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Red blood cell distribution width to predict mortality in heart transplant recipients: a systematic review

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Abstract

Red blood cell distribution width (RDW) has been shown to have prognostic value in a number of different clinical settings, such as cardiovascular disease, including heart failure. However, its prognostic value in heart transplant (HT) recipients remains unknown. The aim of this systematic review is to determine the prognostic value of pre-transplant RDW for mortality in HT recipients. There is a pre-published protocol of this review. The terms "Heart transplant", "Red cell distribution width" and their synonyms were used in the search strategy. PubMed/Medline, Embase, Scopus, Web of Science and LILACS were searched until May 17th, 2022, without date or language restrictions. Two authors independently carried out the selection, first by title and abstract, second by full-text revision. Discrepancies were discussed and resolved with three other authors. Quality of individual studies was assessed with Newcastle Ottawa Scale (NOS) for cohorts. After removing the duplicates, 3885 articles were identified. Four articles were included in the qualitative synthesis. Three studies were classified as "good quality": whereas one as "poor quality" according to NOS scale. All the included articles evaluated long-term mortality and one study also evaluated short-term mortality. In this one, a correlation between higher RDW values and short-term mortality was reported. Meanwhile, in all the studies, a high pre-HT RDW was a marker of long-term mortality following cardiac transplantation. Our review shows that an elevated on-admission RDW is associated with long-term mortality in heart transplantation recipients.

Introduction

Since 1967, heart transplantation (HT) remains the final extraordinary therapeutic option for the treatment of patients with truly irreversible end-stage heart failure, in whom it could offer markedly improved survival and quality of life [1]. Absolute indications for HT change according to the presentation of the disease. Chronic HF patients should be referred for a HT if they are on guideline-directed medical therapy (GDMT) who still have limiting symptoms on exertion (New York Heart Association class III or IV); if they have frequent readmissions for HF exacerbation

despite adherence to GDMT (two or more in 12 months), *etc*. [2]. Meanwhile, acute HF patients usually require an urgent referral for HT, such as in cardiogenic shock despite maximum dose inotropic treatment or despite mechanical circulatory support; in refractory pulmonary edema that does not respond to diuretics and requires ventilation and positive pulmonary pressure; as well as in refractory ventricular arrhythmia that does not respond to medical therapy or electrophysiological procedures [2].

The frequency of HT has been increasing since the 1990s; currently, 4000 to 5000 HT are performed globally per year [3]. This surgical procedure can prolong survival approximately 11 years in end-stage heart failure adult patients [4]; in addition, close to 85% of recipients survive the first year post-HT [5]. There are several factors associated with a poor prognosis in HT recipients, such as mechanical circulatory support [4], history of congenital heart disease, restrictive cardiomyopathy, re-transplantation [4], pre-transplant serum creatinine higher than 2.0 mg/dL [4], pre-transplant total bilirubin higher than 2.0 mg/dL [4], recipient age higher than 55 years old [4], pre-operative clinical instability, defined as Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile I (cardiogenic shock); or profile II (progressive clinical decline despite treatment with inotropes) [6,7]; as well as donor factors, such as advanced donor age and prolonged donor heart ischemia [4]. Even considering these factors, the rate of mortality in HT recipients is high, therefore, determining prognostic markers in these patients will always be helpful in making evidence-based decisions.

Red cell distribution width (RDW) is a biochemical parameter obtained from the routine complete blood count that reflects the variability in the size of circulating erythrocytes [8]. It is calculated by dividing the standard deviation of the mean corpuscular volume (MCV) by the MCV and multiplying by 100, obtaining a percentage value. There is no universal reference range for RDW because methods for measuring RBC size, instruments, experimenters, laboratory standards, and statistical approaches are different in each laboratory. However, the normal RDW reference range used by most laboratories is 11-15% [9]. RDW values are reflected in coefficient of variation of red cell volume distribution width (RDW-CV) and standard deviation of red cell volume distribution width (RDW-SD) levels. Of these two parameters, the one that better correlates with worse outcomes is RDW-CV, it has been shown to have prognostic value in a number of different clinical settings, such as cardiovascular disease, including heart failure [9,10]. In fact, a previous systematic review showed that heart failure patients with higher RDW may have a poorer prognosis [11]; however, the usefulness of pre-HT RDW as a mortality predictor in patients with heart failure after receiving an HT is still unknown. Thus, the main objective of this systematic review is to determine the prognostic value of pre-transplant RDW for mortality in patients who will receive an HT.

