Impact of health literacy in patients with cardiovascular diseases: A systematic review and meta-analysis

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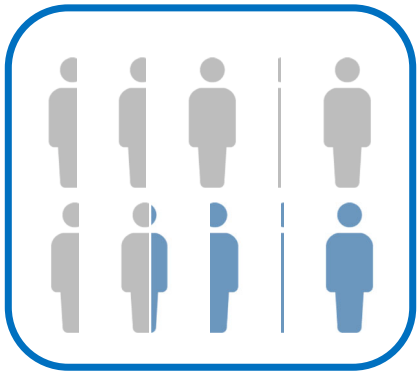
Highlight

- Low health literacy has risk ratio of 1.90 on mortality and 1.35 on readmission.
- All studies focusing on QOL showed significant effects of health literacy.
- The mean rate of low health literacy was 32.8%.
- Low health literacy was significantly related to education level, age, sex.
- S-TOFHLA was the most commonly health literacy assessment tool.



32.8% CVD patients

Low health literacy

Exacerbates prognosis and quality of life…

Relative Risk	
	Mortality: 1.621 (95%CI: 1.089-2.412)
	Readmission: 1.184 (95%CI: 1.035-1.355)

Impact of Health Literacy in Patients with Cardiovascular Diseases: A Systematic Review and Meta-analysis

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Abstract

Objective To clarify the impacts of health literacy on mortality, readmission, and QOL in the secondary or tertiary prevention of CVD through a meta-analysis.

Methods Six electronic database were searched on June 11, 2020. Observational studies involving patients with CVD, health literacy as an exposure factor and mortality, readmission, or QOL as outcomes were included in this study. Two researchers screened the retrieved articles and extracted data independently. The meta-analysis calculated the pooled relative risk of mortality and readmission. We also assessed the body of evidence based on Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Results Following screening of 1616 studies, 16 observational studies were included. The mean rate of low health literacy was 32.8%. All studies focusing on QOL showed significant impacts of health literacy. Pooled relative risk was 1.621 (95% confidence interval: 1.089–2.412) for mortality and 1.184 (95% confidence interval: 1.035–1.355) for readmission, indicating significant effects of health literacy. GRADE assessment showed “LOW” certainty for each outcome.

Conclusions Low health literacy was significantly associated with increased mortality and hospital readmission and decreased QOL in patients with CVD.

Practical value Considering low health literacy in clinical practice is very important to improve prognosis of CVD patients.

Keywords

Health literacy, Cardiovascular diseases, Cardiac rehabilitation, Meta-analysis

1. Introduction

Cardiovascular disease (CVD) was the leading cause of death worldwide in 2017 [1]. The risk of CVD is related to lifestyle risk factors (e.g., smoking, harmful alcohol use, salt intake, obesity, hypertension, elevated blood glucose and diabetes, and physical inactivity) [2]. In such a situation, the American Heart Association propounded “Life’s simple 7” to mitigate the seven major risk factors for CVD as primary prevention [3]. In addition, secondary and tertiary prevention of exacerbations of CVD are also important because CVD tends to cause heart failure with aging that is the final stage of heart disease [4]. Additionally, modification of the risk factors of CVD (lifestyle habits) can improve mortality, hospital readmission rate, and quality of life (QOL) [5–7].

Lifestyle risk factors are related to low health literacy [8], which is defined by Nutbeam as “the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand and use information in ways which promote and maintain health” [9]. Patients with low health literacy tend to have difficulties with complex health tasks and the ability to seek and understand health information, and have poorer uptake of preventive health care, which can perpetuate lifestyle risk factors [8,10]. Although health literacy is an objective concept, both subjective evaluations such as easy-to-use questionnaires and objective performance-based evaluations can be confusing in clinical practice [11].

In patients with CVD, low health literacy causes adverse outcomes, for example, by increasing mortality and hospital readmission and decreasing QOL [12,13]. Previous studies showed the rate of low health literacy to be 39.0% in patients with heart failure [13] and 30.5% in patients with coronary artery disease [12]. Taken together, improving the low level of health literacy in patients with CVD is important to improve adverse outcomes and mitigate the risks of CVD.

However, there is high heterogeneity among studies of health literacy in patients with CVD because target diseases, intervention methods, or follow-up periods vary [12]. For this reason, meta-analyses have been poorly documented, although several meta-analyses focusing on health literacy of patients with heart failure have been published relatively recently [14,15]. Meta-analysis targeting patients with CVD including heart failure is expected to show trends similar to those of these previous studies [14,15]. Low health literacy is hypothesized to associate with adverse events such as increases in mortality and hospital readmission or decreased QOL in patients with CVD as in the previous studies. Thus, the present study aimed to objectively clarify the impact of health literacy in patients with CVD on mortality, readmission, and QOL through a meta-analysis and increase the level of evidence for this topic.

2. Methods

2.1 Eligibility Criteria

The present systematic review and meta-analysis was conducted according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement [16]. This review included only observational studies examining the impacts of health literacy. Experimental studies were excluded because the high heterogeneity between each of these interventions made meta-analysis difficult. Inclusion criteria were defined as follows: 1) patients with low health literacy affected by CVD, 2) health literacy involved as a main topic in observational studies, and 3) mortality, readmission, or QOL as outcomes. We excluded studies not published in English, but we imposed no limitations on publication date and publication status.

We defined CVD to include coronary artery disease, rheumatic heart disease, cardiomyopathy, heart failure, among other heart diseases [17]. Cerebrovascular disease was excluded due to the existence of major differences in patient symptoms, such as those related to higher brain dysfunction [18]. We used the definition of health literacy as stated above by Nutbeam [9] and adopted the criteria used by each study to clarify how the patients were divided into low or high health literacy groups.

2.2 Search Strategy

Studies were identified by searching six electronic databases: PubMed of the U.S. National Library of Medicine, Scopus, Cochrane Controlled Register of Trials, Web of Science, PsycINFO, and the Cumulative Index to Nursing and Allied Health Literature. We formulated an advanced search strategy using search terms related to “CVD”, ”health literacy”, and ”study design” (Supplemental Figure 1). The final search was conducted on June 11, 2020, by one researcher (Y.K.). The references of the study by Cajita et al. [13] were manually searched, which led to six additional studies being included in the present study. Rayyan was used for literature management after searching [19].

