RESEARCH ARTICLE

Association between Red Cell Distribution Width and Cardiovascular Outcomes – Systematic Review and Meta-Analysis

Authors:
Sagar Ranka[a], MD; Shubham Lahan[b], MD; Tarun Dalia[a], MD; Alok Tripathi[c], MD; Amandeep Goyal[a], MD; Jayakumar Sreenivasan[d], MD; Sivasagar Taduru[a], MD; Moghniuddin Muhammed[a], MD & Patrick M. Moriarty[e], MD

Institutional Affiliations:
a. Department of Cardiovascular Medicine, University of Kansas Medical Center, Kansas City, KS, United States.
b. University College of Medical Sciences, New Delhi, India.
c. Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, United States.
d. Department of Cardiology, Westchester Medical Center, Valhalla, NY, United States.
e. Division of Clinical Pharmacology/Atherosclerosis and Lipid-apheresis Center,
Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, United States.

Address for correspondence:
Sagar Ranka, MD
Department of Cardiovascular Medicine,
University of Kansas Medical Center
Kansas City, KS, 66160, United States.
Email: sranka@kumc.edu

Abstract

Background: Increased red cell distribution width (RDW) has been associated with poor prognosis in patients with heart failure (HF) and coronary heart disease (CHD) in multiple observation studies.
Methodology: Literature search of PubMed/Medline, Google Scholar, and Cochrane library databases were conducted from inception till 31st March 2021 to identify studies reporting hazed ratios with 95% CIs for any level of RDW on all-cause mortality in patients with HF and CHD (ST-elevation & non-ST elevation myocardial infarction, coronary artery disease). Two investigators extracted study characteristics using a standard form and pooled data using random-effects meta-analysis.
Results: A total of 30 eligible studies were included with a total of 57, 327 patients. The ages ranged from 49-80 years with females being 2–53% in proportion. Hazard ratios for all-cause mortality among patients with elevated RDW for heart failure (HF) was 1.15 (95% CI 1.09–1.22; $p < 0.001$) and for CHD was 1.19 (95% CI 1.09–1.29; $p = 0.001$). There was 11% elevated hazard for death among HF (HR:1.11 (95% CI, 1.05-1.17; p-value = 0.005) and 18% among CHD (HR,1.18; 95% CI, 1.08–1.30; p-value = 0.007) per 1% increase in RDW levels in studies reporting them. Acute myocardial infarction was associated with elevated hazard with increased RDW (HR, 1.17; 95% CI, 1.01–1.35), whereas no such correlation was demonstrated with acute HF [p= 0.17).
Conclusion: Baseline elevated RDW levels are significantly correlated with the increased all-cause mortality among CHF and CHD patients. Elevated RDW can have prognostic importance in anticipating the risk of death in these subset of patients.

Keywords: Red cell distribution width; congestive heart failure; coronary artery/heart disease; all-cause mortality.

Introduction

The red cell distribution width (RDW) is a simple, rapid and readily available hematological parameter, which measures heterogeneity of the red blood cell size and is now automatically generated by all commercially available hematological analyzers together with the complete blood cells count (CBC).[1] In the past decade, there had been increasing evidence recognizing RDW as an independent marker for anticipating outcomes in patients with cardiovascular diseases such as — coronary heart disease (CHD), congestive heart failure (CHF), atrial fibrillation with higher values correlating with worse outcomes.[2-7] There is no defined universal reference range for the RDW, but most laboratories had used 11-15% as the normal reference range.[8] A recent study showed RDW value > 14.5% was twice as more likely to predict mortality due to CHD with an adjusted hazard ratio (HR) of 2.02 (95% CI 1.04–3.94).[9] Also, RDW when used in conjunction with the conventional Framingham Risk Score increases the predictive accuracy of cardiovascular mortality more than that of traditional cardiovascular risk factors alone.[9] Prior meta-analysis examining the impact of RDW on either CHF patients or CAD patients have lacked a composite comparison. Also, the prior meta-analysis are non-contemporary in the light of newer studies.[10] [11,12] With the availability of new studies, we aimed to perform a systematic review as well as the meta-analysis to study the impact of RDW on cardiovascular outcomes.

Methods

We conducted this systematic review in accordance with the preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines.[13] A PRISMA checklist is provided in ***eTable 1, Data Supplement***.

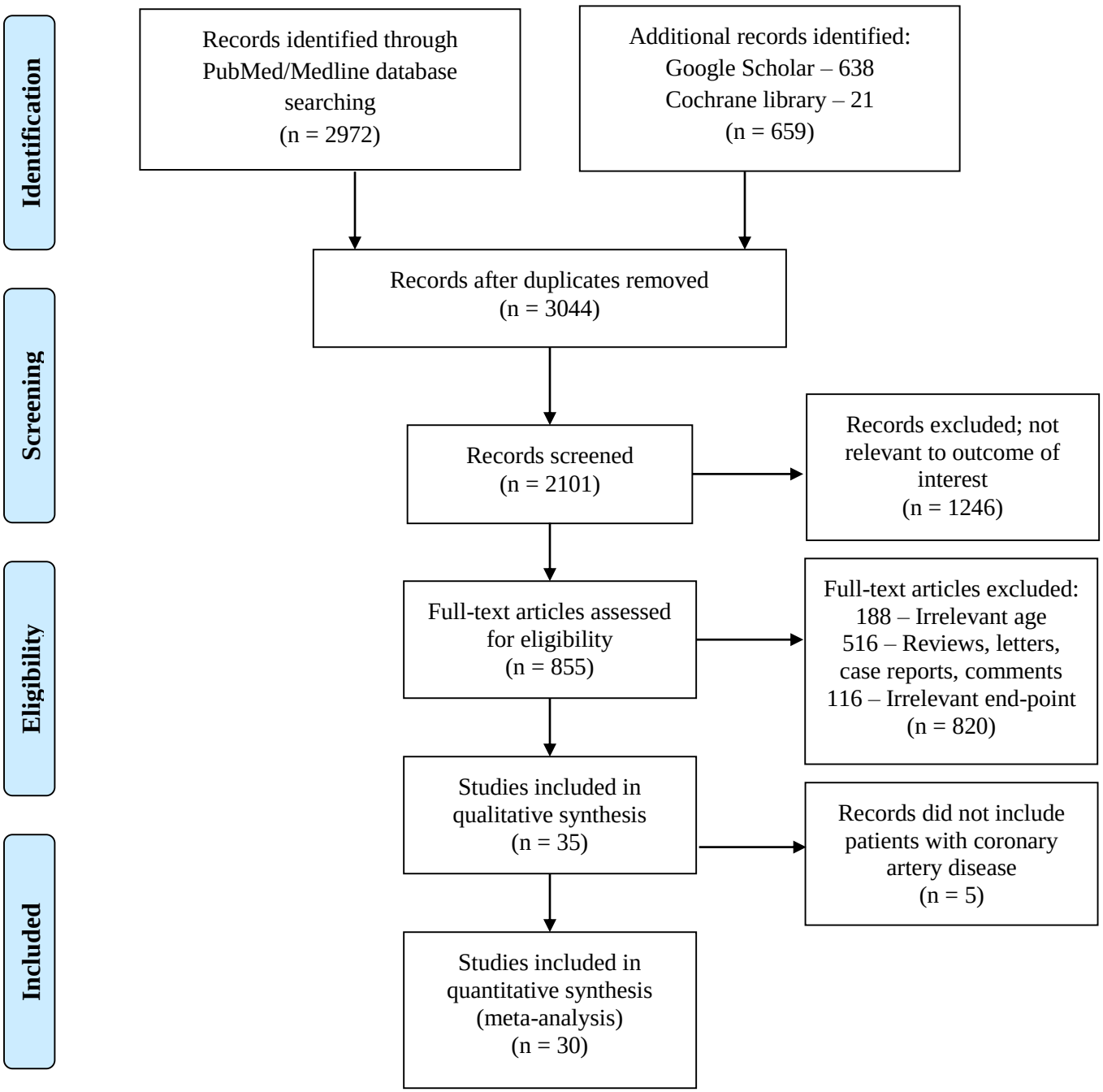
Objectives

1. To summarize the demographic information of patient population and their underlying cardiovascular risk factors from included studies.
2. To estimate the pooled hazard ratio (HR) for all-cause mortality in patients with congestive heart failure (CHF) and atherosclerotic coronary heart disease (CHD) with elevated baseline RDW levels.

Search Strategy

Two authors (S.L. and S.R.) searched PubMed/Medline, Google Scholar, and Cochrane library databases to identify relevant studies conducted from inception till 31st March, 2021 by using the following search terms: "((cardiovascular) OR (Heart)) AND (red cell distribution width); (RDW) AND (cardiovascular mortality); (RDW) AND (card*); (red cell distribution width) AND (heart failure); ((coronary) OR (infarction)) AND (red cell distribution width)." Two authors (S.L. and S.R.) independently reviewed 3631 citations retrieved during literature search and discarded 587 duplicate records. A total of 2101 articles were screened by their title/abstract for eligibility, of which 1246 were recognized as not relevant to our outcome of interest and hence were excluded. Abstracts and full-length texts of 855 articles were evaluated, of which 820 were reviews, letters, correspondence, case reports, had irrelevant patient age or study end-point and were therefore excluded, leaving 35 articles for a qualitative assessment. Five articles were later on excluded as they did not report information on patients with coronary artery disease. Finally, 30 articles in total met the criteria and were quantitatively evaluated and preliminary findings were reported[14] (**Figure 1**). Any conflicts regarding study selection were resolved by a third author (T.D.) and mutual consensus[15].

Figure 1. PRISMA flow diagram for the search strategy.



