

# Association Between Pre-Treatment and Post-Treatment 3-Month Red Cell Distribution Width with Three-Year Prognosis of Prostate Cancer

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**Purpose:** Red cell distribution width (RDW), an inflammation biomarker, has been linked to poor outcomes in patients with different types of cancers. The present study aimed to investigate the relationship between pre-/post-treatment 3-month RDW levels and changes in RDW with 3-year prognosis of prostate cancer.

**Patients and Methods:** A total of 348 patients with prostate cancer were recruited between June 1, 2012 and June 1, 2017 and were followed up for at least 3 years. RDW was measured with the Mindray BC-6800Plus automatic blood counting system at pre- and post-treatment 3-month. Demographic and clinical information of the participants were also collected. The overall survival (OS) and cancer-specific survival (CSS) were analyzed using the Kaplan–Meier method. Cox regression and competing risk regression analyses were performed.

**Results:** During the follow-up period, 51 (14.66%) deaths occurred. The levels of pre- and post-treatment RDW levels were significantly higher in the death group than in the survival group ( $p < 0.001$ ). In the death group, the level of RDW continued to rise in most subjects, and the mean level of RDW was significantly higher at post-treatment than pre-treatment, contrary to the results observed in the survival group. Multivariate Cox regression analysis revealed that high pre-treatment RDW, high post-treatment RDW, and persistently higher RDW were independently associated with OS and CSS ( $p < 0.001$ ). Similar results were observed in the competing risk regression analysis. Kaplan–Meier analysis revealed that patients with higher pre-treatment RDW levels, higher post-treatment RDW levels, and persistently higher RDW levels had poorer 3-year OS and CSS rates ( $p < 0.05$ ).

**Conclusion:** The levels of and changes in RDW before and after treatment were associated with the 3-year prognosis of prostate cancer, suggesting that RDW might be an efficient prognostic predictor in patients with prostate cancer.

**Keywords:** red cell distribution width, prostate cancer, prognostic, overall survival, cohort study

## Introduction

Prostate cancer is the second most common cancer in men,<sup>1</sup> and the worldwide burden of this disease is increasing. The estimated crude incidence and mortality rates of this disease in China are 3.6% and 0.38%, respectively.<sup>2</sup> There is also an increasing trend in the incidence and mortality rates of prostate cancer among older people.<sup>2</sup> Practice trends in the past 10–15 years have shown that radiotherapy and androgen deprivation therapy are the primary treatment methods for patients with

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prostate cancer.<sup>3</sup> Conventional radiotherapy and androgen deprivation therapy result in higher rates of urinary incontinence and sexual dysfunction, worsening bowel function, and significantly affecting the quality of life.<sup>4</sup> Furthermore, there is a decreasing trend in the survival rates of patients with prostate cancer,<sup>2</sup> and the survival rate in Asian countries is relatively lower than that in Europe and North America.<sup>5</sup> Tumor size, histological subtype, grade, and advanced tumor stage, which can only be assessed after surgery, have been predicted as prognostic factors in patients with prostate cancer.<sup>6–8</sup> Therefore, identifying prognostic markers for patients with prostate cancer is important.

Red cell distribution width (RDW) is an index that primarily reflects impaired erythropoiesis and abnormal red blood cell survival.<sup>9</sup> The heterogeneity of red blood cell size has also been found to correlate with inflammation and undernutrition status.<sup>10,11</sup> Recently, numerous studies have proposed RDW as a strong, independent risk factor for death<sup>12–14</sup> and a prognostic factor for different types of cancers.<sup>9,15,16</sup> A population-based study by Borné et al<sup>13</sup> found that a high RDW level was associated with an increased incidence of fatal coronary events. Tonelli et al<sup>14</sup> also reported that higher RDW levels were associated with an increased risk of coronary death/nonfatal myocardial infarction, new symptomatic heart failure, and stroke. Furthermore, a large-sample ( $n = 992$ ) retrospective study by Ichinose et al<sup>17</sup> reported that a high RDW level was significantly associated with high morbidity and reduced survival in elderly patients who underwent resection for non-small cell lung cancer. However, patients with epithelial ovarian cancer and  $RDW > 14.5\%$  have been found to have independent prognostic significance for overall survival (OS).<sup>18</sup>

Only one small-sample case-control study reported that the mean pre-treatment RDW level of patients with prostate cancer was higher than that of the healthy control group ( $14.6\%$  vs  $13.7\%$ ,  $p = 0.001$ ), and higher pre-treatment RDW was associated with an increased risk of cancer progression.<sup>19</sup> However, the association between the changes in RDW levels and the clinical prognosis of prostate cancer has not been sufficiently investigated. Therefore, this study aimed to evaluate the prognostic significance of pre- and post-treatment RDW levels and changes in RDW on OS and cancer-specific survival (CSS) in a large cohort of patients with prostate cancer.

## Materials and Methods

### Study Population

Patients with prostate cancer were recruited from the Department of Urinary Surgery at the Shanghai Xuhui Central Hospital, Shanghai, China, using a primary cohort of consecutive patients who underwent radical prostatectomy or androgen deprivation therapy between June 1, 2012 and June 1, 2017 as their first curative treatment option. This study was approved by the Ethics Committee of the Shanghai Xuhui Central Hospital, Shanghai, China and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants. Subjects were recruited according to the following inclusion criteria.

