



RED BLOOD CELL DISTRIBUTION WIDTH IN HEART FAILURE: PATHOPHYSIOLOGY, PROGNOSTIC ROLE, CONTROVERSIES AND DILEMMAS

Pathology

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ABSTRACT

Red blood cell distribution width (RDW), an integral parameter of the complete blood count (CBC), has been traditionally used for the classification of several types of anemia. However, over the last decade RDW has been associated with outcome in patients with several cardiovascular diseases including heart failure. The role of RDW in acute, chronic and advanced heart failure is the focus of the present work. Several pathophysiological mechanisms of RDW's increase in heart failure have been proposed (i.e., inflammation, oxidative stress, adrenergic stimulation, undernutrition, ineffective erythropoiesis, reduced iron mobilization, etc.); however, the exact mechanism remains unknown. Although high RDW values at admission and discharge have been associated with adverse prognosis in hospitalized heart failure patients, the prognostic role of in-hospital RDW changes (Δ RDW) remains debatable. RDW has been incorporated in recent heart failure prognostic models. Utilizing RDW as a treatment target in heart failure may be a promising area of research.

KEYWORDS

red blood cell distribution width; heart failure; prognosis; mechanisms

INTRODUCTION

Red blood cell distribution width (RDW) is an integral parameter of the complete blood count (CBC), which has been traditionally used for the classification of several types of anemia [1]. It has been defined either as the standard deviation (SD) of erythrocyte volumes (RDW-SD), which is measured by calculating the width at the 20% height level of the red blood cell (RBC) size distribution histogram; or, as the coefficient of variation (RDW-CV) of erythrocyte volumes by dividing the standard deviation (SD) of the red blood cell volume (RBCs) by the mean corpuscular volume (MCV) multiplied by 100 ($SD/MCV \times 100$), and expressing the variability in size of circulating erythrocytes (anisocytosis) (Figure 1) [2]. The normal reference ranges of RDW-SD and RDW-CV are typically 39–46 fL and 11.5–15%, respectively, but often vary depending on the method of RDW calculation and the available hematological analyzers used [3].

Over the last decade, changes in RDW have been associated with outcomes in several discrete populations [4,5], such as in patients with cardiovascular disease [6] including stable coronary artery disease [7], acute coronary syndromes [8], acute myocardial infarction [9], stroke [10] and heart failure (HF). The changes of RDW in HF is the focus of the present work. In this regard, the prevalence, direction and clinical significance of RDW changes, and the contribution of RDW changes to outcome prediction in the relevant HF prognostic models are summarized. Further, the potential underlying mechanisms of RDW changes in acute, chronic and advanced HF as well as the areas of future research regarding this hematological marker will be discussed.

2.(Patho)Physiology of RDW Increase in Heart Failure Erythropoiesis mainly occurs in the bone marrow [11]. Traditionally, it is considered that the main physiological role of RBCs, or erythrocytes, is to transport oxygen and carbon dioxide from the lung to the tissues and to maintain systemic acid/base equilibria [12]. However, recent clinical and experimental evidence suggests that RBCs may be directly involved in nitric oxide (NO) metabolism and control of blood rheology, as well as erythrocyte function (i.e., by releasing nitric oxide (NO), NO metabolites and adenosine triphosphate) [12]. In humans, the life span of RBCs is 120 days. Under normal conditions, approximately 1% of RBCs are synthesized each day, but RBC production can increase substantially during times of acute or chronic stress [11]. The typical mature erythrocyte is disc-shaped, with a diameter between 6–8 μ m and a total volume, also known as mean corpuscular volume (MCV), ranging between 80 and 100 fL [13]. Nevertheless, the mechanical properties and lipid architecture are altered in RBCs from subjects with cardiovascular risk factors, resulting in reduced tissue perfusion, increased oxidative stress, reduced oxygen delivery and an increase in whole blood viscosity which may lead to increased cardiovascular mortality [14]. The

pathophysiological mechanism of RDW's rise (i.e., increased anisocytosis) in HF remains obscure (Figure 2) [13]. It has been suggested that inflammation, neurohormonal and adrenergic system activation may bring about changes in RBC maturation by disturbing the red cell membrane, thereby leading to increased RDW [15]. HF is associated with the activation of both cell- and cytokine-mediated inflammatory pathways, which can impair bone marrow function with the release of premature erythrocytes into the circulation [16]. A correlation between RDW and established inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP) has been reported [17,18].

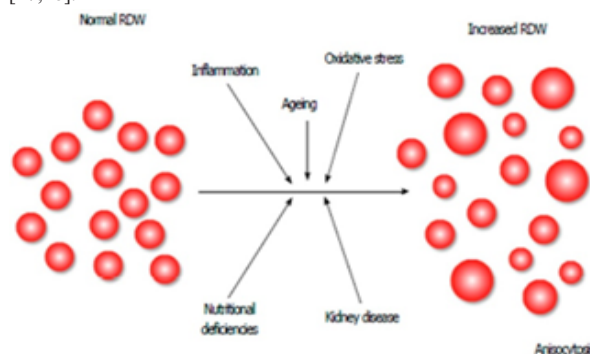


Figure 1: Definition and calculation of the red blood cell distribution width (RDW); in the case of anisocytosis, RDW increases. RDW-CV, coefficient of variation of erythrocyte volumes; RDW-SD, standard deviation of erythrocyte volumes; RBC, red blood cell; MCV, mean corpuscular volume.

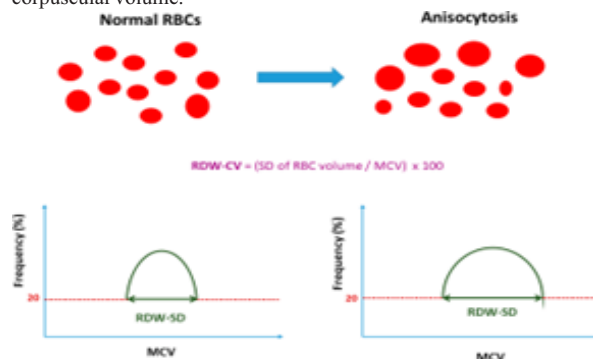


Figure 2. Pathophysiological mechanisms causing anisocytosis.

RDW: red blood cell distribution width [13].

The nervous system emerges as a critical regulatory player of the bone marrow; the primary site of postnatal hematopoiesis and hematopoietic stem cell (HSC) maintenance [19]. Several studies support the central role of the sympathetic nervous system (SNS) in the regulation of hematopoiesis [20]. Norepinephrine is delivered to the bone marrow by the sympathetic nerve in a circadian (diurnal) manner which regulates the expression of core genes in the bone marrow, leading to the fluctuation of immune cell egress in both humans and rodents [21]. A correlation between the proliferation of many HSCs and the circadian oscillation in concentrations of norepinephrine in the bone marrow has also been reported [22]. Therefore, a close communication exists between the SNS and the bone marrow, and dysregulation in this communication may lead to aberrant hematopoietic and immune system responses and increased RDW values [23]. Ineffective erythropoiesis, reduced iron mobilization, oxidative stress, renal failure as well as nutritional deficiencies have been also implicated in the pathophysiology of RDW increase in HF patients [17,18].