Eligibility criteria and study selection

We included studies that reported adjusted hazard ratio for all-cause mortality in relationship with their baseline RDW levels. Certain studies (n = 11) reporting mortality as a composite outcome were also included in the analysis. We excluded studies reporting only univariate or unadjusted outcomes. In studies reporting HR for categorical as well as continuous values for RDW, the latter was selected in our analysis. All hazard ratios were assumed to be per unit increase in RDW unless specified otherwise.

Data extraction and quality assessment

Two authors extracted the data and recorded following variables of interest: Author(s) names; year of publication; region; study design; sample size; underlying co-morbidities of participants; primary end-point; duration of follow-up; and variables adjusted while performing a multivariable time-to-event analysis. The data were extracted based on intention-to-treat. The quality assessment was done by using the Methodological Index for Non-Randomized Studies (MINORS) criteria.[16] The overall scores of studies ranged from 7–12. A detailed assessment of included studies is shown in ***eTable 2, Data Supplement***.

Data synthesis and analyses

The adjusted hazard ratios derived from the Cox proportional hazards models in individual studies were pooled together along with their 95% CI and weighted by using the generic inverse-variance method.[17] Subgroup analyses to ascertain the effect of RDW on certain populations based on — a) presence of acute heart failure; b) acute myocardial infarction; c) follow up duration of short-term (<30- days), mid-term (30-days to 1-year), and long term (>1 year); d) studies reporting HR per 1% increase in RDW were also performed. A random-effects meta-analysis model was used. We used Hartung-Knapp-Sidik-Jonkman method for estimating tau-square (τ^2) over the conventional DerSimonian-Laird method, as it performs better with fewer number of studies and has lower type-I error rates even when combining studies with unequal sample size [18]. Publication bias was assessed by constructing funnel diagrams of the effect size estimate against its standard error (SE) (***eFig. 1 & 2, Data Supplement***), Galbraith plots, and performing Egger's linear regression test of funnel diagram asymmetry. Heterogeneity between studies was quantified by Higgins I^2 statistic. A two-sided p-value <0.05 was considered as statistically significant. We used *meta* and *metafor* packages for conducting our analyses.[19,20] All statistical analyses were conducted in R(v3.6.3).

Results

Demographic findings

We identified 30 studies in total, of which 19 had all-cause mortality as their primary end-point in patients with heart failure (including acute and chronic)[2,4,5,21-36] and 11 included patients with myocardial infarction (ST-segment elevation and non-ST segment elevation) or coronary artery disease,[3,37-46] which we collectively defined as the coronary heart disease (CHD). The pooled sample size was 57,327 patients with ages ranging from 49–80 years; 47%–98% were male participants. The prevalence of hypertension ranged from 35%-87%, and the prevalence of diabetes and smoking ranged from 14%-50% and 11%-63%, respectively. ***eTable 3, Data Supplement*** provides an overview of individual studies and basic demographic information of patients and their co-morbidities along with the duration for which they were followed-up.

Impact on All-cause mortality

We found that the pooled (adjusted) HR estimate for all-cause mortality in heart failure patients was 1.15 (95% CI 1.09–1.22;

p < 0.001) (**Figure 2**). Similar to HF failure patients, increased RDW also increased risk of mortality by 19% in CHD patients (HR, 1.19; 95% CI 1.09–1.29) (p = 0.001) (**Figure 3**).

Figure 2. Forest plot showing pooled hazard ratio for all-cause mortality in heart failure patients.

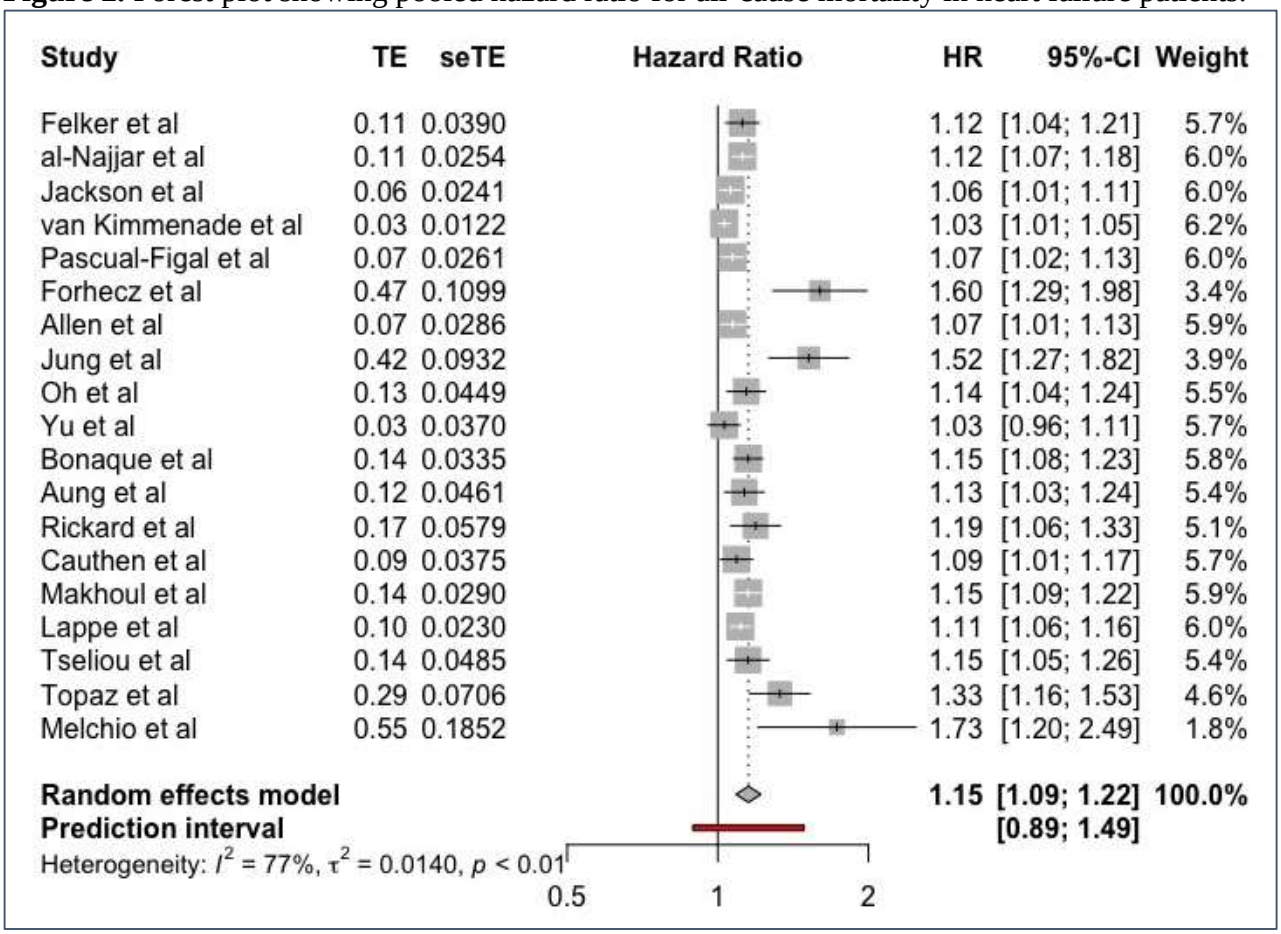
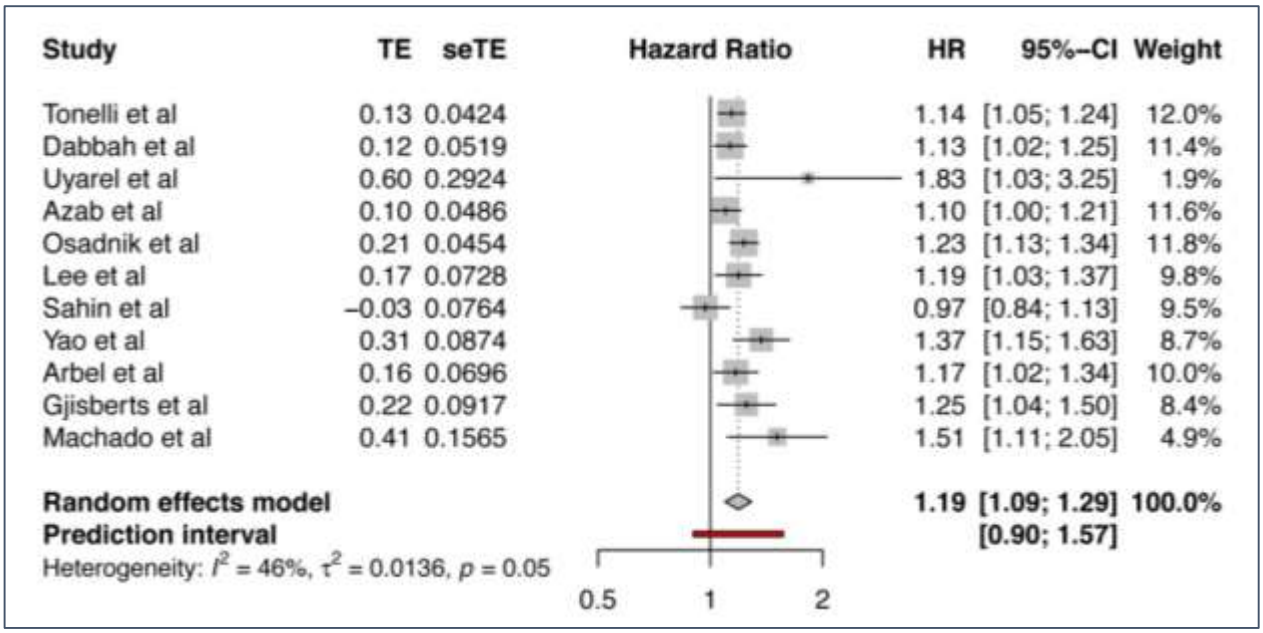


Figure 3. Forest plot showing pooled hazard ratio for all-cause mortality in patients with coronary heart disease.



