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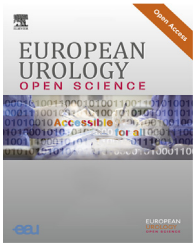

European Association of Urology

Prostate Cancer

Red Blood Cell Distribution Width Is Associated with All-cause Mortality but Not Adverse Cancer-specific Outcomes in Men with Clinically Localized Prostate Cancer Treated with Radical Prostatectomy: Findings Based on a Multicenter Shared Equal Access Regional Cancer Hospital Registry

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Abstract

Background: Recent reports with a small number of patients showed an association of red blood cell distribution width (RDW) with prostate cancer (PCa) progression.

Objective: To investigate whether preoperative RDW can serve as a prognostic marker in patients with PCa undergoing radical prostatectomy (RP) in a large, equal access, and diverse patient cohort.

Design, setting, and participants: Data were retrospectively collected on 4756 men treated with RP at eight Veteran Affairs medical centers within the Shared Equal Access Regional Cancer Hospital (SEARCH) database from 1999 through 2017.

Outcome measurements and statistical analysis: Biochemical recurrence (BCR) was the primary outcome, while metastasis, all-cause mortality (ACM), and prostate cancer–specific mortality (PCSM) were secondary outcomes.

Results and limitations: The mean (standard deviation) age was 62 yr (6.1), and 1589 (33%) men were black. The median (interquartile range) follow-up was 82 mo (46–127). Preoperative RDW either as a continuous variable or when stratified by quartiles was not associated with BCR. Likewise, preoperative RDW was not

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associated with metastases or PCSM. However, higher RDW was significantly associated with higher ACM, both as a continuous variable ($p < 0.001$) and when stratified by quartiles in univariable and multivariable models ($p < 0.001$). RDW was found to be correlated with D'Amico risk classification of PCa. Study limitations include its retrospective nature and lack of data regarding advanced PCa.

Conclusions: Preoperative RDW was not associated with PCa outcomes in men treated with RP but was associated with ACM. While RDW may be a biomarker of overall health, it is not a biomarker for PCa outcomes. These results emphasize the importance of diverse, larger sized studies in genitourinary cancer research.

Patient summary: Prostate cancer includes a wide spectrum of diseases with different genetic, pathological, and oncological behaviors. Red blood cell distribution width is helpful in predicting the overall survival for a localized prostate cancer patient, and hence, it can help inform personalized treatment decisions and operative care.

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1. Introduction

Prostate cancer is the most common noncutaneous malignancy and the second leading cause of cancer-related death among men in the USA [1]. Although prostate cancer is more common in the older population (>65 yr), approximately 10% of young men aged ≤55 yr can be affected [2].

Further, prostate cancer is not a single entity of adenocarcinoma arising from prostate epithelium, but rather it represents a broad spectrum of disease encompassing different histopathological patterns, genetic aberrations, and oncological behaviors [3]. Clinically, it ranges from serendipitously detected disease on transurethrally resected tissue or autopsy to indolent disease that can be monitored, to clinically significant disease that can be treated for survival benefit, to aggressive disease with high mortality. Thus, treatment decisions are variable and dependent on several factors related to both the disease itself and patient preference.

Prostate cancer continues to be complex to manage due to its wide clinical spectrum, availability of many treatment options for each disease stage, and importance of patient decision-making. This is especially paramount for the treatment of clinically localized disease wherein the patient weighs disease control/cure with the possibility of post-treatment complications such as urinary incontinence and sexual dysfunction that impact overall quality of life. Prostate cancer diagnosis and treatment are costly undertakings, and rely on multiple investigations including prognostic biomarkers [4]. There exists an unmet need to have inexpensive, reliable, and convenient biomarkers that could be employed in the prediction of prostate cancer outcomes.

