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Research article

The nonlinear association between red blood cell distribution width (RDW) and bortezomib-related peripheral neurotoxicity (PN): A retrospective cohort study

Yi Ren [a,b], Qian Ding [b], Zan Rui-Si Ding [b], Xing Yang [a,*]

[a] Guizhou Medical University, # 9 Beijing Road, 550004, Gui Yang City, Gui Zhou Province, China
[b] Department of Haematology, Guizhou Provincial People's Hospital, 83#, Zhong Shan East Road, 550004, Gui Yang City, Gui Zhou Province, China

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ABSTRACT

Background: Previous evidence on the association of red blood cell distribution width (RDW) with bortezomib-induced peripheral neuropathy (BIPN) is limited. As a result, in this single-center retrospective cohort analysis, the link between RDW and BIPN was investigated.
Methods: This study4 comprised 376 patients with primary multiple myeloma (MM) who attended the Department of Haematology at Guizhou Provincial People's Hospital between 2013 and 2021. RDW and the occurrence of BIPN were the exposure and outcome variables, respectively. Demographic characteristics, pharmacological agents, co-morbidities, and MM-related indicators were all included as covariates. To investigate the relationship between RDW and BIPN, binary logistic regression and two-piecewise linear regression were utilized.
Results: The relationship between RDW and BIPN was found to be non-linear. RDW was not significantly associated with the risk of BIPN (odds ratio (OR): 0.99; 95% confidence interval (CI): 0.95 to 1.02; p-value: 0.4810) to the left of the inflection point (RDW = 72.3); to the right of the inflection point, each 1 ft increase in RDW was associated with an 7% increase in the risk of BIPN (OR: 1.07; 95% CI: 1.01 to 1.15; p-value: 0.046).
Conclusion: The relationship between RDW and the risk of BIPN demonstrated a threshold effect, with RDW exceeding 72.3 fl, indicating a relatively significant risk of BIPN.

1. Introduction

Multiple myeloma is a rare cancer that affects plasma cells in the bone marrow. It is more common in older males, and black people in the US have a higher incidence rate than white people. From 2004 to 2016, the mortality rate of lymphoma and myeloma in China increased by 4.5% each year [1]. Bortezomib-containing chemotherapy regimens are now the standard of treatment for multiple myeloma patients [2]. The most prevalent or serious side effect of bortezomib is peripheral neurotoxicity [3]. This bortezomib-induced peripheral neurotoxicity (BIPN) can result in dose reduction and treatment discontinuation [4]. Previous studies have revealed that BIPN occurs most frequently during the first 5 cycles of bortezomib treatment, with an incidence of 8.4–85% (median 37%). 1–33.2% (median 8%) of the subjects reported neuropathy of grade C2 or above [5].

Red blood cell width distribution width (RDW) is a traditional biomarker of red blood cell volume variability and one of the most

* Corresponding author.
E-mail address: doctor_yangxing@163.com (X. Yang).

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important indicators of red blood cell homeostasis [6]. RDW is frequently utilized in clinical settings to distinguish various hematologic disorders. Recent studies have discovered that RDW is closely linked to the prognosis of a variety of diseases, including cancer [7–9] (lung, prostate, colorectal, esophageal, etc.), cardiovascular disease [10,11], and immunological connective tissue diseases (rheumatoid arthritis [12], dermatomyositis [13], and systemic lupus erythematosus stain [14]). Research around RDW may become more numerous in the future due to the benefits of simple, inexpensive, rapid, and easily available tests.

