Research Article

Red Cell Distribution Width and Mortality in Hemodialysis Patients: A Single Center Experience in COVID-19 Era

Mustafa Topal*, Ibrahim Guney

Clinic of Nephrology, Konya City Hospital, University of Health Sciences, Turkey.

Abstract: Introduction: Red Cell Distribution width (RDW) is found to be related with mortality in hemodialysis patients. In December 2019, a new corona virus spread was detected in China, which turned into a pandemia with significant mortality. Both RDW and chronic kidney disease were found to be related with mortality in COVID-19 patients. This study investigated if the association of RDW and mortality in hemodialysis patients still existed in the COVID-19 era.

Materials & Methods: This single center study included 117 hemodialysis patients. They were followed for 20 months (between December 2019 and July 2021) or until death. The relation of RDW with all-cause mortality and COVID-19 related deaths were studied.

Results: 21 (17.9%) out of 117 patients died during the follow-up. RDW was found to be an independent risk factor for all-cause mortality (HR:1.35, p=0.009). In post-hoc analyzes, RDW was significantly higher in non-COVID-19 related and cardiovascular deaths.

Conclusion: RDW was found to be an independent and powerful risk factor of all-cause and cardiovascular mortality even in the mortal COVID-19 era.

Keywords: Red cell distribution width, Hemodialysis, Mortality, COVID-19, Chronic kidney disease, Rheumatoid arthtritis.

INTRODUCTION

A progressive decline in glomerular filtration rate for over 3 months is the definition of Chronic Kidney Disease (CKD). Hemodialysis is one of the treatment strategies of renal replacement therapy in end stage kidney failure. Despite the improvement in management of CKD, the mortality rate, especially cardiovascular mortality is still high in hemodialysis patients [1, 2]. Red blood cell distribution width (RDW) is a quantitative measurement of red blood cell size variability. Traditionally it was used to differentiate the types of anemia [3]. RDW is suggested to be related with cancer [4], rheumatoid arthtritis [5], autoimmune liver disease [6], irritable bowel disease [7], thyroiditis [8], diabetes mellitus [9], cobalamin deficiency [10] and inflammation in CKD [11]. In recent studies, RDW was found to be related with mortality in acute kidney injury patients who needed dialysis, in dialysis dependent end stage kidney failure patients and even in the general population [12-14]. In December 2019, a new corona virus spread was detected in Wuhan, China [15, 16]. The disease was named as corona virus infection disease 2019 (COVID-19), which further turned into a pandemia. By 31st March 2021, 128540982 confirmed cases and 2808308 confirmed deaths have been reported by World Health Organisation [17]. Mortality of COVID-19 was found to be associated with RDW, distinct from other risk factors [18]. This study investigated if the association of RDW and mortality in hemodialysis patients still existed in the COVID-19 era.

*Address correspondence to this author at the Clinic of Nephrology, Konya City Hospital, University of Health Sciences, Turkey.
Email: drmustafatopal@yahoo.com

MATERIALS AND METHODS

This was a single center study and was approved by Karatay University Ethics Committee (approval number: 16.03.2021/E-41901325-050.99-4934-040), and has been carried out in compliance with the Helsinki declaration. This study included 117 patients who were on hemodialysis at least for 3 months. Patients who were under 18 years old, who undergone major surgery or had active hemorrhage or had blood transfusion in last 3 months and undergone renal transplantation during the follow-up period were excluded. All patients were followed 20 months (from December 2020 till July 2021) or untill death. Socio-demographic parameters, like gender, age, dialysis vintage, cause of end stage renal disease, co-morbidities like diabetes mellitus (DM), congestive heart failure were noted. Cardiovascular mortality was defined as the deaths due to ischemic heart disease, congestive heart failure, peripheric artery disease and stroke. Body mass indexes were calculated for each patient, weight in kilograms divided by height square as meters (kg/m^2). Serum creatinine (mg/dl), blood urea nitrogen (mg/dl), calcium (mg/dl), phosphorus (mg/dl), potassium (mEq/l), sodium (mEq/l), albumin (g/dl), C-reactive protein (CRP) (mg/l), parathormone (PTH) (ng/l), vitamin B12 (pg/ml), folate (ng/ml), ferritin (µg/dl), bicarbonate, uric acid (mg/dl) and complete blood cell count samples were obtained predialysis and were measured monthly. RDW (%), a routine parameter of complete blood cell count, were noted for each patient. Ferritin, CRP and PTH levels were measured at least quarterly. The blood samples were measured in the laboratory of the hospital in 4 hours. Dialysis sufficiency was calculated as a single pooled Kt/V.