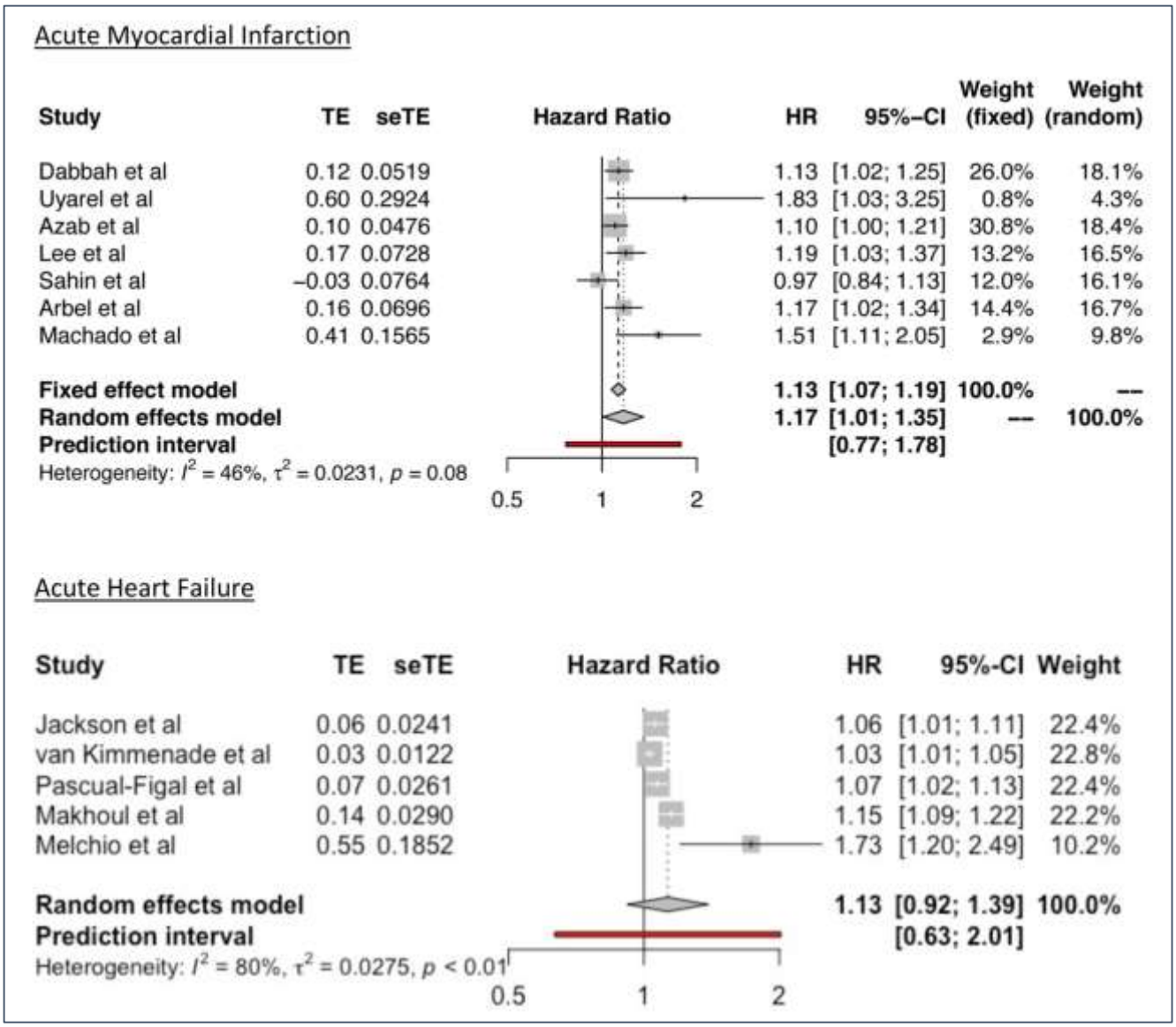
Impact of RDW in Acute HF and MI cohorts

Sub-group analysis of studies including only patients with acute heart failure showed that RDW did not affect the overall mortality [HR, 1.13; (95% CI 0.92–1.36)] (p = 0.17). The risk of mortality was also increased in patients presenting with acute myocardial infarction (HR, 1.17; 95% CI, 1.01–1.35) (**Figure 4**). Furthermore, a subgroup analysis based on follow up duration in HF patients showed that the RDW trended towards significance in the short-term (HR, 1.12; p=0.06; ***eFigure 3, Data Supplement***) but significantly increased the risk of mortality in the mid-term [HR, 1.15 (95% CI, 1.05–1.26)] and long-term [HR, 1.20 (95% CI, 1.03–1.39)] (***eFig. 4 & 5, Data Supplement***). Whereas, among CHD patients, elevated RDW correlated with increased risk of mortality only in long-term [HR, 1.19 (95% CI, 1.07–1.32)] (***eFig. 6 & 7, Data Supplement***).

Per 1% RDW increase

A distinct sub-group analysis including studies that had reported individual HRs per 1% increment in RDW levels showed results similar to composite analysis. The pooled HR for all-cause mortality among heart failure cohort per 1% rise in RDW levels was 1.11 (95% CI, 1.05-1.17) (p-value = 0.005) and among CHD cohort was 1.18 (95% CI, 1.08–1.30) (p-value = 0.007) (***eFig. 8, Data Supplement***).

Figure 4. Forest plot showing the pooled HR for patients presenting with acute myocardial infarction and acute heart failure.



Discussion

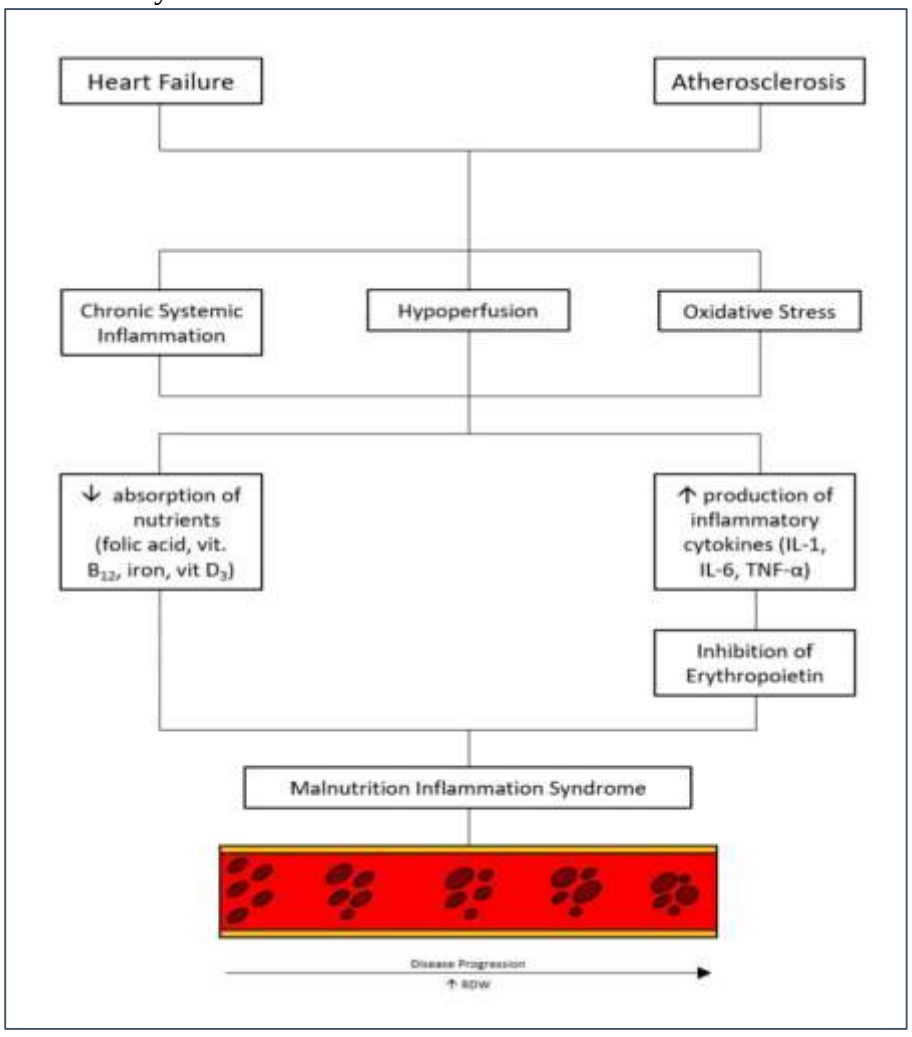
In our systematic review, we observed that elevated RDW levels at the time of admission, during the course of stay in hospital, or at the time of discharge significantly correlate with increased all-cause mortality and the overall occurrence of mortality rises by 15% (HR, 1.15) in CHF patients and 19% (HR, 1.19) in CHD patients, as suggested by their pooled HR estimates. RDW has been recognized as an independent predictor of not only mortality but major adverse cardiovascular events (MACE) as well, which includes any non-fatal/fatal myocardial infarction, re-infarction, stroke, or stent thrombosis.[39,40,43]

RDW, which is a measure of variability of anisocytosis or red cell volume of erythrocytes, is calculated by dividing the standard deviation of mean corpuscular volume (MCV) by the MCV and multiplying by 100 to yield a percentage value.[47] Since different laboratories have different methods of measuring RBC size, dissimilar laboratory standards, and statistical approaches, there is no universal reference range till now. Most laboratories use 11-15% as the normal range but can vary depending upon the technique

used for analysis by different commercially available analyzers.[1,8,47] Several studies have shown value >14.5% is associated with increased all-cause mortality and poor prognosis.[48] [49] We found that if the RDW increases by 1% from the admission baseline value either during the hospital stay or at time of discharge, there is 11% and 18% more risk of mortality in patients with CHF and CHD, respectively.

