Effect of Palliative Care for Patients with Heart Failure
A Systematic Review and Meta-Analysis
Zhili Xu, MD, Linglong Chen, MD, Shuang Jin, MD, Baohua Yang, MD, Xinguo Chen, MD and Zhang Wu, MD

Summary
Palliative care might be beneficial to heart failure. However, the results remain controversial. We conducted a systematic review and meta-analysis to explore the effect of palliative care on heart failure.

PubMed, Embase, Web of Science, EBSCO, and Cochrane library databases were systematically searched. Randomized controlled trials (RCTs) assessing the effect of palliative care versus usual care on heart failure were included. Two investigators independently searched articles, extracted data, and assessed the quality of included studies. The primary outcome was readmission. Meta-analysis was performed using random-effect model.

Five RCTs involving 545 patients were included in the meta-analysis. Overall, compared with control intervention, palliative care intervention was found to significantly reduce the readmission (Std. mean difference = 0.79; 95% confidence intervals (CI) = 0.23 to 1.35; \( P = 0.006 \)), Edmonton Symptom Assessment Scale (ESAS) (Std. mean difference = -2.5; 95% CI = -4.39 to -0.62; \( P = 0.009 \)), and PHQ-9 (Std. mean difference = -1.16; 95% CI = -1.73 to -0.58; \( P < 0.005 \)), as well as improve heart failure questionnaire (Std. mean difference = 4.46; 95% CI = 3.44 to 5.47; \( P < 0.005 \)), but had no influence on mortality (RR = 1.54; 95% CI = 0.80 to 2.96; \( P = 0.19 \)) and quality of life questionnaire (Std. mean difference = 1.81; 95% CI = -0.14 to 3.77; \( P = 0.07 \)).

Compared with control intervention, palliative care intervention was found to significantly reduce readmission, ESAS, PHQ-9, and improve heart failure questionnaire, but showed no influence on mortality and quality of life questionnaire in patients with heart failure.

Key words: Readmission, ESAS, PHQ-9, Mortality, Randomized controlled trials

Heart failure is a worldwide health disease and could result in high mortality rates of 40% within the first 3 years and 75% at 5 years. Patients with advanced heart failure experience marked reductions in health-related quality of life with common fatigue, dyspnea, and swelling of arms and legs. In addition, these patients feel uncertain, feared, isolated, and lonely. They regarded themselves as a burden to their carers because of assistance requirement in daily living.

Patients with heart failure suffer from complicated issues in refractory symptoms, psychological distress, and difficult decision-making involving families. Palliative care would benefit these patients and could be initiated when end-stage heart failure is diagnosed. The ratio of palliative care to life-prolonging care was gradually increased when patients were refractory to treatment. Previous studies reported that palliative care program led to significant reductions in emergency room visits, hospital admissions, hospital days, and costs and enhanced symptom management in patients with cancer, chronic obstructive pulmonary disease, and chronic heart failure. Palliative care was reported to significantly reduce readmission, Edmonton Symptom Assessment Scale (ESAS), and patient health questionnaire-9 (PHQ-9), as well as improve quality of life and heart failure in patients with heart failure.

In contrast to this promising finding, however, some relevant RCTs showed that palliative care had no influence on quality of life and mortality for heart failure. Considering these inconsistent effects, we therefore conducted a systematic review and meta-analysis of RCTs to evaluate the effectiveness of palliative care in patients undergoing heart failure.

Methods
This systematic review and meta-analysis were conducted according to the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-analysis state-
ment and the Cochrane Handbook for Systematic Reviews of Interventions. All analyses were based on previously published studies; thus no ethical approval and patient consent were required.

**Literature search and selection criteria:** PubMed, Embase, Web of Science, EBSCO, and the Cochrane Library were systematically searched from inception to May 2017, with the following keywords: palliative care and heart failure. No limitation was enhanced. To include additional eligible studies, the reference lists of retrieved studies and relevant reviews were also hand-searched and the process above was performed repeatedly until no further article was identified. Conference abstracts meeting the inclusion criteria were also included.

The inclusion criteria were as follows: 1) patients diagnosed with heart failure; 2) intervention treatment was palliative care versus usual care; 3) and the study design was RCT. The exclusion criteria included: 1) diagnosed with severe psychiatric disorders; 2) cognitive impairment; 3) diagnosed with a life-limiting non-heart failure illness.

**Data extraction and outcome measures:** The following information was extracted for the included RCTs: first author, publication year, sample size, baseline characteristics of patients, palliative care control, study design, readmission, mortality, ESAS, PHQ-9, quality of life questionnaire, and heart failure questionnaire. The author would be contacted to acquire the data when necessary.

