

Cognitive impairment associated with increased mortality rate in patients with heart failure: A systematic review and meta-analysis



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Background: Recent systematic review and meta-analysis showed that the prevalence of cognitive impairment was significantly increased in patients with heart failure (HF) when compared to the general population. However, the effect of cognitive impairment on cardiovascular outcome in this population is still unclear. We performed a systematic review and meta-analysis to assess whether cognitive impairment associated with worse outcome in patients with HF.

Methods: We comprehensively searched the databases of MEDLINE and EMBASE from inception to October 2018. Included studies were published cohort (prospective or retrospective) or randomized control trials that evaluate the effect of cognitive impairment mortality in HF patients. Data from each study were combined using the random-effects, generic inverse variance method of DerSimonian and Laird to calculate pooled hazard ratios (HR) and 95% confidence intervals (CI).

Results: Eight studies were included in the analysis involving 3318 participants (951 participants had cognitive impairment). In a random-effects model, our analysis demonstrated that cognitive impairment significantly increased the risk of mortality in HF patients (pooled HR = 1.64, 95% CI = 1.42–1.88, I² = 0.0%, *p* < 0.001).

Conclusion: Our systematic review and meta-analysis showed that the presence of cognitive impairment is strongly associated with an increased mortality risk in the HF population. Further research is needed to explore the pathophysiology of this association.

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1. Introduction

Heart failure (HF) is a very common cardiovascular disease and one of the leading causes of hospitalization and mortality worldwide, especially in older adults [1,2]. The mortality rate from HF has been decreasing significantly in past few decades due to the implementation of beta-blockers, renin-angiotensin-aldosterone system blockers, coronary revascularization, implantable cardioverter-defibrillator, and cardiac resynchronization therapies [3]. However, the mortality rate remained high with 5-year mortality up to 42.3% in patients hospitalized for HF [4]. Identifying clinical prognosticating factors in such patients is among foci of clinical research. Several factors have been found associated with a worse cardiovascular outcome and an increased mortality in patients with HF. These factors include, but not limited to, increased resting heart rate, low ejection fraction, raised creatinine, New York Heart Association Class III/IV, history of left bundle branch block, low systolic blood pressure, and older age [5].

Cognitive dysfunction is a common condition in patients with HF. A systematic review including 4176 participants in 26 cohorts revealed the prevalence of cognitive impairment at 43% in patients with HF [6]. Among such patients, cognitive dysfunction has been found associated with poorer medical adherence [7], lower ability for self-care [8], lower disease awareness [9], increased hospitalization [10], and higher cardiovascular events [11].

Several studies have been conducted to study the impact of cognitive impairment on mortality in patients with HF [12–18]. However, there has been no systematic review or meta-analysis to confirm this relation. This is the first meta-analysis to evaluate the association between cognitive impairment and long-term mortality in patients with HF.

2. Methods

2.1. Search strategy

Two investigators (NP and CK) independently searched for published studies indexed in MEDLINE and EMBASE databases from inception to October 2018 using a search strategy that included the terms “cognitive impairment”, “cognitive dysfunction”, “heart failure”, and “mortality”. Publications in only English language were included. A manual search for additional

Abbreviations

CI	Confidence Interval
HF	Heart Failure
HR	Hazard ratio

pertinent studies and review articles using references from retrieved articles was also completed.

2.2. Inclusion criteria

The eligibility criteria included the following:

- (1) Cohort studies (prospective or retrospective) or randomized controlled trials of HF patients with and without cognitive impairment that compared all-cause mortality rate between the two populations.
- (2) Relative risk, hazard ratio (HR), odds ratio, incidence ratio, or standardized incidence ratio with 95% confidence intervals (CIs) or sufficient raw data for these calculations had to be provided.

Study eligibility was independently determined by two investigators (NP and CK) and differences were resolved by mutual consensus. Newcastle–Ottawa quality assessment scale, ranging from 0 to 9, was used to evaluate each cohort study in three domains: recruitment and selection of the participants, similarity and comparability between the groups, and ascertainment of the outcome of interest among cohort studies [19]. Cochrane Collaboration tool for assessing risk of bias was used to evaluate the quality of each randomized controlled trial [20].

