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Palliative Care Medicine for Patients. With Advanced Heart Failure: A Systematic Review

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RESUMO

Introdução: A insuficiência cardíaca apresenta estimativas de sobrevivência de ~10% após 10 anos de doença. Tendo em conta que se trata de uma doença crónica debilitante, é importante investigar os potenciais benefícios e eficácia de uma abordagem de cuidados paliativos.

Objetivos: Rever de forma sistemática a eficácia dos cuidados paliativos para doentes com insuficiência cardíaca avançada, em termos de qualidade de vida, controlo sintomático, admissões hospitalares e mortalidade.

Métodos: Pesquisa na base de dados MEDLINE, Cochrane e B-on por artigos publicados desde 2010 até Dezembro de 2020, tendo sido incluídos estudos clínicos em humanos com insuficiência cardíaca avançada ou terminal, comparando a integração de cuidados paliativos com a terapêutica standard. Os *outcomes* selecionados para extração de dados foram a qualidade de vida, controlo sintomático, admissões hospitalares e mortalidade.

Resultados: O protocolo de pesquisa resultou em 7 estudos elegíveis para revisão e análise qualitativa. O risco geral de viés foi considerado moderado a alto. A maioria dos estudos demonstrou melhorias com a integração de cuidados paliativos em termos de qualidade de vida e redução de hospitalizações. A evidência de suporte de uma melhoria significativa no controlo sintomático geral não foi tão robusta.

Conclusões: Os cuidados paliativos aparentam ser no geral significativamente eficazes para doentes com insuficiência cardíaca avançada. É necessária investigação futura, com estudos mais rigorosos, para continuar a desenvolver o papel dos cuidados paliativos em doentes com insuficiência cardíaca. Apesar de existir evidência suficiente para suportar os cuidados paliativos, tal ainda não é totalmente aceite e praticado.

Palavras-Chave: Insuficiência cardíaca; Cuidados Paliativos; Qualidade de Vida.

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ABSTRACT

Introduction: Heart failure is a disease with survival estimates of ~10% after 10 years of the disease. Being a chronic and debilitating illness it is important to investigate the potential efficacy of a palliative care approach for these patients.

Objectives: Systematically review the efficacy of integrating palliative care for patients with advanced heart failure, including the outcomes of overall quality of life and well being, overall symptom burden and possible specific symptoms, hospital admission rates and mortality.

Methods: The MEDLINE, Cochrane and B-on databases were searched for articles published from 2010 until December 2020 about palliative care interventions for heart failure. Clinical studies with humans with advanced or end-stage heart failure were included, comparing the integration of palliative care with usual cardiac care.

Results: The search protocol resulted in seven eligible studies for review and qualitative synthesis. The overall risk of bias within studies was moderate to high. The majority of studies demonstrated improvements with the integration of palliative care in terms of quality of life and reduction of admission rates. The evidence to support a significant improvement in overall symptom burden was not so robust among studies.

Conclusion: Palliative care interventions seem to be overall significantly efficacious for patients with heart failure. Future investigation is needed, with more rigorous study designs, to further develop the role of palliative care for heart failure patients. Although, there seems to be evidence to support the early integration of this type of care, this is still not utterly accepted and practiced.

Keywords: heart failure; palliative care; quality of life

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1. INTRODUCTION

1.1. *Rationale*

Heart failure (HF) affects more than 26 million people globally, being responsible for a large number of deaths worldwide, with survival estimates of ~10% after 10 years of the disease (Bloom et al., 2017; Levy et al., 2002). However, more impactful than the mortality associated with HF might be the morbidity associated with this disease. In fact, the quality of life in patients with HF is significantly reduced, given the symptoms of fatigue, dyspnea, pain, cognitive decline and depression (Bloom et al., 2017; Goodlin, 2009; Hoekstra et al., 2013). Indeed, being a chronic illness with increasing survival rates over the last years, HF is responsible for a significant disease burden, with a quality of life as poor as in patients with cancer and a significant health care system economic impact (Dokainish et al., 2017; Goodlin, 2009; Iqbal, Francis, Reid, Murray, & Denvir, 2010; Levy et al., 2002; Roger et al., 2004).