The precise mechanisms responsible for increased RDW in CHF and CHD patients are not fully elucidated. However, existing theories suggest that this elevation in RDW levels is due to a complex interplay between iron deficiency, long-standing inflammation, circulating inflammatory cytokines, and oxidative stress that is seen in both atherosclerosis and heart failure (**Figure 5**). RDW is usually elevated in conditions such as iron, folate or B12 deficiency, malnutrition, and hemolysis[2] — leading to anemia, which is frequently observed in coronary artery disease[50] and heart failure with a prevalence of 4%-55%.[51,52] Furthermore, inflammation, a hallmark of both atherosclerosis and early and late stages of heart failure releases cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and IL-6 into circulation.[53-55]

Figure 5. Mechanisms leading to elevated red cell distribution width in patients with heart failure and coronary atherosclerosis.



The inflammatory stress can lead to dysfunctional bone marrow in multiple ways — inflammatory cytokines inhibit the effect of erythropoietin on erythroid progenitor cells in bone marrow and block its anti-apoptotic effects leading to anemia and increased RDW.[33,37,52] The excess production of reactive oxygen species (oxidative stress) has shown to play pivotal role in pathophysiology of cardiac remodeling leading to CHF and deranged hematopoiesis causing anisocytosis.[1,56] These evidences suggest that increased RDW seen in patients with coronary heart disease and heart failure is not solely due to iron or nutritional deficiency but inflammation induced changes in erythropoiesis also has a key role to play. High sensitivity C-reactive protein (hsCRP) has also been linked with the severity of coronary heart disease.[57] However, it was found to be a weaker predictor of mortality, despite its positive association with the baseline RDW.[58-60]

Elevated RDW's association with poor prognosis in patients with CHD and CHF had been extensively studied.[4,32,61] The reason for poor prognosis in these patients is still unclear but several mechanisms had been postulated. Anemia, which is prevalent in cases of elevated RDW is a well-documented cause of increased mortality in CHD and CHF.[52,62,63] However, elevated RDW had been associated with increased mortality regardless of hemoglobin levels.[41,64] Increased RDW had been shown to correlate with unfavorable lipid profile[65] and reduced deformability of the erythrocytes.[61] This rheological dysfunction of circulating RBCs leads to decreased microvascular perfusion,[60] which can explain the slow coronary flow and decreased post-interventional thrombolysis in myocardial infarction (TIMI) flow in patients with elevated RDW.[66,67] Antioxidants such as vitamin-E are known to reduce the formation of reactive oxygen species and can contribute in improving the abnormal blood rheology.[68] From a therapeutic point of view, approaches dedicated toward reducing the elevated RDW levels in CHD and CHF patients can help lowering the mortality risk.[69] Furthermore, alirocumab (FDA approved second-line treatment for hypercholesterolemia) therapy, demonstrated a significant reduction in MACE and mortality without altering the RDW levels.[60] These interventions may be beneficial for patients with CHD and/or CHF, however, their therapeutic potential still needs to be validated in this particular subset of patients.

Limitations

The foremost limitation of our meta-analysis lies in the study designs of included studies. Due to an absolute unavailability of randomized controlled studies, we had to rely on prospective and retrospective studies for our analyses, which could have resulted in bias. Another limitation is the inconsistency among the adjusted variables across individual studies while estimating the Cox proportional hazards ratio. Additionally, we were unable to adjust for folate or vitamin B12 levels, or high alcohol intake, all of which may act as possible confounders. However, our study involves patients from various geographical regions and still produces results that are concordant to previously conducted meta-analyses, which preserves its external validity.

Conclusion

Elevated RDW levels either at the time of admission, during the course of stay in hospital, or at the time of discharge significantly correlate with the increased all-cause mortality among CHF and CHD patients and have prognostic importance in anticipating the risk of death in these subset of patients. This study also aims to creates awareness among physicians regarding utilizing this easily available tool in these

subsets of patients more to determine prognosis of the disease.

Acknowledgements
None

Declarations

Funding
No sources of funding.

Conflicts of interest
Authors declare that they have no competing interests to disclose.

Availability of data and material
All the data used in this review was extracted from included studies. Additional data and information are provided in the supplementary documents.

CRediT author statement
Sagar Ranka: Conceptualization, Methodology, Resources, Validation, Writing – Review & Editing, Supervision, Project administration.
Shubham Lahan: Methodology, Software, Formal analysis, Data curation, Writing – Original Draft
Tarun Dalia: Methodology, Validation, Data curation, Resources, Writing – Original Draft
Alok Tripathi: Validation, Visualization, Supervision.
Amandeep Goyal: Resources, Data curation, Writing – Review & Editing
Jaykumar Sreenivasan: Data curation, Writing – Review & Editing
Sivasagar Taduru: Writing – Review & Editing, Validation, Project administration.
Moghniuddin Muhammed: Writing – Review & Editing, Resources, Data curation.
Patrick M. Moriarty: Conceptualization, Methodology, Supervision, Funding acquisition.

Ethics approval
Being a systematic review, our study was exempted from review board's approval.

Consent to participate
Not applicable

Consent for publication
Not applicable

ORCID iD
Sagar Ranka – https://orcid.org/0000-0002-2167-6961
Shubham Lahan – https://orcid.org/0000-0002-8192-3629
Tarun Dalia – https://orcid.org/0000-0002-4115-6189
Amandeep Goyal – https://orcid.org/0000-0001-6070-1747

References

1. Lippi G, Turcato G, Cervellin G, Sanchis-Gomar F. Red blood cell distribution width in heart failure: a narrative review. *World journal of cardiology.* 2018;10(2):6.
2. Felker GM, Allen LA, Pocock SJ, 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(1):40-47.
3. Tonelli M, Sacks F, Arnold M, et al. Relation Between Red Blood Cell Distribution Width and Cardiovascular Event Rate in People With Coronary Disease. *Circulation.* 2008;117(2):163-168.
4. van Kimmenade RR, Mohammed AA, Uthamalingam S, van der Meer P, Felker GM, Januzzi JL, Jr. Red blood cell distribution width and 1-year mortality in acute heart failure. *Eur J Heart Fail.* 2010;12(2):129-136.
5. Pascual-Figal DA, Bonaque JC, Redondo B, et al. Red blood cell distribution width predicts long-term outcome regardless of anaemia status in acute heart failure patients. *Eur J Heart Fail.* 2009;11(9):840-846.
6. Zalawadiya SK, Veeranna V, Niraj A, Pradhan J, Afonso L. Red cell distribution width and risk of coronary heart disease events. *Am J Cardiol.* 2010;106(7):988-993.
7. Shao Q, Korantzopoulos P, Letsas KP, et al. Red blood cell distribution width as a predictor of atrial fibrillation. *Journal of clinical laboratory analysis.* 2018;32(5):e22378.
8. Danese E, Lippi G, Montagnana M. Red blood cell distribution width and cardiovascular diseases. *Journal of thoracic disease.* 2015;7(10):E402.
9. Shah N, Pahuja M, Pant S, et al. Red cell distribution width and risk of cardiovascular mortality: Insights from National Health and Nutrition Examination Survey (NHANES)-III. *Int J Cardiol.* 2017;232:105-110.
10. Shao Q, Li L, Li G, Liu T. Prognostic value of red blood cell distribution width in heart failure patients: a meta-analysis. *International Journal of Cardiology.* 2015;179:495-499.
11. Su C, Liao L-Z, Song Y, Xu Z-W, Mei W-Y. The role of red blood cell distribution width in mortality and cardiovascular risk among patients with coronary artery diseases: a systematic review and meta-analysis. *Journal of thoracic disease.* 2014;6(10):1429.
12. Huang Y-L, Hu Z-D, Liu S-J, et al. 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(8):e104861.
13. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.
14. Lahan S, Ranka S, Dalia T, Goyal A, Moriarty P. THE ASSOCIATION BETWEEN RED CELL DISTRIBUTION WIDTH AND CARDIOVASCULAR OUTCOMES-A METANALYSIS. *Journal of the American College of Cardiology.* 2021;77(18_Supplement_1):1629-1629.
15. Biomedicine IoMUCotSaEIoDi. *Society's Choices: Social and Ethical Decision Making in Biomedicine.*