2.3. Data extraction

A standardized data collection form was used to obtain the following information from each study: name of first author, year of the study, country of origin, study type, inclusion and exclusion criteria, number and demographic data of the participants, duration of follow-up, diagnostic method of HF, mortality rate, assessment tools used to identify cognitive impairment, adjusted confounders and conclusion by authors.

To ensure accuracy, two investigators (NP and CK) independently performed this data extraction process. Should there be any data discrepancy, we referred back to the original articles.

2.4. Definition

HF was diagnosed differently as defined in each study (Table 1). Cognitive impairment was defined as an abnormality of at least one of the five domains of the cognitive function [21] or as

Table 1. Study characteristics.

First author	Year	Country	Study type	Inclusion criteria	Exclusion criteria	Mean age (SD)	Male (%)	Follow-up (months)	Total participants (n)	HF diagnostic method	Mortality rate (%)	CI screening method and diagnosis	Patients with CI (%)	Confounder adjustment	Conclusion
Gonz	2014	Spain	Randomized controlled trial	Individuals diagnosed with acute HF and discharged from Geriatric Service of the Caceres Hospital complex	N/A	85 (N/A)	27	12	116	According to the European Society of Cardiology Guidelines 2008	30.1	GDS ≥ 3	19.8	N/A	Participants without CI in disease management program had lower probability of CV event. This effect was not seen in the CI group
Huijts	2013	Netherland	Retrospective cohort	HF patients age ≥ 60 years old with HF, history of HF hospitalization within the past year, NT-proBNP higher than twice the upper limit of normal	Dyspnea not mainly from HF, valvular heart disease, short life expectancy, recent angina, history of revascularization	76 (8)	61.3	18	382	Signs and symptoms of HF or currently NYHA class ≥ 2 and on HF therapy	N/A	AMT ≤ 7	9.2	N/A	CI is often unrecognized in HF patients, but the influence of HF severity and its changes on cognitive function were less than hypothesized
Lan	2018	USA	Retrospective cohort	Outpatient veterans with a clinical diagnosis of HF without previous history of CI	Life expectancy of less than 6 months or documented dementia requiring a caregiver	66.4 (N/A)	98.8	36	250	N/A	25.6	SLUMS < 25	57.6	Demographics data, comorbidity, LVEF, SLUMS score	CI was an independent risk factor for mortality in patients with HF.
McLennan	2006	Australia	Randomized controlled trial	HF patients with EF $\leq 55\%$ and NYHA ≥ 2	Malignancy, documented dementia, unable to be discharged to their own home	75.6 (8)	60.1	60	200	Diagnosed by confirmed LVEF $< 55\%$ and NYHA ≥ 2	96.3	MMSE ≤ 26	13.5	N/A	Mild CI is of prognostic importance in CHF
Murad	2015	USA	Prospective cohort	Participants from the Cardiovascular Health Study who developed HF	N/A	79.2 (6.3)	51.8	120	558	Clinical diagnosis made by a treating physician, and being on medications for HF including both a diuretic and either a digitalis preparation or a vasodilator	83	3MSE < 80	17.4	Demographic data, functional impairment	Some of comorbidities in elderly with incident HF are associated with greater mortality risk

Del Sindaco	2012	Italy	Retrospective cohort	HF patients >70 years old with NYHA ≥ 3	Valvular heart disease, active substance abuse, psychiatric illness, dementia, short life expectancy, non-consent patient, living in nursing care	77 (4.6)	52.0	24	173	Diagnosis was determined according to the European Society of Cardiology Guidelines 2001	31.4	MMSE ≤ 24	41.6	Demographic data, comorbidity	CI is very common and associated with worse prognosis in HF patients
Sokoreli	2018	UK	Prospective observational study	HF patients >18 years old, live in the region served by the Hull and East Yorkshire hospitals NHS trust and hospitalized for HF and on treatment with loop diuretics	Unable to understand and comply with the protocol. Unable or unwilling to give informed consent.	76 (15)	66	12	671	At least one of the following: LVEF $\leq 40\%$, left atrial dimension >4.0 cm, 8 or NT-proBNP $>400/1200$ pg/mL for sinus rhythm/atrial fibrillation	15.6	GPCOG ≤ 4	46.9	Demographic data, comorbidity, LVEF, HADS, serum urea and creatinine	Psychological factors are strongly associated with unplanned recurrent readmissions or mortality following an admission for HF
Zucala	2003	Italy	Retrospective cohort	Patients admitted with principal diagnosis of HF	None	78 (9)	53.9	12	968	Clinically diagnosed by the study researchers	16	AMT <7	24.6	Demographic data, comorbidity, medication	CI is an independent prognostic marker in older patients with HF

