# The prognostic impact of preoperative platelet distribution width-to-platelet count ratio in patients with bladder cancer

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**Research**

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# Abstract

Background Preoperative platelet distribution width-to-platelet count ratio (PDW/PLT) has been discussed about its prognostic value in several malignancies, whereas its role in bladder cancer remains unclear. In this study, we attempt to investigate the relationship between the PDW/PLT and the prognosis of patients with bladder cancer.

Patients and Methods The clinical data of 115 cases of bladder cancer treated in urology department of Nantong tumor hospital from January 2009 to August 2014 were analyzed retrospectively. The best critical value of PDW/PLT was 0.09965 determined by ROC curve. The patients were divided into low PDW/PLT group and high PDW/PLT group. After 5 years of follow-up, survival was observed, and the clinicopathological data of patients were statistically analyzed. Kaplan Meier method and log rank test were used for single factor survival analysis, and Cox regression analysis was used for multiple factors survival analysis.

Results The age of patients in low PDW/PLT group was significantly lower than that in high PDW/PLT group (P=0.008). There was no significant difference between the two groups in gender, TNM stage, grade, lymph node metastasis, distant metastasis, operation method, history of hypertension, history of diabetes, and other operation history (P>0.05). All patients were followed up for 5 years. 89 patients survived, the survival rate was 77.4%, 26 patients died, the mortality rate was 22.6%. There were 94 cases (81.7%) in low PDW/PLT group and 21 cases (18.3%) in high PDW/PLT group. The tumor progression rates of low PDW/PLT group and high PDW/PLT group were 57.4% (54/94) and 71.4% (15/21) respectively. The median PFS was 85 months and 71 months respectively. There was no significant difference between the two groups (P>0.05). Single factor analysis showed that TNM stage, grade, lymph node metastasis, PDW/PLT were the factors affecting OS (P<0.05). The results of Cox multivariate analysis showed that PDW/PLT was an independent risk factor for tumor progression (P□0.05). The increase of PDW/PLT can significantly reduce OS and PFS in patients with bladder cancer.

Conclusions PDW/PLT is an independent prognostic factor in patients with bladder cancer, and it is related to the clinicopathological characteristics. It has a certain value in evaluating the prognosis of patients with bladder cancer.


# Introduction

Bladder cancer is the most common malignant tumor of urinary system. The American Cancer Society predicts that the number of new cases and deaths of bladder cancer in 2019 will be 80470 and 17670 respectively (1). In recent years, the incidence and mortality of bladder cancer in China are also increasing (2). In the management of bladder cancer patients, postoperative tumor recurrence and progression is an important clinical end point(3, 4). The traditional TNM staging system can predict the prognosis of bladder cancer. However, in patients with similar TNM stage, there was significant difference in clinical outcome (5). Although in Europe and the United States, molecular diagnostic tests can be used to obtain

more prognostic information and help guide clinical treatment, they cannot be used in routine clinical practice due to their high cost. Therefore, it is very important to identify the low-cost biomarkers which can be easily obtained by routine blood cell count.

Recent clinical and experimental evidence support that platelets play multiple roles in the progression of malignant tumors. Platelet is a key factor in tumor growth, metastasis and cancer-related thrombosis (6), such as endometrial cancer, gastric cancer, pancreatic cancer, etc. (7–9). Recent studies have found that platelet-related markers, such as the ratio of platelets to lymphocytes, are more significant prognostic factors in patients with bladder cancer (10).

Larger platelets store more granules and receptors, and adhere faster than smaller platelets. Therefore, the activity of platelets is more accurately expressed by their size than by counting (11–13). The ratio of platelet distribution width to platelet count is a commonly used measurement of platelet size and an alternative indicator of platelet activation(14). The ratio of platelet distribution width to platelet count has a significant prognosis in breast cancer patients (15), but its clinical significance in bladder cancer is not clear. Therefore, the purpose of this study is to evaluate the relationship between the ratio of preoperative platelet distribution width to platelet count and the prognosis of patients with bladder cancer.