Red blood cell distribution width (RDW) is an easily obtainable measure for anisocytosis that reflects the heterogeneity of red blood cell dimensions [5]. It has a predictive value in many diseases including malignancy [6–8] and has been reported to be associated with all-cause mortality (ACM) [9]. Investigating its prognostic significance in prostate cancer could be valuable for prediction and clinical decision-making, especially when considering whether and what type of treatment is medically necessary. A previous study in a small number of prostate cancer patients has shown that higher RDW was associated with an increased risk of progression [10]. Another recent study revealed that high RDW is an independent risk factor for clinically significant prostate cancer. However, the authors stressed for the need for a large multicenter study to confirm these results [11]. Hence, we investigated whether there is an association between RDW and biochemical recurrence (BCR) after radical prostatectomy (RP) using a large, diverse, and equal access (Shared Equal Access Regional Cancer Hospital [SEARCH]) database. We also explored whether there is a link between RDW and the development of metastasis, prostate cancer–specific mortality (PCSM), and ACM.

2. Patients and methods

Data with clinical and pathological parameters were collected from the SEARCH database for patients treated with RP in the period from 1999 to 2017. Eight Veteran Affairs medical centers were involved (Greater Los Angeles, Palo Alto, San Diego, and San Francisco, CA; Augusta, GA; Durham and Asheville, NC; and Portland, OR). Institutional review board approval was obtained. Patients with available RDW within 1 yr prior to RP were included in the study. The data contained information about age, race, prostate-specific antigen (PSA; ng/ml), clinical stage, preoperative grade group on prostate biopsy, percentage of biopsy cores with cancer, tumor volume, follow-up interval, Charlson Comorbidity index (CCI), and RDW. Within SEARCH, 5740 men were treated between 1999 and 2017, of whom 5400 had RDW measured within 1 yr prior to RP. After exclusion of patients with missing data, the final study cohort included 4756 patients.

BCR was the primary outcome, defined as PSA >0.2 ng/ml or two consecutive PSA levels at 0.2 ng/ml or secondary treatment for elevated PSA after initial therapy. The development of metastasis, PCSM, and ACM was considered secondary outcomes. Evidence of the presence of metastasis beyond the prostate, seminal vesicle, or pelvic lymph node was based on radiological imaging. PCSM was defined by the presence of progressive metastatic prostate cancer at the time of death not attributable to any other cause. ACM denotes death from any cause.

2.1. Statistical analysis

RDW was categorized into quartiles. Patient characteristics were summarized and stratified by RDW quartiles. Differences were tested using Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables.

Kaplan-Meier curves were created for each outcome, stratified by RDW quartiles: BCR, metastasis, PCSM, and ACM. The association between RDW (quartiles and continuous) and risk of BCR, metastasis, PCSM, and ACM were tested using Cox proportional hazard models. Unadjusted models were fit, as well as those adjusted for the preoperative characteristics listed in Table 1 (age, race, PSA, clinical stage, year of surgery, surgical center, biopsy grade group, percent positive biopsy cores, and CCI) and postoperative pathological characteristics (pathological grade group, extracapsular extension, seminal vesicle invasion, lymph node metastasis, and positive surgical margins). The association between RDW (quartiles and continuous) and D'Amico risk classification was tested using odds ratio models. The p values for trend were calculated by assigning each group's median RDW value to patients in that group and treating the RDW group as continuous. Analyses were performed using Stata 15.0 (StataCorp, College Station, TX, USA). A p value of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics (baseline clinical data)

The mean (standard deviation) age was 62 yr (6.1) and 1589 (33%) men were black. The median follow-up was 82 mo (interquartile range: 46–127 mo). RDW was divided into quartiles: quartile 1 (<12.9%), quartile 2 (12.9–13.3%), quartile 3 (13.4–14%), and quartile 4 (≥14.1%). Percentages of patients in each quartile were as follows: quartile 1, 21.5%; quartile 2, 24.4%; quartile 3, 27.7%; and quartile 4, 26.4%.

The clinical and histopathological characteristics of patients and biopsy samples were stratified by RDW quartiles. There was no difference between the four quartiles regarding age, tumor volume, and clinical stage. However, there was a statistical difference between the four quartiles in regard to PSA, preoperative grade group, percentage of biopsy cores with cancer, and follow-up period (all p < 0.005), although there was no specific trend for that associ-

Table 1 – Characteristics of cohort by RDW.