3MSE = modified mini-mental state exam; AMT = Hodkinson abbreviated mental test; CI = cognitive impairment; CV = cardiovascular; GDS = global deterioration scale; GPCOG = general practitioner assessment of cognition; HADS = hospital anxiety and depression scale; HF = heart failure; LVEF = left ventricular ejection fraction; MMSE = mini-mental state examination; N/A = not available; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart American Classification; SLUMS = The Saint Louis University Mental Status.

defined in each study (Table 1). Mortality was defined by all-cause mortality during the follow-up period.

2.5. Statistical analysis

The meta-analysis was performed using a random-effects model. The extracted studies were excluded from the analysis if they did not justify an outcome in each cohort. We pooled the point estimates from each study using the generic inverse-variance method of Der Simonian and Laird [22]. The heterogeneity of effect size estimates across these studies was measured using the I^2 statistic. The I^2 statistic ranges in value from 0% to 100% ($I^2 < 25%$, low heterogeneity; $I^2 = 25\text{--}50\%$, moderate heterogeneity; $I^2 > 50\%$,

substantial heterogeneity). A sensitivity analysis was also conducted. Publication bias was assessed using a funnel plot and Egger's regression test ($p < 0.05$ was considered significant). All data analyses were performed using the StataCorp 2015, Stata: Release 14, Statistical Software (StataCorp LP, College Station, TX).

3. Results

3.1. Study inclusion and characteristic

In total, 303 potentially relevant studies (full articles) conducted were identified (88 studies from EMBASE, 215 studies from PUBMED). After exclusion of 72 duplicate studies, 231 studies underwent title and abstract review. After the