# 1 Data And Methods

## 1.1 Clinical data

The clinical data of bladder cancer patients admitted to the urology department of Nantong tumor hospital from January 2009 to August 2014 were selected. Inclusion criteria: all patients were diagnosed as bladder cancer for the first time and operated on; no upper respiratory tract infection, urinary tract infection, fever and other factors affecting the results of blood routine examination within 1 month before operation; the last blood routine examination before operation, calculated the ratio of platelet distribution width and platelet count; complete clinical, pathological and follow-up data. Exclusion criteria: patients with positive postoperative pathological margin; patients with history of blood system, autoimmune diseases and other malignant tumors; patients with chronic obstructive pulmonary disease, heart failure, coronary heart disease, high-risk hypertension and other factors affecting postoperative recovery; patients with long-term radiation contact history and neoadjuvant chemotherapy before operation; patients with serious complications during perioperative period; Non urothelial tumor; antibiotics, anticoagulants, hormones and other factors have an impact on the blood test results in the near future. 115 patients were included in the study, including 93 males and 22 females. The average age was (68.5 ± 11.4) years.

## 1.2 Research methods

Through the medical record management system of our hospital, the last blood routine examination and the corresponding clinical pathological data were collected. The platelet distribution width, platelet count and PDW/PLT were recorded. The ROC curve of the relationship between PDW/PLT and postoperative

tumor progression was established, and the Yoden index was calculated. The PDW/PLT corresponding to the maximum value was selected as the best dividing point, and the patients were divided into high PDW/PLT group and low PDW/PLT group. Postoperative OS and PFS were used as survival analysis indexes to compare the clinicopathological data and survival differences between the two groups. At the same time, the single factor and multi factor Prognosis of the patients were analyzed.

### 1.3 Follow up

The follow-up methods were outpatient reexamination, readmission medical record and telephone follow-up. The patients were followed up once every 3 months in the first year, once every half a year in the second year and once a year after the second year. Follow up to August 1, 2019. Follow up items: abdominal and pelvic CT or color ultrasound, chest film, tumor markers, urine routine, liver and kidney function, etc. (additional examination depending on the patient's condition). OUTCOME MEASURES: PFS was defined from the beginning of treatment to any follow-up items indicating disease progression. At the end of follow-up, the data of survival and loss of follow-up were used as the final cut-off time for statistical analysis.

### 1.4 Statistical Analysis

SPSS 22.0 statistical software was used to process the data. Using ROC curve, the maximum value of Yoden index is selected as cut off value of PDW/PLT. The measurement data is expressed by (X±S), the comparison is expressed by t test, the counting data is expressed by % and the comparison is tested by $\chi 2$ test or Fisher's exact probability method. For OS and PFS, Kaplan Meier method and log rank test were used. Factors with statistical significance in single factor analysis were included in the multivariate Cox proportional risk regression model. The difference of $P<0.05$ was statistically significant.

## 2 Results

### 2.1 Relationship between PDW/PLT and tumor progression

ROC curve of the relationship between preoperative PDW/PLT and tumor progression in 115 patients is shown in Figure 1. The optimal cut off value of PDW/PLT determined by ROC curve was 0.09965. According to whether PDW/PLT $\leq$ 0.09965 before operation, the patients were divided into low PDW/PLT group (n = 94) and high PDW/PLT group (n = 21).

### 2.2 Comparison of OS and PFS between the two groups

The tumor progression rates of the low PDW/PLT group and the high PDW/PLT group were 57.4% (54 / 94), 71.4% (15 / 21), respectively, and the median PFS was 85 months and 71 months, respectively. However, due to the relatively small number of patients included in the study, there was no statistical difference between the two groups, while the OS of the low PDW/PLT group was significantly higher than

that of the high PDW/PLT group, the difference was statistically significant (P < 0.05), as shown in Figure 2.

## 2.3 Relationship between PDW/PLT and clinicopathological data

PDW/PLT was only related to the age of patients, but not to gender, TNM stage, grade, lymph node metastasis and other factors. The difference was not statistically significant. See Table 1.