3. RDW Change in Heart Failure

RDW in Incident Heart Failure

Several studies have demonstrated that RDW is an independent predictor of incident HF. In a retrospective population-based cohort analysis including 26,784 middle-aged subjects without history of myocardial infarction, stroke or HF, who participated in the Malmo Diet and Cancer study (1991–1996) and were followed up for up to 15 years, a higher RDW was found to be associated with higher long-term incidence of first hospitalization due to HF (Hazard Ratio (HR): 1.47, 95% Confidence Interval (CI): 1.14–1.89, in the top compared with the bottom quartile of RDW), after adjusting for history of coronary revascularization, biological, lifestyle and socio-economic factors [24]. Emans et al. reported that RDW levels were associated with an increased risk of incidence of HF utilizing data from 17,533 participants from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk cohort [25]. Among them, 640 participants developed HF during a follow-up of 11.2 ± 2.2 years and authors observed that there was a non-linear increase in HF risk as RDW values were increasing [25].

RDW in Chronic HF

The RDW is associated with indices of cardiac function and/or disease severity in HF including the natriuretic peptides [26,27], peak oxygen consumption [28,29], left ventricular end diastolic pressure (LVEDP) [30] and left ventricular deformation [31,32].

The first study examining the predictive value of RDW in chronic HF was conducted by Felker et al. back in 2007 [33]. The authors found that RDW exhibited the strongest association with cardiovascular death or HF hospitalization (adjusted HR 1.17 per 1-SD increase, 95% CI: 1.10–1.25, $p < 0.001$) among 36 laboratory parameters in a cohort of 2679 symptomatic chronic HF patients from the North American CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program. Similar were the findings in the Study of Anemia in a Heart Failure Population (STAMINA-HF) [18,34], as well as in patients post myocardial infarction (MI) [35]. In this regard, it has been proposed that RDW may be a better predictor of outcomes in HF patients than several echocardiographic parameters [36]. It is noteworthy that no association was observed between RDW and HF due to valvular heart disease [37]. A recent study reported an independent association between a low hemoglobin/RDW ratio and the risk of death as well as the combined endpoint of death or cardiovascular hospitalization in a cohort of 6888 HF patients. Interestingly, this association was observed over the whole spectrum of HF types, including HF_{rEF} and HF_{pEF} [38].

RDW in Acute HF

Increased RDW may be associated with a slower diuretic response [39], and elevated LV filling pressure (E/E') [40], and has been shown to predict early mortality in patients presenting with acute dyspnea at the emergency department (ED), irrespective of its etiology [41]. Notably, the addition of RDW to conventional laboratory tests (B-type natriuretic peptide, creatinine, sodium and chloride) may significantly improve the 30-day prognostic assessment (for all-cause mortality) of acute HF patients presenting in the ED [42]. The prognostic value of RDW in acute HF was initially reported in a Spanish study, which included 628 consecutive patients [43]. Pascual-Figal et al. collected

clinical, echocardiographic and laboratory variables at discharge and followed up with patients for ~2¹ years. RDW was found to be a strong and independent marker of all-cause mortality ($p = 0.004$, HR 1.072, 95% CI 1.023–1.124), regardless of anemia status (p for interaction > 0.1 for the entire population). Therefore, this study demonstrated that RDW may be used as an early predictor of adverse outcomes in non-anemic HF patients. Subsequently, it was demonstrated that RDW provided additional prognostic information to natriuretic peptides [44–48], that it may also be useful in the elderly [49] and that it may be a better predictor of outcome in patients with a preserved, than in those with reduced, left ventricular ejection fraction (LVEF) [50,51]. Patients with high RDW and N-terminal pro B-type natriuretic peptide (NT-proBNP) values exhibit the highest mortality rates, whereas those with low RDW and NT-proBNP exhibit the most favorable outcomes. Finally, a significant interaction between diabetes and RDW longitudinal changes from the patient's admission to 1-year post discharge has been reported [52].

RDW in Advanced HF

A retrospective analysis of 367 consecutive patients with advanced HF (New York Heart Association class III–IV) and concomitant diabetes mellitus revealed RDW as an independent predictor of all-cause mortality during the long term follow up [53].

RDW may be useful in risk stratification of patients selected for implantable cardioverter defibrillator (ICD) therapy as it predicts death and appropriate therapy [54]. In patients with advanced HF undergoing cardiac resynchronization therapy (CRT), it has been reported that elevated RDW is associated with lower rates of “positive response” to CRT (defined as a reduction in LV end-systolic volume (LVESV) $\geq 15\%$ or a relative increase in LVEF $\geq 15\%$) [55,56], and that elevated the RDW level before and after CRT implantation is independently associated with all-cause mortality [57].

A retrospective single center analysis of 188 continuous flow left ventricular assist devices (LVADs) implanted from 2004 to June 2014, revealed an independent association between higher pre-implant RDW values and mortality in a more than 1 year follow up [58]. Similarly, in the study by Truby et al. RDW was independently predictive of 90-day mortality (Odds Ratio (OR), 1.16 for 1% increase; CI, 1.04–1.31; $p = 0.010$) in a population of 409 continuous-flow LVADs [59]. Notably, mechanical unloading with continuous-flow LVADs was associated with a reduction in RDW levels. On the contrary, Ahmad et al. reported no change in RDW values, at a median of 135 days after LVAD placement [60]. Poglajen et al. proceeded to a 5-day bone marrow stimulation with granulocyte colony stimulating factor (G-CSF) in 44 patients with advanced HF [61]. On the fifth day, a full blood count and a peripheral blood CD34⁺ cell count were performed. On a multivariable analysis, RDW turned out to be a sole independent predictor of poor stem cell mobilization (HR 8.64, 95% CI: 1.242–60.021, $p = 0.01$). Although the underlying mechanisms are not clearly defined, it appears that RDW may represent a useful tool to improve the selection of candidates for stem cell therapy in this population of patients [61]. Lastly, increased RDW in advanced HF patients immediately before orthotopic heart transplantation is an independent predictor of post-operative mortality during an average follow-up of 45.5 months [62]. 4.

4. RDW Longitudinal Changes in HF

Acute HF

Several studies have reported the association between an increase in RDW longitudinal values (Δ RDW) during HF hospitalization and adverse short [63,64] as well as long-term outcomes [65–67]. Enlarging RDW during hospitalization has added valuable prognostic information on top of hemoconcentration [68], whereas patients with positive Δ RDW between admission and 1 month after discharge have demonstrated a significantly higher cardiovascular mortality and HF re-hospitalizations compared with those with no positive RDW changes [69]. Núñez et al. reported the longitudinal association of RDW with mortality and anemia in 1702 patients recently hospitalized for AHF [70]. The investigators utilizing sophisticated statistical methods found that the RDW trajectory differs according to the patient's outcome, with relatively stable RDW levels over time for those patients who remained alive during the follow up (median follow-up = 1.5 years), and with a steeper slope near its occurrence for those who died [70].

Chronic HF

In a cohort of 6159 ambulatory chronic HF patients, RDW's positive change from baseline to 1-year follow up was associated with all-cause mortality over a mean period of 4.4 ± 2.4 years (risk ratio for +1% increase in changes in RDW was 1.08 (95% CI 1.03–1.13; $p = 0.001$)) [71]. This effect was independent of anemia status or other baseline cardiac or renal indices, and particularly strong in those with a lower baseline RDW. In another study of 274 chronic HF patients, the combination of expanding RDW value and the evolving iron deficiency (falling MCV) over time conferred a three-fold escalated risk of mortality independently of changes in hemoglobin and RDW [72].