Previous studies have suggested that high red blood cell distribution width (RDW) levels are associated with poor prognosis in multiple myeloma patients [15]. However, there is limited literature on the relationship between pretreatment RDW and bortezomib-induced peripheral neuropathy (BIPN). Considering bortezomib's ability to inhibit erythropoiesis and elevate RDW [16], which has been linked to neurological disorders, we hypothesize that patients with multiple myeloma who receive bortezomib and have high RDW levels may be at a higher risk of developing BIPN. Furthermore, the neurological damage induced by bortezomib's oxidative stress and inflammatory responses [17] may exacerbate this risk. As such, we hypothesize that elevated RDW levels may be associated with increased risk of BIPN in patients undergoing bortezomib treatment, based on the aforementioned factors [18]. To investigate this further, we conducted a retrospective cohort study to examine the relationship between baseline RDW levels and the occurrence of BIPN. As bortezomib has become the primary treatment for MM in China and is incorporated into Chinese MM clinical guidelines due to the country's vast population [19–21], identifying a correlation between RDW and BIPN may provide valuable clinical evidence for risk stratification and the response to BIPN therapy. Additionally, exploring the correlation between RDW and Bortezomib-induced peripheral neuropathy may offer valuable insights and strategies for predicting and preventing adverse effects of Bortezomib.

2. Patients and methods

2.1. Study population

This is a retrospective cohort study. We retrieved patient data from the hospital's electronic medical record system. All individuals with a primary diagnosis of multiple myeloma who visited the Department of Haematology at Guizhou Provincial People's Hospital from March 2013 to October 2021 were eligible for the study. Data collection for these patients is non-selective and consecutive. We collected data from the hospital's HIS system database manually entered into an electronic data capture system (EDC). The following were the inclusion criteria for this study: (1) Patients with a primary diagnosis of multiple myeloma; (2) No signs or symptoms of peripheral neuropathy prior to chemotherapy; and (3) Adherence to a 4-cycle bortezomib-containing chemotherapy plan. The following patients were excluded from this study: (1) those whose chemotherapy regimen did not include bortezomib; (2) those who were administered with other proteasome inhibitors; and (3) those who were transferred to the institution or died during treatment. The hospital ethics committee approved the study. No informed consent was needed because patient information was obtained in a retrospective cohort and was anonymized and de-identified.

2.2. Variable

2.2.1. Outcome variable

In this study, the outcome variable was BIPN, which was recorded as a dichotomous variable. The occurrence of BIPN grade 2 or higher was recorded as 1 in the database, whereas those below grade 2 were recorded as 0. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) was used to assess BIPN. The scale grades sensory symptoms from 0 (none) to 4 (disabling). The NCI-CTCAE scale is used to assess patients at the start and end of each cycle of chemotherapy by fully skilled nursing staff.

2.2.2. Exposure variables

This study's exposure variable of interest was pre-treatment (baseline) RDW-SD (reference value: 35.0–56.0 fl). RDW was included in a routine blood test conducted by the hospital's clinical center. At the time of the routine blood test, the testers had no idea if the subject had BIPN or if the results would be used in a retrospective cohort research.

2.2.3. Covariates

In this study, covariates included age, gender, smoking and drinking status, diabetic burden status, DS stage, RISS stage, inclusion of vincristine or immunomodulators (thalidomide + lenalidomide) in the chemotherapy regimen, body mass index and immunophenotyping for MM, and beta2-microglobulin. Data on all covariates were collected at baseline. The selection of covariates was justified primarily by our previous work, clinical experience, and previous literature [5,22,23] that also used BIPN as an outcome variable. It is worth noting that the total bortezomib dose was not used as a covariate. This is because, in clinical practice, when patients have grade 2 or higher BIPN, we reduce the dose and, if necessary, transition to a bortezomib-free chemotherapeutic regimen (although this did not occur in this study). As a result, the inverse of BIPN influences the overall dose of bortezomib.

2.3. Description of chemotherapy regimen

In this research, all patients underwent bortezomib-containing chemotherapy. Bortezomib dosage was all standardized to a 21-day chemotherapy cycle: a single hypodermic injection of 1.3 mg/m^2 was administered on days 1, 4, 8, and 11 of each chemotherapy cycle,

followed by a 10-day rest (days 12–21). When grade 3 non-haematological toxicity or any grade 4 haematological toxicity (except BIPN) occurs, use is temporarily halted and then resumed once symptoms have improved, but the dose is lowered to 1.0–1.1 mg/m^2. Other chemotherapeutic agents in the regimen are primarily based on standardised protocols developed in the "Expert Consensus on Integrative Medicine in the Treatment of Multiple Myeloma (2019)". These chemotherapeutic medicines were designed as dummy variables (use or not) and served as covariates for adjustment and stratified analysis.