2.3 Study Selection

Two researchers (Y.K. and T.S.) independently conducted screening of the studies in a standardized blinded manner. First, we screened by reading titles and abstracts of each study. After integrating each result from the first screening, the full text of the remaining studies was screened. Experimental studies were excluded in this phase because severe heterogeneity of study design made it unable to perform a meta-analysis. Cohen’s d was calculated as the index of inter-rater reliability in each screening phase. We adopted the criteria of Cohen’s d advocated by Landis and Koch [20]: “< 0 as indicating no agreement and 0–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1 as almost

perfect agreement". Conflicts regarding inclusion of studies were reconciled via consensus between the two researchers.

2.4 Data Extraction and Quality Assessment

We conducted data extraction of the included studies independently according to the Cochrane Consumers and Communication Review Group's data extraction template [21]. The score of health literacy was the value accepted in the univariate analysis, and the relationship between health literacy and confounders or comorbidities was focused on. Confounders consisted of age, sex, race, monthly income/economic situation, insurance type, education level, marriage status, employment status, New York Heart Association functional classification (NYHA), CVD knowledge, self-care, medical adherence, cognitive impairment, and depression. Comorbidities included hypertension, diabetes, chronic obstructive pulmonary disease (COPD), cerebrovascular diseases, renal diseases, and atrial fibrillation. We contacted two authors to get full-text, and four authors to get additional data for meta-analysis in the present study. However we could not get a reply from them.

Assessment of the risk of bias in each included study was conducted with the Risk of Bias Assessment tool for Non-randomized studies (RoBANS) [22]. RoBANS consists of 6 items that are evaluated by three grades: "low risk of bias", "high risk of bias " or "unclear". Further, assessment of the body of evidence was performed according to the Grading of

Recommendations Assessment, Development and Evaluation (GRADE) approach [23]. By referring to this guideline, the certainty of included studies was assessed and a table summarizing the findings was created (Table 1).

2.5 Statistical Analysis

Meta-analysis of a random effects model for pooled relative ratio of mortality and readmission was calculated by Open-meta [24]. Meta-analysis of QOL was not performed because there were major differences in the methods of QOL assessment in the included studies. Because specific findings on mortality and readmission were rare in the included studies, the odds ratio was approximated to the relative rate [25]. We assessed statistically significant differences with a 2-tailed test with $p < 0.05$. If an event did not occur, we performed zero correction in the meta-analysis [25]. Follow-up time of outcomes and differences in health literacy assessment tools used were not considered in this meta-analysis. The patients were divided according to health literacy into the low/inadequate group vs. the marginal + high/adequate group based on the definition in each included study [14,26]. We adopted the definition for low health literacy used in each study because a variety of health literacy assessment tools were used in the included studies. Heterogeneity assessment was also conducted by the I^2 test, in which heterogeneity was defined for each variability value as follows: “less than 30%: mild, 30 to 50%: moderate, and more than 50%: severe” [27].

Publication bias was assessed by Funnel plots and Begg's test [28]. Additionally, we performed a sensitivity analysis after removing the included studies with no events of death or readmission because these studies tended to have outliers in the meta-analysis that distorted the results.

3. Results

3.1 Overview of Included Studies

We identified 1616 studies through the electronic database search, and 132 studies remained after removing duplicates and screening the titles and abstracts. Of these remaining studies, 119 were available as full-text articles. After screening the full text of each article, 16 observational studies were included in the present study (Figure 1) [29–44]. We excluded six experimental studies and summarized them in Supplemental Table 1. Cohen's kappa was 0.41 in the first screening and 0.65 in the second screening.

Of the 16 included studies, 3 cross-sectional studies researched the effects on QOL [29–31], and 10 prospective [32–41] and 3 retrospective cohort studies [42–44] researched the impacts on mortality or readmission (Table 1). The oldest included study was published in 2011, and 11 of the studies were conducted in the USA. The included studies involved 95 to 7733 patients with CVD, and their mean age ranged from 59.2 to 85.6 years old. Heart failure was the most common disease in the included studies, but ischemic heart disease, acute

coronary syndrome, and acute myocardial infarction were also confirmed. The included studies tended to exclude patients with dementia and psychiatric disorders. The rate of low health literacy ranged from 9.9 to 68.6% (mean 32.8%). Eight health literacy assessment tools were used, with the Short Test of Functional Health Literacy in Adults (S-TOFHLA) as an objective assessment and the Brief Health Literacy Screening Scale (BHLS) as an subjective assessment often used. The rate of low health literacy was higher with the S-TOFHLA than that with the BHLS. The confirmed QOL assessments used in the studies were the 12-Item Short Form Health Survey, Minnesota Living with Heart Failure Questionnaire, and The Improving Chronic Illness Care Evaluation/Heart Failure Symptom Scale.

Three quarters of the studies showed that health literacy had significant impacts on mortality, readmission, or QOL. In addition, all studies focusing on QOL showed significant effects of health literacy although a meta-analysis could not be performed [29–31].

3.2 Relationship Between Health Literacy and Confounders

The included studies showed that low health literacy was significantly related to patient demographic factors such as education level, age, sex, and economic situation, and contents regarding CVD such as NYHA and CVD knowledge. Self-care was covered in five studies, but only two studies showed a significant relationship between health literacy and self-care

[32,33]. Four studies showed a relation between low health literacy and diabetes [33,38,42,43] or hypertension [33,42].

3.3 Trend of Included Studies Except for Heart Failure

Four studies targeted patients with CVD other than heart failure [30,35,39,43]. Three studies focusing on readmission rate [35,39,43] and one study focusing on QOL [30] showed significant effects of health literacy. The characteristics of the included studies are summarized for heart failure and other CVD as follows: for sample size, heart failure: 95–2647 vs. other CVD: 203−6620; for mean age, heart failure: 59.2−85.6 vs. other CVD: 60.0−72.0 years; for the ratio of males, heart failure: 0.38−0.77 vs. other CVD: 0.41−0.62; and for the rate of low health literacy, heart failure: 0.10−0.53 vs. other CVD: 0.14−0.37.

