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Patients with heart failure and reduced ejection fraction after sacubitril/valsartan treatment may be at risk for major adverse cardiovascular events according to ΔRDW.

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Abstract:

The objective of this study was to assess the correlation between alterations in the distribution width of red blood cells (RDW) and the incidence of major adverse cardiovascular events (MACEs) in patients with heart failure with reduced ejection fraction (HFRF) receiving sacubitril/valsartan therapy. **Implementing Methods:** After obtaining permission from the Institutional Ethics Committee, the present study was initiated. This study retrospectively examined the medical records of hospitalized patients diagnosed with HFRF. The patients were allocated into two distinct groups, namely, the traditional group and the sacubitril/valsartan group, based on whether sacubitril/valsartan was incorporated into their individual pharmacological treatment regimen. The RDW values before and after treatment with sacubitril/valsartan are documented as RDW1 and RDW2, respectively. ΔRDW is defined as the value obtained by subtracting RDW1 from RDW2. Based on ΔRDW >0 or ≤0, patients in the sacubitril/valsartan group were categorized into two subgroups. MACEs, including mortality and readmission for myocardial infarction, acute myocardial infarction, and ischemic stroke, were documented in each cohort throughout the one-year follow-up period. **Findings:** Patients who received sacubitril/valsartan exhibited a reduced incidence of MACE compared to those who received conventional therapy (log-rank, P<0.001). During the follow-up period, the incidence of cardiac events was significantly higher in the ΔRDW >0 group than in the ΔRDW ≤ 0 group (Breslow, P<0.001). There was a significant positive correlation between increased RDW and a decreased likelihood of developing MACE (odds ratio [OR] = 3.044, 95% confidence interval [CI]:1.592–

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4.357). Furthermore, for every unit increase in RDW, the risk of developing MACE increased by 23.2% (OR=2.332, 95% CI:1.185–2.499). Treatment with sacubitril/valsartan effectively reduced the incidence of MACEs in HFRF patients. In addition, variations in RDW serve as predictors of MACEs after sacubitril/valsartan treatment.

Key words: distribution width of red blood cells, heart failure with reduced ejection fraction, major adverse cardiovascular events, sacubitril, valsartan

Introduction:

Heart failure (HF) with a diminished ejection fraction is distinguished by the impaired capacity of the heart to efficiently circulate blood, resulting in lethargy, fluid retention, and fatigue [1,2]. HF continues to be a significant public health issue, impacting millions of people globally and placing considerable financial strain on the health care system. The annual incidence of symptomatic HF in patients' disease (CHD) patients in India ranges from 0.4% to 2.3% [3,4]. This means that 120,000–690,000 Indians could develop HF annually due to CHD if no one had HF at baseline and that the at-risk population remained constant [1]. Among the diverse subtypes of heart failure, heart failure with reduced ejection fraction (HFRF) is a particularly formidable clinical entity [5]. Patients with HFRF may benefit from sacubitril/valsartan, an innovative therapeutic agent that has surfaced as a viable alternative treatment [6]. The sacubitril/valsartan combination has been shown to improve the prognosis of patients with HFRF by inhibiting the renin-angiotensin-aldosterone system and increasing natriuretic peptide levels [3]. Nonetheless, even after the initiation of sacubitril/valsartan therapy, a considerable proportion of patients with HFRF develop major adverse cardiovascular events (MACE), including myocardial infarction, cerebrovascular accident, and fatalities from the cardiovascular system [3]. Notwithstanding its established effectiveness in mitigating hospitalization and mortality, this medication does not elicit a favorable response in all patients [2]. Recent studies have indicated that ΔRDW (change in red cell distribution width), an uncomplicated and economically viable biomarker, might be able to identify individuals who are susceptible to MACE after treatment with sacubitril/valsartan [2].