Therefore, interventions directed to improve quality of life, either physical or psychological, and to better accept the disease might be of interest since 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 (Hoekstra et al., 2013; Iqbal et al., 2010; Obieglo, Uchmanowicz, Wleklík, Jankowska-Polanska, & Kusmierz, 2014). In fact, it was been shown that quality of life is placed equally or even more importantly than longevity by patients, with approximately 50% of them being willing to prefer therapies that improve quality of life while shortening life expectancy (Kraai et al., 2013; Stevenson et al., 2008).

Considering recent evidence that comprehensive and integrative HF care with palliative intervention based on the patient's quality of life can have such an important effect for both patients and health care systems, several current HF guidelines have stated the importance of this type of approach (Bloom et al., 2017). According to the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure, it is recognized that palliative and end of life care should ideally be introduced early in the disease trajectory (Sionis, 2016). Palliative care interventions for HF include both symptom relief (such as increasing inspired oxygen concentration, diuretic management and lowering drugs that reduce blood pressure) as well as

psychological and spiritual support with concomitant advanced care planning (Gibbs, Addington-Hall, & Gibbs, 2011; Goodlin, 2009; McCarthy, Addington Hall, & Ley, 1997; Sionis, 2016).

Although palliative care approaches for HF are ever more considered of interest in parallel with evidence-based-disease-modifying interventions, there are still some barriers regarding the referral of patients to this type of integrative care (Goodlin, 2009). Therefore, further evidence and review of evidence is still needed to assess the effects of early palliative care intervention for HF patients.

1.2. *Palliative Care Interventions for Heart Failure and Symptom Management*

The palliative care approach to the patient is based on an interdisciplinary management of the patients and their families, focused on improving the quality of life. This includes treatment of distressing symptoms, promotion of psychological and spiritual well-being and offering a support system for patients and their environment that facilitates coping with the disease and its uncertainty. The coordination of care allows for the improvement of communication and assistance of shared decision making and advanced care planning. Planification of care options is particularly important for heart failure in the way that there are several available devices that may artificially prolong lifetime with complex trade-offs, namely the implantable cardioverter-defibrillator (ICD) and the Left Ventricular Assist Device (LVAD). This type of devices may not be indicated for frail older patients and can even impact their mode of death, but the decisions regarding their implantation are highly preference-sensitive (Krumholz, 2011), which reflects the importance of an appropriate channel of communication.

Having in mind the overall importance of palliative care for heart failure, and given the fact that it is a highly symptomatic disease, with a high risk of death and important decision making, it should be integrated early in the course of the illness. Identifying patients in need of palliative care assessment can be helped by using some published criteria like a negative answer to the “surprise question” (Would I be surprised if the patient died within 12 months?), frequent hospital admissions for heart failure, difficult-to-control and prolonged symptoms, functional dependency, feeding intolerance, history of out-of-hospital cardiac arrest or the absence of an advanced care planning document (Weissman & Meier, 2011).

Advanced care planning for HF is of the utmost importance to define goals of care with the help of palliative interventions. The major decisions required are related to the use or withdrawal of ICD, inotropic support, the LVAD and disease modifying pharmacological therapy. In particular, ICDs pose a real challenge in palliative care, with several studies showing that patients are not properly informed about their use and that doctors infrequently discuss deactivation of the ICD with patient (Kirkpatrick, Gottlieb, Sehgal, Patel, & Verdino, 2012), which ultimately frequently leads to the ICD being active during death and shocking patients in the end of life (Goldstein, Carlson, Livote, & Kutner, 2010). If repeated shocks happen during the dying process, emergency deactivation with a magnet placement on top of the ICD can be achieved.