3.4 Assessment of Risk of Bias in Individual Studies and Assessment Across a Body of Evidence

Of the 16 included studies, nine had low risk of bias for all contents (Supplemental Figure 2) [29,30,33,34,37,39,41,42,44]. Selection of participants, blinding of outcome assessments, and selective outcomes reporting contributed to the low risk of bias in all included studies. Among the 16 included studies, three studies were assessed as having high risk of bias due to incomplete outcome data [35,40,43], and two other studies as having an unclear risk of bias [36,38]. Certainty of each outcome by GRADE assessment was LOW in all studies (Figure

2). We included cohort or cross-sectional studies, which have low certainty in the GRADE assessment. However, the included studies did not show serious problems in terms of risk of bias, inconsistency, indirectness and imprecision, so the certainty of each outcome by GRADE assessment did not further decrease and remained LOW in all studies (Figure 2).

3.5 Meta-analysis

A meta-analysis was performed on five studies for mortality [34,37,40,42,44] and eight studies for readmission [33–36,39,40,42,44] after removing the studies with data deficits. Low health literacy had significantly adverse impacts on both mortality and readmission (Figure 3). Pooled relative risk was calculated as 1.621 (95% confidence interval [CI]: 1.089–2.412) for mortality and 1.184 (95% CI: 1.035–1.355) for readmission. The I^2 test showed high heterogeneity for mortality (83.96%) and readmission (57.59%). After excluding one studies with no death and readmission events in the marginal + high health literacy group [40], sensitivity analysis of the remaining studies clarified the significant impact of health literacy only for readmission as indicated by the calculated pooled relative risk of 1.584 (95% CI: 1.058–2.370) for mortality and 1.167 (95% CI: 1.040–1.310) for readmission. (Figure 4) Although subjectively, the Funnel plot appeared to be asymmetric (Supplemental Figure 3), Begg's test clarified that no significant publication bias existed in regard to mortality (Kendall's tau=0.40, p=0.48) or readmission (Kendall's tau=0.14, p=0.72).

4. Discussion and Conclusion

4.1 Brief Summary

The present systematic review and meta-analysis showed that low health literacy has adverse impacts on mortality, hospital readmission, and QOL in patients with CVD, meeting the hypothesis. Remedying low health literacy may make it possible to improve clinical aspects of prognosis, such as mortality, and the psychological aspect of QOL in patients with CVD.

4.2 Comparison with Previous Studies

In the studies included in the meta-analysis, almost one-third of the CVD patients showed inadequate health literacy, and the relative risk for mortality was 1.62 and for readmission was 1.18. In previous meta-analyses targeting heart failure, the mean rate of patients with low health literacy was 39% [13], with relative risks for mortality of 1.67 and for readmission of 1.19 [14,15]. Some systematic reviews targeting patients with heart failure and coronary artery disease remarked that health literacy and QOL showed a positive correlation [12,13]. The results of the present meta-analysis are agreement with these previous meta-analyses in showing the adverse effects of low health literacy on mortality, readmission, and QOL.

Heart failure accounted for most of the CVD in the studies reviewed. However, low health literacy remained influential in affecting adverse outcomes even after excluding the

studies focusing on heart failure. Comparison of the heart failure studies with the other CVD studies showed that the patients with heart failure tended to have higher mean age and rate of low health literacy. Heart failure is more likely to occur with aging [4], leading to the above situation.

As mentioned above, we did not consider cerebrovascular disease in the present analysis because of major differences in patient symptoms [18]. Patients with cerebrovascular disease such as stroke and low health literacy may have less disease knowledge, and the contents of patient education may be difficult to acquire [45]. Therefore, including stroke studies in the present systematic review would likely have produced similar results. Collectively, low health literacy requires attention and must be considered during interventions or treatment of patients with CVD.

4.3 Practice Implications

Only 14% of CVD patients with low health literacy were reported to understand the context of patient education provided by the medical profession [46]. The present study showed that low health literacy was related with CVD knowledge [29,32,33,37]. In fact, the CVD patients with low health literacy could not reach a level of lifestyle modification after medical examination or patient education due to their low health literacy, which led to avoidance of their health problems. Thus, a patient's poor understanding of their disease state can lead to

progression of CVD and cause adverse events related to mortality and readmission. When educating patients, it is necessary to avoid medical terms, use illustrations to enhance their understanding, repeat and limit the essential information they need to remember, and use a "teach back" approach to confirm their understanding [46].

Inadequate health literacy was related to patient demographic factors of educational level, age, sex, and economic status, suggesting that understanding the patient's background is important when assessing health literacy. Among comorbidities, diabetes especially showed a better correlation with low health literacy than did other comorbidities. Diabetes patients with inadequate health literacy have poor disease knowledge, which leads to insufficient self-care [47]. The rate of low health literacy is 38% in patients with diabetes [47], similar to that of patients with CVD, and there may be some overlap between them. As diabetes is involved in the risk of CVD [2], patients with both CVD and diabetes need to receive priority intervention for inadequate health literacy.

Several of the analyzed studies excluded patients with cognitive impairment. A previous study showed that cognitive impairment is related with low health literacy [13], and the rate of cognitive impairment is about 30%, similar to that in patients with CVD [48]. Screening for intercurrent cognitive impairment is important in patients with CVD. Additionally, because ageing leads to a decline in cognitive function [49] and increased morbidity from heart failure [4], assessment of health literacy in older patients with CVD is essential.

Low health literacy was revealed to be a factor affecting the adverse prognosis of CVD patients in the present study. Medical professionals tend to overestimate the level of a patient's health literacy [46]. It is thus important for medical professionals to be aware of this fact and grasp the level of a patient's health literacy before interventions. Inadequate health literacy was related with aging and NYHA severity. In general, heart diseases gradually worsen with aging [4], and health literacy may worsen as well. As secondary prevention, assessment of health literacy may discover that it is low and thus allow earlier intervention. CVD commonly has a high recurrence rate, and accurate disease knowledge and self-care after discharge can help to prevent adverse events [50]. The present analysis showed that low health literacy is correlated with disease knowledge and self-care. Taken together, health literacy should be assessed during hospitalization, and patients found to have low health literacy should receive priority interventions to modify their risk of CVD as tertiary prevention. Specifically, it is necessary to convey the information in a way that allows patients to understand the importance of such self-care actions as limiting salt intake at meals, adhering to medications, performing regular physical activity, and monitoring weight and symptoms every day. Collectively, assessment of health literacy is important and helpful in the secondary and tertiary prevention of CVD [33].