To optimize patient care and outcomes, it is critical to identify factors that predict adverse outcomes [1]. Recently, there has been increased interest in the notion of ΔRDW, which signifies

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the temporal variation in RDW, as a potentially valuable prognostic indicator for cardiovascular ailments, such as HFRF [3]. Complete blood count (CBC) tests routinely measure RDW, which reflects the heterogeneity in the size of blood cells. Various cardiovascular and non-cardiovascular diseases have historically been linked to elevated RDW, which also functions as an indicator of inflammation, oxidative stress, and erythropoiesis impairment [4]. There are numerous justifications for investigating RDW in the context of sacubitril/valsartan treatment in patients with HFRF [3]. First, the ever-evolving characteristics of ΔRDW enable instantaneous surveillance of alterations in a patient's state, which may provide valuable insights regarding the likelihood of MACE [5]. Furthermore, ΔRDW may serve as an indicator of drug efficacy in mitigating cardiac stress and enhancing hemodynamics [6]. This information is critical for identifying non-responders or patients who remain at an elevated risk of adverse events despite treatment. Furthermore, ΔRDW is an easily accessible economic indicator, rendering it a pragmatic instrument for risk stratification in healthcare environments with limited resources [8].

Several studies have investigated the correlation between RDW and adverse cardiovascular outcomes in patients with HFRF [9-12]. Although these inquiries have produced encouraging outcomes, additional research is required to validate and enhance our understanding of how ΔRDW can be incorporated into clinical practice [13]. This study aimed to fill this gap in the literature by systematically assessing the association between ΔRDW and MACE in patients with HFRF who received sacubitril/valsartan treatment. Hence, the objective of this study was to assess the correlation between alterations in RDW and the incidence of MACEs in patients with HFRF receiving sacubitril/valsartan therapy.

Materials & methods:

After obtaining permission from the Institutional Ethics Committee, the present study was initiated. The study was conducted in the department of Medicine, VIMSAR, Burla, Odisha. This study retrospectively examined the medical records of hospitalized patients diagnosed with HFRF. Sex, age, and medical history, including hypertension, diabetes, prior smoking, alcohol consumption, and medication usage, were also recorded. Medication history included antiplatelet drugs, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs),

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cardiac glycosides, β-blockers, thrombin inhibitors, lipid-lowering drugs, calcium channel blockers (CCBs), and angiotensin receptor blockers (ARBs). The patients were allocated into two distinct groups, namely, the traditional group and the sacubitril/valsartan group, based on whether sacubitril/valsartan was incorporated into their individual pharmacological treatment regimen. The RDW values before and after treatment with sacubitril/valsartan are documented as RDW1 and RDW2, respectively. ΔRDW is defined as the value obtained by subtracting RDW1 from RDW2. Based on ΔRDW >0 or ≤0, patients in the sacubitril/valsartan group were categorized into two subgroups. MACEs, including mortality and readmission for myocardial infarction, acute myocardial infarction, and ischemic stroke, were documented in each cohort throughout the one-year follow-up period.

The parameters analyzed were platelet count (PLT), D-dimer, white blood cell count, low-density lipoprotein, hemoglobin, triglyceride, neutrophil percentage, RDW, fasting blood glucose, alanine aminotransferase, hematocrit, aspartate aminotransferase, blood urea nitrogen, serum potassium, total cholesterol, creatinine, and homocysteine. The ejection fraction of the left ventricle (LVEF) was derived from the cardiac ultrasound report. The RDW1 value was assigned to blood parameter values assessed upon initial admission for patients receiving sacubitril/valsartan treatment. ΔRDW was established to represent the discrepancy between the initial and final values (RDW = RDW2–RDW1). After discharge, the 1-year incidence of MACE was determined via telephone and review of the medical records.

Statistical analysis:

The reported values are means and standard deviations. A comparative analysis was conducted on the baseline characteristics of the traditional and sacubitril/valsartan groups. Categorical variables were analyzed using the chi-square test, whereas continuous variables were analyzed using the Mann–Whitney U-test or Student's t–test. Statistical significance was set at $p < 0.05$.

Results & Discussion:

The present research has unveiled a multitude of noteworthy discoveries. First, the treatment regimens for patients with HFRF differ in their potential to induce cardiac events. The drug

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regimen consisting of sacubitril, and valsartan protected against the development of MACE, as evidenced by the more pronounced decrease in RDW observed in this group. Furthermore, analysis conducted on the sacubitril/valsartan group indicated that cardiac events occurred with greater frequency in the positive ΔRDW group (ΔRDW > 0) than in the negative ΔRDW group (ΔRDW ≤ 0). According to these findings, prognostic factors may be associated with RDW alterations in patients with HFRF treated with sacubitril/valsartan drugs.

