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Red blood cell distribution width and renal cell carcinoma: A comparative analysis of peer-reviewed studies

Dear editors

We read the article entitled "Preoperative red blood cell distribution width as an independent prognostic factor in metastatic renal cell carcinoma" by Z. Wei et al, which has recently been published in *Translational Oncology* [1]. We thank Wei and colleagues for their contribution to the literature exploring the potential use of the red blood cell distribution width (RDW) as a biomarker in renal cell carcinoma (RCC). We have written this letter to add (1) additional comparative data regarding the utility of the RDW in RCC derived from previous studies reported in the peer-review medical literature and (2) technical comments regarding the practical utilization and limitations of the RDW that would be of interest to the readership of *Translational Oncology* who are considering the use of the RDW in their clinical practice.

Since we used publicly available data, our work did not require ethical board approval. A search was conducted using Medline (PubMed interface), Scopus, and Web of Science for the keywords "renal cell carcinoma" AND "red blood cell distribution width" OR "red cell distribution width" OR "RDW" without restrictions. The search date was July 25, 2022. We then screened titles and abstracts, and the full text of all potentially relevant articles was obtained. After we identified all relevant studies, we reviewed the reference lists from each paper for additional potentially relevant studies and we searched the PubMed and Google Scholar databases for citations of each paper to identify additional eligible articles.

Our search identified seven studies [1–7] (Table 1), which were conducted in Turkey ($n = 3$), China ($n = 2$), Singapore ($n = 1$), and Poland ($n = 1$) and were published between 2014–2022. The design of the studies was retrospective cohort ($n = 6$) or case-control ($n = 1$), with sample sizes ranging from to 103–687 patients. These studies made claims regarding the potential use for RDW in (1) distinguishing RCC from benign renal lesions (renal cysts) [6]; (2) predicting pathologic features of the tumor (e.g. grade, tumor size, stage) [3–7]; and (3) predicting clinical behavior, including progression-free survival, overall survival, cancer-specific survival) [1,2,5,7]. The RDW cutoff values for these studies ranged from 13.1–15.65%. Although differences in study design, including the choice to include all RCC patients or to restrict a study to patients with metastatic or nonmetastatic disease, almost certainly contributed to the variability of the cutoff values, the potential role of preanalytical and analytical phase biases in the RDW, which were not reported in any of these studies, may also be a factor.

The RDW is reported by all blood analyzers in clinical use as the standard deviation (RDW-SD) or coefficient of variability (RDW-CV) of the red blood cell histogram. The RDW may be biased by several preanalytical variables including time between phlebotomy and analysis, storage temperature, tube type, and transport conditions (e.g. tube transport) [8]. Moreover, since an internationally recognized standard for the RDW does not exist, there is a lack of standardization of the RDW among the different instrumentation manufacturers [9]. The biases introduced by these variables may be sufficient to skew individual results and may be a concern for patient samples with borderline elevated

Table 1
Characteristics of studies analyzing RDW in RCC.

Study (Ref number)	Year	Country	Study Design	RCC sample size and special features	Control group(s), size and clinical features	Age (y, mean and range)	Major finding
Aktepe (2)	2021	Turkey	Retrospective, cohort	104, metastatic disease	none	58 (52–64)	RDW > 15.4% associated with lower OS
Arda (3)	2018	Turkey	Retrospective, cohort	103	none	NR	RDW not associated with FG or tumor size
Kisa (4)	2019	Turkey	Retrospective, cohort	283	none	61 (25–89)	RDW > 15.65% associated with high FG; RDW > 14.3 associated with high stage
Lee (5)	2020	Singapore	Retrospective, cohort	687, nonmetastatic CC RCC	none	58.3 ± 11.7	RDW ≥ 14.3% associated with high FG, tumor size, no association with CSS
Wang (6)	2014	China	Retrospective, case-control	318	238, renal cyst	56.83 (13–83)	High RDW associated with RCC compared to controls; RDW > 13.15% associated with high stage
Wei (1)	2022	China	Retrospective, cohort	230, metastatic disease	none	50 (low RDW), 61 (high RDW)	RDW > 13.1% associated with reduced PFS and OS
Zyczkowski (7)	2017	Poland	Retrospective, cohort	434	none	62 (54–69)	RDW ≥ 13.9% associated with lower CSS, larger tumor size

Abbreviations: RDW - red blood cell distribution width; RCC - renal cell carcinoma; y – years; Ref – reference; OS - overall survival; NR – not reported; FG - Fuhrman grade; CC - clear cell ; CSS - cancer-specific survival; PFS - progression-free survival.

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RDWs. In addition, studies with a retrospective design that collected data over a long period from one or more sites may be prone to these confounders. For these reasons, we would recommend that studies reporting the use of complete blood cell count-derived analytes, such as the RDW, report these potential preanalytical and analytical phase variables to (1) indicate that the authors attempted to minimize the impact of these potential sources of bias and (2) allow readers to determine the degree to which the findings could be implemented in their clinical environment.

Again, we thank Z. Wei et al. for their contribution to the literature and hope that these additional comments provide useful context to the readership of *Translational Oncology* who are interested in the clinical application of the RDW. We would welcome a response from the authors, which would give them an opportunity to provide the technical details of their study, in the interest of greater transparency.

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John L Frater: Conceptualization, Writing – original draft. **M Yadira Hurley:** Writing – review & editing.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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John L Frater[a,*], M Yadira Hurley[b]

[a] *Department of Pathology and Immunology, Washington University, 660 South Euclid Avenue, Box 8118, St Louis, MO 63110-1093, USA*

[b] *Departments of Pathology and Dermatology, Saint Louis University, St Louis, MO, USA*

[*] Corresponding author.

E-mail address: jfrater@wustl.edu (J.L. Frater).