4.4 Limitations

This study has several limitations. First, this study was meta-analysis of observational studies having unadjusted potential confounders. Therefore, the results of meta-analysis did not reflect the pure effects of health literacy on outcomes. Second, sensitivity analysis showed poor reliability in the results of the meta-analysis, especially for mortality, although the results require care when interpreting the impacts of health literacy. In addition, the analyzed studies only showed correlations between health literacy and outcomes, and thus, further interventional studies of patients with low health literacy are required. In agreement with previous reviews, there was heterogeneity between the included studies. Various health literacy assessment tools were used, and there were differences in age, sex, and diseases in the patients with CVD. We also have not considered the effects of the combination of CVD and comorbidities on health literacy. Finally, health literacy is greatly influenced by the environment, and many of the included studies were conducted in the USA. The results presented in these studies may involve regional bias, and attention must be paid when applying the findings to other regions.

4.5 Conclusion

In summary, the present systematic review and meta-analysis showed that low health literacy in patients with CVD correlated with increased mortality and hospital readmissions and decreased QOL. It is necessary to understand a patient's health literacy to grasp their risk of

CVD. Screening for health literacy would help to prioritize additional counselling or patient education. However, there remain unanswered questions concerning effective interventions for low health literacy. Further study will be required to examine effective interventions to improve health literacy and modify the prognosis of patients with CVD.

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Declaration of interest

The Authors declare that there is no conflict of interest.

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Figure Legends

Figure 1. Flow Diagram of Study Selection

Abbreviation: CVD; cardiovascular disease.

Figure 2. GRADE Assessment

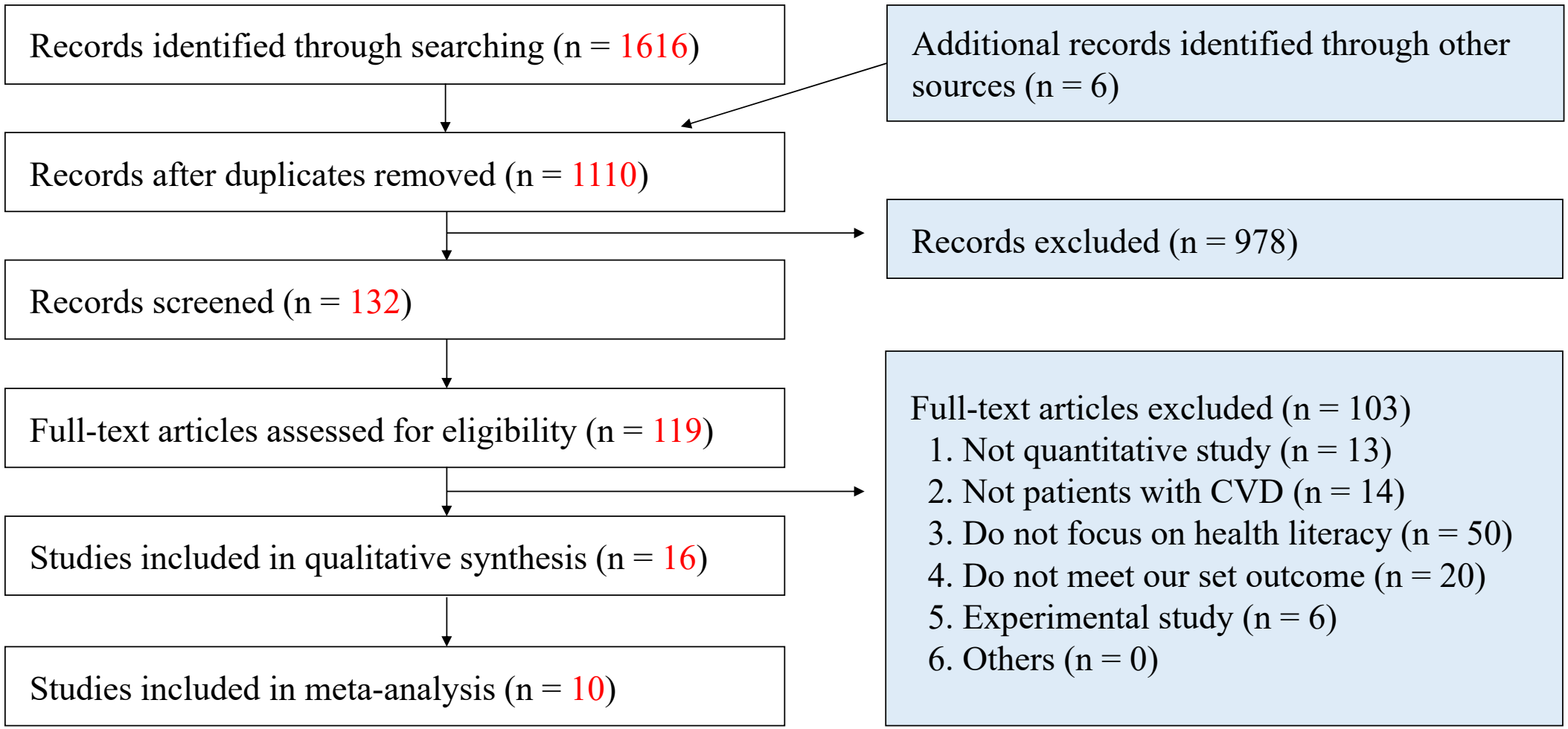
Abbreviations: CI, confidence interval; RR, relative risk.

Figure 3. Meta-analysis

Abbreviations: CI, confidence interval; HL, health literacy.

Figure 4. Sensitive Analysis

Abbreviations: CI, confidence interval; HL, health literacy.