Table 1. Relationship between PDW/PLT and clinicopathological data of patients

| e | Total number | PDW/PLT≤0.09965 | PDW/PLT0.09965 | P-value |
|---|---|---|---|---|
| | n%) | n%) | n%) | |
| | | | | 0.008 |
| ≤65 | 52(45.2) | 48(51.1) | 4(19.0) | |
| 65 | 63(54.8) | 46(48.9) | 17(81.0) | |
| | | | | 0.216 |
| male | 93(80.9) | 74(78.7) | 19(90.5) | |
| female | 22(19.1) | 20(21.3) | 2(9.5) | |
| | | | | 0.290 |
| T1 | 77(67.0) | 65(69.1) | 12(57.1) | |
| T2+T3 | 38(33.0) | 29(30.9) | 9(42.9) | |
| | | | | 0.458 |
| G1+G2 | 79(68.7) | 66(70.2) | 13(61.9) | |
| G3 | 36(31.3) | 28(29.8) | 8(38.1) | |
| node metastasis | | | | 0.094 |
| Yes | 4(3.5) | 2(2.1) | 2(9.5) | |
| No | 111(96.5) | 92(97.9) | 19(90.5) | |
| metastases | | | | 0.635 |
| Yes | 1(0.9) | 1(1.1) | 0(0.0) | |
| No | 114(99.1) | 93(98.9) | 21(100.0) | |
| on method | | | | 0.279 |
| lical resection | 39(33.9) | 34(36.2) | 5(23.8) | |
| surgical resection | 76(66.1) | 60(63.8) | 16(76.2) | |
| of hypertension | | | | 0.730 |
| Yes | 19(16.5) | 15(16.0) | 4(19.0) | |
| No | 96(83.5) | 79(84.0) | 17(81.0) | |
| of diabetes | | | | 0.723 |
| Yes | 4(3.5) | 3(3.2) | 1(4.8) | |
| No | 111(96.5) | 91(96.8) | 20(95.2) | |
| peration history | | | | 0.820 |
| Yes | 24(20.9) | 20(21.3) | 4(19.0) | |
| No | 91(79.1) | 74(78.7) | 17(81.0) | |

## 2.4 Log rank single factor analysis

TNM stage, grade, lymph node metastasis, PDW/PLT ≤ 0.09965 are the risk factors of OS in patients with bladder cancer (P < 0.05) (Table 2).

Table 2. Single factor analysis of patients' OS by clinical factors

| Variable | HR | （95%CI） | p-value |
|---|---|---|---|
| Age | | | |
| ≤65 | 2.006 | （0.871-4.619） | 0.102 |
| 65 | 1 | | |
| Gender | | | |
| male | 0.801 | （0.276-2.323） | 0.682 |
| female | 1 | | |
| TNM | | | |
| T1 | 2.727 | （1.260-5.902） | 0.011 |
| T2+T3 | 1 | | |
| Grade | | | |
| G1+G2 | 5.377 | （2.390-12.098） | P＜0.001 |
| G3 | 1 | | |
| Lymph node metastasis | | | |
| Yes | 0.088 | （0.026-0.301） | P＜0.001 |
| No | 1 | | |
| Distant metastases | | | |
| Yes | 20.382 | （0.000-2718726421） | 0.752 |
| No | 1 | | |
| Operation method | | | |
| Radical resection | 0.652 | （0.299-1.420） | 0.282 |
| Electrosurgical resection | 1 | | |
| History of hypertension | | | |
| Yes | 0.916 | （0.345-2.432） | 0.860 |
| No | 1 | | |
| History of diabetes | | | |
| Yes | 1.026 | （0.139-7.582） | 0.980 |
| No | 1 | | |
| Other operation history | | | |
| Yes | 0.528 | （0.229-1.214） | 0.133 |
| No | 1 | | |
| PDW/PLT | | | |
| ≤0.09965 | 5.087 | （2.323-11.137） | P＜0.001 |
| 0.09965 | 1 | | |

## 2.5 Cox regression analysis

The statistically significant risk factors of single factor analysis were gradually included in Cox regression analysis. The results showed that grading, lymph node metastasis, PDW/PLT ≤ 0.09965 were independent risk factors affecting the postoperative progression time of bladder cancer patients, as shown in Table 3.