Taken all together, the above studies suggest that monitoring changes in RDW may serve as a robust longitudinal indicator for outcomes in the entire HF spectrum. Nevertheless, these findings were not replicated in a recent study which analyzed data from two cohorts with AHF patients [73]. In particular, the Δ RDW (admission RDW—discharge RDW) was similar between patients who developed [0.2 (–0.2 to 0.7)] and those who did not develop [0.0 (–0.1 to 0.5)] the study endpoint all-cause death or HF rehospitalization at 1 year (p not adjusted for ties = 0.863; p adjusted for ties = 0.271). The contradictory findings between the latter study and previous studies indicating that Δ RDW during hospitalization has clinical significance are incompletely understood. A potential explanation might be that the value of Δ RDW is small and may lie within the laboratory (assay) variation. Moreover, there is compelling evidence indicating that RDW may reflect inflammation [74]. Interestingly, inflammatory markers remain practically unaffected in the short term in hospitalized HF patients [75]. Nevertheless, whether RDW is the glycated hemoglobin (HbA1c) of the HF patient or not needs to be answered in future studies.

5. Systematic Reviews and Meta-Analyses

A systematic review and meta-analysis of 17 cohort studies with a total of 18,288 patients hospitalized for HF showed that RDW on admission and RDW at discharge, as well as its change during treatment, were of prognostic significance for HF patients [76]. In particular, a 1% increase in baseline RDW was associated with a 10% higher risk of all-cause mortality [76]. Similarly, in the meta-analysis by Shao Q et al. (17 studies and 41,311 patients), for every 1% increase in RDW, the risk of all-cause mortality increased by 12% (HR 1.12, 95% CI 1.08–1.16) [77]. In addition, every 1% increase in RDW was associated with a 9.1% increase in the risk of HF hospitalization (HR 1.091, 95% CI 1.025–1.162, $I^2 = 52.8\%$). Lastly, the meta-analysis by Hou H et al. consisting of 28 studies and 102,689 participants, revealed an HR of 1.12 (95% CI = 1.09–1.15) for all-cause mortality and an HR of 1.12 (95% CI = 1.08–1.17) for major adverse cardiac events, per 1% increase of RDW [78].

6. RDW and Prognostic Scores in HF

Risk prediction in HF provides information about patient prognosis, guides decision making and enables better understanding of provider performance [79]. A number of prognostic models have been developed both in acute and chronic HF [80,81]. RDW has been incorporated in some of them. For example, the Larissa Heart Failure Risk Score (LHFRS) is a simple prognostic model consisting of three variables, namely, history of hypertension, history of coronary artery disease/myocardial infarction and $\text{RDW} \geq 15\%$ [82,83]. Recently, this score has been externally validated in a cohort of 1670 consecutive AHF patients enrolled in The Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure (REALITY-AHF) [84] and found to be an independent predictor of 1-year all cause-death or HF rehospitalization (adjusted HR per 1-point increase, 95%CI: 1.17 [1.04–1.32], $p = 0.011$) [84].

A risk score derived from the machine learning assessment of risk and early mortality in heart failure (MARKER-HF) model accurately discriminated between low and high-risk of death ($\text{AUC} = 0.88$) by identifying eight variables, including RDW [85]. Lastly, RDW was included in the sex-specific intermountain inpatient heart failure model (iHF) for males [86]. The latter was derived during an inpatient admission (within 24h of hospitalization) and effectively predicted post-discharge 30-day readmission in independent validation populations.

7. RDW and Congenital Heart Disease

Congenital heart disease (CHD) is a common cause of HF and several studies have examined the association between RDW and outcomes in

CHD patients. Increased RDW is a predictor of worse outcome in children undergoing surgery for CHD [87], in children with HF due to CHD [88] and in children with Tetralogy of Fallot undergoing corrective repair [89]. Interestingly, RDW is associated with central venous pressure and SVO₂ in pediatric patients with Fontan circulation [90]. In adult patients with CHD, elevated RDW has been associated with increased IL-6 [91], low exercise capacity [92], as well as adverse cardiovascular events and poor survival [93–95].

8. RDW And Anemia

Nutritional deficiencies and heterozygous hemoglobinopathies are present in many forms of anemia and are characterized by different degrees of anisocytosis [13]. However, several studies in the general population [5,24,25], as well as in acute [43,46,66,70], chronic [33,96] and advanced [97] heart failure have demonstrated the independent (of anemia) prognostic value of RDW. Nevertheless, keeping in mind that RDW is strongly inversely associated with anemia, its interpretation in anemic patients should be made with caution.

Table 1. Facts And Open Issues About RDW.

Facts	Open Issues/Controversies
RDW is an integral marker of the complete blood count and can be calculated by automatic hematology analyzers.	No universal consensus on the recommended method of RDW calculation (standard deviation or coefficient of variation) currently exists.
The typical reference range value of RDW-CV is 11.5–15% and of RDW-SD is 39–46 fL	No universal reference range values exist. Those often vary depending on the method of RDW calculation and the available hematology analyzers used.
RDW is an established simple prognostic marker in heart failure (acute, chronic and advanced).	There are limited data on the role of RDW in cardio-oncology.
Several pathophysiological mechanisms of the RDW increase in heart failure have been proposed (inflammation, adrenergic stimulation, undernutrition, etc.).	The exact pathophysiological mechanism of RDW increase in heart failure remains unknown.
RDW values at hospital admission and discharge have been associated with prognosis in heart failure patients.	There is a debate on the prognostic value of in-hospital RDW changes (Δ RDW).
The current RDW indications include the classification of several types of anemia and the estimation of patients' risk in cardiovascular diseases (including heart failure).	RDW may be used in the future to guide therapy in heart failure.

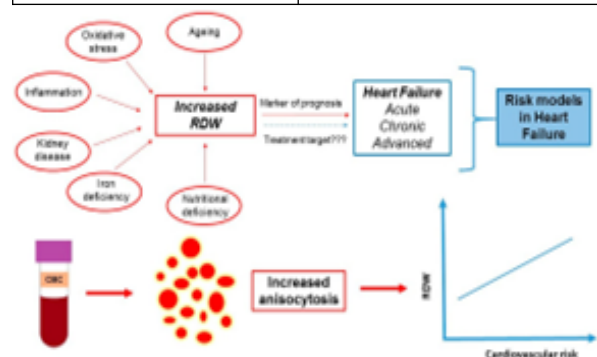


Figure 3. The role of RDW in heart failure. RDW is a simple parameter derived from the complete blood count (CBC) and expresses the variability in red blood cell size (anisocytosis). RDW has been used as a marker of prognosis in acute, chronic and advanced heart failure either as a sole variable or as a variable included in risk models. Higher RDW has been associated with increased risk of death and/or re-hospitalization. Several (patho)physiological mechanisms such as ageing, oxidative stress, inflammation, kidney disease, iron deficiency and nutritional deficiency have been implicated in the reported RDW increase in patients with heart failure. Whether or not RDW can be used as a treatment target remains to be elucidated in future studies.