	Quartile 1, RDW <12.9% (N = 1021)	Quartile 2, RDW 12.9–13.3% (N = 1160)	Quartile 3, RDW 12.4–14% (N = 1319)	Quartile 4, RDW ≥14.1% (N = 1256)	p value
Age					0.689 [a]
Median	62.0	62.0	62.0	62.0	
Q1, Q3	57.0, 66.0	58.0, 66.0	58.0, 66.0	58.0, 66.0	
Year of surgery					<0.001 [a]
Median	2009.0	2010.0	2010.0	2010.0	
Q1, Q3	2004.0, 2013.0	2006.0, 2013.0	2006.0, 2013.0	2006.0, 2013.0	
Race, n (%)					<0.001 [b]
Nonblack	786 (77)	860 (74)	901 (68)	620 (49)	
Black	235 (23)	300 (26)	418 (32)	636 (51)	
PSA (ng/ml)					0.002 [a]
Median	6.5	6.1	6.2	6.8	
Q1, Q3	4.7, 9.3	4.7, 8.9	4.8, 9.4	4.9, 10.0	
Clinical stage, n (%)					0.611 [b]
T1	638 (62)	721 (62)	813 (62)	805 (64)	
T2–T4	383 (38)	439 (38)	506 (38)	451 (36)	
Surgery center, n (%)					<0.001 [b]
West LA	127 (12)	153 (13)	181 (14)	188 (15)	
Palo Alto	111 (11)	113 (10)	118 (9)	71 (6)	
San Francisco	54 (5)	54 (5)	59 (4)	40 (3)	
Augusta	139 (14)	194 (17)	268 (20)	337 (27)	
Durham	210 (21)	169 (15)	196 (15)	224 (18)	
San Diego	115 (11)	154 (13)	172 (13)	144 (11)	
Asheville	126 (12)	126 (11)	91 (7)	75 (6)	
Portland	139 (14)	197 (17)	234 (18)	177 (14)	
Preop grade group, n (%)					0.003 [b]
1	421 (41)	410 (35)	461 (35)	409 (33)	
2–3	444 (43)	541 (47)	618 (47)	616 (49)	
4–5	156 (15)	209 (18)	240 (18)	231 (18)	
Percent of biopsy cores with cancer					<0.001 [1a]
Median	33.3	33.3	33.3	33.3	
Q1, Q3	16.7, 50.0	16.7, 50.0	20.8, 50.0	19.0, 53.8	
Tumor volume					0.080 [a]
Median	5.3	6.3	6.4	6.3	
Q1, Q3	2.9, 11.2	3.3, 11.7	3.3, 12.0	3.0, 11.6	
Follow-up					<0.001 [a]
Median	91.9	84.9	80.2	73.8	
Q1, Q3	48.5, 145.9	47.0, 127.7	45.1, 124.3	41.5, 116.7	
CCI at surgery, n (%)					<0.001 [b]
0	490 (48)	518 (45)	549 (42)	466 (37)	
1	246 (24)	297 (26)	342 (26)	339 (27)	
2	122 (12)	144 (12)	177 (13)	168 (13)	
3+	163 (16)	201 (17)	251 (19)	283 (23)	

CCI = Charlson Comorbidity Index; PSA = prostate-specific antigen; Q1 = 25th percentile; Q3 = 75th percentile; RDW = red blood cell distribution width.
[a] Kruskal-Wallis test.
[b] Chi-square test.

ation. There was also a statistical difference among RDW quartiles and the CCI (Table 1).

3.2. Biochemical recurrence

A Kaplan-Meier curve showed that there was no association between BCR and RDW (p = 0.71; Fig. 1). On an unadjusted analysis using Cox proportional hazard models, there was no association between RDW (whether as a continuous variable or by quartiles) and BCR (p = 0.887 and 0.778, respectively). On multivariable adjusted models, there was still no significant association (p = 0.078 and 0.088 for continuous variable and by quartiles, respectively, for model I [based on preoperative characteristics; footnote a in Table 2] and p = 0.759 and 0.472, respectively, for model II [based on pathological findings; footnote b in Table 2]; Table 2).