2.4. Statistical analysis

In this study, continuous variables are presented as mean ± standard deviation (Gaussian distribution) or median (minimum, maximum) (skewed distribution), while categorical variables are presented as rates. We trisected RDW (tertile) and examined trends in baseline characteristics across different RDW subgroups. To evaluate the differences of continuous variables across RDW groups, one-way ANOVA (Gaussian distribution) or Kruskal Whallis H (skewed distribution) tests were employed; chi-square tests were used to assess the differences of categorical variable distribution across RDW groups. Our primary goals in this study were as follows: (1) Is there a independent relationship between RDW and BIPN? (2) Is this association linear or non-linear? (3) If non-linear, how will we accurately understand this non-linear association? As a result, we used a multivariate binary logistic regression model to investigate whether RDW was independently associated with BIPN after controlling for covariates, and we presented odds ratio and 95% confidence intervals. Second, because the binary logistic regression model is ineffective at dealing with non-linear associations, we used a smoothing curve (penalty function method) along with a generalized additive model (GAM) to determine whether RDW is non-linearly associated with BIPN, and we calculated the inflection point using a recursive algorithm and bootstrapping. In contrast to the binary logistic regression model, the GAM fit a non-linear relationship between RDW and BIPN using a non-linear smoothing term (Logit (BIPN) = aX1 + S(RDW)). The implementation is based on the mgcv package's gam() function. The two-piecewise linear model was then utilized to construct a segmented linear model on both sides of the inflection point, and the odds ratio and 95% confidence intervals were reported.

2.5. Sensitivity analysis

We carried out the following sensitivity analyses to strengthen the robustness of our findings: (1) We presented the unadjusted model, the adjust 1 model (which only adjusted for gender and age), and the adjust 2 model (which adjusted for all covariates), and we observed whether OR values are reliable across the various adjustment strategies. (2) We converted RDW from a continuous to a categorical variable (according to tertile) and computed P for trend. The goal was to check if the results when RDW was a continuous variable matched those when RDW was a categorical variable. (3) We additionally present the GAM model, which accounts for non-linear correlations between continuous variables in the covariates used for adjustment.

2.6. Missing data addressing

We show the number of cases and the proportion of missing data for each variable (supplementary tab. 1). Multiple imputation was

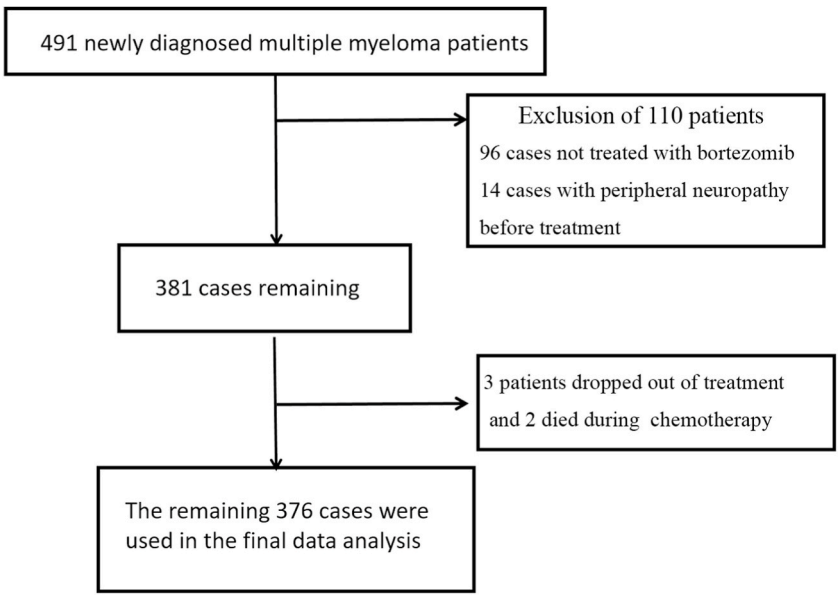

Fig. 1. Shows the flow chart of the study. The flowchart is intended to depict the patient screening at the time of data collection.

not utilized for missing data because the proportion missing was less than 5%.