9.Future Perspectives

A fruitful area of research may be the evaluation of the prognostic value of RDW in cardio-oncology [98]. Until now, RDW has been used mainly for the assessment of prognosis, either as a sole marker or as a part of risk models, in HF patients. Nevertheless, keeping in mind that RDW reflects several mechanisms of HF development may expand its indications from a marker of prognosis to a treatment target (Table 1). Interestingly, data from the BIOSTAT-CHF (Biology Study to Tailored Treatment in Chronic Heart Failure) showed that up-titrating patients with HF based on biomarker values might have resulted in fewer deaths or hospitalizations compared with a hypothetical scenario in which all patients were successfully up-titrated [99]. Lastly, mechanistic studies regarding RDW increase in HF would be of great interest.

CONCLUSIONS

RDW is a simple marker of the CBC initially used for the classification of different types of anemia. It has an established prognostic role in acute, chronic and advanced HF (Table 2, Figure 3). A controversy exists regarding the prognostic value of in-hospital RDW changes in acute HF. Utilizing RDW as a treatment target in HF may be a promising area of research.

REFERENCES

- Bessman, J.D.; Gilmer, P.R.; Gardner, F.H., Jr. Improved classification of anemias by MCV and RDW. *Am. J. Clin. Pathol.* **1983**, *80*, 322–326. [CrossRef] [PubMed]
- Salvagno, G.L.; Sanchis-Gomar, F.; Picanza, A.; Lippi, G. Red blood cell distribution width: A simple parameter with multiple clinical applications. *Crit. Rev. Clin. Lab. Sci.* **2015**, *52*, 86–105. [CrossRef] [PubMed]
- Buttarelli, M.; Plebani, M. Automated blood cell counts: State of the art. *Am. J. Clin. Pathol.* **2008**, *130*, 104–116. [CrossRef] [PubMed]
- Uyarel, H.; Isik, T.; Ayhan, E.; Ergelen, M. Red cell distribution width (RDW): A novel risk factor for cardiovascular disease. *Int. J. Cardiol.* **2012**, *154*, 351–352. [CrossRef]
- Fava, C.; Cattazzo, F.; Hu, Z.D.; Lippi, G.; Montagnana, M. The role of red blood cell distribution width (RDW) in cardiovascular risk assessment: Useful or hype? *Ann. Transl. Med.* **2019**, *7*, 581. [CrossRef]
- Talarico, M.; Manicardi, M.; Vitolo, M.; Malavasi, V.L.; Valenti, A.C.; Sgreccia, D.; Rossi, R.; Boriani, G. Red cell distribution width and patient outcome in cardiovascular disease: A “real-world” analysis. *J. Cardiovasc. Dev. Dis.* **2021**, *8*, 120. [CrossRef]
- Tonelli, M.; Sacks, F.; Arnold, M.; Moye, L.; Davis, B.; Pfeffer, M.; For the Cholesterol and Recurrent Events Trial Investigators. Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. *Circulation* **2008**, *117*, 163–168. [CrossRef]
- Abraham, L.L.T.; Ramos, J.D.A.; Cunanan, E.L.; Tiongson, M.D.A.; Punzalan, F.E.R. Red cell distribution width and mortality in patients with acute coronary syndrome: A meta-analysis on prognosis. *Cardiol. Res.* **2018**, *9*, 144–152. [CrossRef]
- Sahin, O.; Akpek, M.; Sarli, B.; Baktir, A.O.; Savas, G.; Karadavut, S.; Elcici, D.; Saglam, H.; Kaya, M.G.; Arinc, H. Association of red blood cell distribution width levels with severity of coronary artery disease in patients with non-ST elevation myocardial infarction. *Med. Princ. Pract.* **2015**, *24*, 178–183. [CrossRef]
- Feng, G.H.; Li, H.P.; Li, Q.L.; Fu, Y.; Huang, R.B. Red blood cell distribution width and ischaemic stroke. *Stroke Vasc. Neurol.* **2017**, *2*, 172–175. [CrossRef]
- Hattangadi, S.M.; Wong, P.; Zhang, L.; Flygare, J.; Lodish, H.F. From stem cell to red cell: Regulation of erythropoiesis at multiple levels by multiple proteins, RNAs, and chromatin modifications. *Blood* **2011**, *118*, 6258–6268. [CrossRef] [PubMed]
- Kuhn, V.; Diederich, L.; Stevenson Keller, T.C., IV; Kramer, C.M.; Luckstadt, W.; Panknin, C.; Suvorova, T.; Isakson, B.E.; Kelm, M.; Cortese-Krott, M.M. Red blood cell function and dysfunction: Redox regulation, nitric oxide metabolism, anemia. *Antioxid. Redox. Signal.* **2017**, *26*, 718–742. [CrossRef] [PubMed]
- Lippi, G.; Turcato, G.; Cervellini, G.; Sanchis-Gomar, F. Red blood cell distribution width in heart failure: A narrative review. *World J. Cardiol.* **2018**, *10*, 6–14. [CrossRef] [PubMed]
- Pernow, J.; Mahdi, A.; Yang, J.; Zhou, Z. Red blood cell dysfunction: A new player in cardiovascular disease. *Cardiovasc. Res.* **2019**, *115*, 1596–1605. [CrossRef]
- Cole, J.; Ertoy, D.; Lin, H.; Sutliff, R.L.; Egan, E.; Guyene, T.T.; Capechchi, M.; Corvol, P.; Bernstein, K.E. Lack of angiotensin II-facilitated erythropoiesis causes anemia in angiotensin-converting enzyme-deficient mice. *J. Clin. Invest.* **2000**, *106*, 1391–1398. [CrossRef]
- Hullin, R.; Barras, N.; Abdurashidova, T.; Monney, P.; Regamey, J. Red cell distribution width and prognosis in acute heart failure: Ready for prime time? *Intern. Emerg. Med.* **2019**, *14*, 195–197. [CrossRef]
- Forhecz, Z.; Gombos, T.; Borgulya, G.; Pozsonyi, Z.; Prohaszka, Z.; Janoskuti, L. Red cell distribution width in heart failure: Prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. *Am. Heart J.* **2009**, *158*, 659–666. [CrossRef]
- Allen, L.A.; Felker, G.M.; Mehra, M.R.; Chiong, J.R.; Dunlap, S.H.; Ghali, J.K.; Lenihan, D.J.; Oren, R.M.; Wagoner, L.E.; Schwartz, T.A.; et al. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. *J. Card. Fail.* **2010**, *16*, 230–238. [CrossRef]
- Leitao, L.; Alves, C.J.; Sousa, D.M.; Neto, E.; Conceicao, F.; Lamghari, M. The alliance between nerve fibers and stem cell populations in bone marrow: Life partners in sickness and health. *FASEB J.* **2019**, *33*, 8697–8710. [CrossRef]
- Cosentino, M.; Marino, F.; Maestroni, G.J. Sympathoadrenergic modulation of hematopoiesis: A review of available evidence and of therapeutic perspectives. *Front. Cell Neurosci.* **2015**, *9*, 302. [CrossRef]
- Mendez-Ferrer, S.; Chow, A.; Merad, M.; Frenette, P.S. Circadian rhythms influence hematopoietic stem cells. *Curr. Opin. Hematol.* **2009**, *16*, 235–242. [CrossRef] [PubMed]
- Katayama, Y.; Battista, M.; Kao, W.M.; Hidalgo, A.; Peired, A.J.; Thomas, S.A.; Frenette, P.S. Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow. *Cell* **2006**, *124*, 407–421. [CrossRef] [PubMed]
- Xanthopoulos, A.; Trypskiadis, K.; Dimos, A.; Bourazana, A.; Zagouras, A.; Iakovis, N.; Papamichalis, M.; Giamouzis, G.; Vassilopoulos, G.; Skoularigis, J.; et al. Red blood cell distribution width in elderly hospitalized patients with cardiovascular disease. *World J. Cardiol.* **2021**, *13*, 503–513. [CrossRef] [PubMed]
- Borne, Y.; Smith, J.G.; Melander, O.; Hedblad, B.; Engstrom, G. Red cell distribution