3.3. Secondary outcomes

Kaplan-Meier curves were analyzed according to RDW as a continuous variable and as quartiles. It showed that the higher the RDW, the worse the survival (p < 0.001; Fig. 2A), but no significant difference was found in PCSM or development of metastasis (p = 0.26 and 0.12, respectively; Fig. 2B and 2C). On unadjusted analysis using Cox proportional hazard models, no association of RDW (whether as a continuous variable or by quartiles) with PCSM (p = 0.699 and 0.980, respectively) and freedom from metastasis (p = 0.360 and 0.352, respectively; Table 2) was detected. On multivariable adjusted models also, no association was identified in case of PCSM (p = 0.711 and 0.890 for model I [adjusting for preoperative variables; footnote a in Table 2] and p = 0.499 and 0.634 for model II [adjusting for operative pathological findings; footnote b in Table 2], respectively; Table 2). Regarding freedom from metastasis, no association was observed on multivariable adjusted models (p = 0.152 and 0.110 for model I [footnote a in Table 2] and p = 0.232 and 0.166 for model II [footnote b in Table 2], respectively; Table 2). Both adjusted and unadjusted models showed that there was a significant correlation between ACM and RDW; patients with high RDW had worse ACM than those with low RDW (p < 0.001; Table 2).

RDW was found to be significantly associated with an increased D'Amico risk on an unadjusted model (p = 0.001 and 0.002 as a continuous variable and by quartiles respectively; Table 3). On multivariable adjusted analysis, this association was maintained when RDW was assessed as a continuous variable (p = 0.021; Table 3) and lost when it was analyzed by quartiles (p = 0.116; Table 3).

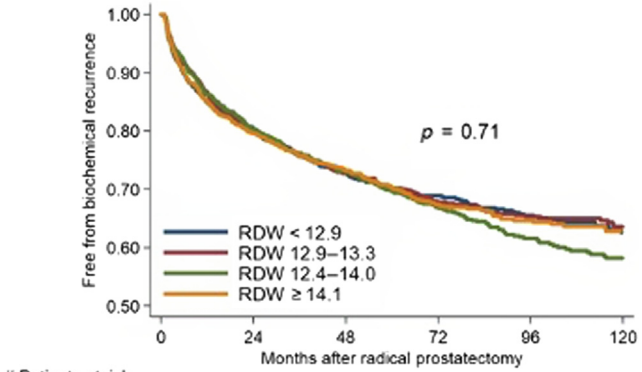

Fig. 1 – Kaplan-Meier curves for biochemical recurrence as a primary outcome, stratified by RDW quartiles. RDW = red blood cell distribution width.

4. Discussion

RDW is a readily available test in the complete blood count assay. Red blood corpuscles typically have a diameter of 6–8 μm, and variation in size is common. RDW assesses size variance between the largest and the smallest red blood cell diameter, and has utility for a number of medical conditions including chronic disease (eg, Crohn's, diabetes, etc.), blood dyscrasias (eg, thalassemia or anemia), heart or liver disease, and cancer. RDW has been investigated in many urological malignancies with conflicting results regarding its prognostic significance. In renal cell carcinoma (RCC), RDW was tested to determine whether it could predict the presence of RCC and its relation to stage and grade [12]. It was found that there is a positive correlation between RDW and clinical stage of RCC, and Fuhrman grade in clear cell type. This may be explained by the role of inflammatory cytokines in RCC and the association with increased RDW values [13,14]. In another study of patients with RCC treated with nephrectomy, RDW was not positively associated with tumor stage or grade, while tumor necrosis and larger tumor size were more often identified in patients. Życzkowski et al [15] found RDW to be an independent prognostic factor of cancer-specific survival (CSS).

In patients with upper tract urothelial carcinoma, it was observed that those with higher RDW had worse overall survival [16]. In a subgroup analysis, this prognostic importance was restricted to localized disease. This positive correlation, however, was not found in CSS [16]. On the contrary, in urothelial carcinoma of the bladder, there were no associations between RDW and tumor stage, tumor size, or grade [17].

There are few contradictory reports about the prognostic value of RDW in prostate cancer. In one study of 62 patients, high RDW was found to be associated with an increased risk of disease progression [10]. In another study of 226 prostate cancer patients, RDW had no significant association with overall or disease-free survival. Apart from older age, higher RDW was not associated with a high risk of progression [18].

In our study of men with localized prostate cancer treated with RP, there was no association between preoperative RDW and BCR, development of metastasis, or PCSM. The possible explanations for the association between malignancies and RDW are not clear. It has been suggested that inflammation and poor nutrition may be causing higher RDW [10] and are also risk factors for cancer development [19]. Regarding genitourinary neoplasms, chronic inflammation can lead to some, but not all, cancers [20,21]. The

Table 2 – Hazard ratios for the association between red blood cell distribution width and risk of prostate cancer outcomes.