Table 3. Cox regression analysis of prognostic factors in 115 patients

| Variable | HR | （95%CI） | p-value |
|---|---|---|---|
| TNM | | | |
| T1 | | | 0.969 |
| T2+T3 | | | |
| Grade | | | |
| G1+G2 | 0.182 | （0.079-0.418） | P＜0.001 |
| G3 | | | |
| Lymph node metastasis | | | |
| Yes | 9.228 | （2.032-41.911） | 0.004 |
| No | | | |
| PDW/PLT | | | |
| ≤0.09965 | 0.202 | （0.088-0.467） | P＜0.001 |
| 0.09965 | | | |

# 3 Discussion

This study found that PDW/PLT was associated with survival and was an independent risk factor for the prognosis of bladder cancer. Our findings suggest the potential importance of combining clinicopathological features with PDW/PLT to assess the prognosis of bladder cancer.

Although there are many recent studies on the clinical significance of activated platelets in cancer, the range of available data is still limited by the type of cancer and the clinical results studied. Platelet is rich in TGF-β and PDGF. These platelet-derived growth factors are usually produced in large quantities by cancer cells and contribute to their development. Thrombocytopenia is associated with reduced survival in patients with a variety of tumor types, including colorectal, lung, kidney, stomach, ovarian, brain, endometrial, pancreatic and breast cancers. Elevated platelets promote cancer progression and metastasis by shielding circulating tumor cells from immune surveillance and killing (16). For bladder cancer, the increased expression of platelet-derived endothelial growth factor is significantly related to the tumor progression of bladder cancer (17).

PDW is a more specific marker of platelet activation, because it will not increase due to platelet swelling [(18)], and it is also a method to measure platelet heterogeneity caused by megakaryocyte heterogeneity delineation (19). The high value of this index indicates that there are both mature and immature cells in the circulation. This means that the increase of PDW may be accompanied by abnormal thrombosis and / or the result of heterogeneous boundary of megakaryocyte (20). The causes of poor prognosis in patients with high PDW/PLT are not clear. Inflammation may be a link between PDW/PLT and survival. There is a strong link between inflammation and cancer (21). All kinds of proinflammatory cytokines are up-regulated with the development of tumor, and at the same time, they promote the maturation of allomegakaryocytes, leading to the production and release of immature platelets with various characteristics and sizes into the circulatory system, so as to meet the growing needs of tumor (22). However, further research is needed to better understand the causes of poor prognosis of bladder cancer patients with high PDW/PLT.

This study also has some limitations, including single center design and relatively small sample size. At the same time, this is a retrospective study, which may also lead to data selection and analysis deviation. Despite these limitations, this study is still the first to reveal that the increase of PDW/PLT indicates the poor prognosis of bladder cancer patients.

# 4 Conclusion

Although there are some limitations in this study, the data clearly show that the increase of preoperative PDW/PLT measurement is an unfavorable prognostic factor for bladder cancer patients. It is necessary to further study the mechanism of PDW/PLT in bladder cancer.

# Abbreviations

PDW platelet distribution width

PLT platelet count

OS overall survival

PFS progression-free survival

AUC area under the curve

HR hazard ratio

CI confidence interval

# Declarations


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Not applicable.

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### Availability of data and materials

The datasets used or analyzed during the present study are available from the corresponding author on reasonable request.

### Authors' contributions

JCW, HFX and XLW designed the study. MDG and HJ analyzed and interpreted the patient data. JCW was a major contributor in writing the manuscript. JJS, XLW, JFZ analyzed and interpreted the patient data. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The study was approved by The Ethics Committee of the Tumor Hospital Affiliated to Nantong University (Nantong, China). Written informed consent was obtained from all individual participants included in the study.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