Another important aspect of palliative care is symptom burden control. It has been demonstrated that for patients diagnosed with HF the single most important determinant of health-related quality of life is the physical symptom burden (Heo, Doering, Widener, & Moser, 2008). The most common reported symptoms by patients are dyspnea, pain, decreased exercise tolerance, depression and fatigue (Heo et al., 2008).

Dyspnea refractory to diuretics, nitrates and inotropes is one of the major HF symptoms and its management in palliative care is achieved mainly with opioids. Low-dose morphine (10 to 20mg, orally) is generally effective in reducing breathlessness and improving exercise tolerance for both chronic stabilized and advanced HF patients. (Johnson, McDonagh, Harkness, McKay, & Dargie, 2002). Due to the possibility of severe chronic cardiorenal syndrome in patients with important disease burden, there might be a preference towards oxycodone, which does not lead to excretion of active metabolites as morphine does. Despite the fact that opioids are the first line of treatment, there are also other available options like benzodiazepines, rehabilitation and oxygen therapy for patients with persistent hypoxia.

Although HF is not directly associated with musculoskeletal pain in early stages of disease, the majority of patients with chronic HF report pain, mostly in the legs, below the knees (Walke, Gallo, Tinetti, & Fried, 2004). Considering the World Health Organization pain ladder, pain treatment should begin with a nonopioid drug. However, for patients with HF it is extremely important to have in mind the side effects of analgesics, like nonsteroidal anti-inflammatory drugs, which are contraindicated

because of the risk of worsening kidney function, leading to further fluid retention and worsening symptom burden. Therefore, once again, opioids emerge as a very appropriate treatment option, covering control of both dyspnea and pain, being the only class of medication that showed effective reduction of pain in the PAIN-HF Study (Goodlin et al., 2012).

Fatigue and depression are two symptoms that often arise in association in HF patients, given the fact that decreased cardiac output causes deconditioning and cachexia, thus limiting life activities, exacerbating depressive symptoms and loss of sense of self-efficacy. Muscle strengthening, especially in the thigh region, alleviates fatigue (Quittan et al., 2001). Treatment for depression is primarily based on controlling other contributing physical symptoms. This is because several trials have failed to demonstrate improvement with standard antidepressants, like sertraline or escitalopram (O'Connor et al., 2010). However, very frequently, treatment with stimulants such as methylphenidate, selective serotonin reuptake inhibitors or tricyclic antidepressants is tried despite the lack of evidence (Bekelman DB, 2008).

Although it is very important to start specific treatment towards the palliation of symptoms in HF patients, disease-modifying drugs and interventions are still one of the major components of symptom management, even if there is a goal shift towards palliation rather than life prolongation. This is because symptoms are mostly determined by the degree of volume overload, controlled with targeted pharmacological therapy. However, if in end-stage disease renin-angiotensin-aldosterone inhibitors and beta-blockers become intolerable due to hypotension, they should be discontinued.

1.3. Barriers to Palliative Care

There is evidence that referral of HF patients to palliative care is still lacking, especially in comparison with other diseases such as cancer (Kavalieratos et al., 2014). There are several barriers to referral identified, mainly based on the lack of knowledge regard this type of care and planning. This includes limitations in available evidence, uncertainty and difficulty of prognosis definition by doctors, lack of knowledge on how to initiate a “bad news” and prognostic disclosure with patients and lack of understanding that

palliative care interventions may be useful for all patients with HF and not only those with terminal illness (Dunlay et al., 2015).

1.4. Objectives

The aim of this study is to systematically review the literature for qualitative evidence in order to evaluate outcomes of palliative care for heart failure patients. To this end, the proposed systematic review will focus on three main questions, which are whether palliative care is more effective than the usual HF care in the improvement of different health-related quality of life (HRQL) aspects and symptomatic control, being chosen specifically as outcomes the overall quality of life and well being, overall symptom burden and possible specific symptoms, hospital admission rates and mortality.

Having in mind the barriers to palliative care referral for patients with HF, this work intends to contribute with further knowledge on this subject, decrease the limitations of evidence and alert ever more health care professionals to the need of palliation for this patients, improving the overall acceptance and inclusion of this type of care.

