Heart failure (HF) affects more than 26 million people worldwide, with survival estimates of around 10% after 10 years of the disease. Indeed, being a chronic illness with increasing survival rates, HF is responsible for a significant disease burden, with a QOL as poor as in patients with cancer and has a significant economic impact.\textsuperscript{2,3,5–7} Therefore, interventions directed to the improvement of physical or psychological QOL and disease acceptance might be of interest. It has been shown that the extent of the patient’s coping strategies and acceptance of the diagnosis correlates with more positive outcomes, such as hospitalization rates and disease burden.\textsuperscript{4,5,6} Moreover, it is relevant to have in mind that QOL is considered equally or even more important than longevity by patients. Approximately 50% of the patients are willing to prefer therapies that improve QOL, with patients having in mind that QOL is considered equally or even more important than longevity by patients. Approximately 50% of the patients are willing to prefer therapies that improve QOL.
even though at the cost of shortening life expectancy. Considering recent evidence that comprehensive and integrative HF care, including palliative interventions, can have such an important effect for both patients and health care systems, several current HF guidelines have stated the importance of this approach. According to the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF, it is recognized that palliative and end of life care should ideally be introduced early in the disease trajectory. Palliative care (PC) interventions for HF include symptom relief, such as increasing inspired oxygen concentration, diuretic management and decreasing the use of drugs that reduce blood pressure. However, these interventions occur in parallel with advanced care planning, as well as psychological and spiritual support.

Although PC approaches for HF are increasingly considered of interest in addition to evidence-based-disease-modifying interventions, there are still some barriers regarding the referral of patients to this type of integrative care. Therefore, further evidence and review of evidence is still needed to assess the effects of timely PC intervention for HF patients.

Objectives

The aim of this study is to systematically review the literature for qualitative evidence to evaluate outcomes of PC for HF patients. To this end, the proposed systematic review will focus on three main questions, which are whether PC is more effective than the usual HF care in the improvement of different health related QOL aspects and symptomatic control. Specifically, the chosen outcomes were the overall QOL and well-being, overall symptom burden and possible specific symptoms, hospital admission rates and mortality. Quantitative synthesis and meta-analysis were not performed due to the heterogeneity and various types of outcome assessment between studies.

MATERIAL AND METHODS

Protocol and registration

This systematic review is not registered.

Eligibility criteria

The articles were selected based on several characteristics, as explained below.

Study design

We anticipated a reduced number of randomized controlled trials (RCT) concerning PC interventions. Therefore, we included as possible study designs RCT as well as other clinical study types, such as controlled clinical trials (CCT), interrupted time series (ITS) studies, prospective and retrospective cohort studies and case-control studies.

Participants

The participants in the included studies were adults of any age or gender diagnosed with symptomatic HF (New York Heart Association Class II or higher). We anticipated a reduced number of studies about PC interventions in HF. Therefore, studies with participants being functionally classified as class II HF, or higher, were included, as opposed to only including patients with advanced or end-stage HF. This also allowed to further qualify the impact and outcomes of earlier referral of patients with HF to palliative medicine.

Interventions

Studies related to PC interventions with assessment of symptom burden, QOL, hospital admission rates or mortality were included. For inclusion, an objective description about the intervention provided was required. PC interventions included were integrative care in addition to evidence-based HF care, home-based PC programs, transitional PC models and hospice enrollment.

Comparators

In the included controlled studies, the control group received usual care for HF patients.

Outcomes

The most common outcomes regarding PC interventions for HF and the most important for decision-making are based on overall QOL assessment and well-being, overall symptom burden and possible specific symptom control, hospital admission rates and mortality. Studies that involved this type of outcomes were included. Eligible studies should have clear recognized and validated QOL and symptom assessment scales, such as the Edmonton Symptom Assessment scale (ESAS), the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Hospital Anxiety and Depression Scale (HADS).

Information sources, search strategy and study selection

MEDLINE, Cochrane, EMBASE and CINAHL databases were researched for articles published between January 2010 and December 2020. No manual search was performed, and article authors were not contacted. The search included free-text terms and database specific headings, according to the structure of: Heart failure AND (palliative care OR terminal care OR hospice care OR end of life). Filters for clinical studies and randomized controlled trials were applied. All the identified titles and abstracts during the search process were screened by the first author. The articles considered potentially eligible were selected for full-text analysis by two independent reviewers. The process of study selection was described in a flow diagram, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.