### Inclusion Criteria

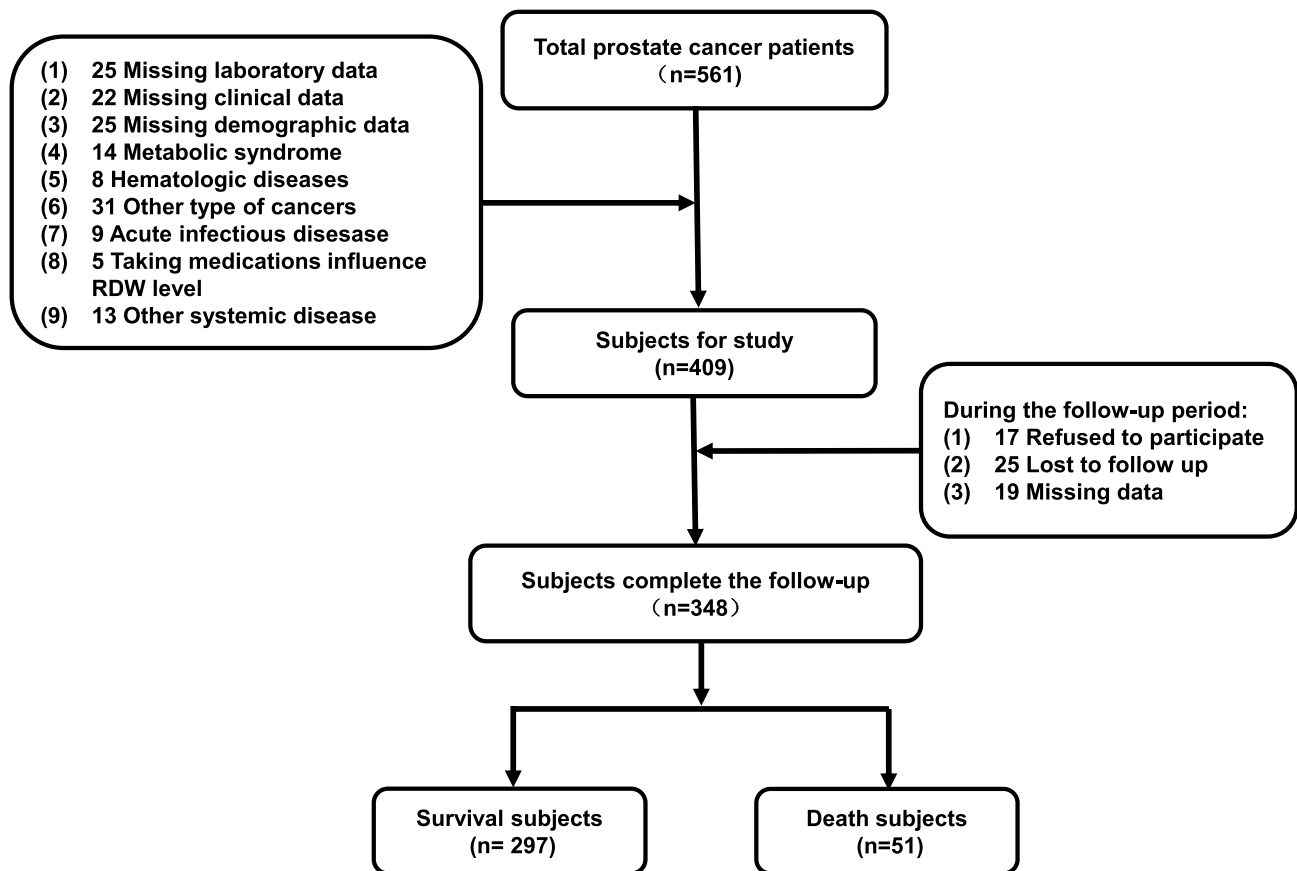
A total of 561 patients with prostate cancer who visited the Department of Urinary Surgery at the Shanghai Xuhui Central Hospital between June 1, 2012 and June 1, 2017, were enrolled. Of these, 152 patients were excluded, resulting in a sample size of 409. During the follow-up period, 61 patients were excluded from the study. Finally, only 348 subjects were included. Figure 1 presents the flow diagram of the study cohort.

The inclusion criteria for patients with prostate cancer included the following:

1. Patients with histologically proven prostate cancer confirmed by pathology
2. Patients aged  $>18$  years
3. Patients whose blood samples were used to measure RDW
4. Patients with detailed clinical, laboratory, and follow-up data
5. Patients who provided signed informed consent
6. Patients who were free from systemic diseases, hematologic diseases, or other cancers
7. Patients who did not take medications that could influence RDW levels
8. Patients who underwent radical prostatectomy or androgen deprivation therapy

### Data Collection

Clinical information, including medical history, date of diagnosis, tumor size, clinical stage, Gleason score, histological grading, and therapy experienced, were collected from the medical data platform of the Shanghai Xuhui Central



**Figure 1** The study cohort flow diagram.

Hospital by trained staff. Demographic information, including age, height, weight, alcohol drinking habits, diabetes, hypertension, and smoking habits, were obtained through interviews conducted by a trained assistant.

## Follow-Up

All patients were followed up through their outpatient records, which were obtained every 3 months until death to remain up-to-date on patient survival status, disease progression, and time of death. During the follow-up period, the participants were interviewed by a trained doctor until their death. The final follow-up was on June 30, 2020. CSS was estimated as the date of surgery until death due to prostate cancer and intercurrent disease of prostate cancer within the follow-up period, while OS was estimated as the date of treatment until death.

## Laboratory Examination

Laboratory examination was performed twice at the Department of Clinical Laboratory, Shanghai Xuhui Central

Hospital. The first blood examination was the pre-treatment, and a second blood examination was the post-treatment after 3 months. Blood samples (4 mL) for routine blood examination were collected in a coagulation-promoting tube via standard venipuncture in the antecubital fossae (anterior elbow veins). The samples were centrifuged for 10 min at 3000 r/min. Serum levels of the total prostate-specific antigen (TPSA) were measured using a Mindray CL-6000 automatic chemiluminescence analyzer (Shenzhen, China). Another 2 mL of blood was collected in an EDTA anticoagulant tube. RDW was measured with the Mindray BC-6800Plus automatic blood counting system (Shenzhen, China) within 0.5 h after blood collection. Persistently higher RDW levels mean post-treatment RDW minus pre-treatment RDW > 0. Persistently lower RDW levels mean post-treatment RDW minus pre-treatment RDW < 0.

## Statistical Analysis

The data were analyzed using SPSS 23.0 (SPSS, Chicago, IL, USA). GraphPad Prism 6 software was also used to

generate the figures. Normality was assessed using the Kolmogorov–Smirnov test. Chi-square tests and independent samples *t*-tests were used to compare categorical and continuous variables, respectively, between groups. Paired *t*-tests were performed to compare RDW levels between pre-treatment and post-treatment, while Cox proportional hazard models were used to obtain hazard ratios (HRs) and 95% confidence intervals (CIs). Cox regression analyses and competing risk regression analyses were performed to analyze the relationship between the variables and OS and CSS. Patient clinical endpoints were also calculated using the Kaplan–Meier method and compared using the Log rank test. Statistical significance was set at  $p < 0.05$  (two-sided).

