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ORIGINAL ARTICLE

Diagnostic and Prognostic Value of Red Blood Cell Distribution Width in Children with Respiratory Tract Infections

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SUMMARY

Background: **Respiratory tract infections (RTIs) are the most common disorders among children. Red blood cell distribution width (RDW) was proven to be associated with the prognosis of many diseases, including chronic obstructive pulmonary disease.**
Methods: **We aimed to evaluate the diagnostic and prognostic value of RDW level in children with RTIs. A total of 1,044 RTI cases and 115 healthy controls in our center were involved in this study. We compared the differences of RDW level among different groups of RTI cases and controls. Receiver operating curve (ROC) analysis was applied to determine the predictive value of RDW level in the risk of various groups of RTIs. Clinical and laboratory parameters were compared between RTIs with RDW > 14% and ≤ 14%. Correlation analyses were conducted to investigate the relationship between RDW and RTIs' clinical and laboratory parameters.**
Results: **Significant differences of RDW levels between tonsillitis without suppression and with suppression ($p = 0.024$), bronchitis and pneumonia ($p = 0.008$), non-mycoplasma pneumonia and mycoplasma pneumonia ($p < 10^{-4}$), and total RTIs and healthy controls ($p < 10^{-4}$) were observed. Significant associations between RDW level and pneumonia, mycoplasma pneumonia, and total RTI risk were observed (ROC = 0.560, $p = 0.022$; ROC = 0.537, $p = 0.043$; ROC = 0.863, $p < 10^{-4}$). Significant differences of WBC, PLT, ESR, Scr, and CK levels were observed between RTIs with RDW > 14% and ≤ 14%. RDW level was significantly associated with WBC, PLT, Scr, ALT, LDH, and CKMB.**
Conclusions: **RDW was a non-invasive, low-cost, and widely available predictor for the risk and progression of RTIs. RDW level may reflect the disease course among RTIs.**
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KEY WORDS

respiratory tract infections, red blood cell distribution width, children

LIST OF ABBREVIATIONS

RTIs - respiratory tract infections
RDW - red blood cell distribution width
ROC - receiver operating curve
WBC - white blood cell
CRP - c-reactive protein
ESR - erythrocyte sedimentation rate
PLT - platelet

PCT - procalcitonin
BUN - blood urea nitrogen
Scr - serum creatinine
uRBC - urine red blood cell count
ALT - alanine aminotransferase
AST - aspartate aminotransferase
LDH - lactate dehydrogenase
CK - creatine kinase
CKMB - creatine kinase isoenzyme
SD - standard deviation

INTRODUCTION

Respiratory tract infections (RTIs) are the most common disorders among children [1]. RTIs are likely to occur during the epidemic season among the cases with poor immunity. Meanwhile, frequent RTIs may result in severe complications, such as nephritis and myocarditis [2,3]. Currently, aggressive therapy is applied among certain RTIs cases due to their complications. However, long-term intravenous antibiotics therapy may induce side effects, such as enteritis [4]. Hence, identification of the early biomarkers of RTIs may be helpful for the prevention and therapy of RTIs.

Red blood cell distribution width (RDW), a parameter of standard full blood count tests, reflects the size variability of erythrocytes [5]. RDW was previously applied in the diagnosis of anemia-associated diseases [6]. Recently, RDW level was found to be associated with cardiac disorders, including ischemic heart disease, atherosclerosis, and heart failure [7]. RDW was also a predictor of mortality and readmission in critically ill patients [8]. RDW was associated with the prognosis of chronic obstructive pulmonary disease [9]. This evidence indicated that RDW level was closely associated with the risk and prognosis of various diseases. In the adult studies, RDW change was proven to predict poor in-hospital outcomes in community-acquired pneumonia cases [10]. RDW level was associated with hsCRP/ESR independent confounding factors [11]. In terms of the high occurrence and complications of RTIs in children, we speculated that RDW level also reflected the risk of RTIs to some extent.

We decided to perform this retrospective study to analyze the differences of RDW level between RTIs and healthy controls. We also determined the differences of RDW level among various types of RT cases, including the comparisons between tonsillitis with and without suppression, ordinary and severe pneumonia, and bronchitis and pneumonia. The predictive value of RDW in the risk of various types of RTIs was tested. Additional correlation analyses were conducted to investigate the relationship between RDW level and RTIs' clinical and laboratory parameters.