Data management

Full-text articles of the included studies were assessed for eligibility criteria and methodological quality by two independent reviewers. Any disagreement between reviewers was resolved by discussion until a consensus was reached.
Table 1 – Individual study’s characteristics (n = 7)

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Population</th>
<th>Intervention</th>
<th>Control</th>
<th>Main outcomes</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brännström and Boman, 2014</td>
<td>Single-center, open non-blinded, prospective randomized controlled trial</td>
<td>Patients with chronic HF (NYHA III-IV)</td>
<td>Person-centered integrated PC and active HF care combined with PC at home</td>
<td>Usual HF care</td>
<td>Symptom burden (according to the ESAS) and health-related QOL (according to the EQ-5D and the KCCQ)</td>
<td></td>
</tr>
<tr>
<td>Ng and Wong, 2018</td>
<td>Multi-center, non-blinded, randomized controlled trial</td>
<td>Patients with HF with two of the following: NYHA class III-IV; one year life expectancy; repeated hospitalizations due to HF-related symptoms and physical or psychological symptoms</td>
<td>Home-based palliative HF program</td>
<td>Usual HF care</td>
<td>QOL; symptom burden; functional status; patient satisfaction and caregiver burden</td>
<td>Data collected four and 12 weeks after hospital discharge</td>
</tr>
<tr>
<td>Wong et al, 2016</td>
<td>Multi-center, randomized controlled trial</td>
<td>End stage HF patients (NYHA III-IV) after hospital discharge</td>
<td>Home-based transitional PC</td>
<td>Placebo calls (light conversation topics unrelated to clinical issues)</td>
<td>Readmission rates and symptom burden (according to the ESAS)</td>
<td>Data collected at baseline, four and 12 weeks after hospital discharge</td>
</tr>
<tr>
<td>Hua et al, 2017</td>
<td>Randomized, controlled cohort study</td>
<td>Chronic HF patients</td>
<td>Collaborative care model</td>
<td>Usual care</td>
<td>Self-care ability; QOL; Left ventricle ejection fraction; NT-proBNP levels and the six-minute walk test performance</td>
<td>Intervention lasted for three months</td>
</tr>
<tr>
<td>Rogers et al, 2017</td>
<td>Single-center, randomized, controlled, unblinded clinical trial</td>
<td>Advanced HF patients</td>
<td>Interdisciplinary PC intervention in addition to evidence-based care</td>
<td>Usual care</td>
<td>QOL measurements (according to the KCCQ and the FACIT-Pal); depression and anxiety (according to the HADS); spiritual well-being; hospitalizations and mortality</td>
<td></td>
</tr>
<tr>
<td>Lewin et al, 2017</td>
<td>Nonrandomized, controlled prospective study</td>
<td>End-stage HF patients</td>
<td>PC, in addition to standard cardiac care alone</td>
<td>Advanced care planning documentation; Emergency department visits; hospital readmissions</td>
<td>Outcomes were compared over a six-months period. All patients in the Intervention group had a PC consult before starting</td>
<td></td>
</tr>
<tr>
<td>Yim et al, 2017</td>
<td>Longitudinal, observational, uncontrolled cohort study</td>
<td>Advanced HF patients</td>
<td>Hospice care enrollment</td>
<td>Number of hospital admissions; intensive care unit stay and Emergency room visits</td>
<td>Comparison was made between before and after six months of hospice enrollment</td>
<td></td>
</tr>
</tbody>
</table>

The second evaluator allowed for resolution of potential disagreements regarding the quality of the included studies.

Risk of bias in individual studies and across studies

For randomized studies, the risk of bias was assessed via Cochrane tools for RCT. For nonrandomized studies, ROBINS-I was used to evaluate risk of bias. Two independent reviewers were responsible for quality evaluation of studies and any disagreements were discussed between reviewers until consensus was achieved. The risk of bias across studies was not performed due to the lack of information.

Summary measures, synthesis of results and analysis

Since a small number of studies and a high level of heterogeneity was expected between studies, it was chosen not to perform a meta-regression analysis. Therefore, a qualitative analysis of studies was preferred, considering the methodological differences between included studies. For a better understanding of the different results among studies, summary tables referring to study variables, characteristics and key findings were made for a better visual comparison of results (Table 1).

RESULTS

Study selection

A total of 549 references from the MEDLINE, Cochrane, EMBASE and CINAHL databases were identified (Fig. 1). No other references were added through manual search or other sources. After removal of duplicates, 405 references remained. Of the 405 screened papers, fourteen full-text articles were examined and seven records were eligible for review and qualitative synthesis. In these seven studies the total number of patients included who received PC interventions was 5388.