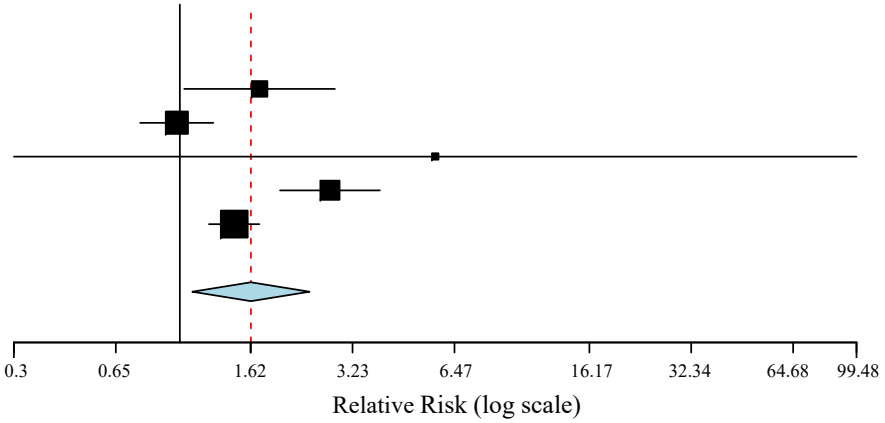


<outcome> mortality: n= 5, readmission: n=7 (duplicate: n=2)

Certainty assessment							No. of patients		Effect		Certainty
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low health literacy	High health literacy	Relative (95% CI)	Absolute (95% CI)	
Mortality (follow up: mean 14.6 months)											
5	Cohort studies	Not serious	Not serious	Not serious	Not serious	None	253/946 (26.7%)	485/3158 (15.4%)	RR 1.902 (1.097 to 3.299)	139 more per 1000 (15 to 353)	⨁⨁◯◯ LOW
Readmission (follow up: mean 7.4 months)											
7	Cohort studies	Not serious	Not serious	Not serious	Not serious	None	462/1320 (35.0%)	800/3437 (23.3%)	RR 1.354 (1.052 to 1.742)	82 more per 1000 (12 to 173)	⨁⨁◯◯ LOW
Quality of life											
3	Observational studies	Not serious	Not serious	Not serious	Not serious	None	All studies showed that low health literacy was significantly related to low quality of life, especially the physical component.				⨁⨁◯◯ LOW

<Mortality>

Studies	Estimate (95%CI)	Events/low HL	Events/high HL
Moser DK, 2015	1.718 (1.029, 2.869)	17/100	46/465
León-González R, 2018	0.979 (0.764, 1.255)	61/182	128/374
Oscalices MIL, 2019	5.672 (0.323, 99.479)	5/63	0/32
Peterson PN, 2011	2.773 (1.976, 3.893)	46/262	78/1232
McNaughton CD, 2015	1.447 (1.220, 1.717)	124/324	279/1055
Overall	**1.621 (1.089, 2.412)**	**253/931**	**531/3158**
(I^2=83.96%, p<0.001)			



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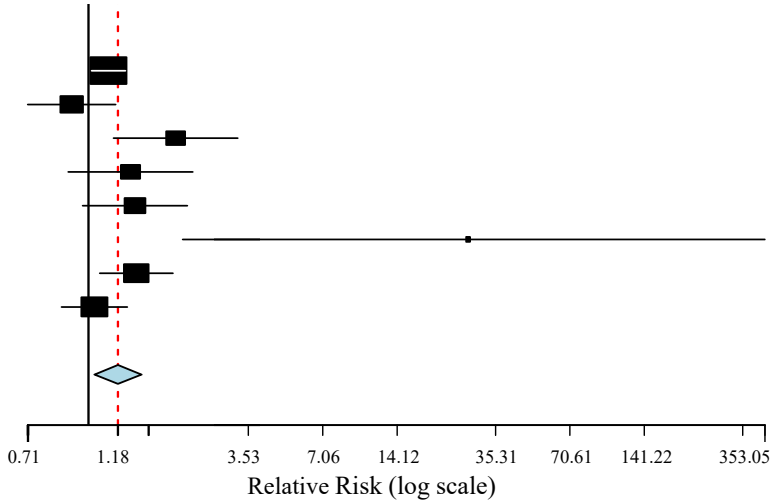
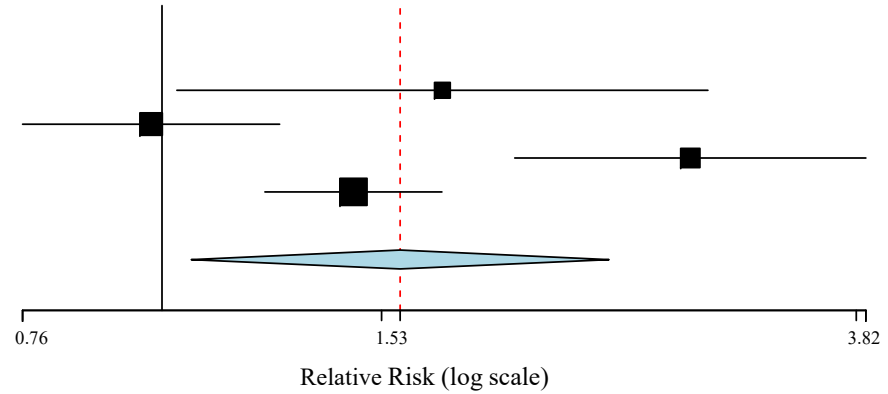
Studies	Estimate (95%CI)	Events/low HL	Events/high HL
Wu JR, 2013	1.121 (1.019, 1.234)	173/220	263/375
Moser DK, 2015	0.907 (0.706, 1.166)	44/110	205/465
McManus DD, 2016	1.648 (1.156, 2.350)	52/300	53/504
Cox SR, 2017	1.272 (0.891, 1.816)	33/89	51/175
Sterling MR, 2018	1.305 (0.968, 1.760)	38/127	160/698
Oscalices MIL, 2019	27.33 (1.72, 434.43)	26/63	0/32
Peterson PN, 2011	1.315 (1.067, 1.621)	80/262	286/1232
McNaughton CD, 2015	1.034 (0.857, 1.247)	100/324	315/1055
Overall	**1.184 (1.035, 1.355)**	**546/1495**	**1333/4536**
(I^2=57.59%, p=0.002)			



<Mortality>

Studies	Estimate (95%CI)	Events/low HL	Events/high HL
Moser DK, 2015	1.718 (1.029, 2.869)	17/100	46/465
León-González R, 2018	0.979 (0.764, 1.255)	61/182	128/374
Peterson PN, 2011	2.773 (1.976, 3.893)	46/262	78/1232
McNaughton CD, 2015	1.447 (1.220, 1.717)	124/324	279/1055
Overall	**1.584 (1.058, 2.370)**	**248/868**	**531/3126**
(I^2=87.54%, p<0.001)			