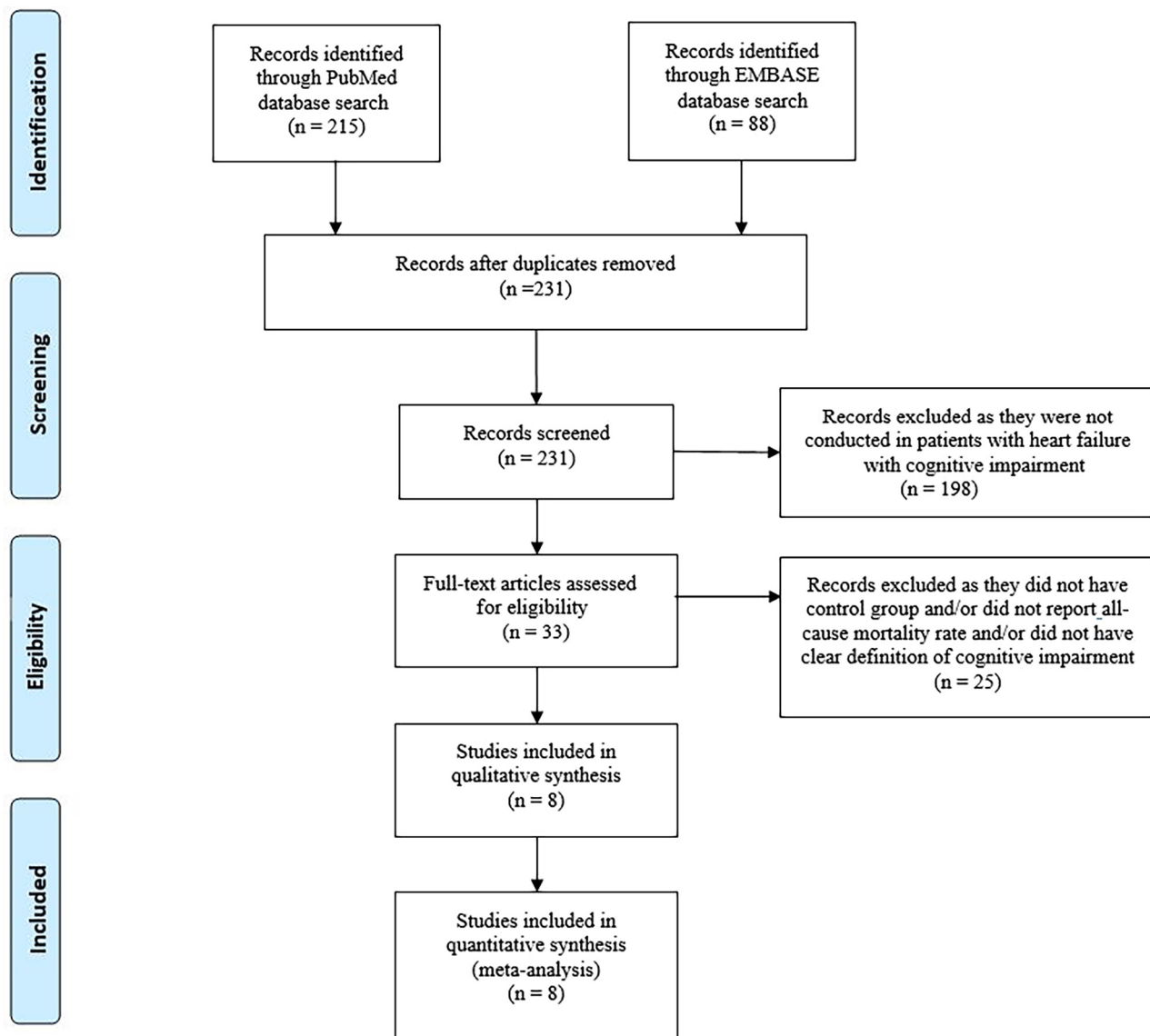


Figure 1. PRISMA flow diagram demonstrating search strategy and selection process.

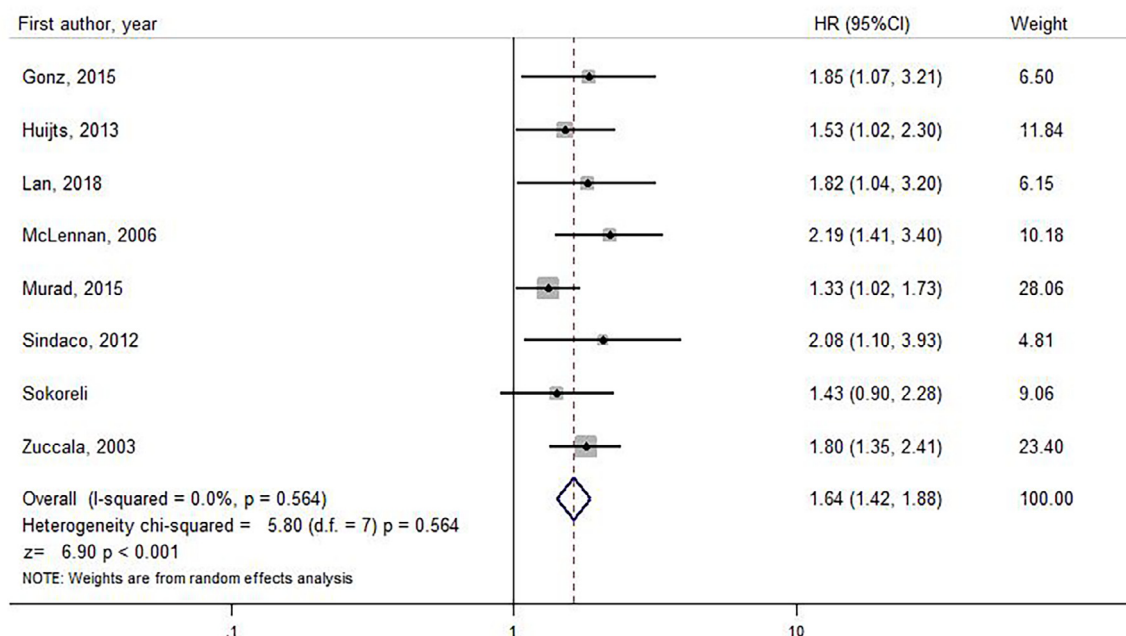


Figure 2. Forest plot of included studies assessing the association between cognitive impairment and mortality rate in patients with heart failure. CI = confidence interval; HR = hazard ratio.

initial reviewed, 198 studies were excluded as they were not conducted in HF patients with cognitive impairment, and 33 studies underwent full-article review. A further 25 studies were excluded as they did not have a control group and/or did not report all-cause mortality rate and/or did not have a clear definition of cognitive impairment. Therefore, eight eligible studies with a total of 3318 participants (951 participants had cognitive impairment) were included for meta-analysis. The PRISMA diagram flow is demonstrated in Fig. 1. Mortality rate was compared between HF patients with and without cognitive impairment. The prevalence of cognitive impairment ranged from 9.2% to 57.6% across the included studies. Characteristics of the included studies in the meta-analysis are summarized in Table 1.