## Results

### Characteristics of the Study Population

A total of 348 patients with prostate cancer were recruited for this study. During a mean longitudinal follow-up period of 33.02 months after baseline, 51 (14.66%) deaths occurred. The mean age of the patients was 74.42 years (range, 44–90 years). The mean level of pre-treatment RDW among the participants was 14.73% (11.8–22.9%), while the mean level of post-treatment RDW was 14.20% (10.1–24.0%). The demographic information and clinical characteristics of the participants are presented in Table 1.

### Comparison of Baseline Demographic and Lifestyle Characteristics Between Death and Survival Patients

Patients were divided into the survival ( $n = 297$ ) and death ( $n = 51$ ) groups. The levels of pre-treatment ( $14.05\% \pm 1.63\%$  vs  $18.18\% \pm 2.31\%$ ) and post-treatment ( $13.37 \pm 1.60\%$  vs  $19.10 \pm 2.48\%$ ) RDW levels were significantly higher in the death group compared with those in the survival group ( $p < 0.001$ ) (Table 2). Furthermore, lower body mass index, higher levels of TPSA, advanced tumor stage, and higher Gleason score ( $p < 0.05$ ) were significantly correlated with higher death events (Table 2).

### Comparison of RDW According to Demographics and Clinical Characteristics

The patients were further divided into two groups according to the mean RDW (RDW  $< 14.73\%$  subgroup,  $n = 196$ ; RDW  $\geq 14.73\%$  subgroup,  $n = 156$ ). Higher

**Table 1** Baseline Demographic and Lifestyle Characteristics of Prostate Cancer Patients

| Covariates                                   | Number of Patients/<br>Mean |
|--|-----------------------------|
| No. individuals                              | 348                         |
| Age at diagnosis(years), mean, range         | 74.42, 44–90                |
| <74  | 168                         |
| $\geq 74$                                    | 180                         |
| BMI (kg/m <sup>2</sup> ), mean, range        | 22.81, 15.57–30.11          |
| <22.81                                       | 159                         |
| $\geq 22.81$                                 | 189                         |
| Death Events                                 | 51                          |
| Duration of follow-up, median, range(months) | 33.02, 3–36                 |
| Smoking history (yes/no)                     | 186/162                     |
| Drinking history (yes/no)                    | 86/262                      |
| Hypertension (yes/no)                        | 109/239                     |
| Diabetes (yes/no)                            | 77/271                      |
| T Stage                                      |                             |
| T <sub>1-2</sub>                             | 145                         |
| T <sub>3-4</sub>                             | 203                         |
| N Stage                                      |                             |
| N <sub>0</sub>                               | 310                         |
| N <sub>1</sub>                               | 38                          |
| TNM Stage                                    |                             |
| I–II   | 196                         |
| III–IV                                       | 152                         |
| IVA  | 36                          |
| IVB  | 54                          |
| Tumor size, mean, range (cm)                 | 2.30, 1.2–6.5               |
| <2.3cm                                       | 199                         |
| $\geq 2.3$ cm                                | 149                         |
| Histological grading                         |                             |
| II   | 19                          |
| III  | 188                         |
| IV   | 141                         |
| Gleason score, mean, range                   | 7.24, 3–9                   |
| <8   | 170                         |
| $\geq 8$                                     | 178                         |
| Therapy method                               |                             |
| Radical prostatectomy                        | 64                          |
| Androgen deprivation therapy                 | 284                         |
| Pre-treatment RDW (%), mean, range (%)       | 14.73, 11.8–22.9            |
| <14.73                                       | 192                         |
| $\geq 14.73$                                 | 156                         |

(Continued)

**Table 1** (Continued).

| Covariates                              | Number of Patients/<br>Mean |
|---|-----------------------------|
| Post-treatment RDW (%), mean, range (%) | 14.20, 10.1–24.00           |
| <14.20                                  | 186                         |
| ≥14.20                                  | 162                         |
| TPSA, mean, range                       | 90.77, 0.117–117.663        |
| <90.77                                  | 255                         |
| ≥90.77                                  | 93                          |

**Abbreviations:** BMI, body mass index; RDW, red cell distribution width; TPSA, total prostate specific antigen.

death events, a long duration of follow-up, hypertension, increased tumor size, and advanced tumor stage ( $p < 0.05$ ) were significantly correlated with high RDW levels (Table 3).

## Changes in RDW at Pre-Treatment and Post-Treatment

Figure 2 shows the levels of RDW between the death and survival groups at different time points. In the death group, the level of RDW continued to rise in most subjects, and the mean level of RDW was significantly higher at the post-treatment point than at the pre-treatment point ( $p = 0.007$ ). However, converse results were observed in the survival group. The level of RDW continued to decrease in most subjects, and the mean level of RDW was significantly lower at the post-treatment point than at the pre-treatment point ( $p < 0.001$ ).

## Univariate Cox Regression Analysis

Univariate analysis identified that high pre-treatment RDW, high post-treatment RDW, and persistently higher RDW were associated with OS. Furthermore, older age, drinking history, hypertension, advanced tumor stage (III and IV),

**Table 2** Comparison of Baseline Demographic and Lifestyle Characteristics Between Death and Survival Patients

|   | Survival (n=297) | Death (n=51)  | t value        | p value        |
|---|------------------|---------------|----------------|----------------|
| Age (years)   | 73.73±10.04      | 76.04±8.52    | 1.202          | 0.228          |
| BMI (kg/m <sup>2</sup> )  | 23.25±2.21       | 22.24±2.97    | 2.300          | 0.025          |
| Pretreatment RDW (%)  | 14.05±1.63       | 18.18±2.31    | 14.045         | <0.001         |
| Posttreatment RDW (%)   | 13.37±1.60       | 19.10±2.48    | 15.729         | <0.001         |
| TPSA  | 28.17±50.21      | 132.18±152.72 | 4.773          | <0.001         |
| Duration of follow-up (months)  | 36.00±0.00       | 22.68±10.03   | 9.385          | <0.001         |
| Smoking history (yes/no)  | 155/142          | 31/20         | 1.293          | 0.256          |
| Drinking history (yes/no)   | 74/223           | 12/39         | 0.045          | 0.832          |
| Hypertension (yes/no)   | 94/203           | 15/36         | 0.101          | 0.750          |
| Diabetes (yes/no)   | 64/233           | 13/38         | 0.392          | 0.531          |
| T Stage<br>T <sub>1-2</sub> / T <sub>3-4</sub>                        | 112/185          | 33/18         | 13.050         | <0.001         |
| N Stage<br>N <sub>0</sub> / N <sub>1</sub>                            | 277/20           | 33/18         | 36.50          | <0.001         |
| TNM Stage<br>I-II/ III-IV<br>IVA/ IVB                                 | 167/130<br>27/38 | 29/22<br>9/16 | 0.007<br>0.231 | 0.933<br>0.631 |
| Tumor size (cm)   | 2.27±0.43        | 2.47±0.97     | 2.432          | 0.016          |
| Gleason score   | 7.36±1.24        | 8.30±1.01     | 5.940          | <0.001         |
| Therapy method<br>Radical prostatectomy/ Androgen deprivation therapy | 56/241           | 8/43          | 0.291          | 0.589          |