Figure 1 – Flow diagram
Study characteristics

Table 1 summarizes the characteristics of the included studies. Different study designs and PC approaches for advanced HF were included. All of them compared usual HF care with a PC approach. Overall, four RCT,\textsuperscript{17–19,21} one cohort study,\textsuperscript{20} as well as two other non-randomized prospective clinical studies were included.\textsuperscript{22,23}

Risk of bias

The overall risk of bias within studies was moderate to high. Considering the included randomized studies,\textsuperscript{17–21} blinding of outcome assessment (detection bias) was the only item that was considered of high risk in all included studies (Fig. 2). This was mostly attributable to the fact that the studies were not blinded. However, even in an unblinded scenario, the performance bias was considered of low risk in three of the included studies,\textsuperscript{17,18,21} taking into account that this methodology was not likely to influence the results. In fact, blinded PC interventions for HF are not feasible, given the fact that they require a comprehensive and integrated approach with both symptomatic control and psychosocial support, based on resources such as communication.\textsuperscript{3} This was also referred in the Methods section.

Random sequence generation was considered of low risk in every included randomized study, except for Hua et al,\textsuperscript{20} because there was no available information regarding this topic. In both Brännström and Boman\textsuperscript{17} and Hua et al,\textsuperscript{20} there was some risk of selection bias. However, in the other three studies\textsuperscript{16,18,21} there was a low risk of selection bias, because sealed opaque envelopes\textsuperscript{18} and a computer software randomizer were used for randomization.\textsuperscript{19}

In all of the five included studies\textsuperscript{17–21} there was, in general, a low risk of incomplete outcome data and selective reporting.

Additionally, there were two studies\textsuperscript{18,20} with other potential sources of bias. In Hua et al\textsuperscript{20} there was the risk of using an unusual population given the fact that not all patients had advanced III-IV NYHA class HF. In the study by Ng and Wong there was the additional risk of using blocked randomization in an unblinded trial.\textsuperscript{18}

Considering the included nonrandomized studies (Table 2),\textsuperscript{22,23} the risk of bias was considered serious in both studies which are not comparable to randomized trials in terms of methodology. In general, the description of the

Figure 2 – Risk of bias summary for randomized studies included for review (n = 5)
interventions was less clear in these two studies and there was a higher discrepancy in the number of patients included.

**Results of individual studies**

The main results of individual studies for the outcomes included in this review are presented in Table 3.

All of the analyzed studies with outcomes regarding overall QOL, measured through different scores and questionnaires, showed significant improvement when PC was used versus the control interventions.\(^{17-21}\) It is important to state that different scales of QOL assessment were used between studies, which decreases the homogeneity of evidence and makes a global quantitative assessment more difficult. Therefore, we chose to pursue only a qualitative analysis and synthesis of studies. A specific quantitative analysis by Brännström and Boman showed a 26% percent improvement in QOL with PC, compared with only 3% with standard care.\(^{17}\) Quantitative evidence in Rogers et al showed that patients who received PC had higher scores in the KCCQ, with a difference of 9.49 in QOL when compared to standard care.\(^{21}\)

Regarding hospital readmission rates, whereas Brännström and Boman,\(^{17}\) Wong et al,\(^{19}\) and Yim et al\(^{23}\) found significant reduction of the number of hospital admissions when PC approaches where used, all the other studies which analyzed this outcome failed to demonstrate significant reductions. Specific independent quantitative analysis of outcomes in the study by Brännström and Boman indicates that standard care was responsible for 3.5 times more hospital readmissions than the PC approach.\(^{17}\) In the study by Wong et al,\(^{19}\) PC allowed for a reduction in hospital admissions of 55%. These examples reflect the quantitative magnitude of these results, even though only a qualitative analysis was carried out.