MATERIALS AND METHODS

Subjects

The study case population were from outpatients and hospitalized patients in the Department of Pediatrics, Shanghai Sixth People's Hospital, China. The healthy children examined in outpatient service were enrolled as controls. The ages of enrolled participants were no more than 14 years. RTIs were diagnosed according to the international criteria [12]. The study period was between January 2016 and July 2018.

Patients with systemic diseases and other disorders that may affect the risk of RTIs were excluded. All the guardians of enrolled participants signed an informed consent according to the ethics requirement.

Data collection

We extracted the clinical and laboratory parameters from the out and inpatient medical records. We collected the clinical parameters, including age, gender, and hospitalization days. Meanwhile, the laboratory parameters, including red blood cell distribution width (RDW), white blood cell (WBC), c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelet (PLT), procalcitonin (PCT), blood urea nitrogen (BUN), serum creatinine (Scr), urine red blood cell (uRBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), and creatine kinase isoenzyme (CKMB). All the laboratory indexes were tested in the first day after hospital visit.

Statistical analysis

The data of all the enrolled clinical and laboratory parameters were expressed as means ± standard deviation (SD). Independent one-sample *t*-test was applied to compare the difference of RDW level between different groups, including tonsillitis without suppression vs. tonsillitis with suppression, bronchitis vs. pneumonia, ordinary pneumonia vs. severe pneumonia, non-mycoplasma pneumoniae vs. mycoplasma pneumoniae, respiratory virus infection vs. non-virus infection, and RTIs vs. controls. ROC analysis was used to test the predictive value of RDW level in the risk of various RTIs, including tonsillitis with suppression, pneumonia, severe pneumonia, mycoplasma pneumoniae, respiratory virus infection and whole RTIs. Independent one-sample *t*-test was applied to test the differences of clinical and laboratory parameters between RTIs with RDW > 14% and ≤ 14%. Spearman's correlation analysis was used to determine the association between RDW level and clinical and laboratory parameters. All the analyses were performed by using SPSS version 19. $p < 0.05$ was considered statistically significant, except where otherwise specified.

Table 1. Baseline characteristics of recruited subjects.

Groups	n	Age (years)	Boy/girl ratio
Tonsillitis without suppression	171	5.08 ± 3.04	1.32
Tonsillitis with suppression	201	5.15 ± 2.89	1.29
Bronchitis	165	4.81 ± 2.88	1.38
Pneumonia	507	4.45 ± 2.40	1.28
Ordinary pneumonia	447	4.57 ± 2.46	1.29
Severe pneumonia	60	3.95 ± 2.32	1.25
Non-mycoplasma pneumoniae	575	4.18 ± 2.37	1.14
Mycoplasma pneumoniae	469	5.41 ± 2.68	1.39
Respiratory virus infection	429	4.66 ± 2.62	1.14
Non-virus infection	615	4.78 ± 2.59	1.25
RDW ≤ 14%	654	5.15 ± 2.68	1.03
RDW > 14%	390	4.08 ± 2.25	1.41
Control	115	5.13 ± 1.99	1.12

RDW - red blood cell distribution width.

Table 2. Comparison of RDW level between different groups.

Index	RDW	p
Tonsillitis without suppression vs. Tonsillitis with suppression	13.04 ± 0.72 vs. 13.48 ± 1.28	0.024
Bronchitis vs. Pneumonia	13.27 ± 1.13 vs. 13.65 ± 1.71	0.008
Ordinary pneumonia vs. Severe pneumonia	13.25 ± 1.12 vs. 13.48 ± 1.32	0.192
Non-mycoplasma pneumoniae vs. Mycoplasma pneumoniae	13.31 ± 1.15 vs. 13.44± 1.43	$< 10^{-4}$
Respiratory virus infection vs. Non-virus infection	13.31 ± 1.15 vs. 13.44 ± 1.43	0.118
RTIs vs. controls	13.38 ± 1.32 vs. 11.75 ± 0.84	$< 10^{-4}$

RTIs - respiratory tract infections, RDW - red blood cell distribution width.