3. Results

3.1. Description of the patient screening process

Out of the 491 patients initially included in the study, 96 were excluded due to financial difficulties preventing them from receiving a bortezomib-containing chemotherapy regimen; 14 were excluded because they had symptoms of peripheral neuropathy prior to treatment, leaving 381 patients. Of these 381 patients, 3 patients did not complete treatment; 2 patients died during chemotherapy, leaving 376 patients for the final data analysis. Details are shown in the flow chart (Fig. 1).

3.2. Patient characteristics at baseline

Table 1 shows the baseline characteristics of the patients. We divided the RDW into three sub-groups according to tertile(low, middle, high). The patients' mean age was 61.02 ± 11.14 years, the male percentage was 53.99% (203/376), and the incidence of BIPN was 13.82% (68/376). We found no significant statistical differences among RDW subgroups in the distribution of gender, smoking and drinking status, diabetes burden status, body mass index, vincristine and immunomodulators use status (all P values > 0.05). The middle and high RDW groups were older, had higher beta2-microglobulin, a higher number of patients with high D-S and RISS staging, and a higher proportion of patients with IgA type than the low RDW group.

3.3. The findings of univariate and multivariate analyses

There was no significant connection between RDW and risk of BIPN in the unadjusted model (Odds ratio: 1.00, 95% CI: 0.98 to

Table 1
Baseline characteristics of involved patients.

Red blood cell distribution width	Low (30.40–48.20 fl)	Middle (48.30–56.90 fl)	High (57.00–108.80 fl)	P-value
N	132	128	116	
Age, mean ± sd, year	58.24 ± 11.31	62.46 ± 10.59	62.97 ± 11.46	0.001
beta2-microglobulin, mean ± sd, (mg/l)	8.25 ± 10.47	10.04 ± 8.44	12.60 ± 14.48	0.015
Sex, n (%)				0.268
Female	60 (45.45%)	53 (41.41%)	60 (51.72%)	
Male	72 (54.55%)	75 (58.59%)	56 (48.28%)	
Smoking status, n (%)				0.333
Current smoker	67 (50.76%)	58 (45.67%)	64 (55.17%)	
Non-smoker	65 (49.24%)	69 (54.33%)	52 (44.83%)	
Drinking status, n (%)				0.820
No	61 (46.21%)	55 (42.97%)	54 (46.55%)	
Yes	71 (53.79%)	73 (57.03%)	62 (53.45%)	
Diabetes duration, n (%)				0.675
No	125 (94.70%)	116 (92.06%)	109 (93.97%)	
Yes	7 (5.30%)	10 (7.94%)	7 (6.03%)	
DS-Staging, n (%)				0.047
I	4 (3.03%)	2 (1.56%)	0 (0.00%)	
II	21 (15.91%)	12 (9.38%)	8 (6.90%)	
III	107 (81.06%)	114 (89.06%)	108 (93.10%)	
R–ISS staging, n (%)				<0.001
I	33 (25.00%)	23 (17.97%)	4 (3.48%)	
II	65 (49.24%)	65 (50.78%)	67 (58.26%)	
III	34 (25.76%)	40 (31.25%)	44 (38.26%)	
Vincristine use, n (%)				0.866
No	127 (96.21%)	122 (95.31%)	110 (94.83%)	
Yes	5 (3.79%)	6 (4.69%)	6 (5.17%)	
Immunomodulators use, n (%)				0.795
No	87 (65.91%)	88 (68.50%)	81 (69.83%)	
Yes	45 (34.09%)	40 (31.50%)	35 (30.17%)	
Peripheral neurotoxicity, n (%)				0.841
No	109 (82.58%)	106 (82.81%)	93 (80.17%)	
Yes	23 (17.42%)	22 (17.19%)	23 (19.83%)	
Body mass index, n (%)				0.473
Low + normal	47 (35.61%)	45 (35.16%)	50 (43.10%)	
Overweight	62 (46.97%)	67 (52.34%)	50 (43.10%)	
Obesity	23 (17.42%)	16 (12.50%)	16 (13.79%)	
Immunophenotypes, n (%)				0.006
IgG type	67 (50.76%)	75 (59.06%)	57 (50.00%)	
IgA type	23 (17.42%)	29 (22.83%)	37 (32.46%)	
Other (Light-chain + IgM + IgD type)	42 (31.82%)	23 (18.11%)	20 (17.54%)	