Long-term overall symptom burden and specific symptom control showed significant improvement versus control interventions when PC was used in three of the included studies, as specified in Table 3, with the appropriate indication of statistical significance.\(^{17,19,21}\) However, one of the included studies did not show any significant improvement.\(^{18}\)

**DISCUSSION**

**Summary of evidence and limitations**

This systematic review focused on PC interventions for advanced HF patients, and looked specifically at outcomes such as QOL, symptom burden, hospital admission and mortality. First, it is important to recognize that there was a lot of heterogeneity between studies, both clinically and methodologically, which limits the efficacy analysis of these outcomes. However, there were convergences among studies, namely towards the significant efficacy of PC interventions when it comes to the improvement of the overall QOL. In fact, every included article that evaluated this outcome\(^{17-21}\) suggested a significant difference between PC

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### Table 2 – Risk of bias in nonrandomized studies (n = 2)

<table>
<thead>
<tr>
<th>Study</th>
<th>Domain 1: Confounding bias</th>
<th>Domain 2: Selection</th>
<th>Domain 3: Classification of intervention</th>
<th>Domain 4: Deviation from interventions</th>
<th>Domain 5: Missing data</th>
<th>Domain 6: Measurement of outcomes</th>
<th>Domain 7: Selection of reporter result</th>
<th>ROBINS-I Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewin et al, 2017(^{22})</td>
<td>1</td>
<td>1-2</td>
<td>1-2</td>
<td>3-4</td>
<td>1</td>
<td>3-4</td>
<td>1-2</td>
<td>3 Serious</td>
</tr>
<tr>
<td>Yim et al, 2017(^{23})</td>
<td>1</td>
<td>3-4</td>
<td>1-2</td>
<td>3-4</td>
<td>1</td>
<td>2-3</td>
<td>1-2</td>
<td>3 Serious</td>
</tr>
</tbody>
</table>

### Table 3 – Key findings of individual studies (n = 7)

<table>
<thead>
<tr>
<th>Study</th>
<th>Significant difference</th>
<th>No significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brännström and Boman, 2014(^{17})</td>
<td>Health related QOL (p = 0.02); nausea (p = 0.02); number of Hospitalizations (p = 0.009) and days spent in the hospital (p = 0.011).</td>
<td>Symptom burden (the ESAS; the KCCQ).</td>
</tr>
<tr>
<td>Ng and Wong, 2018(^{18})</td>
<td>QOL (the MQOL, p = 0.016); overall symptom burden at 4 weeks (the CHFQ, p = 0.01).</td>
<td>Overall symptom burden at 12 weeks (the CHFQ and the ESAS).</td>
</tr>
<tr>
<td>Wong et al, 2016(^{19})</td>
<td>Hospital readmission rate at 12 weeks (p = 0.009); depression (p &lt; 0.05), dyspnea (p &lt; 0.05) and symptom burden (Total ESAS, p &lt; 0.05); QOL (the CHFQ, p &lt; 0.01; the MQOL, p &lt; 0.05).</td>
<td>Hospital readmission rate at 4 weeks.</td>
</tr>
<tr>
<td>Hua et al, 2017(^{20})</td>
<td>Self-care maintenance ability (p &lt; 0.05); mental QOL (p &lt; 0.05) and physical QOL (p &lt; 0.01).</td>
<td>-</td>
</tr>
<tr>
<td>Rogers et al, 2017(^{21})</td>
<td>Improvement in the KCCQ and the FACIT-Pal functional and QOL scores; depression (p = 0.020); anxiety (0.048); spiritual well-being (p = 0.027).</td>
<td>Hospital readmission rates and mortality.</td>
</tr>
<tr>
<td>Lewin et al, 2017(^{22})</td>
<td>-</td>
<td>Hospital readmissions.</td>
</tr>
<tr>
<td>Yim et al, 2017(^{23})</td>
<td>Hospital Admissions and Emergency Room visits (p &lt; 0.001).</td>
<td>-</td>
</tr>
</tbody>
</table>

KCCQ: Kansas City Cardiomyopathy questionnaire; MQOL: McGill Quality of Life questionnaire; QOL: quality of life
and standard HF care, with better QOL with a palliative approach. This could be explained because the quality of care in palliative medicine is mainly evaluated and measured by the improvement in the overall QOL of both patients and their families, even though it is difficult to measure objectively.\textsuperscript{24} Therefore, this allows for more focus on the individual patient, including the social sphere, family problems and the fear of death,\textsuperscript{24} all of which are present in advanced HF patients and are a cause of serious suffering that mandates intervention.