**Notes:** Data are expressed as mean± standard deviation (SD). Chi-square test and independent sample t-test was used.

**Abbreviations:** BMI, body mass index; RDW, red cell distribution width.

**Table 3** Comparison of Pretreatment RDW in Patients with Prostate Cancer, Stratified According to Demographics and Clinical Characteristic

|   | RDW<14.73% (n=192) | RDW≥14.73% (n=156) | t value       | p value        |
|---|--------------------|--------------------|---------------|----------------|
| Age (years)   | 73.58±9.52         | 76.28±8.96         | 1.627         | 0.106          |
| BMI (kg/m <sup>2</sup> )  | 22.62±2.54         | 23.21±3.17         | 1.198         | 0.233          |
| Death Events (Yes/No)   | 13/179             | 38/118             | 21.287        | <0.001         |
| Duration of follow-up (months)  | 34.97±4.93         | 28.69±9.79         | 4.118         | <0.001         |
| Smoking history (yes/no)  | 105/87             | 81/75              | 0.264         | 0.607          |
| Drinking history (yes/no)   | 52/140             | 34/122             | 1.294         | 0.255          |
| Hypertension (yes/no)   | 61/131             | 48/108             | 0.04          | 0.841          |
| Diabetes (yes/no)   | 41/151             | 36/120             | 0.148         | 0.700          |
| T Stage<br>T <sub>1-2</sub> / T <sub>3-4</sub>                        | 84/108             | 59/97              | 1.25          | 0.264          |
| N Stage<br>N <sub>0</sub> / N <sub>1</sub>                            | 178/14             | 132/24             | 5.79          | 0.016          |
| TNM Stage<br>I-II/ III-IV<br>IVA/ IVB                                 | 56/102<br>20/14    | 50/50<br>16/40     | 5.36<br>8.067 | 0.021<br>0.005 |
| Tumor size (cm)   | 1.99±0.56          | 2.44±1.01          | 3.469         | 0.001          |
| Gleason score   | 7.11±1.37          | 7.52±1.57          | 1.582         | 0.116          |
| Therapy method<br>Radical prostatectomy/ Androgen deprivation therapy | 44/148             | 20/136             | 5.845         | 0.016          |

**Notes:** Data are expressed as mean± standard deviation (SD). Chi-square test and independent sample t-test was used.

**Abbreviations:** BMI, body mass index; RDW, red cell distribution width.

high histological grade (IV), high Gleason score, and high TPSA were also poor prognostic factors for OS in this study cohort. Similarly, these factors were found to be poor prognostic factors for CSS (Table 4).

## Multivariate Cox Regression Analysis

After the univariate Cox regression analysis, multivariate Cox regression analysis was performed. After adjusting for age, body mass index, smoking, drinking, hypertension, tumor size, histological grading, Gleason score, tumor stage, therapy method, and TPSA, multivariate Cox regression analysis revealed that high pretreatment RDW, high post-treatment RDW, and persistently higher RDW were independently associated with OS and CSS ( $p < 0.001$ ). Furthermore, older age, drinking history, hypertension, and advanced tumor stage (III and IV) were also predicted to be poor prognostic factors for OS and CSS ( $p < 0.05$ ) (Table 5).

## Competing Risk Regression Analyses

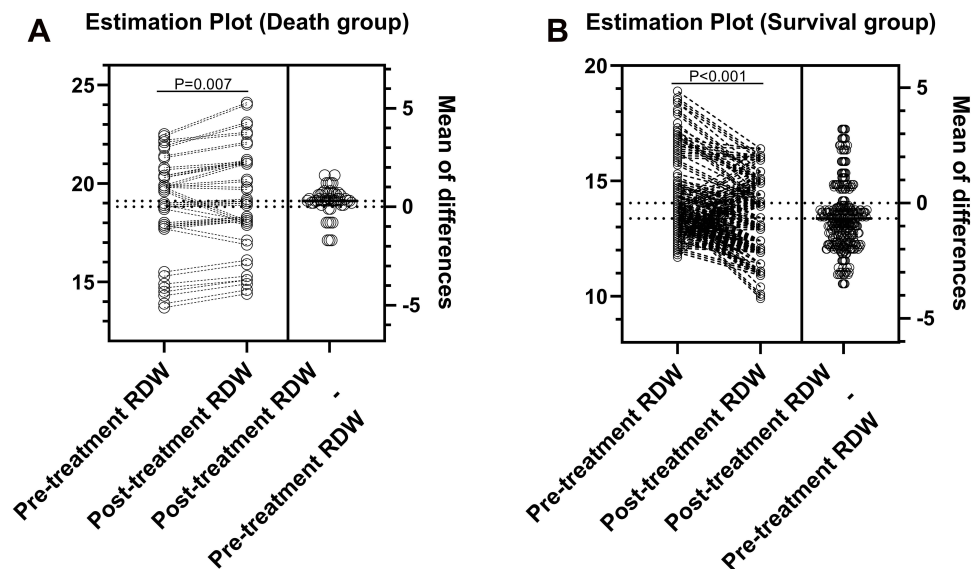
After multivariate Cox regression analysis, competing risk regression analyses were performed. The results showed that high pre-treatment RDW, high post-treatment RDW, persistently higher RDW, and advanced tumor stage (III and IV) were poor prognostic factors for survival of prostate cancer (Table 6).