1.03, p-value: 0.7815). Even after controlling for demographic characteristics (adjusted-I model), there was no substantial relationship between RDW and risk of BIPN (Odds ratio: 1.00, 95% CI: 0.98 to 1.03, p-value: 0.8802). The adjusted-II model achieves the same results. We found no significant association between RDW and BIPN after controlling for the variables listed in Table 1 (odds ratio: 1.01, 95% CI: 0.98 to 1.03, p-value: 0.6901). We converted RDW into a categorical variable based on tertiles for sensitivity analysis and calculated P for trend. The results demonstrated that when RDW was utilized as a continuous variable, the findings were in line with when RDW was used as a categorical variable (Table 2). The results of the GAM model indicate that even when adjusting for smooth terms of continuous variables in covariates, there is no significant change observed in the OR value of RDW and BIPN.

3.4. The non-linearity addressing

The researchers used smoothed curve fitting and a generalized additive model to investigate the non-linear relationship between RDW and risk of BIPN. Our findings (Fig. 2) show that after controlling for the covariates listed in Table 1, the relationship between RDW and BIPN seems to have a threshold effect (Table 3). We calculate an inflection point for RDW of 72.3 (95% CI: 61.9 to 76.7) using the recursive algorithm. Using a two-piecewise linear model, we observed that there was no connection between RDW and risk of BIPN to the left of the inflection point (OR: 0.99; 95% CI: 0.95 to 1.02; p-value: 0.4810). In contrast to the right of the inflection point, each 1 fL increase in RDW is associated with an incremental risk of BIPN of 8% (OR: 1.07; 95% CI: 1.01 to 1.15; p-value: 0.046) (Table 3). We compared the two-piecewise linear model to the binary logistic regression model for sensitivity analysis. The log-likelihood ratio test revealed that the two-piecewise linear model fitted the relationship between RDW and BIPN risk better than the standard binary logistic regression model. In addition, we used the use of immunomodulators as a stratification factor to fit the curves in the population with/without the use of immunomodulators, respectively. The results of the sensitivity analysis (Supplemental Fig. 1) showed that the association between RDW and PN is linear and attenuated in the population using immunomodulators. In contrast, the non-linear association remained in patients who did not use immunomodulation. This suggests that our findings are more appropriate for application to patients who are not using immunomodulators.

4. Discussion

This single-center retrospective cohort study examined the link between RDW and BIPN in individuals with diagnosed MM. We observed that the relationship between RDW and BIPN risk was non-linear and had a threshold impact by analyzing clinical data from 376 individuals. The results suggest that RDW is only associated with a higher risk of BIPN when it exceeds 72.3 fL.

Although we only discovered a link between RDW and BIPN in clinical data and did not investigate the mechanisms involved, the relationship is available for interpretation based on the literature. We discovered a common relationship between RDW and BIPN, which is oxidative stress and inflammation [3]. First, oxidative stress causes red blood cell death and, as a compensating response, increases the body's haematopoietic function. As a result of compensatory proliferation, erythrocyte volume increases, as demonstrated by an increase in RDW [24]. Bortezomib, on the other hand, causes aberrant mitochondrial morphology in the peripheral nervous system (PNS) [25–27]. Bortezomib has been demonstrated in studies to drastically lower mitochondrial respiration and adenosine triphosphate (ATP) levels in cells [3,28]. Furthermore, manganese superoxide dismutase is an important mitochondrial antioxidant enzyme, and bortezomib over-nitrates it and reduces its activity; thus, treatment with the reactive oxygen species (ROS) scavenger phenyl-N-tert-butylnitrone may be effective in reducing bortezomib-induced mechanical nociceptive hypersensitivity [29]. Another link between RDW and BIPN is inflammation. RDW can signify the degree of inflammation in the body [24]. It is significantly increased in several inflammatory disorders (sepsis, chronic obstructive pulmonary disease, inflammatory bowel disease, primary dry syndrome, polymyositis, etc.) [24,30]. Similarly, inflammation plays a significant role in the development of BIPN [31]. In animal experiments, bortezomib has been shown to enhance the expression of inflammatory cytokines and chemokines, most notably tumor