Washington (DC): National Academic Press (US); 1995.
16. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg.* 2003;73(9):712-716.
17. Deeks JJ, Higgins J, Altman DG. Cochrane Training. Chapter 10.3.: Analysing data and undertaking meta-analyses. https://training.cochrane.org/handbook/current/chapter-10#section-10-3 Accessed.
18. IntHout J, Ioannidis JP, Borm GF. The Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis is straightforward and considerably outperforms the standard DerSimonian-Laird method. *BMC Med Res Methodol.* 2014;14:25.
19. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health.* 2019;22(4):153-160.
20. W V. Conducting Meta-Analyses in R with the metafor Package. *Journal of Statistical Software.* 2010;36(3):1-48.
21. Al-Najjar Y, Goode KM, Zhang J, Cleland JG, Clark AL. Red cell distribution width: an inexpensive and powerful prognostic marker in heart failure. *Eur J Heart Fail.* 2009;11(12):1155-1162.
22. Allen LA, Felker GM, Mehra MR, et al. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. *J Card Fail.* 2010;16(3):230-238.
23. Bonaque JC, Pascual-Figal DA, Manzano-Fernandez S, et al. Red blood cell distribution width adds prognostic value for outpatients with chronic heart failure. *Rev Esp Cardiol (Engl Ed).* 2012;65(7):606-612.
24. Cauthen CA, Tong W, Jain A, Tang WH. Progressive rise in red cell distribution width is associated with disease progression in ambulatory patients with chronic heart failure. *J Card Fail.* 2012;18(2):146-152.
25. Jackson CE, Dalzell JR, Bezlyak V, et al. Red cell distribution width has incremental prognostic value to B-type natriuretic peptide in acute heart failure. *Eur J Heart Fail.* 2009;11(12):1152-1154.
26. Lappe J, Anderson J, Kfoury A, et al. The Red Cell Distribution Width Predicts 30-Day Readmission Risk among Patients with a Primary Diagnosis of Heart Failure. *J Am Coll Cardiol.* 2013;61(10).
27. Makhoul BF, Khourieh A, Kaplan M, Bahouth F, Aronson D, Azzam ZS. Relation between changes in red cell distribution width and clinical outcomes in acute decompensated heart failure. *Int J Cardiol.* 2013;167(4):1412-1416.
28. Melchio R, Rinaldi G, Testa E, 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(2):239-247.
29. Oh J, Kang SM, Won H, et al. Prognostic value of change in red cell distribution width 1 month after discharge in acute decompensated heart failure patients. *Circ J.* 2012;76(1):109-116.
30. Rickard J, Kumbhani DJ, Gorodeski EZ, et al. 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(2):79-84.
31. Topaz G, Haim M, Kusniec J, et al. Association between Red Cell Distribution Width and Mortality after Cardiac Resynchronization Therapy. *Isr Med Assoc J.* 2015;17(8):505-509.
32. Tseliou E, Terrovitis JV, Kaldara EE, 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(6):457-461.
33. 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(4):659-666.
34. Aung N, Ling HZ, Cheng AS, 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(3):1997-2002.
35. Jung C, Fujita B, Lauten A, et al. Red blood cell distribution width as useful tool to predict long-term mortality in patients with chronic heart failure. *Int J Cardiol.* 2011;152(3):417-418.
36. Yu SB, Cui HY, Qin M, et al. [Impact of red cell distribution width on outcome of 16 681 patients with chronic systolic heart failure]. *Zhonghua Xin Xue Guan Bing Za Zhi.* 2012;40(3):237-242.
37. Arbel Y, Shacham Y, Finkelstein A, et al. Red blood cell distribution width (RDW) and long-term survival in patients with ST elevation myocardial infarction. *Thromb Res.* 2014;134(5):976-979.
38. Azab B, Torbey E, Hatoum H, et al. Usefulness of red cell distribution width in predicting all-cause long-term mortality after non-ST-elevation myocardial infarction. *Cardiology.* 2011;119(2):72-80.
39. Gijsberts CM, den Ruijter HM, de Kleijn DP, et al. Hematological Parameters Improve Prediction of Mortality and Secondary Adverse Events in Coronary Angiography Patients: A Longitudinal Cohort Study. *Medicine (Baltimore).* 2015;94(45):e1992.
40. Machado GP, de Araujo GN, Carpes CK, et al. Long-term Pattern of Red Cell Distribution Width in Patients With ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. *Crit Pathw Cardiol.* 2020;19(1):43-48.
41. Osadnik T, Strzelczyk J, Hawranek M, et al. Red cell distribution width is associated with long-term prognosis in patients with stable coronary artery disease. *BMC Cardiovasc Disord.* 2013;13:113.
42. Sahin O, Akpek M, Sarli B, et al. 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(2):178-183.
43. Yao HM, Sun TW, Zhang XJ, et al. Red blood cell distribution width and long-term outcome in patients undergoing percutaneous coronary intervention in the drug-eluting stenting era: a two-year cohort study. *PLoS One.* 2014;9(4):e94887.
44. Dabbah S, Hammerman H, Markiewicz W, Aronson D. Relation between red cell distribution width and clinical outcomes after acute

myocardial infarction. *Am J Cardiol.* 2010;105(3):312-317.
45. Lee JH, Yang DH, Jang SY, et al. Incremental predictive value of red cell distribution width for 12-month clinical outcome after acute myocardial infarction. *Clin Cardiol.* 2013;36(6):336-341.
46. Uyarel H, Ergelen M, Cicek G, et al. Red cell distribution width as a novel prognostic marker in patients undergoing primary angioplasty for acute myocardial infarction. *Coron Artery Dis.* 2011;22(3):138-144.
47. Li N, Zhou H, Tang Q. Red blood cell distribution width: a novel predictive indicator for cardiovascular and cerebrovascular diseases. *Disease markers.* 2017;2017.
48. Bazick HS, Chang D, Mahadevappa K, Gibbons FK, Christopher KB. Red Cell Distribution Width and all cause mortality in critically ill patients. *Critical care medicine.* 2011;39(8):1913.
49. Hou H, Sun T, Li C, et al. An overall and dose-response meta-analysis of red blood cell distribution width and CVD outcomes. *Scientific reports.* 2017;7(1):1-10.
50. Rymer JA, Rao SV. Anemia and coronary artery disease: pathophysiology, prognosis, and treatment. *Coron Artery Dis.* 2018;29(2):161-167.
51. Felker GM, Adams KF, Jr., Gattis WA, O'Connor CM. Anemia as a risk factor and therapeutic target in heart failure. *J Am Coll Cardiol.* 2004;44(5):959-966.
52. Anand IS, Gupta P. Anemia and Iron Deficiency in Heart Failure: Current Concepts and Emerging Therapies. *Circulation.* 2018;138(1):80-98.
53. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N Engl J Med.* 1990;323(4):236-241.
54. Munger MA, Johnson B, Amber IJ, Callahan KS, Gilbert EM. Circulating concentrations of proinflammatory cytokines in mild or moderate heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol.* 1996;77(9):723-727.
55. Tousoulis D, Oikonomou E, Economou EK, Crea F, Kaski JC. Inflammatory cytokines in atherosclerosis: current therapeutic approaches. *Eur Heart J.* 2016;37(22):1723-1732.
56. Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart failure. *American Journal of Physiology-Heart and Circulatory Physiology.* 2011.
57. Speidl WS, Graf S, Hornykewycz S, et al. High-sensitivity C-reactive protein in the prediction of coronary events in patients with premature coronary artery disease. *Am Heart J.* 2002;144(3):449-455.
58. Loprinzi PD. Comparative evaluation of red blood cell distribution width and high sensitivity C-reactive protein in predicting all-cause mortality and coronary heart disease mortality. *Int J Cardiol.* 2016;223:72-73.
59. Veeranna V, Zalawadiya SK, Panaich S, Patel KV, Afonso L. Comparative analysis of red cell distribution width and high sensitivity C-reactive protein for coronary heart disease mortality prediction in multi-ethnic population: findings from the 1999-2004 NHANES. *Int J Cardiol.* 2013;168(6):5156-5161.
60. Moriarty PM, Steg PG, Gorby LK, et al. Relation of Red Blood Cell Distribution Width to Risk of Major Adverse Cardiovascular Events,

Death, and Effect of Alirocumab After Acute Coronary Syndrome. *Circulation.* 2019;140.

61. Bujak K, Wasilewski J, Osadnik T, et al. The prognostic role of red blood cell distribution width in coronary artery disease: a review of the pathophysiology. *Disease markers.* 2015;2015.
62. Muzzarelli S, Pfisterer M, Investigators T. Anemia as independent predictor of major events in elderly patients with chronic angina. *American heart journal.* 2006;152(5):991-996.
63. Anand IS. Anemia and chronic heart failure: implications and treatment options. *Journal of the American College of Cardiology.* 2008;52(7):501-511.
64. 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. *Experimental and therapeutic medicine.* 2014;8(2):600-606.
65. Tziakas D, Chalikias G, Grapsa A, Gioka T, Tentes I, Konstantinides S. Red blood cell distribution width–a strong prognostic marker in cardiovascular disease–is associated with cholesterol content of erythrocyte membrane. *Clinical hemorheology and microcirculation.* 2012;51(4):243-254.
66. Akpinar I, Sayin MR, Gursoy YC, et al. Plateletcrit and red cell distribution width are independent predictors of the slow coronary flow phenomenon. *Journal of cardiology.* 2014;63(2):112-118.
67. Karabulut A, Uyarel H, Uzunlar B, Çakmak M. Elevated red cell distribution width level predicts worse postinterventional thrombolysis in myocardial infarction flow reflecting abnormal reperfusion in acute myocardial infarction treated with a primary coronary intervention. *Coronary artery disease.* 2012;23(1):68-72.
68. Kobayashi S, Moriya H, Aso K, Ohtake T. Vitamin E-bonded hemodialyzer improves atherosclerosis associated with a rheological improvement of circulating red blood cells. *Kidney Int.* 2003;63(5):1881-1887.
69. Meital LT, Windsor MT, Ramirez Jewell RML, et al. n-3 PUFAs improve erythrocyte fatty acid profile in patients with small AAA: a randomized controlled trial. *J Lipid Res.* 2019;60(6):1154-1163.