3.2. Quality of eligible studies

The quality of the included cohort studies and randomized controlled trials were evaluated by the Newcastle–Ottawa Scale and the Cochrane Collaboration tool for assessing risk of bias, respectively (Supplementary file 2 and 3).

3.3. Quantitative analyses

In random-effect model, our analysis showed that the presence of cognitive impairment significantly increased the risk of mortality in HF patients with pooled HR of 1.64 (95% CIs: 1.42, 1.88, $I^2 = 0.0%$, $p < 0.001$; Fig. 2).

3.4. Sensitivity analysis

We assessed the stability of the meta-analysis results. We conducted a sensitivity analysis by excluding one study at a time. None of the results were significantly altered, as the results after removing one study at a time were consistent with the main meta-analysis. This indicated that our results were robust.

3.5. Publication bias

Funnel plot and Egger’s test were performed to confirm absent of publication bias. The funnel plot (Fig. 3) was symmetric indicating no publication

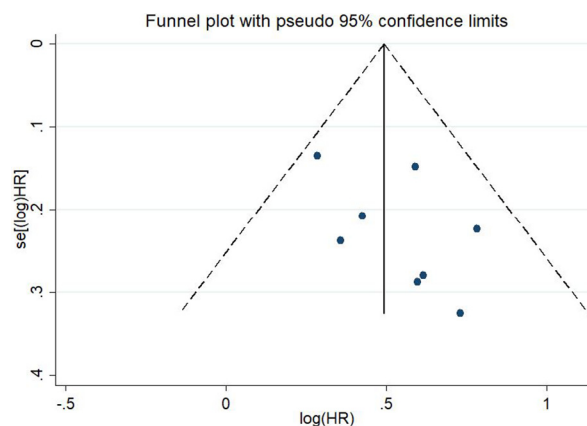


Figure 3. Funnel plot of cognitive impairment and mortality. Circles represent published studies. HR = hazard ratio.

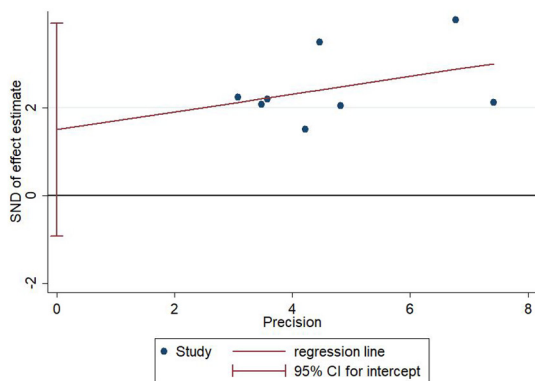


Figure 4. Egger's test. CI = confidence interval, SND = Standardized.

bias, and Egger's test reported no small studies effect (95% CI: $-0.91, 3.93$, $p = 0.179$; Fig. 4).

4. Discussion

To the best of our knowledge, this is the first meta-analysis examining the association between cognitive impairment and mortality in the HF population. Our meta-analysis showed a 1.64-fold increase in mortality rate among HF patients with cognitive impairment compared with that among those without cognitive impairment.

Huijts et al. [13] reported the lowest cognitive impairment prevalence at 9.2%, whereas the study by Lan et al. [14] showed the highest cognitive impairment prevalence at 57.6%. This major difference was likely due to a variation in participants' demographic and screening instruments. Every included study reported a significant association between the presence of cognitive impairment and an increased mortality rate in HF patients. Despite the highest reported cognitive impairment prevalence in the study by Lan et al. [14], the highest mortality rate was found in the study by McLennan et al. [15] (96.3%), which followed patients up to 60 months. The study by Murad et al. [17] had the longest follow-up duration (120 months) and reported the relatively high mortality rate of 83%. The study by Zuccala et al. [18], which had the highest number of participants ($n = 968$), reported the cognitive impairment prevalence and mortality rate at 24.6% and 16%, respectively.