RESULTS

Patient characteristics

A total of 1,044 RTI cases and 115 healthy controls were involved in our study. There were 171 tonsillitis without suppression, 201 tonsillitis with suppression, 165 bronchitis, 507 pneumonia, 447 ordinary pneumonia, 60 severe pneumonia, 575 non-mycoplasma pneumonia, 469 mycoplasma pneumonia, 429 respiratory virus infection, 615 non-virus infection, 654 RTIs with RDW ≤ 14% and 390 RTIs with RDW > 14%. The mean age and boy/girl ratios were all presented in Table 1.

Differences of RDW level between different groups

There was a significant difference in the RDW level between tonsillitis without suppression and tonsillitis with suppression ($p = 0.024$, Table 2). A marked difference in RDW level between bronchitis and pneumonia was observed ($p = 0.008$, Table 2). There was no significant difference in RDW level between ordinary and severe pneumonia ($p = 0.192$, Table 2). A significant difference in RDW level between non-mycoplasma pneumonia and mycoplasma pneumonia cases was noted ($p < 10^{-4}$, Table 2). No marked difference in RDW level between respiratory virus infection and non-virus infection was observed ($p = 0.118$, Table 2). A marked difference in RDW level between RTIs and healthy controls was noted ($p < 10^{-4}$, Table 2).

Table 3. Predictive value of RDW level in the risk of various RTIs.

Groups	Sensitivity	1-Specificity	ROC area	95% CI	p	Cutoff point
Tonsillitis with suppression	0.250	0.386	0.424	0.323 - 0.526	0.146	13.45
Pneumonia	0.376	0.280	0.560	0.505 - 0.614	0.022	13.65
Severe pneumonia	0.417	0.400	0.446	0.364 - 0.529	0.179	13.35
Mycoplasma pneumoniae	0.284	0.256	0.537	0.501 - 0.572	0.043	13.75
Respiratory virus infection	0.263	0.269	0.484	0.448 - 0.520	0.448	13.75
RTIs	0.299	0.000	0.863	0.769 - 0.957		13.65

ROC - receiver operating characteristic curve, RDW - red blood cell distribution width.

Table 4. Comparison of clinical and laboratory parameters between RDW > and ≤ 14%.

Index	Value	p
WBC	8.95 ± 7.01 vs. 7.42 ± 4.76	$< 10^{-4}$
CRP	26.04 ± 38.71 vs. 22.42 ± 33.61	0.129
PLT	255.75 ± 93.82 vs. 237.69 ± 99.54	0.004
PCT	0.48 ± 0.97 vs. 0.57 ± 1.74	0.314
ESR	23.75 ± 20.16 vs. 19.76 ± 16.09	0.002
Day	6.99 ± 2.47 vs. 7.00 ± 2.03	0.912
uRBC	8.92 ± 3.73 vs. 6.99 ± 2.52	0.264
BUN	3.40 ± 0.99 vs. 3.47 ± 1.01	0.320
Scr	27.71 ± 7.08 vs. 31.06 ± 8.79	$< 10^{-4}$
ALT	22.93 ± 47.07 vs. 20.08 ± 36.18	0.327
AST	38.29 ± 39.67 vs. 34.33 ± 21.42	0.085
LDH	304.55 ± 102.55 vs. 294.90 ± 97.88	0.153
CK	120.43 ± 127.39 vs. 106.06 ± 92.94	0.047
CKMB	23.27 ± 11.21 vs. 22.01 ± 9.59	0.079

RTIs - respiratory tract infections, RDW - red blood cell distribution width, WBC - white blood cell, CRP -c-reactive protein, PLT - platelet, PCT - procalcitonin, ESR - erythrocyte sedimentation rate, uRBC - urine red blood cell, BUN- blood urea nitrogen, Scr - serum creatinine, ALT - alanine aminotransferase, AST - aspartate aminotransferase, LDH - lactate dehydrogenase, CK - creatine kinase, CKMB - creatine kinase isoenzyme.