Table 2
The findings of univariate and multivariable analyses.

	Non-adjusted model (OR, 95%CI, P value)	Adjust I model (OR, 95%CI, P value)	Adjust II model (OR, 95%CI, P value)	GAM (OR, 95%CI, P value)
RDW-SD	1.00 (0.98, 1.03) 0.7815	1.00 (0.98, 1.03) 0.8802	1.01 (0.98, 1.03) 0.6901	1.01 (0.98, 1.04) 0.4952
RDW grouped by tertile				
Low	Reference	Reference	Reference	
Middle	0.98 (0.52, 1.87) 0.9598	0.84 (0.43, 1.62) 0.5964	0.91 (0.44, 1.90) 0.8034	
Higth	1.17 (0.62, 2.22) 0.6273	1.06 (0.55, 2.05) 0.8660	1.14 (0.53, 2.46) 0.7389	
P for trend	1.08 (0.78, 1.50) 0.6327	1.03 (0.73, 1.44) 0.8665	1.07 (0.72, 1.57) 0.7465	

RDW: Red blood cell distribution width.
95%CI: 95% confidence interval.
OR: odds ratio.
Non-adjusted model: No covariates were adjusted for.
Adjust I model: we only adjusted for age and sex.
Adjust II model: we adjusted for covariates presented in Table 1.
GAM: We adjusted for the continuous variables in the covariates using smooth terms.

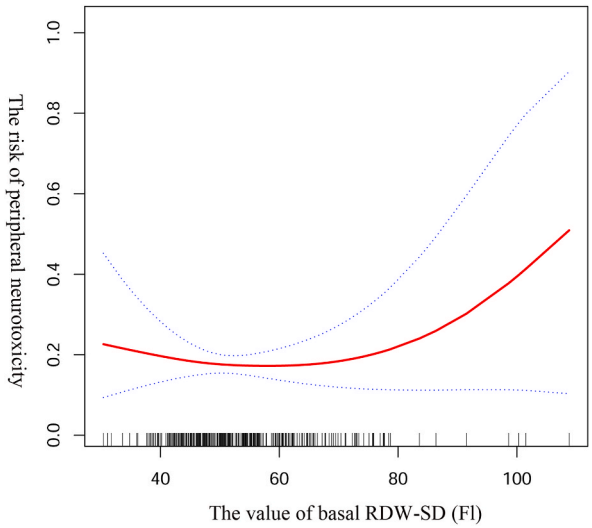

Fig. 2. Shows the smoothed curve fit. The horizontal coordinate is the value of the baseline RDW; the vertical coordinate is the risk of BIPN. The two dashed curves represent confidence intervals.

Table 3
Nonlinearity addressing between RDW and the risk of peripheral neurotoxicity.

	OR, 95%CI, P value
Fitting model by standard logistic regression model	1.01 (0.98, 1.03) 0.6901
Fitting model by two-piecewise linear model	
Inflection point of RDW	72.3 (95%CI:61.9 to 76.7)
<72.3 fl	0.99 (0.95, 1.02) 0.4810
≥.99 (fl	1.07 (1.01, 1.15) 0.0313
P for log likely ratio test	0.046

Our covariate adjustment strategy is similar to that used in the Adjust II model.

necrosis factor alpha (TNF-α), CC chemokine ligand 2 (CCL2), interleukin-6 (IL-6), and prokineticin-2 [32–35]. Furthermore, bortezomib causes direct damage to Schwann cells and dorsal root ganglion neurons, as well as increased ion channel sensitivity and significant macrophage infiltration in the spinal cord, all of which contribute to the advancement of neuropathic pain [31]. Therefore, based on the mechanisms described above, it is plausible that elevated RDW is associated with a high risk of BIPN. Of course, we must admit that diabetes, in addition to bortezomib, can cause peripheral neuropathy. Similarly, the chemotherapy medicines immunomodulators and vincristine are neurotoxic. As a result, we used standard binary logistic regression models and two-piece linear models for the confounders to tightly control for confounding of the results by the important confounders of diabetes load status, immunomodulators, and vincristine.