Although the differences in study characteristics were obvious, the low level of heterogeneity among studies is particularly interesting suggesting that the effect of cognitive impairment on mortality is consistent despite the variation in demographics, screening tools, and follow-up duration. As there is still not enough evidence

regarding the most sensitive and specific method and the optimal timing for cognitive screening in HF population [23], this could imply that different instrument may be equally effective in screening for cognitive impairment, and the diverse cognitive impairment prevalence was mainly from the difference in participants' demographics. Moreover, the effect of cognitive impairment on mortality could be similar on both short- and long-term follow-up. Nevertheless, this further strengthens the result of our meta-analysis and confirms the existence of this relation.

Recent evidence from a systematic review and meta-analysis found a significant association between cognitive impairment and HF [6]. Several mechanisms have been suggested to explain this finding. One is the low systolic blood pressure found to be associated with the presence of cognitive impairment in the HF population [24]. In addition to cardiogenic emboli and other comorbidities, this leads to chronic poor cerebral perfusion and progressive degeneration of the brain [25]. Some factors, such as anemia, chronic kidney disease, older age, and lower left ventricular ejection fraction, were also found relating to the presence of cognitive impairment in HF patients [26–28]. Despite the recommendation to screen for cognitive impairment in HF patients, the dysfunction of cognition in the majority of HF patients was still undetected [29]. One study revealed that by the time of discharge, as little as 23% of HF patients with impaired cognition had it documented [30].

Management of cognitive impairment in HF is still in debate. Patients with cognitive impairment were found to have less effective self-care and medical non-compliance [31–33]. However, there is no data showing that improving HF knowledge or lifestyle could reduce cardiovascular outcome in the HF population with cognitive impairment. Currently, delaying the progression of cognitive impairment by targeting comorbidities, such as hypertension, atrial fibrillation and depression seem to be beneficial [34]. More research is needed to explore an effective intervention in reducing cardiovascular outcome in HF patients with cognitive impairment.

4.1. Strengths and limitations

The strength of this meta-analysis is that most studies were prospective studies. The result from our analysis showed heterogeneity of 0.0%, which demonstrated the consistency of the results among the included studies.

We also found limitations. First, the included studies did not report the type or classification of

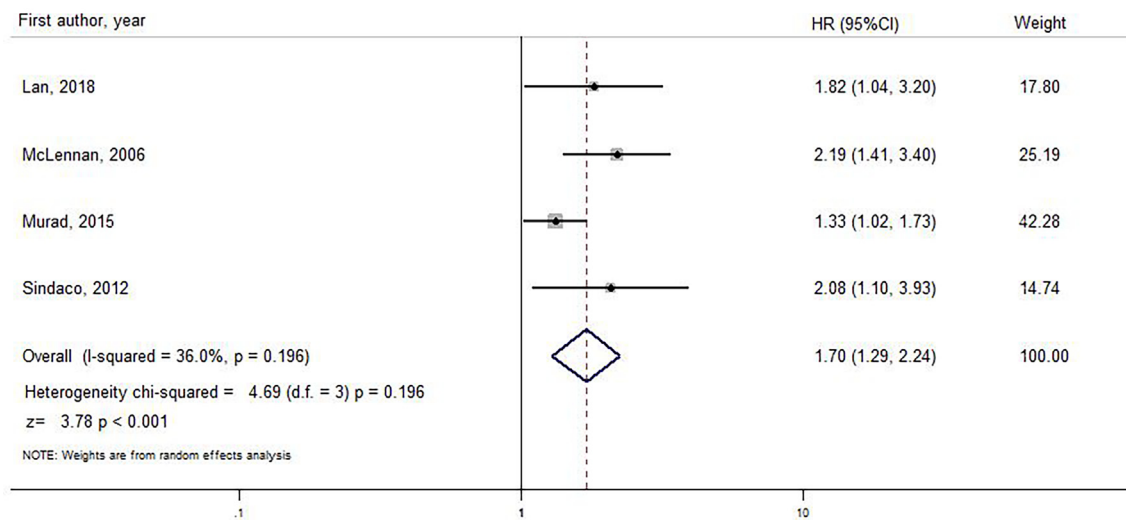


Figure 5. Subgroup analysis of studies with adjusted hazard ratio of cognitive impairment and mortality rate in patients with heart failure. CI = confidence interval.

the HF. Secondly, HRs from the study by Gonz et al. [35], Huijts et al. [13], and Zuccala et al. [18] were not adjusted for other variables, and outcome from the study by Sokoleri et al. [36] also included re-hospitalization rate. However, subgroup analysis without the four studies still showed a significant association between cognitive impairment and mortality in HF patients (Fig. 5). Lastly, each study used different cognitive screening tools and had various follow-up durations. Nevertheless, the absence of heterogeneity implied that each study reported comparable HR and could be combined for meta-analysis.