Data Supplement

eTable 1. PRISMA Checklist reporting necessary items.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Data Supplement
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8

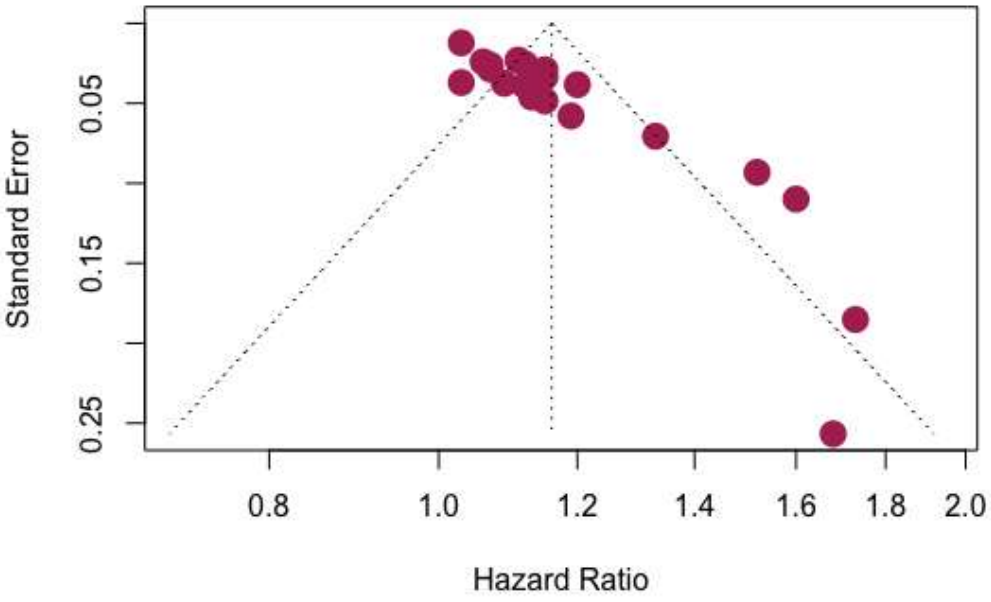
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	-
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Data Supplement
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Data Supplement
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

eTable 2. Quality assessment of studies included using Methodological Index for Non-Randomized Studies (MINORS) criteria.

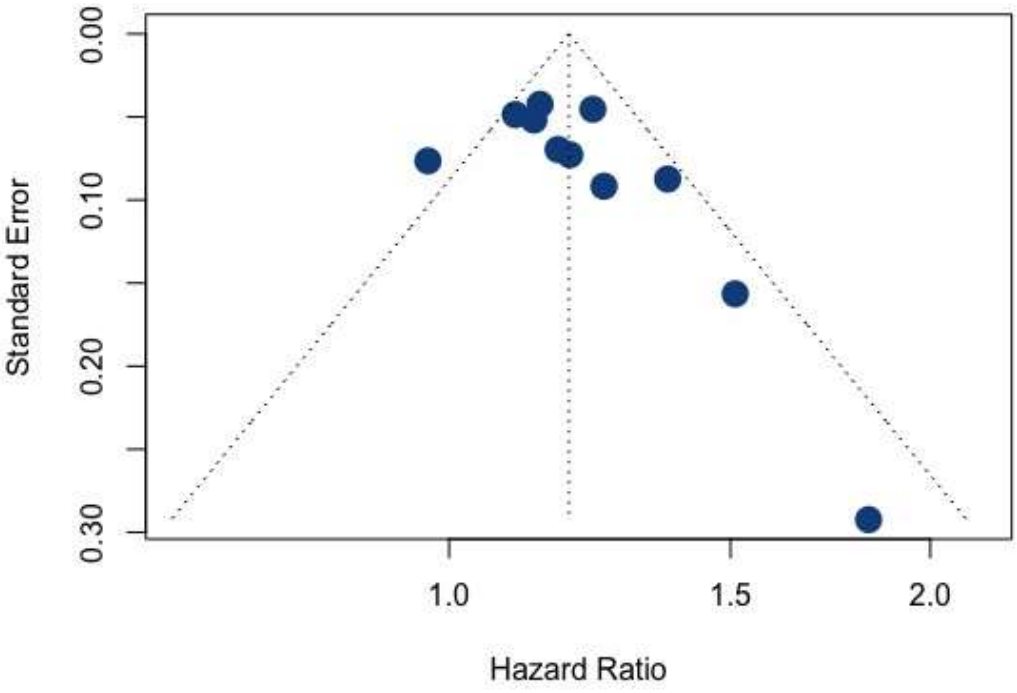
	Clearly stated aim	**Inclusion of consecutive patients**	**Prospective collection of data**	**Endpoints appropriate to the aim of the study.**	**Unbiased assessment of study endpoint**	**Follow-up period appropriate to the aim of the study**	**Loss to follow-up < 5%**	**Prospective calculation of the study size**	**Total score**
Study author (year)									
Felker et al (2007)	2	1	2	2	0	2	2	0	**11**
Al Najjar et al (2009)	2	2	1	2	2	2	0	0	**11**
Jackson et al (2009)	2	0	2	2	0	2	0	0	**8**
Van Kimmenade et al (2009)	1	0	2	2	0	2	2	0	**9**
Pasqual-Figal et al (2009)	2	2	2	2	0	2	2	0	**12**
Forhecz et al (2009)	2	2	2	2	0	2	2	0	**12**
Allen et al (2010)	2	2	2	2	0	2	1	0	**11**
Jung et al (2011)	1	0	2	2	0	2	0	0	**7**
Oh et al (2012)	2	0	2	2	0	2	1	0	**9**
Yu et al (2012)	2	1	0	2	0	2	0	0	**7**
Bonaque et al (2012)	2	2	2	2	0	2	2	0	**12**
Aung et al (2012)	2	0	1	2	0	2	2	0	**9**
Rickard et al (2012)	2	1	2	2	1	2	0	0	**10**
Cauthen et al (2012)	2	0	2	2	0	2	1	0	**9**
Makhoul et al (2012)	2	1	2	2	0	2	2	0	**11**
Lappe et al (2013)	2	1	0	2	0	2	2	0	**9**
Tseliou et al (2014)	2	0	0	2	0	2	2	0	**8**
Topaz et al (2015)	2	0	2	2	0	2	1	0	**9**

Melchio et al (2019)	2	0	2	2	0	2	1	0	**9**
Tonelli et al (2008)	2	2	2	2	0	2	2	0	**10**
Dabbah et al (2010)	2	0	2	2	0	2	0	0	**8**
Uyarel et al (2011)	2	0	1	2	0	2	2	0	**9**
Azab et al (2011)	2	0	0	2	0	2	1	0	**7**
Osadnik et al (2013)	2	2	2	2	0	2	2	0	**12**
Lee et al (2013)	2	2	0	2	0	2	0	0	**8**
Sahin et al (2014)	2	0	0	2	1	2	0	0	**7**
Yao et al (2014)	2	0	2	2	0	2	1	0	**9**
Arbel et al (2014)	2	0	2	2	0	2	0	0	**8**
Gijsberts et al (2015)	2	1	2	2	0	2	1	0	**10**
Machado et al (2020)	2	2	2	2	0	2	0	0	**10**

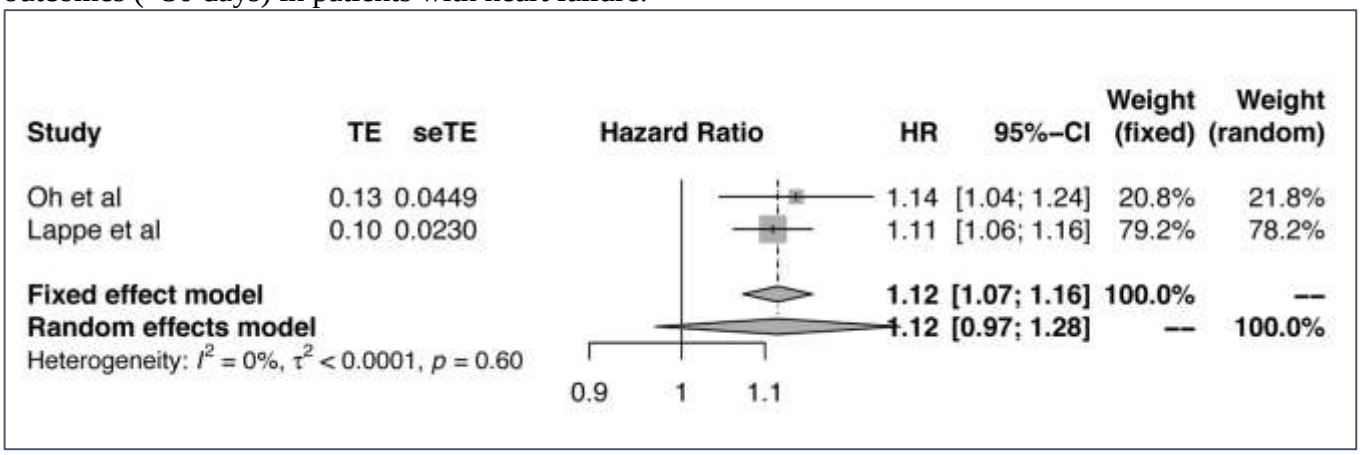
eFigure 1. Funnel plot showing effect size of different studies against its standard error for HF.