width and risk for first hospitalization due to heart failure: A population-based cohort study. *Eur. J. Heart Fail.* **2011**, *13*, 1355–1361. [CrossRef]

- Emans, M.E.; Gaillard, C.A.; Pfister, R.; Tanck, M.W.; Boekholdt, S.M.; Wareham, N.J.; Khaw, K.T. Red cell distribution width is associated with physical inactivity and heart failure, independent of established risk factors, inflammation or iron metabolism; the EPIC-Norfolk study. *Int. J. Cardiol.* **2013**, *168*, 3550–3555. [CrossRef]
- Al-Najjar, Y.; Goode, K.M.; Zhang, J.; Cleland, J.G.; Clark, A.L. Red cell distribution width: An inexpensive and powerful prognostic marker in heart failure. *Eur. J. Heart Fail.* **2009**, *11*, 1155–1162. [CrossRef]
- Su, J.L.; Zhang, S.G.; Gao, R.J.; Han, Q.F.; Wang, L.H.; Zhou, Y.H.; Li, T.; Yao, H.C. Red cell distribution width is a predictor of mortality in patients with chronic heart failure. *Int. J. Cardiol.* **2016**, *212*, 79–81. [CrossRef]
- Van Craenenbroeck, E.M.; Pelle, A.J.; Beckers, P.J.; Possemiers, N.M.; Ramackers, C.; Vrints, C.J.; Van Hoof, V.; Denollet, J.; Conraads, V.M. Red cell distribution width as a marker of impaired exercise tolerance in patients with chronic heart failure. *Eur. J. Heart Fail.* **2012**, *14*, 54–60. [CrossRef]
- Hong, S.J.; Youn, J.C.; Oh, J.; Hong, N.; Lee, H.S.; Park, S.; Lee, S.H.; Choi, D.; Kang, S.M. Red cell distribution width as an independent predictor of exercise intolerance and ventilatory inefficiency in patients with chronic heart failure. *Yonsei Med. J.* **2014**, *55*, 635–643. [CrossRef]
- Senthong, V.; Hudec, T.; Neale, S.; Wu, Y.; Hazen, S.L.; Tang, W.H. Relation of red cell distribution width to left ventricular end-diastolic pressure and mortality in patients with and without heart failure. *Am. J. Cardiol.* **2017**, *119*, 1421–1427. [CrossRef]
- Eroglu, E.; Kilicgedik, A.; Kahveci, G.; Bakal, R.B.; Kirma, C. Red cell distribution width and its relationship with global longitudinal strain in patients with heart failure with reduced ejection fraction: A study using two-dimensional speckle tracking echocardiography. *Kardiol. Pol.* **2018**, *76*, 580–585. [CrossRef] [PubMed]
- Fang, S.; Zhang, Z.; Wang, Y.; Jiang, F.; Yang, K.; He, F.; Zhang, C. Predictive value of left ventricular myocardial strain by four-dimensional speckle tracking echocardiography combined with red cell distribution width in heart failure with preserved ejection fraction. *Echocardiography* **2019**, *36*, 1074–1083. [CrossRef] [PubMed]
- Felker, G.M.; Allen, L.A.; Pocock, S.J.; Shaw, L.K.; McMurray, J.J.; Pfeffer, M.A.; Swedberg, K.; Wang, D.; Yusuf, S.; Michelson, E.L.; et al. Red cell distribution width as a novel prognostic marker in heart failure: Data from the CHARM program and the Duke Databank. *J. Am. Coll. Cardiol.* **2007**, *50*, 40–47. [CrossRef] [PubMed]
- Wolowiec, L.; Rogowicz, D.; Banach, J.; Buszko, K.; Surowiec, A.; Blazejewski, J.; Bujak, R.; Sinkiewicz, W. Prognostic significance of red cell distribution width and other red cell parameters in patients with chronic heart failure during two years of follow-up. *Kardiol. Pol.* **2016**, *74*, 657–664. [CrossRef]
- Bozorgi, A.; Mehrabi Nasab, E.; Khoshnevis, M.; Dogmehchi, E.; Hamze, G.; Goodarzynajad, H. Red Cell Distribution width and severe left ventricular dysfunction in ischemic heart failure. *Crit. Pathw. Cardiol.* **2016**, *15*, 174–178. [CrossRef]
- Vizzardi, E.; Sciatti, E.; Bonadelli, I.; Pezzali, N.L.; Lombardi, C.M.; Metra, M. Red cell distribution width and chronic heart failure: Prognostic role beyond echocardiographic parameters. *Monaldi Arch. Chest Dis.* **2016**, *84*, 59. [CrossRef]
- Zhang, Y.; Wang, Y.; Kang, J.S.; Yu, J.X.; Yin, S.J.; Cong, X.F.; Chen, X. Differences in the predictive value of red cell distribution width for the mortality of patients with heart failure due to various heart diseases. *J. Geriatr. Cardiol.* **2015**, *12*, 647–654.
- Rahamim, E.; Zwas, D.R.; Keren, A.; Elbaz-Greener, G.; Ibrahimli, M.; Amir, O.; Gotsman, I. The ratio of hemoglobin to red cell distribution width: A strong predictor of clinical outcome in patients with heart failure. *J. Clin. Med.* **2021**, *11*, 886. [CrossRef]