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Wu JR, 2013	1.121 (1.019, 1.234)	173/220	263/375
Moser DK, 2015	0.907 (0.706, 1.166)	44/110	205/465
McManus DD, 2016	1.648 (1.156, 2.350)	52/300	53/504
Cox SR, 2017	1.272 (0.891, 1.816)	33/89	51/175
Sterling MR, 2018	1.305 (0.968, 1.760)	38/127	160/698
Peterson PN, 2011	1.315 (1.067, 1.621)	80/262	286/1232
McNaughton CD, 2015	1.034 (0.857, 1.247)	100/324	315/1055
Overall	**1.167 (1.040, 1.310)**	**520/1432**	**1333/4504**
(I^2=47.59%, p=0.075)			

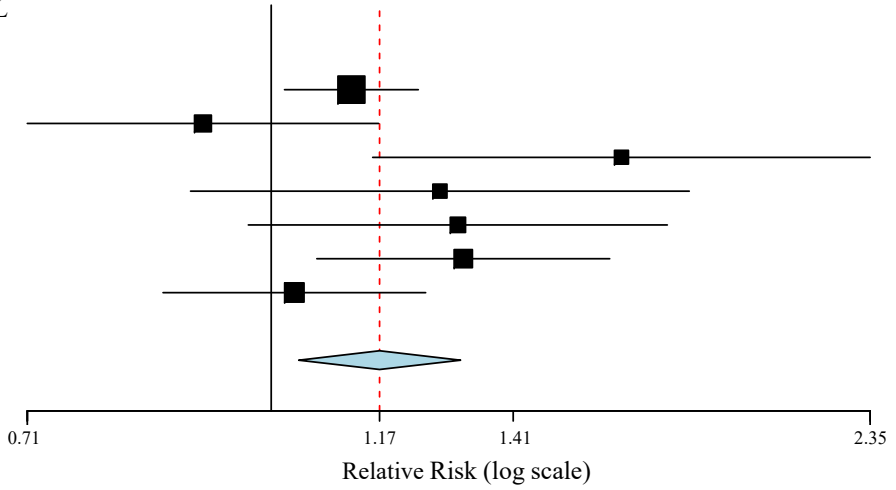

Table 1. Summary of Included Studies

Study	Design, country	Diagnosis, sample size	Mean age, Low HL rate (%)	Main results
Macabasco-O'Connell A, 2011	Cross-sectional study, USA	Heart failure, 605	60.7, 37.2	Low literacy was significantly associated with worse heart failure-related QOL even after adjusting for potential confounders.
González-Chica DA, 2016	Cross-sectional study, Australia	Ischemic heart disease, 574	72.0, 14.3	Inadequate health literacy had adverse effects on the physical component of health-related QOL in patients with ischemic heart diseases, especially in older age groups and those with disadvantaged socioeconomic position.
Zhang J, 2020	Cross-sectional study, China	Chronic heart failure, 299	61.9, 52.5	There was a significant relationship between health literacy and QOL in chronic heart failure patients without adjusting for covariates.

Dennison CR, 2011	Prospective cohort study, USA	Heart failure, 95	59.2, 42.1	Participants with marginal health literacy had the highest 30-day readmission rate, although this trend was not statistically significant (p=.116).
Wu J-R, 2013	Prospective cohort study, USA	Heart failure, 595	60.6, 37.0	Low literacy was associated with higher risk of all-cause hospitalizations or death (RR=1.39, 95% CI: 0.99–1.94), HF-related hospitalization (RR=1.36, 95% CI: 1.11–1.66) for patients with HF.
Moser DK, 2015	Prospective cohort study, USA	Heart failure, 575	65.9, 19.1	Inadequate or marginal health literacy was associated with higher risk of earlier heart failure hospitalization (HR=1.94, 95% CI: 1.43–2.63) or all-cause death (HR=1.91, 95% CI :1.36–2.67) among rural patients with heart failure.
McManus DD, 2016	Prospective cohort study, USA	Acute coronary syndrome, 804	73.0, 37.3	Low health literacy during the index hospitalization was associated with early readmission. (OR=1.83, 95% CI: 1.21–2.75).

Cox SR, 2017	Prospective cohort study, USA	Heart failure, 264	66.6, 33.7	More patients with low health literacy were readmitted (OR=1.80, 95% CI: 1.04–3.11). The regression identified low health literacy that significantly increase the risk of 30-day readmission or ED visit (p=0.035).
León-González R, 2018	Prospective cohort study, Spain	Heart failure, 556	85.6, 32.7	Among very old patients, no association was found between health literacy and 12-month mortality. (HR=1.00, 95% CI: 0.66–1.51).
Fabbri M, 2018	Prospective cohort study, USA	Heart failure, 2647	69.0, 9.9	After adjusting for covariates, low health literacy was associated with increased mortality (HR=1.91, 95% CI: 1.38–2.65) and hospitalizations (HR=1.30, 95% CI: 1.02–1.66).
Sterling MR, 2018	Prospective cohort study, USA	ACS or ADHF, 825	60.0, 24.6	Although low health literacy was associated with 30-day readmission in unadjusted models (p=0.04), there was no association in adjusted models (RR=0.95, 95% CI: 0.80–1.13).

Oscalices MIL, 2019	Prospective cohort study, Brazil	Decompensated heart failure, 100	63.3, 68.0	Those with inadequate health literacy had a higher numbers of readmissions ($p<0.01$) and death ($p<0.01$) during the 3-month follow-up after hospital discharge.
Son Y, 2020	Prospective cohort study, South Korea	Heart failure, 286	75.4, 61.5	Limited health literacy increased the risk of 1-year hospital readmission in both men (OR=5.27, 95% CI: 2.04–13.6) and women (OR=10.17, 95% CI: 2.19–47.2) even after controlling for other factors.
Peterson PN, 2011	Retrospective cohort study, USA	Heart failure, 1494	75.0, 17.5	Low health literacy is associated with higher mortality (HR=1.61, 95% CI: 1.06–2.43), even among those with health insurance and access to health information.
Bailey SC, 2015	Retrospective cohort study, USA	AMI, 7733	-, 14.4	Patients with above basic literacy according to derived health literacy estimates had an 18% lower risk of a 30-day readmission (RR=0.82, 95% CI; 0.73–0.92).