STATISTICAL ANAYLSIS

The statistical analysis were done by SPSS (Statistical Package for the Social Sciences, SPSS Inc, Chicago, IL, USA.) for Windows version 22. After Kolmogorov-Smirnov normality test, correlation was done by Pearson correlation for parametric and Spearman correlation for non-parametric data. We performed Mann-Whitney U test according to survival. Chi-square test was done to analyze the relation of categoric parameters with mortality. Then, cox regression analysis was performed with survival related parameters. After grouping the cause of deaths according to COVID-19 related or not, a Kruskal-Wallis and post-hoc analysis were run to reveal the relation of RDW values with survivors, non-COVID-19 related and COVID-19 related deaths. Kruskal-Wallis and post-hoc analysis were also run after grouping for cardiovascular and non-cardiovascular deaths. Statistically significance was designated as a p value of <0.05.

RESULTS

117 hemodialysis patients including 60 (51.28%) women and 57 (48.72%) men with mean age of 53.57±16.95 years were studied. 46 (39.32%) patients were diabetic. Patient characteristics are shown in Table **1**. 21 (17.95%) of patients died during the follow-up period. Out of 21 deaths, the causes were cardiovascular (n=10, 47.62%), upper gastrointestinal bleeding (n=1, 4.76%), cancer (n=1, 4.76%), infectious diseases other than COVID-19 (n=1, 4.76%) and complications of COVID-19 (n=8, 38.1%). Some parameters of survivors and non-survivors are shown in Table **2**. Mortality was found to be associated with age (p=0.005), male gender (p=0.029), DM (p<0.001), systolic blood pressure (p=0.019), serum CRP (p=0.007), albumin (p=0.001), RDW (p=0.022) and PTH (p=0.026) levels. After cox regression analysis, mortality was independently associated with male gender (p=0.023, HR=3.61, 95% CI:1.113-14.117), diabetes mellitus (p=0.034, HR=3.96, 95% CI: 1.198-10.877), age (p=0.003, HR=1.06, 95% CI: 1.022-1.108), systolic blood pressure (p=0.005, HR=1.05, 95% CI: 1.015-1.086) and RDW (p=0.009, HR=1.35, 95% CI: 1.079-1.692) (Table **3**).

Kruskal-Wallis analysis were performed after grouping for survivors, COVID-19 related and COVID-19 non-related deaths. According to post-hoc analysis, the RDW values of non-COVID-19 related deaths were significantly higher compared to RDW values of survivors (17.10±2.12 vs 15.04±1.48 respectively, p<0.001). No significant relationship was found between the RDW levels of survivors and COVID-19 related deaths (15.04±1.48 vs 14.83±1.51 respectively, p>0.05). Kruskal-Wallis analysis were also performed after grouping for survivors, cardiovascular and non-cardiovascular deaths. RDW values of cardiovascular deaths were significantly higher compared to survivors according to post-hoc analysis (p=0.006) (Table **4**). There were no significant relation in terms of RDW between non-cardiovascular deaths and survivors. Median RDW value was 15.1%. RDW had a negative correlation with serum PTH (p=0.003, r=-0.276) and ferritin levels (p=0.030, r=-0.2). RDW values were not correlated with hemoglobin (r=-0.062,p=0.507) serum vitamin B12 (r=0.083, p=0.376) and folate levels and (=0.008, p=0.929).

Table 1. Patient Characteristics.