Predictive value of RDW level in the risk of various RTIs

No marked association was noted between RDW level and the risk of tonsillitis with suppression (ROC = 0.424, p = 0.146, Table 3, Figure 1). Significant association between RDW level and pneumonia risk was observed (ROC = 0.560, p = 0.022, Table 3, Figure 1). No significant association between RDW level and the risk of severe pneumonia was noted (ROC = 0.446, p = 0.179, Table 3, Figure 1). There was significant association between RDW level and mycoplasma pneumonia risk (ROC = 0.537, p = 0.043, Table 3, Figure 1). No marked association between RDW level and respiratory virus infection cases was noted (ROC = 0.484, p = 0.448, Table 3, Figure 1). RDW level was significantly associated with RTI risk (ROC = 0.863, $p < 10^{-4}$, Table 3, Figure 1).

Differences in clinical and laboratory parameters between RTIs with RDW > and ≤ 14%

We chose the upper limit of reference value of RDW (14%) as the testing point. Significant differences in WBC, PLT, ESR, Scr, and CK levels were observed between RTIs with RDW > and ≤ 14% (Table 4). There

Table 5. Correlation between RDW level and clinical and laboratory parameters.

Index	R	p
WBC	0.196	$< 10^{-4}$
CRP	0.050	0.110
PLT	0.138	$< 10^{-4}$
PCT	0.006	0.859
ESR	0.048	0.142
Day	0.096	0.103
uRBC	0.037	0.245
BUN	-0.013	0.680
Scr	-0.155	$< 10^{-4}$
ALT	0.091	0.005
AST	0.019	0.549
LDH	0.090	0.005
CK	0.049	0.138
CKMB	0.073	0.026

RDW - red blood cell distribution width, WBC - white blood cell, CRP - c-reactive protein, PLT - platelet, PCT: procalcitonin, ESR - erythrocyte sedimentation rate, uRBC - urine red blood cell, BUN - blood urea nitrogen, Scr - serum creatinine, ALT - alanine aminotransferase, AST - aspartate aminotransferase, LDH - lactate dehydrogenase, CK - creatine kinase, CKMB - creatine kinase isoenzyme.

were no marked differences in CRP, PCT, hospitalization days, uRBC, BUN, ALT, AST, LDH, and CKMB between RTIs with RDW > and ≤ 14% (Table 4).

Association between RDW level and RTI parameters
RDW level was significantly associated with WBC, PLT, Scr, ALT, LDH, and CKMB (Table 5). No marked association between RDW level and CRP, PCT, ESR, hospitalization days, uRBC, BUN, AST, and CK was observed (Table 5).

DISCUSSION

RTIs are likely to occur in children with lower immunity during the epidemic season. Many RTIs may lead to significant morbidity, such as respiratory and heart failure, or even death [13]. Hence, early prevention and treatment of RTIs seems important. For children, identification of non-invasive biomarkers for RTI risk and progression is of great clinical significance.
RDW, a simple and widely available laboratory parameter, reflects the deregulation of erythrocyte homeostasis. A high RDW level has been shown to be associated with cardiac diseases, chronic obstructive pulmonary disease, and acute kidney injury [14]. To our knowledge, this is the first study focusing on the association between RDW level and RTIs in children. We found that significant differences of RDW level between tonsillitis without and with suppression, bronchitis and pneumonia, non-mycoplasma pneumoniae and mycoplasma pneumoniae, and total RTIs and healthy controls were observed. The RDW level was of predictive value for the risk of pneumonia, mycoplasma pneumonia, and total RTIs, which indicated that monitoring of RDW level was helpful for the prevention of RTIs. We also noted that marked differences of WBC, PLT, ESR, Scr, and CK levels were observed between RTIs with RDW > and ≤ 14%. The RDW level was significantly associated with WBC, PLT, Scr, ALT, LDH, and CKMB. This evidence suggested that RDW level was closely associated with the disease course of RTIs.
Several facts may account for our findings. First, erythrocytes function mainly delivering the oxygen to the peripheral tissues from the lung, meeting the demand of the body [15]. Aging erythrocytes shrink and are more equally sized compared with the younger red blood cells [16]. Pathological conditions, such as oxidative stress, reduce the survival length of erythrocytes, which leads to the increased number of small and large red blood cells [17]. RDW reflects the degree of heterogeneity of erythrocyte volume. Hence, an increased level of RDW indicates the deregulation of erythrocyte homeostasis, which may be attributed to various disorders. Our findings were consistent with the above-mentioned evidence that a higher RDW level was observed in RTIs compared with controls. Second, an increased level of RDW was closely associated with inflammation, which accounted for tonsillitis with suppression, pneumonia, and mycoplasma pneumonia cases showing higher levels of