# References


1. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2019. CA Cancer J Clin 69: 7-34, 2019.
2. Li K, Lin T, Chinese Bladder Cancer C, et al.: Current status of diagnosis and treatment of bladder cancer in China - Analyses of Chinese Bladder Cancer Consortium database. Asian J Urol 2: 63-69, 2015.
3. Alfred Witjes J, Lebret T, Comperat EM, et al.: Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. Eur Urol 71: 462-475, 2017.
4. Chang SS, Bochner BH, Chou R, et al.: Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline. J Urol 198: 552-559, 2017.
5. Mitra AP and Daneshmand S: Molecular Prognostication in Bladder Cancer. Cancer Treat Res 175: 165-191, 2018.
6. Mege D, Aubert M, Lacroix R, Dignat-George F, Panicot-Dubois L and Dubois C: Involvement of Platelets in Cancers. Semin Thromb Hemost 45: 569-575, 2019.
7. Ekici H, Malatyalioglu E, Kokcu A, Kurtoglu E, Tosun M and Celik H: Do Leukocyte and Platelet Counts Have Benefit for \Preoperative Evaluation of Endometrial Cancer? Asian Pac J Cancer Prev 16: 5305-5310, 2015.
8. Suzuki K, Aiura K, Kitagou M, et al.: Platelets counts closely correlate with the disease-free survival interval of pancreatic cancer patients. Hepatogastroenterology 51: 847-853, 2004.
9. Wu Y, Jiang M, Qin Y, Lin F and Lai M: Single and combined use of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and carcinoembryonic antigen in diagnosing gastric cancer. Clin Chim Acta 481: 20-24, 2018.
10. Wang X, Ni X and Tang G: Prognostic Role of Platelet-to-Lymphocyte Ratio in Patients With Bladder Cancer: A Meta-Analysis. Front Oncol 9: 757, 2019.
11. Lembeck AL, Posch F, Klocker EV, et al.: Large platelet size is associated with poor outcome in patients with metastatic pancreatic cancer. Clin Chem Lab Med 57: 740-744, 2019.
12. Zhou Q, Huang F, He Z and Zuo MZ: Clinicopathological and prognostic significance of platelet count in patients with ovarian cancer. Climacteric 21: 60-68, 2018.
13. Huang Y, Cui MM, Huang YX, et al.: Preoperative platelet distribution width predicts breast cancer survival. Cancer Biomark 23: 205-211, 2018.
14. Gasparyan AY, Ayvazyan L, Mikhailidis DP and Kitas GD: Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des 17: 47-58, 2011.
15. Takeuchi H, Abe M, Takumi Y, et al.: The prognostic impact of the platelet distribution width-to-platelet count ratio in patients with breast cancer. PLoS One 12: e0189166, 2017.

16. Meikle CK, Kelly CA, Garg P, Wuescher LM, Ali RA and Worth RG: Cancer and Thrombosis: The Platelet Perspective. Front Cell Dev Biol 4: 147, 2016.
17. Li N, Kanda K, Fukumori T, et al.: Expression of vascular endothelial growth factor isoforms and platelet-derived endothelial cell growth factor in bladder cancer. Urol Oncol 6: 10-15, 2000.
18. Vagdatli E, Gounari E, Lazaridou E, Katsibourlia E, Tsikopoulou F and Labrianou I: Platelet distribution width: a simple, practical and specific marker of activation of coagulation. Hippokratia 14: 28-32, 2010.
19. Paulus JM: Recent advances in the story of megakaryocyte physiology. Pathol Biol (Paris) 29: 133-135, 1981.
20. Matsuo K, Tang SH, Sharifi B, Rubin SA, Schreck R and Fagin JA: Growth factor production by human thyroid carcinoma cells: abundant expression of a platelet-derived growth factor-B-like protein by a human papillary carcinoma cell line. J Clin Endocrinol Metab 77: 996-1004, 1993.
21. Mantovani A, Allavena P, Sica A and Balkwill F: Cancer-related inflammation. Nature 454: 436-444, 2008.
22. Kaushansky K: Growth factors and hematopoietic cell fate. A new feature: controversies in hematology. Blood 92: 345-344, 1998.