- Freireira, J.P.; Santos, M.; Almeida, S.; Marques, I.; Bettencourt, P.; Carvalho, H. Tailoring diuretic therapy in acute heart failure: Insight into early diuretic response predictors. *Clin. Res. Cardiol.* **2013**, *102*, 745–753. [CrossRef]
- Oh, J.; Kang, S.M.; Hong, N.; Choi, J.W.; Lee, S.H.; Park, S.; Shin, M.J.; Jang, Y.; Chung, N. Relation between red cell distribution width with echocardiographic parameters in patients with acute heart failure. *J. Card. Fail.* **2009**, *15*, 517–522. [CrossRef]
- Hong, N.; Oh, J.; Kang, S.M.; Kim, S.Y.; Won, H.; Youn, J.C.; Park, S.; Jang, Y.; Chung, N. Red blood cell distribution width predicts early mortality in patients with acute dyspnea. *Clin. Chim. Acta* **2012**, *413*, 992–997. [CrossRef]
- Turcato, G.; Cervellini, G.; Bonora, A.; Prati, D.; Zorzi, E.; Ricci, G.; Salvagno, G.L.; Maccagnani, A.; Lippi, G. Red blood cell distribution width improves reclassification of patients admitted to the emergency department with acute decompensated heart failure. *J. Med. Biochem.* **2018**, *37*, 299–306. [CrossRef]
- Pascual-Figal, D.A.; Bonaque, J.C.; Redondo, B.; Caro, C.; Manzano-Fernandez, S.; Sanchez-Mas, J.; Garrido, I.P.; Valdes, M. Red blood cell distribution width predicts long-term outcome regardless of anaemia status in acute heart failure patients. *Eur. J. Heart Fail.* **2009**, *11*, 840–846. [CrossRef] [PubMed]
- Jackson, C.E.; Dalzell, J.R.; Bezlyak, V.; Tzorlalis, I.K.; Myles, R.C.; Spooner, R.; Ford, I.; Petrie, M.C.; Cobbe, S.M.; McMurray, J.J. Red cell distribution width has incremental prognostic value to B-type natriuretic peptide in acute heart failure. *Eur. J. Heart Fail.* **2009**, *11*, 1152–1154. [CrossRef] [PubMed]
- Zalawadiya, S.K.; Zmily, H.; Farah, J.; Daifallah, S.; Ali, O.; Ghali, J.K. Red cell distribution width and mortality in predominantly African-American population with decompensated heart failure. *J. Card. Fail.* **2011**, *17*, 292–298. [CrossRef] [PubMed]
- Dai, Y.; Konishi, H.; Takagi, A.; Miyauchi, K.; Daida, H. Red cell distribution width predicts short- and long-term outcomes of acute congestive heart failure more effectively than hemoglobin. *Exp. Ther. Med.* **2014**, *8*, 600–606. [CrossRef]
- He, W.; Jia, J.; Chen, J.; Qin, S.; Tao, H.; Kong, Q.; Xue, Q.; Zhang, D. Comparison of prognostic value of red cell distribution width and NT-proBNP for short-term clinical outcomes in acute heart failure patients. *Int. Heart J.* **2014**, *55*, 58–64. [CrossRef]
- Van Kimmenade, R.R.; Mohammed, A.A.; Uthamalingam, S.; Van Der Meer, P.; Felker, G.M.; Januzzi, J.L., Jr. Red blood cell distribution width and 1-year mortality in acute heart failure. *Eur. J. Heart Fail.* **2010**, *12*, 129–136. [CrossRef]
- Salvatori, M.; Formiga, F.; Moreno-Gonzalez, R.; Chivite, D.; Migone De Amicis, M.; Cappellini, M.D.; Corbella, X. Red blood cell distribution width as a prognostic factor of mortality in elderly patients firstly hospitalized due to heart failure. *Kardiol. Pol.* **2019**, *77*, 632–638. [CrossRef]
- Sotiropoulos, K.; Yerly, P.; Monney, P.; Garnier, A.; Regamey, J.; Hugli, O.; Martin, D.; Metrich, M.; Antonietti, J.P.; Hullin, R. Red cell distribution width and mortality in acute heart failure patients with preserved and reduced ejection fraction. *ESC Heart Fail.* **2016**, *3*, 198–204. [CrossRef]
- Imai, R.; Uemura, Y.; Okumura, T.; Takemoto, K.; Uchikawa, T.; Koyasu, M.; Ishikawa, S.; Iwamiya, S.; Ozaki, Y.; Shibata, R.; et al. Impact of red blood cell distribution width on non-cardiac mortality in patients with acute decompensated heart failure with preserved ejection fraction. *J. Cardiol.* **2017**, *70*, 591–597. [CrossRef] [PubMed]
- Xanthopoulos, A.; Giamouzis, G.; Melidonis, A.; Kitai, T.; Paraskevopoulou, E.; Paraskevopoulou, P.; Patsilinas, S.; Triposkiadis, F.; Skoularigis, J. Red blood cell distribution width as a prognostic marker in patients with heart failure and diabetes mellitus. *Cardiovasc. Diabetol.* **2017**, *16*, 81. [CrossRef] [PubMed]
- Siedlecki, L.; Szygula-Jurkiewicz, B.; Szczurek, W.; Pyka, L.; Niedziela, J.; Gasior, M. Mortality risk factors in patients with advanced heart failure and diabetes mellitus.