## Kaplan–Meier Survival Analysis

Patients with pre-treatment RDW levels  $\geq 14.73\%$  had poorer 3-year OS (95.73% vs 70.52%,  $p < 0.001$ ) and CSS rates (95.19% vs 60.45%,  $p < 0.001$ ) than those with RDW levels  $< 14.73\%$  (Figure 3). Furthermore, the Kaplan–Meier curves for OS and CSS revealed that advanced tumor stage (III and IV) could also be risk factors that are consistent with poor prognosis in patients with prostate cancer ( $p < 0.05$ , Log rank test) (Figure 3).

Patients with post-treatment RDW levels  $\geq 14.20\%$  had poorer 3-year OS (98.68% vs 75.00%,  $p < 0.001$ ) and CSS





**Figure 2** The levels of RDW between the groups at different points. Paired t-test were used. (A) Death group. (B) Survival group.

rates (99.28% vs 73.91%,  $p < 0.001$ ) compared with patients with RDW levels  $< 14.20\%$  (Figure 4).

Moreover, patients with persistently higher RDW levels had poorer 3-year OS (96.28% vs 61.32%,  $p < 0.001$ ) and CSS rates (97.06% vs 63.37%,  $p < 0.001$ ) compared with patients with persistently lower RDW levels (Figure 5).

## Discussion

Our findings demonstrated that several factors impact the likelihood of survival of patients with prostate cancer, including a high level of RDW, persistently higher RDW levels, older age, drinking history, hypertension, and advanced tumor stage. To the best of our knowledge, this is the first study to explore the association between pre-treatment RDW, post-treatment RDW, and change in RDW with prostate cancer prognosis. Considering RDW as a prognostic marker, comparable and stable values are vital. At the pre-treatment time point, the RDW levels were not affected by radiotherapy or androgen deprivation therapy. Three months after treatment, the inflammation subsided. The post-treatment 3-month was chosen to exclude the effect of radical prostatectomy, which led to systemic inflammation on RDW. We found that high pre-treatment RDW, high post-treatment RDW, and persistently higher RDW were independently associated with OS and CSS ( $p < 0.001$ ). Thus, the levels of and changes in RDW before and after treatment were associated with the 3-year prognosis of prostate cancer, suggesting that

RDW might be an efficient prognostic predictor in patients with prostate cancer.

Inflammation plays a key role in the therapeutic response and survival of patients with prostate cancer.<sup>20,21</sup> Many research groups have investigated the predictive and prognostic roles of peripheral blood inflammatory parameters in prostate cancer.<sup>22–24</sup> Cho et al<sup>23</sup> reported that the lymphocyte-to-monocyte ratio is a predictor of clinically significant prostate cancer on prostate biopsy. Bauckneht et al<sup>24</sup> also found that a higher neutrophil-to-lymphocyte ratio and systemic inflammation index predicted worse OS in patients with prostate cancer. RDW, as an inflammation biomarker, has been linked to poor outcomes in patients with different types of cancer.

Several previous studies that have investigated the relationship between pre-treatment RDW and prognosis in various types of cancer<sup>9,11,15–18</sup> have consistently reported that RDW could be a useful marker for poor prognosis prediction in patients with cancer. In line with these findings, our study also found that a high pre-treatment RDW level is a poor prognostic factor for OS and CSS in patients with prostate cancer. Interestingly, we further found that post-treatment RDW and changes in RDW (persistently higher RDW) were associated with the prognosis of prostate cancer. To the best of our knowledge, this is the first study to explore the relationship between changes in RDW before and after treatment and the prognosis of prostate cancer. Limited data are available

**Table 4** Univariate Cox Regression Analysis for Overall Survival and Cancer Specific Survival in Patients with Prostate Cancer

|                              | OS                   |        | CSS                  |        |
|------------------------------|----------------------|--------|----------------------|--------|
|                              | HR(95% CI)           | P      | HR(95% CI)           | P      |
| Age                          | 1.062 (1.016–1.110)  | 0.008  | 1.049 (1.003–1.097)  | 0.036  |
| BMI                          | 0.873 (0.762–1.001)  | 0.051  | 0.897 (0.779–1.034)  | 0.136  |
| Smoking history              |                      |        |                      |        |
| No                           | I                    |        | I                    |        |
| Yes                          | 2.087 (0.929–4.687)  | 0.075  | 2.180(0.922–5.156)   | 0.076  |
| Drinking history             |                      |        |                      |        |
| No                           | I                    |        | I                    |        |
| Yes                          | 2.902(1.416–5.949)   | 0.004  | 3.180(1.488–6.798)   | 0.003  |
| Hypertension                 |                      |        |                      |        |
| No                           | I                    |        | I                    |        |
| Yes                          | 4.718 (2.098–10.607) | <0.001 | 4.953(2.092–11.725)  | <0.001 |
| Diabetes                     |                      |        |                      |        |
| No                           | I                    |        | I                    |        |
| Yes                          | 1.995(0.933–4.263)   | 0.075  | 1.997(0.897–4.448)   | 0.090  |
| T Stage                      |                      |        |                      |        |
| T <sub>1-2</sub>             | I                    |        | I                    |        |
| T <sub>3-4</sub>             | 2.875(1.570–5.265)   | 0.001  | 3.110(1.644–5.884)   | <0.001 |
| N Stage                      |                      |        |                      |        |
| N <sub>0</sub>               | I                    |        | I                    |        |
| N <sub>1</sub>               | 1.541(0.467–5.079)   | 0.478  | 1.746(0.526–5.800)   | 0.363  |
| TNM Stage                    |                      |        |                      |        |
| I–II                         | I                    |        | I                    |        |
| III–IV                       | 2.053(1.289–3.270)   | 0.002  | 1.960(1.209–3.178)   | 0.006  |
| IVA                          | 3.047 (1.597–5.816)  | 0.001  | 3.260 (1.646–6.457)  | 0.001  |
| IVB                          | 4.535 (1.943–10.586) | <0.001 | 4.724 (1.918–11.631) | 0.001  |
| Histological grading         |                      |        |                      |        |
| II–III                       | I                    |        | I                    |        |
| IV                           | 2.126(1.094–4.133)   | 0.026  | 2.023(1.009–4.057)   | 0.047  |
| Gleason score                | 1.657 (1.132–2.317)  | 0.003  | 1.495(1.115–2.120)   | 0.008  |
| Therapy method               |                      |        |                      |        |
| Radical prostatectomy        | I                    |        | I                    |        |
| Androgen deprivation therapy | 0.219(0.051–1.918)   | 0.653  | 0.223(0.112–1.827)   | 0.644  |
| Tumor size                   | 0.918 (0.615–1.371)  | 0.667  | 0.915 (0.599–1.396)  | 0.679  |
| Pretreatment RDW (%)         | 1.782 (1.545–2.054)  | <0.001 | 1.864 (1.591–2.182)  | <0.001 |
| Posttreatment RDW (%)        | 1.922 (1.343–2.584)  | <0.001 | 2.010 (1.411–2.772)  | <0.001 |
| Change in RDW                |                      |        |                      |        |
| Persistent lower RDW (%)     | I                    |        | I                    |        |
| Persistent higher RDW (%)    | 2.110 (1.544–2.877)  | <0.001 | 2.445 (1.650–2.335)  | <0.001 |
| TPSA                         | 1.006 (1.004–1.008)  | <0.001 | 1.007 (1.004–1.009)  | <0.001 |