McNaughton CD, 2015	Retrospective cohort study, USA	Acute heart failure, 1379	63.1, 23.5	Patients with a lower level of health literacy had an increased risk of all-cause death (HR=1.32, 95% CI: 1.05–1.66), and this risk rose with decreasing health literacy.

Abbreviations: HL, health literacy; ACS, acute coronary syndrome; ADHF, acute decompensated heart failure; S-TOFHLA, Short Test of Functional Health Literacy in Adults; BHLS, Three-item Brief Health Literacy Scale; NVS, newest vital sign; REALM, Rapid Estimate of Adult Literacy in Medicine; QOL, quality of life; RR, relative risk; OR, odds ratio; HR, hazard risk; CI, confidence interval; ED, emergency department.

#1	[Health Literacy]:MeSH
#2	(health literac*):ti,ab,kw
#3	(functional literacy):ti,ab,kw
#4	(communicative literacy):ti,ab,kw
#5	(critical literacy):ti,ab,kw
#6	("health information" NEAR/4 need*):ti,ab,kw
#7	("health information" NEAR/4 seek*):ti,ab,kw
#8	("health information" NEAR/4 util*):ti,ab,kw
#9	("health information" NEAR/4 literac*):ti,ab,kw
#10	("health information" skill*):ti,ab,kw
#11	("health information" access):ti,ab,kw
#12	("health information" dissemination):ti,ab,kw
#13	("health information" storage):ti,ab,kw
#14	("health information" retrieval):ti,ab,kw
#15	("health information" service):ti,ab,kw
#16	#1 - #15
#17	[Cardiovascular Diseases]:MeSH
#18	("heart disease*"):ti,ab,kw
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#20	("coronary artery disease*"):ti,ab,kw
#21	("heart failure"):ti,ab,kw
#22	("ischemic heart failure"):ti,ab,kw
#23	#17 - #22
#24	("randomized controlled trial"):pt
#25	("controlled clinical trial"):pt
#26	[Randomized Controlled Trial]:MeSH
#27	[Random Allocation]:MeSH
#28	[Double-Blind Method]:MeSH
#29	[Single-Blind Method]:MeSH
#30	("clinical trial"):pt
#31	(Clin* NEAR/25 Trial*):ti,ab,kw
#32	[Cohort Studies]:MeSH
#33	[Comparative Study]:MeSH
#34	[Cross-Sectional Studies]:MeSH
#35	#24 - #34
#36	#16 AND #23 AND #35


Selection of participants
Confounding variables
Measurement of exposure
Blinding of outcome assessments
Incomplete outcome data
Selective outcome reporting
Macabasco-O'Connell A, 2011
González-Chica DA, 2016
Zhang J, 2020
Dennison CR, 2011
Wu J-R, 2013
Moser DK, 2015
McManus DD, 2016
Cox SR, 2017
León-González R, 2018
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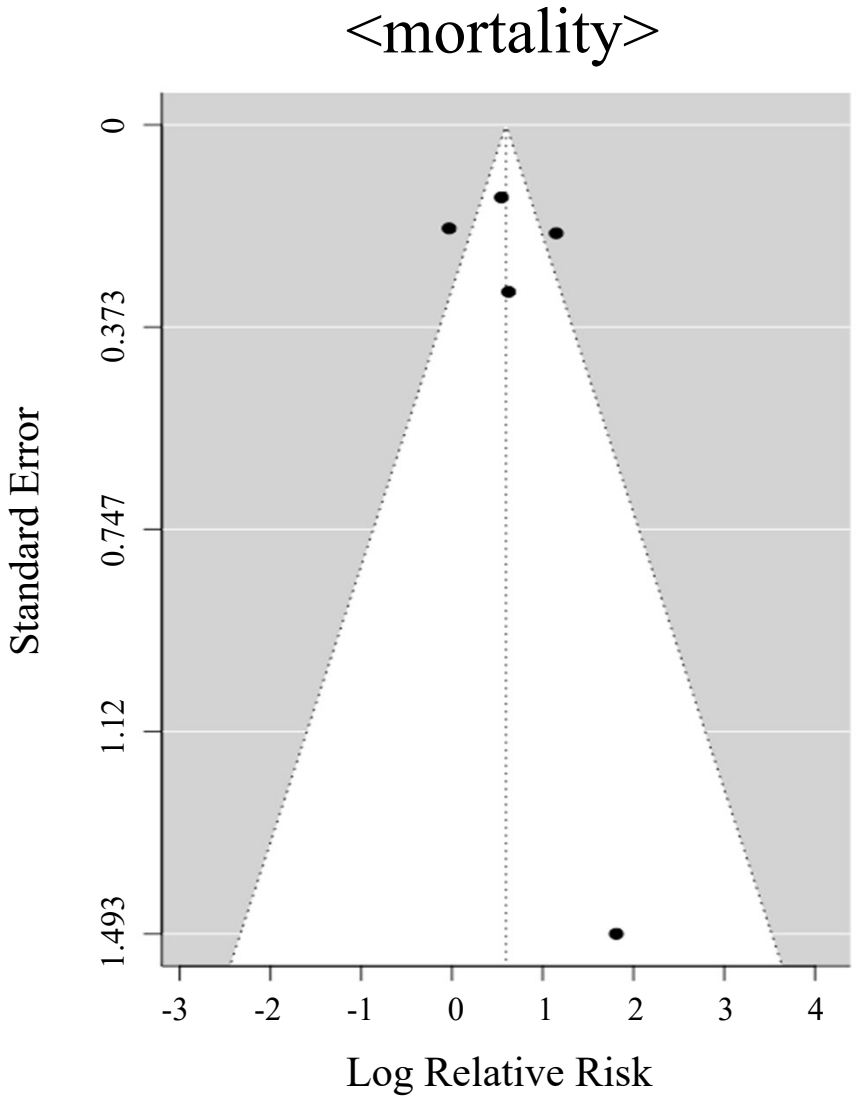
Sterling MR, 2018
Oscalices MIL, 2019
Son Y, 2020
Peterson PN, 2011
Bailey SC, 2015
McNaughton CD, 2015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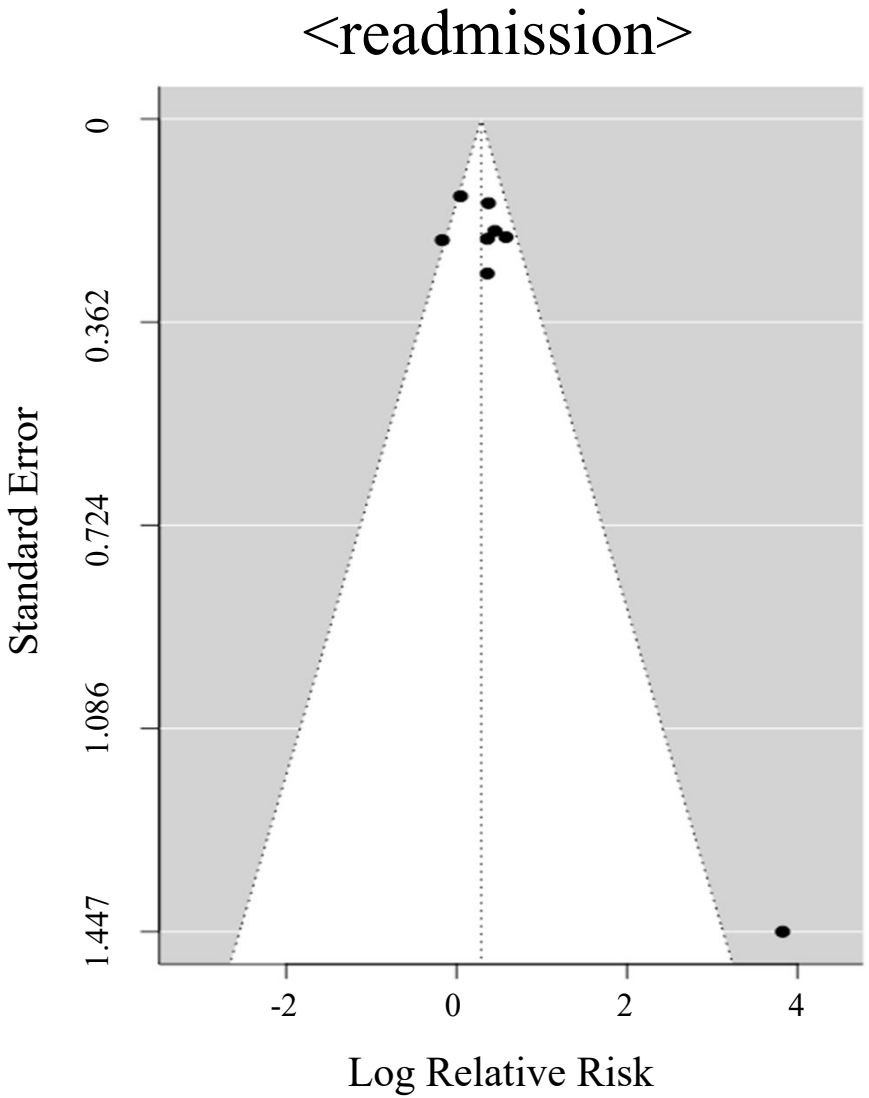
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2
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Log Relative Risk