Sacubitril-valsartan decreases the risk of rehospitalization for heart failure by 21% in comparison to conventional treatment approaches, according to related studies [9]. Significantly, both cohorts demonstrated that elderly males are particularly susceptible to developing HF.

RDW predicted 1-year mortality in patients with acute and chronic HF independently [10]. For every unit increase in RDW, the risk of developing MACE increased by 23.2% (OR=2.332, 95% CI:1.185–2.499). The precise mechanism underlying RDW abnormalities in cardiovascular disease remains unknown. Among numerous potential factors, chronic inflammation, oxidative stress, and neurohormonal activation are crucial components. Inflammation suppresses bone marrow function, inhibits renal erythropoietin synthesis, and induces apoptosis of erythroid precursors in the bone marrow, according to previous research. These effects manifest as variations in the volume and size of red blood cells (RBCs) and elevated RDW values in laboratory analyses [11,12].

Based on a single RDW measure, the role of RDW in HF continues to be investigated; however, owing to a lack of attention and in-depth studies, no research has been reported on the influence of RDW changes before and after HF treatment on predicting patient prognosis. Recently, ΔRDW, a novel concept, was introduced to account for the dynamic nature of variations in the RDW. Its potential applications include documenting the disparity between RDW values at the onset of clinical treatment and at different time intervals thereafter or assigning unit variations in RDW within the study population a designation by the investigator. Aslam et al. [13] demonstrated that in patients who survived within 30 days, ΔRDW was stable and modest, with negative changes in RDW serving as a more accurate indicator of treatment efficacy. Our study monitored the incidence of MACEs in HFRF patients treated for one year with sacubitril/valsartan. During the

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observation period, the increased RDW group had a higher probability of experiencing a significant adverse cardiac event than the decreased RDW group, as determined by analysis. Forward ΔRDW levels were significantly associated with cardiac events, as determined by analysis (hazard ratio 3.172, 95% CI, 2.423–4.364; P<0.05). A significant correlation between the forward ΔRDW level and cardiac events was identified in a multivariate model that accounted for potential confounding factors (smoking, RDW, and diabetes). The hazard ratio for this association was 3.166 (95% confidence interval [CI], 2.412–4.357; P< 0.05). In this study, fatalities occurred within the negative ΔRDW group, even though their prognosis was more favorable than that of the positive ΔRDW group. Retrospective data indicated that this patient underwent a reexamination period of 10 weeks, with a ΔRDW of -6. The duration until patient mortality was three months; therefore, it was hypothesized that significant changes in RDW (either increased or decreased) would lead to a higher incidence of cardiac events. However, further validation is required.

Table 1: ΔRDW versus MACE

Variable	P value	OR (95% CI)
RDW	< 0.05	2.287 (2.144 – 2.668)
Smoking	< 0.05	2.722 (2.159 – 3.589
Diabetes	< 0.05	1.778 (1.036 – 2.818

The significant difference in blood pressure between patients in the traditional group and those in the sacubitril/valsartan group was attributable to the antihypertensive effect that patients produced while receiving sacubitril/valsartan treatment for HF in this study. Hypertension and heart failure are well-known to be associated, and renal impairment, arteriosclerosis, and left ventricular hypertrophy are all plausible contributors to the development of this syndrome [14]. To manage sodium and water retention in heart failure, diuretics are frequently necessary; therefore, they are the treatment of choice for comorbid hypertension.

Conclusion:

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HF with reduced ejection fraction is a complex clinical syndrome with a considerable burden of morbidity and mortality. Sacubitril/valsartan has emerged as a valuable therapeutic option; however, its efficacy varies among patients. The identification of patients at risk for major adverse cardiovascular events is crucial for tailoring treatment strategies. ΔRDW, a dynamic and easily accessible biomarker, has the potential to enhance the risk stratification in this population. This study aimed to contribute to the growing body of evidence on the role of ΔRDW in predicting MACE in HFRF patients receiving sacubitril/valsartan therapy, with the goal of improving patient outcomes and guiding clinical decision-making.

Conflict of interest:

The authors declare that they have no conflict of interest.

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