Methods

Studies in which pre-transplant RDW has been determined to assess mortality in patients who underwent heart transplantation were searched. There is a pre-published protocol of this systematic review registered in PROSPERO (CRD42021271074) [12]. This review was conducted in accordance with PRISMA guidelines [13] as shown in Supplementary Table 1.

Data sources and searches

We conducted a systematic search of electronic databases Pubmed/Medline, Embase, Scopus, Web of Science, LILACS and Cochrane until May 17th, 2022. The terms "Red blood cell distribution width", "Heart transplant" and their synonyms were used. There were no date or language restrictions. The full electronic search strategy can be found in Supplementary Table 2.

Study selection

One author (CCB) downloaded references to EndNote to eliminate duplicates. Then, those references were exported to Rayyan QCRI (https://www.rayyan.ai/) to continue with the selection, carried out independently by two authors (LMAC, CQV), first by title and abstract, second by full-text revision (LMAC, CCB, CQV, MAV). Discrepancies were discussed and resolved with three other authors (MAV, PSS, JCP).

Data abstraction

Data were extracted and verified by all the authors. The following data were extracted: principal author, country, publication year, study design, characteristics of patients, exclusion criteria, exposition, follow-up (short term 30 days and long term 1 year and above) and outcomes, controlled factors, measures of association, and results.

Quality assessment of individual studies

The quality of included studies was assessed using the Newcastle Ottawa Scale (NOS) for cohort studies [14]; then, studies were classified in good, fair or poor quality according to the

Table 1. Quality assessment of the included studies according to Newcastle-Ottawa scale for cohorts.

Study	Newcastle Ottawa scale								
	Selection				Comparability		Outcome		Overall quality°
	Representativeness of the exposed cohort	Selection of non-exposed	Ascertainment of exposure	Outcome not present at start		Assessment of outcome	Adequate follow-up length	Adequacy of follow-up	
Lechiancole *et al.* [16]	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	⋆	Good
Poglajen *et al.* [17]	⋆	⋆	⋆	⋆	-	⋆	⋆	-	Poor
Szygula *et al.* [18]	⋆	⋆	⋆	⋆	⋆	⋆	⋆	-	Good
Truby *et al.* [19]	⋆	⋆	⋆	⋆	-	⋆	⋆	⋆	Poor

The star (⋆) is granted to each component according to its risk of bias; °overall quality was considered according to Agency for Healthcare Research and Quality (AHRQ) criteria.

Agency for Healthcare Research and Quality (AHRQ) thresholds, suggested in a previous publication [15] as follows, i) good quality: 3 or 4 stars in selection domain, and 1 or 2 stars in comparability domain, and 2 or 3 stars in outcome/exposure domain; ii) fair quality: 2 stars in selection domain, and 1 or 2 stars in comparability domain, and 2 or 3 stars in outcome/exposure domain; and iii) poor quality: 0 or 1 star in selection domain, or 0 stars in comparability domain, or 0 or 1 stars in outcome/exposure domain.

Data synthesis

Due to heterogeneity in follow-up and statistical analysis across studies, it was not possible to meta-analyze the results. However, we present a qualitative synthesis of them.

RESULTS

Selected studies

A total of 4218 articles were obtained from PubMed/Medline (n=3018), Embase (n=538), Scopus (n=394), Web of Science Core Collection (n=223) and LILACS (n=45). Removal of duplicates resulted in a total of 3885 articles. In the selection by title and abstracts, 3875 articles were eliminated. With the remaining 10, a full-text review was carried out, in which 6 articles were excluded for the reasons given in Figure 1, where the flowchart of the selection process according to PRISMA guidelines is shown [13]. As the findings in the search included two conference abstracts, we decided to create a Funnel plot, it showed that even with or without the inclusion of these two studies there is not a publication bias (Supplementary Figure 1).

Finally, four articles were considered in this review for qualitative synthesis [16-19].

Quality assessment of individual studies

NOS scale for cohort studies was used. According to AHRQ criteria, three articles received the maximum score, classified as "Good quality"; on the other hand, one article did not perform a regression adjustment for confounders, so was classified as "Poor quality". Similarly, another article affirms to have performed a multivariate regression analysis but does not mention which variables were included in it. The NOS scores for each individual study can be found in Table 1.

