,10] indicate that RDW may be linked to the immune-nutritional status of patients with pancreatic cancer. Specifically, patients with high RDW demonstrate poorer immune-nutritional status (as assessed using the Controlling Nutritional Status score) and unfavorable prognosis,

indicating that RDW may influence the progression of the tumor by modulating systemic inflammatory responses and nutritional metabolism[9]. Existing literature suggests[11,12] that elevated RDW may be associated with dysregulated erythropoietin (EPO) signaling under hypoxia within the TME, although the underlying pathophysiological mechanisms are not yet fully elucidated. EPO may promote tumor development in pancreatic cancer through the activation of signaling pathways such as AKT/ β -catenin[11,12]. Moreover, the fibrotic microenvironment characteristic of pancreatic cancer may influence erythropoiesis dynamics through mechanical stress, with RDW serving as an inflammation-related marker that reflects this process[13,14]. Additional research has suggested a possible association between pancreatic fat deposition and RDW, indicating that disorders in lipid metabolism may contribute to elevated RDW levels by influencing erythrocyte maturation *via* oxidative stress[15].

From the perspective of clinical translation, it is essential to compare it with existing risk stratification systems to enhance the clinical applicability of the model. Currently, the Fukuoka Consensus Guidelines and the American Gastroenterological Association guidelines primarily rely on imaging features (such as main pancreatic duct dilation and mural nodules) and results from EUS-FNA for risk stratification. In contrast, as a simple and low-cost combination of blood-based indicators, the "age plus RDW" model proposed in this study may serve as an auxiliary tool for initial screening in situations where imaging findings are atypical or medical resources are limited. It could help clinicians in identifying high-risk patients who need further invasive examinations. This will further optimize the allocation of medical resources and reduce unnecessary invasive procedures.

Moreover, one of the key directions for future validation is whether RDW can provide incremental predictive value over existing biomarkers such as CA19-9 or NLR. Although RDW is influenced by various factors such as inflammation and nutritional status, it is somewhat non-specific. However, its potential link to systemic inflammatory responses and the TME suggests that it may indicate malignant transformation from a perspective different from that of traditional biomarkers. To reduce false-positive

results due to elevated RDW and avoid unnecessary invasive procedures, RDW should be used as an initial screening tool rather than a standalone diagnostic criterion. To enhance overall discriminative performance, its combined use with imaging evaluations, clinical symptoms, and other serum biomarkers (*e.g.*, CA19-9) should be emphasized. The integration of artificial intelligence or radiomics technologies in the future could lead to the development of intelligent decision-support systems that synergize clinical features, laboratory indicators, and imaging data, enhancing the risk stratification of PCNs.

CONCLUSION

This study, presented by Martli *et al.*, proposes a promising, straightforward, and economical approach for assessing preoperative malignancy risk in PCNs. If validated through further research, the combination of age and RDW could significantly improve individualized diagnosis and treatment, establishing a foundation for ongoing investigations into risk stratification in this area.

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