- Kardiol. Pol.* **2019**, *77*, 604–609. [CrossRef] [PubMed]
54. Dabbah, S.; Chertin, L.; Khateeb, A.; Rosenfeld, I.; Suleiman, M.; Halabi, M. Red cell distribution width predicts death and appropriate therapy in patients with implantable cardioverter defibrillator: A simple measurement with prognostic value in a variety of diseases, may help in better selection of patients who will benefit the most from this device. *Pacing Clin. Electrophysiol.* **2017**, *40*, 1384–1388.
 55. Rickard, J.; Kumbhani, D.J.; Gorodeski, E.Z.; Martin, D.O.; Grimm, R.A.; Tchou, P.; Lindsay, B.D.; Tang, W.H.; Wilkoff, B.L. Elevated red cell distribution width is associated with impaired reverse ventricular remodeling and increased mortality in patients undergoing cardiac resynchronization therapy. *Congest. Heart Fail.* **2012**, *18*, 79–84. [CrossRef]
 56. Celikyurt, U.; Agacdiken, A.; Sahin, T.; Kozdag, G.; Vural, A.; Ural, D. Association between red blood cell distribution width and response to cardiac resynchronization therapy. *J. Interv. Card. Electrophysiol.* **2012**, *35*, 215–218. [CrossRef]
 57. Topaz, G.; Haim, M.; Kusniec, J.; Kazum, S.; Goldenberg, G.; Golovchiner, G.; Kornowski, R.; Strasberg, B.; Eisen, A. Association between red cell distribution width and mortality after cardiac resynchronization therapy. *Isr. Med. Assoc. J.* **2015**, *17*, 505–509.
 58. Miller, P.E.; Houston, B.A.; Schneider, A.L.; Bush, A.L.; Whitman, G.J.; Stevens, G.R.; Tedford, R.J.; Russell, S.D. Associations of preimplant red blood cell distribution width with clinical outcomes among individuals with left ventricular assist devices. *ASAIO J.* **2016**, *62*, 677–683. [CrossRef]
 59. Truby, L.K.; Sridharan, L.; Flores, R.J.; Garan, A.R.; Jennings, D.; Yuzefpolskaya, M.; Takeda, K.; Takayama, H.; Naka, Y.; Colombo, P.C.; et al. Red cell distribution width predicts 90 day mortality in continuous-flow left ventricular assist device patients. *ASAIO J.* **2019**, *65*, 233–240. [CrossRef]
 60. Ahmad, T.; Wang, T.; O'Brien, E.C.; Samsky, M.D.; Pura, J.A.; Lokhnygina, Y.; Rogers, J.G.; Hernandez, A.F.; Craig, D.; Bowles, D.E.; et al. Effects of left ventricular assist device support on biomarkers of cardiovascular stress, fibrosis, fluid homeostasis, inflammation, and renal injury. *JACC Heart Fail.* **2015**, *3*, 30–39. [CrossRef]
 61. Pogljajen, G.; Sever, M.; Cernelc, P.; Haddad, F.; Vrtovec, B. Increased red cell distribution width is associated with poor stem cell mobilization in patients with advanced chronic heart failure. *Biomarkers* **2015**, *20*, 365–370. [CrossRef] [PubMed]
 62. Szygula-Jurkiewicz, B.; Szczurek, W.; Skrzypek, M.; Nadziakiewicz, P.; Siedlecki, L.; Zakliczynski, M.; Gasior, M.; Zembala, M. Red blood cell distribution width in end-stage heart failure patients is independently associated with all-cause mortality after orthotopic heart transplantation. *Transplant. Proc.* **2018**, *50*, 2095–2099. [CrossRef] [PubMed]
 63. Muhlestein, J.B.; Lappe, D.L.; Anderson, J.L.; Muhlestein, J.B.; Budge, D.; May, H.T.; Bennett, S.T.; Bair, T.L.; Horne, B.D. Both initial red cell distribution width (RDW) and change in RDW during heart failure hospitalization are associated with length of hospital stay and 30-day outcomes. *Int. J. Lab. Hematol.* **2016**, *38*, 328–337. [CrossRef] [PubMed]
 64. Turcato, G.; Zorzi, E.; Prati, D.; Ricci, G.; Bonora, A.; Zannoni, M.; Maccagnani, A.; Salvagno, G.L.; Sanchis-Gomar, F.; Cervellini, G.; et al. Early in-hospital variation of red blood cell distribution width predicts mortality in patients with acute heart failure. *Int. J. Cardiol.* **2017**, *243*, 306–310. [CrossRef]
 65. Makhoul, B.F.; Khourieh, A.; Kaplan, M.; Bahouth, F.; Aronson, D.; Azzam, Z.S. Relation between changes in red cell distribution width and clinical outcomes in acute decompensated heart failure. *Int. J. Cardiol.* **2013**, *167*, 1412–1416. [CrossRef]
 66. Uemura, Y.; Shibata, R.; Takemoto, K.; Uchikawa, T.; Koyasu, M.; Watanabe, H.; Mitsuda, T.; Miura, A.; Imai, R.; Watarai, M.; et al. Elevation of red blood cell distribution width during hospitalization predicts mortality in patients with acute decompensated heart failure. *J. Cardiol.* **2016**, *67*, 268–273. [CrossRef]
 67. Melchior, R.; Rinaldi, G.; Testa, E.; Giraud, A.; Serraino, C.; Bracco, C.; Spadafora, L.; Falceitta, A.; Leccardi, S.; Silvestri, A.; et al. Red cell distribution width predicts mid-term prognosis in patients hospitalized with acute heart failure: The RDW in Acute Heart Failure (RE-AHF) study. *Intern. Emerg. Med.* **2019**, *14*, 239–247. [CrossRef]
 68. Ferreira, J.P.; Girend, N.; Arrigo, M.; Medeiros, P.B.; Ricardo, M.B.; Almeida, T.; Rola, A.; Tolpanen, H.; Laribi, S.; Gayat, E.; et al. Enlarging red blood cell distribution width during hospitalization identifies a very high-risk subset of acutely decompensated heart failure patients and adds valuable prognostic information on top of hemocrit. *Medicine* **2016**, *95*, e3307. [CrossRef]
 69. Oh, J.; Kang, S.M.; Won, H.; Hong, N.; Kim, S.Y.; Park, S.; Lee, S.H.; Jang, Y.; Chung, N. Prognostic value of change in red cell distribution width 1 month after discharge in acute decompensated heart failure patients. *Circ. J.* **2012**, *76*, 109–116. [CrossRef]
 70. Nunez, J.; Nunez, E.; Rizopoulos, D.; Minana, G.; Bodi, V.; Bondanza, L.; Huser, O.; Merlos, P.; Santos, E.; Pascual-Figal, D.; et al. Red blood cell distribution width is longitudinally associated with mortality and anemia in heart failure patients. *Circ. J.* **2014**, *78*, 410–418. [CrossRef]
 71. Cauthen, C.A.; Tong, W.; Jain, A.; Tang, W.H. Progressive rise in red cell distribution width is associated with disease progression in ambulatory patients with chronic heart failure. *J. Card. Fail.* **2012**, *18*, 146–152. [CrossRef]
 72. Aung, N.; Ling, H.Z.; Cheng, A.S.; Aggarwal, S.; Flint, J.; Mendonca, M.; Rashid, M.; Kang, S.; Weissert, S.; Coats, C.J.; et al. Expansion of the red cell distribution width and evolving iron deficiency as predictors of poor outcome in chronic heart failure. *Int. J. Cardiol.* **2013**, *168*, 1997–2002. [CrossRef] [PubMed]
 73. Xanthopoulos, A.; Papamichalis, M.; Zajichek, A.; Milinovich, A.; Kattan, M.W.; Skoularigis, J.; Starling, R.C.; Triposkiadis, F. In-hospital red blood cell distribution width change in patients with heart failure. *Eur. J. Heart Fail.* **2019**, *21*, 1659–1661. [CrossRef] [PubMed]
 74. Lippi, G.; Targher, G.; Montagnana, M.; Salvagno, G.L.; Zoppini, G.; Guidi, G.C. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Arch. Pathol. Lab. Med.* **2009**, *133*, 628–632. [CrossRef] [PubMed]
 75. Boulogne, M.; Sadoune, M.; Launay, J.M.; Baudet, M.; Cohen-Solal, A.; Logeart, D. Inflammation versus mechanical stretch biomarkers over time in acutely decompensated heart failure with reduced ejection fraction. *Int. J. Cardiol.* **2017**, *226*, 53–59. [CrossRef]