Characteristics of selected studies

Four retrospective cohort studies were included for qualitative synthesis. We got access to the full text of two of them [16,18], while the other two were available only in conference abstract format [17,19]. The cohorts were performed in Poland (2018)[18], Italy (2019) [16], Slovenia (2015) [17] and United States (2017)[19]. Characteristics of individual studies are reported in Table 2. The number of participants ranged from 115 to 708 and follow up

Table 2. Characteristics of the included studies.

Study	Design	Country	Publication year	Number of HT recipients	Age	Exclusion criteria	Follow-up	Outcome
Lechiancole *et al.* [16]	Retrospective cohort	Italy	2019	218	- RDW <14.6 group: 54±11° years. - 14.6 ≤ RDW ≤16.4 group: 56±10° years. - RDW>16.4 group: 56±11° years.	- Urgent HT. - Age <18 years old. - Bridge with mechanical circulatory support. - Mechanical ventilation. - Multiple-organ transplantation. - Re-HT.	6.6±4. 2° years	- In-hospital 30-day mortality. - In-hospital long-term mortality. - Long-term survival.
Poglajen *et al.* [17]	Retrospective cohort	Slovenia	2015	115	- Normal RDW group: 49.1±11.3° years. - High RDW group: 52.9 ± 6.5° years.	- Iron deficiency (serum ferritin 100-200 µg/L, transferrin saturation <20%). - Anemia (hemoglobin <12 mg/mL). - Short or long-term mechanical circulatory support prior HT.	1 year	Mortality
Szygula *et al.* [18]	Retrospective cohort	Poland	2018	173	54 (41-59)# years	- Anemia. - Previous red blood cell transfusion. - Patients receiving treatment for anemia (supplemental iron, folate, or erythropoiesis-stimulating agents).	3.79±2. 36° years.	All-cause mortality
Truby *et al.* [19]	Retrospective cohort	United States	2017	708	Not reported	None.	1 year.	Mortality

°Mean ± SD; #median (interquartile rank); HT, heart transplant; RDW, red blood cell distribution width.

ranged from 1 to more than 6 years. The population was defined as "heart transplantation recipients" in the four studies. Pre-transplant RDW-CV was measured by the automatized hemogram taken on hospital admission in the four included studies. Mortality and survival were assessed as the principal outcomes.

RDW as a mortality predictor in HT recipients

The individual results of each study are described in Table 3. All the included studies evaluated long-term post-HT mortality, and just one study also evaluated short-term mortality. The rates of post-HT 30-day mortality were shown to be greater in patients with higher on-admission RDW values [16]. Two studies assessed 1-year mortality following HT. Poglajen *et al*. [17] calculated 1-year mortality rates in two groups according to a RDW cut-off value of 14.5 (RDW³ 14.5, and RDW< 14.5). They reported greater mortality rates in the higher RDW group than in the normal RDW group. In addition, Truby *et al*. [19] performed a multivariable analysis in which the RDW predicted 1-year post-HT mortality. On the other hand, other two studies followed HT-recipients for more than 1 year. Szygula *et al*. [18] predicted mortality with the on-admission RDW value, both at univariate and multivariate analysis in a cohort of post-HT patients followed for 3.79±2.36 (mean ± SD) years. Lechiancole *et al*. [16] followed their HT recipients for 6.6±4.2 years and also showed a statistically significant correlation with mortality at univariate and multivariate analysis. This regression model was adjusted for creatinine, diabetes mellitus, previous

Table 3. Red blood cell distribution width as a mortality predictor in heart transplant recipients.

Study	Short-term mortality	Long-term mortality
Lechiancole *et al.* [16]	30-day mortality rates: RDW <14.6: 1.4% 14.6 < RDW <16.4: 4% RDW >16.4: 9%	Univariate analysis: HR 1.15, 95% CI 1.06-1.25 Multivariate analysis: HR 1.11, 95% CI 1.06-1.22
Poglajen *et al.* [17]°	Not performed.	1-year mortality rates: RDW < 14.5 (1/27, 4%) RDW > 14.5 (15/88, 17%)
Szygula *et al.* [18]	Not performed.	Univariate analysis HR 1.408, CI 1.309-1.514 Multivariate analysis HR 1.381, CI: 1.251-1.467
Truby *et al.* [19]	Not performed.	Multivariate analysis# OR: 1.15, CI: 1.06-1.25

°Conference abstract; #the variables included in the regression were not mentioned; HR, hazard ratio; OR, odds ratio; CI, confidence interval; RDW, red blood cell distribution width.