2. METHODS

2.1. Protocol and Registration

This systematic review is not registered

2.2. Eligibility Criteria

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

Study Designs

We anticipated a few number of randomized controlled trials (RCTs) concerning palliative care interventions. Therefore, we included as possible study designs RCTs as well as other clinical study types, such as controlled clinical trials (CCTs), interrupted time series (ITS) studies, prospective and retrospective cohort studies and case-control studies, both randomized and nonrandomized.

Participants

The participants in the included studies are adults of any age or gender diagnosed with advanced or end-stage heart failure. We anticipated a few number of studies regarding palliative care interventions in heart failure. Therefore, studies with the majority of participants being functionally classified as class II or higher according to the New York Heart Association were also included.

Interventions

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

Comparators

In the included controlled studies, the controlled group included usual cardiac care for heart failure patients.

Outcomes

The most common outcomes regarding palliative care interventions for heart failure are based on overall quality of life assessment and well being, overall symptom burden and possible specific symptoms, hospital admission rates and mortality. Studies that involved this type of outcomes were included. Eligible studies should have clear recognized and validated quality of life and symptom assessment scales, such as the Edmont Symptom Assessment scale (ESAS), Kansas City Cardiomyopathy Questionnaire (KCCQ) and Hospital Anxiety and Depression Scale (HADS).

2.3. Information Sources, Search Strategy and Study Selection

The MEDLINE, Cochrane and B-on databases were searched for articles published after 2010 and the last date searched was December 2020. No manual search was performed and article authors were not contacted. The search included free-text terms and database specific headings, according 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.(Moher, 2015)

2.4. 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 solved by discussion until a consensus was reached. The second evaluator allowed for resolution of potential disagreements regarding the quality of the included studies.

2.5. Risk of bias in Individual Studies and Across Studies

For randomized studies, the risk of bias was assessed via Cochrane tools for RCT.(Higgins et al., 2011) For nonrandomized studies, ROBINS-I was used to evaluate risk of bias.(Sterne et al., 2016) 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.