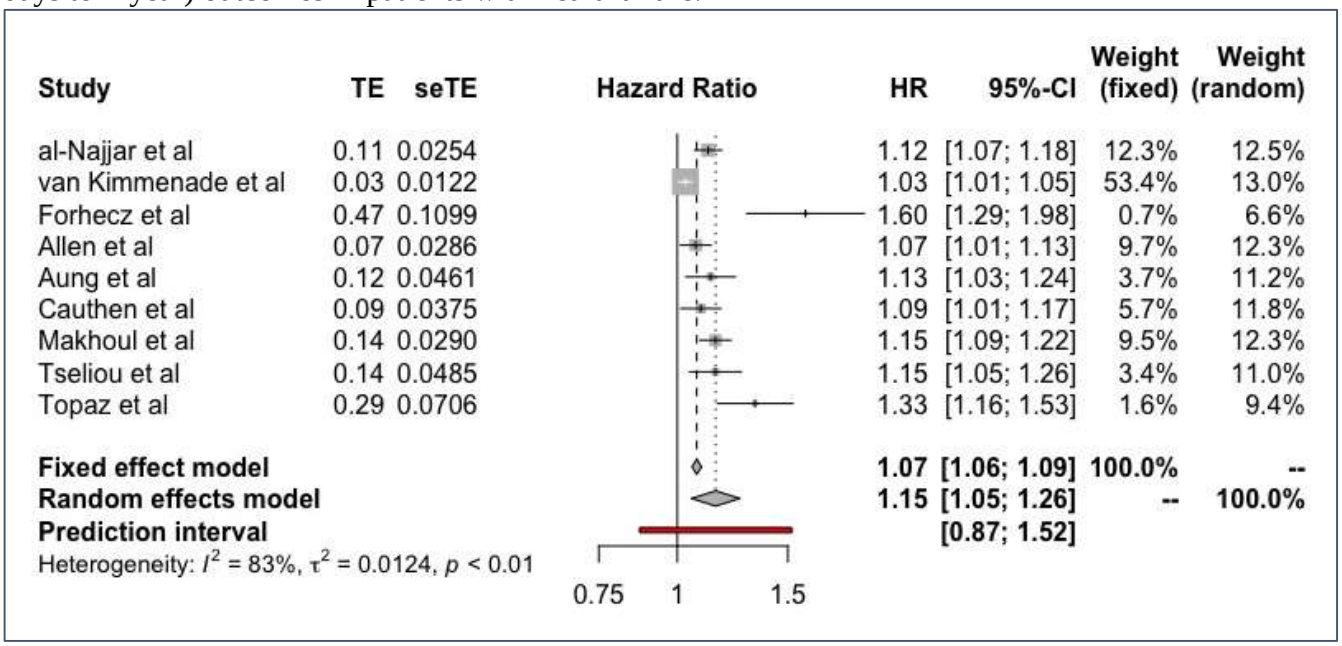
eFigure 2. Funnel plot showing effect size of different studies against its standard error for CHD.



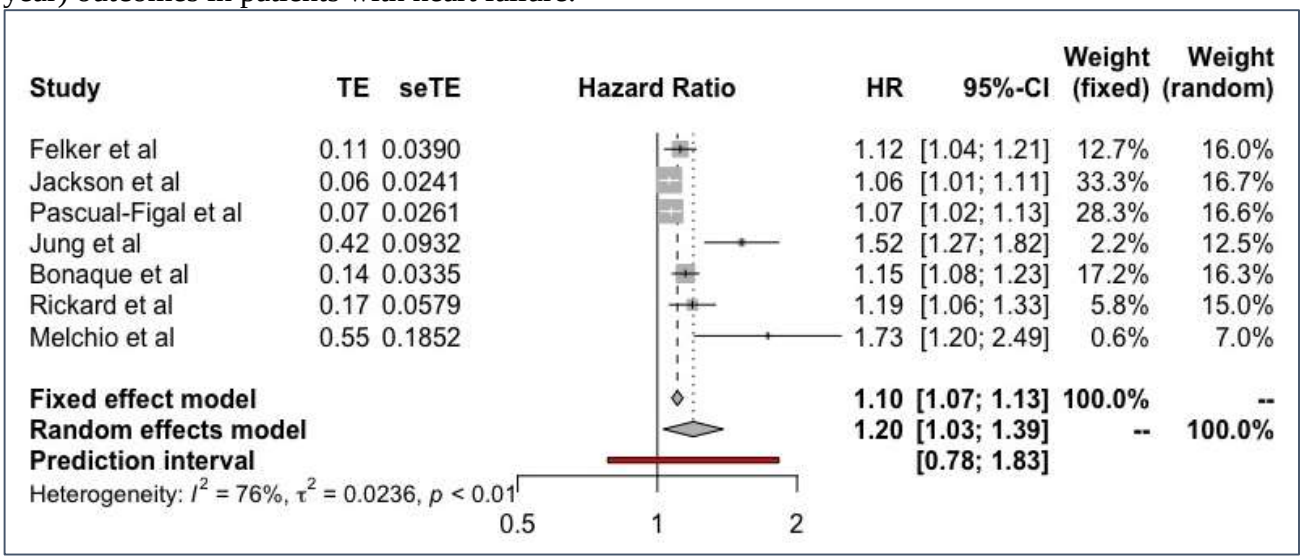
eFigure 3. Forest plot showing pooled HR obtained on sub-group analysis for the short-term outcomes (<30 days) in patients with heart failure.



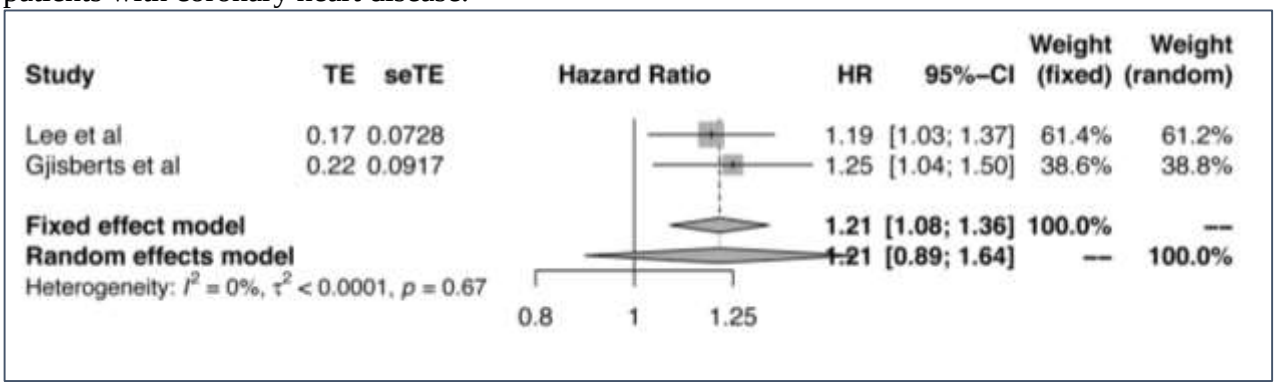
eFigure 4. Forest plot showing pooled HR obtained on sub-group analysis for the mid-term (30-days to 1-year) outcomes in patients with heart failure.



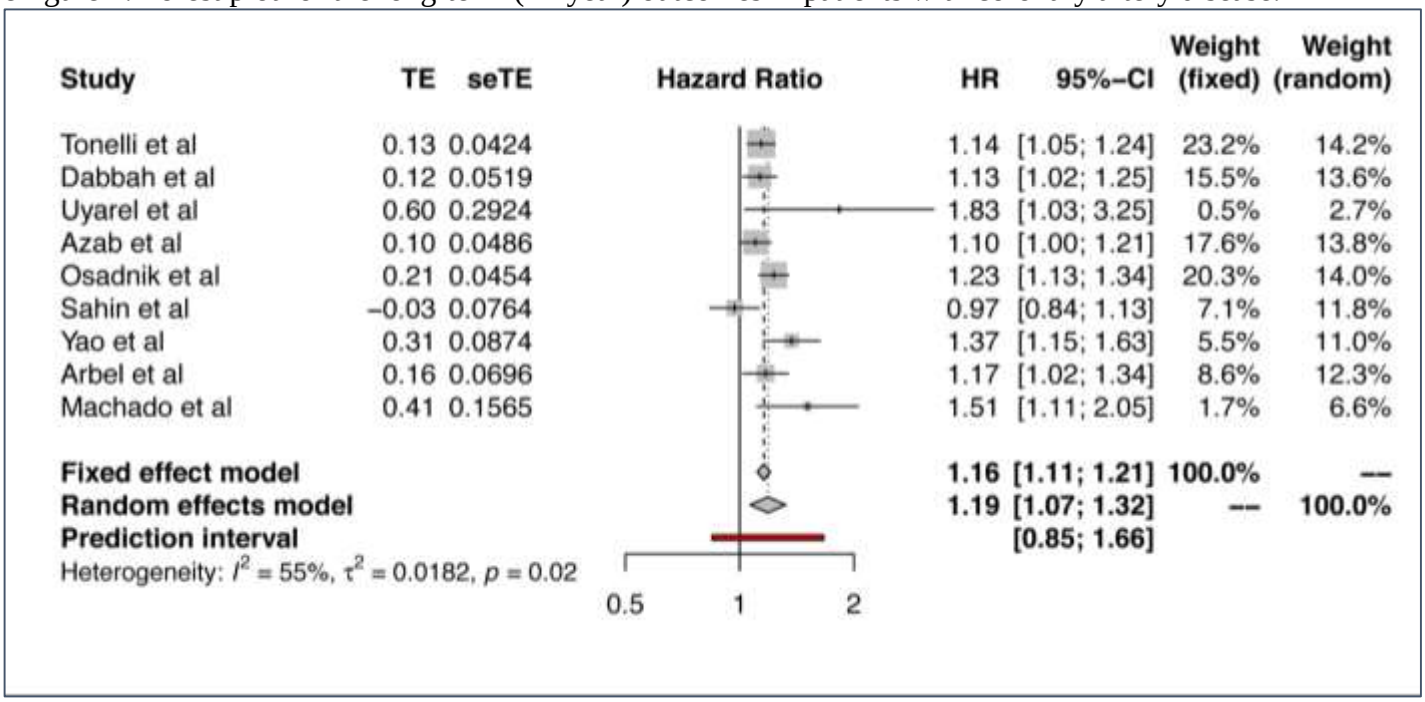
eFigure 5. Forest plot showing pooled HR obtained on sub-group analysis for the long-term (>1 year) outcomes in patients with heart failure.