Unlike the health related QOL, the evidence related to the outcome of symptom burden is not so robust. Although two studies revealed significant improvement in long-term overall symptom burden with PC,\textsuperscript{19,20} other studies showed similar results with standard care. However, it is important to recognize some aspects, namely that PC may provide earlier symptomatic control, as suggested by Ng and Wong,\textsuperscript{18} and possibly explained by the importance attributed to the prevention of expected symptoms in palliative medicine, with a faster approach. Moreover, although the overall symptomatic control may be similar, there is a tendency for PC to significantly better improve specific psychological symptoms, such as depression and anxiety, contributing to a better spiritual well-being.\textsuperscript{19-21} This further reinforces the fact that PC professionals tend to be more experienced in dealing with this type of psychological symptoms, having already been demonstrated that psychotherapy plays an important role in these patients.\textsuperscript{25}

The number of hospital admissions, duration of hospital stay and emergency room visits are also very important outcomes nowadays, especially considering that the economics of care are a worldwide priority due to the lack of financial resources.\textsuperscript{26} Several of these studies\textsuperscript{17,19,23} showed that referral of patients to palliative medicine had a significantly positive effect in reducing the pressure on healthcare systems, whether in terms of readmission rates, emergency room visits or duration of hospital stay, which can contribute to reducing costs and better healthcare allocation. Moreover, in a recent study, it has been shown that for non-cancer patients who received PC while hospitalized with a serious illness there was a statistically significant reduction of cost of US$2105 per patient.\textsuperscript{27} Therefore, palliative medicine must and has become a concern and an increasing public health priority.\textsuperscript{28,29}

The fact that reducing mortality is not a necessary goal of PC approaches makes it a less studied outcome, which was only evaluated in one included study. However, it is an interesting topic and further studies could help establishing if it is beneficial.

Our systematic review has both strengths and limitations. On one hand, it shows evidence of benefit of PC in HF patients across various outcomes. On the other hand, it has several limitations, as already stated, such as a moderate to high risk of bias among studies, and the presence of different methodologies and approaches between studies, which limits the comparison between them.

The findings of this review have implications for future research and planning. We identified several PC interventions that should be further integrated in future HF treatment guidelines. It is also important to investigate whether early referral of patients to PC will allow for a reduction in the number of hospital deaths from HF, considering that the last six months of life for these patients are still often marked by frequent hospital admissions, culminating in hospital deaths.\textsuperscript{30} Also, this review identified that more rigorous studies and study designs are needed in order to further continue to develop PC approaches for advanced HF.

Another important issue in this review was to evaluate how soon HF patients received PC interventions. Only three of the selected studies\textsuperscript{10,21,23} included patients with early-stage HF, namely NYHA class I to II or weakly symptomatic patients. Therefore, robust conclusions regarding the effectiveness of early PC interventions in HF cannot yet be made, because that was not the major factor studied in most articles. However, having in mind that these studies indicated effectiveness with PC interventions, a tendency towards an advantage in early referral of HF patients can be assumed, with the concomitant disease-modifying treatments.

In parallel with the development of PC approaches for advanced HF patients, there have been developments in terms of new treatments and devices for these patients. This is the case of the left ventricle assist device, which can be used for patients not expected to survive without further hemodynamic support, either as a bridge to transplant or a destination therapy, although with strict eligibility criteria and a high cost.\textsuperscript{31,32} Furthermore, vericiguat, a novel guanylate cyclase stimulator, has been shown to reduce incidence of death due to cardiovascular causes and the hospitalization of patients with high-risk HF.\textsuperscript{33} In fact, palliative medicine should take into account all the novel advances that can benefit advanced HF patients. It is mandatory to integrate all the best possible care, PC included, in the relief of suffering of HF patients.

In line with our outcomes for this review, PC seems effective in advanced HF patients, especially when we consider the overall QOL of the patients and the pressure imposed upon healthcare systems. A PC approach in HF patients should include advance care planning, routine evaluation of QOL indexes, symptom burden, and shared decision-making.

CONCLUSION

The readiness for healthcare services to provide PC for patients with chronic diseases, such as HF, has never been more imperative, considering the disease burden. Nevertheless, this review showed that there are still few studies on PC Interventions in HF with more rigorous designs such as RCT. However, several other studies with other designs were included. PC for HF patients improves the QOL and reduces the number of hospital admissions and number of emergency room visits, when compared to standard care alone. The evidence related with the efficacy of symptom burden control and reduction in mortality is not so robust.
Studies focusing on early referral of HF patients to palliative medicine are still lacking, even though this is recommended in most guidelines. Therefore, this review highlights that this topic is still understudied and that studies are heterogeneous.

AUTHORS CONTRIBUTION

JFP: Draft of the manuscript, approval of the final version of the paper
PRP: Design of the review protocol, data analysis, critical review and final approval of the paper

REFERENCES


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