	N	Univariable		Multivariable model I [a]		Multivariable model II [b]	
		HR (95% CI)	*p* value [c]	HR (95% CI)	*p* value [c]	HR (95% CI)	*p* value [c]
BCR			0.778		0.088		0.472
RDW Q1	306/1020	Ref.		Ref.		Ref.	
RDW Q2	333/1160	0.97 (0.83–1.14)		0.94 (0.81–1.10)		0.97 (0.83–1.14)	
RDW Q3	406/1319	1.06 (0.91–1.23)		0.99 (0.85–1.15)		0.96 (0.83–1.12)	
RDW Q4	348/1256	1.00 (0.86–1.17)		0.86 (0.73–1.01)		0.94 (0.81–1.10)	
Continuous	1393/4755	1.00 (0.96–1.06)	0.887	0.96 (0.91–1.01)	0.078	0.99 (0.94–1.04)	0.759
Metastasis			0.360		0.110		0.166
RDW Q1	49/1021	Ref.		Ref.		Ref.	
RDW Q2	43/1160	0.83 (0.55–1.26)		0.80 (0.53–1.20)		0.76 (0.50–1.16)	
RDW Q3	37/1319	0.65 (0.42–0.99)		0.58 (0.38–0.90)		0.55 (0.35–0.85)	
RDW Q4	43/1256	0.84 (0.56–1.27)		0.72 (0.47–1.11)		0.75 (0.50–1.14)	
Continuous	172/4756	0.93 (0.81–1.08)	0.352	0.89 (0.77–1.04)	0.152	0.91 (0.78–1.06)	0.232
PCSM			0.980		0.890		0.634
RDW Q1	22/1021	Ref.		Ref.		Ref.	
RDW Q2	19/1160	0.87 (0.47–1.61)		0.77 (0.41–1.44)		0.75 (0.40–1.41)	
RDW Q3	11/1319	0.46 (0.22–0.96)		0.39 (0.19–0.83)		0.35 (0.16–0.75)	
RDW Q4	21/1256	1.05 (0.58–1.91)		0.99 (0.53–1.85)		0.89 (0.48–1.63)	
Continuous	74/4756	0.96 (0.77–1.19)	0.699	0.96 (0.76–1.21)	0.711	0.92 (0.73–1.17)	0.499
ACM			<0.001		<0.001		<0.001
RDW Q1	163/1021	Ref.		Ref.		Ref.	
RDW Q2	148/1160	0.97 (0.78–1.21)		1.00 (0.80–1.26)		0.97 (0.77–1.22)	
RDW Q3	198/1319	1.20 (0.97–1.48)		1.21 (0.98–1.50)		1.16 (0.94–1.44)	
RDW Q4	243/1256	1.68 (1.38–2.06)		1.64 (1.33–2.01)		1.65 (1.35–2.03)	
Continuous	752/4756	1.22 (1.15–1.28)	<0.001	1.21 (1.15–1.28)	<0.001	1.21 (1.15–1.27)	<0.001

ACM = all-cause mortality; BCR = biochemical recurrence; CI = confidence interval; HR = hazard ratio; PCSM = prostate cancer–specific mortality; PSA = prostate-specific antigen; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile; RDW = red blood cell distribution width; Ref. = reference.

[a] Model I adjusted for age, race, PSA, clinical stage, year of surgery, surgical center, biopsy grade group, Charlson Comorbidity score, and percent positive cores.

[b] Model II adjusted for pathological grade group, extracapsular extension, seminal vesicle invasion, lymph node metastasis, and positive surgical margins.

[c] The *p* values for trend were calculated by assigning each group's median RDW value to patients in that group and treating RDW group as continuous.

discrepancy between the association of RDW with high risk factors in prostate cancer and other malignancies can be explained by the different function/role of RDW and inflammation among the various types of cancers. Additionally, the variation in study design, sample size, and power of the study may explain the difference in outcomes among these studies. Our study was large and diverse, including 4756 patients of different ethnic backgrounds, and thus provides strong evidence that in early-stage localized disease, RDW does not predict outcomes after RP.