2.6. Summary measures, Synthesis of Results and Analysis

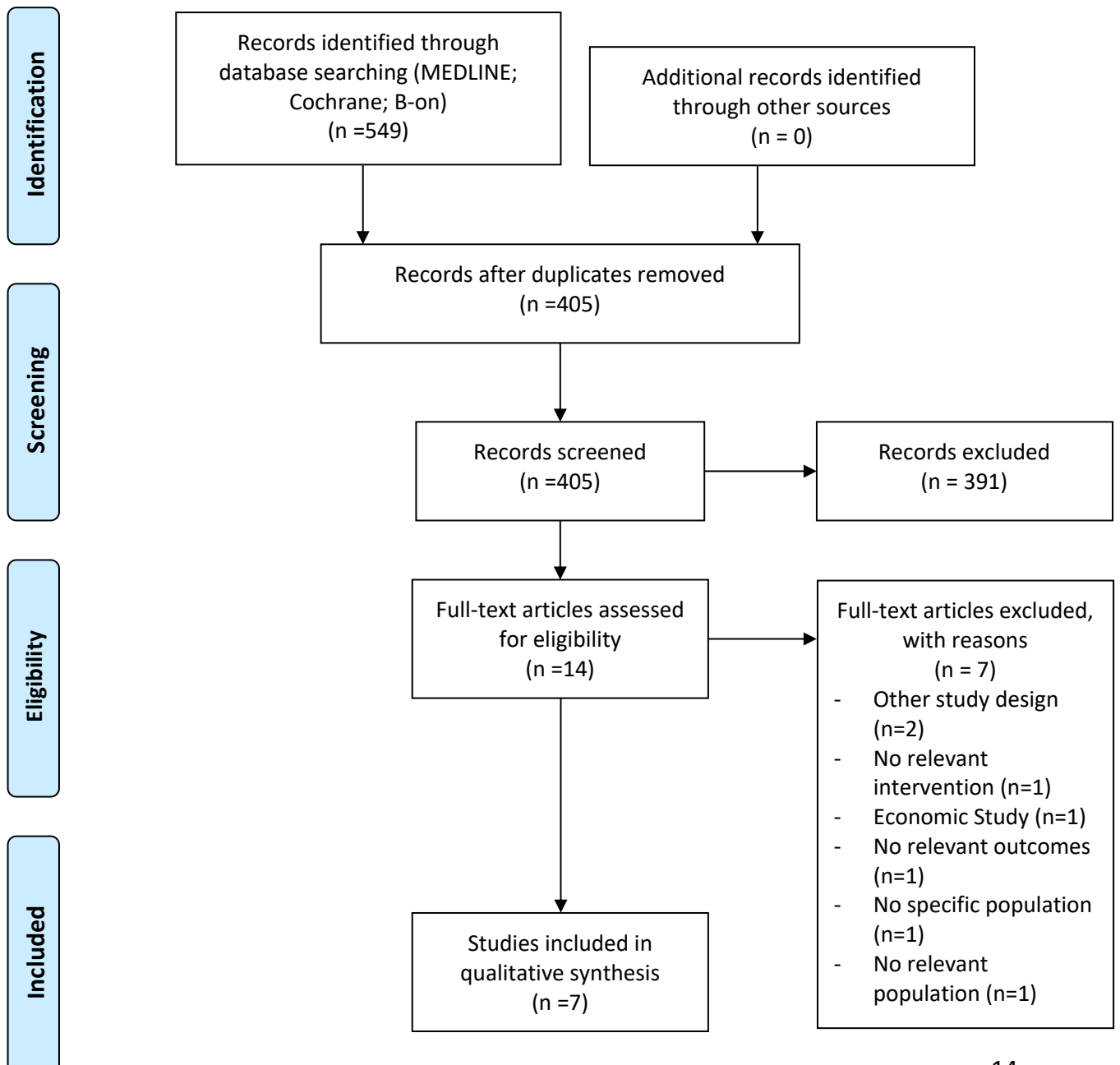
According to the fact that a small number of studies was anticipated and that an elevated level of heterogeneity was expected between studies, it was chosen not to perform a meta-regression analysis. Therefore, a qualitative analysis of studies was preferred, taking into account the methodological differences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

3. RESULTS

3.1. Study Selection

Following the research protocol, a total of 549 references from electronic MEDLINE, Cochrane, EMBASE and CINAHL databases were identified (Figure 1). No other references were added through manual research 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 of patients included who received PC interventions were 5388.

Figure 1 – Flow Diagram



3.2. Study Characteristics

Table 1 summarizes the included study's characteristics.

Different study designs and palliative care approaches for advanced HF were included and all of them compared usual HF care with a palliative care approach. Overall, 4 RCTs (Brännström & Boman, 2014; Ng & Wong, 2018; Rogers et al., 2017; Wong et al., 2016) were included and 3 prospective clinical studies (Hua et al., 2017; Lewin et al., 2017; Yim et al., 2017).

Table 1 - Individual Study's Characteristics

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

EQ-5D – EuroQol's Quality of Life (Five dimensions); ESAS – Edmonton Symptom Assessment Scale; FACIT-Pal – Functional Assessment of Chronic Illness Therapy-Palliative Care; HADS – Hospital Anxiety and Depression Scale; HF – Heart Failure; KCCQ – Kansas City Cardiomyopathy Questionnaire; NT-proBNP – N-terminal prohormone of brain natriuretic peptide; NYHA – New York Heart Association; PC – Palliative Care; QOL – Quality of Life.

3.3. Risk of Bias

The overall risk of bias within studies was moderate to high.