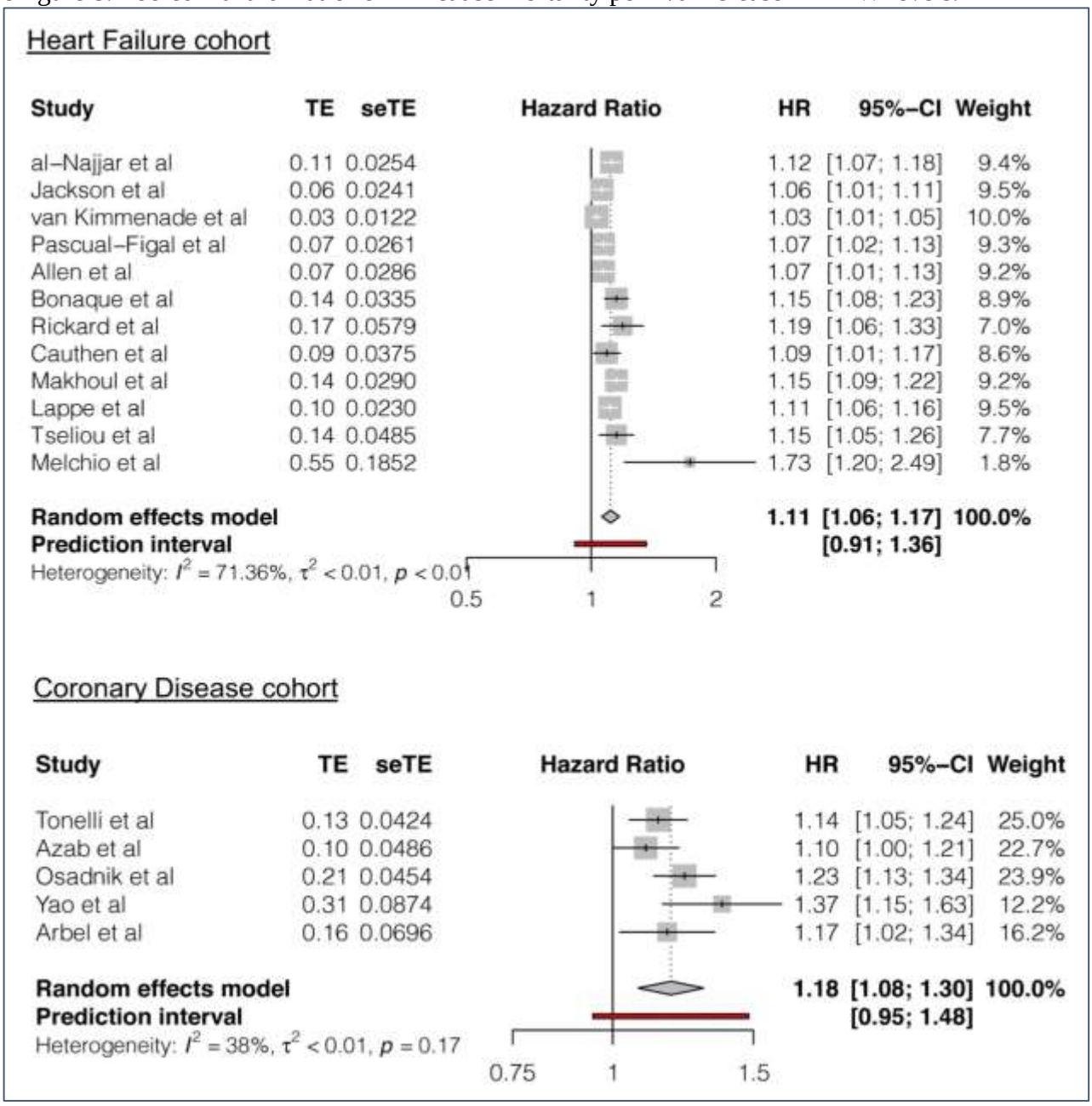
eFigure 6. Forest plot illustrating the pooled HR for the mid-term (30-days to 1-year) outcomes in patients with coronary heart disease.



eFigure 7: Forest plot for the long-term (>1 year) outcomes in patients with coronary artery disease.



eFigure 8. Pooled Hazard Ratio for All-cause mortality per 1% increase in RDW levels.



eTable 3. Details of studies and baseline characteristics of their patient cohorts included in this systematic review.

Authors	Study period	Year	Country	Study design	Underlying cardiac condition	Sample size (n)	Age (years)	Male (%)	HTN (%)	Diabetes (%)	Smokers (%)	Primary End-point
Felker et al	Not specified	2007	US	Prospective cohort	Heart Failure	2679	65	67	67	40	NA	All-cause mortality
Al Najjar et al	2001-2008	2009	UK	Prospective cohort	Heart Failure	1087	72	74.3	35.5	19.6	NA	All-cause mortality
Jackson et al	2006 – 2008	2009	UK	Prospective cohort	Acute HF	707	73	52	NA	31	NA	All-cause mortality
Van Kimmenade et al	Not specified	2009	US	Retrospective cohort	Acute HF	205	73	51	65	42	49.5	All-cause mortality
Pasqual-Figal et al	2002-2003	2009	Spain	Prospective cohort	Acute HF	628	71	68	57	39	NA	All-cause mortality
Forhecz et al	2005-2006	2009	Hungary	Prospective cohort	Heart Failure	195	70	74.4	68.7	37	NA	All-cause mortality and hospital readmission
Allen et al	Not specified	2010	US	Prospective cohort	Heart Failure	1012	64	58	69	38	11	All-cause mortality and all-cause hospitalization or mortality.
Jung et al	1999-2005	2011	Germany	Prospective cohort	Heart Failure	354	49	75.7	NA	NA	NA	All-cause mortality or Heart transplant
Oh et al	2005-2009	2012	Korea	Retrospective cohort	Heart Failure	261	62.6	54.8	50.2	31	NA	CV events including CV mortality and re-admission for HF.

Yu et al	Not specified	2012	China	Prospective cohort	Acute HF	16,681	66	49	NA	NA	NA	All-cause mortality
Bonaque et al	2003-2005	2012	Spain	Prospective cohort	Heart Failure	698	71	63	63	42.2	NA	Hospitali-zation and mortality
Aung et al	2006-2010	2012	UK	Retrospective cohort	Heart Failure	274	69	69	NA	NA	NA	All-cause mortality
Rickard et al	2001-2006	2012	US	Retrospective cohort	Heart Failure	217	64	73.3	57	36.9	63	All-cause mortality
Cauthen et al	2001-2006	2012	US	Retrospective cohort	Heart Failure	6052	66	64	41	28	NA	All-cause mortality
Makhoul et al	2008-2010	2012	Israel	Prospective cohort	Acute HF	614	76.7	48.2	82.5	50	NA	All-cause mortality or re-admission
Lappe et al	Not specified	2013	US	Retrospective cohort	Heart Failure	6616	71.4	47.7	NA	NA	NA	30-day re-admission
Tseliou et al	Not specified	2014	Greece	Prospective cohort	Heart Failure	80	57.8	97.6	NA	NA	NA	All-cause mortality or LVAD implantation
Topaz et al	2004-2008	2015	Israel	Retrospective cohort	Heart Failure	156	69	80.8	68	41	NA	All-cause mortality

Melchio et al	2014	2019	Italy	Retrospective cohort	Acute HF	451	80	52	53	29	NA	All-cause death rate & composite death or re-admission
Tonelli et al	NA	2008	US	Post-hoc analysis	CAD	4111	58.2	86.2	42.7	14	16	All-cause mortality
Dabbah et al	2001-2007	2010	Israel	Prospective cohort	MI	1709	61	78	50	29	12.8	All-cause mortality
Uyarel et al	2003-2008	2011	Turkey	Prospective cohort	MI	2506	58.5	82	41	25	55	MACE (mortality, re-infarction, repeat target vessel revascularization
Azab et al	2004-2006	2011	US	Observational	CAD	619	64	67	71.5	35	56.3	All-cause mortality
Osadnik et al	2007-2011	2013	Poland	Retrospective cohort	CAD	2535	64	70.5	71.6	37	34.5	All-cause mortality

Lee et al	2005-2010	2013	Korea	Observational	MI	1596	64.5	67	46	28.8	43	Death and non-fatal MI
Sahin et al	2010-2012	2014	Turkey	Cross-sectional	MI	335	63	67	51	32	35	All-cause mortality
Yao et al	2009-2011	2014	China	Prospective cohort	CAD	2169	60	67	50	22.7	NA	All-cause mortality MACE
Arbel et al	Not specified	2014	Israel	Prospective cohort	MI	535	61	77	43	47	44	All-cause mortality
Gijsberts et al	2011-2014	2015	Netherland	Retrospective cohort	MI	1760	64	72	57.6	22	47.3	All-cause mortality MACE
Machado et al	2011-2018	2020	Brazil	Prospective cohort	MI	485	61	63	62	26	62	MACE (all-cause death, new MI, stent thrombosis, and stroke after primary PCI)

ACEI: Angiotensin convertase enzyme inhibitors; ACS: Acute coronary syndrome; ARB: Angiotensin receptor blockers; BMI: Basal metabolic index; BNP: Brain natriuretic peptide; BUN: Blood urea nitrogen; CAD: Coronary artery disease; CHD: Coronary heart disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; DBP: Diastolic blood pressure; EF: Ejection fraction; GFR: Glomerular filtration rate; HDL: High-density lipoprotein; HF: Heart failure; HTN: Hypertension; IHD: Ischemic heart disease; JVP: Jugular venous pressure; LDL: Low-density lipoprotein; LVEF: Left ventricular ejection fraction; MCV: Mean corpuscular volume; MI: Myocardial infarction; NYHA: New York Heart Association; PCI: Percutaneous coronary intervention; PCWP: Pulmonary capillary wedge pressure; RAS: Renin-angiotensin system; SBP: Systolic blood pressure; TIMI: Thrombolysis in myocardial infarction; WBC: White blood cells.