The current study also demonstrated that preoperative RDW was positively correlated with ACM in patients treated with RP for localized prostate cancer. This was consistent with the observations found in many malignancies including upper tract urothelial cancer [16,22]. RDW has been observed to be associated with and increased risk of mortality, particularly with cardiovascular disease [22,23]. Although the mechanism of action remains unknown, this observation may be explained by chronic inflammation, poor nutrition, and anomalous erythropoiesis that can cause high RDW values [24–26]. Chronic inflammation and nutritional deficiency can accompany the malignant state, particularly in advanced cancers. Our study included 5740 patients who were treated with RP for localized prostate cancer, with 4756 men having RDW information in the study cohort. This gives our study the power over the previous studies [10,11] and highlights the need for large-sample, diverse, multicenter studies in oncology.

The CCI is indexed to predict the risk of death within 1 yr of hospitalization for patients with specific comorbid conditions [27,28]. It is a method of classifying the comorbidities of patients based on International Classification of Diseases. CCI was found to be inversely correlated with overall survival in patients with localized prostate cancer [29]. In our study, RDW was significantly associated with ACM independent of CCI in a multivariable logistic regression model. This indicates that RDW is considered an independent predictor of ACM.

While we tested the prognostic significance of RDW in patients with localized prostate cancer, RDW has also been investigated in castrate-resistant prostate cancer [30]. It has been suggested that RDW can be a predictor of treatment response and survival in patients with castration-resistant prostate cancer taking androgen receptor axis–targeted agents: the higher the RDW, the worse the treatment response and survival. Although the number of patients in this study who progressed to PCSM was limited, it draws attention to the possible prognostic significance of RDW in different stages of prostate cancer, particularly with advanced disease, and thus further studies in late-stage disease may be warranted.

This study has many strengths supporting its conclusions, including a large patient cohort, different ethnic groups, its multicenter nature with equal access to health care, and long-term follow-up. Limitations to our study include its retrospective nature that makes it challenging to determine whether RDW is causally related to the process of prostate cancer oncogenesis. Additionally, this study lacks granularity of data regarding measurable cytokines and other inflammatory biomarkers. The cohort studied comprised men with localized prostate cancer treated with surgery as we did not query men with more advanced or