Considering the included randomized studies (Brännström & Boman, 2014; Hua et al., 2017; Ng & Wong, 2018; Rogers et al., 2017; Wong et al., 2016), blinding of outcome assessment (detection bias) was the only item that was considered of high risk in all included studies (**Figure 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 (Brännström & Boman, 2014; Ng & Wong, 2018; Rogers et al., 2017) of the included studies taking into account that this methodology was not likely to influence the outcome results. In fact, blinded palliative care 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 as communication. (Goodlin, 2009) This is also referred in the study's Methods section. Random sequence generation was considered of low risk in every included randomized study except for Hua et al. (Hua et al., 2017) because there was no available information on this topic. In both Brannstrom et al. (Brännström & Boman, 2014) and Hua et al. (Hua et al., 2017) there was some risk of selection bias. However, in the other three (Ng & Wong, 2018; Rogers et al., 2017; Wong et al., 2016) studies there was a low risk of selection bias through methods as sealed opaque envelopes (Ng & Wong, 2018) or usage of a computer software research randomizer (Wong et al., 2016).

In all of the five included studies (Brännström & Boman, 2014; Hua et al., 2017; Ng & Wong, 2018; Rogers et al., 2017; Wong et al., 2016) there was in general a low risk of incomplete outcome data and selective reporting.

Also, there were two studies (Hua et al., 2017; Ng & Wong, 2018) with other potential sources of bias. In Hua et al. (Hua et al., 2017) there was the risk of using an usual population, given the fact that not all patients had advanced, III-IV NYHA class. In Man Ng et al. (Ng & Wong, 2018) there was the additional risk of using blocked randomization in an unblinded trial.

Considering the included nonrandomized studies (Lewin et al., 2017; Yim et al., 2017) (Table 2), the risk of bias was considered serious in both studies which are not comparable to randomized controlled trials in methodology.

Risk of bias across studies was not evaluated due to the lack of information and no additional analysis was performed.

Figure 2 – Risk of bias summary for randomized studies included for Review

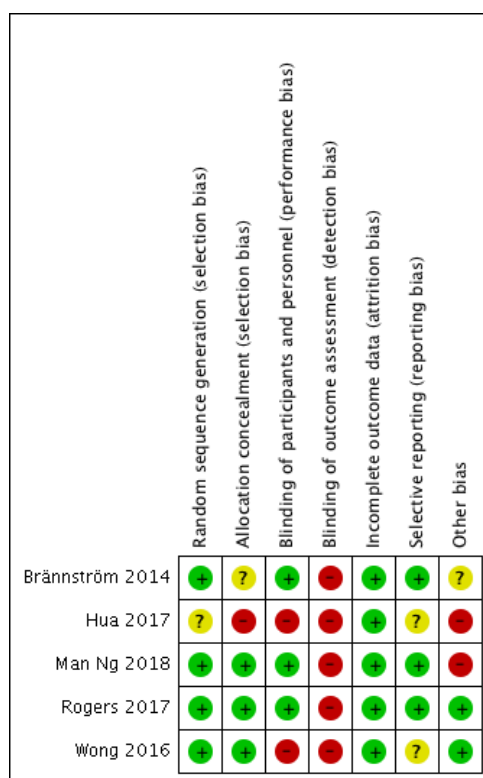


Table 2 – Risk of bias in nonrandomized studies

Study	Domain 1: Confounding Bias	Domain 2: Selection	Domain 3: classification of intervention	Domain 4: Deviation from interventions	Domain 5: missing data	Domain 6: measurement of outcomes	Domain 7: selection of reporter result	ROBINS-I Overall
Lewin 2017	1	1-2	1-2	3-4	1	3-4	1-2	3 Serious
Yim 2017	1	3-4	1-2	3-4	1	2-3	1-2	3 Serious

3.4. Results of Individual Studies

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

All of the analyzed studies with an outcome regarding overall quality of life, measured through different scores and questionnaires, showed significant improvement when

palliative care was used versus the control interventions. It is important to state that different scales of quality of life assessment were used between studies, which decreases the homogeneity of evidence and makes a global quantitative assessment impossible. Specific quantitative analysis of Brännström and Boman showed a 26% percent improvement in quality of life with palliative care, compared with only 3% with standard care. Quantitative evidence in Rogers et al. showed that patients who received palliative care had higher scores in the KCCQ, with a difference of 9.49, when compared to standard care.