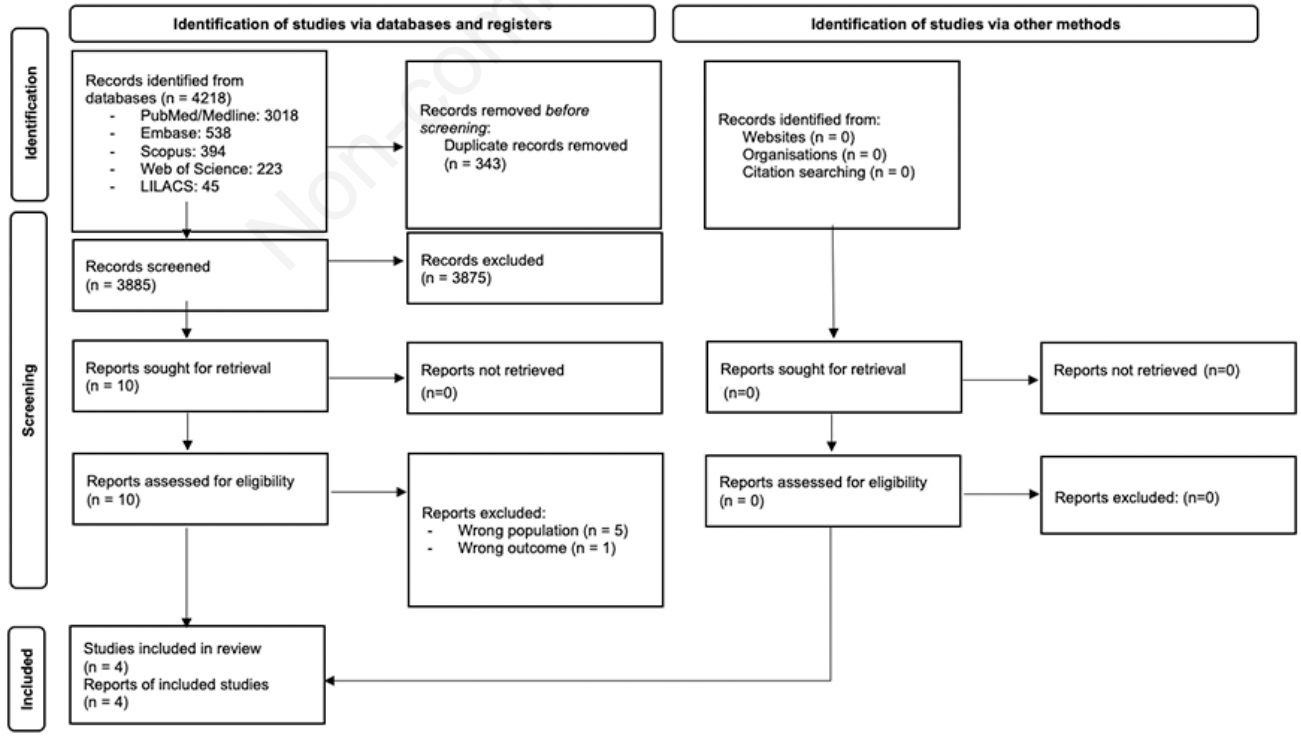

Figure 1. PRISMA flow-chart of included studies.

cardiac surgery, mean pulmonary pressure, systolic pulmonary pressure and pulmonary-capillary wedge pressure. In this study the authors also performed a Kaplan-Meyer analysis that shows a statistically significant difference among the survival curves and survival probabilities at 4, 8 and 12 years between the groups with RDW less than 14.6% (90, 84 and 74%, respectively) and greater than 16.4% (72, 60 and 42%, respectively), HR 3.29, 95% CI: 1.74-6.24. Additionally, they calculated a cut-off value for RDW of 16.15%, with an area under the curve of 0.607, 95% CI: 0.524-0.691; specificity of 68.2% and sensitivity of 55.2% to predict prognosis.