To the best of our knowledge, this is the first investigation to describe a non-linear relationship between RDW and the risk of BIPN in a Chinese population, and a recursive algorithm was used to precisely find the inflection point (72.3 fl, 95% CI:62.3 to 77). Only after this inflection point will we be able to see that a high RDW is strongly associated with an increased likelihood of developing BIPN. This gives us some helpful experience and data for better monitoring toxicities during bortezomib chemotherapy. However, it is important to note that we have just discovered a relationship and that a significant number of clinical trials are required to support this as a "specific marker."

The study's primary strengths are that (1) more appropriate, advanced algorithms and sensitivity analyses improve the robustness of our findings and better reflect the solid relationship between RDW and BIPN risk. (2) In this study, there are some important confounding factors that can interfere with the connection between RDW and BIPN. However, we used a rigorous adjustment strategy to control for these confounding factors. (3) This was a retrospective cohort research, RDW testers had no idea that their data would be used in future clinical investigations, and the status of BIPN was unclear at the time of testing. As a result, the data are more objective, and the possibility of observational bias is reduced. (4) Retrospective cohort studies are prone to recall bias, which is an inherent drawback. However, in this study, all information was objectively recorded in the case system, which minimizes the possibility of recall bias.

The following are the study's limitations: (1) Because our study sample only included patients getting bortezomib-containing chemotherapy regimens, our findings do not apply to patients receiving other types of proteasome inhibitors. (2) Because this was an observational study, confounding was unavoidable; however, we rigorously adjusted for confounders and assessed the robustness of the results using sensitivity analyses; (3) due to the nature of observational studies, we could only observe associations, not causality;

and (4) we could only adjust for measurable confounders, not non-measurable ones. Therefore, future validation of our findings from diverse ethnic, regional, and institutional settings is necessary; (5) theoretically, RDW-CV is considered more sensitive and accurate for clinical diagnosis and monitoring than RDW-SD because it eliminates the impact of hemoglobin concentration changes on erythrocyte volume variation. However, in this particular study, RDW-SD was the only available blood test at our institution and was thus the only measurement used as an exposure variable. As a result, we were unable to utilize RDW-CV in our analysis. It is important to note, however, that despite the limitation posed by the availability of only RDW-SD, our study still provides valuable insights into the association between RDW and bortezomib-induced peripheral neuropathy; (6) furthermore, the single-center design constrained the generalizability and external validity of our study.

In conclusion, By analysing data from a retrospective cohort, we identified a non-linear association between RDW and BIPN risk. The non-linear association showed a threshold effect: when RDW exceeded 72.3 fL, an increasing value of RDW was associated with a high risk of BIPN occurrence.

Author contribution statement

Yi Ren: Performed the experiments; Wrote the paper.
Qian Ding; Rui-Zan Si Ding: Performed the experiments; Contributed reagents, materials, analysis tools or data.
Xing Yang: Conceived and designed the experiments; Analyzed and interpreted the data.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e15994.

Abbreviations

RDW	red blood cell distribution width
BIPN	bortezomib-induced peripheral neuropathy
MM	multiple myeloma
OR	odds ratio
CI	confidence interval
NCI-CTCAE	The National Cancer Institute Common Terminology Criteria for Adverse Events
PNS	peripheral nervous system\
ATP	adenosine triphosphate
ROS	reactive oxygen species
TNF-α	tumor necrosis factor alpha
CCL2	CC chemokine ligand 2
Interleukin-6	IL-6

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