Regarding hospital readmission rates, whereas Brännström and Boman, Wong et al., and Yim et al. found significant reduction of the number of hospital admissions when palliative care approaches were used, all the other studies which analyzed this outcome failed to demonstrate significant reductions. Specific independent quantitative analysis of outcomes in Brännström and Boman indicates that standard care was responsible for 3,5 times more hospital readmissions than the palliative care approach. In Wong et al. palliative care allowed for a reduction in hospital admissions of 55%. These examples reflect the quantitative magnitude of these results, despite only a qualitative analysis having been pursued.

Long term overall symptom burden and specific symptoms control showed significant improvement versus control interventions when palliative care was used, in three of the included studies (Brännström & Boman, 2014; Rogers et al., 2017; Wong et al., 2016). However, one of the included studies didn't show any significant improvement. (Ng & Wong, 2018).

Table 3 – Key Findings of individual Studies

Study	Key Findings (Relative to control)
Brännström and Boman, 2014	<p>Significant Difference (post-intervention): 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).</p> <p>No Significance Difference: Symptom Burden (the ESAS; the KCCQ).</p>
Ng and Wong, 2018	<p>Significant Difference: QOL (the MQOL, P=0,016); Overall symptom burden at 4 weeks (the CHFQ, P=0,01).</p> <p>No Significance Difference: Overall symptom burden at 12 weeks (the CHFQ and the ESAS).</p>
Wong et al., 2016	<p>Significant Difference: Hospital Readmission Rate at 12 weeks (P=0,009); Depression (P<0,05), Dyspnea (P<0,05) and symptom burden (Total ESAS, P<0,05); QOL (the CHFQ, P<0,01; the MQOL, P<0,05).</p> <p>No significance Difference: Hospital Readmission Rate at 4 weeks.</p>
Hua et al., 2017	<p>Significant Difference: Self-care maintenance ability (P<0,05); Mental QOL (P<0,05) and Physical QOL (P<0,01).</p>
Rogers et al., 2017	<p>Significant Difference: 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).</p> <p>No significance Difference: Hospital readmission rates and Mortality.</p>
Lewin et al., 2017	<p>No significance Difference: Hospital readmissions.</p>
Yim et al., 2017	<p>Significant Difference: Hospital Admissions and Emergency Room visits (P<0,001).</p>
<p>CHFQ – Chronic Heart Failure Questionnaire; ESAS – Edmonton Symptom Assessment Scale; FACIT-Pal – Functional Assessment of Chronic Illness Therapy-Palliative Care; KCCQ – Kansas City Cardiomyopathy Questionnaire; MQOL – McGill Quality of Life Questionnaire; QOL – Quality of Life.</p>	

4. Discussion

This systematic review is focused on palliative care interventions for advanced heart failure patients, taking interest specifically in outcomes such as quality of life, symptom burden, hospital admission and mortality. First of all, it is important to recognize that there was a lot of heterogeneity between studies, both clinically and methodologically, which limits the analysis of efficacy of these outcomes.

However, there were observed convergences among studies, namely towards the significant efficacy of palliative care interventions when it comes to the improvement of the overall quality of life. In fact, every included article that evaluated this outcome (Brännström & Boman, 2014; Hua et al., 2017; Ng & Wong, 2018; Rogers et al., 2017; Wong et al., 2016) suggested a significant difference between palliative care and

standard HF care, with better quality of life with a palliative care approach. This could be explained because the quality of care in palliative medicine is mainly evaluated and measured by the improvement in the overall quality of life of both patients and their families, even though it is difficult to measure objectively. (Daire, Donabédian, Tambouras, & Sagot, 2019) Therefore, this allows for aiming more precisely at the individual, including the social sphere, family problems and the fear of death,(Daire et al., 2019) all of which are present in advanced heart failure patients and are a cause of serious suffering that mandates intervention.