 76. Huang, Y.L.; Hu, Z.D.; Liu, S.J.; Sun, Y.; Qin, Q.; Qin, B.D.; Zhang, W.W.; Zhang, J.R.; Zhong, R.Q.; Deng, A.M. Prognostic value of red blood cell distribution width for patients with heart failure: A systematic review and meta-analysis of cohort studies. *PLoS ONE* **2014**, *9*, e104861. [CrossRef]
 77. Shao, Q.; Li, L.; Li, G.; Liu, T. Prognostic value of red blood cell distribution width in heart failure patients: A meta-analysis. *Int. J. Cardiol.* **2015**, *179*, 495–499. [CrossRef]
 78. Hou, H.; Sun, T.; Li, C.; Li, Y.; Guo, Z.; Wang, W.; Li, D. An overall and dose-response meta-analysis of red blood cell distribution width and CVD outcomes. *Sci. Rep.* **2017**, *7*, 43420. [CrossRef]
 79. Rahimi, K.; Bennett, D.; Conrad, N.; Williams, T.M.; Basu, J.; Dwight, J.; Woodward, M.; Patel, A.; McMurray, J.; MacMahon, S. Risk prediction in patients with heart failure: A systematic review and analysis. *JACC Heart Fail.* **2014**, *2*, 440–446. [CrossRef]
 80. Passantino, A.; Monitillo, F.; Iacoviello, M.; Scrutinio, D. Predicting mortality in patients with acute heart failure: Role of risk scores. *World J. Cardiol.* **2015**, *7*, 902–911. [CrossRef]
 81. Ferrero, P.; Iacovoni, A.; D'Elia, E.; Vaduganathan, M.; Gavazzi, A.; Senni, M. Prognostic scores in heart failure—Critical appraisal and practical use. *Int. J. Cardiol.* **2015**, *188*, 1–9. [CrossRef] [PubMed]
 82. Xanthopoulos, A.; Giamouzis, G.; Tryposkiadis, K.; Paraskevopoulou, E.; Paraskevopoulou, P.; Karagiannis, G.; Patsilinos, S.; Parissis, J.; Farmakis, D.; Butler, J.; et al. A simple score for early risk stratification in acute heart failure. *Int. J. Cardiol.* **2017**, *230*, 248–254. [CrossRef] [PubMed]
 83. Xanthopoulos, A.; Tryposkiadis, K.; Giamouzis, G.; Konstantinou, D.; Giannakoulas, G.; Karvounis, H.; Kattan, M.W.; Skoularigis, J.; Parissis, J.; Starling, R.C.; et al. Larissa Heart Failure Risk score: A proposed simple score for risk stratification in chronic heart failure. *Eur. J. Heart Fail.* **2018**, *20*, 614–616. [CrossRef] [PubMed]
 84. Kitai, T.; Xanthopoulos, A.; Tang, W.H.W.; Kaji, S.; Furukawa, Y.; Oishi, S.; Akiyama, E.; Suzuki, S.; Yamamoto, M.; Kida, K.; et al. Validation of the Larissa Heart Failure Risk score for risk stratification in acute heart failure. *Int. J. Cardiol.* **2020**, *307*, 119–124. [CrossRef]
 85. Adler, E.D.; Voors, A.A.; Klein, L.; Macheret, F.; Braun, O.O.; Urey, M.A.; Zhu, W.; Sama, I.; Tadel, M.; Campagnari, C.; et al. Improving risk prediction in heart failure using machine learning. *Eur. J. Heart Fail.* **2020**, *22*, 139–147. [CrossRef]
 86. Horne, B.D.; Budge, D.; Masica, A.L.; Savitz, L.A.; Benuzzillo, J.; Cantu, G.; Bradshaw, A.; McCubrey, R.O.; Bair, T.L.; Roberts, C.A.; et al. Early inpatient calculation of laboratory-based 30-day readmission risk scores empowers clinical risk modification during index hospitalization. *Am. Heart J.* **2017**, *185*, 101–109. [CrossRef]
 87. Massin, M.M. Relation between red cell distribution width and clinical outcome after surgery for congenital heart disease in children. *Pediatr. Cardiol.* **2012**, *33*, 1021–1025. [CrossRef]
 88. Mawlawi, W.; Donia, A.; Elamrousy, D. Relation between red cell distribution width and left ventricular function in children with heart failure. *ISRN Pediatr.* **2014**, *2014*, 234835. [CrossRef]
 89. Kumar, S.; Sudhakar, A.; Mohan, M.; Balachandran, R.; Raj, B.; Sumangala, S.G.; Kumar, R.K. Elevated red cell distribution width is associated with delayed postoperative recovery after correction of Tetralogy of Fallot. *Ann. Pediatr. Cardiol.* **2013**, *6*, 121–125. [CrossRef]
 90. Kojima, T.; Yasuhara, J.; Kumamoto, T.; Shimizu, H.; Yoshida, S.; Kobayashi, T.; Sumitomo, N. Usefulness of the red blood cell distribution width to predict heart failure in patients with a fontan circulation. *Am. J. Cardiol.* **2015**, *116*, 965–968. [CrossRef]
 91. Miyamoto, K.; Inai, K.; Takeuchi, D.; Shinohara, T.; Nakanishi, T. Relationships among red cell distribution width, anemia, and interleukin-6 in adult congenital heart disease. *Circ. J.* **2015**, *79*, 1100–1106. [CrossRef] [PubMed]
 92. Tomkiewicz-Pajak, L.; Plazak, W.; Kolcz, J.; Pajak, J.; Kopec, G.; Dlużniewska, N.; Olszowska, M.; Moryl-Bujakowska, A.; Podolec, P. Iron deficiency and hematological changes in adult patients after Fontan operation. *J. Cardiol.* **2014**, *64*, 384–389. [CrossRef] [PubMed]
 93. Baggen, V.J.M.; Van Den Bosch, A.E.; Van Kimmenade, R.R.; Eindhoven, J.A.; Witsenburg, M.; Cuypers, J.; Leebeck, F.W.G.; Boersma, E.; Roos-Hesselink, J.W. Red cell distribution width in adults with congenital heart disease: A worldwide available and low-cost predictor of cardiovascular events. *Int. J. Cardiol.* **2018**, *260*, 60–65. [CrossRef]
 94. Yang, T.; Sun, Y.J.; Xiong, C.M.; Zeng, W.J.; Ni, X.H.; Zhao, Z.H.; Liu, Z.H.; Gu, Q.; He, J.G. Red blood cell distribution width predicts survival in patients with Eisenmenger syndrome. *Clin. Chem. Lab. Med.* **2014**, *52*, 743–750. [CrossRef] [PubMed]
 95. Martinez-Quintana, E.; Estupinan-Leon, H.; Riano-Ruiz, M.; Rodriguez-Gonzalez, F.; Tugores, A. Red blood cell distribution width in addition to N-terminal pro-B-type natriuretic peptide concentration improves assessment of risk of cardiovascular events in adult patients with congenital heart disease. *Arch. Cardiovasc. Dis.* **2020**, *113*, 607–616. [CrossRef] [PubMed]
 96. Bonaque, J.C.; Pascual-Figal, D.A.; Manzano-Fernandez, S.; Gonzalez-Canovas, C.; Vidal, A.; Munoz-Esparza, C.; Garrido, I.P.; Pastor-Perez, F.; Valdes, M. Red blood cell distribution width adds prognostic value for outpatients with chronic heart failure. *Rev. Esp. Cardiol.* **2012**, *65*, 606–612. [CrossRef] [PubMed]
 97. Tseliou, E.; Terrovitis, J.V.; Kaldara, E.E.; Ntalians, A.S.; Repasos, E.; Katsaros, L.; Margari, Z.J.; Matsouka, C.; Toumanidis, S.; Nanas, S.N.; et al. Red blood cell distribution width is a significant prognostic marker in advanced heart failure, independent of hemoglobin levels. *Hellenic J. Cardiol.* **2014**, *55*, 457–461.
 98. Yaegashi, D.; Oikawa, M.; Yokokawa, T.; Misaka, T.; Kobayashi, A.; Kaneshiro, T.; Yoshihisa, A.; Nakazato, K.; Ishida, T.; Takeishi, Y. Red blood cell distribution width is a predictive factor of anthracycline-induced cardiotoxicity. *Front. Cardiovasc. Med.* **2020**, *7*, 594685. [CrossRef]
 99. Ouwerkerk, W.; Zwiderman, A.H.; Ng, L.L.; Demissei, B.; Hillege, H.L.; Zannad, F.; Van Veldhuisen, D.J.; Samani, N.J.; Ponikowski, P.; Metra, M.; et al. Biomarker-guided versus guideline-based treatment of patients with heart failure: Results from BIOSTAT-CHF. *J. Am. Coll. Cardiol.* **2018**, *71*, 386–398. [CrossRef]