Parameters	**Mean ± Standard Deviation or Frequency (%)**
Age (Years)	53.57±16.95
Female Gender	60 (51.28)
Diabetes Mellitus	46 (39.32)
Dialysis Vintage (Months)	46.77±40.56
Hemoglobin (g/dl)	10.57±1.78
C-reactive Protein (mg/l)	11.75±21.72
Albumin (g/dl)	3.66±0.33
Vitamin B12 (pg/ml)	480.21±273.50
Folate (ng/ml)	9.86±6.22
RDW (%)	15.26±1.68
Systolic Blood Pressure (mmHg)	125.89±16.90
Diastolic Blood Pressure (mmHg)	75.80±9.83
Body Mass Index (kg/m²)	25.99±6.10
Calcium (mg/dl)	8.55±0.71
Phosphorus (mg/dl)	4.90±1.63
Parathormone (ng/l)	552.19±463.91
Ferritin (µg/dl)	566.57±331.55
Uric Acid (mg/dl)	5.73±1.18

Table 2. Patient Characteristics among Survivors and Non-Survivors.

Parameters	Survivors	Non-survivors	P value
C-reactive Protein (mg/l)	11.10±23.28	14.70±12.27	0.319
Albumin (g/dl)	3.70±0.33	3.48±0.22	0.001
Age (years)	51.44±17.03	63.33±12.91	0.001
RDW (%)	15.04±1.48	16.23±2.19	0.026
Body Mass İndex (kg/m²)	25.58±6.15	27.65±5.74	0.164
Hemoglobin (g/dl)	10.61±1.77	10.39±1.82	0.615
Systolic Blood Pressure (mmHg)	124.09±16.76	134.74±15.04	0.01
Dialysis Vintage (months)	48.29±43.49	39.81±22.24	0.202
Uric Acid (mg/dl)	5.76±1.17	5.57±1.26	0.519
Parathormone (ng/l)	586.94±464.30	339.31±438.12	0.079

Table 3. Cox Regression Analysis for all Cause Mortality.

	Backwards stepwise Model 1(R2=39.654)		Backwards stepwise Model 4 (R2=37.375)	
Parameters	HR (CI%95)	p	HR (CI%95)	p
Diabetes mellitus	3.71 (1.024-13.442)	0.046	3.96 (1.113-14.117)	0.034
Male gender	3.54 (1.172-10.669)	0.025	3.61 (1.198-10.877)	0.023
Age	1.06 (1.012-1.106)	0.013	1.06 (1.022-1.108)	0.003
Systolic blood pressure	1.05 (1.012-1.089)	0.009	1.05 (1.015-1.086)	0.005
RDW	1.37 (1.083-1.733)	0.009	1.35 (1.079-1.692)	0.009
Albumin	0.37 (0.068-2.013)	0.25		
C-reactive protein	0.99 (0.976-1.019)	0.83		
Parathormone	1.00 (0.999-1.002)	0.64		

Table 4. Post-Hoc Analysis after Grouping for Survivors, Cardiovascular Deaths and COVID-19 Related Deaths.

Multiple Comparisons		Significance
Survivors	Cardiovascular deaths	p=0.006
	Non-cardiovascular deaths	p=0.485
Non-Cardiovascular Deaths	Cardiovascular deaths	p=0.314
	Survivors	p=0.485
Cardiovascular Deaths	Non-cardiovacular deaths	p=0.314
	Survivors	p=0.006

DISCUSSION

In this study we found that RDW is an independent predictor of all cause and cardiovascular mortality in hemodialysis patients and still existed even in the mortal COVID-19 era. Each 1% increase in RDW value was associated with an increase in all cause mortality by 35%. On 100 hemodialysis patients, Sicaja *et al*. found an independent relationship between RDW and mortality. 25 out of 100 patients died at the end of the follow-up, which was 12 months. The all cause mortality for 12 months was increased by 54% for each 1% increase in RDW [13].

In a mixed group of patients undergoing both hemodialysis and periton dialysis, Yoon *et al*. also showed a relationship between RDW and mortality. In a total group of 326 dialysis patients, 75 patients died in 12 months follow-up. Increasing RDW values were independently related with all cause mortality, at a hazard ratio of 1.75 [19].

In a retrospective study with a cohort of 109675 adult HD patients, Vashista *et al*. found a powerful and lineer relation between RDW and all cause mortality [20]. They also concluded that RDW was a robust mortality predictor compared to hemoglobin, ferritin and iron saturation.