**Abbreviations:** BMI, body mass index; OS, overall survival; CSS, cancer-specific survival; RDW, red cell distribution width; TPSA, total prostate specific antigen; persistent lower RDW, post-treatment RDW-Pre-treatment RDW<0; persistent higher RDW, post-treatment RDW-Pre-treatment RDW>0.



**Table 5** Multivariate Cox Regression Analysis for Overall Survival and Cancer Specific Survival in Patients with Prostate Cancer

|                           | OS                   |        | CSS                  |        |
|---------------------------|----------------------|--------|----------------------|--------|
|                           | HR (95% CI)          | P      | HR (95% CI)          | P      |
| Age                       | 1.070 (1.005–1.151)  | 0.048  | 1.055 (0.981–1.135)  | 0.148  |
| Drinking history          |                      |        |                      |        |
| No                        | 1                    |        | 1                    |        |
| Yes                       | 1.396 (1.101–4.194)  | 0.044  | 1.786 (0.962–3.522)  | 0.061  |
| Hypertension              |                      |        |                      |        |
| No                        | 1                    |        | 1                    |        |
| Yes                       | 1.279 (1.002–4.628)  | 0.025  | 1.503 (0.602–10.405) | 0.207  |
| T Stage                   |                      |        |                      |        |
| T <sub>1-2</sub>          | 1                    |        | 1                    |        |
| T <sub>3-4</sub>          | 0.861 (0.259–2.857)  | 0.806  | 1.252 (0.338–4.634)  | 0.737  |
| TNM Stage                 |                      |        |                      |        |
| I–II                      | 1                    |        | 1                    |        |
| III–IV                    | 3.252 (1.771–11.636) | 0.001  | 3.556 (1.411–8.758)  | 0.003  |
| IVA                       | 3.617 (1.360–9.619)  | 0.010  | 3.786 (1.362–10.522) | 0.011  |
| IVB                       | 3.709 (1.046–4.887)  | 0.002  | 3.894 (1.116–4.923)  | 0.003  |
| Histological grading      |                      |        |                      |        |
| II–III                    | 1                    |        | 1                    |        |
| IV                        | 1.429 (1.096–1.920)  | 0.269  | 1.325 (0.902–4.131)  | 0.325  |
| Gleason score             | 0.718 (0.396–1.304)  | 0.277  | 0.718 (0.393–1.311)  | 0.281  |
| Pretreatment RDW (%)      | 1.306 (1.022–1.669)  | 0.033  | 1.331 (1.031–1.718)  | 0.028  |
| Posttreatment RDW (%)     | 1.385 (1.131–1.564)  | 0.004  | 1.425 (1.163–1.624)  | 0.001  |
| Chang in RDW              |                      |        |                      |        |
| Persistent lower RDW (%)  | 1                    |        | 1                    |        |
| Persistent higher RDW (%) | 1.659 (1.244–2.077)  | <0.001 | 1.990 (1.350–2.544)  | <0.001 |
| TPSA                      | 1.007 (1.001–1.228)  | 0.008  | 0.998 (0.992–1.005)  | 0.068  |

**Abbreviations:** OS, overall survival; CSS, cancer-specific survival; RDW, red cell distribution width; TPSA, total prostate specific antigen; persistent lower RDW, Post-treatment RDW-Pre-treatment RDW<0; persistent higher RDW, Post-treatment RDW-Pre-treatment RDW>0.

in the literature regarding the association between RDW and prostate cancer prognosis. An early case-control study conducted by Sebahattin et al<sup>19</sup> found that patients with prostate cancer had higher pre-treatment RDW levels than normal control subjects.

Based on our results, different factors might explain the prognostic value of RDW. Recent evidence indicates that the host inflammatory response plays an important role in tumor progression.<sup>25</sup> Meanwhile, the heterogeneity of red blood cell size (high RDW) correlates with inflammation and undernutrition status.<sup>10,11</sup> A higher tumor stage can lead to significant systemic inflammation through the secretion of cytokines and release of tumor-degradation products, which, in turn, increases RDW levels.<sup>19</sup> In our study, we also found an

association between increased tumor size, advanced tumor stage, and high RDW levels.