The primary outcome was readmission. Secondary outcomes included mortality, ESAS, PHQ-9, quality of life questionnaire, and heart failure questionnaire. ESAS included eight symptoms: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, sense of well-being, and dyspnea using a 0-100 mm visual analog scale with established validity and Cronbach’s α reliability of 0.8. PHQ-9 was a validated tool that measured depression severity and higher scores denoted higher levels of depression severity.

**Quality assessment in individual studies:** The Jadad Scale was used to evaluate the methodological quality of each RCT included in this meta-analysis. This scale consisted of three evaluation elements: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). One point would be allocated to each element if they have been mentioned in article, and another one point would be given if the methods of randomization and/or blinding had been detailedly and appropriately described. If methods of randomization and/or blinding were inappropriate, or dropouts and withdrawals had not been recorded, then one point was deducted. The score of Jadad Scale varied from 0 to 5 points. An article with Jadad score ≤ 2 was considered to be of low quality. If the Jadad score was ≥ 3, the study was thought to be of high quality.

**Statistical analysis:** Standard Mean differences (Std. MDs) with 95% confidence intervals (CIs) for continuous outcomes (ESAS, PHQ-9, quality of life questionnaire, and heart failure questionnaire), and risk ratios (RRs) with 95% CIs for dichotomous outcomes (readmission and mortality) were used to estimate the pooled effects. All meta-analyses were performed using random-effects models with DerSimonian and Laird weights. Heterogeneity was tested using the Cochran Q statistic (P < 0.1) and quantified with the I² statistic, which described the variation of effect size that was attributable to heterogeneity across studies. An I² value greater than 50% indicated significant heterogeneity. Sensitivity analysis was performed to detect the influence of a single study on the overall estimate via omitting one study in turn when necessary. Owing to the limited number (< 10) of included studies, publication bias was not assessed. P < 0.05 in two-tailed tests was considered statistically significant. All statistical analyses were performed with Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK) or Stata 12.0 software (StataCorp, College Station, TX, USA).

**Results**

**Literature search, study characteristics, and quality assessment:** The flow chart for the selection process and detailed identification is presented in Figure 1. In total, 781 publications were identified through the initial search of databases. Ultimately, five RCTs were included in the meta-analysis.

The baseline characteristics of the five eligible RCTs in the meta-analysis were summarized in Table. The five studies were published between 2012 and 2016, and sample sizes ranged from 72 to 232 with a total of 545. There was no significant difference of age, the number of married patients and employed patients between palliative care group and control group at baseline. Two included RCTs involved chronic heart failure, one RCT for acute exacerbation of chronic heart failure, one RCT for acute heart failure and another RCT for symptomatic heart failure.

Among the five RCTs, two studies reported the readmission, two studies reported the mortality, three studies reported the ESAS, two studies reported the PHQ-9, three studies reported the quality of life questionnaire, and two studies reported the heart failure questionnaire.

**Primary outcome--readmission:** This outcome data was
Table. Characteristics of included studies

<table>
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<th>NO.</th>
<th>Author, Year</th>
<th>Palliative care group</th>
<th>NYHA functional class, I/II (n)</th>
<th>Age (years)</th>
<th>Sex (Male/Female)</th>
<th>Type of heart failure</th>
<th>NYHA functional class, I/II (n)</th>
<th>Age (years)</th>
<th>Sex (Male/Female)</th>
<th>Type of heart failure</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>Wong, 2016</td>
<td>Control group</td>
<td>78/3±16.8 18 27</td>
<td>41</td>
<td>66</td>
<td>Chronic heart failure</td>
<td>78/4±100 25 28</td>
<td>1</td>
<td>78/4±100 25 28</td>
<td>Chronic heart failure</td>
</tr>
<tr>
<td>2</td>
<td>Hopp, 2016</td>
<td>Control group</td>
<td>67/0±110 136 26</td>
<td>42</td>
<td>680±113.0 18</td>
<td>Acute heart failure</td>
<td>70/9±13.6 67 22</td>
<td>4</td>
<td>70/9±13.6 67</td>
<td>Acute heart failure</td>
</tr>
<tr>
<td>3</td>
<td>Slabbenstrom, 2015</td>
<td>Control group</td>
<td>76/0±119 55 26</td>
<td>116</td>
<td>76/6±102 25</td>
<td>Acute exacerbation of chronic heart failure</td>
<td>76/6±102 25</td>
<td>22</td>
<td>Acute exacerbation of chronic heart failure</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Brannstrom, 2014</td>
<td>Control group</td>
<td>81.9±8.9 26</td>
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<td>Symptomatic heart failure</td>
<td>53±9.8</td>
<td>12</td>
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</tbody>
</table>