5. Conclusions

In conclusion, our systematic review and meta-analysis showed that the presence of cognitive impairment is strongly associated with an increased mortality rate among patients with HF. This emphasizes the necessity for cognitive assessment among HF population. Further research is needed to explore the pathophysiology and to appropriately manage the dysfunction of cognition in this population.

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Conflict of interest

The authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jsha.2019.06.001>.

References

- [1] van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail* 2016;18:242–52.
- [2] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics–2015 update: a report from the American Heart Association. *Circulation* 2015;131:e29–e322.
- [3] Merlo M, Pivetta A, Pinamonti B, Stolfo D, Zecchin M, Barbati G, et al. Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: changing mortality over the last 30 years. *Eur J Heart Fail* 2014;16:317–24.
- [4] Chang PP, Chambless LE, Shahar E, Bertoni AG, Russell SD, Ni H, et al. Incidence and survival of hospitalized acute decompensated heart failure in four US communities (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol* 2014;113:504–10.
- [5] Ford I, Robertson M, Komajda M, Böhm M, Borer JS, Tavazzi L, et al. Top ten risk factors for morbidity and mortality in patients with chronic systolic heart failure and elevated heart rate: the SHIFT Risk Model. *Int J Cardiol* 2015;184:163–9.
- [6] Cannon JA, Moffitt P, Perez-Moreno AC, Walters MR, Broomfield NM, McMurray JJ, et al. Cognitive impairment and heart failure: systematic review and meta-analysis. *J Card Fail* 2017;23:464–75.
- [7] Mixon AS, Myers AP, Leak CL, Jacobsen JM, Cawthon C, Goggins KM, et al. Characteristics associated with postdischarge medication errors. *Mayo Clin Proc* 2014;89:1042–51.
- [8] Harkness K, Heckman GA, Akhtar-Danesh N, Demers C, Gunn E, McKelvie RS. Cognitive function and self-care management in older patients with heart failure. *Eur J Cardiovasc Nurs* 2014;13:277–84.
- [9] Dennison CR, McEntee ML, Samuel L, Johnson BJ, Rotman S, Kielty A, et al. Adequate health literacy is

