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The association between red cell distribution width and poor outcomes in hospitalized patients with influenza

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ABSTRACT

Purpose: To examine an association between red blood cell distribution width (RDW) and the prognosis of influenza patients.
Methods: We conducted a retrospective analysis of patients hospitalized with influenza during 2012–2015 in the internal medicine wards of one medical center. RDW measurements during hospitalization were analyzed. Primary outcome was complicated hospitalization (defined as at least one of: length of stay ≥7 days, need for mechanical ventilation, septic shock, transfer to intensive-care, or 30-day mortality). Secondary outcome was 30-day mortality.
Results: 153 patients were included, mean age: 62.5 ± 1, 82 (54%) male; 84 (55%) had a high RDW value (>14.5%) during hospitalization. Patients with high and low RDW (≤14.5%) had similar age and comorbidity profiles, but those with high RDW had lower hemoglobin and higher creatinine levels. Patients with high RDW had a higher rate of complicated hospitalization (32.5% vs. 10.3%, $p < 0.01$) and a trend for increased 30-day mortality. In a multivariate regression model, high RDW was a predictor of complicated hospitalization (OR 5.03, 95% CI 1.81–13.93, $p < 0.01$). Each 1-point increase in RDW was associated with a 29% increase in the risk for the primary outcome.
Conclusion: RDW > 14.5% was a predictor of severe hospital complications in patients with influenza.

1. Introduction

Influenza infection is usually self-limited, but occasionally may lead to substantial morbidity and even to mortality, especially in an elderly and immunocompromised population [1]. Seasonal influenza occurs mainly during winter and is responsible for an estimated 3–5 million cases of severe illness and up to 500,000 deaths annually world-wide [2].

Red blood cell distribution width (RDW) is a measure of the degree of heterogeneity of erythrocyte volume. Prior studies have shown that elevated RDW is associated with increased mortality among patients with various disease states, such as cardiovascular disease [3-5], stroke [6], renal disease [7], chronic obstructive pulmonary disease [8], septic shock [9] and community acquired pneumonia [10].To the best of our knowledge, RDW levels among influenza patients have not been evaluated previously. This study examined the association between RDW levels and short-term outcomes among influenza patients.

2. Materials and methods

2.1. Study population and design

We analyzed the data of all adult patients (age > 18) hospitalized with the diagnosis of influenza infection in the5 internal medicine wards of Meir Medical Center from January 1, 2012 through December 31, 2015. Meir Medical Center is a 760-bed, tertiary care university hospital. Influenza was diagnosed using polymerase chain reaction kit (3 M integrated cycler, Focus Diagnostics, Cypress, CA, USA). During the study period, RDW and other laboratory tests were analyzed in a single central laboratory using standardized automated kits (Advia 2120, Siemens, Erlangen, Germany). Data were collected from electronic medical records. Mortality data were confirmed using the Israel Central Bureau of Statistics. Data collection was approved by the hospital ethics committee.

2.2. Definitions

For analysis, patients were categorized according to RDW values during hospitalization: high RDW (at least one RDW > 14.5%) and low RDW (no RDW value > 14.5%). The cutoff of 14.5% was determined as the upper limit of normal values provided by our laboratory. Primary

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outcome was complicated hospitalization, defined as at least one of the following: hospital stay > 7 days, need for mechanical ventilation, septic shock, transfer to the Intensive Care Unit (ICU) and 30-day mortality. Secondary outcome was 30-day, all-cause mortality. Patients were followed until December 31, 2015 for all-cause mortality. Patients were further subdivided according to the change in RDW levels during hospitalization (discharge RDW minus baseline RDW). A significant change was defined as more than ± 0.6%.

2.3. Statistical analysis

Data are presented as numbers and percentages for nominal data and as means and standard deviations for continuous parameters. Differences between the high RDW and low RDW groups were analyzed with chi-square or Fisher's exact test, as appropriate. Continuous variables were examined for normality (Shapiro-Wilk test) and data were analyzed accordingly. The *t*-test was used for normally distributed variables and the Mann-Whitney for non-parametric variables. Receiver operating characteristic (ROC) curves were used to evaluate the ability of maximum RDW and the change in RDW to predict unfavorable outcomes. A logistic regression model was applied to estimate odds ratios for complicated hospitalization. In a multivariate logistic regression model, the following variables were accounted forage, gender, high RDW, change in RDW > ±0.6% and hemoglobin levels at admission. A Cox proportional hazard model was applied to estimate hazard ratios for all-cause mortality until the end of the follow-up period. The variables accounted for in this model were diabetes mellitus, creatinine at admission, hemoglobin at admission, high RDW and complicated hospitalization. $p < 0.05$ was considered statistically significant. Data were analyzed with SPSS Version 21 (IBM Corporation, Armonk, NY, USA).

3. Results

Among 162 patients hospitalized with a diagnosis of influenza during the study period, 9 were excluded from the analysis due to incomplete data. A total of 153 influenza patients were included in this analysis (mean age 62.5 ± 1 years, 53.6%men). Eighty-four (55%) patients were categorized in the high RDW group and 69 (45%) in the low RDW group. Patients in the two groups were of similar age and had similar comorbidity profiles. The mean hemoglobin level at admission was lower and the mean creatinine level was higher for patients in the high RDW than in the low RDW group (11.2 ± 1.8 vs. 12.9 ± 1.3, $p = 0.00$ and 1.9 ± 2.0 vs. 1.2 ± 0.6, $p < 0.01$, respectively) (Table 1).