24 months follow-up of 356 hemodialysis patients by Chen *et al*. also showed a lineer association between RDW and all cause death. 56 patients died in this study during follow-up and the hazard ratio of RDW was 1.34 [21].

Following 80 hemodialysis patients for over a 5 years, Fukasawa *et al*. showed that a cut-off RDW level indepently predicted all cause and cardiovascular mortality. 34 patients died during follow-up, mostly due to cardiovascular diseases. Every 1% increase in RDW value showed 25% increased risk of all cause death [22].

In a meta-analysis including 117047 hemodialysis patients, RDW value was also shown as an independent predictor of all cause death in hemodialysis patients [23]. They found that the risk of death in hemodialysis patients elevated by 36% for every 1% increase in RDW values.

RDW was also found to be independently related with mortality in peritoneal dialysis. Peng *et al*. found that RDW values were related with mortality, especially cardiovascular mortality in peritoneal dialysis patients [24]. 249 patients out of 613 patients died during a median of 34.3 months follow-up. In another study of Sun *et al*. on 136 patients, RDW was shown to be an independent risk factor for all cause death [25]. On 313 peritoneal dialysis patients, Hsieh *et al*. showed that RDW had a robust prediction of all cause and cardiovascular death, than classic laboratory markers [26]. Soohoo *et al.* found a lineer association between baseline RDW and all cause death on 14323 peritoneal patients [27].

Taken together, all these studies showed the relation of RDW and all cause death in dialysis patients. Yet, the cause of deaths were not identified. The study of Fukasawa *et al*. was the only one to show a relation between RDW and cardiovascular deaths, as well as all cause mortality [22]. Similarly, we found that RDW was an independent risk factor of all cause and cardiovascular death.

The exact mechanism how RDW values affects mortality is not clear. It is hypothesized that inflammation, which is frequent in hemodialysis patients, leads to impaired iron metabolism and erythropoietin resistance [3, 26]. This further leads to presentation of immature erythrocytes in circulation, resulting in increased RDW. The RDW values of infected people are expected to be elevated. However, the impact of COVID-19 era on RDW values of hemodialysis patients has not been studied till now.

In this study, RDW was found to be an independent risk factor of death in hemodialysis patients. However, baseline RDW values of COVID-19 related deaths were not associated with mortality. In fact, the mean RDW values of COVID-19 related deaths were lower than the survivors. This shows that the mortality of COVID-19 is independent of baseline RDW values. Lorente *et al*. showed higher RDW levels were associated with mortality in patients treated for COVID-19 in intensive care units. RDW values were obtained on admission at intensive care units, when they were already infected and COVID-19 complications were present [18]. As mentioned before, RDW is a sign of inflammation [28]. So the acute infection could have been the primer cause of higher RDW values, especially in those with complicated disease. Chronic renal failure is a risk factor of mortality in patients with COVID-19 and COVID-19 is a mortal infection even in healthy subjects [29-31]. The pandemic era is a state of unpredictable deaths, away from traditional risk factors. We found that baseline RDW values of non-COVID deaths, particularly cardiovascular deaths, were independently associated with mortality.

LIMITATION

The main limitation of this study was the relatively small number of patients from a single center. However, to our knowledge, this was the first study to investigate the relation of RDW and mortality in hemodialysis patients in COVID-19 era.

CONCLUSION

In conclusion, in this study we showed that RDW was a

powerful and independent risk factor of all cause and cardiovascular death in hemodialysis patients that even mortal COVID-19 era could not change it. Multi-center studies with high number of patients are needed to investigate the relationship of RDW and mortality in hemodialysis patients in COVID-19 era.

AUTHORS' CONTRIBUTION

Mustafa Topal: Contributed to concept, design, definition of intellectual content, data collection, literature search, data analysis, manuscript preparation, manuscript editing.
Ibrahim Guney: Contributed to manuscript review and performed statistical analysis.

CONFLICT OF INTEREST

Declared none.

ACKNOWLEDGEMENTS

Declared none.

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Received: October 11, 2021 Revised: December 03, 2021 Accepted: December 03, 2021