Undernutrition is common among patients with cancer and can influence the prognosis of patients,<sup>26</sup> and a higher rate of cancer-related undernutrition status might impair erythropoiesis and influence abnormal red blood cell survival. Dietary factors (folate, vitamin B12, and iron) are fundamental to the generation of red blood cells, and low concentrations of any of these factors can lead to changes in red blood cell morphology and cause anemia.<sup>27</sup> Meanwhile, cancer can cause anemia by producing cytokines (leading to iron sequestration),<sup>28</sup> which, in turn, can cause a further increase in RDW levels. Furthermore, Price et al<sup>29</sup> reported that folate, vitamin B12, and iron are associated with prostate cancer risk. Therefore, our results

**Table 6** Multivariate Cox Regression Analysis for Overall Survival and Cancer Specific Survival in Patients with Prostate Cancer Using the Competing-Risks Model

|                           | sdHR (95% CI)       | P      |
|---------------------------|---------------------|--------|
| Age                       | 1.090 (0.934–1.849) | 0.062  |
| Drinking history          |                     |        |
| No                        | I                   |        |
| Yes                       | 2.099 (0.804–4.842) | 0.175  |
| Hypertension              |                     |        |
| No                        | I                   |        |
| Yes                       | 2.279 (0.602–8.628) | 0.225  |
| T Stage                   |                     |        |
| T <sub>1-2</sub>          | I                   |        |
| T <sub>3-4</sub>          |                     |        |
| TNM Stage                 |                     |        |
| I–II                      | I                   |        |
| III–IV                    | 2.838 (1.262–6.379) | 0.012  |
| IVA                       | 3.099 (1.404–6.842) | 0.005  |
| IVB                       | 3.175 (1.250–7.262) | 0.001  |
| Histological grading      |                     |        |
| II–III                    | I                   |        |
| IV                        | 1.429 (0.096–1.920) | 0.269  |
| Gleason score             | 0.632 (0.371–1.077) | 0.092  |
| Pretreatment RDW (%)      | 1.390 (1.141–1.695) | 0.001  |
| Posttreatment RDW (%)     | 1.450 (1.180–1.890) | <0.001 |
| Change in RDW             |                     |        |
| Persistent lower RDW (%)  | I                   |        |
| Persistent higher RDW (%) | 1.825 (1.442–2.340) | <0.001 |
| TPSA                      | 0.997 (0.991–1.004) | 0.388  |

**Abbreviations:** RDW, red cell distribution width; TPSA, total prostate specific antigen; sdHR, sub-distribution hazard ratio; persistent lower RDW, post-treatment RDW-Pre-treatment RDW<0; persistent higher RDW, Post-treatment RDW-Pre-treatment RDW>0.

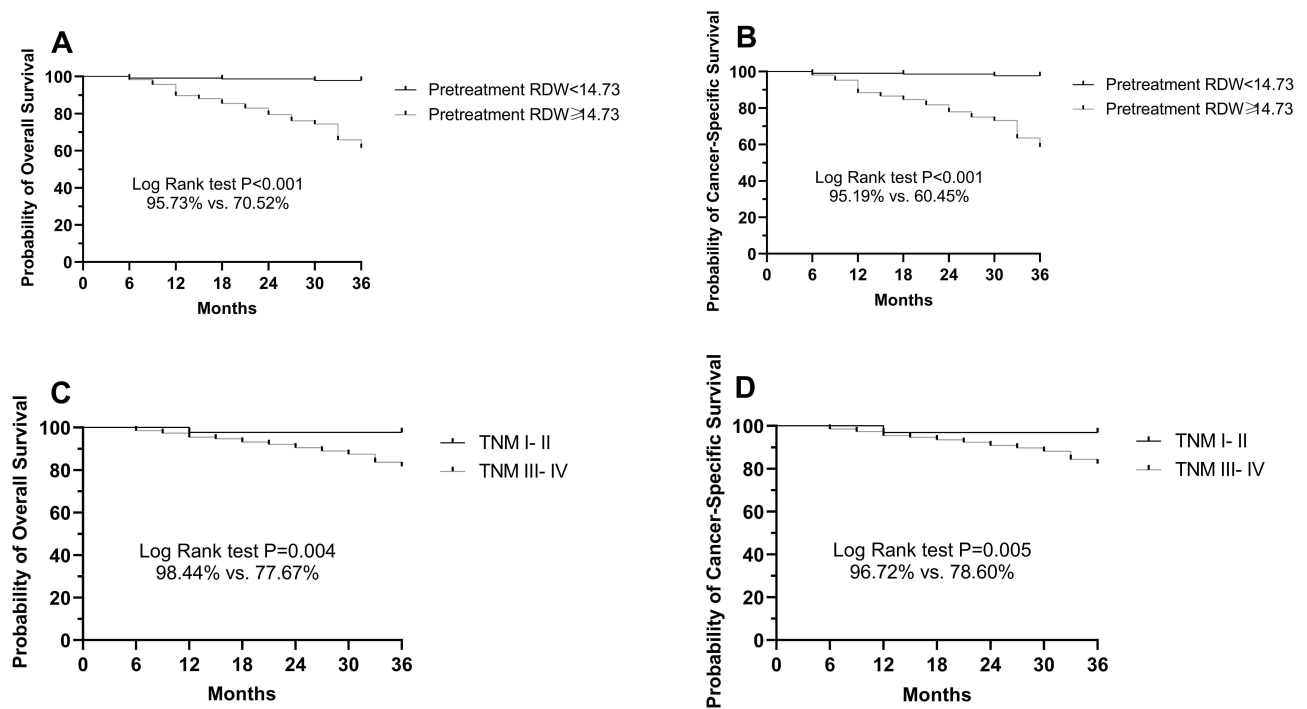
are consistent with prior hypotheses that elevated RDW levels could reflect the biological properties of cancer cells. We also speculate that high RDW levels may represent a response secondary to tumor necrosis and local tissue damage, which is caused by the tumor–host cell interaction and reflects a high tumor burden.<sup>30</sup> The inflammatory response, which is indicated by a high RDW level, results in tumor microenvironment dysfunction that promotes tumor growth, angiogenesis, and metastasis.<sup>31</sup> Higher post-treatment RDW levels and changes in RDW (persistently higher RDW) also represent patients with a high systemic inflammation status. In this study, post-treatment RDW levels and changes in RDW (persistently higher RDW) were associated with the prognosis of

prostate cancer. Thus, high RDW levels can be considered a biomarker for poor tumor biology and adverse prognosis in patients with prostate cancer.