# Figures

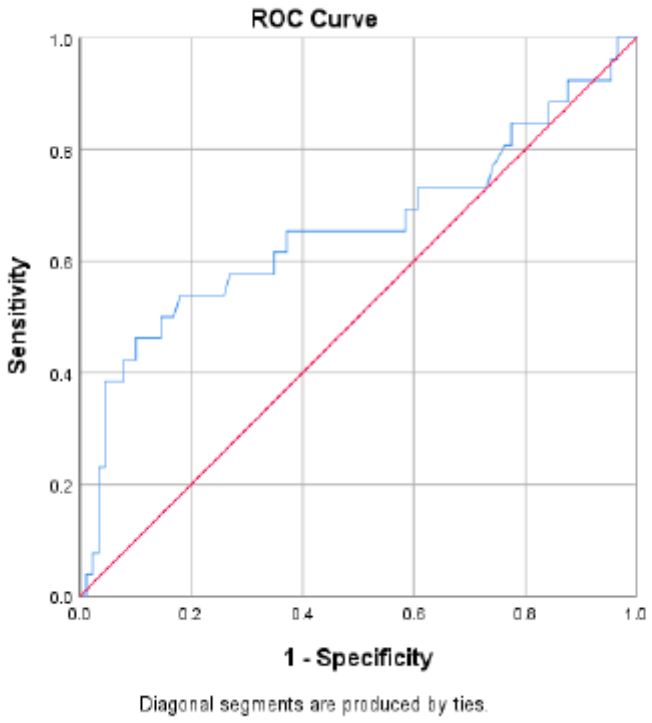
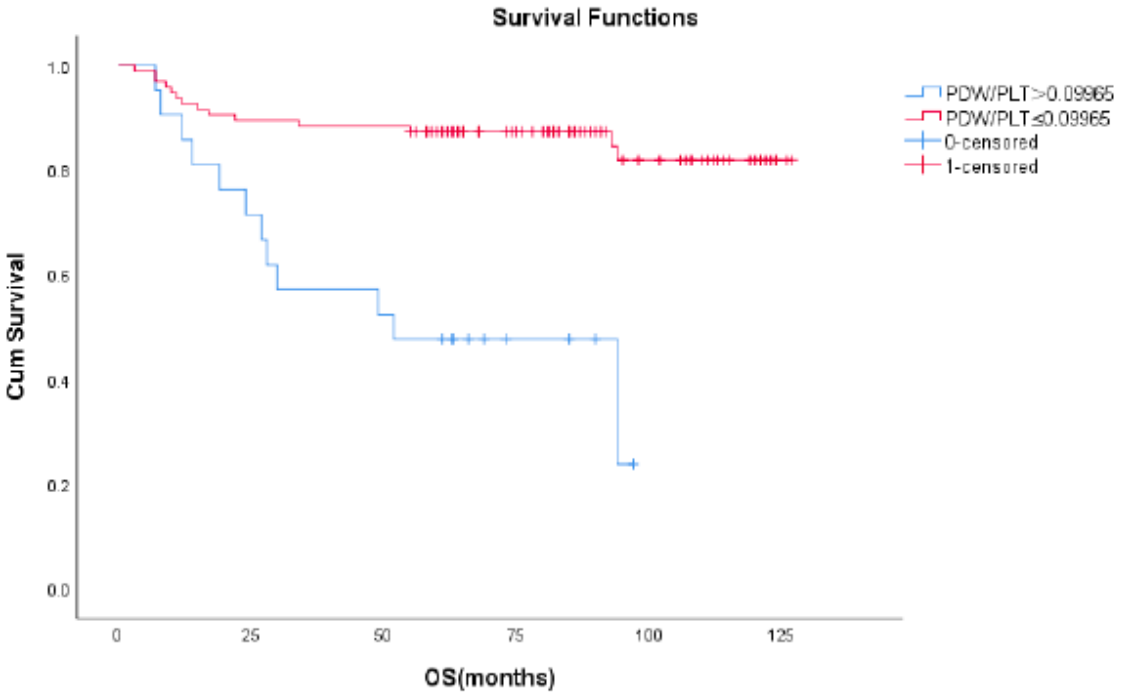



**Figure 1**

ROC curve shows the relationship between PDW/PLT ratio and tumor progression (AUC= 0.657, P = 0.015)




## Figure 2

Comparison of OS curves between the two groups