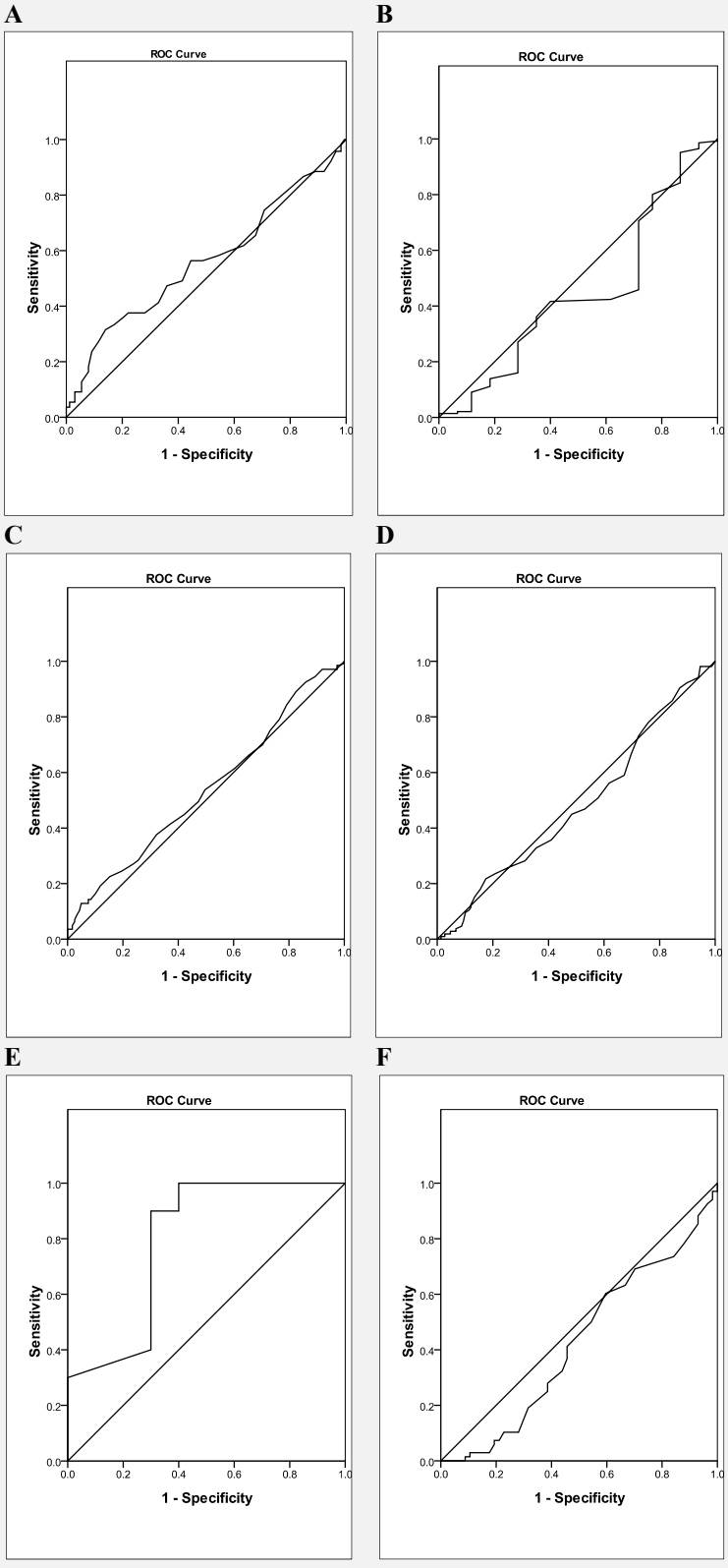

Figure 1. Predictive value of RDW in the risk of various RTIs.

A - RDW and risk of pneumonia, B - RDW and risk of severe pneumonia, C - RDW and risk of mycoplasma pneumoniae, D - RDW and risk of respiratory virus infection, E - RDW and risk of total RTIs, F - Figure 1. Predictive value of RDW in the risk of various RTIs.