Supplemental Table 1. Summary of Excluded Studies

Study	Design	Number	Diagnosis	Intervention	Results
DeWalt DA et al. (2006)	RCT	121	Heart failure	1) One-hour educational session 2) Management plan in the patient's notebook to help the patient better manage weight fluctuations and self-adjust the diuretic dose based on weight	Self-management program designed for patients with low literacy did not significantly reduce the rate of the combined endpoint of hospitalization or death (IRR=0.69, 95% CI: 0.40-1.19) and increased quality of life (3.5 points, p=0.36).
Baker DW et al. (2011)	RCT	605	Heart failure	1) Single in-person education session 2) Series of follow-up education phone calls, including teaching adjusted-dose diuretics to maintain a target weight	The TTG program resulted in slightly greater knowledge (p=0.008), substantially better achievement of self-care goals (p<0.001), higher self-efficacy (p=0.006), and greater improvement in heart failure-related quality of life (p<0.001)
DeWalt DA et al. (2012)	RCT	605	Heart failure	1) More intensive education 2) Self-care training intervention 3) More specific instruction using daily weights to guide diuretic self-adjustment 4) Follow-up phone calls	A more intensive multisession intervention did not decrease the incidence of hospitalizations compared with a single session only (IRR=1.01, 95% CI: 0.83–1.22); however, effect modification by literacy suggests that more intensive interventions may hold benefit for specific subgroups.
Dracup K et al. (2014)	RCT	602	Heart failure	1) Daily weight and heart failure symptom diaries to be completed and weight scales. 2) An educational session lasting 50 minutes 3) 2 phone calls at 2-week intervals to reinforce the information in the educational session.	Intervention program did not significantly decrease the cardiac death or re-hospitalization for heart failure (p=0.058), although self-care behaviors increased and cardiac mortality was significantly decreased (p=0.003).

Bell SP et al. (2016)	RCT	851	Acute coronary syndrome or acute decompensated heart failure	1) Reconciled preadmission medications and discharge medications with the patient 2) Tailored counseling about medication 3) Inquired about general health, symptoms, and any medication-related problems after discharge	This intervention resulted in no significant difference in time to first hospital readmission or emergency room visit (HR=1.04, 95% CI: 0.78-1.39). However, it was effective in reducing unplanned health care utilization among individuals with inadequate health literacy, primarily through an effect on emergency room visits.
Palo KED et al. (2017)	Non-RCT	94	Acute myocardial infarction or heart failure	1) Intake assessment 2) Patients education 3) Medication counseling 4) Guideline-directed Medical Therapy recommendations	The diligent effort to identify hospitalized heart failure patients led to interventions that ultimately reduced the readmission rate, but not significantly (p=0.15). Designated interventions of a nurse and clinical pharmacist allowed for effective delivery and a patient-centered approach.
Abbreviations: CI; confidence interval, HR; hazard ratio, IRR; incident rate ratio, RCT; randomized controlled trial.					