Unlike the health related quality of life, the evidence related to the outcome of symptom burden is not so robust. Although two studies(Hua et al., 2017; Wong et al., 2016) revealed significant improvement in long term overall symptom burden with palliative care, other studies showed similar results as with the standard care. However, it is important to recognize some aspects, such as that palliative care may provide earlier symptomatic control, as suggested by Man Ng 2018,(Ng & Wong, 2018) 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 palliative care to significantly better improve specific psychological symptoms, such as depression and anxiety, contributing to a better spiritual well-being.(Hua et al., 2017; Rogers et al., 2017; Wong et al., 2016) This further promotes that palliative care professionals are more experienced with dealing with this type of psychological symptoms, having already been demonstrated that psychotherapy plays an important role in this patients.(Fulton, Newins, Porter, & Ramos, 2018)

The number of hospital admissions, duration of hospital stay and emergency room visits is also a very important outcome nowadays, especially considering that economics of care are a worldwide priority due to the scarcity of monetary resources.(Smith, Brick, O'Hara, & Normand, 2014) Several of these studies (Brännström & Boman, 2014; Wong et al., 2016; Yim et al., 2017) showed a significantly positive effect of referral of patients to palliative care medicine in reducing the pressure imposed upon the Health Systems, whether in terms of readmission rates, emergency room visits or duration of hospital stay, which can contribute to reduce costs and provide better healthcare allocation. Moreover, in a recent study, it has been shown that for non-cancer patients who

received palliative care while hospitalized with a serious illness there was a statistically significant reduction of cost of -\$2105 per patient.(May et al., 2018) Therefore, palliative care must and has become a concern and an increasing priority of Public Health.(Callaway, Connor, & Foley, 2018; Dzingina & Higginson, 2015)

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

Our systematic review has both strengths and limitations. On one hand, it definitely shows evidence of benefit of palliative care in multiple outcomes. On the other hand, it has several limitations, as already stated, such as a moderate to high level of risk of bias among studies and the presence of different methodologies and approaches between studies, which limits the comparison amongst them but which also is an inherent characteristic of palliative care.

The findings of this review have also implications for future research and planning. We identified several palliative care interventions that should be further integrated in the future treatment guidelines for heart failure. It is also important to investigate whether early referencing of patients to palliative care will allow for a reduction in the number of hospital deaths from heart failure, considering that the last six months of life for these patients are still often marked by frequent hospital admissions culminating in hospital deaths (Unroe et al., 2011). Also, this review identified that more rigorous studies and research designs are needed to further continue to develop palliative care approaches to advanced heart failure.

In parallel with the development of palliative care approaches for advanced heart failure patients, there have been several innovative treatments and devices emerging for this 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.(Miller & Rogers, 2018; Warraich et al., 2019) 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 heart failure.(Armstrong et al., 2020) In fact, the palliative care approach should take into

account all the novel advances that can benefit advanced heart failure patients and it is possible to integrate all the best possible care for the relief of suffering.

According with our outcomes for this review, palliative care seems efficacious for advanced heart failure patients, especially considering the overall quality of life and the pressure imposed upon health systems. A palliative care approach should include advanced care planning, routine evaluation of quality of life indexes and symptom burden and shared decision-making process.

5. CONCLUSION

The preparation for health services to provide PC for patients with chronic diseases, such as HF, has never been more imperative, considering the disease burden. Nevertheless, this review demonstrated that there is still a few of studies on PC Interventions in HF with more rigorous designs that translate in more evidence, such as RCT. However, several other studies with other designs were included, therefore having been considered with enough methodological quality to figure in this review. Current evidence makes clear that PC for HF patients improves the QOL and reduces the number of hospital admissions, duration of hospital stay and number of emergency room visits, when compared to standard care alone. Evidence related to the efficacy controlling symptom burden and decreasing mortality is not so robust. Studies focusing on early referral of HF patients to palliative medicine are still lacking, despite this being recommended in most guidelines. Therefore, this review highlights that this topic is still understudied and with a lot of heterogeneity between studies.

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