RDW [18]. Notably, we found that virus infection did not affect the RDW level, which may be because the virus did not affect the energy metabolism and inflammation directly. On the other hand, no difference in RDW level was observed between ordinary and severe pneumonia, which may be due to the fact that often severe pneumonia was induced by a virus or mixed infections [19]. Finally, the close association between RDW and inflammation explained the correlation between RDW and WBC/PLT/LDH. Interestingly, we found that the length of hospitalization was not associated with RDW level, which may be due to that multiple factors determine the hospitalisation days, and most parents decided to discharge with mild inflammation. Erythrocytes function by mainly transferring the oxygen to the various tissues participating in metabolism. Therefore, a higher RDW level is likely to lead to nutritional and metabolic disorders, which accounted for the correlation between RDW and ALT/CKMB. Notably, the negative correlation between Scr and RDW may be due to that an increased RDW level affecting the nutritional status, leading to decreased appetite which lowers the Scr level. The role of RDW was the differential diagnosis of anemia first reported in 1980's [20]. Our study generalized its utility in RTIs in children. Based on our findings, several questions merit attention. First, the specific role of RDW in RTIs requires further investigation. For example, the immunity and calcium/phosphorus metabolism may influence the prognosis of RTIs [21]. An in-depth analysis of the association between RDW and various indexes should be performed in the future. Second, besides the common types of RTIs, we should also pay attention to the relationship between RDW level and other types of RTIs, such as herpangina and pharyngo-conjunctival fever. On the other hand, the RTI-associated immunological disorders, such as asthma, merit investigation due to their high incidence in children. Finally, the follow-up of RDW level may be helpful for understanding the dynamic association between RDW level and RTIs.

In the past, a number of studies were conducted to investigate the association between RDW and various disorders. Ramby et al. [22] reported that increased RDW was associated with outcome in pediatric critical illness. Bello et al. and Braun et al. [23,24] reported that RDW was closely associated with long-term mortality of community-acquired pneumonia. Topaz et al. [25] reported that RDW > 14.5% was a predictor of poor outcome in patients with influenza. This evidence all supported the idea that RDW level was closely associated with prognosis of respiratory tract infections. Our investigation added the value of RDW level in the risk of specific RTI cases and recent conditions. Zhan et al. reported that RDW level > 13.16% was an independent risk factor for left atrial thrombus/left atrial spontaneous echo contrast in patients with non-valvular atrial fibrillation [26]. Our findings also showed that the RDW cutoff point was between 13.35 and 13.75. The comparison of indexes between RDW > 14% and ≤ 14% showed positive results. Zou et al. reported that elevated RDW may be an independent prognostic factor for the severity and poor prognosis of acute kidney injury after cardiac surgery [14]. Blaslov et al. [27] reported that RDW was associated with the risk of diabetic retinopathy development and progression. Our findings showed that RDW level was associated with inflammation, liver and cardiac injury markers, influencing the disease prognosis. Soohoo et al. [28] reported that RDW was associated with a higher risk of time to first hospitalization and a higher rate of hospitalizations in peritoneal dialysis patients. Conversely, our finding showed that RDW level was not associated with the length of hospitalization, which may be because dialysis cases were likely to be complicated with anemia. An increased RDW will aggravate anemia. Hence, increased RDW level may affect the anemia risk and progression, leading to the extension of hospitalization. Our findings had important clinical implications that RDW level reflected the disease course of RTIs in children. Future, larger studies may focus on the in-depth analysis and mechanism. Several limitations should be considered in our study. First, our investigation was cross-sectional, retrospective study, which limited the analysis of longer follow-up of cases, such as the association between RDW level and clinical outcomes, including shock and death. Second, the disease severity may affect the level of RDW. We only investigated the relationship between RDW level and specific diseases. Further studies should be performed to address this issue. Finally, a larger number of participants enrolled in our study would have increased the statistical power. Nevertheless, our study had important clinical implications.

CONCLUSION

Our investigation indicated that RDW was a non-invasive, low-cost, and widely available predictor for the risk and progression of RTIs. RDW level may reflect the disease course among RTIs.

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Declaration of Interest:
There is no conflict of interest for all authors.

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