Table 1
Characteristics of patients hospitalized with influenza virus infection.

Variables	RDW > 14.5% (*n* = 84)	RDW ≤ 14.5% (*n* = 69)	Total (*n* = 153)	*p*-Value
Age	64 ± 12.7	60.9 ± 15.7	62.5 ± 14.2	0.19
Male gender	51.2	56.5	53.6	0.52
Comorbidities				
Asthma	4.8	7.2	5.9	0.73
COPD	7.1	2.9	5.2	0.29
Diabetes mellitus	27.4	20.3	24.2	0.31
Hypertension	28.6	30.4	29.4	0.8
Hyperlipidemia	28.6	37.7	32.7	0.23
CRF	13.1	5.8	9.8	0.17
Tobacco use	13.1	14.5	13.7	0.8
Baseline laboratory values				
Hemoglobin (g/dl)	11.2 ± 1.8	12.9 ± 1.3	11.9 ± 1.8	0.00
WBC (K/microL)	6.8 ± 4.8	6.8 ± 3.1	6.8 ± 4.1	0.89
PLT (K/microL)	186 ± 88	193 ± 62	189.4 ± 77.3	0.56
Creatinine (g/dL)	1.9 ± 2.0	1.2 ± 0.6	1.36 ± 1.4	0.00
Bilirubin (mg/dL)	0.61 ± 0.35	0.68 ± 0.68	0.64 ± 0.5	0.43
CRP (mg/dL)	11.2 ± 7.9	9.8 ± 6.1	9.9 ± 6.1	0.31
Baseline RDW (%)	15.3 ± 1.6	13.4 ± 0.6	14.5 ± 1.6	0.00

WBC, white blood cells; PLT, platelets; RDW, red blood cell distribution width; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure.
Data are presented as means ± SD or percentages of presented cases.
Normal ranges of values of laboratory data: Hemoglobin (12–16), WBC (4.8–10.8), PLT (150–400), creatinine (0.5–1.2), bilirubin (0.2–1.5), CRP (0.0–0.5).

3.1. RDW and in-hospital complications

Complicated hospitalization rates were significantly higher in the high than in the low RDW group (32.5% vs. 10.3%, $p < 0.01$). In-hospital characteristics and complications are depicted in Table 2. ROC curve analysis revealed that the maximum RDW of 14.5% was the optimal cut-off value associated with complicated hospitalization. Risk assessment using RDW level as a continuous variable demonstrated that each 1-point increase in RDW was associated with a 29% increase in the risk for the primary endpoint of complicated hospitalization. A multivariate logistic regression model revealed that high RDW was the only factor examined that was an independent predictor of complicated hospitalization (OR 5.03, 95% CI 1.81 to 13.93, $p < 0.01$).

A sub-analysis of the 35 patients with complicated hospitalization revealed a high RDW value in 27 (77%). The mean maximum RDW of patients with complicated hospitalization was significantly higher than that of patients with a non-complicated hospitalization (15.9 ± 1.9 vs. 14.9 ± 1.8, $p < 0.01$). The same trend was noted when comparing patients with and without complicated hospitalization, with mean RDW levels at baseline and at discharge higher in the complicated hospitalization group (14.8 ± 1.6 vs. 14.4 ± 1.6, $p = 0.2$ and 15.3 ± 2.0 vs. 14.8 ± 1.8, $p = 0.13$, respectively).

3.2. RDW and mortality

Thirty-day mortality rates were higher for patients with a high RDW value than for those without (2.4% vs. 0%, $p = 0.5$). Two patients died due to complications related to influenza infection. Four patients (2.7%) died within 90 days due to influenza complications, 3 had a high RDW value (3.6% vs. 1.5%, $p = 0.63$). During a mean follow-up of 21 ±10 months, 24 patients (15.9%) died. A high RDW was associated with higher long-term all-cause mortality (21.7% vs. 8.8%, $p = 0.04$). However, a multivariate Cox regression model analysis demonstrated that only complicated hospitalization, and not high RDW, was

Table 2
In-hospital characteristics and outcomes of patients hospitalized with influenza virus infection according to RDW levels.

Variables	RDW > 14.5% (*n* = 84)	RDW ≤ 14.5% (*n* = 69)	Total (*n* = 153)	*p*-Value
Acute renal failure	10.7	8.8	9.9	0.7
Septic shock	3.6	0	2.0	0.25
Syncope	2.4	5.9	3.9	0.41
COPD exacerbation	4.8	0	2.6	0.13
Max fever, °C	38.1 ± 0.88	38.0 ± 0.9	38.0 ± 0.8	0.03
ICU transfer	4.9	2.9	4.0	0.69
Mechanical ventilation	2.4	0	1.3	0.5
Oseltamivir treatment	76.2	77.9	77.0	0.08
Hospitalization length, days	6.4 ± 5.9	4.6 ± 2.9	5.6 ± 4.9	0.02
30-day mortality rate	2.4	0	1.3	0.5

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; RDW, red blood cell distribution width; Max, maximum.
Data are presented as means ± SD or percentages of presented cases.