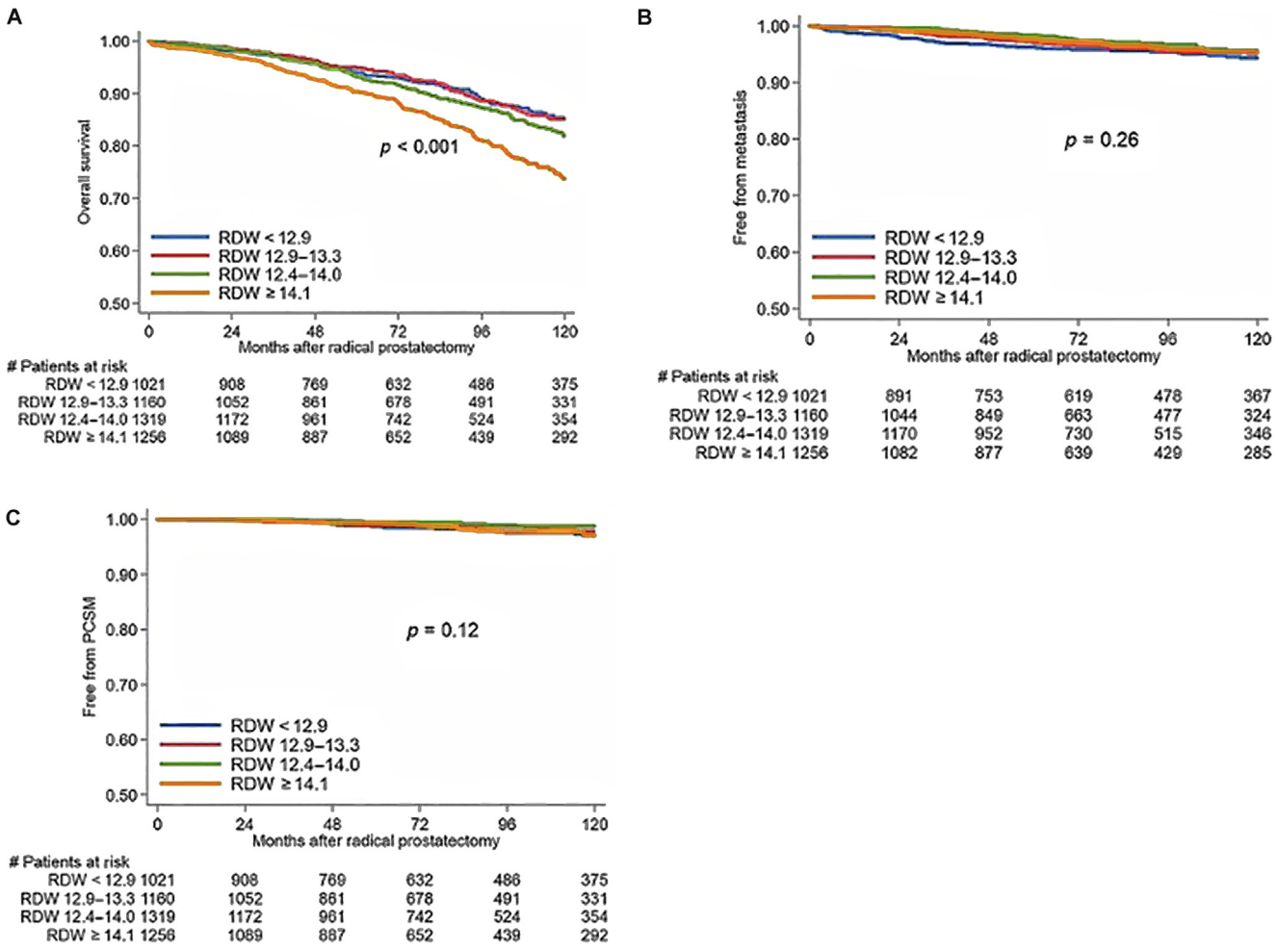

Fig. 2 – Kaplan-Meier curves for secondary outcomes: (A) ACM outcome, stratified by RDW quartiles; (B) freedom-from-metastasis outcome, stratified by RDW quartiles; and (C) PCSM outcome, stratified by RDW. ACM = all-cause mortality; PCSM = prostate cancer–specific mortality; RDW = red blood cell distribution width.

Table 3 – Odds ratios for the association between red blood cell distribution width and D'Amico risk (N = 4756).

	N	D'Amico risk (*n*)			Univariable		Multivariable	
		Low	Intermediate	High	OR (95% CI)	*p* value	OR (95% CI)	*p* value
RDW						0.002		0.116
RDW Q1	1021	327	447	247	Ref.		Ref.	
RDW Q2	1160	325	539	296	1.15 (0.98–1.35)		1.09 (0.93–1.27)	
RDW Q3	1319	350	610	359	1.25 (1.07–1.45)		1.15 (0.99–1.34)	
RDW Q4	1256	304	607	345	1.33 (1.14–1.55)		1.21 (1.03–1.42)	
Continuous	4756	1306	2203	1247	1.08 (1.03–1.14)	0.001	1.06 (1.01–1.11)	0.021

CI = confidence interval; OR = odds ratio; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile; RDW = red blood cell distribution width; Ref. = reference.
Multivariable model adjusted for age, race, surgical center, and Charlson Comorbidity Index.

known metastatic cancer. Finally, we were not able to corroborate overall health and inflammation due to heart disease or other factors that might impact the ACM.

5. Conclusions

Preoperative RDW was not associated with adverse prostate cancer outcomes in men treated with RP, including BCR, development of metastasis, and PCSM. However, this study showed that there was a significant correlation between ACM and RDW. Future studies are required to confirm whether RDW predicts overall survival in varying stages of prostate cancer particularly late-stage disease and whether this information can help optimize the overall health care plan of our patients. A large number multicenter studies are of high importance and have an impact in the field of urological cancer as these provide more accurate mean values and a smaller margin of error.

***Author contributions*:** Thomas J. Polascik had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Orabi, Polascik.
Acquisition of data: All authors.
Analysis and interpretation of data: Orabi, Howard, Polascik, Freedland.
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