- associated with higher heart failure knowledge and self-care confidence in hospitalized patients. *J Cardiovasc Nurs* 2011;26:359-67.
- [10] Wu JR, Holmes GM, DeWalt DA, Macabasco-O'Connell A, Bibbins-Domingo K, Ruo B, et al. Low literacy is associated with increased risk of hospitalization and death among individuals with heart failure. *J Gen Intern Med* 2013;28:1174-80.
- [11] Gelow JM, Mudd JO, Chien CV, Lee CS. Usefulness of cognitive dysfunction in heart failure to predict cardiovascular risk at 180 days. *Am J Cardiol* 2015;115:778-82.
- [12] Del Sindaco D, Pulignano G, Di Lenarda A, Tarantini L, Cioffi G, Tolone S, et al. Role of a multidisciplinary program in improving outcomes in cognitively impaired heart failure older patients. *Monaldi Arch Chest Dis* 2012;78:20-8.
- [13] Huijts M, van Oostenbrugge RJ, Duits A, Burkard T, Muzzarelli S, Maeder MT, et al. Cognitive impairment in heart failure: results from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF) randomized trial. *Eur J Heart Fail* 2013;15:699-707.
- [14] Lan H, Hawkins LA, Kashner M, Perez E, Firek CJ, Silvet H. Cognitive impairment predicts mortality in outpatient veterans with heart failure. *Heart Lung* 2018;47:546-52.
- [15] McLennan SN, Pearson SA, Cameron J, Stewart S. Prognostic importance of cognitive impairment in chronic heart failure patients: does specialist management make a difference? *Eur J Heart Fail* 2006;8:494-501.
- [16] O'Donnell M, Teo K, Gao P, Anderson C, Sleight P, Dans A, et al. Cognitive impairment and risk of cardiovascular events and mortality. *Eur Heart J* 2012;33:1777-86.
- [17] Murad K, Goff Jr DC, Morgan TM, Burke GL, Bartz TM, Kizer JR, et al. Burden of Comorbidities and Functional and Cognitive Impairments in Elderly Patients at the Initial Diagnosis of Heart Failure and Their Impact on Total Mortality: The Cardiovascular Health Study. *JACC Heart Fail* 2015;3:542-50.
- [18] Zuccala G, Pedone C, Cesari M, Onder G, Pahor M, Marzetti E, et al. The effects of cognitive impairment on mortality among hospitalized patients with heart failure. *Am J Med* 2003;115:97-103.
- [19] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603-5.
- [20] Higgins JP, Altman DG, Gotzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- [21] Knopman DS, Petersen RC. Mild cognitive impairment and mild dementia: a clinical perspective. *Mayo Clin Proc* 2014;89:1452-9.
- [22] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
- [23] Cameron J, Gallagher R, Pressler SJ. Detecting and managing cognitive impairment to improve engagement in heart failure self-care. *Curr Heart Fail Rep* 2017;14:13-22.
- [24] Zuccala G, Onder G, Pedone C, Carosella L, Pahor M, Bernabei R, et al. Hypotension and cognitive impairment: Selective association in patients with heart failure. *Neurology* 2001;57:1986-92.
- [25] Georgiadis D, Sievert M, Cencetti S, Uhlmann F, Krivokuca M, Zierz S, et al. Cerebrovascular reactivity is impaired in patients with cardiac failure. *Eur Heart J* 2000;21:407-13.
- [26] Pulignano G, Del Sindaco D, Di Lenarda A, Tinti MD, Tarantini L, Cioffi G, et al. Chronic renal dysfunction and anaemia are associated with cognitive impairment in older patients with heart failure. *J Cardiovasc Med* 2014;15:481-90.
- [27] Jurgens CY, Faulkner KM, Lee CS. Phenotypic profiling of cognitive impairment risk among patients with heart failure: a literature review of the usefulness of cardiac-related variables. *Eur J Cardiovasc Nurs* 2013;12:109-31.
- [28] Dardiotis E, Giamouzis G, Mastrogiannis D, Vogiatzi C, Skoularigis J, Triposkiadis F, et al. Cognitive impairment in heart failure. *Cardiol Res Prac* 2012;2012 595821.
- [29] Moyer VA. Screening for cognitive impairment in older adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014;160:791-7.
- [30] Dodson JA, Truong TT, Towle VR, Kerins G, Chaudhry SI. Cognitive impairment in older adults with heart failure: prevalence, documentation, and impact on outcomes. *Am J Med* 2013;126:120-6.
- [31] Currie K, Rideout A, Lindsay G, Harkness K. The association between mild cognitive impairment and self-care in adults with chronic heart failure: a systematic review and narrative synthesis. *J Cardiovasc Nurs* 2015;30:382-93.
- [32] Hawkins LA, Kilian S, Firek A, Kashner TM, Firek CJ, Silvet H. Cognitive impairment and medication adherence in outpatients with heart failure. *J Crit Care* 2012;41:572-82.
- [33] Davis KK, Mintzer M, Dennison Himmelfarb CR, Hayat MJ, Rotman S, Allen J. Targeted intervention improves knowledge but not self-care or readmissions in heart failure patients with mild cognitive impairment. *Eur J Heart Fail* 2012;14:1041-9.
- [34] Yzeiraj E, Tam DM, Gorodeski EZ. Management of cognitive impairment in heart failure. *Cur Treat Options Cardiovasc Med* 2016;18:4.
- [35] Gonzalez-Guerrero JL, Alonso-Fernandez T, Garcia-Mayolin N, Gusi N, Ribera-Casado JM. Effect of A Follow-Up Program in Elderly Adults with Heart Failure with Cognitive Impairment After Hospital Discharge. *Journal of the American Geriatrics Society*. 2015;63 (9):1950-1.
- [36] Sokoreli I, Pauws SC, Steyerberg EW, de Vries GJ, Riistama JM, Tesanovic A, Kazmi S, Pellicori P, Cleland JG, Clark AL. Prognostic value of psychosocial factors for first and recurrent hospitalizations and mortality in heart failure patients: insights from the OPERA-HF study. *Eur J Heart Fail*. 2018;20(4):689-96.