Discussion

The results of this systematic review indicate that a high pre-HT RDW is a marker of poor prognosis in patients who will receive a HT. In fact, the pre-operative RDW has previously been shown to be a poor prognostic marker in cardiovascular surgery, as well as in other types of organ transplants; for example, Duchnowski *et al*. [20] showed an association between pre-operative RDW and mortality, as well as adverse events following elective valvular surgery. In addition, Mucsi *et al*. [21] reported that higher RDW collected at baseline predicts mortality in kidney transplant recipients. On the other hand, a meta-analysis carried out by Yuan-Lan et al. [11] indicates that for each 1% increase in RDW on admission there is a 10% associated increase in the risk of mortality events in heart failure (HF) patients.

RDW is an independent predictor of mortality in patients with acute heart failure [22] and cardiogenic shock [23]. In addition, pre-transplantation clinical instability, *i.e*., INTERMACS profile I (cardiogenic shock), is also associated in-hospital post-operative mortality in HT recipients [6]. Thus, clinically unstable HT recipients with an elevated on-admission RDW could be at an even higher risk of death. Lechiancole *et al*. [16] excluded urgent HT patients, as well as those who needed mechanical circulatory support. In addition, Szygula *et al*. [18] defined their participants as "end-stage heart failure patients undergoing HT". On the other hand, there are many other factors that could affect the post-operative prognosis in HT recipients such as congenital heart diseases, pre-transplant serum creatinine or bilirubin higher than 2.0 mg/dL, *etc*. Only Lechiancole et al. [16] adjusted their regression model to serum creatinine. This fact could hide other important factors that could worsen the prognosis of patients after HT.

In addition, there are some factors that could affect the RDW value. There are certain conditions in which RDW tends to increase, *i.e*., heterozygous thalassemia, hemolytic anemia, hereditary spherocytosis, vitamin B12 or folate deficiency anemia and myelodysplastic syndrome. Two of the included studies in this review excluded patients with anemia [17,18]. However, one of the included studies [19] reported that patients with elevated RDW had significantly lower hemoglobin (11.0±2.0 *vs* 12.5±1.8 mg/dL, p=0.001). This fact could probably increase the RDW value. Moreover, patients over 60 years old might have a RDW higher than other patients under that age [24,25]. The average age in the four included studies in this review was around 50 years. There are many other factors that could affect the RDW value, such as sex, genetics, renal function and dyslipidemia [26].

The exact biological mechanism by which RDW could predict mortality in patients undergoing HT is unknown. Previous studies suggest that RDW levels tend to increase in proinflammatory states, such as systemic inflammatory response syndrome, metabolic syndrome, among others [27,28]. Likewise, cytokines such as tumor necrosis factor alpha, interleukin 1B, among others, play an important role in the development of heart failure by promoting myocardial hypertrophy [29]. Thus, the increase in RDW could be a hematological manifestation of the inflammatory response, which induces the development and severity of heart failure leading to heart transplantation. Further studies are needed to confirm this pathophysiological hypothesis. On the other hand, it should be noted that the RDW could lose its prognostic value if its value after HT is used, especially after the start of immunomodulatory therapy because it is known that some immunomodulatory drugs, *i.e*., azathioprine [30], can suppress bone marrow activity, causing anemia and disrupting erythrocyte homeostasis. In this way, the value of the RDW is altered as a side effect of the therapy and its prognostic value would be lost.

There are some limitations in this systematic review. First, two of the included studies did not specify HT indications in their sample. As mentioned above, the post-transplant prognosis in patients with acute heart failure is much more limited than in chronic heart failure. Second, there are several conditions in which RDW may be increased that were not considered for exclusion or regression in all the included articles; *i.e*., some types of anemia (iron deficiency, folate deficiency, vitamin B12 deficiency, hemolytic anemia and sickle cell anemia), blood transfusions, chronic hepatobiliary disease, beta thalassemia, *etc*. [9]. Third, two of the included studies were available only in conference abstract format. The reason why we decided to include the two studies was because the number of publications in this very important topic is scarce. This fact limits the quality and the amount of information that could be extracted. On the other hand, only one of them adjusted the regression for intervening factors with epidemiological and statistical criteria that could also predict death. Fourth, each study was conducted in a different country, this could impact in RDW can be different among different ethnic groups. Finally, despite its limitations, this systematic review is the only most in-depth analyses that systematically examined the available evidence, additionally, we suggest the development of a global open access data registry on heart transplantation, so secondary-data studies could be conducted to identify more easily accessible prognostic indicators available in health centers around the world.

Conclusions

The red blood cell distribution width is an accessible tool obtained from the routine complete blood count. According to our results, an elevated on-admission RDW is highly predictive of long-term mortality in heart transplantation recipients.

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