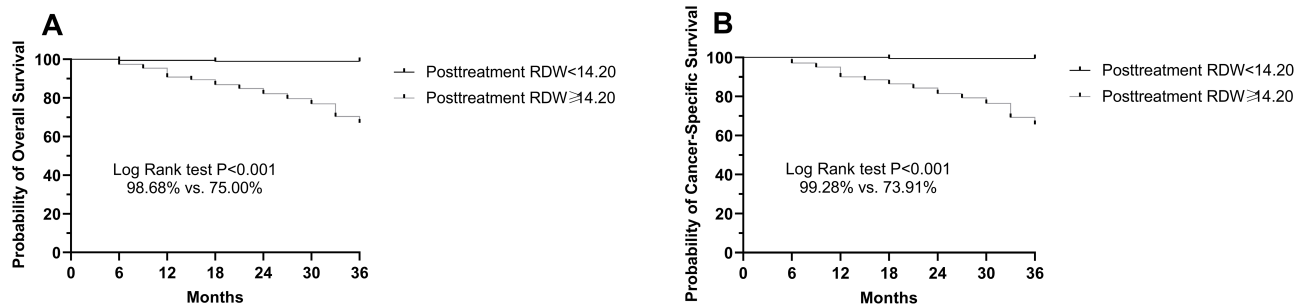
Our study also suggests that older age, drinking history, hypertension, and advanced tumor stage are biomarkers for poor prognosis in patients with prostate cancer. Consistent with our findings, Kamel et al<sup>32</sup> and Valero et al<sup>33</sup> both reported that older age and advanced tumor stage are considered independent predictors affecting the prognosis of patients with prostate cancer. Liang et al<sup>34</sup> performed a systematic review and meta-analysis and found that hypertension may be associated with an increased risk of prostate cancer. In addition, according to Dickerman et al<sup>35</sup> and Zuccolo et al,<sup>36</sup> heavy regular alcohol consumption and binge drinking patterns are associated with increased prostate cancer risk and advanced tumor stage.

Furthermore, there are different types of treatment for patients with prostate cancer, but radiotherapy and androgen deprivation therapy are the primary treatment methods for patients with prostate cancer.<sup>3</sup> The number of patients with prostate cancer who underwent other types of treatment was limited to this study. If patients with prostate cancer who underwent other types of treatment were included in this study, this will lead to potential bias in the results. In this study, only patients who underwent radical prostatectomy and/or androgen deprivation therapy were included. Thus, our findings may not be applicable to patients undergoing other types of treatment. Further multicenter, large-sample studies including all types of treatment for patients with prostate cancer are needed to confirm our results.

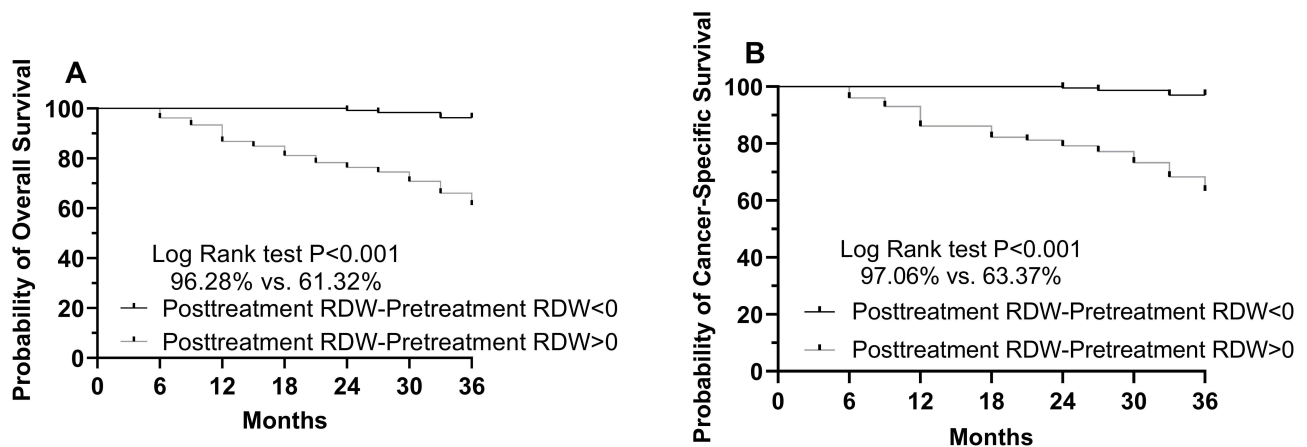
As this was the first study to assess the association between pre-treatment RDW, post-treatment RDW levels, and changes in RDW with prostate cancer prognosis, it had some limitations. First, undernutrition status was associated with RDW levels, but we were unable to evaluate the nutritional status of patients in our study. Second, although patients with obvious infectious diseases were excluded, subclinical infection, which cannot be found by physical examination, could influence RDW levels. Third, this was a single-center retrospective study; future studies should consider conducting a controlled prospective clinical trial. Fourth, death was considered as the primary outcome. Tumor recurrence and other indicators are usually regarded as secondary outcomes. However, our study failed to explore the relationship between RDW, tumor recurrence, and other



**Figure 3** Kaplan-Meier overall survival (OS) and cancer specific survival (CSS) curves stratified by the mean value in terms of pre-treatment red cell distribution width (RDW), and TNM stage. **(A)** OS curves stratified based on RDW category. **(B)** CSS curves stratified based on RDW category. **(C)** OS curves stratified based on TNM category. **(D)** CSS curves stratified based on TNM category.



**Figure 4** Kaplan-Meier overall survival (OS) and cancer specific survival (CSS) curves stratified by the mean value in terms of post-treatment red cell distribution width (RDW). **(A)** OS curves stratified based on RDW category. **(B)** CSS curves stratified based on RDW category.



**Figure 5** Kaplan-Meier overall survival (OS) and cancer specific survival (CSS) curves stratified by the mean value in terms of change in red cell distribution width (RDW). **(A)** OS curves stratified based on RDW change category. **(B)** CSS curves stratified based on RDW change category.

indicators. Finally, the optimal cut-off value for the RDW was determined by the mean value of the RDW and not by the receiver operating characteristics (ROC). ROC curves are graphical schemes for an ensemble. The ROC curve represents the true positive rate as a function of the false-positive rate. Therefore, this deficiency may have caused bias in the interpretation of data.

## Conclusion

RDW, as a readily available, accurate, and inexpensive parameter, was demonstrated to be a prognostic factor for OS and CSS in patients with prostate cancer.

## Data Sharing Statement

Available from the corresponding author upon reasonable request.

## Ethics Approval Statement

This study was approved by the Ethics Committee of the Shanghai Xuhui Central Hospital, Shanghai, China, and was conducted in accordance with the Declaration of Helsinki.

## Patient Consent Statement

Informed consent was obtained from all the patients.

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## Disclosure

The authors declare no competing interests.

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