Discussion

Previous studies reported that palliative care could result in higher satisfaction, fewer hospitalization, and better quality of life than usual care for heart failure and chronic obstructive pulmonary disease. Palliative home-based support enabled patients to reduce hospital use and stay well in the community after an episode of hospitalization, and thus was cost-effective among general medical patients. Patients with heart failure could obtain symptom control and psychosocial support through palliative care. Our meta-analysis suggests that compared with control intervention, palliative care intervention substantially reduced readmission, ESAS, PHQ-9, and improved heart failure questionnaire but had no influence on mortality and quality of life questionnaire for heart failure. When analyzing the quality of life, two included RCTs showed the benefit of palliative care to patients, but one included RCT demonstrated no increase in the quality of life after the intervention of palliative care. The pooled results concluded a contradictory result in the context of no benefits of palliative care on quality of life, which was mainly caused by significant heterogeneity because of different types of heart failure and cardiac function. But the proportion of using palliative care for heart failure was low, with 10%-12% for heart failure and 5% for non-cancer disease. The reasons for low use of palliative care among patients with heart failure were multifactorial, disease-related, person-related, and system-related. Accurate prognostication was difficult because of the unpredictable disease trajectories in heart failure. Care providers (e.g., cardiologists and primary care physicians) lacked appreciation of the palliative concept and analyzed with a random-effects model; the pooled estimate of the two included RCTs suggested that compared with control group, palliative care intervention was associated with a significantly decreased readmission (Std. mean difference = -0.79; 95% CI = 0.23 to 1.35; P = 0.006), with no heterogeneity among the studies (I² = 0%, heterogeneity P = 0.463, Figure 2). However, palliative care was not associated with decreased mortality (RR = 1.54; 95% CI = 0.80 to 2.96; P = 0.19) compared with control group, with no heterogeneity among the studies (I² = 0%, heterogeneity P = 0.57, Figure 3).

Sensitivity analysis: No heterogeneity was observed among the included studies for the readmission and mortality. Thus, we did not perform sensitivity analysis by omitting one study in each turn or perform subgroup analysis to detect the source of heterogeneity.

Secondary outcomes: Compared with control intervention, palliative care intervention showed significantly reduced ESAS (Std. mean difference = -9.39 to -0.62; P = 0.009; Figure 4) and PHQ-9 (Std. mean difference = -1.16; 95% CI = -1.73 to -0.58; P < 0.005; Figure 5) but had no influence on quality of life questionnaire (Std. mean difference = 1.81; 95% CI = -0.14 to 3.77; P = 0.07; Figure 6). In addition, palliative care could substantially improve heart failure questionnaire (Std. mean difference = 4.46; 95% CI = 3.44 to 5.47; P < 0.005; Figure 7).
failed to recognize specialist palliative care as a tangible service. Patients were often unaware of the treatment important of palliative care. Clearer guidelines of how and when specialist palliative care should be integrated into advanced heart failure management and benefit to the good collaboration of both palliative care and medical specialists.

Palliative care not only played a role in alleviating specific symptoms but also helped patients and their caregivers make complex medical decision. Advance care planning could serve as one tool to help patients in this process for heart failure. Completion of the advance care planning process focused on enabling proxies to be able to make decisions in alignment with patient preferences and was also associated with increased hospice use at the end of life.

Several limitations should be taken into account. Firstly, our analysis was based on five RCTs but four of them have a relatively small sample size (n < 100). Over-estimation of the treatment effect was more likely in smaller trials compared with larger samples. More clinical trials with large sample were needed to explore this issue. The types of heart failure and cardiac function in included RCTs were different, and it probably affected the pooling results. During search terms for palliative care, a variety of interventions should have been included in the palliative care group due to the lack of standardized method. Next, the palliative care team in included RCTs did not have all of the designated team members recommended by the Joint Commission. Finally, some unpublished and missing data might lead bias to the pooled effect.

**Conclusion**

Palliative care showed an important ability to reduce readmission, ESAS, PHQ-9, and improve heart failure questionnaire. Palliative care was recommended to be administered for heart failure, but more studies should confirm its efficacy.
Figure 4. Forest plot for the meta-analysis of ESAS.

Figure 5. Forest plot for the meta-analysis of PHQ-9.
Figure 6. Forest plot for the meta-analysis of quality of life questionnaire.

Figure 7. Forest plot for the meta-analysis of heart failure questionnaire.

Disclosures

Conflicts of interest: The authors declare no conflict of interest.

Research involving human participants and/or animals: Not applicable.

References


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